7-2-2011

Comparison of monotherapy with angiotensin-converting enzyme inhibitors or angtiotensin receptor blockers in improving health outcomes among veteran patients with type 2 diabetes

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COMPARISON OF MONOTHERAPY WITH ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS IN IMPROVING HEALTH OUTCOMES AMONG VETERAN PATIENTS WITH TYPE 2 DIABETES

BY

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Pharm.D., University of New Mexico, 2004

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy

Pharmaceutical Sciences

The University of New Mexico
Albuquerque, New Mexico

May, 2011

DEDICATION

I wholeheartedly dedicate the completion of this dissertation to my parents, grandfathers, and great-grandfather. You are all dedicated and loyal hard workers, people who worked two to three jobs simultaneously to provide for what's most important in life: family. You taught me the "American Dream" that so many people talk about, something that conjures hope and motivation. Each of you embodies the American Spirit. Early in my life you taught me the advantage of being an opportunist and a forerunner in addition to the importance of independence as a female. Combining these attributes with dedication, loyalty, hard work, hope, and motivation means anyone should be able to accomplish anything, regardless of background, socioeconomic status, gender, or for that matter, anything else. Indeed, without these characteristics and this belief I never would have accomplished this feat. Thank you all for instilling this in me at such a young age and throughout my life.

ACKNOWLEDGEMENTS

I sincerely thank Dr. Nasreen Khan, my primary advisor and dissertation chair, for demanding nothing less than perfection. Early on we recognized we shared the same determination and drive. Without this, the dissertation never would have received funding for that all-too-critical programmer. I appreciate her encouragement through the years of classroom teachings, one-on-one sessions, and writing and re-writing these chapters. Her vast amount of knowledge about methods and data analysis has made me a better researcher. Even after her departure from the University of New Mexico, she found time to give me feedback and push me to finish. Her guidance and professional style will remain with me as I continue my career.

I also thank the guidance I have received from Dr. Dennis Raisch, my secondary advisor and dissertation chair. He taught me a lot about the research process specific to the VA and gave me continuing encouragement as my fellowship preceptor, which founded trust upon which a strong relationship was forged. I realize the advantage he afforded me by learning skills like critical literature review. He introduced me to other well-known researchers in this field, a wonderful opportunity. His reminders of reality and the end goal helped me continue despite the dissertation taking longer than I originally planned. His different perspective has helped in areas outside of this dissertation and will continue to do so.

I thank Dr. Matthew Borrego in continuing my development by steering me to the Robert J. Wood Foundation in addition to the classroom teachings and associated projects. His feedback and attention to detail from early on helped balance correcting

mistakes in the context of deadlines throughout this process. With more of a perspective on rural life, socioeconomic status, and race and ethnic disparities, he has given me a good understanding of these issues. I continue to be amazed how, even though these topics have not been my primary research interests, they keep appearing as important factors, requiring substantial discussion.

I thank Dr. Glen Murata for his extensive clinical and research expertise. He was invaluable in his understanding of clinical practice in the VA for patients with type 2 diabetes in terms of the disease state, dual care, and bringing my dissertation back to the clinicians' point-of-view since they are the individuals who are responsible for optimizing care in patients. His patience and optimism very much helped with my motivation.

I thank Dr. Mike Sather for his insight into randomized clinical trials among a majority of health services researchers. I appreciate the opportunity he afforded me to help him take his own dissertation one step further as my first exposure to research. His flexibility and levelheadedness have always given me perspective. His traditional values are similar to my own and seem to be getting rarer by the day.

I thank Zachary Taylor, the programmer for this study. I appreciate his attention-to-detail and conscientiousness to ensure he not only upheld, but also improved, the data integrity to the level at which it was received from the VA. Without his help, this process would have easily taken another year.

I thank Kathy Boardman, a fellow graduate student and colleague. I cannot tell her how much it helps to have someone to relate to. Going through similar educational experiences, we've certainly spent quite a bit of time talking.

I thank the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, my employer throughout my graduate studies, for flexibility in tour schedule so I could attend the classes that were only offered during the day. I also thank them for their general support and encouragement.

Gratitude is extended to the American Society for Health-system Pharmacy (ASHP) Foundation for the funding to pursue this research.

Lastly, I thank my husband, Kyle. Your love is the greatest gift of all. That's the only rational reason why you would be so patient while I spend time in front of a computer instead of time with you.

“Life is a gift, and it offers us the privilege, opportunity, and responsibility to give something back by becoming more.” - Anthony Robbins

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ABSTRACT

Diabetes is a world-wide epidemic; 90-95% of diabetes cases are type 2 in nature. Albuminuria and hypertension are risk factors of diabetes complications, specifically nephropathy and cardiovascular disease. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended as monotherapy to reduce albuminuria and hypertension. Because of this, we sought to compare patients with type 2 diabetes (P2DM) who received neither therapy to those who received either monotherapy for end-stage renal disease (ESRD), cardio- and cerebro- vascular disease, and all-cause mortality. Additionally, because there are very limited data on comparisons between ACEI and ARB therapies, none of which compare occurrence of incident cardio- or cerebro- vascular disease or mortality, these monotherapies were compared. Moreover, because diabetes incidence is expected to increase, healthcare utilization was also analyzed. This longitudinal study followed P2DM maximally for five years. Comparisons between patients receiving neither therapy and either monotherapy were

performed with multivariate logistic or negative binomial regression, while comparisons between ACEI and ARB patients were performed with propensity score weighted logistic or negative binomial regression. Compared to neither therapy, ACEI patients were associated with lower odds of ESRD, higher odds of incident cardio- or cerebro- vascular disease events, lower odds of mortality, and higher incidence rates of healthcare utilization. Treatment selection existed between ACEI and ARB monotherapies in P2DM, necessitating propensity score analysis (PSA). Fortunately, the PSA balanced between group characteristics and had substantial overlap in propensity scores between groups, allowing for precise estimates of causal interpretation. No differences were found between ACEI and ARB monotherapies for all endpoints studied. Since only associations can be found between comparisons of ACEI and ARB patients with neither patients and because ACEIs or ARBs are recommended in guidelines, significance is focused on comparisons between ACEI and ARB patients. This is the second study lasting more than a year comparing outcomes of ACEI and ARB monotherapies for nephropathy and the first study comparing ACEI and ARB monotherapies for other endpoints. This study confirms that ACEIs and ARBs have no significant difference in effects for two years mean follow-up. Until this study, similar effects have only been assumed.

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CHAPTER 1: INTRODUCTION

Type 2 diabetes is a public health concern; its prevalence is expected to increase substantially. The disease causes a plethora of complications, including morbidity due to macro- and micro- vascular outcomes, and mortality. ACEI or ARB monotherapy is recommended in clinical practice guidelines for prevention of progressive nephropathy in patients with type 2 diabetes (P2DM) by reducing albuminuria levels and by reducing blood pressure. Albuminuria and hypertension are risk factors for cardio- and cerebro-vascular disease events and all-cause mortality. There have been few well-controlled head-to-head comparisons of ACEI and ARB monotherapy for end-stage renal disease (ESRD) and no head-to-head comparisons of ACEI and ARB monotherapy for cardio- and cerebro- vascular disease events or all-cause mortality in P2DM. These clinical outcomes are the most relevant long-term outcomes for this comparison in this population. Also important from a public health perspective is the comparison of outpatient visits, emergency department (ED) visits, and hospitalizations as healthcare resources are already strained. With an expected increase of people afflicted with type 2 diabetes, answers to these questions are of utmost importance Lastly, because of the few studies of ACEI or ARB monotherapy compared to placebo yielding disputed findings for cardio- and cerebro- vascular disease and all-cause mortality, the current study extends knowledge about these outcomes in P2DM receiving ACEI or ARB monotherapy or neither therapy.

Type 2 Diabetes Burden

Type 2 diabetes is already heralded as a national epidemic,[1] it is currently the sixth leading cause of death nationally.[2] Approximately 20.8 million Americans had diabetes in 2005;[3] of which, 90%-95% of had type 2 diabetes.[3] The prevalence of diabetes has increased by 80% in the last ten years,[4] and between the years 2000 and 2050, projections estimate its prevalence to increase by more than 2.5 fold.[5] If current trends concerning diabetes continue, 33% of Americans born in the year 2000 will develop diabetes in their lifetime.[6]

The escalating prevalence and incidence of type 2 diabetes are due to an aging population, a more ethnically diverse population, consumption of many foods with high sugar and fat content, a sedentary lifestyle, and overeating. For instance, 23.8% of people at least 60 years of age have diabetes[7] and as baby boomers continue to age, the number of elders will increase;[8] thus the absolute number of American elders with diabetes will also increase. The number of people at least 65 years of age has already increased 2.3 fold between the years 1970 and 2006.[9] In addition to an increasingly aged population, genetics place Hispanics, American Indians, and African Americans at higher risk than non-Hispanic whites.[10] Specifically, Hispanics, American Indians/Alaska Natives, and African Americans have a 1.7, 2.2, and 1.9 times higher prevalence rate, respectively, compared to non-Hispanic whites.[11] Obesity is also strongly associated with diabetes, yet, in terms of prevention, only 23% eat 5 servings of fruits and vegetables daily and 22% of Americans exercise regularly.[12] These habits are evident based on the increasing prevalence of people who are overweight or obese.[13] The National Health and Nutrition Examination Survey found a 55.9% prevalence rate of

people who were overweight in 1988-1994 versus 64.5% in 1999-2000 and a 22.9% prevalence rate of people who were obese versus 30.5% in the same time periods, respectively.[13]

Diabetes is progressive and its complications result in high morbidity and mortality.[14] Diabetes-related complications are attributed to more than 200,000 deaths annually.[3] In the United States (U.S), if a man is diagnosed with diabetes at age 40, he will lose 11.6 years of life after having diabetes for 28.0 years.[6] Corresponding numbers for a woman are 14.3 years of lost life after having diabetes for 38.4 years.[6]

Complications

The incidence and severity of end-stage renal disease (ESRD) in patients with diabetes is also expected to increase as the U.S. population becomes more diverse. For instance, Hispanics and African Americans with diabetes have a much higher risk of acquiring ESRD compared to non-Hispanic whites with diabetes.[15] At least in the Southwest U.S., lower extremity amputation from diabetes has been found to be 3.5-fold higher in Native Americans compared to non-Hispanic whites.[16] Evidence also exists that African Americans with diabetes have a 27% higher mortality rate compared to non-Hispanic whites.[17]

Following natural history of the disease, one to two in every five microalbuminuric (2-20mg/dL or 30-300mg/g) patients with type 2 diabetes (P2DM) become macroalbuminuric (>20mg/dL or >300mg/g) without intervention; approximately one in five macroalbuminuric P2DM will develop ESRD.[18] Since the majority of deaths in patients with diabetes are currently attributed to cardiovascular disease (CVD) events, prevention of CVD events may place more people in ESRD.[18] Diabetes is the leading

health condition contributing to incident ESRD cases according to the U.S. Renal Data System (USRDS); 45% of ESRD patients have type 2 diabetes.[19] Dialysis patients with diabetes have a 27.2% and 23.3% five-year survival rate for hemodialysis and peritoneal dialysis, respectively.[19]

In addition to nephropathy events, CVD complications are important in this disease. People who are afflicted with diabetes have two times the risk of developing CVD compared to the general population[20] and patients with diabetes and a history of CVD have more than double the risk of subsequent CVD events.[20] Patients with diabetes also have a 2-4 times higher risk of stroke compared to patients without diabetes.[3] Approximately 65% of deaths in patients with diabetes result from heart disease and stroke in the U.S.[3]

Hypertension, a risk factor for complications, has a 73% prevalence rate in the American diabetes population.[3] Compared to normotensive patients, hypertensive patients have a 22 times higher risk of developing ESRD.[21] Patients with type 2 diabetes mellitus (P2DM) and hypertension are at higher risk for diabetic nephropathy and CVD.[22,23] In P2DM and nephropathy, patients with lower blood pressure have slower progression of renal dysfunction.[24] Blood pressure reduction and antihypertensives have been shown to decrease microvascular and macrovascular complications in type 2 diabetes.[25-27]

Cost Implications

Complications are also more costly than ever, and with the increasing prevalence of diabetes, are continuing to rise. At the individual level, development of ESRD can cause costs to increase by 771% while suffering a CVD event can cause costs to increase

by 360%.[28] Additionally, healthcare expenditures have been increasing at a rate higher than inflation for several years,[29-32] and healthcare organizations have been tightening their budgets.[33]

The Department of Veterans Affairs (VA) and Diabetes

In the U.S., the VA healthcare system is the largest provider of healthcare services.[34] About 20% of veteran patients have been diagnosed with diabetes, which is considerably higher than 5.8% of the general U.S. population with diabetes diagnosis.[7] Patients with diabetes in the VA or in the general U.S. population, compared to patients without diabetes, have twice the mortality rate.[3,35] Mirroring racial disparities observed in the general U.S. population, African American veteran patients were found to be more likely to have renal disease.[36] Higher prevalence makes diabetes a large burden for the VA while the similar patterns of mortality rates and racial disparities give credence that the VA population may not be that different from health maintenance organization populations, apart from being overwhelmingly male.

Theoretical Framework

In normal physiological functioning, people should be normoalbuminuric (<2mg/dL of albumin in their urine or < 30mg/g of albumin to creatinine (also known as the albumin-to-creatinine ratio)). Albuminuria is progressive in diabetes. Although a continuous measure of nephropathy, in the diabetes literature, it has been categorized into normoalbuminuria, microalbuminuria (2-20mg/dL or 30-300mg/g), and macroalbuminuria (> 20mg/dL or > 300mg/g). Thus, ESRD is not defined by an amount of albumin in urine. Instead, ESRD is an administrative term signaling dialysis initiation,

which is characterized by a reduction in glomerular filtration and the quantity and duration of albuminuria.

More than one-fourth of type 2 diabetes patients have microalbuminuria or macroalbuminuria upon diagnosis.[37] All P2DM are prone to increasing levels of albuminuria as a result of progressive loss of beta cell functioning, which deteriorates with duration of diabetes.[38] Worsening beta cell function leads to poorer blood glucose control, which, in turn, contributes to progressive nephropathy,[39] ultimately leading to ESRD.

There is a gradient effect between level of albuminuria and cardiorenal risk, starting at the upper end of the normal albumin excretion rate,[40] which is associated with a 1.83 times higher likelihood of major CVD events.[40] Albuminuria is a continuous independent predictor for CVD events, congestive heart failure (CHF), and all-cause mortality.[40] It is associated with hospitalization, left ventricular dysfunction, stroke, and myocardial infarction (MI).[41]

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) effectively reduce albuminuria. At the molecular level, ACEIs and ARBs work by inhibiting angiotensin II from stimulating angiotensin II type 1 (AT1) receptors. ACEIs prevent conversion of angiotensin I to angiotensin II while ARBs compete with angiotensin II for AT1 receptor sites.[42,43] When followed downstream, AT1 receptor stimulation increases urinary albumin excretion through vasoconstriction, which increases intraglomerular pressure.[44] Vasoconstriction also leads to increased systemic pressure, causing increased blood pressure. As monotherapy, ACEIs and ARBs have shown attenuation in the progression of albuminuria throughout the disease

process.[45-49] Additionally, studies have shown ACEIs or ARBs negate disease progression by causing P2DM to revert to the previous albuminuric state.[45,50,51]

Overall Hypothesis

Diabetes increases patients' risk of vascular disease, including cardiovascular disease (CVD), i.e., left ventricular dysfunction and MI, and cerebrovascular disease, i.e., ischemic stroke. Diabetes also increases patients' risk of kidney damage via increased albumin excretion, which is characteristic of ESRD. Additionally, many P2DM have hypertension, a risk factor for ESRD, cardio- and cerebro- vascular disease, and mortality.

P2DM are prescribed ACEIs and ARBs for two reasons: to reduce blood pressure and to reduce albuminuria. Albuminuria, the amount of albumin in urine, has been found to be the strongest predictor of ESRD.[52] Albuminuria expressed as mg/g creatinine adjusts for hydration while mg/dL does not, so the creatinine ratio is preferred as it is more accurate (Personal communication, G. Murata, March 11, 2009). Since there is preliminary evidence of a larger reduction in albuminuria exhibited with ACEI monotherapy compared to ARB monotherapy, ACEI monotherapy may lead to decreased incidence of ESRD, cardio- and cerebro- vascular disease events, and mortality. Avoiding clinical outcomes with ACEI monotherapy may lead to decreased resource utilization.

Few randomized controlled trials have established the efficacy of ACEIs or ARBs in reducing albuminuria; including development of ESRD; in P2DM.[46,49,53] Further, there are no studies comparing cardio- and cerebro- vascular disease events, all-cause

mortality, outpatient visits, emergency department (ED) visits, or hospitalizations in P2DM. Comparing these event rates between therapeutic classes will provide meaningful answers for ensuring optimal care of P2DM. This naturally extends to gaining knowledge about preventing complications, including deaths, in the diabetes population. However, there is scant evidence on long-term effectiveness, and little data on head-to head comparisons between ACEIs and ARBs as monotherapy.

This study will fill this gap by studying clinical outcomes in veteran P2DM who have received ACEIs or ARBs for development of ESRD; reduction of albuminuria; incident vascular disease events (IVDE), incorporating cardio- and cerebro- vascular disease outcomes MI, LVH, and stroke; and all-cause mortality over a maximum of 5 years. Resource utilization will also be assessed in this sample over the time period via number of outpatient visits, ED visits, and hospitalizations.

Specific Aims

Specific Aim 1: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing the incidence of ESRD.

H_{01}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing the incidence of ESRD in P2DM.

Specific Aim 2a: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria.

H_{02a}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria in P2DM.

Specific Aim 2b: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria in those with baseline microalbuminuria.

H_{02b}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria in P2DM with microalbuminuria at baseline.

Specific Aim 2c: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria in those with baseline macroalbuminuria.

H_{02c}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing albuminuria in P2DM with macroalbuminuria at baseline.

Specific Aim 3: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing the incidence of vascular disease events (IVDEs): left ventricular hypertrophy, MI, and stroke.

H_{03}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing the incidence of IVDEs in P2DM.

Specific Aim 4: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing all-cause mortality.

H_{04}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing all-cause mortality in P2DM.

Specific Aim 5: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing outpatient visits.

H_{05}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing outpatient visits in P2DM.

Specific Aim 6: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing emergency department (ED) visits.

H_{06}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy for reducing ED visits in P2DM.

Specific Aim 7: To determine the difference in effectiveness between ACEIs or ARBs and neither therapy in reducing hospital admissions.

H_{07}: There will be no difference in effectiveness between ACEIs or ARBs and neither therapy in reducing hospital admissions in P2DM.

Specific Aim 8: To determine the difference in effectiveness between ACEIs and ARBs in reducing the incidence of ESRD.

H_{08}: There will be no difference in effectiveness between ACEIs and ARBs for reducing the incidence of ESRD in P2DM.

Specific Aim 9a: To determine the difference in effectiveness between ACEIs and ARBs in reducing albuminuria.

H_{09a}: There will be no difference in effectiveness between ACEIs and ARBs for reducing albuminuria in P2DM.

Specific Aim 9b: To determine the difference in effectiveness between ACEIs and ARBs in reducing albuminuria for those with baseline microalbuminuria.

H_{09b}: There will be no difference in effectiveness between ACEIs and ARBs in reducing albuminuria in P2DM with microalbuminuria at baseline.

Specific Aim 9c: To determine the difference in effectiveness between ACEIs and ARBs in reducing albuminuria for those with baseline macroalbuminuria.

H_{09c}: There will be no difference in effectiveness between ACEIs and ARBs in reducing albuminuria in P2DM with microalbuminuria at baseline.

Specific Aim 10: To determine the difference in effectiveness between ACEIs and ARBs in reducing the IVDEs.

H_{010}: There will be no difference in effectiveness between ACEIs and ARBs for reducing the IVDEs in P2DM.

Specific Aim 11: To determine the difference in effectiveness between ACEIs and ARBs in reducing all-cause mortality.

H_{011}: There will be no difference in effectiveness between ACEIs and ARBs for reducing all-cause mortality in P2DM.

Specific Aim 12: To determine the difference in effectiveness between ACEIs and ARBs in reducing outpatient visits.

H_{012}: There will be no difference in effectiveness between ACEIs and ARBs for reducing outpatient visits in P2DM.

Specific Aim 13: To determine the difference in effectiveness between ACEIs and ARBs in reducing ED visits.

H_{013}: There will be no difference in effectiveness between ACEIs and ARBs for reducing ED visits in P2DM.

Specific Aim 14: To determine the difference in effectiveness between ACEIs and ARBs in reducing hospital admissions.

H_{014}: There will be no difference in effectiveness between ACEIs and ARBs for reducing hospital admissions in P2DM.

Significance

Choice Between ACEIs and ARBs

The results of this study are important for the prevention and treatment of albuminuria in U.S. P2DM. In patients with microalbuminuria or macroalbuminuria, the American Diabetes Association (ADA) guidelines recommend monotherapy with ACEIs or ARBs as interventional strategies against progressive nephropathy.[54] Unfortunately, there is hardly any available information about which treatment strategy is better in reducing albuminuria and no information about which is better in slowing progression to ESRD, preventing IVDEs, or reducing all-cause mortality. ACEIs may be associated with a persistent, dry cough (1-10% prevalence),[55] if bothersome enough, individuals switch medications within the therapeutic class or replace them with ARBs.[56] ARBs do not typically produce a cough.[57] In addition to cough, ACEIs have a higher incidence of angioedema[58] and hyperkalemia[56] (>5.0mEq/L serum potassium) than ARBs. Formulary status also comes into play when deciding between ACEIs and ARBs; in this study, both therapeutic classes have been available on the VA national formulary throughout the study period. [59] Although on the national formulary, Veterans Integrated Service Network (VISN) formularies and institution formularies are allowed to deviate. During this study period, patent expiration occurred sooner with ACEIs than ARBs, perhaps making prescription cost a local formulary consideration.

High Complication Rate among P2DM

Almost half of ESRD cases occur in P2DM.[19] The U.S. has the highest incidence and second-highest prevalence of ESRD compared to 11 other developed countries.[60] Over the last 10 years, incidence of ESRD in the U.S. has doubled,[61] a reflection of

diabetes prevalence increasing by 80% in the same time period.[4] Patients with ESRD have a low quality of life leaving few ESRD patients with the ability to work.[62] Preventing P2DM from progressing to ESRD will reduce the burden of ESRD, especially since projections estimate diabetes prevalence to increase by 2.5 times between the years 2000 and 2050.[5] Dialysis patients who have diabetes have a 25% and 23%, 5-year survival rate, for hemodialysis and peritoneal dialysis, respectively.[63] Additionally, diabetes patients with ESRD have a worse prognosis than patients with ESRD due to other conditions, both in terms of vascular disease events and mortality.[64,65] Furthermore, two-thirds of P2DM die from vascular disease.[3] Clearly, cardio- and cerebro- vascular disease is currently placing a larger burden on healthcare resources as many P2DM die from cardio- and cerebro- vascular disease before ESRD has time to develop. At the patient level, development of ESRD can cause costs to increase almost 8-fold while suffering a CVD event can cause costs to increase 3.5 fold.[28] In 2006, diabetes was the seventh leading cause of death in the U.S.[7] Even more interesting to this statistic, diabetes is underreported on death certificates 60% to 65% of the time.[7]

Significance in Terms of Public Policy

The results of this study also have potential implications on health policy relating to P2DM. Healthy People 2010, priorities for health as determined by the U.S. Department of Health and Human Services, acknowledges the need for reducing nephropathy and CVD in patients with diabetes.[10] To decrease the onset of ESRD, Healthy People 2010 proposes two objectives. The first objective relevant to Healthy People, 4-7, is to reduce the number of patients with incident cases of ESRD by 31%. In 1996, there were 113 incident cases of ESRD per million diabetes patients. Objective 4-8

is an extension of Objective 4-7, which stipulates the need for increasing the proportion of patients with diabetes and proteinuria who receive medical treatment to attenuate progression to chronic renal insufficiency.[10] In addition to these objectives, Healthy People 2010 seeks a 10% reduction in CVD-related deaths, an 11% reduction in diabetes-related mortality, and a 43% reduction in all-cause mortality in P2DM. It is evident from this public policy document that more clinical and research efforts should be directed toward the prevention of these complications in patients with diabetes. This study, by seeking to determine the therapy that has the largest reduction in albuminuria, will provide information on which treatment is effective at preventing cases of ESRD, IVDE, and all-cause mortality. For instance, patients with diabetes and microalbuminuria, compared to normoalbuminuria, have a 1.97 times; 2.15 times; and 3.70 times increased likelihood of MI, stroke, or death due to CVD; all-cause mortality; and hospitalization associated with congestive heart failure, respectively.[40]

Significance to the VA

In the U.S., the VA healthcare system is the largest provider of healthcare services.[34] Annually, an average of 4.1 million veterans use the VA to access healthcare. Since prevalence of diabetes in the VA is higher than the national average, examination of clinical outcomes provides valuable information in this setting.

Direct VA costs attributed to diabetes is in the billions. Based on our sample size calculations, potential identification of cost savings of minimally $29.6 million in the study sample just by identifying the best strategy for a significant reduction in ESRD is of importance to the VA. Based on the 20% prevalence of diabetes in the VA population[35] and knowledge that 90-95% of patients with diabetes have type 2,[3] if we

extrapolate the sample to the VA population of roughly 1 million P2DM, we could potentially prevent upwards of 10,323 patients from reaching ESRD. Using costs associated with ESRD in 2005 from the USRDS, this equates to $2.8 billion due to ESRD over 4.25 years.[66] Similarly, finding a significant reduction in IVDE in our sample could lead to identification of an absolute risk reduction of up to 5.5%, which could lead to a cost savings due to prevented events of another $2.3 million in the study sample. If we extrapolate the sample to the VA population, we could prevent upwards of 55,000 IVDEs. Using 2005 costs from a pharmacoeconomic analysis of newly-diagnosed P2DM using ACEIs, $2.1 billion could be saved due to prevented costs within in one year of IVDEs.[67] Assuming 12.4 times more CVD events than strokes,[34] this would lead to prevention of up to 33,082 CVD-related deaths in the VA. Finally, studying veteran patients will provide insight into the effects of long duration of therapy, as this study will document patients who were prescribed ACEIs or ARBs for maximally 5 years.

Significance to the Literature

The additional significance of this study is its uniqueness in duration of therapy for treatments that attenuate renal disease progression, the country of study, and the effectiveness data it will yield. In particular, information about hard outcomes, rather than surrogate markers, will be extremely valuable. As recently publicized in a population of type 2 diabetes, analysis of hard outcomes may yield unexpected results compared to previously-examined short-term surrogate outcomes which formed previously- and widely- held expert opinion.[68] Additionally, this study will have the benefit of determining effectiveness without exclusion of patients with common comorbidities. By examining patients longitudinally and without them receiving

additional attention by investigators, we can also see the effect of the medications when used in patients' daily routines: true effectiveness data. This will be the first population study comparing effectiveness of ACEI and ARB monotherapy. It will also be the first study conducted in the U.S.

CHAPTER 2: REVIEW OF THE LITERATURE

Introduction

This chapter presents a detailed literature review. I begin by providing a brief review of diabetes. Then, a review of diabetes in the Department of Veterans Affairs is presented. Next, drug treatment in diabetes is discussed. This is followed by a more in-depth look at the natural history of diabetes and complications of interest.

Together, these topics lead into the importance of using ACEIs and ARBs for reduction of ESRD, albuminuria, IVDE, and mortality. As there are no effectiveness studies, the review of studies that have examined the impact of ACEIs and ARBs on health is presented as follows. First, studies establishing the efficacy of ACEIs or ARBs compared to placebo are discussed. Second, studies comparing ACEIs or ARBs to active controls are examined. From here, head-to-head studies of ACEI and ARB monotherapy are presented. Next, studies comparing combination therapy to monotherapy with these agents are reviewed. Although the primary analysis is comparing ACEI and ARB monotherapies, it is important to contextualize the combination versus mono- therapy studies since this is the most recent direction that studies in this field seem to be headed.

Diabetes Classification and Etiology

To put type 2 diabetes in context, it is first important to differentiate it from normal physiologic functioning and from the other types of diabetes. Diabetes mellitus is a multi-factoral disease. Diabetes results from an insulin abnormality, leading to

hyperglycemia. There are three major types of diabetes: type 1, type 2, and gestational.[7] Type 1; formerly known as Insulin Dependent Diabetes Mellitus (IDDM), childhood-onset diabetes, or juvenile diabetes; is caused by pancreatic beta cell damage. This damage leads to the body's inability to produce insulin, leaving high amounts of glucose in the blood as it is unable to be transported to cells. Type 1 diabetes is unavoidable while type 2 diabetes is preventable. Type 2 diabetes, formerly known as Non-Insulin Dependent Diabetes Mellitus (NIDDM) or adult-onset diabetes, reflects a reduction in insulin release from pancreatic beta cells, increased insulin resistance, and/or increased hepatic glucose output.[69] Women who are diagnosed with gestational diabetes, meaning diagnosed during pregnancy, are more likely to develop type 2 diabetes during their lifetime.[3]

Approximately 90%-95% of patients with diabetes have type 2.[3] Approximately 23.6 million (7.8%) Americans had diabetes in 2007.[7] Of these, an estimated 5.7 million were undiagnosed. People with type 2 diabetes usually do not become diagnosed until they become symptomatic or suffer complications.[54] This explains why a higher proportion of patients newly-diagnosed with type 2 diabetes, compared to type 1 diabetes, have microalbuminuria or macroalbuminuria.[18]

Diabetes Diagnosis

A person can be diagnosed with diabetes through three different methods.[54] The first method uses a threshold of plasma glucose level of $\geq$ 200mg/dL. Diagnosis is made at this level regardless of meal timing when symptoms of unexplained weight loss, frequent urination (polyuria), and frequent drinking (polydipsia) are present. The second method, the oral glucose tolerance test, is performed by measuring a patient's blood

glucose 2 hours after fasting and consuming a high-glucose drink. If the person has a blood glucose level of ≥ 200mg/dL at that time, diabetes is confirmed. Third, a person can be diagnosed with the fasting plasma glucose test with a blood glucose level of ≥120mg/dL. The American Diabetes Association recommends the last test due to its ease, timeliness, and cost.[54]

Microvascular and Macrovascular Complications

Complications of diabetes are microvascular and macrovascular in nature. Microvascular complications include retinopathy (an eye complication), neuropathy (nerve complications), and nephropathy (kidney complications). Macrovascular complications include CVD, cerebrovascular disease, and peripheral vascular/artery disease.

Standards of Practice for Diabetes Care

A person with diabetes has higher risk of cardiovascular and renal disease compared to people without diabetes[54] due to elevated HbA1c, hypertension, increased albumin excretion, and poorer lipid profile.

HbA1c is a long-term indicator of blood glucose control. It is recommended that HbA1c is tested at a frequency of every 6 months in patients meeting goals with stable glycemia and every 3 months in patients who are not.[39] Whereas a healthy individual has an HbA1c of 4%-6%, it is rarely this level in a person with diabetes. The target is < 7% in diabetes patients.

People with diabetes have a high prevalence of hypertension (75%),[7] which contributes to poor HbA1c and increased albumin excretion. The Seventh Report of the

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7 report) recommends a hypertension goal of < 130/80mm Hg.[70]

Normal albumin excretion is < 2mg/dL or < 30mg/g; if a test is positive for microalbuminuria, 2 of 3 tests over 6 months need to be positive before microalbuminuria is diagnosed. Annual testing of albumin excretion should be performed. Focusing on macrovascular complications in diabetes patients, LDL and triglyceride tests should be performed annually in most adults, with goals of < 100mg/dL and < 150mg/dL, respectively.[54]

Diabetes and ESRD

Type 2 diabetes is the leading condition contributing to incident ESRD cases in the U.S.[19] More than one-fourth of P2DM have microalbuminuria or macroalbuminuria upon diagnosis.[37] Over one's lifetime, 20% to 40% of P2DM with microalbuminuria progress to macroalbuminuria without intervention; about 20% of these people will develop ESRD.[18] In a randomized controlled trial of P2DM with microalbuminuria, 17.5% of subjects randomized to placebo progressed to macroalbuminuria in 2 years.[45] In a separate randomized trial of type 2 diabetes patients of mostly non-Hispanic white ancestry, an annual rate of 2.0% was seen for progression from normoalbuminuria to microalbuminuria, an annual rate of 2.8% was seen for microalbuminuria to macroalbuminuria, and an annual rate of 2.3% was seen from macroalbuminuria to ESRD.[71] Also noteworthy for this study was a 0.1% annual progression from normoalbuminuria to macroalbuminuria and a 0.3% annual progression from microalbuminuria to ESRD. Furthermore, in a cohort study of 1,832 mostly non-

Hispanic Whites in Minnesota, researchers found P2DM progress from start of macroalbuminuria to ESRD in a mean interval of 7 years (range: 2 months-22 years).[72]

It is well-documented that minority groups with diabetes tend to develop renal complications more frequently and more severely. American Pima Indians with diabetes have been extensively studied for their relatively short progression to ESRD,[73-81] and as of 1993, incidence of ESRD among Pima Indians was 23-fold higher than the general U.S. population.[82] P2DM who are Native American, Hispanic, and African-American have a much higher risk of acquiring ESRD compared to Caucasians.[83] Specifically, Native Americans, Hispanics, African Americans, and Asians had 1.9, 1.4, 1.9, and 1.8 higher odds of developing ESRD, respectively, compared to non-Hispanic whites.[84] Additionally, Native Americans and African Americans had 1.5 and 1.3 higher odds of developing early diabetic nephropathy, respectively, compared to non-Hispanic whites.[84]

All P2DM are prone to increasing levels of albuminuria as a result of progressive loss of beta cell functioning, which deteriorates with duration of diabetes.[38] Increasing beta cell dysfunction leads to worsening blood glucose control, which, in turn, contributes to progressive nephropathy states (microalbuminuria and macroalbuminuria),[39] ultimately leading to ESRD. More specifically, hyperglycemia leads to glycosylated proteins, which at first, are reversible.[85] However, when advanced glycosylation end products are formed via irreversible covalent bonding, the proteins pass through the glomerular basement membrane despite the membrane previously repelling the protein.[86] This cycle progresses, resulting in glomerular basement membrane thickening, allowing for more proteins to pass into the urine.[86] Angiotensin II stimulation

of AT1 receptors also increases albuminuria excretion through vasoconstriction, which increases intraglomerular pressure.[44,85]

Based on this mechanism, controlling hyperglycemia, blood pressure, and albuminuria will aid in slowing the decline of progressive nephropathy. Other risk factors include genetic predisposition, smoking, and dyslipidemia; dietary consumption of protein may also be a risk factor.[87] According to a meta-analysis of randomized controlled trials of subjects with type 1 or 2 diabetes eating a low protein diet significantly reduced albuminuria. However, the reduction, compared to a normal diet, was only seen in two of the eight trials and results of this meta-analysis contradict findings of three other meta-analyses.[88] The VA and Department of Defense cite further evidence to back this comment, stating that there is lack of support because the trials were not blinded and were "not optimally designed to test this hypothesis."[89]

In a study of 75 VA and non-VA patients on dialysis, patients were categorized by condition leading to dialysis and followed for mortality.[64] The group that had hypertension (10 of 45) or diabetes (35 of 45) had a worse mortality rate at 2 and 3 years (41% and 63%, respectively) then those who suffered from primary nephropathy (11% and 19%, respectively). This finding that diabetes patients with ESRD have higher mortality has been corroborated by another study.[65] In that study, non-VA patients with ESRD were followed for survival. No one with diabetes survived after 7 years, 27% of people who had ESRD as a result of hypertension survived 12 years, and 40% of patients with ESRD due to other causes survived 12 years.[65]

More recently, a randomized controlled trial of VA patients with advanced chronic kidney disease or ESRD undergoing hemodialysis or peritoneal dialysis followed

patients for all-cause mortality.[90] Fifty-five percent of patients had diabetes. Among those who had ESRD, 42% died within 4.5 years. (There was no breakout of diabetes patients in this group.) Collectively, these 3 studies demonstrate the importance of preventing ESRD among veteran patients with diabetes.

Diabetes and Cardio- and Cerebro- Vascular Disease

The Framingham Study, a longitudinal U.S. population-based study, revealed diabetes doubles the risk of CVD in men and triples the risk in women.[91] It is also widely-known that patients with diabetes are 2-4 times more likely to have a stroke compared to those without diabetes.[3] P2DM have higher levels of albuminuria compared to other patients. Like hypertension, albuminuria is also a predictor for cardio- and cerebro- vascular disease events.[40] As albuminuria increases, there is an increase in the number of cardio- and cerebro- vascular disease events. Higher levels of albuminuria have been shown to be associated with hospitalization, left ventricular dysfunction, MI, and stroke.[41] In addition, there is a gradient effect between level of albuminuria and cardiorenal risk, starting at the upper end of the normal albumin excretion rate,[40] which is associated with a 1.83 times higher likelihood of major CVD events.[40] Cardiac remodeling (i.e., left ventricular hypertrophy) is at least partly attributed to angiotensin II stimulating AT1 receptors.[42,92]

Diabetes and Mortality

Compared to the general population in the U.S., patients with diabetes have a 2-fold higher mortality rate.[3] Albuminuria is a predictor for all-cause mortality.[40] There is an increase in mortality rates with increasing albuminuria. This is based on the HOPE trial, a 4.5 year study with a sample consisting of high-risk patients with diabetes, of whom 32.00% had microalbuminuria and 68.00% had normoalbuminuria at baseline. Investigators found those with microalbuminuria were twice as likely to die from all-causes compared to those who were normoalbuminuric.[40] A U.S. study found that, compared to those with normoalbuminuria, P2DM with microalbuminuria and macroalbuminuria were 1.68-1.97 and 2.47-3.28 times as likely to die from all causes, were 2.20-2.45 and 2.33-3.05 times as likely to die from stroke, and were 1.96-2.39 and 2.73-3.85 times as likely to die from coronary heart disease, respectively.[93]

Risk and Preventive Factors for ESRD, IVDEs, and Mortality

Differences in age, gender, and race/ethnicity are generally documented to be associated with poorer health outcomes across disease states. Similarly, patients with lower income tend to have poorer health while those living in rural areas are more likely to have access to care issues, leading to poorer health outcomes. Smoking, hypertension, and obesity are health conditions predisposing patients to poorer health outcomes while higher levels of HbA1c, LDL cholesterol, and triglycerides are risk factors for ESRD in P2DM. Compliance with ACEIs and ARBs need to be controlled to obtain a realistic picture of benefit of these therapies, and thus, differences between these therapies.

Duration of therapy with NSAIDs is a risk factor: NSAIDs inhibit vasodilator prostaglandins, leading to decreased renal perfusion in P2DM.[94]

For IVDEs and all-cause mortality, risk factors are age, gender, obesity, race/ethnicity, income, rural versus urban/suburban living, history of MI/stroke, family history of CVD, smoking, hypertension, compliance of ACEIs or ARBs, HbA1c, LDL cholesterol, and triglycerides. HbA1c, LDL cholesterol, and triglycerides are also risk factors for cardio- and cerebro- vascular disease and all-cause mortality in P2DM.

Diabetes in the Department of Veterans Affairs (VA)

As the population of this study comprises of VA patients with type 2 diabetes, the following section is devoted to the VA Health Care System.

History

Since 1974, the VA has been making strides towards caring for its diabetes patients.[95] In that year, Congress mandated the VA and 22 other federal organizations to coordinate activities involving research, education, and public service.[95] Fourteen years later, the VA became the first federal organization to have ADA accreditation for its education program.[95]

Process and Outcome Measures

In a random sample of diabetes patients from every VA facility, between October 1, 2004 and September 30, 2005, 85% of patients had yearly HbA1c tests with results of ≤9%, 77% had LDL and triglyceride levels performed biennially with an LDL < 120mg/dL, and 75% had blood pressure ≤140/90mmHg.[96] In a cohort study of patients receiving VA or commercial managed care health services from 6 states, researchers compared processes of care between the two healthcare entities. After adjusting for

covariates, compared to patients in commercial managed care, a higher percentage of VA patients received annual HbA1c tests (93% and 83%, respectively, p=0.006), received annual proteinuria screening (92% and 81%, respectively, p=0.005), received annual lipid screenings (79% and 63%, respectively, p=0.02), had better LDL levels (< 100mg/dL for 52% and 36%, respectively, p=0.003), and had better HbA1c levels (< 8.5% for 83% and 65%, respectively, p=0.009). The two groups had similar blood pressure control (<130/85mmHg for 29% and 29%, respectively, p>0.2).[97] These data confirm the VA commitment to diabetes care.

Between 1999 and 2000, prevalence of diagnosed diabetes in the general population was estimated to be 5.9%.[98] Between 1998 and 2000, prevalence of diagnosed diabetes was 3.4 times higher in the VA population, at about 20% indicating the importance of studying diabetes in this population.[3,35] A substantial amount of VA resources are spent on diabetes patients. Approximately 19% of all VA hospitalizations are associated with diabetes.[34] In one study, 10.7% of veterans diagnosed with diabetes were found to have macroalbuminuria or ESRD in 1998.[36] One-year mortality for this group was approximately 3.7 times higher compared to those without these conditions (10.7% versus 2.9%, respectively).[36] Paralleling racial disparities observed in the general U.S. population, African Americans were found to be more likely to have renal disease.[36]

Drug Treatment in Diabetes

People with diabetes have a high prevalence of hypertension and hyperlipidemia. It is typical for patients with diabetes to be prescribed several medications as multiple risk factors for complications need to be controlled. Accordingly, oral hypoglycemics and

insulin are commonly prescribed agents. In addition, patients may be prescribed antihypertensives and antihyperlipidemics. Table 1 lists FDA approved medications commonly used among P2DM. Monotherapy with ACEIs or ARBs are recommended as first-line antihypertensive agents among P2DM with microalbuminuria or macroalbuminuria. Table 2 provides a list of FDA approved ACEIs and ARBs.

Table 1: Common Therapeutic Classes Used in Diabetes Patients

Therapeutic class **Subclass (if applicable)**	**Generic medication names**
	Oral hypoglycemics
Sulfonylureas	Acetohexamide, chlorpropamide, tolazamide, tolbutamide, glipizide, glyburide, glimiperide
Short-acting insulin secretagogues	Nateglinide, repaglinide
Biguanides	Metformin
Thiazolidinediones	Pioglitazone, rosiglitazone
Alpha-glucosidase inhibitors	Acarbose, miglitol
Dipeptidyl peptidase-IV inhibitors	Sitagliptin
	Insulin
Rapid-acting	Insulin lispro, insulin aspart, insulin glulisine, inhaled human insulin
Short-acting	Regular
Intermediate-acting	Neutral Protamine Hagadern
Long-acting	Insulin glargine, insulin detemir
	Antihypertensives
ACEIs	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
ARBs	Eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Direct rennin inhibitor	Aliskiren
Diuretics	
Thiazides	Chlorthalidone, hydrochlorothiazide, indapamide, metolazone
Loop	Bumetanide, furosemide, torsemide
Potassium sparing	Amiloride, triamterene
Aldosterone antagonist	Eplerenone, spironolactone
Beta-blockers	
Cardioselective	Atenolol, betaxolol, bisoprolol, metoprolol
Nonselective	Nadolol, propranolol, timolol
Intrinsic sympathomimetic activity	Acebutolol, carteolol, penbutolol, pindolol
Mixed alpha- and beta- blockers	Carvedilol, labetalol
Calcium channel blockers	
Dihydropyridines	Amlodipine, felodipine, isradipine, nicardipine, nisoldipine

Table 1 (cont.)

Therapeutic class **Subclass (if applicable)**	**Generic medication names**
Nondihydropyridines	Diltiazem, verapamil
Alpha-blockers	Doxazosin, prazosin, terazosin
Central alpha$_2$ agonists	Clonidine, methyldopa
Peripheral adrenergic antagonist	Reserpine
Direct arterial vasodilators	Minoxidil, hydralazine
Antihyperlipidemics	
Bile acid resins	Cholestyramine, colestipol, colesevelam
Fibrates	Clofibrate, fenofibrate, gemfibrozil
HMG-CoA reductase inhibitors ("Statins")	Lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin
Niemann-Pick C1-Like 1 inhibitor	Ezetimibe
Niacin	Niacin

Table 2: List of Food and Drug Administration (FDA)-approved ACEIs and ARBs

ACEIs		**ARBs**	
Generic Name	***Trade Name(s)***	***Generic Name***	***Trade Name(s)***
Benazepril, Benazepril + hydrochlorothiazide (HCTZ), Benazepril + amlodipine	Lotensin, Lotensin HCT, Lotrel	Candesartan, Candesartan + HCTZ	Atacand, Atacand HCT
Captopril, Captopril + HCTZ	Capoten, Capozide	Eprosartan, Eprosartan + HCTZ	Teveten, Teveten HCT
Enalapril, Enalapril + Felodipine	Vasotec, Lexxel	Irbesartan, Irbesartan + HCTZ	Avapro, Avalide
Fosinopril, Fosinopril + HCTZ	Monopril, Monopril HCT	Losartan, Losartan + HCTZ	Lozaar, Hyzaar
Lisinopril, Lisinopril + HCTZ	Prinivil; Zestril, Prinzide; Zestoretic	Olmesartan, Olmesartan + HCTZ	Benicar, Benicar HCT
Moexipril	Univasc	Telmisartan, Telmisartan + HCTZ	Micardis, Micardis HCT
Perindopril	Aceon	Valsartan, Valsartan + HCTZ, Valsartan + amlodipine	Diovan, Diovan HCT, Exforge
Quinapril	Accupril		
Ramipril	Altace		
Trandolapril, Trandolapril + Verapamil	Mavik, Tarka		

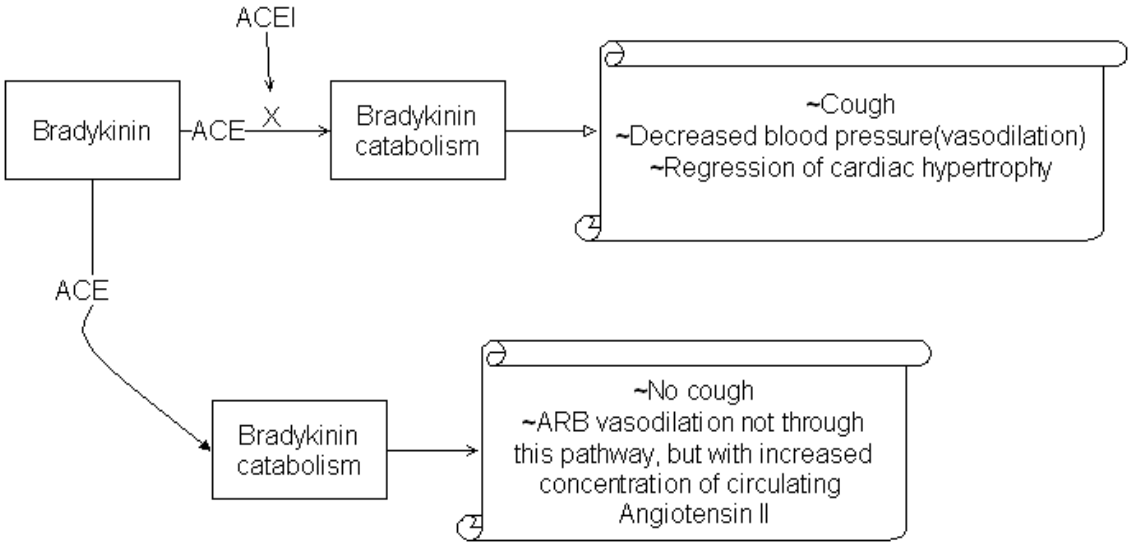
In a study that examined a cohort of 22,954 patients in the VA who were diagnosed with type 2 diabetes and hypertension, 22,477 patients (97.92%) were prescribed ACEIs while 1,542 patients (6.85%) were prescribed ARBs in the year 2000.[99] Of the 22,954 patients, 28.3%, 7.1%, and 11.2% were also receiving oral hypoglycemics, insulin, and antihyperlipidemics, respectively.[99] Other prescribed antihypertensive therapies in P2DM in the year 2000 included beta-blockers, calcium channel blockers, diuretics, and alpha-blockers.[99]

Mechanism of Action of ACEIs and ARBs

In patients with microalbuminuria or macroalbuminuria, the ADA guidelines recommend monotherapy with ACEIs or ARBs as interventional strategies against progressive nephropathy and hypertension.[54] ACEIs may be associated with a persistent, dry cough; if bothersome enough, patients may replace them with ARBs.[56] The cough attributed to ACEIs is a result of blocking bradykinin breakdown, which causes blood pressure lowering and regression of cardiac hypertrophy.[57] ARBs, on the other hand, do not block bradykinin catabolism and do not produce a cough.[57] Although ARBs do not reap the benefits of bradykinin afforded to ACEIs, through specific blockade of angiotensin II type 1 (AT1) receptors, they may lead to increased systemic levels of angiotensin II, which, in turn, could lead to enhanced stimulation of angiotensin II type 2 (AT2) receptors[56] (Figure 1). This may be beneficial, leading to augmented vasodilation and enhanced tissue repair.[57] In addition to cough, ACEIs have a higher incidence of angioedema[58] and hyperkalemia[56] (>5.0mEq/L serum potassium) than ARBs.

In practice, patients usually have initial therapy with ACEIs[100] although there are no conclusive data establishing efficacy or effectiveness of ACEIs over ARBs for P2DM.[101] Due to the higher incidence of cough with ACEIs, clinicians may be more likely to prescribe ARBs to patients who are more likely to cough (Personal communication, G. Murata, August 25, 2008). For instance, those who smoke (Personal communication, G. Murata, August 25, 2008),[102] have asthma, allergic rhinitis, gastroesophageal reflux disease, chronic obstructive pulmonary disease, chronic bronchitis, postnasal drip,[103] and are initiated on therapy during winter months are more likely to be prescribed ARBs (Personal communication, G. Murata, August 25, 2008). Lastly, clinician choice is dependent on the availability of ACEIs and ARBs on a formulary. In the VA population, both therapeutic classes have been available on the national formulary throughout the study period.[59]

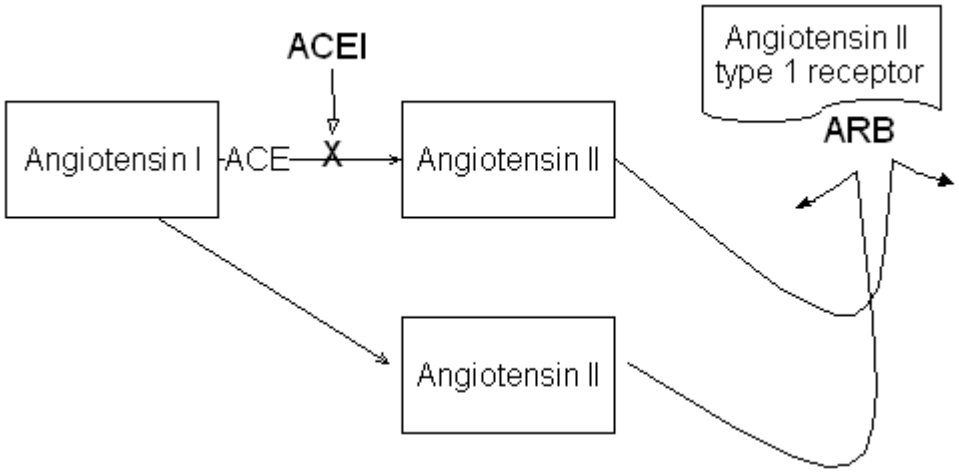
Figure 1: Effects of ACEI and ARB Blockade.
The top pathway depicts the effects of ACE blockade with an ACEI. The bottom pathway depicts the effects of an ARB



ACEIs and ARBs work by inhibiting angiotensin II from stimulating AT1 receptors. ACEIs prevent conversion of angiotensin I to angiotensin II while ARBs compete with angiotensin II for AT1 receptor sites (blockade).[42,43] AT1 receptors are located in the blood vessels, heart, kidney, adrenal gland, and nerves.[43] When stimulated by angiotensin II, AT1 receptors lead to vasoconstriction, sodium retention, cardiac fibrosis, sympathetic nervous system stimulation, arrhythmia induction, plasminogen activator inhibitor 1 stimulation, and renal perfusion alteration through systemic resistance (i.e., vasoconstriction) and afferent and efferent arteriole resistance.[42,43,92]

Intuitively, ARBs more effectively block the deleterious effects of the renin-angiotensin-aldosterone system since angiotensin II is made by ACE-dependent and ACE-independent pathways.[42,92] It has been estimated that about one-third of angiotensin II is generated through ACE-independent pathways.[104] ARBs, through blockade of the AT1 receptor, inhibit the negative effects of angiotensin II, regardless of the pathway used in its formation[105] (Figure 2). Inhibition of angiotensin II with ACEIs or ARBs has been shown to be both cardioprotective[92] and renoprotective.[42,92] The slight difference in mechanisms of action between the two classes, however, may lead to different levels of albuminuria.

Figure 2: Differences in Mechanisms of Action between ACEI and ARB Monotherapies
Depiction of ACE-dependent (top) and ACE-independent (bottom) pathways. An ACEI can only reduce angiotensin II in an ACE-dependent pathway while an ARB competitively blocks angiotensin II from stimulating the AT1 receptor in both types of pathways.



Dose response of these therapeutic classes has been based on antihypertensive results in patients without diabetes rather than antiproteinuric effects in patients with diabetes, which indicates the possibility of underdosing for renoprotective effects.[106,107] In fact, in one study, researchers compared the urinary albumin excretion rates of the optimal dosage for blood pressure control of an ARB, irbesartan 300mg daily, with irbesartan 900mg daily; they found the 900mg dosage decreased urinary albumin excretion 15% more than the 300mg dosage.[108]

ACEIs, ARBs and Development of ESRD, Cardio- and Cerebro- Vascular Disease, and All-cause Mortality

ACEIs or ARBs Compared to Placebo

Effect on Albuminuria

Several clinical trials have indicated that ACEIs and ARBs in monotherapy are efficacious in reducing the progression of albuminuria throughout the disease process.[45-49] This is evidenced by a reduction in risk of progression to macroalbuminuria from normoalbuminuria or microalbuminuria by 1.9% (6.5% versus 8.4%) over 4.5 years for ramipril 10mg daily (ACEI) compared to placebo.[46] This is further shown by a reduction in risk of progression from microalbuminuria to macroalbuminuria by 5.2% (14.9% versus 9.7%) and 9.7% (14.9% versus 5.2%) over 2 years for irbesartan 150mg and irbesartan 300mg daily (ARB) compared to placebo.[45] Similarly, losartan 50-100mg daily (ARB) when compared to placebo during a 4 year period reduced the risk of progression from macroalbuminuria to ESRD by 5.9% (25.5% versus 19.6%).[49] Additionally, one study has shown ACEIs or ARBs negate disease progression by

causing P2DM to revert to the previous albuminuric state.[45] Three other studies found similar results.[47,48,53]

Effect on Cardio- and Cerebro- Vascular Disease and Mortality

Cardio- and cerebro- vascular disease and mortality were examined in 3 articles representing 2 studies.[46,53,109] In the first study, HOPE, ramipril 10mg daily (ACEI) was found to reduce risk of developing the composite endpoint of MI, stroke, or cardiovascular death by 4.5% at 4.5 years (15.3% versus 19.8%).[46] Analysis of the components found ramipril conferred a reduced risk in each of them compared to placebo. The trial also found ramipril reduced the risk of all-cause mortality at 4.5 years by 3.2% (10.8% versus 14.0%).[46] In IDNT, the researchers found a nonsignificant difference between irbesartan 300mg daily (ARB) and placebo for the composite endpoint of death from cardiovascular disease, nonfatal MI, hospitalization for heart failure, permanent neurological defect from a cerebrovascular event, or lower limb amputation above the ankle.[53] Similarly, the trial did not demonstrate irbesartan to be more effective at reducing the risk of death than placebo. In a separate article discussing the results of IDNT, an analysis of each component of the composite endpoint revealed that irbesartan was only more effective than placebo at reducing the risk of developing CHF (13.8% versus 19.9%).[109]

In summary, the use of ACEIs or ARBs has been associated with better renal outcomes;[45-49,53] however, there has been fewer and less consistent data regarding cardio- and cerebro- vascular disease and mortality in P2DM.[46,53,109] Please see Appendix B for more information about study results.

ACEIs or ARBs Compared to Active Controls

Effect on Albuminuria

Therapeutic agents such as beta-blockers (BBs) and calcium channel blockers (CCBs) are called active controls as studies have used these medications as comparison therapies with some theoretical basis that the medications will work for the outcome of interest. BBs and CCBs have had conflicting information regarding renal protection when compared with ACEIs or ARBs. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), P2DM and hypertension had similar incidence of microvascular complications when given atenolol 50-100mg daily (BB) or captopril 25 to 50mg twice daily (ACEI).[110] In a randomized double-blind trial of P2DM, hypertension, and either normoalbuminuria or microalbuminuria, cilazapril 2.5mg daily (ACEI) and amlodipine 5mg daily (CCB) had similar blood pressure effects and similar decreases in albumin excretion rate.[111] In a randomized trial of P2DM, hypertension, microalbuminuria, and diabetic glomerulopathy, the investigators found a significant reduction in urinary albumin excretion in patients receiving enalapril 5 to 20mg daily (ACEI) compared to nitrendipine 10-40mg daily (CCB) despite similar blood pressure reduction at 98 days.[112] Interestingly, at 1 year after these first 98 days, urinary albumin excretion was similar between groups.[112] In the same vein, investigators of a blinded randomized parallel study of P2DM, hypertension, and nephropathy showed similar renoprotection with atenolol 50 to100mg daily (BB) or lisinopril 10 to 20mg daily (ACEI).[113] In a randomized study with 6 year follow-up of P2DM, hypertension, retinopathy, and proteinuria, the researchers found significantly better decreases in albumin excretion with lisinopril (ACEI) or diltiazem/verapamil (nondihydropyridine

CCB group) compared with atenolol (BB) (dosages not reported).[114] There are two important issues to note. No published study was identified in which a protective benefit was observed in BBs or CCBs when compared to ACEIs, and a similar or protective benefit was observed for BBs or CCBs when compared to ARBs.

Effect on Cardio- and Cerebro- Vascular Disease and Mortality

Despite the previous studies showing similar promise for renal protection with BBs and CCBs compared to ACEIs, the following studies show a cardiorenal advantage for ACEIs or ARBs compared to BBs or CCBs. In a randomized study, although nitrendipine 20mg daily (CCB) and ramipril 5mg daily (ACEI) similarly lowered blood pressure, ramipril decreased urinary albumin excretion at an earlier point in time and to a greater extent.[115] In another randomized clinical trial, P2DM and microalbuminuria had a significant decrease in urinary albumin excretion in the enalapril 10mg daily (ACEI) group compared to the nifedipine 20mg twice daily (CCB) group.[116] The same study found attenuation of renal function decline in macroalbuminuric patients randomized to enalapril compared to nifedipine.[116] In the Microalbuminuria Reduction with Valsartan (MARVAL) study, yet another randomized clinical trial, despite similar blood pressure reduction in valsartan 80mg daily (ARB) and amlodipine 5mg daily (CCB) groups, a renoprotective effect was seen in normotensives and hypertensives in the valsartan group compared to the amlodipine group.[117] Again, these studies lack a hard endpoint measuring renal effects.

In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, a randomized clinical trial of patients with diabetes, hypertension, and left ventricular hypertrophy, losartan 50 to 100mg daily (ARB), compared to atenolol 50 to

100mg daily (BB), reported hazard ratios of 0.63, 0.59, and 0.61 for CVD mortality, hospitalizations for heart failure, and all-cause mortality, respectively.[50] This trial also found losartan conferred an absolute risk reduction of 14.4% of the composite outcome of CVD mortality, MI, or stroke compared to those taking atenolol over 4.7 years (incidence of 39.2% and 53.6%, respectively). In the Appropriate Blood Pressure Control in Diabetics (ABCD) trial, the enalapril 40mg daily group (ACEI) had significantly fewer MIs than nisoldipine 60mg daily (CCB) group.[118] In the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET), an open-label randomized clinical trial of hypertensive P2DM with normoalbuminuria, although subjects in the amlodipine 10mg daily (CCB) group achieved a larger reduction in systolic blood pressure, patients in the fosinopril 20mg daily (ACEI) group were less likely to develop a CVD event.[119] Specifically, fosinopril achieved an absolute risk reduction of the composite outcome of MI, stroke, or hospitalized angina of 6.7% compared to patients receiving amlodipine over 3.5 years (incidence of 7.4% and 14.1%, respectively).[119] This body of literature points to the need for controlling for beta-blocker and CCB use in determining the effects of monotherapy with ACEIs and ARBs.

In addition to cardiorenal protection, a double-blind trial of hypertensive diabetic patients with left ventricular hypertrophy comparing losartan 50-100mg daily (ARB) to atenolol 50-100mg daily (BB) over 4.7 years, losartan achieved a reduction in risk of mortality of 14.7% (22.5% versus 37.2%).[50]

In summary, ACEIs were consistently better at reducing the progression of albuminuria compared to BBs despite conflicting evidence between ACEIs and CCBs for this outcome.[110-116,118-120] None of the studies comparing ACEIs and BBs assessed

cardio- or cerebro- vascular endpoints or mortality. Two of the studies comparing ACEIs and CCBs examined cardio- and cerebro- vascular endpoints and both indicated ACEIs were better at reducing risk of vascular endpoints, but none of the endpoints were the same across studies.[118,119] Even though the researchers of the ABCD trial found ACEIs were better at preventing nonfatal MI or nonfatal and fatal MI, they found ACEIs was no better at preventing CVAs, CHF, CVD death, or all-cause mortality.[118] This is the only study of active controls compared to ACEI or ARB monotherapy where all-cause mortality was assessed as an outcome.

We have been unable to identify a head-to-head comparison of ARBs and BBs to be able to say anything about this outcome, cardio- or cerebro- vascular disease, or mortality. For the two studies comparing ARBs to CCBs, both found ARBs reduced the risk of albuminuria progression; only one of these studies analyzed vascular events or mortality, which showed no difference between the two therapeutic strategies.[53,109,117] Please see Appendix C for more details about the studies comparing active controls to ACEI or ARB monotherapy.

ACEI Monotherapy Compared to ARB Monotherapy

We were able to identify sixteen studies that examined the efficacy or effectiveness of ACEIs compared to ARBs in P2DM in attenuating albuminuria. None statistically examined the effect on cardio- or cerebro- vascular outcomes or mortality. Appendix D provides a description of these studies.

Effect on Albuminuria

Sixteen studies compared ACEI and ARB monotherapy in attenuating albuminuria. These studies were randomized, mostly consisting of double-blind trials or

crossover studies with sample sizes ranging from 20 to 250 subjects. The results from these studies indicated that few had controlled for baseline albuminuria. Next, we expand on the three studies controlling for baseline albuminuria.

The study by Barnett et al. (2004) was a double-blind randomized controlled trial of 250 subjects who had microalbuminuria or macroalbuminuria at baseline. The sample consisted of 98.4% non-Hispanic whites. Median baseline urinary albumin excretion rates were 60.0 and 46.2µg/min for enalapril (ACEI) and telmisartan (ARB), respectively. The study had 5 years of duration. Researchers found enalapril reduced albuminuria by 4.0% (enalapril reduced albuminuria by 3.0% while telmisartan increased it by 1.0%) (p-value not reported). The study had a drop-out rate of 30.4% and 33.6% for telmisartan 40mg daily and enalapril 10mg daily, respectively.[121] Numbers reflecting albuminuria levels at baseline or study end were not reported.

The study by Mogensen et al. (2000), compared lisinopril 20mg daily (ACEI) to candesartan 16mg daily (ARB) in 197 subjects who were microalbuminuric at baseline.[122] This was a double-blind randomized controlled trial. Mean baseline albumin-to-creatinine ratios were 5.9 and 6.6mg/mmol for candesartan and lisinopril, respectively. Compared to baseline, there were significant reductions in albuminuria of 30% and 46% for candesartan and lisinopril monotherapy, respectively, at week 12 ($p<0.001$ each). This equates to a 30% difference between lisinopril and candesartan at week 12 ($p=0.058$) after controlling for baseline value, site, weight, and change in diastolic blood pressure.[122] At week 24, these reductions remained significant ($p<0.001$ for lisinopril, $p=0.05$ for candesartan).

The third study was a randomized, open-label, crossover study of 219 subjects who were microalbuminuric at baseline by Sengul.[123] The study compared lisinopril 20mg (ACEI) with telmisartan 80mg (ARB) in subjects with mean urinary albumin excretion rates of 264 and 256mg/d for lisinopril and telmisartan, respectively. Investigators reported an 18% relative reduction in albuminuria with lisinopril 20mg compared to telmisartan at week 24 (p=0.12). For this study, subjects were advised to limit ingestion of sodium and maintain ingestion of protein at 1.2g/kg. Due to the relatively short duration of the study and the more intensive following compared to clinical practice, the diet specifications in themselves may not make this generalizable to practice. While it suffers external invalidity because of this fact, it also suffers more internal invalidity compared to double-blind clinical trials.

Studies by Rosei et al. (2005) and Lim et al. (2007) did not control for baseline albuminuria. Their results showed ARBs led to a statistically significantly reduction in albuminuria compared to ACEIs.[124,125] Rosei et al. did not mention albuminuria as an endpoint, leaving one to assume it was a *post hoc* analysis.[124] The researchers of this randomized double-blind trial found, among 118 microalbuminuric patients, candesartan led to an additional 80.2mg/g reduction in albuminuria at 24 weeks compared to enalapril. At baseline, the mean albuminuria of the ARB group was 82mg/g higher. The researchers in the second study enrolled 41 patients at microalbuminuria or macroalbuminuria for 4 weeks in a randomized single-blind crossover study.[125] The authors mention losartan conferred an additional 44mg/g reduction in albuminuria compared to quinapril. At baseline, the mean albuminuria of the ACEI group was 79mg/g higher than the ARB group.

The 4 studies that were reviewed by the Agency for Healthcare Research and Quality (AHRQ) were only found to be of "fair" quality.[126] As AHRQ is the Federal agency in charge of improving the effectiveness, quality, efficiency, and safety, the fact that the studies reviewed were of only "fair" quality is important to note. Only three studies described above controlled for baseline differences in albuminuria between ACEIs and ARBs. Controlling for such differences at baseline is important in these studies when the outcome is reduction in albuminuria. In particular, a group that has a larger albuminuria value at baseline may have more of a potential to have a larger reduction in albuminuria. Alternatively, it may be indicative of a group that is further along in nephropathy progression, perhaps making it less likely for that group to have a similar reduction in albuminuria. This is an especially important consideration as many of the studies had substantial differences in baseline albuminuria. In each of these studies, ACEIs demonstrated greater reduction in albuminuria compared to ARBs, but the difference was statistically insignificant.[121-123] For ACEIs, the relative reduction in albuminuria ranged from 4%-30% compared to ARBs.

Conversely, two of the 13 studies not controlling for baseline albuminuria found ARBs significantly lowered albuminuria compared to ACEIs. What is particularly intriguing about this fact is that the mean baseline between group difference in albuminuria was approximately 80mg/g, but with one study having the ACEI group with higher albuminuria and the other study having the ARB group with higher albuminuria.

To the best of our knowledge, these 16 small studies are the only published data comparing ACEIs to ARBs: all only statistically compare the surrogate endpoint of reduction in albuminuria. In these trials, all measured albuminuria continuously. None

of these studies enrolled patients from the U.S. As is the case in most clinical trials, subjects were healthier than the general population. For instance, of the studies reporting exclusion criteria, 80% excluded patients with severe hypertension or enrolled patients who had a mean systolic blood pressure <140mmHg, 60% excluded patients with recent CVD events or strokes, and 60% excluded patients with cancer.[51,121-123,125,127-133] Moreover, as there is evidence for discrepancies in effects of angiotensin blockade across race/ethnic groups in left ventricular hypertrophy or hypertension,[134,135] there is a gap in the studies analyzing effects across race/ethnic groups, especially in light of the fact that individuals in minority groups are among those who are most likely to develop progressive albuminuria. As a result, data are not available to inform us which treatment is more effective in preventing nephropathy progression, or development of ESRD, in U.S. clinical practice.

Effect on Cardio- and Cerebro- Vascular Disease and Mortality

There are no published studies making statistical comparisons of ACEIs to ARBs in terms of cardio- or cerebro- vascular disease outcomes. One study, a 5 year double-blind randomized controlled trial conducted by Barnett and colleagues,[121] combined stroke; nonfatal MI; and death from stroke, MI, or cardiac insufficiency to evaluate safety profiles of enalapril 10mg daily and telmisartan 40mg daily. Investigators found a 15.0% incidence in the telmisartan group and a 10.8% incidence in the enalapril group. Similarly, there was a 7.5% and 5.4% incidence of congestive heart failure in the telmisartan and enalapril groups, respectively. This study suggests a relative risk reduction of each adverse event of 39% with ACEIs compared to ARBs.

Finally, no studies were identified comparing all-cause mortality or healthcare utilization.

ACEI and ARB Combination versus Mono-therapy

There were 11 studies that compared ACEI and ARB combination to mono-therapy in P2DM. All were conducted outside the U.S., had small sample sizes, and followed patients for a short time. Two studies had patients on one year of therapy, but most studies only had patients on therapy for a maximum of four months. The majority of these studies did not control for baseline albuminuria between groups. Appendix E provides more information about these studies.

Four studies controlled for baseline differences in albuminuria. Two of these studies also compared ACEI and ARB in monotherapy and were mentioned previously. The study by Mogensen et al. (2000)[122] was a double-blind randomized controlled trial comparing lisinopril 20mg plus candesartan 16mg to each as a monotherapy for 12 weeks. The results indicated that combination therapy reduced albuminuria significantly by 34% (95% confidence interval: 3%-55%) when compared to candesartan ($p=0.04$). However, the combination therapy was less effective when compared to lisinopril. Although it reduced albuminuria by 18% (95% confidence interval: -20% to 44%), the results were nonsignificant ($p>0.20$).

Sengul et al. (2006)[123] was an open-label randomized crossover study of 219 microalbuminuric subjects with hypertension. Treatment with lisinopril 20mg plus telmisartan 80mg or each monotherapy continued for 28 weeks. The investigators of this study reported a significant reduction in albuminuria between the combination therapy

and each monotherapy (p=0.04). No details regarding magnitude of reduction were reported.

The third study was an open-label before-and-after study of 27 microalbuminuric and macroalbuminuric patients with hypertension conducted by Fujisawa.[136] In that study, investigators switched monotherapy for combination therapy at half-doses. If a subject received 8mg candesartan at the beginning of the study, the patient would receive combination therapy of 4mg candesartan and 5mg imidapril. The same holds true of a patient initially on 10mg imidapril. The monotherapies were pooled for analysis. Combination therapy led to a 34% reduction in albuminuria (14%-49%) compared to the monotherapies ($p<0.01$). The researchers were able to determine combination therapy reduced albuminuria independent of individual albuminuria or blood pressure at baseline.

The last study, conducted by Song,[137] was a double-blind randomized crossover study of 18 macroalbuminuric patients without hypertension. Combination therapy with candesartan 4-8mg plus ramipril at a dosage over 5mg led to a 0.8% reduction in albuminuria over 16 weeks compared to taking ramipril alone ($p>0.05$). The researchers concluded there was no difference while controlling for blood pressure reduction.

Of the studies not controlling for baseline albuminuria, there was also a mixture of positive and negative findings. Two studies found nonsignificant differences between combination and monotherapies, two studies found significant differences between combination therapy and ACEI monotherapy, and three studies found significant differences between combination therapy with each monotherapy.

From what was identified in our exhaustive literature review of studies comparing combination therapy to monotherapy, these 11 studies are the only data available on the

subject. All of these studies examined the surrogate endpoint of reduction in albuminuria. Every study measured albuminuria continuously rather than looking at progression or reversion from one albuminuric state to another. All studies had small sample sizes and short treatment durations, with the sample sizes ranging from 17-219 subjects and treatment durations lasting 2-12 months. No studies were conducted in the U.S. As to be expected, subjects in these studies were healthier than the general population. Specifically, 67% excluded patients with severe hypertension or enrolled patients with a mean systolic blood pressure <140mmHg; 60% excluded patients with uncontrolled diabetes, severe diabetes complications, or who used insulin; 50% excluded patients with recent CVD or stroke; and 50% excluded patients with cancer.[51,122,123,130-132,136-140] Additionally, no study assessed the treatment strategies across race/ethnic groups. These limitations do not permit prescribers to know if combination therapy is superior, equal, or inferior to each monotherapy in preventing nephropathy progression in U.S. clinical practice.

To the best of our knowledge no studies examined the impact of these therapies on ESRD, cardio- or cerebro- vascular disease, all-cause mortality, or healthcare utilization.

Summary

There is undisputed evidence that type 2 diabetes has already reached epidemic proportions, with incidence expected to continue to rise for the next four decades. The disease is more prevalent and more severe in minority populations. The VA has a diverse population and has been a forerunner in combating this disease state over the last four

decades. With a diabetes incidence 4-times higher than the general population, it is essential to study type 2 diabetes among this population. Process and outcome measures demonstrate VA patients are tested more frequently for HbA1c, proteinuria, and lipids; and have better LDL and HbA1c levels compared to managed care patients. Despite this, complications remain high among veterans, straining available resources. As the argument can be made that VA patients receive better care, one can speculate if a difference is seen between treatments in this population, that a larger difference would be seen in managed care patients.

Overwhelming evidence exists about the seriousness of complications arising from type 2 diabetes. Duration since diabetes diagnosis has a positive relationship with diabetes complications as a result of increasing likelihood of hypertension, which leads to worsening HbA1c and albuminuria. ACEIs and ARBs have proven to be effective at reducing blood pressure and albuminuria, although there is no consensus of whether the albuminuria effects are independent or dependent of blood pressure lowering. A possible reason for this is that doses regularly given to P2DM are based on the FDA-approved indication for hypertension.

Literature Review Summary

This literature review provides a historical record of the literature relating to ACEI and ARB therapy. First, efficacy was demonstrated in ACEI or ARB monotherapy in studies using placebo and active controls. From there, researchers and clinicians started comparing the two monotherapies to each other. Recently, interest has sparked in comparing each monotherapy to combination therapy.

In terms of monotherapy comparisons, more valid conclusions can be made with the studies controlling for baseline albuminuria. Of these 3 studies, although no significant differences were found, a 4%-30% relative reduction in albuminuria was seen with ACEIs versus ARBs. The only study lasting over 6 months assessed reduction in albuminuria as a secondary outcome. Interestingly, of the 13 studies not controlling for baseline albuminuria, the 2 studies that showed a significant difference between groups had a treatment effect favoring ARBs. None of the 16 studies have analyzed the clinical outcomes ESRD, cardio- or cerebro- vascular disease, or all-cause mortality to know if ACEI or ARB monotherapy provides clinically significant differences in patient outcomes. Simply no evidence exists for comparisons of monotherapies with these important events, making research into these outcomes critical.

Among the studies comparing combination with mono- therapy, there is also lack of consensus. Only 4 of these 11 studies controlled for baseline albuminuria, which again places more weight on findings from these 4 studies. The 2 open-label studies found combination therapy to be better than both monotherapy while the 2 double-blind randomized studies found no difference between combination therapy and ACEI monotherapy. Only 1 of the 2 double-blind studies compared combination therapy to ARB monotherapy, which found ARB monotherapy to be significantly less effective at reducing albuminuria. The 7 studies that did not control for albuminuria differences at baseline yielded a similar picture of mixed results. None of the 11 studies analyzed ESRD, vascular disease, or all-cause mortality to know if combination therapy is clinically different than either monotherapy.

Whittling down the studies to only those controlling for albuminuria at baseline, we need to collectively analyze the findings from the 3 monotherapy comparison studies and the 4 combination versus mono- therapy studies. By doing this, we can say that there is evidence that ACEI monotherapy may work better at reducing albuminuria than ARB monotherapy, despite lack of statistically significant differences. The first part of this picture is that relative reductions of 4%-30% for attenuation of albuminuria are seen for ACEI monotherapy compared to ARB monotherapy. The second is that the 2 double-blind randomized studies comparing combination and mono- therapy show no significant difference between ACEI monotherapy and combination therapy. As these conclusions do not rely on a particularly large number of studies, further research into reduction in albuminuria is essential.

CHAPTER 3: METHODS

The beginning of this chapter talks about human subjects and VA approval and the pilot study. The research design, data sources, and data storage follow this. Next, inclusion and exclusion criteria, sample size, and the pilot study are described. Lastly, data management, data cleaning, data coding, and statistical analyses are discussed.

Human Subjects Approval

We submitted for two departmental reviews, one through the University of New Mexico College of Pharmacy and one through the VA Research and Development (R&D) Committee on March 14, 2008. After obtaining each of their approvals, we applied for expedited review through the University of New Mexico Health Sciences Center Human Research Review Committee (HRRC), which occurred on March 21, 2008. The HRRC approved the study on April 4, 2008 (see Appendix A for HRRC approval letter). We requested an informed consent waiver and a Health Insurance Portability and Accountability Act (HIPAA) waiver as we felt the research would be more harmful to patients if we actually obtained their consent: we would need their social security number to do so, which would cause a larger risk to confidentiality.

VA Approval

After obtaining HRRC approval, we submitted our proposal to National Data Systems division of Information Assurance, Veterans Health Administration (VHA)

Office of Information and Decision Support Office, the division in charge of Decision Support Systems. From this point, National Data Systems forwarded our proposal to VHA Office of Research Oversight and VHA Office of Research and Development. All approvals were given in October 2008, which had to be obtained before any data were provided.

Research Design

This was a quasi-experimental retrospective longitudinal secondary database analysis. The aim of this study was to compare the effectiveness of two treatments (ACEIs and ARBs) used in P2DM. As mentioned earlier, the VA is an ideal setting for this comparison; we used national VA data for our analysis. The study period for observing outcomes at any Department of Veterans Affairs (VA) healthcare facilities is October 1, 2002-September 30, 2007. A patient would only be counted as newly-diagnosed between fy2003 and fy2006 if there was no mention of type 2 diabetes the year before. A main reason we picked this time frame is because provider ID (for the intended instrumental variables analysis) was not available until October 1, 2002. This means recorded patient data was potentially used from October 1, 2001 to define patients as newly-diagnosed, new users of ACEIs or ARBs, and having comorbidities. Similarly, because we wanted minimally one year of follow-up for each patient the last day someone could have his first date of healthcare utilization documenting type 2 diabetes was September 30, 2006. The analysis plan is described later.

Data Sources

The data provide information on outpatient visits, emergency department (ED) visits, and hospitalizations for services provided by the VA, including prescription utilization and lab results. The datasets are available in different files. Scrambled social security number, date of service, and date of birth linked patients across these files unless otherwise noted.

In particular, we used the following datasets available at the VA Corporate Franchise Data Center. National Data Systems provided the VHA Medical SAS Outpatient files, the VHA Medical Inpatient files, and the death files. The Decision Support Office provided the VHA Decision Support System National Data Extract files. Table 3 summarizes the data sets and the variables used in the analysis. We briefly list these files below by type of information extracted:

Outpatient Care and Emergency Department (ED) Visits at the VA

a) The VHA Medical SAS Outpatient Event dataset: This dataset contains information pertaining to outpatient encounters in the VA. Specifically, it has ICD-9 codes, CPT-4 codes, date of outpatient encounter, and provider identification number (ID).

b) The VHA Medical SAS Outpatient Visit dataset: This dataset contains information pertaining to outpatient encounters in the VA and demographic variables such as age, race, and detailed income information.

Inpatient Care at the VA

c) The VHA Medical Inpatient Main dataset: This dataset contains information on diagnostic codes, admission and discharge dates, length of stay, demographic information, and date of death.

d) The VHA Medical Inpatient Procedure dataset: This dataset contains ICD-9 codes and dates pertaining to procedures.

e) The VHA Medical Inpatient Surgery dataset: This dataset contains ICD-9 codes and dates pertaining to surgeries.

Laboratory Results at the VA

f) The VHA Decision Support System National Data Extract Clinical Laboratory Results (VHA DSS NDE LAR) dataset: This dataset contains information on laboratory results and includes information about lab name, date, lab result, date of lab procedure, and date lab procedure was ordered for inpatient and outpatient laboratory procedures.

Pharmacy Utilization at the VA

g) The VHA Decision Support System National Data Extract Clinical Pharmacy (VHA DSS NDE PHA) dataset: This dataset contains information about medication name, dose, quantity, and days supply for inpatient and outpatient prescriptions. Information was requested from October 1, 2002-September 30, 2007.

h) The Pharmacy Benefits Management (PBM) dataset: This dataset was requested from the PBM/Strategic Health Group (SHG). The Group regularly extracts data requested by researchers, with a usual turnaround time of 6 months. Information

was requested from October 1, 1998 to October 1, 2002. This is because data are unavailable in the VHA DSS NDE PHA dataset before October 1, 2002. Looking before the index date allows us to distinguish between new users and longer-term users of ACEIs or ARBs. There are 3 separate PBM extracts, but only one is given to researchers[141]. This is the prescription extract, PBM PRE EXT, which refers to outpatient prescriptions only.

Deaths

j) The Beneficiary Identification Records Locator Subsystem (BIRLS) Death File, Social Security Administration (SSA) Death Master File, and the VHA Medical Inpatient Main datasets: These datasets were requested from National Data Systems at the VA Corporate Data Franchise Center. These files were used for date of death.

k) The VA-Medicare Vital Status file: This file contains dates of death and was requested from the VA Corporate Data Franchise Center.

Table 3: Name of Datasets and Variables to Extract

Dataset	Variable
VHA Medical SAS Outpatient Event	Outpatient data: Dates of office visits, Diagnosis (ICD-9) and Procedure (CPT-4) codes Demographic and patient characteristics: Gender, Zip code of patient's residence, Race/ethnicity, Income, Provider
VHA Medical SAS Outpatient Visit	Demographic and patient characteristic: Income
VHA Medical SAS Inpatient Main	Inpatient data: Admission and discharge dates, length of stay, ICD-9 codes, Diagnosis related groups (DRGs) Demographic and patient characteristics: Gender, Race/ethnicity, Income, Zip code of patient's residence, Dates of birth and death
VHA Medical SAS Inpatient Bedsection, Medical Surgery	Inpatient data: Admission and discharge dates, Admission and discharges dates for bedsection
VHA Medical SAS Inpatient Bedsection, Non-medical Surgery	Inpatient data: Admission and discharge dates, Admission and discharges dates for bedsection
VHA Medical SAS Inpatient Procedure	Inpatient data: Admission and discharge dates, ICD-9 codes relating to procedures, Procedure dates
VHA Medical SAS Inpatient Surgery	Inpatient data: Admission and discharge dates, ICD-9 codes relating to surgeries, Surgery dates

Table 3 (cont.)

Dataset	Variable
VHA DSS NDE LAR	Visit data: Admission and discharge dates (if inpatient), Date of outpatient visit Test data: Test name, Test results, Units of results, Date lab procedure was performed, Date lab procedure was ordered
VHA DSS NDE PHA	Visit data: Admission and discharge dates (if inpatient), Date of outpatient visit Pharmacy data: Medication name, Dose, Days supply, Quantity, Dispensing date, Provider
PBM PRE EXT	Pharmacy data: Medication name, Dose, Days supply, Quantity, Dispensing date, Provider
VA-Medicare Vital Status File	Demographic and patient characteristics: Race/ethnicity, Dates of birth and death
BIRLS Death File	Demographic and patient characteristics: Dates of death
SSA Death Master File	Demographic and patient characteristics: Dates of death

Data Storage, Patient Confidentiality

Scrambled social security numbers (SCRSSNs) are generated by the National Data Systems at the VA. All SCRSSNs are based on an algorithm used throughout the datasets to ensure appropriate linkages across datasets without use of true social security numbers. The investigators neither had access to true social security numbers nor to the crosswalk that provides the conversion from SCRSSNs to true social security numbers. Further, it is part of the Information Technology security guidelines at the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center for no investigator to ever have true social security numbers.

In terms of maintaining confidentiality of subjects, all compact discs (CDs) that contained patient-level data were stored in a locked CD cabinet in a locked office at the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center. To comply with VA guidelines, all analyses were conducted at this VA facility, which is a limited access facility. Before data could be collected from the CDs, the researcher needed a password from the programmer extracting the data at the National Data Systems. This password was relayed via telephone to the researcher; email was not acceptable as it is not considered a secure means of communication. After data had been extracted from the CD and the data had been placed on the network for management and analysis, the data were stored on a restricted access network drive behind a VA firewall. This network drive is only accessible by the researchers of this study.

Study Population and Sample Size Estimation

The sample was restricted to VA beneficiaries continuously receiving VA care who have type 2 diabetes. P2DM were identified through ICD-9-CM codes 250.X0 or 250.X2.

Although consistent information exists in the literature for ACEI or ARB monotherapy comparisons to placebo for effect on albuminuria, which has led to guidelines recommending ACEI or ARB monotherapy for P2DM, there has been less information about cardio- and cerebro- vascular disease and all-cause mortality. Therefore, it is also of importance to compare those who have not received therapy to those who have received either monotherapy. We planned to study patients who did not receive ACEIs or ARBs through the VA in an effort to describe the proportion of patients who fit this description. Since the guidelines advocate their use in diabetes patients with hypertension, heart failure, or at least microalbuminuria, all patients should be receiving therapy.[54,89,142-146]

Inclusion and Exclusion Criteria

It was identified *a priori* that it would be better to have an analysis of only new users of ACEIs or ARBs who were newly-diagnosed with type 2 diabetes. This was done to limit bias associated with differences in duration of therapy, and secondarily, any unobserved bias related to duration since diabetes diagnosis. Additionally, each P2DM must have had baseline microalbuminuria or macroalbuminuria for two reasons: 1. patients with normoalbuminuria were not expected to have many events compared to those with microalbuminuria and macroalbuminuria and 2. patients with ESRD could not be followed since ESRD is an endpoint. To increase generalizability to the VA

population and maintain data integrity, patients younger than 30 years of age were excluded as individuals are usually not diagnosed with type 2 diabetes until at least 30 years of age.[147] Patients also must not have had renal insufficiency/failure due to a nondiabetic cause to rule out confounding of ESRD development. These include patients with documented ICD-9-CM codes of 593.89, 599.6, 599.60, 599.69 (urinary obstruction), 600.01, 600.11, 600.21, 600.31, 600.41, 600.51, 600.61, 600.61, 600.71, 600.81, 600.91 (urinary obstruction due to hyperplasia of prostate), 592.0, 592.1, 592.9 (kidney or ureter stone) were excluded from analysis as these diagnostic codes reflect nondiabetic causes of renal insufficiency/failure. Finally, patients who did not have at least one test result for albuminuria, HbA1c, LDL, and triglycerides were inherently excluded from analysis as individuals with missing information are dropped from statistical analysis. Since albuminuria was the emphasis of this study, all patients had to have albuminuria at baseline to be included. See Figure 3.

Figure 3: Inclusion/exclusion Criteria

Inclusion Criteria: patients documented as having newly-diagnosed type 2 diabetes during the study timeframe

Exclusion Criteria:

1. prevalent use of ACEIs or ARBs
2. patients with normoalbuminuria at baseline
3. age <30 years
4. female gender
5. patients with ESRD at baseline
6. diagnosis of renal failure/insufficiency due to a nondiabetic cause
7. combination therapy
8. 0 test results for albuminuria, HbA1c, LDL, or triglycerides
9. missing baseline albuminuria value

Sample Size Calculation

The sample size calculation is based on the difference in the primary dependent variable, onset of ESRD.

Hsieh et al. recommend using the formula $n<4P(1-P)(Z_{1-\alpha/2} + Z_{1-\beta})^2/(P1-P2)^2$ for logistic regression.[148]

Where P = probability of occurrence of the dependent variable,

$Z_{1-\alpha/2}$ = the standard normal deviate for $1-\alpha/2$ (i.e., 1.96 for $\alpha=0.05$),

$Z_{1-\beta}$ = the standard normal deviate for $1-\beta$ (i.e., 0.84 for 80% power, 1.28 for 90% power),

P1 = event rate for ARB monotherapy, and

P2 = event rate for ACEI monotherapy.

Previous studies of combination therapy compared to monotherapy have documented 11% to 26% reduction in albuminuria in the combination therapy regimen.[122,136-140] Since these were determined to be significant in combination versus mono- therapy studies and since there are no studies demonstrating significance in ACEI versus ARB monotherapy for reduction in albuminuria with comparable baseline albuminuria,[51,121-123,125,127-133] the significance criteria for combination versus mono-therapy comparisons were used for calculating significance associated with difference in onset of ESRD associated with ACEI or ARB monotherapy.

Table 4 below displays the sample size calculations based on the aforementioned combination therapy versus monotherapy studies as applied to this study. All of the calculations assume an annual incidence of onset of ESRD of 0.06 for monotherapy patients who are macroalbuminuric at baseline and an annual incidence of onset of ESRD

of 0.00 for monotherapy patients who are microalbuminuric at baseline. This is a conservative estimate as 1) RENAAL, a randomized clinical trial, showed monotherapy can lead to a 0.068 annual incidence of ESRD in those who are microalbuminuric at baseline[49] and 2) those who are microalbuminuric at baseline are expected to have progressively worsening albuminuria. If the independent variable (treatment) is correlated with covariates, the sample size needs to be multiplied by $1/(1- \rho^2)$ where ρ is the multiple correlation coefficient between the independent variable and the covariates. This is done to account for variance inflation that would occur in this circumstance.[148]

Table 4: Sample Size Calculations for ESRD

Power	**Relative risk reduction**	**Absolute risk reduction**	**Sample size, ρ = 0.0**	**Sample size, ρ = 0.1**	**Sample size, ρ = 0.2**	**Sample size, ρ = 0.3**
80%	13%	1.59%	10,516	10,623	10,955	11,557
80%	17%	2.46%	6,150	6,213	6,407	6,759
80%	21%	3.03%	4,030	4,071	4,198	4,429
90%	13%	1.59%	14,080	14,223	14,667	15,473
90%	17%	2.46%	8,234	8,318	8,578	9,049
90%	21%	3.03%	5,396	5,451	5,621	5,930

IVDEs are important to study in this population as well. Therefore, following the same sample size formula and, this time, estimating treatment effect based on studies demonstrating significance between ACEIs or ARBs and controls,[46,49,109,118] we verify that we will have adequate power to detect a statistically significant difference in IVDEs (Table 5).

Table 5: Sample Size Calculations for IVDEs

Power	**Relative risk reduction**	**Absolute risk reduction**	**Sample size, ρ = 0.0**	**Sample size, ρ = 0.1**	**Sample size, ρ = 0.2**	**Sample size, ρ = 0.3**
80%	17%	2.40%	1,078	1,089	1,123	1,185
80%	21%	2.55%	708	716	738	779
80%	37%	5.50%	322	326	336	354
90%	17%	2.40%	2,709	2,737	2,822	2,977
90%	21%	2.55%	1,777	1,795	1,852	1,953
90%	37%	5.50%	430	435	448	473

In the absence of available data we believed we would have adequate sample size based on the study by Wang (2006)[99] and our pilot study. The former study was focused on P2DM who were new users of antihypertensive therapy in 2000. The study identified 695,586 patients between October 1, 1998 and September 30, 2004. Among those who were new users of antihypertensive drugs (44,534), 22,477 were either prescribed an ACEI while 1,542 were prescribed an ARB in 2000. Assuming a similar number are on ACEIs and ARBs in other years, our estimated sample size is 72,057 for similar patients started on an ACEI or ARB between October 1, 2000 and October 1, 2003. Note we did not restrict analysis to new users of antihypertensive agents.

Pilot Study

We conducted a pilot study using local VA data to further assess patients fitting our inclusion and exclusion criteria. The point of this study was to determine the numbers and proportions of patients receiving ACEI monotherapy, ARB monotherapy, both therapies, and neither therapy in later years of the study's follow-up period. The researcher had a de-identified set of data and conducted a descriptive analysis.

At the Raymond G. Murphy VA Medical Center in Albuquerque, 7,648 patients with type 2 diabetes (newly diagnosed and those who have had it for years) were identified. Among these individuals, 47.72% of patients were on ACEI monotherapy in 2006, which increased to 51.16% in 2007. Whereas only 8.64% received ARB monotherapy in 2006, in 2007 11.07% were on ARB monotherapy. The percentage of patients receiving neither therapy decreased from 38.93% in 2006 to 32.06% in 2007. (In this circumstance patients receiving neither therapy received absolutely zero prescriptions

for ACEI or ARB monotherapy.) Only 2.35% received combination therapy in 2006, which increased to 2.85% in 2007. The pilot study gives us confidence that we would have a large enough sample size when extending the study to all VA facilities. A concern that we had was the amount of patients receiving combination therapy as that was the emerging trend in the literature among P2DM.

Data Management and Cleaning

Data Management

The VA datasets each consisted of hundreds of thousands to millions of records for each requested year for P2DM. The reason for this is a record is created for each outpatient visit, each ED visit, day of hospitalization, inpatient procedure, inpatient surgery, transfer between bedsections, prescription fill, and laboratory result. Therefore, to make this data easier to work with, a programmer placed each dataset on a VA server to create a summary of each patient's care, diagnoses, and outcomes for each year of patient data. This lead to the creation of person-time observations.

Speed of query results is dependent upon the number of columns and the number of rows. The first two steps reduced the number of columns while the next two steps reduced the number of rows. Data were optimized, meaning one field was created from the 10 ICD-9 code fields among the variables that relied on documentation of an ICD-9 code in any of the fields. Next, variables that were not needed specifically for this analysis were deleted to make the queries run faster. After this, because the population of type 2 diabetes patients has a majority who is normoalbuminuric, these patients were deleted. Following this, records not having ICD-9, CPT-4, or DRG codes of interest

were dropped. The last step was not involved with directly reducing the number of rows or columns. Rather, normalizing data indirectly reduces the number of rows the computer processor has to analyze. Normalizing data basically orders words alphabetically and numbers from smallest to largest. A flag signifies the start of another letter or number. When the processor finds the record of interest is in between two tabs, it starts at the earlier of the two tabs, bypassing the previous records.

Data Cleaning

After completion of the processes involved to make queries run faster, data cleaning began. Instances of more than one date of birth, gender, or race/ethnicity for a subject were treated similarly. For a subject with more than one date of birth, the decision was made to use the date of birth appearing most frequently for that patient, making the assumption that data entry error would occur with the less frequent date of birth. For the five patients with more than one date of birth that appeared with equal frequencies, the decision was made to take the midpoint of the two dates of birth as long as the two dates of birth did not exceed twenty years of separation. In that case, the age was coded as missing. For a patient with more than one value for gender or race/ethnicity documented across visits, the patient was labeled with the most frequently occurring value. If more than one value was documented with equal frequency, the respective variable was coded as missing. Additionally for race/ethnicity, values of "unknown" were coded as missing.

Albuminuria and albumin:creatinine ratio results were extracted from the datasets. These values were character/string rather than numeric. A value with the letter "O" was transformed to number "0". A values such as "<4" was transformed to the closest integer

("3" in this example). A value with a range was transformed to the number in the middle of the range (for instance, "30-300" would become "135"). Values with words that could not be easily translated were deleted. From here, because the albumin:creatinine ratio is more exact than albuminuria, we used albumin:creatinine ratio preferentially at baseline and in each year of observation for each patient. When there was no value for the ratio, we used the albuminuria values rather than considering it missing data. If neither value was present for a patient in a year, it became a missing value. If more than one test was performed in a given year the mean of the values was recorded for study purposes.

HbA1c, LDL, and triglyceride test results were obtained similarly as albuminuria and albumin:creatinine ratios, meaning that the data were directly lifted from the datasets, so similar translations occurred. Also similar to albuminuria and albumin:creatinine ratio, if, within a test, more than one test was run in a given year of observation, the mean of the values was taken. Rarely did this happen. For more details about coding Elixhauser comorbidities, covariates, variables used to control selection bias, and dependent variables, please see Appendix F, Tables 1, 2, 3, and 4, respectively.

Empirical Analysis

Introduction

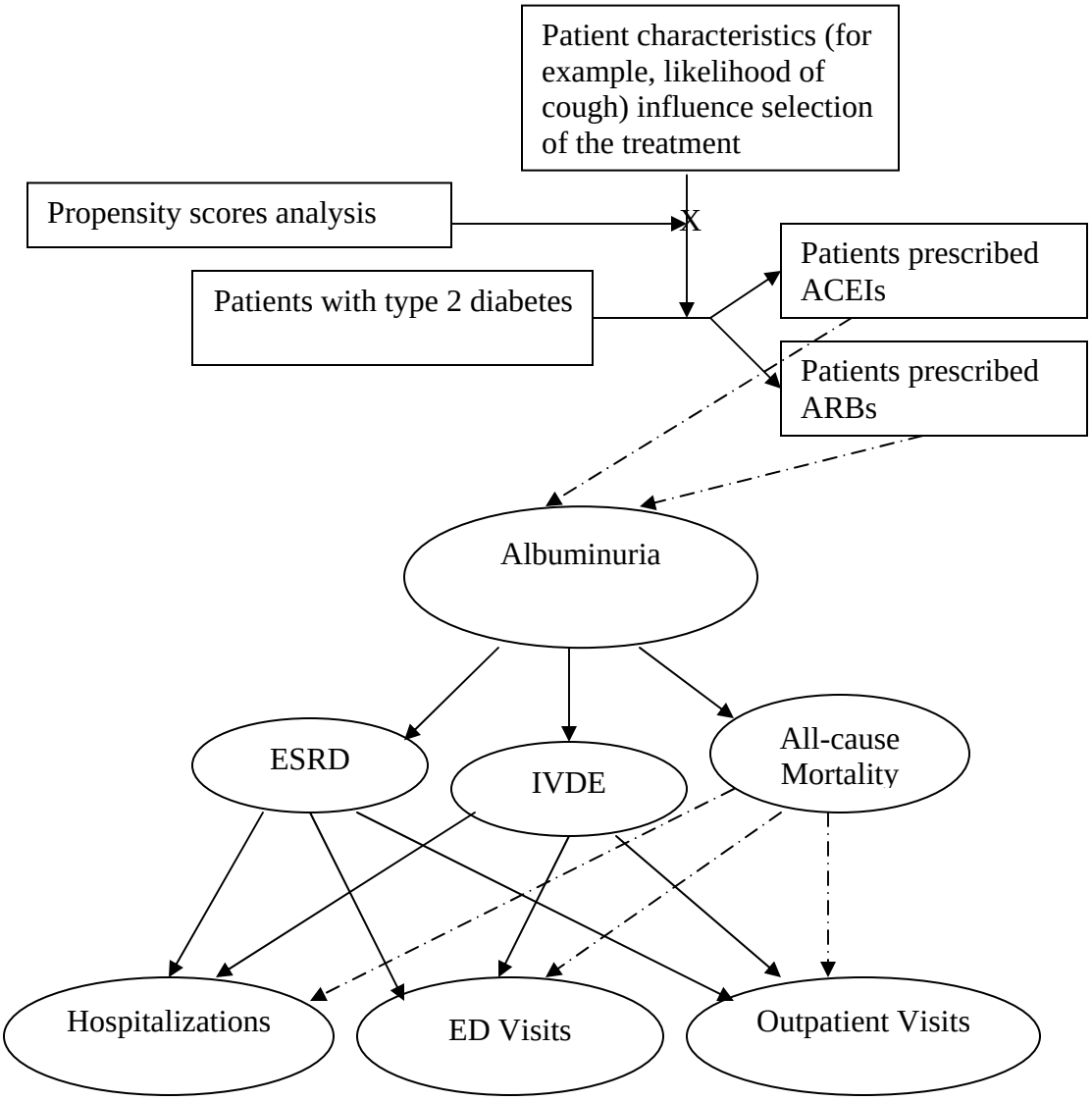
In this section we first present the advantages of propensity score analysis compared to OLS. Then, we discuss propensity score analysis; including regression, stratification, and matching; comparing and contrasting these techniques. Then we talk about sensitivity analysis of propensity score analysis results. From this topic we explain how we incorporated propensity score analysis into logistic regression as well as regressions specific to count variables. In the context of regression models for count variables we explain the advantages of count regression models over OLS, then we recount the controversy in the different models, and discuss different model fit diagnostics. Next we talk about how we dealt with non-independence of observation, how we followed patients, and how we accounted for multiple comparisons in assessing significance. Since there were univariate comparisons in our analysis, but these are much more common techniques, a short overview is included. From here, we talk about construction of independent and dependent variables and covariates. Lastly, we summarize all the techniques as applied to this study and report a timeline of activities.

Theory suggests that choice of treatment is associated with patient characteristics. Treatment selection reflects clinical practice; expert opinion exists for preferential selection of ARBs based upon patient propensity for cough due to the much higher rate of cough witnessed with ACEIs. We expect differences between groups in patient characteristics as confounding by indication naturally exists in clinical practice: those who are expected to receive the most benefit from a treatment are more likely to receive that treatment. In an observational design, treatment selection can produce biased

estimates. Use of longitudinal data and quasi-experimental design helps us to control for this selection bias. Specifically, we used one method to control for selection bias: propensity scores analysis (Figure 4).

Propensity score analysis controls observable variables that could lead to selection bias. Observable patient characteristics can potentially be confounders. In order for this to happen, a characteristic must be correlated with both the independent and dependent variables while not being an intermediate step in the path. If there is no evidence of selection bias, ordinary least squares (OLS) with robust standard errors is more efficient, so would be preferred.

Figure 4: Conceptual Framework.
The top diagram acknowledges selection bias and how we will control for selection bias. Basically, controlling for selection bias through propensity scores analysis should make therapy groups similar. From here, we will be able to assess how ACEIs and ARBs influence albuminuria and the other outcomes of interest.



Propensity Scores Analysis

Propensity scores analysis (PSA) has been used to control for selection bias associated with treatment assignment by adjusting for the propensity score, defined as "the conditional probability a patient will be treated based on observed covariates."[149] The limitation with propensity scores analysis is that it only controls for observed variables, unlike other approaches such as instrumental variables analysis.[150] That being said, the theory behind PSA is that if all observed covariates are included in the model predicting odds of treatment selection, this reduces the association between treatment assignment and prognosis.[149] Further, if people between groups are similar on observed variables, they should be similar on unobserved variables as well. Therefore, PSA may lead to more precise estimates than OLS regression, which may underestimate treatment effect. The last ideal of PSA is that matching patients on propensity scores leads to exclusion of patients that are at tails of the distribution. This leads to identification of patients who have a low or high probability of one treatment or another based on their covariates, meaning there is no clinical equipoise for these patients. Thus, it could be postulated that these patients should not be included in the analysis.[151] In fact, there is evidence that using PSA to account for treatment selection provides similar treatment effect estimates obtained from randomized clinical trials.[152]

In the propensity scores method, a logistic regression is first run to determine the odds of receiving each treatment strategy, the propensity score, for each patient based on observed covariates.[153] More technically:

$P(Tr|\mathbf{X}, Y_{obs}, Y_{mis}) = P(Tr|\mathbf{X})$ for all $Y_{mis,}$ Y_{obs} is the probability an individual assigned a particular treatment is only related to observed variables $\mathbf{X}$.[154] Since Y_{obs} is

the outcome observed for a patient given his/her assigned treatment and Y_{mis} is the outcome observed in a patient with the same propensity score assigned the alternate treatment (i.e., the counterfactual outcome), the equation explicitly states treatment assignment is not dependent on recorded outcomes of treatment assigned nor is it dependent on unrecorded outcomes of treatments not assigned. Extending this to each patient: $p_i=P(Tr_i|X_i, Y_{obs})$ is the propensity score.[154]

Accordingly, enough overlap in the propensity scores between the groups needs to be present to provide valid estimates of the treatment effect.[149] PSA, in an attempt to make groups equal, extracts the variation in therapy not related to, at least, observed characteristics. In STATA, this is accomplished by including only those patients identified as having common support equal to one, which restricts analyses to any combination of observables that can be observed in both treatment groups.[155] In other words, analysis is restricted to matched patients. Said yet another way, if people are matched on similar propensity scores, since these patients had similar probability of treatment, as far as we can tell from comparable baseline observable characteristics, a coin was flipped to determine treatment assignment.[156]

A model explaining treatment assignment is necessary for causal inference.[154] This points to the usual regression assumptions that if model misspecification is present or if covariates are measured with error, the treatment effect estimates are biased; the same holds true for PSA.[153] Additionally, bias from between group differences in baseline observed covariates is inherent in regression without propensity score adjustment.[157] For PSA, it is believed to be better to include a weak confounder, thus allowing for some inefficiency, than to omit it and create bias.[158] The first stage of the

PSA should include all variables believed to be associated with the outcome regardless of their association to treatment.[159,160] If the model predicting treatment selection is correctly specified, it will result in a consistent estimator.[161] The benefit of collapsing all potential observed covariates into a single predictor variable is improved efficiency[149] as possible multicollinearity from inclusion of many observed covariates will make the standard error larger than if just incorporating one predictor into the next step of the analysis.

Regression adjustment with propensity score can be accomplished by using a large set of baseline observable covariates to estimate the propensity score, and then using a subset of the covariates with the propensity score in the second stage regression.[162] In the second stage, the regression can be weighted by the inverse of the propensity score for each patient.[160] Weighting by the inverse of the propensity score removes the imbalance of observed covariates between the treatment groups as well as the associated bias.[163] This approach provides a relatively simple way to incorporate propensity scores into longitudinal data.[160] Weighting may also allow for more patients to be included in the second stage PSA, providing for more generalizability.[152]

In this study, we reweighted the second stage regression model by using a logit regression of drug therapy to estimate the conditional probability, p_i, of being in the ACEI monotherapy group, with weight of $p_i/(1- p_i)$.[164] This implies we only applied this weight to patients receiving ARB monotherapy in order to make the outcomes that occurred in the ARB monotherapy group represent the counterfactual outcomes of the ACEI monotherapy group "by making the two groups similar with respect to observable characteristics."[165] "A weighted regression of outcome on treatment is thus a comparison

of means across treatment and control groups, but the control group is reweighted to represent the average outcome that the treatment group would have exhibited in the absence of treatment. That is, every control group observation is contributing to an estimate of the mean counterfactual outcome for all treated observations (rather than specific observations being matched)."[165] Reweighting with this method provided the average treatment effect on the treated (ATT of ACEI monotherapy), which allows for direct comparison to the other techniques used to derive ATT.[164] These techniques, stratification and matching, are described below.

The creators of PSA, Rosenbaum and Rubin, recommend to balance the nonequivalent groups using stratification (5 strata) or matching,[166] which is the original intent of the technique.[150] Stratifying or matching across treatment groups allows the treatment effect to be estimated as observed covariates are similar between the groups. Stratification is different than regression as it obtains propensity scores through iterative testing to see if there is balance between groups on the propensity score; if not, the stratum is halved to see if the propensity score is then balanced between groups.[165] Once equal, if the F ratios of any variables are large, interactions with these variables need to be added and/or squares of these variables need to be added and the process repeated until variables are balanced.[167] Obtaining this balance in propensity scores effectively creates a 90-95% reduction in bias.[167] An alternate strategy that can be employed as a next step is to use propensity scores generated in the first stage as part of the second stage PSA.[160] Matching on propensity score is usually less efficient than weighting, meaning fewer observations are generally included with the former method.[157] Additionally, matching can make it complicated to make confidence intervals incorporating the

propensity score obtained in the first stage.[157] We compared the PSA methods of stratification, nearest-neighbor matching, and two stage regression in this study.

Using a weighted second stage regression does not guarantee the distributions of propensity scores are identical between the two treatment groups, for those who are on common support, but it does balance the majority of the propensity score data across the groups.[165] Another thing to touch on is the lack of confidence in attaining standard errors (SEs) in nearest-neighbor matching while they are known (and not controversial) in stratification. Since the t-statistic is derived from dividing the mean difference between groups by the SE, a different SE (for instance, obtained through bootstrapping) may have yielded significant results. Nearest-neighbor matching yields SEs that do not take propensity score into account. Based on the limited information about this that I can find, this causes SEs to be biased downward, leading to larger t-statistics, which would overestimate significance.[168] Although this seems to be the case and an alternative is to bootstrap to find the SE, there is literature saying that bootstrapping will lead to miscalculation of the SE as well.[169] The ATT derived through stratification is based on a weighted average of treatment effect of each of the strata[170] while the ATT derived through nearest-neighbor matching is calculated by comparing an ACEI patient's outcome to the ARB patient's outcome with the closest propensity score. Given this information the reader may ask why we want to assess outcomes with nearest-neighbor matching. The reason is because nearest-neighbor matching permits the researcher to conduct sensitivity analyses. As can be inferred, there is some underlying controversy in the techniques, and because different techniques have the potential to yield different

results, we sought to compare ATT obtained from each second stage PSA technique: regression, stratification, and matching.

Validity of PSA Approach

To assess the stability of the propensity score we used sensitivity analyses in case unknown unobserved heterogeneity (hidden bias) was present. According to Rosenbaum (2002), presence of unobserved variables that affect treatment assignment and dependent variable may result in a hidden bias.[171] Rosenbaum bounds calculates the difference in treatment effect of the dependent variable (i.e., outpatient visits) between the two treatment groups if various levels of hidden bias did exist, meaning this technique indicates the robustness of PSA results.[171,172] It is important to point out that it is impossible to test that unobserved variables are truly not confounders, which is a PSA assumption.[167,171]

Specifically:

$P_i = P(\mathbf{x}_i, \mu_i) = F(ß\mathbf{x}_i+\gamma\mu_i)$ where P_i is the probability of the outcome, $\mathbf{x}_i$ are the observed variables for the individual, μ_i is the unobserved variable, and γ is the effect of μ_i on the outcome.[172] If unobserved heterogeneity is absent, γ will be zero, meaning the outcome is determined by $\mathbf{x}_i$ only.[172] Conversely, if unobserved heterogeneity is present, two people with the same observed variables have different chances of assignment to a treatment group by a factor γ, meaning γ does not equal zero.[172] Since patients are matched on propensity score, $\mathbf{x}_i$ drops out of this equation. Converting this into a logistic regression for individuals with the same observed variables gives the following:[172]

$$\frac{\frac{P_i}{1-P_i}}{\frac{P_j}{1-P_j}} = \frac{P_i(1-P_j)}{P_j(1-P_i)} = \exp[\gamma(\mu_i-\mu_j)]$$

From this thought, Rosenbaum (2002) places bounds on the odds ratio that two matched individuals from PSA will be assigned the same treatment:

$$\frac{1}{e^{\gamma}} \leq \frac{P_i(1-P_j)}{P_j(1-P_i)} \leq e^{\gamma}$$

where e^{γ} only is one when matched individuals will have the same outcome.[171,172] (If = 1.5 it means that individuals with the same observed variables could have up to a factor 1.5 difference in treatment assignment.)[172]

This technique provides the Wilcoxon signrank tests that give upper and lower bound estimates of significance levels at given levels of unobserved heterogeneity at different levels of γ (γ =1 means no heterogeneity).[173] It also calculates Hodges-Lehmann point estimates and confidence intervals for the ATT.[173]

A similar sensitivity analysis was developed for dichotomous variables: Mantel-Haenszel bounds.[172] This technique uses the Mantel and Haenszel test statistic, Q_{MH}, to compare the actual, versus expected, number of successful patients in the treatment group, for treatment effect equal to zero.[172] Since Q_{MH} can be bounded by two known distributions we use the bounds of no unobserved heterogeneity and some unobserved heterogeneity and run several scenarios with increasing levels of unobserved heterogeneity.[172] A positive Q_{MH} is the test statistic assuming overestimation of

treatment effect; conversely, a negative Q_{MH} is the test statistic assuming underestimation of treatment effect.[172]

Other Statistical Considerations

We have mentioned the techniques used to most accurately depict effect of therapy on outcome. Next, we need to mention how we incorporated these previous techniques in analysis of the dependent variables. The latter techniques in this section are independent of the previous of these techniques.

Type of Dependent Variables: Dichotomous Variables

We performed logistic regression for the clinical outcomes ESRD, IVDEs, and all-cause mortality. Exponentiating the coefficient (β) provides the odds ratio that the outcome will occur for the independent variable conditional on covariates. The equation is:

$$Y = \frac{e^{A + B\mathbf{X}}}{1 + e^{A + B\mathbf{X}}}$$

Where Y is the outcome (ESRD, IVDEs, or all-cause mortality), A is the intercept and B is the estimate of effect for each variable in a vector of predictors, **X**.

Type of Dependent Variables: Count Variables

Although OLS is sometimes used to model count data when there are more zero values than other values in the data, power is decreased as OLS assumptions are violated, while at the same time, using the central limit theorem as a justification to use OLS may lead to incorrectly rejecting the null hypothesis.[174] One could also transform dependent variables to achieve a normal distribution, but these transformed variables generally are

not interpretable (i.e., what is the inverse of a hospitalization or the natural logarithm of ED visits?).[174] Additionally, "there is a very real danger that the log scale results may provide a very misleading, incomplete, and biased estimate of the impact of covariates on the untransformed scale, which is usually the scale of interest."[175] Another important consideration is there is no transformation that can "spread out a stack of zeroes".[174] "Transforming the outcome fundamentally alters the structure of residuals, and it is possible to transform the residuals to normality while concurrently violating a different assumption, such as unequal variances".[174] Lastly, OLS or OLS with transformed dependent variables can be biased and inefficient with count data.[176] Manning (1998) and Mullahy (1998) add that OLS methods can lead to biased estimates in the presence of heteroskedasticity if not retransformed appropriately.[175,177] Manning (2001) also mentions that generalized linear models (GLM) may have more precise estimates than OLS when heteroskedasticity is absent.[178]

Instead, a family of different models are recommended for analysis of count variables. The Poisson distribution is referred to as a log-linear model since the natural logarithm of the conditional mean is linear in the parameters, $\ln E[y_i|x_i]=\mathbf{x}_i'ß$. It is a generalized linear model with a natural logarithm link function and Poisson distribution (in contrast, logistic regression has a logit link and binomial distribution).[174] It is a better choice than the normal distribution for count data. For example, while count data are necessarily positive, the normal distribution extends from negative infinity to positive infinity.[174] For Poisson regression, correct specification of the conditional mean is required to obtain consistent estimates.[179] Alternatively, consistent estimates are independent of Poisson distribution of the dependent variables.[179] Although statistical

inference is still valid in the presence of data that are not equidispersed with correct specification of the conditional mean, Poisson regression will result in less efficient estimators than other distributions.[179] In particular, the standard errors will be biased downward, giving large z-values, which will overestimate significance.[180] Poisson's equidispersion property (i.e., mean = variance) is akin to the homoskedastacity assumption in OLS. As already alluded to, count variables often have overdispersion (i.e., variance > mean). One cause of overdispersion is not taking heterogeneity of mean rate across individuals into account.[181] Although observed heterogeneity is indicated with μ in Poisson regression, the negative binomial regression allows for unobserved heterogeneity through introduction of the dispersion parameter, α.[181] It is this larger variance that makes the negative binomial distribution have more low counts, one of which would be zero values.[181]

In this circumstance, there are alternative methods to pursue. The first is to conduct a Poisson regression, but with adjustment to the standard errors with a robust sandwich estimator (a.k.a. Huber-White estimator), called Poisson-pseudo maximum likelihood estimate.[179] This takes overdispersion into account.

The second alternative is to use the negative binomial distribution, of which the Poisson distribution is a special case.[179] The negative binomial distribution inherently assumes the data are overdispersed since the variance is a multiple of the mean. This model is the standard parametric model to account for overdispersion.[179] Specifically, while the Poisson distribution assumes variance=$\mu=\exp(\mathbf{x_i}'ß)$, the conditional variance of Y_i given x_i, $\omega_i=\mu_i+\alpha_i^p$ where p is specified. The NB1 function holds p at 1, making

$\omega_i=(1+\alpha)$ while the NB2 function holds p at 2, making $\omega_i=\mu_i+\alpha\mu_i^2$. In either case, α needs to be estimated. If $\alpha=0$ then the negative binomial distribution reduces to the Poisson.[179]

Overdispersion can be detected by comparing the variance and mean, which was done before running each regression so we knew what to anticipate before running any formal tests of overdispersion. The likelihood ratio test statistic is a more formal test of overdispersion. Since the Poisson model is nested in the negative binomial, "the test statistic is twice the difference in log-likelihoods between the two models, which is distributed as a χ^2 random variable with degrees of freedom equal to the difference in number of parameters between the two models."[174] This test assesses if there is a difference between the two models; if there is not a difference, the test will have a nonsignificant p-value indicating lack of overdispersion. When the dependent variable is overdispersed the negative binomial model's standard errors will be larger and more appropriate; said a different way, using Poisson regression in these circumstances would result in lower p-values and narrower confidence intervals than should be.[174]

Zero-inflated Models

Zero-inflated models introduce two more methods to our repertoire to depict count variables; however, their use is more controversial. For instance, Manning (2001) says parsimony may be more advantageous than achieving a better fit.[178] The rationale behind using zero-inflated models is that patients use healthcare through two distinct processes: some patients will not use healthcare resources while others clearly will, but the amount of care used among those using it needs to be estimated differently from whether or not patients are using healthcare resources.[177] Since we do not know who tried to access care and did not versus who did not try to access care, modeling this way,

by forming two different groups, accounts for this unobserved heterogeneity.[181] The overall probability of zeroes is formed from the probability of zeroes in each group weighted by the probability of each individual being in that group.[181] The first part uses all count values to estimate the mean with a Poisson distribution, then the second part uses individual characteristics, ψ, to estimate zeroes with a logit or probit model.[177,181] Zero-inflated Poisson and zero-inflated negative binomial models lower the expected count by $\mu\psi$, which also changes the conditional variance.[181] The zero-inflated Poisson model has conditional variance= $\mu_i(1- \psi_i)(1+ \mu_i\psi_i)$ while the zero-inflated negative binomial model has conditional variance = $\mu_i(1- \psi_i)[1+ \mu_i(\psi_i+\alpha)]$.[181] If $\psi =0$ for the zero-inflated Poisson, the model reduces to a Poisson regression and if $\psi =0$ for the zero-inflated negative binomial, the model reduces to a negative binomial regression.[181] The Vuong test can be used to assess which model is favored (zero-inflated Poisson versus Poisson or zero-inflated negative binomial versus negative binomial),[181] but cannot be used with clustered robust standard errors, as we have used in this study.

At least in the non-robust standard error situation, standard errors should be larger for the negative binomial than the Poisson and for the zero-inflated negative binomial than the zero-inflated Poisson.[174,182] Similarly, for non-robust standard errors, standard errors for zero-inflated Poisson tend to be larger than for Poisson.[183]

The same overdispersion test that compared Poisson and negative binomial models can be used to compare zero-inflated Poisson and zero-inflated negative binomial.[174]

Model Fit Diagnostic Tests

Just as there is controversy with use or non-use of zero-inflated models due to their lack of parsimony and difficulty in interpretation, there is controversy in what diagnostic tests should be used to determine the count model with the best fit of the data. Kibria (2006) says the model with the lowest Akaike's information criterion (AIC) should be selected.[184] AIC=-2L+2k where L is the log likelihood and k is the number of parameters in the model. In contrast, Basu et al (2004) used the Hosmer and Lemeshow goodness-of-fit test, Pregibon's Link Test, and Pearson's correlation for the predicted and residual on the raw scale to determine the best model fit for the dependent variables length of stay and inpatient expenditure.[185] In contrast, the Statistical Consulting Group at University of California, Los Angeles says if we're between a negative binomial and zero-inflated negative binomial to look at the log likelihoods and the Bayesian information criterion (BIC); if similar, they advise to go with the negative binomial model because it has fewer degrees of freedom.[186]

Since the Vuong test cannot be used in this study to determine best model choice of each count variable and because controversy surrounds zero-inflated models due to their lack of parsimony and difficult interpretation, we report negative binomial regression in Results. The researchers performed Poisson, negative binomial, zero-inflated Poisson, and zero-inflated negative binomial regression analyses for each count variable and provide summary tables of model fit diagnostics of each model in Appendix F.

Non-independence of Observations

Incorporating time-varying covariates means we have multiple observations per person, a violation of OLS regression. To account for this we used the Huber-White

Sandwich Estimator and clustered by patient to account for non-independence of observation.[187] This is because we expect heteroskedasticity between groups since variance in variables changes across treatments.[187] Heteroskedasticity is a violation of OLS, biasing variance, which means we cannot correctly test for significance with OLS procedures.[187] Although the Huber-White Sandwich Estimator does not fix the heteroskedasticity problem, it is robust to its implications.[187]

Intention-to-Treat Analysis

We performed an intention-to-treat analysis to maintain balance achieved at baseline through PSA between monotherapy groups, meaning if a patient switched from an ACEI to an ARB, this analysis counted that patient as receiving an ACEI. This type of analysis evaluates the decision to assign the patient to one therapy or the other. Intention-to-treat is a conservative estimate of effect due to treatment crossovers.

Multiple Comparisons

It is well-described in the literature that using the same sample to answer multiple questions results in inflation of alpha.[188] Thus, in the researchers' eyes variables were only significant at $p<0.017$ ($p=0.05/3$) for analyses involving three group comparisons and $p<0.05$ for comparisons limited to ACEI and ARB monotherapies, which follows advice of having a conservative value of α in the context of multiple comparisons.[189] There are several techniques that can be used to adjust for multiple comparisons and we acknowledge the controversy around Bonferroni adjustment. ANOVAs used Tukey Honestly Significant Difference pairwise comparisons because it is the most conservative approach of the other pairwise comparisons.[188] Pairwise comparisons using this method

are significant when the studentized range critical value is less than the observed value.[188] Kruskal-Wallis tests used Bonferroni adjustment for control of family-wise error associated with pairwise comparisons.[190]

Univariate Comparisons

Analysis of Variance (ANOVA) and Kruskal-Wallis Test

ANOVA was performed for between group comparisons of continuous and count variables. If the Levene test showed homogeneity of variance, the results were retained. However, if the Levene test detected heterogeneity of variance, the Kruskal-Wallis test was conducted to detect between group differences as there are more relaxed assumptions about the distribution in this non-parametric test as compared to the parametric ANOVA.[191]

Chi-square Test

Chi-square tests were performed for between group comparisons of categorical variables to assess differences in proportions of baseline characteristics.[192]

Construction of Variables

Independent Variable

Drug therapy is a mutually exclusive and exhaustive categorical variable in our sample. ACEI, ARB, neither, and combination therapy status was defined by looking at the original prescription and subsequent refill pharmacy records, thus compliance is inherently embedded in this. Specifically, the days supply in each year that each patient received an ACEI or ARB was first calculated. (Note this is the medication possession ratio.[193]) Then, looking across each day of the observation period, if any overlap in ACEI or ARB prescription days supply existed, these patients were considered to be taking

combination therapy during that time. If patients received less than enough medication to last one-half of the year, those patients were considered to be on neither therapy. Patients receiving neither therapy in any year were excluded from subgroup analysis. Alternately, if a patient had at least enough of a days supply of an ACEI (excluding any combination therapy with concomitant days supply of an ARB), to cover one-half of the year, that person was considered to have received ACEI monotherapy. In a similar vein, ARB monotherapy was calculated. If patients had overlapping ACEI and ARB prescriptions that covered at least one-half of any year of observation, those patients were excluded from analysis as they were considered taking combination therapy.

Dependent Variables

Development of ESRD is a mutually exclusive and exhaustive categorical variable in our sample. This is dichotomous in nature: people who developed ESRD were coded as "1"s while people who did not develop ESRD were coded as "0"s. Patients with ICD-9-CM codes of 585.6(, V45.1, or V56 or CPT codes 36800, 36810, 36815, 90935, 90937, or 90947, 90989, 90993; 50300, 50340, 50360, 50365; 90920, 90921, 90924, 90925, 90945, 90997, 90999) were classified as having ESRD (dialysis; kidney transplant; ESRD-related services, respectively). Those identified as having ESRD at baseline were excluded.

Change in albuminuria is a categorical variable reflecting the change in albuminuria during the observation period.

IVDE is a mutually exclusive and exhaustive categorical variable in our sample. This is dichotomous in nature: people who suffered an IVDE were coded as "1"s while people who did not will be coded as "0"s. Patients with MI or ischemic stroke were

identified with ICD-9 codes 410.00-.02, 410.10-.12,410.30-.32, 410.40-.42, 410.50-.52, 410.60-.62, 410.70-.72, 410.80-.82, 410.90-.92 or ICD-9 codes 433, 433.0, 433.1, 433.2, 433.3, 434, 434.0, 434.1, 434.9, 434.91. Patients with LVH were identified with ICD-9-CM code 429.3. If a patient had one or more MIs in the same year that patient was documented as having an MI in that year and subsequent years. Ischemic stroke had the same logic as MI. Since once a patient has LVH the person has it the rest of his life, LVH was documented in the year it occurred as well as subsequent years of observation. If ICD-9 codes 438 or V12.59 were coded with ICD-9-CM code 434.91 (or, if before occurrence of another stroke, if coded by themselves), these patients were classified as having a history of stroke. Similarly, if ICD 9(-CM) codes 412 or 429.7 were found, these patients were classified as having a history of MI. Individuals with a family history of CVD were identified with ICD-9 codes V17.1, V17.3, and V17.4. These people were included; history of CVD will be a covariate.

All-cause mortality is a mutually exclusive and exhaustive categorical variable in our sample. This is dichotomous in nature: people who died were coded as "1"s while people who did not were coded as "0"s.

Number of outpatient visits is the number of times a patient was seen by a provider during an outpatient visit. Determined by unique visit date, it is the subset of unique outpatient visits that do not have a CPT-4 code denoting an ED visit. Range can be 0 to 365 in each year.

Number of ED visits is the number of times a patient was admitted to the emergency department. Determined by unique visit date, it is the subset of unique

outpatient visits that have a CPT-4 code denoting an ED visit (CPT-4 codes 99281-8). Range can be 0 to 365 in each year.

Number of hospitalizations is the number of hospitalizations a patient encountered. After the initial admission date, every additional admission date signifies another hospitalization. Range can be 0 to 365 in each year.

Other Variables

The majority of other variables were created based upon presence of ICD-9-CM, DRG, and/or CPT-4 codes (see Tables 6-8). The following variables, however, were not as straightforward.

New user is a dichotomous variable of ACEI or ARB monotherapy patients. A patient received a "1" if there was no documented prescription of an ACEI or ARB in the six months before the index date. If a prescription for an ACEI or ARB was found in this time period, the variable was coded as "0".

Newly-diagnosed is a dichotomous variable. A patient received a "1" if there was no documentation of type 2 diabetes in the year previous to the first date of healthcare utilization for type 2 diabetes in the study period. If there was such documentation, the patient received a "0".

Cohort is a mutually exclusive and exhaustive categorical variable. The cohort in which a person belongs is based on the fiscal year within the study period in which the first date of healthcare utilization for type 2 diabetes occurred. A patient was classified into cohort 2003, 2004, 2005, or 2006.

Time is a mutually exclusive and exhaustive categorical variable. For each patient, it corresponds to each year for which information on healthcare utilization was

available after the first date of healthcare utilization for type 2 diabetes. Time t corresponds to year 1, time (t+1) to year 2, time (t+2) to year 3, time (t+3) to year 4, and time (t+4) to year 5. (The maximum amount of follow-up a patient can have is dependent upon the cohort to which he belongs since patients were not followed after September 30, 2007).

Urban/suburban versus rural living is dichotomous variable determined from zip codes based on census tract information.[194] Rural Urban Commuting Area Codes (RUCA) for 2006 were used. Specifically, RUCA2 codes with zip codes were used to differentiate between urban/suburban and rural status. Zip codes were retained in the dataset as well.

Treatment initiated in winter is a dichotomous variable of ACEI or ARB monotherapy patients. A patient received a "1" if he received his first prescription for an ACEI or ARB between December 1 and February 28 (or 29 if a leap year) of the year. If he did not, this variable was coded as "0".

Covariates Used in Regression Analyses

For ESRD, covariates were compliance of ACEIs or ARBs; time; age; income (<$6,000, $6,000-17,999, $18,000-34,999, ≥$35,000, missing); rural versus urban/suburban living; smoking (current versus former versus never smoker); HbA1c; LDL cholesterol; triglycerides; Elixhauser comorbidities, including hypertension and obesity; cohort; and metropolitan area/county. Compliance with ACEIs and ARBs needs to be controlled to obtain a realistic picture of benefit of these therapies, and thus, differences between these therapies. Time was taken into account as that is the strength

longitudinal studies have over cross-sectional. Differences in age are generally documented to be associated with poorer health outcomes across disease states. Similarly, patients with lower income tend to have poorer health while those living in rural areas are more likely to have access to care issues, leading to poorer health outcomes. Smoking, hypertension, and obesity are health conditions along with the other Elixhauser comorbidities predisposing patients to poorer health outcomes. Higher levels of HbA1c, LDL cholesterol, and triglycerides are risk factors for ESRD in P2DM. Cohort was controlled in case there was a difference in health status based on year of type 2 diabetes diagnosis. To account for between group differences in local formulary status metropolitan area/county were entered into the first-stage PSA.

For IVDE, all-cause mortality, number of outpatient visits, number of ED visits, and number of hospitalizations, covariates were compliance of ACEIs or ARBs, time, age, income (<$6,000, $6,000-17,999, $18,000-34,999, ≥$35,000, missing), rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking (current versus former versus never smoker), HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county. The reasons for inclusion of these covariates for IVDE and all-cause mortality are similar to those for ESRD. HbA1c, LDL cholesterol, triglycerides, history of MI, history of stroke, and family history of CVD are also risk factors for cardio- and cerebro- vascular disease and all-cause mortality in P2DM. Since they are risk factors for these dependent variables, referring to Figure 4, we would want to control for these for number of outpatient visits, number of ED visits, and number of hospitalizations.

Smoking status was determined with ICD-9-CM codes of 305.1, 989.84, 491.0, and V15.82, which identify current tobacco dependence, toxic effect of tobacco, smoker's cough, and history of tobacco use, respectively. Patients with hypertension were identified with ICD-9 code 401 while obese patients were identified with ICD-9 code 278.

Elixhauser Case-Mix Index

In all specifications, to help control health status among different treatment strategies that might be associated with treatment selection, we constructed an Elixhauser index of comorbidities, which identifies 30 different conditions.[195] There are many severity of illness indices; none have been identified for predicting ESRD or cardio- or cerebro- vascular disease. The advantages to using the Elixhauser case-mix index include its development based upon about 1.8 million patients from 439 hospitals, its ability to assess effects of each comorbidity (which would otherwise be missed in a single index that combines all comorbidities into one measure), and its increased model power. For instance, a comparison of the Charlson comorbidity index to Elixhauser found Elixhauser to be better due to the aforementioned differences as well as the fact that Elixhauser accounts for a greater number of comorbidities.[196,197]

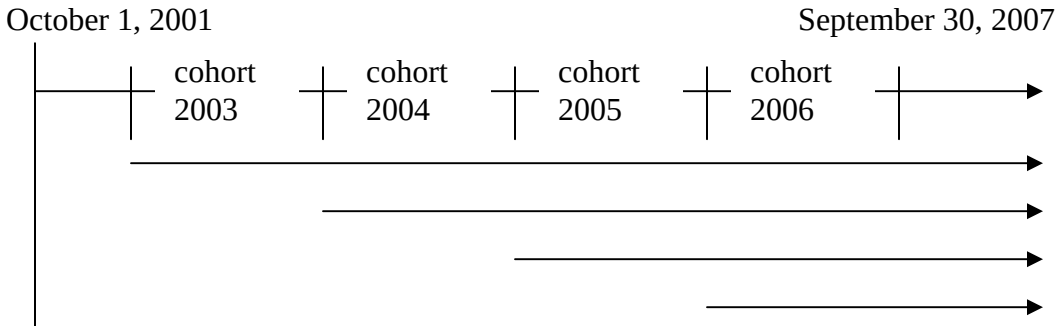
The Charlson comorbidity index includes conditions that occurred in <600 patients in 1 hospital in 1 month.[197] It also adds weights for comorbidities from relative weights in Cox regression despite relative weights not being additive. The Nursing Severity Index is similar to the Charlson comorbidity index in creating one number from patient comorbidities[198] and has less published literature supporting its use. RxRisk,

formerly known as the Chronic Disease Score, was found to be less consistent than the diagnosis-based models to which it was compared.[199]

Since diabetes is one of the 30 conditions identified in Elixhauser and the purpose of its use is to identify comorbidities rather than complications or the disease of interest, we did not include diabetes-related complications occurring after the index date or diabetes as comorbidities. Specifically, complications of interest were captured as outcomes and diabetes at baseline was excluded as a comorbidity. However, history of CVD or any other conditions potentially identifiable as complications at baseline were considered as comorbidities. Comorbidities were captured when codes documenting each comorbidity were found in the three months before the first date of healthcare utilization documenting type 2 diabetes.

Figure 5 provides a summary of data collection and patient follow-up. Table 6 shows the statistical techniques used in each analysis. Table 7 depicts the time allocated to each study activity.

Figure 5: Summary of Data Collection, Patient Follow-up



- Determined eligibility criteria for veteran P2DM.
  - New diagnosis of type 2 diabetes: looked back one year from first date of healthcare utilization in which type 2 diabetes was documented during time period
  - New user of ACEI or ARB: looked back 6 months from first date of healthcare utilization in which type 2 diabetes was documented during time period
- Characterized included patients.
  - Comorbidities: looked back 3 months from first date of healthcare utilization in which type 2 diabetes was documented during time period
- Followed patients for outcomes, healthcare utilization October 1, 2002-September 30, 2007

Table 6: Summary of Study Hypotheses and Statistical Techniques

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
ACEI Monotherapy or ARB Monotherapy versus neither				
1. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing the incidence of ESRD in P2DM.	Development of ESRD (categorical)	Drug therapy (ACEIs, ARBs, or neither)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, smoking status HbA1c, LDL cholesterol triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient
2a. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing albuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Drug therapy (ACEIs, ARBs, or neither)		Univariate comparison

Table 6 (cont.)

Null hypothesis	**Dependent variable**	**Independent variable**	**Covariates**	**Statistical technique**(s)
2b. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing progression albuminuria for those with baseline microalbuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Drug therapy (ACEIs, ARBs, or neither)		Univariate comparison
2c. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing progression albuminuria for those with baseline macroalbuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Drug therapy (ACEIs, ARBs, or neither)		Univariate comparison

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
3. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing incident vascular disease events (IVDEs) in P2DM.	IVDEs: LVH, MI, ischemic stroke (categorical)	Drug therapy (ACEIs, ARBs, or neither)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient
4. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing all-cause mortality in P2DM.	All-cause mortality (categorical)	Drug therapy (ACEIs, ARBs, or neither)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
5. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing outpatient visits in P2DM.	Number of outpatient visits (count)	Drug therapy (ACEIs, ARBs, or neither)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial
6. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing ED visits in P2DM.	Number of ED visits (count)	Drug therapy (ACEIs, ARBs, or neither)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
7. There will be no difference in effectiveness in ACEIs or ARBs compared to neither therapy for reducing hospital admissions in P2DM.	Number of outpatient visits (count)	Drug therapy (ACEIs, ARBs, or neither therapy)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial)
ACEI Monotherapy versus ARB Monotherapy				
8. There will be no difference in effectiveness between ACEIs and ARBs for reducing the incidence of ESRD in P2DM.	Development of ESRD (categorical)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, smoking status HbA1c, LDL cholesterol triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient; propensity scores analyses; intention-to-treat analysis

Table 6 (cont.)

Null hypothesis	**Dependent variable**	**Independent variable**	**Covariates**	**Statistical technique**(s)
9a. There will be no difference in effectiveness between ACEIs and ARBs for reducing albuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Therapy (ACEIs or ARBs)		Univariate comparison
9b. There will be no difference in effectiveness between ACEIs and ARBs for reducing progression albuminuria for those with baseline microalbuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Therapy (ACEIs or ARBs)		Univariate comparison

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
9c. There will be no difference in effectiveness between ACEIs and ARBs for reducing progression albuminuria for those with baseline macroalbuminuria in P2DM.	Change in albuminuria over study time period (categorical)	Drug therapy (ACEIs or ARBs)		Univariate comparison
10. There will be no difference in effectiveness between ACEIs and ARBs for reducing IVDEs in P2DM.	Development of IVDEs during study time period (categorical)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient; propensity scores analyses; intention-to-treat analysis

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
11. There will be no difference in effectiveness between ACEIs and ARBs for reducing all-cause mortality in P2DM.	All-cause mortality (categorical)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	Multivariate logistic regression with robust SEs clustered by patient; propensity scores analyses; intention-to-treat analysis
12. There will be no difference in effectiveness between ACEIs and ARBs for reducing outpatient visits in P2DM.	Number of hospitalizations (count)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial); propensity scores analyses; intention-to-treat analysis

Table 6 (cont.)

Null hypothesis	Dependent variable	Independent variable	Covariates	Statistical technique(s)
13. There will be no difference in effectiveness between ACEIs and ARBs for reducing ED visits in P2DM.	Number of ED visits (count)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial); propensity scores analyses; intention-to-treat analysis
14. There will be no difference in effectiveness between ACEIs and ARBs for reducing hospital admissions in P2DM.	Number of outpatient visits (count)	Drug therapy (ACEIs or ARBs)	Compliance of ACEIs or ARBs, time, age, income, rural versus urban/suburban living, history of MI, history of stroke, family history of CVD, smoking status, HbA1c, LDL cholesterol, triglycerides, Elixhauser comorbidities (including hypertension and obesity), cohort, and metropolitan area/county	All count models with robust SEs clustered by patient (Poisson, negative binomial, zero-inflated Poisson, zero-inflated negative binomial); propensity scores analyses; intention-to-treat analysis

Table 7: Timeline of Study Activities

Activity	**Date(s)**
VA R&D Application	03/14/2008
VA R&D Conditional Approval	03/20/2008
UNM HRRC Application	03/21/2008
UNM HRRC Approval	04/04/2008
National VA Data Application	04/07/2008
VA R&D Full Approval	06/2008
National VA Data Approvals	10/2008
Data Extraction	10/2008-12/2008
Data Management, Cleaning, and Coding	12/15/2008-05/31/2010
Data Analysis	03/02/2009-01/18/2011
UNM Continuing Approval Applications	02/09/2009, 03/08/2010
UNM Continuing Approvals	04/14/2009, 04/14/2010
VA R&D Committee Annual Reviews	11/19/2009
VA Research Compliance Officer Audit	02/26/2010-03/05/2010

CHAPTER 4: RESULTS

Sample Selection and Size

We identified 1,719,387 P2DM who received care at a VA facility between fy2000 and fy2007. As the data were too large for our SQL server (programmer) and/or our desktop (researcher) to handle without "crashing" we started with fy2003 (i.e., October 1, 2002) patients and accrued annual cohorts of patients through fy2006, which yielded 671,411 patients. Patients were followed through fy2007 (i.e., September 30, 2007). Of newly-diagnosed type 2 diabetes patients, there were 145,078 (21.61%) incident users and 526,333 (78.39%) prevalent users. To avoid confounding associated with duration of ACEI or ARB treatment, we included only incident users. Our final sample size, after exclusion criteria were applied, was a total of 124,296 person-year observations corresponding to 40,669 patients in our sample. Figure 6 shows patient flow and respective number of person-year observations through the study. Of the 124,296 person-years, 40,669 (32.72%) occurred in the first year of follow-up, 40,133 (32.29%) occurred in the second, 27,021 (21.74%) occurred in the third, 14,342 (11.54%) occurred in the fourth, and 2,124 (1.71%) occurred in the fifth. (Please see Table 8.) Table 9 presents this information by cohort.

Figure 6: Patient Flow through Study for Patients with Documented Newly-diagnosed Type 2 Diabetes, Fy2003-06

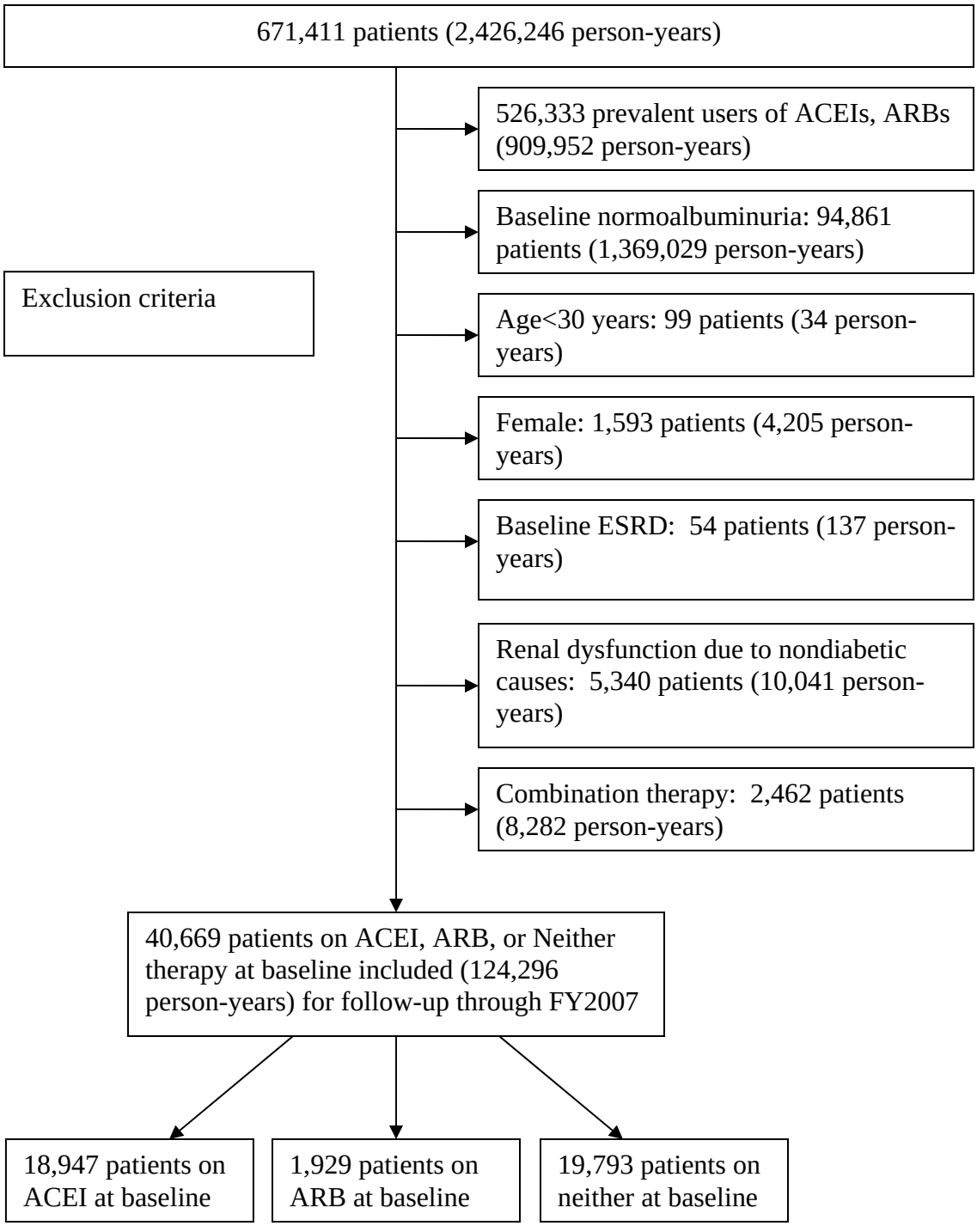


Table 8: Person-year Observations by Time Since Identification

Year	Frequency	Percent
Year 1	40,669	32.72
Year 2	40,133	32.29
Year 3	27,021	21.74
Year 4	14,349	11.54
Year 5	2,124	1.71
Total Person-years	124,296	100.00

Table 9: Number of Observations by Cohort

Cohort[a]	Frequency	Percentage
2003	11,331	9.12
2004	51,192	41.19
2005	37,427	30.11
2006	24,346	19.59
Total	124,296	100.00

[a]Cohort defined by fiscal year patients were first identified as having type 2 diabetes

Tables 10 and 11 illustrate percentage of patients on each drug therapy. Overall, ACEI monotherapy was present in 38.24% of person-years, ARB monotherapy in 4.10%, and neither therapy in 57.66%. Table 11 shows that 84.13% of patients receiving ACEI monotherapy in one year of follow-up are also on ACEI in the second; corresponding numbers for ARB and neither groups are 75.99% and 65.03%, respectively. We verify that all subsequent years of each patient are compared to his first year as the total number of patient-years shown in Table 11, 83,627, when subtracted by the total number of patient-years in the study sample, 124,296, yields 40,669 person-years. (Note this also relates to Table 10 because multiplying the percentages that appear within a drug therapy at each year of follow-up by the respective sample size in each year of follow-up for all years except year 1 yields the column total of the drug therapy in Table 11. Also note the reason for what appears as a possible discrepancy between Tables 10 and 11 is due to the fact that if someone died, they would appear to have received neither therapy in Table 10.)

Table 10: Drug Therapy Percentages, by Time Since Identification

	Sample Overall	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
ACEI	38.24	46.59	39.34	34.76	23.21	3.44
ARB	4.10	4.74	4.23	3.94	2.80	0.28
Neither	57.66	48.79	56.43	61.30	73.98	96.28
Sample Size	124,296	40,669	40,133	27,021	14,349	2,124

Table 11: Mean Drug Therapy Switch over Time (Two Subsequent Years at a Time)

	ACEI, Year 2 Frequency, (%)	**ARB, Year 2 Frequency, (%)**	**Neither, Year 2 Frequency, (%)**	**Total**
ACEI, Year 1	24,049 (84.13)	167 (5.27)	16,326 (31.47)	40,542
ARB, Year 1	72 (0.25)	2,408 (75.99)	1,813 (3.50)	4,293
Neither, Year 1	4,465 (15.62)	594 (18.74)	33,733 (65.03)	38,792
Sample Size	28,586	3,169	51,872	83,627

Table 12 depicts the mean and standard deviation of days supply of medication that patients had on-hand in each year within each drug therapy. It also shows 81.42% of patients classified as neither patients received less than a 30 days supply of ACEI or ARB monotherapy (mean±standard deviation=22.03±42.07 days) while more ACEI and ARB patients received 270-360 days supply of monotherapy compared with 180-270 days (mean±standard deviation=298.13±49.17 and 291.68±51.66 days, respectively).

Table 12: Description of Patient Days Supply/Medication Possession Ratio

Days Supply	**ACEI Patients**	**ARB Patients**	**Neither Patients**
<30	0	0	81.40%
30-60	0	0	1.99%
61-90	0	0	1.57%
91-121	0	0	6.50%
122-151	0	0	2.22%
152-181	0	0	6.32%
182-212	6.41%	8.24%	0
213-242	7.83%	9.28%	0
243-272	14.68%	14.98%	0
273-303	17.19%	17.73%	0
304-333	19.91%	21.00%	0
334-365	33.98%	28.77%	0
Mean±standard deviation	298.13±49.17	298.68±51.66	22.03±42.07

Descriptive Characteristics

The sample was 63.78 ± 11.17 years of age and reported an annual income of $35,082.20 ± $67,166.40. At baseline 78.03% had microalbuminuria, 21.97% had macroalbuminuria, 70.96% were hypertensive, 13.67% suffered from diabetes complications, and 16.53% were obese according to VA records (Table 14). In terms of clinical parameters, mean ± standard deviation baseline HbA1c, LDL, and triglycerides were 7.29 ± 1.84%, 97.82 ± 33.63 mg/dL, and 195.50 ± 175.00 mg/dL, respectively.

Univariate comparisons of baseline characteristics revealed several between group differences (Tables 13 and 14). As expected, there were fewer between group differences for ACEI and ARB than either monotherapy compared to neither therapy. In more detail, ARB patients were the oldest, followed by neither patients, followed by ACEI patients ($p<0.0083$ each); ACEI patients had higher HbA1c values at baseline than the other groups ($p<0.001$ each); and all groups were significantly different from each other for LDL values ($p<0.001$ each). In this circumstance, patients in the neither group had the highest LDL values, followed by ACEI, followed by ARB.

As Table 14 shows, the ACEI group had more patients with macroalbuminuria compared to the neither group (23.37% versus 20.57%, $p<0.001$). Also noteworthy, patients in the ARB group had the highest percentage of never smokers (81.18%), followed by neither (79.30%), followed by ACEI (76.40%) ($p<0.001$ each). More patients in the ACEI group had a history of stroke or MI versus neither patients (1.44% versus 1.06% and 2.83% versus 2.21%, $p<0.001$ each). The ARB group had the highest amount of patients with peripheral vascular disorders at baseline: 7.52% compared to 6.02% of ACEI patients and 5.80% of neither patients ($p<0.01$ each). An extremely

interesting finding is significantly fewer patients receiving neither therapy were hypertensive compared to ACEI or ARB monotherapy (60.30% versus 80.80% and 83.51%, $p<0.001$ each).

A *post hoc* analysis comparing number of comorbidities by drug therapy with Kruskal-Wallis test found similar numbers of comorbidities between ACEI and ARB patients, both of whom have significantly higher comorbidities than neither patients ($p<0.0083$). Another item to note is each of the conditions that may lead to propensity to cough, (i.e., smoking, allergic rhinitis, GERD, treatment initiated in winter, and chronic pulmonary disease) were not present at a significantly higher rate for ARB patients compared to ACEI patients (Table 14). We expected clinicians would preferentially prescribe ARBs to patients presenting with these conditions since ACEIs have higher rates of cough than ARBs.

Table 13: Differences in Baseline Characteristics by Drug Therapy, Continuous Variables

Variable	All patients (n=40,669) Mean (SD)	ACEI (n=18,947) Mean (SD)	ARB (n=1,929) Mean (SD)	Neither (n=19,793) Mean (SD)
Age***	63.78 (11.17)	63.42 (10.65)	65.82 (10.27)	64.16 (11.78)
HbA1c†††	7.30 (3.19)	7.32 (1.82)	7.21 (3.24)	7.27 (1.66)
LDL‡‡‡	94.56 (33.45)	96.19 (32.64)	91.66 (30.32)	100.20 (34.79)
Triglycerides‖	189.96 (177.86)	197.70 (169.70)	198.00 (182.50)	193.00 (179.50)

***$p<0.001$, drug therapy group comparisons for Kruskal-Wallis test. Pairwise comparisons finds three differences in rank means. Rank Mean difference = 2,610.60, critical value = 671.72, finds a significant difference between ACEI and ARB groups (rank mean = 19,810.26 and 22,420.87, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 1,786.84, critical value = 670.39, finds a significant difference between ARB and neither groups (rank mean = 22,420.87 and 20,634.02, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 823.76, critical value = 285.66, finds a significant difference between ACEI and neither groups (rank mean = 19,810.26 and 20,634.02, respectively, $p<0.0083$ (adjusted p-value)).

†††$p<0.001$, drug therapy group comparisons for Kruskal-Wallis test. Pairwise comparisons find two differences in rank means. Rank Mean difference = 1,265.91, critical value = 649.98, finds a significant difference between ACEI and ARB groups (rank mean = 19,256.85 and 17,990.94, respectively, $p<0.00083$ (adjusted p-value)). Rank Mean difference = 887.25, critical value = 274.29, finds a significant difference between ACEI and neither groups (rank mean = 19,256.85 and 18,369.60, respectively, $p<0.00083$ (adjusted p-value)).

‡‡‡ $p<0.001$, drug therapy group comparisons for ANOVA. Pairwise comparisons find three differences in rank means. Rank Mean difference = 1,469.30, critical value = 602.72, finds a significant difference between ACEI and ARB groups (rank mean = 16,507.80 and 15,038.49, respectively, $p<0.00083$ (adjusted p-value)). Rank Mean difference = 2,549.73, critical value = 604.37, finds a significant difference between ARB and neither groups (rank mean = 15,038.49 and 17,588.22, respectively, $p<0.00083$ (adjusted p-value)). Rank mean difference = 1,080.42, critical value = 260.95, finds a significant difference between ACEI and neither groups (rank mean = 16,507.80 and 17,588.22, respectively, $p<0.00083$ (adjusted p-value)).

‖$p<0.05$, drug therapy group comparisons for ANOVA. Tukey's Honestly Significant Difference finds no difference between the three comparisons as the studentized range critical value (.05, 3, 36793) = 3.315. Of the four variables in the table, this is the only one that did not fail the Levene Test, so ANOVA was retained.

Table 14: Differences in Baseline Characteristics by Drug Therapy, Categorical Variables

Variable	**All patients (n=40,669) Frequency (%)**	**ACEI (n=18,947) Frequency (%)**	**ARB (n=1,929) Frequency (%)**	**Neither (n=19,793) Frequency (%)**
Albuminuria Stage				
Microalbuminuria	31,734 (78.03)	14,520 (76.63)	1,493 (77.40)[a]	15,721 (79.43)[b]
Macroalbuminuria	8,935 (21.97)	4,427 (23.37)	436 (22.60)	4,072 (20.57)
Smoking Status				
Never	31,727 (78.01)	14,476 (76.40)[c]	1,566 (81.18) [d]	15,696 (79.30) [e]
Ever	1,146 (2.83)	574 (3.00)	68 (3.53)	505 (2.50)
Current	7,796 (19.17)	3,903 (20.60)	295 (15.29)	3,602 (18.20)
Family History of CVD	267 (0.66)	140 (0.74)[f]	28 (1.45) [g]	99 (0.50) [h]
History of Stroke	497 (1.22)	273 (1.44)[i]	15 (0.78)	210 (1.06) [j]
History of MI	1,018 (2.50)	536 (2.83)	44 (2.28)	437 (2.21) [k]
NSAID user[*]	3,160 (36.22)	1,727 (38.59)	156 (37.30) [l]	1,276 (33.31) [m]
Annual Household Income				
< $6000	9,555 (23.49)	4,085 (21.56)[n]	470 (24.36) [o]	5,000 (25.26) [p]
$6,000-17,999	9,696 (23.84)	4,730 (24.96)	398 (20.63)	4,568 (23.08)
$18,000-34,999	10,200 (25.08)	4,847 (25.58)	462 (23.95)	4,891 (24.71)
≥$35,000	9,894 (24.33)	4,674 (24.67)	537 (27.84)	4,683 (23.66)
Income missing	1,324 (3.26)	611 (3.22)	62 (3.21)	651 (3.29)

Table 14 (cont.)

Variable	All patients (n=40,669) Frequency (%)	ACEI (n=18,947) Frequency (%)	ARB (n=1,929) Frequency (%)	Neither (n=19,793) Frequency (%)
Urban/suburban	28,935 (71.15)	13,282 (70.10)	1,391 (72.11)	14,271 (72.10) [q]
CHF	2,096 (5.15)	1,040 (5.49)[r]	163 (8.45) [s]	893 (4.51) [t]
Cardiac Arrhythmias	2,084 (5.12)	999 (5.27)[u]	131 (6.79) [v]	954 (4.82) [w]
Valvular Disease	278 (0.68)	125 (0.66)	21 (1.09)	132 (0.67)
Pulmonary Circulation Disorders	73 (0.18)	33 (0.17)	4 (0.21)	36 (0.18)
Peripheral Vascular Disorders	2,434 (5.98)	1,141 (6.02)[x]	145 (7.52) [y]	1,148 (5.80)
Hypertension	28,857 (70.96)	15,309 (80.80)[z]	1,611 (83.51) [aa]	11,935 (60.30) [bb]
Paralysis	138 (0.34)	50 (0.26)	3 (0.16)	85 (0.43) [cc]
Other Neurological Disorders	368 (0.90)	147 (0.78)	15 (0.78)	206 (1.04) [dd]
Chronic Pulmonary Disease	4,151 (10.21)	1,849 (9.76)[ee]	216 (11.20)	2,078 (10.50) [ff]
Hypothyroidism	1,951 (4.80)	866 (4.57)	99 (5.13)	986 (4.98)

Table 14 (cont.)

Variable	All patients (n=40,669) Frequency (%)	ACEI (n=18,947) Frequency (%)	ARB (n=1,929) Frequency (%)	Neither (n=19,793) Frequency (%)
Diabetes Complicated	5,560 (13.67)	2,785 (14.70)	264 (13.69)	2,514 (12.70) [gg]
Liver Disease	612 (1.50)	252 (1.33)	24 (1.24)	336 (1.70) [hh]
Peptic Ulcer Disease	378 (0.93)	167 (0.88)	26 (1.35)	185 (0.93)
AIDS	72 (0.18)	23 (0.12)	0 (0.00) [ii]	49 (0.25) [jj]
Lymphoma	165 (0.41)	58 (0.31)	6 (0.31)	101 (0.51) [kk]
Metastatic Cancer	74 (0.18)	24 (0.13)	2 (0.10)	48 (0.24) [ll]
Solid Tumor Without Metastasis	2,883 (7.09)	1,237 (6.53)	141 (7.31)	1,504 (7.60) [mm]
Rheumatoid Arthritis/Collagen Vascular Diseases	331 (0.81)	133 (0.70)	14 (0.73)	184 (0.93) [nn]
Coagulopathy	449 (1.10)	193 (1.02)	28 (1.45)	228 (1.15)
Obesity	6,722 (16.53)	3,543 (18.70)	334 (17.31) [oo]	2,850 (14.40) [pp]
Weight Loss	40 (0.10)	11 (0.06)	0 (0.00)	29 (0.15) [qq]

Table 14 (cont.)

Variable	All patients (n=40,669) Frequency (%)	ACEI (n=18,947) Frequency (%)	ARB (n=1,929) Frequency (%)	Neither (n=19,793) Frequency (%)
Fluid and Electrolyte Disorders	765 (1.88)	341 (1.80)	33 (1.71)	392 (1.98)
Blood Loss Anemia	30 (0.07)	14 (0.07)	3 (0.16)	13 (0.07)
Deficiency Anemias	1,386 (3.41)	591 (3.12)	69 (3.58)	724 (3.66) [rr]
Alcohol Abuse	1,268 (3.12)	563 (2.97)	50 (2.59)	655 (3.31)
Drug Abuse	566 (1.39)	237 (1.25)[ss]	11 (0.57) [tt]	319 (1.61) [uu]
Psychoses	1,809 (4.45)	807 (4.26)[vv]	58 (3.01) [ww]	942 (4.76) [xx]
Depression	3,847 (9.46)	1,825 (9.63)	178 (9.23)	1,845 (9.32)
Other Considerations for Propensity to Cough (Used Only in PSA)				
Allergic Rhinitis	162 (0.40)	96 (0.51)	14 (0.73) [yy]	52 (0.26) [zz]
Gastroesophageal Reflux Disease	2,699 (6.64)	1,618 (8.54)	158 (8.19) [aaa]	932 (4.71) [bbb]
Postnasal Drip	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14 (cont.)

Variable	All patients (n=40,669) Frequency (%)	ACEI (n=18,947) Frequency (%)	ARB (n=1,929) Frequency (%)	Neither (n=19,793) Frequency (%)
ACEI/ARB Started in Winter	7,877 (19.37)	4,680 (24.70)	475 (24.62) [ccc]	2,731 (13.80) [ddd]

*NSAID user had 8,724 observations: 4,475 observations for ACEI, 418 observations for ARB, and 3,831 observations for neither. NSAID user was defined as having received enough medication to cover ≥ 50% of the days in the first year.

[a] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 4.402$.
[b] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 44.071$.
[c] $p<0.001$, ACEI versus ARB for chi-square test. $\chi^2(1) = 31.246$.
[d] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 15.333$.
[e] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 48.250$.
[f] $p<0.01$, ACEI versus ARB for chi-square test. $\chi^2(1) = 11.138$.
[g] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 27.370$.
[h] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 8.998$.
[i] $p<0.05$, ACEI versus ARB for chi-square test. $\chi^2(1) = 5.661$.
[j] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 11.674$.
[k] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 15.496$.
[l] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(1) = 6.992$.
[m] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 76.094$.
[n] $p<0.001$, ACEI versus ARB for chi-square test. $\chi^2(4) = 28.566$.
[o] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(4) = 18.375$.
[p] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(4) = 78.015$.
[q] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 19.040$.
[r] $p<0.001$, ACEI versus ARB for chi-square test. $\chi^2(1) = 28.143$.
[s] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 59.148$.
[t] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 19.918$.
[u] $p<0.01$, ACEI versus ARB for chi-square test. $\chi^2(1) = 7.885$.

[v] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 14.392$.
[w] p<0.05, ACEI versus neither for chi-square test. $\chi^2(1) = 4.145$.
[x] p<0.01, ACEI versus ARB for chi-square test. $\chi^2(1) = 6.767$.
[y] p<0.01, ARB versus neither for chi-square test. $\chi^2(1) = 9.254$.
[z] p<0.01, ACEI versus ARB for chi-square test. $\chi^2(1) = 8.283$.
[aa] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 403.915$.
[bb] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 2.00 \text{ X } 10^3$.
[cc] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 7.640$.
[dd] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 7.525$.
[ee] p<0.05, ACEI versus ARB for chi-square test. $\chi^2(1) = 4.034$.
[ff] p<0.05, ACEI versus neither for chi-square test. $\chi^2(1) = 6.289$.
[gg] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 30.552$.
[hh] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 8.749$.
[ii] p<0.05, ARB versus neither for chi-square test. $\chi^2(1) = 4.786$.
[jj] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 8.307$.
[kk] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 9.872$.
[ll] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 7.003$.
[mm] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 16.683$.
[nn] p<0.05, ACEI versus neither for chi-square test. $\chi^2(1) = 6.182$.
[oo] p<0.01, ARB versus neither for chi-square test. $\chi^2(1) = 11.835$.
[pp] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 133.110$.
[qq] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 7.344$.
[rr] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 8.545$.
[ss] p<0.01, ACEI versus ARB for chi-square test. $\chi^2(1) = 6.829$.
[tt] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 12.742$.
[uu] p<0.01, ACEI versus neither for chi-square test. $\chi^2(1) = 9.188$.
[vv] p<0.01, ACEI versus ARB for chi-square test. $\chi^2(1) = 6.966$.
[ww] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 12.352$.
[xx] p<0.05, ACEI versus neither for chi-square test. $\chi^2(1) = 5.603$.
[yy] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 12.441$.
[zz] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 15.138$.

[aaa] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 44.546$.
[bbb] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 230.895$.
[ccc] p<0.001, ARB versus neither for chi-square test. $\chi^2(1) = 163.401$.
[ddd] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 747.111$.

To provide insight into albuminuria progression over time, within the first year of follow-up, 4.91 ± 0.11% of our sample regressed to normoalbuminuria (data not shown). At years 2, 3, 4, and 5 of follow-up, 26.34 ± 0.35%, 27.89 ± 0.46%, 29.90 ± 0.72%, and 24.31 ± 2.53% had normoalbuminuria, respectively (data not shown). The next two tables reveal categories of albuminuria (i.e., normoalbuminuria, microalbuminuria, macroalbuminuria) within each drug therapy at each year of follow-up. Table 15 compares drug therapy within each year of follow-up while Table 16 compares changes over time in albuminuria within each drug therapy. Table 15 presents data indicating that albuminuria was only significantly different between therapies at year 1. ACEI or ARB patients each have a wider spectrum of albuminuria than neither patients; ACEI and ARB patients had comparable albuminuria levels. Table 16 shows, within each drug therapy, there are significant differences between the first year of follow-up and each subsequent year of follow-up. In particular, because baseline normoalbuminuria was an exclusion criterion for study entry, we see a small proportion of patients with normoalbuminuria within each drug therapy at first year of follow-up, with attenuation of albuminuria across follow-up. For more detail about changes in clinical parameters across time, please see Appendix F Tables 5-10.

Table 15: Albuminuria by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)[c]	Time (t+2)[c]	Time (t+3)[c]	Time (t+4)[c]	Total
ACEI						
Normoalbuminuria	0.05[a]	0.27	0.29	0.32	0.16	0.15
Microalbuminuria	0.72	0.53	0.51	0.46	0.59	0.63
Macroalbuminuria	0.23	0.20	0.21	0.22	0.25	0.22
ARB						
Normoalbuminuria	0.06[b]	0.25	0.31	0.30	0.50	0.16
Microalbuminuria	0.71	0.56	0.48	0.50	0.25	0.63
Macroalbuminuria	0.23	0.19	0.21	0.21	0.25	0.22
Neither						
Normoalbuminuria	0.04	0.26	0.27	0.29	0.25	0.14
Microalbuminuria	0.75	0.54	0.52	0.51	0.56	0.66
Macroalbuminuria	0.21	0.19	0.22	0.21	0.19	0.21

Notes: values represent proportions

[a] $p<0.001$, albuminuria, ACEI versus neither, within time t for chi-square test. $\chi^2(2) = 49.99$.
[b] $p<0.01$, albuminuria, ARB versus neither, within time t for chi-square test. $\chi^2(2) = 13.61$.
[c] p=nonsignificant for albuminuria within time period across drug therapies

Table 16: Albuminuria by Drug Therapy and Time Since Identification, Comparisons by Time

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Normoalbuminuria	0.05[a,b,c,d]	0.27[e,f]	0.29[g]	0.32	0.16	0.15
Microalbuminuria	0.72	0.53	0.51	0.46	0.59	0.63
Macroalbuminuria	0.23	0.20	0.21	0.22	0.25	0.22
ARB						
Normoalbuminuria	0.06[h,i,j,k]	0.25[l]	0.31	0.30	0.50	0.16
Microalbuminuria	0.71	0.56	0.48	0.50	0.25	0.63
Macroalbuminuria	0.23	0.19	0.21	0.21	0.25	0.22
Neither						
Normoalbuminuria	0.04[m,n,o,p]	0.26[q,r]	0.27	0.29	0.25	0.14
Microalbuminuria	0.75	0.54	0.52	0.51	0.56	0.66
Macroalbuminuria	0.21	0.19	0.22	0.21	0.19	0.21

Notes: values represent proportions

[a] $p<0.001$, albuminuria, time t and time (t+1), within ACEI for chi-square test. $\chi^2(2) = 2.40 \times 10^3$.
[b] $p<0.001$, albuminuria, time t and time (t+2), within ACEI for chi-square test. $\chi^2(2) = 2.30 \times 10^3$.
[c] $p<0.001$, albuminuria, time t and time (t+3), within ACEI for chi-square test. $\chi^2(2) = 1.60 \times 10^3$.
[d] $p<0.05$, albuminuria, time t and time (t+4), within ACEI for chi-square test. $\chi^2(2) = 7.03$.
[e] $p<0.01$, albuminuria, time t and time (t+2), within ACEI for chi-square test. $\chi^2(2) = 10.12$.
[f] $p<0.001$, albuminuria, time t (t+1) and time (t+4), within ACEI for chi-square test. $\chi^2(2) = 30.31$.
[g] $p<0.01$, albuminuria, time t (t+2) and time (t+3), within ACEI for chi-square test. $\chi^2(2) = 9.79$.

[h] $p<0.001$, albuminuria, time t and time (t+1), within ARB for chi-square test. $\chi^2(2) = 210.28$.
[i] $p<0.001$, albuminuria, time t and time (t+2), within ARB for chi-square test. $\chi^2(2) = 263.65$.
[j] $p<0.001$, albuminuria, time t and time (t+3), within ARB for chi-square test. $\chi^2(2) = 137.17$.
[k] $p<0.01$, albuminuria, time t and time (t+4), within ARB for chi-square test. $\chi^2(2) = 14.89$.
[l] $p<0.05$, albuminuria, time t (t+1) and time (t+2), within ARB for chi-square test. $\chi^2(2) = 8.94$.
[m] $p<0.001$, albuminuria, time t and time (t+1), within neither for chi-square test. $\chi^2(2) = 2.70 \text{ X } 10^3$.
[n] $p<0.001$, albuminuria, time t and time (t+2), within neither for chi-square test. $\chi^2(2) = 2.30 \text{ X } 10^3$.
[o] $p<0.001$, albuminuria, time t and time (t+3), within neither for chi-square test. $\chi^2(2) = 1.80 \text{ X } 10^3$.
[p] $p<0.01$, albuminuria, time t and time (t+4), within neither for chi-square test. $\chi^2(2) = 236.88$.
[q] $p<0.01$, albuminuria, time t (t+1) and time (t+2), within neither for chi-square test. $\chi^2(2) = 10.13$.
[r] $p<0.05$, albuminuria, time t (t+1) and time (t+4), within neither for chi-square test. $\chi^2(2) = 8.08$.

Outcomes of Interest

The next set of tables describes the outcomes of interest to the study. As Table 17 depicts, 0.79% of our patients developed ESRD, 7.54% suffered an IVDE, and 9.06% died over follow-up. ACEI patients had the lowest proportion of patients who developed ESRD over follow-up. ACEI and ARB patients had higher rates of development of LVH and stroke than neither patients ($p<0.001$ each). When each of the components of IVDE (i.e., MI, LVH, stroke) were incorporated into the composite endpoint, the same pattern was observed. Despite ACEI and ARB patients having comparable mortality rates, neither patients were dying at an approximately 12 times higher rate than ACEI or ARB patients ($p<0.001$ each).

Table 17: Descriptive Statistics by Drug Therapy, Categorical Outcomes

Variable	**All patients (n=124,296 person-years; n=40,669 patients) Frequency, (%)**	**ACEI (n=47,533 person-years; n=18,947 patients) Frequency, (%)**	**ARB (n=5,098 person-years; n=1,929 patients) Frequency, (%)**	**Neither (n=71,665 person-years; n=19,793 patients) Frequency, (%)**
ESRD	320 (0.79)	80 (0.42) [a]	17 (0.88)	223 (1.13) [b]
MI	433 (1.07)	236 (1.25)	21 (1.09) [c]	176 (0.89) [d]
LVH	1,240 (3.05)	523 (2.76) [e]	74 (3.84) [f]	643 (3.25) [g]
Stroke	1,490 (3.66)	823 (4.34)	84 (4.36) [h]	583 (2.95) [i]
IVDE*	3,065 (7.54)	1,529 (8.07)	169 (8.76) [j]	1,367 (6.91) [k]
Mortality	3,685 (9.06)	192 (1.01)	20 (1.04) [l]	3,473 (17.55) [m]

*Although IVDE is a composite of MI, LVH, and Stroke, IVDE does not equal the sum of these components. For instance, if a person had an MI in year 2 and a Stroke in year 3, that person was documented as having a IVDE event in year 2. Also note once a patient had IVDE he is documented as having IVDE in subsequent years.

[a] $p<0.01$, drug therapy comparison of ACEI versus ARB for chi-square test. $\chi^2(1) = 6.83$.
[b] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 23.01$.
[c] $p<0.05$, drug therapy comparison of ARB versus neither for chi-square test. $\chi^2(1) = 5.15$.
[d] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 52.23$.
[e] $p<0.05$, drug therapy comparison of ACEI versus ARB for chi-square test. $\chi^2(1) = 5.07$.
[f] $p<0.001$, drug therapy comparison of ARB versus neither for chi-square test. $\chi^2(1) = 15.81$.
[g] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 12.17$.
[h] $p<0.001$, drug therapy comparison of ARB versus neither for chi-square test. $\chi^2(1) = 38.45$.

[i] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 206.58$.
[j] $p<0.001$, drug therapy comparison of ARB versus neither for chi-square test. $\chi^2(1) = 48.09$.
[k] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 206.64$.
[l] $p<0.001$, drug therapy comparison of ARB versus neither for chi-square test. $\chi^2(1) = 217.37$.
[m] $p<0.001$, drug therapy comparison of ACEI versus neither for chi-square test. $\chi^2(1) = 1.90 \text{ X } 10^3$.

Tables 18 and 19 depict changes in rates of outcomes across time and drug therapy. Table 18 shows the only difference between ACEI and ARB patients was for ESRD at year 4, when ACEI patients had a lower rate of acquiring ESRD than ARB patients ($p<0.001$). For cardio- and cerebro- vascular events, ACEI patients had a higher rate of MI at years 1, 2, and 3 than neither patients. The first four years of observation showed more ACEI patients suffered strokes compared to neither patients; this was also true for ARB patients at years 2 and 3. Since we saw a similar pattern for acquiring LVH, but only for the first three years for ACEI patients and only for year 3 for ARB patients; ACEI and ARB patients had a higher proportion develop IVDE compared to neither patients in the first four years. This analysis gives us a clearer picture of what we saw earlier in terms of between group comparisons for all-cause mortality: neither patients are dying at about ten times the rate of ACEI or ARB patients for each year of years 1 through 4.

Table 19 portrays these same dependent variables across time. Among ACEI patients ESRD increased progressively through years 1 and 3 of follow-up. Rates of LVH increased progressively the first four years of follow-up; year 5 was comparable to year 1. All-cause mortality increased progressively through year 4. ARB patients were more stable across follow-up. The only difference seen was an increase in acquiring ESRD from year 1 to year 2. Patients receiving neither therapy experienced a rise in the rate of acquiring ESRD from years 1 through 4. Development of LVH progressively increased across time. Lastly, all-cause mortality significantly increased from first through fourth years of follow-up.

Table 18: Categorical Outcomes by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
ESRD	0.001	0.002	0.003	0.002[a]	0.00	0.002
	(0.03)	(0.04)	(0.06)	(0.04)	(0.00)	(0.04)
MI	0.006	0.004	0.005	0.003	0.00	0.005
	(0.08)	(0.06)	(0.07)	(0.06)	(0.00)	(0.07)
LVH	0.008	0.01	0.01	0.02	0.01	0.01
	(0.09)	(0.10)	(0.12)	(0.13)	(0.12)	(0.10)
Stroke	0.02	0.02	0.02	0.01	0.00	0.02
	(0.14)	(0.13)	(0.13)	(0.11)	(0.00)	(0.13)
IVDE	0.03	0.03	0.04	0.03	0.01	0.03
	(0.18)	(0.17)	(0.18)	(0.18)	(0.12)	(0.18)
Mortality	0.003	0.004	0.004	0.01	0.03	0.004
	(0.05)	(0.07)	(0.07)	(0.08)	(0.16)	(0.06)
ARB						
ESRD	0.001	0.004	0.003	0.01[b]	0.00	0.003
	(0.03)	(0.06)	(0.05)	(0.11)	(0.00)	(0.06)
MI	0.01[c]	0.002	0.003	0.002	0.00	0.004
	(0.08)	(0.05)	(0.05)	(0.05)	(0.00)	(0.06)
LVH	0.01[d]	0.01[e]	0.02[f]	0.03	0.00	0.02
	(0.10)	(0.12)	(0.14)	(0.16)	(0.00)	(0.12)
Stroke	0.02[g]	0.02[h]	0.02[i]	0.01	0.00	0.02
	(0.12)	(0.13)	(0.13)	(0.11)	(0.00)	(0.13)
IVDE	0.03[j]	0.03[k]	0.04[l]	0.04[m]	0.00	0.03
	(0.17)	(0.18)	(0.19)	(0.20)	(0.00)	(0.18)
Mortality	0.003[n]	0.004[o]	0.005[p]	0.005[q]	0.00	0.004
	(0.06)	(0.06)	(0.07)	(0.07)	(0.00)	(0.06)
Neither						
ESRD	0.002[r]	0.003	0.005	0.004[s]	0.002	0.003
	(0.04)	(0.05)	(0.07)	(0.06)	(0.05)	(0.06)

Table 18 (cont.)

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
MI	0.004[t] (0.06)	0.003[u] (0.05)	0.002[v] (0.04)	0.002 (0.04)	0.00 (0.00)	0.002 (0.05)
LVH	0.006[w] (0.08)	0.01[x] (0.09)	0.01[y] (0.10)	0.01 (0.12)	0.02 (0.13)	0.01 (0.10)
Stroke	0.01[z] (0.10)	0.01[aa] (0.09)	0.01[bb] (0.09)	0.005[cc] (0.07)	0.003 (0.06)	0.01 (0.09)
IVDE	0.02[dd] (0.14)	0.02[ee] (0.14)	0.02[ff] (0.14)	0.02[gg] (0.14)	0.01 (0.12)	0.02 (0.14)
Mortality	0.02[hh] (0.15)	0.06[ii] (0.23)	0.06[jj] (0.24)	0.06[kk] (0.23)	0.04 (0.19)	0.05 (0.22)

[a] $p<0.001$, ACEI versus ARB for chi-square test. $\chi^2(1) = 16.06$.
[b] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 6.56$.
[c] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 4.74$.
[d] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 6.46$.
[e] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 6.62$.
[f] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(1) = 6.83$.
[g] $p<0.05$, ARB versus neither for chi-square test. $\chi^2(1) = 4.03$.
[h] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 17.83$.
[i] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(1) = 11.58$.
[j] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(1) = 8.32$.
[k] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 18.89$.
[l] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 17.81$.
[m] $p<0.01$, ARB versus neither for chi-square test. $\chi^2(1) = 7.52$.
[n] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 35.32$
[o] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 89.03$.
[p] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 58.21$.
[q] $p<0.001$, ARB versus neither for chi-square test. $\chi^2(1) = 20.17$.
[r] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 6.86$.
[s] $p<0.05$, ACEI versus neither for chi-square test. $\chi^2(1) = 4.55$.
[t] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 12.60$.
[u] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 7.06$.
[v] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 18.64$.
[w] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 9.69$.
[x] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 7.84$.
[y] $p<0.01$, ACEI versus neither for chi-square test. $\chi^2(1) = 8.72$.
[z] $p<0.001$, ACEI versus neither for chi-square test. $\chi^2(1) = 46.64$.

[aa] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 56.00$.
[bb] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 52.14$.
[cc] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 19.55$.
[dd] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 63.95$.
[ee] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 59.83$.
[ff] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 65.41$.
[gg] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 15.23$.
[hh] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 316.14$.
[ii] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 766.70$.
[jj] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 493.23$.
[kk] p<0.001, ACEI versus neither for chi-square test. $\chi^2(1) = 148.24$.

Table 19: Categorical Outcomes by Drug Therapy and Time Since Identification, Comparisons by Time

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
ESRD***	0.001[a,b] (0.03)	0.002 (0.04)	0.003 (0.06)	0.002 (0.04)	0.00 (0.00)	0.002 (0.04)
MI	0.006 (0.08)	0.004 (0.06)	0.005 (0.07)	0.003 (0.06)	0.00 (0.00)	0.005 (0.07)
LVH†††	0.01[c,d,e] (0.09)	0.01[f,g] (0.10)	0.01 (0.12)	0.02 (0.13)	0.01 (0.12)	0.01 (0.10)
Stroke	0.02 (0.14)	0.02 (0.13)	0.02 (0.13)	0.01 (0.11)	0.00 (0.00)	0.02 (0.13)
IVDE	0.03 (0.18)	0.03 (0.17)	0.04 (0.18)	0.03 (0.18)	0.01 (0.18)	0.03 (0.18)
Mortality‡‡‡	0.003[h,i,j] (0.05)	0.004 (0.07)	0.004 (0.07)	0.007 (0.08)	0.03 (0.16)	0.004 (0.06)
ARB						
ESRD‖‖	0.001[k] (0.03)	0.004 (0.06)	0.003 (0.05)	0.01 (0.11)	0.00 (0.00)	0.003 (0.06)
MI	0.007 (0.08)	0.002 (0.05)	0.003 (0.05)	0.002 (0.05)	0.00 (0.00)	0.004 (0.06)
LVH	0.01 (0.10)	0.01 (0.12)	0.02 (0.14)	0.03 (0.16)	0.00 (0.00)	0.02 (0.12)
Stroke	0.02 (0.12)	0.02 (0.13)	0.02 (0.13)	0.01 (0.11)	0.00 (0.00)	0.02 (0.13)
IVDE	0.03 (0.17)	0.03 (0.18)	0.04 (0.19)	0.04 (0.20)	0.00 (0.00)	0.03 (0.18)
Mortality	0.003 (0.06)	0.004 (0.06)	0.005 (0.07)	0.005 (0.07)	0.00 (0.00)	0.004 (0.06)

Table 19 (cont.)

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
Neither						
ESRD§§§	0.002[l,m] (0.04)	0.003 (0.05)	0.005 (0.07)	0.004 (0.06)	0.002 (0.05)	0.003 (0.06)
MI¶¶¶	0.004[n,o,p] (0.06)	0.003[q] (0.05)	0.002[r] (0.04)	0.002 (0.04)	0.00 (0.00)	0.002 (0.05)
LVH$$$	0.006[s,t,u,v] (0.08)	0.008[w,x,y] (0.09)	0.01[z,aa] (0.10)	0.013 (0.12)	0.02 (0.13)	0.01 (0.09)
Stroke πππ	0.011[bb,cc,dd, ee] (0.10)	0.008[ff,gg] (0.09)	0.007[hh] (0.09)	0.005 (0.07)	0.003 (0.06)	0.008 (0.09)
IVDE	0.02 (0.02)	0.02 (0.14)	0.02 (0.14)	0.02 (0.14)	0.02 (0.14)	0.02 (0.14)
Mortality ΔΔΔ	0.02[ii,jj,kk] (0.15)	0.06 (0.23)	0.06 (0.24)	0.06 (0.23)	0.04 (0.19)	0.05 (0.22)

Notes: mean (standard deviation)

***p<0.001, time comparisons for chi-square test. χ^2 (4) = 19.02.
††† p<0.001, time comparisons for chi-square test. χ^2 (4) = 34.13.
‡‡‡ p<0.001, time comparisons for chi-square test. χ^2 (4) = 23.09.
‖‖ p<0.01, time comparisons for chi-square test. χ^2 (4) = 13.51.
§§§ p<0.001, time comparisons for chi-square test. χ^2 (4) = 68.01.
¶¶¶ p<0.001, time comparisons for chi-square test. χ^2 (4) = 20.33.
$$$ p<0.001, time comparisons for chi-square test. χ^2 (4) = 65.82.
πππ p<0.001, time comparisons for chi-square test. χ^2 (4) = 30.69.
ΔΔΔ p<0.001, time comparisons for chi-square test. χ^2 (4) = 379.62.
[a] p<0.05, time comparison of first and second years of observation for chi-square test. χ^2 (1) = 3.85.
[b] p<0.001, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 18.70.
[c] p<0.05, time comparison of first and second years of observation for chi-square test. χ^2 (1) = 6.53.
[d] p<0.001, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 22.81.
[e] p<0.001, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 23.20.
[f] p<0.05, time comparison of second and third years of observation for chi-square test. χ^2 (1) = 5.69.

[g] $p<0.01$, time comparison of second and fourth years of observation for chi-square test. χ^2 (1) = 8.77.
[h] $p<0.05$, time comparison of first and second years of observation for chi-square test. χ^2 (1) = 5.20.
[i] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 12.50.
[j] $p<0.001$, time comparison of first and fifth years of observation for chi-square test. χ^2 (1) = 14.29.
[k] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 14.44.
[l] $p<0.001$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 20.34.
[m] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 10.26.
[n] $p<0.01$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 8.30.
[o] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 10.09.
[p] $p<0.01$, time comparison of first and fifth years of observation for chi-square test. χ^2 (1) = 7.26.
[q] $p<0.05$, time comparison of second and fifth years of observation for chi-square test. χ^2 (1) = 5.25.
[r] $p<0.05$, time comparison of third and fifth years of observation for chi-square test. χ^2 (1) = 3.96.
[s] $p<0.01$, time comparison of first and second years of observation for chi-square test. χ^2 (1) = 9.58.
[t] $p<0.001$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 24.84.
[u] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 49.69.
[v] $p<0.001$, time comparison of first and fifth years of observation for chi-square test. χ^2 (1) = 33.57.
[w] $p<0.05$, time comparison of second and third years of observation for chi-square test. χ^2 (1) = 4.68.
[x] $p<0.001$, time comparison of second and fourth years of observation for chi-square test. χ^2 (1) = 20.13.
[y] $p<0.001$, time comparison of second and fifth years of observation for chi-square test. χ^2 (1) = 15.26.
[z] $p<0.05$, time comparison of third and fourth years of observation for chi-square test. χ^2 (1) = 5.53.
[aa] $p<0.01$, time comparison of third and fifth years of observation for chi-square test. χ^2 (1) = 6.80.
[bb] $p<0.05$, time comparison of first and second years of observation for chi-square test. χ^2 (1) = 6.06.
[cc] $p<0.01$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 10.20.

[dd] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 20.62.
[ee] $p<0.01$, time comparison of first and fifth years of observation for chi-square test. χ^2 (1) = 9.64.
[ff] $p<0.01$, time comparison of second and fourth years of observation for chi-square test. χ^2 (1) = 7.72.
[gg] $p<0.05$, time comparison of second and fifth years of observation for chi-square test. χ^2 (1) = 5.62.
[hh] $p<0.05$, time comparison of third and fifth years of observation for chi-square test. χ^2 (1) = 4.11.
[ii] $p<0.001$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 314.14.
[jj] $p<0.001$, time comparison of first and third years of observation for chi-square test. χ^2 (1) = 221.49.
[kk] $p<0.001$, time comparison of first and fourth years of observation for chi-square test. χ^2 (1) = 12.25.

In terms of healthcare utilization, veterans had 10.52 ± 13.37 outpatient visits, 0.18 ± 0.71 ED visits, and 0.13 ± 0.55 hospitalizations per year (Table 20). (Note the percentages for outpatient visits are not limited to the conventional range of 0% to 100% because, on average, patients have more than one outpatient visit in a given year.)

Comparisons by drug therapy show ACEI patients had the highest amount of outpatient visits of the three therapy groups; ARB patients had a higher amount of outpatient visits than neither patients ($p<0.001$ each). In terms of ED visits, patients on neither therapy had significantly fewer ED visits than those on ACEI or ARB therapy ($p<0.001$ each). ACEI patients had a significantly higher rate of hospitalization than neither patients ($p<0.001$), but they were comparable to ARB patients.

Table 20: Descriptive Statistics by Drug Therapy, Count Outcomes

Variable	**All patients (n=124,296 person-years; n=40,669 patients) Frequency, [mean (SD)]/person-year**	**ACEI (n=47,533 person-years; n=18,947 patients) Frequency, [mean (SD)]/person-year**	**ARB (n=5,098 person-years; n=1,929 patients) Frequency,[mean (SD)]/person-year**	**Neither (n=71,665 person-years; n=19,793 patients) Frequency, [mean (SD)]/person-year**
Outpatient visits[***,a]	1,307,141 [10.52 (13.37)]	661,523 [13.92 (13.93)]	70,691 [13.87 (15.00)]	574,927 [(8.02 (12.27)]
ED visits[†††]	21,737 [0.18 (0.71)]	10,356 [0.22 (0.79)]	945 [0.19 (0.68)]	9,536 [0.15 (0.64)]
Hospitalizations[‡‡‡]	15,503 [0.13 (0.55)]	7,364 [0.16 (0.60)]	637 [0.13 (0.51)]	7,402 [0.11 (0.52)]

[a]Outpatient visits look very different from Hospitalizations and ED visits. Remember, although we do not expect every patient to have a hospitalization or ED visit every year, that every patient has to have at least one outpatient visit every year or we would not have a medical record available for them for this year unless he received an ACEI or ARB at least 50% of the year.

[***]$p<0.001$, drug therapy comparisons, for Kruskal-Wallis test. Pairwise comparisons found three significant differences in rank means. Rank Mean difference = 1,611.60, critical value = 1,302.48, found a significant difference between ACEI and ARB groups (rank mean = 80,950.33 and 79,338.73, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 27,149.58, critical value = 1,279.08, found a significant difference between ARB and neither groups (rank means = 79,338.73 and 52,189.15, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 28,761.18, critical value = 517.85, found a significant difference between ACEI and neither groups (rank mean = 80,950.33 and 52,189.15, respectively, $p<0.0083$, (adjusted p-value)).

[†††]$p<0.001$, drug therapy comparisons, for Kruskal-Wallis test. Pairwise comparisons found two significant differences in rank means. Rank Mean difference = 1,640.44, critical value = 1,279.08, found a significant difference between ARB and neither groups (rank mean = 64,513.30 and 62,872.86, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 2,770.06, critical value = 517.85, found a significant difference between ACEI and neither groups (rank mean = 65,642.92 and 62,872.86, respectively, $p<0.0083$ (adjusted p-value)).

‡‡‡$p<0.001$, drug therapy comparisons, for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 2,295.86, critical value = 517.85, finds a significant difference between ACEI and neither groups (rank mean = 65,360.46 and 63,064.62, respectively, $p<0.0083$ (adjusted p-value)).

The following two tables compare hospitalization, ED visit, and outpatient visit rates across time and drug therapy for each year of follow-up. At year 1, ACEI patients had more hospitalizations, ED visits, and outpatient visits than those on neither therapy (Table 21). The only difference involving ARB patients at this time point is that they also had more outpatient visits than those receiving neither therapy. During the second year of follow-up we see a similar pattern: ACEI patients had more hospitalizations, ED visits, and outpatient visits than neither patients, again with ARB patients having more outpatient visits than neither patients. Neither patients had about one-half the outpatient visits as those in the ACEI or neither groups. Similar patterns were revealed in the third and fourth years of follow-up. In the last year of follow-up the only difference found is ACEI patients had more outpatient visits than neither patients.

Table 22 shows among ACEI patients there is a progressive decrease in the rate of hospitalization and ED visits across follow-up as evidenced by year 1 having a significantly higher rate than years 2, 3, and 4. There is even more evidence for a continuous decline in hospitalizations across follow-up for ACEI patients as each year of follow-up is significantly different from another. It should be noted that the number of outpatient visits in year 5 is approximately one-third of those in year 1. ARB patients only had one significant difference in rates across follow-up: there were fewer outpatient visits in year 5 than year 1. Patients receiving neither therapy had decreasing rates of hospitalization, ED visits, and outpatient visits across the follow-up period.

Table 21: Count Outcomes by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Hospitalization	0.18[a] (0.64)	0.15[b] (0.60)	0.14[c] (0.58)	0.11[d] (0.50)	0.03 (0.23)	0.16 (0.60)
ED visits	0.25[e] (0.84)	0.20[f] (0.79)	0.19[g] (0.72)	0.18[h] (0.71)	0.11[i] (0.39)	0.22 (0.79)
Outpatient Visits	15.96[j] (13.88)	12.87[k] (13.88)	12.53[l] (13.88)	11.32[m] (13.18)	5.671[n] (5.58)	13.92 (13.93)
ARB						
Hospitalization	0.16 (0.58)	0.12 (0.51)	0.10 (0.42)	0.09 (0.42)	0.00 (0.00)	0.13 (0.51)
ED visits	0.22 (0.72)	0.17 (0.68)	0.17 (0.67)	0.15 (0.54)	0.00 (0.00)	0.19 (0.68)
Outpatient Visits	16.08 (14.75)	12.70 (13.19)	12.71 (17.89)	11.37 (13.71)	4.67 (4.32)	13.87 (15.00)
Neither						
Hospitalization	0.16 (0.64)	0.10 (0.51)	0.09 (0.47)	0.06 (0.37)	0.02 (0.20)	0.11 (0.52)
ED visits	0.22 (0.82)	0.13 (0.61)	0.11 (0.54)	0.09 (0.49)	0.05 (0.35)	0.15 (0.64)
Outpatient Visits	12.93 (13.99)	7.20 (11.90)	6.17 (11.23)	4.66 (8.89)	2.07 (4.11)	8.02 (12.27)

Notes: mean (standard deviation)

[a] $p<0.01$, drug therapy comparisons within time t for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Means difference = 404.46, critical value = 285.66, found a significant difference between ACEI and neither (rank mean = 20,546.88 and 20,142.42, respectively, $p<0.0083$ (adjusted p-value)).
[b] $p<0.01$, drug therapy comparisons within time (t+1) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Means difference = 598.12, critical value = 287.56, found one significant difference between ACEI and neither (rank mean = 20,418.68 and 19,820.57, respectively, $p<0.0083$ (adjusted p-value)).
[c] $p<0.001$, drug therapy comparisons within time (t+2) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference =

419.44, critical value = 241.20, found a significant difference between ACEI and neither groups (rank mean = 13,775.91 and 13,356.46, respectively, $p<0.0083$ (adjusted p-value)).

[d] $p<0.001$, drug therapy comparisons within time (t+3) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 225.96, critical value = 196.94, found one significant difference between ACEI and neither groups (rank mean = 7,344.56 and 7,118.59, respectively, $p<0.0083$ (adjusted p-value)).

[e] $p<0.001$, drug therapy comparisons within time t for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 386.28, critical value = 285.66, found a significant difference between ACEI and neither groups (rank mean = 20,541.91 and 20,155.63, respectively, $p<0.0083$ (adjusted p-value)).

[f] $p<0.001$, drug therapy comparisons within time (t+1) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 660.14, critical value = 287.56, found a significant difference between ACEI and neither groups (rank mean = 20,453.96 and 19,793.82, respectively, $p<0.0083$ (adjusted p-value)).

[g] $p<0.001$, drug therapy comparisons within time (t+2) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 595.62, critical value = 241.20, found a significant difference between ACEI and neither groups (rank mean = 13,884.96 and 13,289.34, respectively, $p<0.0083$ (adjusted p-value)).

[h] $p<0.001$, drug therapy comparisons within time (t+3) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 342.42, critical value = 196.94, found a difference between ACEI and neither groups (rank mean = 7,429.24 and 7,086.82, respectively, $p<0.0083$ (adjusted p-value)).

[i] $p<0.05$, drug therapy comparisons within time (t+4) for Kruskal-Wallis test. Pairwise comparisons found no significant difference in rank means.

[j] $p<0.001$, drug therapy comparisons within time t for Kruskal-Wallis test. Pairwise comparisons found two significant differences in rank means. Rank Mean difference = 3,917.54, critical value = 670.39, found a significant difference between ARB and neither groups (rank mean = 22,054.75 and 18,137.21, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 4,318.63, critical value = 285.66, found a significant difference between ACEI and neither groups (rank mean = 22,455.84 and 18,137.21, respectively, $p<0.0083$ (adjusted p-value)).

[k] $p<0.001$, drug therapy comparisons within time (t+1) for Kruskal-Wallis test. Pairwise comparisons found two significant differences in rank means. Rank Mean difference = 8,236.89, critical value = 698.05, found a significant difference between ARB and neither groups (rank mean = 24,554.68 and 16,317.79, respectively, $p<0.0083$ (adjusted p-value)). Rank Mean difference = 8,644.57, critical value = 287.56, found a significant difference between ACEI and neither groups (rank mean = 24,962.36 and 16,317.17, respectively, $p<0.0083$ (adjusted p-value)).

[l] $p<0.001$, drug therapy comparisons within time (t+2) for Kruskal-Wallis test. Pairwise comparisons found two significant differences in rank means. Rank Mean difference = 6,345.98, critical value = 590.59, found a significant difference between ARB and neither

groups (rank mean = 17,262.87 and 10,916.88, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 6,743.69, critical value = 241.20, found a significant difference between ACEI and neither groups (rank mean = 17,660.57 and 10,916.88, respectively, p<0.0083 (adjusted p-value)).

[m] p<0.001, drug therapy comparisons within time (t+3) for Kruskal-Wallis test. Pairwise comparisons found two significant differences in rank means. Rank Mean difference = 3,836.26, critical value = 503.88, found a significant difference between ARB and neither groups (rank mean = 9,977.09 and 6,140.83, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 3,991.95, critical value = 196.94, found a significant difference between ACEI and neither groups (rank mean = 10,132.78 and 6,140.83, respectively, p<0.0083 (adjusted p-value)).

[n] p<0.001, drug therapy comparisons within time (t+4) for Kruskal-Wallis test. Pairwise comparisons found one significant difference in rank means. Rank Mean difference = 580.14, critical value = 174.88, found a significant difference between ACEI and neither groups (rank mean = 1,621.17 and 1,041.03, respectively, p<0.0083 (adjusted p-value)).

Table 22: Count Outcomes by Drug Therapy and Time Since Identification, Comparisons by Time

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Hospitalization***	0.18 (0.64)	0.15 (0.60)	0.14 (0.58)	0.11 (0.50)	0.03 (0.23)	0.16 (0.60)
ED visits†††	0.25 (0.84)	0.20 (0.79)	0.19 (0.72)	0.18 (0.71)	0.11 (0.39)	0.22 (0.79)
Outpatient Visits‡‡‡	15.96 (13.88)	12.87 (13.88)	12.53 (13.88)	11.32 (13.18)	5.671 (5.575)	13.92 (13.93)
ARB						
Hospitalization‖	0.16 (0.58)	0.12 (0.51)	0.10 (0.42)	0.09 (0.42)	0.00 (0.00)	0.13 (0.51)
ED visits	0.22 (0.72)	0.17 (0.68)	0.17 (0.67)	0.15 (0.54)	0.00 (0.00)	0.19 (0.68)
Outpatient Visits§§§	16.08 (14.75)	12.70 (13.19)	12.71 (17.89)	11.37 (13.71)	4.67 (4.32)	13.87 (15.00)
Neither						
Hospitalization¶¶¶	0.16 (0.64)	0.10 (0.51)	0.09 (0.47)	0.06 (0.37)	0.02 (0.20)	0.11 (0.52)
ED visits$$$	0.22 (0.82)	0.13 (0.61)	0.11 (0.54)	0.09 (0.49)	0.05 (0.35)	0.15 (0.64)
Outpatient Visits¤¤¤	12.93 (13.99)	7.20 (11.90)	6.17 (11.23)	4.66 (8.89)	2.07 (4.11)	8.02 (12.27)

Notes: mean (standard deviation)

*** $p<0.001$, time comparisons within ACEI for Kruskal-Wallis test. Pairwise comparisons found three significant differences in rank means. Rank Mean difference = 472.45, critical value = 415.05, found a difference between the first and second years of follow-up (rank mean = 24,116.92 and 23,644.47, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 620.17, critical value = 486.05, found a difference between the first and third years of follow-up (rank mean = 24,116.92 and 23,496.76, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 955.86, critical value = 723.66, found a difference between the first and fourth years of follow-up (rank mean = 24,116.92 and 23,161.06, respectively, $p<0.0025$ (adjusted p-value)).

††† $p<0.001$, time comparisons within ACEI for Kruskal-Wallis test. Pairwise comparisons found three significant differences in rank means. Rank Mean difference =

686.05, critical value = 415.05, found a significant difference between the first and second years of follow-up (rank mean = 24,194.69 and 23,508.64, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 700.37, critical value = 486.05, found a significant difference in the first and third years of follow-up (rank mean = 24,194.69 and 23,494.33, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 845.02, critical value = 723.66, found a significant difference in the first and fourth years of follow-up (rank mean = 24,194.69 and 23,349.67, respectively, p<0.0025 (adjusted p-value)).

‡‡‡ p<0.001, time comparisons within ACEI for Kruskal-Wallis test. Pairwise comparisons found ten significant differences in rank means. Rank Mean difference = 5,223.30, critical value = 415.05, found a significant difference in the first and second years of follow-up (rank mean = 27,197.06 and 21,973.76, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 5,789.55, critical value = 486.05, found a significant difference in the first and third years of follow-up (rank mean = 27,197.06 and 21,407.51, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 7,510.41, critical value = 723.66, found a significant difference in the first and fourth years of follow-up (rank mean = 27,197.06 and 19,686.65, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 16,052.63, critical value = 4,516.80, found a significant difference between the first and fifth years of follow-up (rank mean = 27,197.06 and 11,144.43, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 566.25, critical value = 501.91, found a significant difference in the second and third years of follow-up (rank mean = 21,973.76 and 21,407.51, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,287.11, critical value = 734.41, found a significant difference between the second and fourth years of follow-up (rank mean = 21,973.76 and 19,686.65, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 10,829.33, critical value = 4,518.53, found a significant difference between the second and fifth years of follow-up (rank mean = 21,973.76 and 11,144.43, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,720.86, critical value = 776.75, found a significant difference in the third and fourth years of follow-up (rank mean = 21,407.51 and 19,686.65, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 10,263.08, critical value = 4,525.60, found a significant difference in the third and fifth years of follow-up (rank mean = 21,407.51 and 11,144.43, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 8,542.22, critical value = 4,557.25, found a significant difference in the fourth and fifth years of follow-up (rank mean = 19,686.65 and 11,144.43, respectively, p<0.0025 (adjusted p-value)).

‖ p<0.05, time comparisons within ARB for Kruskal-Wallis test. Pairwise comparisons found no differences.

§§§ p<0.001, time comparisons for ANOVA. Tukey's Honestly Significant Difference finds one comparison is greater than the studentized range critical value (.05, 5, 5093) = 3.859. Among ARB users, the first year of observation had more outpatient visits than the fifth year (HSD test statistic = 4.140).

¶¶¶ p<0.001, time comparisons within neither for Kruskal-Wallis test. Pairwise comparisons found six significant differences in rank means. Rank Mean difference = 1,058.26, critical value = 565.06, found a significant difference in the first and second years of follow-up (rank mean = 36,821.22 and 35,762.95, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,323.35, critical value = 611.54, found a

significant difference in the first and third years of follow-up (rank mean = 36,821.22 and 35,497.86, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,839.39, critical value = 698.61, found a significant difference between the first and fourth years of follow-up (rank mean = 36,821.22 and 34,981.82, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,644.00, critical value = 1,348.87, found a significant difference in the first and fifth years of follow-up (rank mean = 36,821.22 and 34,177.21, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 781.13, critical value = 683.07, found a significant difference between the second and fourth years of follow-up (rank mean = 35,762.95 and 34,981.82, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,585.74, critical value = 1,340.89, found a significant difference in the second and fifth years of follow-up (rank mean = 35,762.95 and 34,177.21, respectively, p<0.0025 (adjusted p-value)).

[$$$] p<0.001, time comparisons within neither for Kruskal-Wallis test. Pairwise comparisons found seven significant differences in rank means. Rank Mean difference = 1,528.16, critical value = 565.06, found a significant difference in the first and second years of follow-up (rank mean = 37,200.27 and 35,672.12, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,949.72, critical value = 611.54, found a significant difference in the first and third years of follow-up (rank mean = 37,200.27 and 35,250.55, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,287.79, critical value = 698.61, found a significant difference in the first and fourth years of follow-up (rank mean = 37,200.27 and 34,912.49, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 3,322.81, critical value = 1,348.87, found a significant difference in the first and fifth years of follow-up (rank mean = 37,200.27 and 33,877.46, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 759.63, critical value = 683.07, found a significant difference in the second and fourth years of follow-up (rank mean = 35,672.12 and 34,912.49, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,794.66, critical value = 1,340.89, found a significant difference in the second and fifth years of follow-up (rank mean = 35,672.12 and 33,877.46, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,373.09, critical value = 1,361.13, found a significant difference in the third and fifth years of follow-up (rank mean = 35,250.55 and 33,877.46, respectively, p<0.0025 (adjusted p-value)).

[πππ] p<0.001, time comparisons within neither for Kruskal-Wallis test. Pairwise comparisons found ten significant differences in rank means. Rank Mean difference = 15,585.01, critical value = 565.06, found a significant difference in the first and second years of follow-up (rank mean = 49,337.50 and 33,752.49, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 18,990.24, critical value = 611.54, found a significant difference in the first and third years of follow-up (rank mean = 49,337.50 and 30,347.26, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 22,507.56, critical value = 698.61, found a significant difference in the first and fourth years of follow-up (rank mean = 49,337.50 and 26,829.94, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 30,000.93, critical value = 1,348.87, found a significant difference in the first and fifth years of follow-up (rank mean = 49,337.50 and 19,336.57, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 3,405.23, critical value = 593.72, found a significant difference in the second and third years of follow-up (rank mean = 33,752.49 and 30,347.26, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 6,922.55, critical value = 683.07, found a

significant difference in the second and fourth years of follow-up (rank mean = 33,752.49 and 26,829.94, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 14,415.92, critical value = 1,340.89, found a significant difference in the second and fifth years of follow-up (rank mean = 33,752.49 and 19,336.57, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 3,517.32, critical value = 721.99, found a significant difference in the third and fourth years of follow-up (rank mean = 30,347.26 and 26,829.94, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 11,010.69, critical value = 1,361.13, found a significant difference in the third and fifth years of follow-up (rank mean = 30,347.26 and 19,336.57, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 7,493.37, critical value = 1,402.41, found a significant difference in the fourth and fifth years of follow-up (rank mean = 26,829.94 and 19,336.57, respectively, $p<0.0025$ (adjusted p-value)).

Multivariate Regression Results

ACEI or ARB Monotherapy versus neither

The following six tables present multivariate regression results for comparisons between ACEI or ARB monotherapy and neither therapy. Table 23 shows the results for the logistic regression of ACEI monotherapy's effect and ARB monotherapy's effect, compared to neither therapy, on development of ESRD. Several patient characteristics were simultaneously entered in the model to control for their effects.

With robust standard errors we only have Pregibon's Link Test and Hosmer and Lemeshow goodness-of-fit test for diagnostic tests of logistic regression. The Pregibon's Link Test was nonsignificant (p=0.95) as was Hosmer and Lemeshow (p=0.53, $\chi^2(8)=7.05$).

The interaction between ACEI and time (t+4), the interaction between ARB and time (t+4), pulmonary circulation disorders, AIDS, lymphoma, metastatic cancer, and rheumatoid arthritis/collagen vascular diseases were dropped because each of these variables have no observations with an ESRD value of one. Time (t+2), annual income $18,000-34,999, CHF, diabetes complicated, fluid and electrolyte disorders, and deficiency anemias were associated with higher odds of ESRD development. ACEI monotherapy, age, and LDL were associated with lower odds of ESRD ($p<0.017$ each). Focusing on ACEI monotherapy, with an odds ratio (OR)=0.43 (95% CI: 0.23-0.80), patients were associated with having 57% (20-77%) lower odds of ESRD development compared to patients receiving neither therapy. Particular emphasis should be placed on diabetes complicated (OR=3.40, 2.39-4.84), fluid and electrolyte disorders (OR=4.19, 2.44-7.19), and deficiency anemias (OR=4.25, 2.56-7.07). Note although all conditions

have high point estimates, the confidence intervals for the latter two are wider, indicating fewer patients with these conditions compared to diabetes complicated. The model was significant [Wald $\chi^2(49) = 499.17$, $p<0.001$] and explained 13.24% of the variance in ESRD development. It also has a 0.82 probability of correctly classifying a randomly selected pair of cases from those developing and not developing ESRD based on the area under the receiver operating characteristic (ROC) curve. (Note this value varies from 0.5 to 1.0, chance to perfect prediction, respectively).

Table 23: Logistic Regression, ACEI or ARB versus Neither, for Variables Predicting ESRD (N=72,153 person-years; N=35,475 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	0.43	0.14	<0.01	0.23	0.80
ARB[a]	0.50	0.37	0.35	0.12	2.13
Time (t+1) [b]	1.00	0.28	0.99	0.57	1.74
Time (t+2) [b]	2.76	0.67	<0.001	1.71	4.45
Time (t+3) [b]	0.89	0.38	0.78	0.38	2.04
Time (t+4) [b]	2.28	1.86	0.31	0.46	11.28
ACEI*time (t+1) [c]	1.30	0.61	0.58	0.52	3.27
ACEI*time (t+2) [c]	0.84	0.36	0.69	0.36	1.96
ACEI*time (t+3) [c]	1.95	1.36	0.34	0.50	7.66
ARB*time (t+1) [d]	3.12	2.38	0.14	0.70	13.92
ARB*time (t+2) [d]	0.73	0.76	0.77	0.10	5.66
ARB*time (t+3) [d]	2.99	3.93	0.40	0.23	39.28
Age	0.97	0.01	<0.01	0.96	0.99
Annual income $6,000-17,999[e]	1.63	0.42	0.06	0.98	2.71
Annual income $18,000-34,999[e]	1.86	0.46	0.01	1.14	3.03
Annual income ≥$35,000[e]	1.10	0.33	0.74	0.61	1.98
Income missing[e]	1.46	0.72	0.44	0.56	3.84
Urban/suburban[f]	1.52	0.33	0.06	0.99	2.33
Never smoker[g]	0.46	0.81	0.04	0.22	0.96
Ever smoker[g]	0.66	0.30	0.04	0.45	0.97
HbA1c	0.89	0.07	0.11	0.77	1.03
LDL	0.99	0.00	<0.01	0.99	1.00
Triglycerides	1.00	0.00	0.17	1.00	1.00
CHF[h]	2.63	0.68	<0.001	1.59	4.35
Cardiac arrhythmias[i]	1.38	0.49	0.37	0.69	2.76
Valvular disease[j]	1.25	1.07	0.79	0.24	6.63
Peripheral vascular disorders[k]	2.01	0.58	0.02	1.14	3.54
Hypertension[l]	1.32	0.27	0.17	0.89	1.97
Paralysis[m]	1.51	1.60	0.70	0.19	12.12
Other neurological disorders[n]	0.52	0.52	0.52	0.07	3.72
Chronic pulmonary disease[o]	0.69	0.21	0.23	0.38	1.26
Hypothyroidism[p]	0.99	0.34	0.98	0.50	1.95
Diabetes complicated[q]	3.40	0.61	<0.001	2.39	4.84
Liver disease[r]	1.84	0.83	0.18	0.76	4.43

Table 23 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Peptic ulcer disease[s]	0.81	0.66	0.80	0.17	3.98
Solid tumor without metastasis[t]	1.98	0.63	0.03	1.07	3.69
Coagulopathy[u]	1.68	1.08	0.42	0.48	5.89
Obesity[v]	0.57	0.16	0.04	0.33	0.98
Weight loss[w]	5.16	5.88	0.15	0.55	48.21
Fluid and electrolyte disorders[x]	4.19	1.15	<0.001	2.44	7.19
Blood loss anemia[y]	4.06	4.59	0.22	0.44	37.19
Deficiency anemias[z]	4.25	1.10	<0.001	2.56	7.07
Alcohol abuse[aa]	1.22	0.55	0.66	0.50	2.97
Drug abuse[bb]	0.67	0.47	0.57	0.17	2.68
Psychoses [cc]	0.96	0.33	0.91	0.49	1.88
Depression [dd]	1.32	0.32	0.25	0.82	2.12
Cohort 2004[ee]	0.82	0.30	0.58	0.40	1.67
Cohort 2005 [ee]	1.13	0.41	0.74	0.55	2.30
Cohort 2006 [ee]	0.69	0.29	0.38	0.30	1.57

McFadden's Pseudo $R^2 = 0.13$
Wald $\chi^2(49) = 499.17$, $p<0.001$, Log pseudolikelihood = -1008.18
Area under the ROC curve = 0.82

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = No CHF, [I] Reference category = No cardiac arrhythmias, [j] Reference category = No valvular disease, [k] Reference category = No peripheral vascular disorders, [l] Reference category = Normotension, [m] Reference category = No paralysis, [n] Reference category = No other neurological disorders, [o] Reference category = No chronic pulmonary disease, [p] Reference category = No hypothyroidism, [q] Reference category = No diabetes complicated, [r] Reference category = No liver disease, [s] Reference category = No peptic ulcer disease, [t] Reference category = No solid tumor without metastasis, [u] Reference category = No coagulopathy, [v] Reference category = No obesity, [w] Reference category = No weight loss, [x] Reference category = No fluid and electrolyte disorders, [y] Reference category = No blood loss anemia, [z] Reference category = No deficiency anemias, [aa] Reference category = No alcohol abuse, [bb] Reference category = No drug abuse, [cc] Reference category = No psychoses, [dd] Reference category =No depression, [ee] Reference category =Cohort 2003

Table 24 displays results of the logistic regression of ACEI monotherapy's and ARB monotherapy's effect, compared to neither, on having an IVDE. Several patient characteristics were simultaneously entered in the model to quantify their effects.

After running the original model, diagnostic tests were checked; Pregibon's Link test was significant (p=0.004), so another model was constructed by iteratively adding age squared; income divided by 100,000; the interactions between HbA1c and LDL, HbA1c and triglycerides, LDL and triglycerides, albuminuria and HbA1c, albuminuria and triglycerides, albuminuria and LDL, age and triglycerides, age and LDL, and age and HbA1c. Only those variables that were significant at their time of entry and contributed to a larger p-value for the Pregibon's Link Test were retained. This model resulted in a significant Pregibon's Link Test (p=0.01) and nonsignificant Hosmer and Lemeshow goodness-of-fit ($\chi^2(8) = 10.10$, p=0.26). Accordingly, we conducted a Box-Tidwell estimation to determine if there were any other transformations of variables that we should include that we did not. Box-Tidwell did not provide any meaningful transformations. (For instance, it specified that dividing several dummy codes by a number and then multiplying them by a decimal would help with fit; however, this goes against common sense.) Due to this, we kept the model with the significant iteratively added variables mentioned above.

The interaction between ARB and time (t+4) was dropped because no observations with that characteristic had an IVDE during the study period. Age squared, never smoker, ever smoker, LDL, and the interaction between LDL and triglycerides were associated with lower odds while ACEI monotherapy, age, history of MI, history of stroke, CHF, peripheral vascular disorders, chronic pulmonary disease, fluid and

electrolyte disorders, and deficiency anemias were associated with higher odds of IVDE occurrence ($p<0.017$ each). Particular attention should be paid to patients with history of MI or stroke (OR=1.98 (1.51-2.58) and OR=2.70 (1.96-3.71) as well as patients with fluid and electrolyte disorders (OR=1.99 (1.44-2.76) and peripheral vascular disorders (OR=2.93 (2.46-3.49). The model was significant [Wald $\chi^2(66) = 700.48$, $p<0.001$] and explained 5.30% of the variance in IVDE occurrence. It also has a 0.68 probability of correctly classifying a randomly selected pair of cases from those who did and did not experience an IVDE.

Table 24: Logistic Regression Analysis, ACEI or ARB versus Neither, for Variables Predicting IVDE (N=55,526 person-years; N=34,060 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.54	0.12	<0.001	1.33	1.79
ARB[a]	1.35	0.22	0.07	0.98	1.86
Time (t+1) [b]	1.04	0.11	0.72	0.84	1.28
Time (t+2) [b]	1.17	0.15	0.22	0.91	1.50
Time (t+3) [b]	1.40	0.22	0.03	1.03	1.91
Time (t+4) [b]	1.38	0.58	0.45	0.60	3.16
ACEI*time (t+1) [c]	0.85	0.12	0.24	0.65	1.11
ACEI*time (t+2) [c]	0.95	0.15	0.73	0.69	1.29
ACEI*time (t+3) [c]	0.78	0.17	0.24	0.51	1.18
ACEI*time (t+4) [c]	0.73	0.81	0.77	0.08	6.36
ARB*time (t+1) [d]	1.29	0.32	0.31	0.79	2.10
ARB*time (t+2) [d]	1.01	0.32	0.98	0.54	1.89
ARB*time (t+3) [d]	0.68	0.35	0.45	0.25	1.86
Age	1.20	0.04	<0.001	1.12	1.28
Age squared	1.00	0.00	<0.001	1.00	1.00
Annual income $6,000-17,999[e]	1.20	0.11	0.05	1.00	1.44
Annual income $18,000-34,999[e]	1.17	0.11	0.08	0.98	1.40
Annual income ≥$35,000[e]	1.08	0.10	0.43	0.89	1.30
Income missing[e]	0.86	0.18	0.48	0.57	1.30
Urban/suburban[f]	1.02	0.07	0.79	0.89	1.16
Never smoker[g]	0.47	0.30	<0.001	0.35	0.61
Ever smoker[g]	0.65	0.11	<0.001	0.56	0.75
Baseline microalbuminuria[h]	0.99	0.09	0.89	0.82	1.18
Microalbuminuria in follow-up[i]	0.65	0.14	0.04	0.43	0.98
Macroalbuminuria in follow-up[i]	0.54	0.22	0.13	0.24	1.20
HbA1c	0.92	0.06	0.19	0.81	1.00
Albuminuria*HbA1c	1.06	0.03	0.04	1.00	1.12
LDL	1.00	0.00	<0.001	0.99	1.00
Triglycerides	1.00	0.00	0.17	1.00	1.00
Albuminuria*triglycerides	1.00	0.00	0.09	1.00	1.00
LDL*triglycerides	1.00	0.00	<0.01	1.00	1.00
History of MI[j]	1.98	0.27	<0.001	1.51	2.58
History of stroke[k]	2.70	0.44	<0.001	1.96	3.71
Family history of CVD[l]	1.65	0.43	0.06	0.98	2.75
CHF[m]	1.41	0.17	<0.01	1.12	1.79

Table 24 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Cardiac arrhythmias[n]	1.32	0.17	0.03	1.03	1.70
Valvular disease[o]	1.70	0.52	0.08	0.94	3.10
Pulmonary circulation disorders[p]	2.70	1.17	0.02	1.15	6.31
Peripheral vascular disorders[q]	2.93	0.26	<0.001	2.46	3.49
Hypertension[r]	1.10	0.08	0.19	0.95	1.27
Paralysis[s]	0.54	0.32	0.30	0.16	1.76
Other neurological disorders[t]	1.76	0.46	0.03	1.05	2.95
Chronic pulmonary disease[u]	1.27	0.12	0.01	1.05	1.52
Hypothyroidism[v]	1.06	0.15	0.68	0.80	1.41
Diabetes complicated[w]	1.12	0.09	0.16	0.95	1.32
Liver disease[x]	1.28	0.29	0.27	0.83	1.99
Peptic ulcer disease[y]	0.88	0.27	0.67	0.48	1.61
AIDS[z]	1.46	1.06	0.61	0.35	6.03
Lymphoma[aa]	0.59	0.36	0.39	0.18	1.93
Metastatic cancer[bb]	1.68	1.48	0.56	0.30	9.40
Solid tumor without metastasis[cc]	0.95	0.12	0.65	0.74	1.20
Rheumatoid arthritis/ collagen vascular diseases[dd]	1.34	0.36	0.28	0.79	2.28
Coagulopathy[ee]	1.05	0.28	0.86	0.63	1.75
Obesity[ff]	1.02	0.08	0.82	0.87	1.20
Weight loss[gg]	0.63	0.67	0.66	0.08	5.01
Fluid and electrolyte disorders[hh]	1.99	0.33	<0.001	1.44	2.76
Blood loss anemia[ii]	1.40	1.01	0.64	0.34	5.79
Deficiency anemias[jj]	1.50	0.21	<0.01	1.14	1.97
Alcohol abuse[kk]	1.03	0.20	0.90	0.70	1.49
Drug abuse[ll]	1.09	0.31	0.77	0.63	1.89
Psychoses[mm]	1.05	0.16	0.75	0.78	1.40
Depression[nn]	1.18	0.12	0.09	0.97	1.43
Cohort 2004[oo]	0.94	0.12	0.61	0.73	1.20
Cohort 2005[oo]	0.91	0.12	0.45	0.70	1.17
Cohort 2006[oo]	0.98	0.13	0.86	0.75	1.27

McFadden's PseudoR^2 = 0.05
Wald $\chi^2(65)$ = 700.48, p<0.001, Log pseudolikelihood=-6753.45

Area under the ROC curve = 0.68

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = Baseline macroalbuminuria, [i]Reference category = Normoalbuminuria in follow-up, [j] Reference category = No history of MI, [k] Reference category = No history of stroke, [l] Reference category = No family history of CVD, [m] Reference category = No CHF, [n] Reference category = No cardiac arrhythmias, [o] Reference category = No valvular disease, [p] Reference category = No pulmonary circulation disorders, [q] Reference category = No peripheral vascular disorders, [r] Reference category = Normotension, [s] Reference category = No paralysis, [t] Reference category = No other neurological disorders, [u] Reference category = No chronic pulmonary disease, [v] Reference category = No hypothyroidism, [w] Reference category = No diabetes complicated, [x] Reference category = No liver disease, [y] Reference category = No peptic ulcer disease, [z] Reference category = No AIDS, [aa] Reference category = No Lymphoma [bb] Reference category = No metastatic cancer, [cc] Reference category = No solid tumor without metastasis, [dd] Reference category = No rheumatoid arthritis/collagen vascular diseases, [ee] Reference category = No coagulopathy, [ff] Reference category = No obesity, [gg] Reference category = No weight loss, [hh] Reference category = No fluid and electrolyte disorders, [ii] Reference category = No blood loss anemia, [jj] Reference category = No deficiency anemias, [kk] Reference category = No alcohol abuse, [ll] Reference category = No drug abuse, [mm] Reference category = No psychoses, [nn] Reference category = No depression, [oo] Reference category = Cohort 2003

Table 25 displays the results of the logistic regression of ACEI monotherapy's effect and ARB monotherapy's effect, compared to neither's effect, on all-cause mortality. Several patient characteristics were simultaneously entered in the model to control for their effects.

After running the model, diagnostic tests were checked. The model had a nonsignificant Pregibon's Link Test ($p = 0.45$) as well as a nonsignificant Hosmer and Lemeshow goodness-of-fit [$\chi^2(8) = 9.63$, $p = 0.29$].

The interaction between ACEI monotherapy and time (t+4), the interaction between ARB monotherapy and time (t+4), and blood loss anemia were dropped as none of their observations had a value of one for all-cause mortality. ACEI monotherapy, ARB monotherapy, times (t+1) and (t+2), and income missing were associated with lower odds while the interaction between ACEI monotherapy and times (t+1), (t+2), and (t+3), age, urban/suburban living, HbA1c, CHF, peripheral vascular disorders, chronic pulmonary disease, metastatic cancer, coagulopathy, fluid and electrolyte disorders, and cohorts 2004, 2005, and 2006 were associated with higher odds of all-cause mortality ($p<0.017$ each). (Note the large odds ratios and robust standard errors for cohorts 2004, 2005, and 2006, something to be cautious of when interpreting results of a logistic regression.) Worth pointing out, patients with chronic pulmonary disease were associated with a 107% (62-164%) higher odds of dying. Because the Wald test for time (t+4) cannot be reported as it is dependent on the (robust) standard error for that variable and the Wald statistic for the model is dependent upon the Wald test for the variable, no Wald statistic (or associated p-value) is reported for the model. The model explained

13.50% of the variance in all-cause mortality and has a 0.82 probability of correctly classifying a randomly selected pair of cases from those who did and did not die.

Table 25: Logistic Regression Analysis, ACEI or ARB versus Neither, for Variables Predicting All-Cause Mortality (N=55,457 person-years; N=34,034 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	0.16	0.03	<0.001	0.11	0.22
ARB[a]	0.11	0.06	<0.001	0.03	0.33
Time (t+1) [b]	0.43	0.08	<0.001	0.30	0.60
Time (t+2) [b]	0.59	0.12	<0.01	0.39	0.88
Time (t+3) [b]	0.85	0.23	0.55	0.49	1.45
Time (t+4) [b]	1.22×10^7	.	.	.	.
ACEI*time (t+1) [c]	2.58	0.88	<0.01	1.32	5.05
ACEI*time (t+2) [c]	2.92	1.11	<0.01	1.38	6.14
ACEI*time (t+3) [c]	5.78	2.61	<0.001	2.39	14.00
ARB*time (t+1) [d]	1.97	2.32	0.56	0.20	19.77
ARB*time (t+2) [d]	6.14	5.78	0.05	0.97	38.84
ARB*time (t+3) [d]	8.48	10.22	0.08	0.80	89.88
Age	1.04	0.01	<0.001	1.03	1.05
Annual income $6,000-17,999[e]	1.34	0.20	0.05	1.00	1.79
Annual income $18,000-34,999[e]	1.35	0.20	0.04	1.01	1.79
Annual income ≥$35,000[e]	1.10	0.17	0.55	0.81	1.47
Income missing[e]	0.16	0.12	0.01	0.04	0.67
Urban/suburban[f]	1.32	0.16	<0.02	1.04	1.66
Never smoker[g]	0.55	0.22	0.13	0.25	1.19
Ever smoker[g]	0.98	0.15	0.88	0.73	1.31
Baseline microalbuminuria[h]	0.93	0.20	0.70	0.65	1.33
Microalbuminuria in follow-up[i]	1.44	0.27	0.05	1.00	2.08
Macroalbuminuria in follow-up[i]	1.63	0.42	0.05	0.99	2.69
HbA1c	1.02	0.00	<0.001	1.01	1.02
LDL	1.00	0.00	0.42	0.99	1.00
Triglycerides	1.00	0.00	0.14	1.00	1.00
History of MI[j]	1.62	0.40	0.05	0.99	2.63
History of stroke[k]	1.77	0.55	0.07	0.96	3.27
Family history of CVD[l]	0.48	0.44	0.42	0.08	2.85
CHF[m]	2.46	0.39	<0.001	1.81	3.35
Cardiac arrhythmias[n]	1.05	0.20	0.79	0.73	1.52
Valvular disease[o]	0.52	0.37	0.36	0.13	2.13

Table 25 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Pulmonary circulation disorders[p]	1.48	1.17	0.62	0.31	6.96
Peripheral vascular disorders[q]	1.51	0.24	0.01	1.10	2.06
Hypertension[r]	0.86	0.09	0.15	0.70	1.06
Paralysis[s]	1.80	1.10	0.33	0.55	5.94
Other neurological disorders[t]	1.65	0.61	0.18	0.80	3.39
Chronic pulmonary disease[u]	2.07	0.26	<0.001	1.62	2.64
Hypothyroidism[v]	1.33	0.26	0.14	0.91	1.93
Diabetes complicated[w]	1.08	0.15	0.55	0.83	1.42
Liver disease[x]	1.54	0.51	0.19	0.80	2.96
Peptic ulcer disease[y]	0.40	0.28	0.20	0.10	1.60
AIDS[z]	4.15	2.98	0.05	1.02	16.98
Lymphoma[aa]	2.68	1.18	0.03	1.13	6.36
Metastatic cancer[bb]	9.29	4.27	<0.001	3.77	22.87
Solid tumor without metastasis[cc]	1.30	0.21	0.10	0.95	1.78
Rheumatoid arthritis/collagen vascular diseases[dd]	1.69	0.68	0.20	0.76	3.73
Coagulopathy[ee]	2.33	0.69	<0.01	1.31	4.14
Obesity[ff]	0.89	0.14	0.46	0.66	1.21
Weight loss[gg]	1.48	1.83	0.75	0.13	16.68
Fluid and electrolyte disorders[hh]	2.00	0.52	<0.01	1.20	3.32
Deficiency anemias[ii]	1.15	0.25	0.51	0.76	1.75
Alcohol abuse[jj]	1.92	0.53	0.02	1.11	3.30
Drug abuse[kk]	1.45	0.61	0.38	0.63	3.30
Psychoses[ll]	1.02	0.26	0.94	0.62	1.66
Depression[mm]	1.37	0.22	0.05	1.00	1.87
Cohort 2004[nn]	3.00×10^7	3.03×10^7	<0.001	4.14×10^6	2.17×10^8
Cohort 2005[nn]	4.06×10^7	4.10×10^7	<0.001	5.61×10^6	2.94×10^8
Cohort 2006[nn]	3.57×10^7	3.61×10^7	<0.001	4.93×10^6	2.59×10^8

McFadden's Pseudo $R^2 = 0.14$
Wald $\chi^2(58)$ and its p-value were not reported, Log pseudolikelihood = -2144.450
Area under the ROC curve = 0.82

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = Baseline macroalbuminuria, [i]Reference category = Normoalbuminuria in follow-up, [j] Reference category = No history of MI, [k] Reference category = No history of stroke, [l] Reference category = No family history of CVD, [m] Reference category = No CHF, [n] Reference category = No cardiac arrhythmias, [o] Reference category = No valvular disease, [p] Reference category = No pulmonary circulation disorders, [q] Reference category = No peripheral vascular disorders, [r] Reference category = Normotension, [s] Reference category = No paralysis, [t] Reference category = No other neurological disorders, [u] Reference category = No chronic pulmonary disease, [v] Reference category = No hypothyroidism, [w] Reference category = No diabetes complicated, [x] Reference category = No liver disease, [y] Reference category = No peptic ulcer disease, [z] Reference category = No AIDS, [aa] Reference category = No Lymphoma [bb] Reference category = No metastatic cancer, [cc] Reference category = No solid tumor without metastisis, [dd] Reference category = No rheumatoid arthritis/collagen vascular diseases, [ee] Reference category = No coagulopathy, [ff] Reference category = No obesity, [gg] Reference category = No weight loss, [hh] Reference category = No fluid and electrolyte disorders, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

Table 26 presents the results of the negative binomial regression for variables predicting outpatient visits. Times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, income missing, never smoker, microalbuminuria in follow-up, LDL, hypertension, and cohorts 2005 and 2006 were associated with lower incidence rates of outpatient visits ($p<0.017$ each). ACEI monotherapy, ARB monotherapy, the interaction between ACEI monotherapy and times (t+1), (t+2), and (t+3), the interaction between ARB monotherapy and time (t+3), annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, history of stroke, CHF, cardiac arrhythmias, valvular disease, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression were associated with higher incidence rates of outpatient visits ($p<0.017$ each). Taking a closer look at ACEI monotherapy, with an incidence rate ratio (IRR)=1.19 (95%CI: 1.16-1.21), we see that patients taking ACEI monotherapy were associated with 19% (16-21%) more outpatient visits than patients receiving neither therapy. Special mention should be given to metastatic cancer (IRR=1.94, (1.59-2.36)), fluid and electrolyte disorders (IRR=1.32, (1.23-1.42)), drug abuse (IRR=1.69, (1.53-1.87)), and psychoses (IRR=1.54, (1.46-1.63)). The model resulted in Wald $\chi2(62) = 8269.50$, $p<0.001$, log pseudolikelihood = -192329.35. Note for models involving robust standard errors, a p-value is not reported in the regression output for the likelihood-ratio test of alpha. Model fit diagnostic tests for all count variables are in Appendix F.

Table 26: Negative Binomial Regression Analysis, ACEI or ARB versus Neither, for Variables Predicting Outpatient Visits (N=55,530 person-years; N=34,060 patients)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.19	1.01	<0.001	1.16	1.21
ARB[a]	1.25	1.02	<0.001	1.20	1.30
Time (t+1)[b]	0.80	1.02	<0.001	0.77	0.82
Time (t+2)[b]	0.75	1.02	<0.001	0.72	0.77
Time (t+3)[b]	0.61	1.03	<0.001	0.58	0.64
Time (t+4)[b]	0.34	1.07	<0.001	0.30	0.39
ACEI*time (t+1)[c]	1.05	1.02	0.01	1.01	1.09
ACEI*time (t+2)[c]	1.08	1.02	<0.01	1.03	1.13
ACEI*time (t+3)[c]	1.19	1.04	<0.001	1.11	1.27
ACEI*time (t+4)[c]	1.05	1.20	0.80	0.73	1.50
ARB*time (t+1)[d]	1.05	1.04	0.17	0.98	1.13
ARB*time (t+2)[d]	1.17	1.07	0.03	1.02	1.34
ARB*time (t+3)[d]	1.30	1.09	<0.01	1.10	1.53
ARB*time (t+4)[d]	1.12	1.46	0.77	0.53	2.35
Age	0.99	1.00	<0.001	0.99	0.99
Annual income $6,000-17,999[e]	1.23	1.01	<0.001	1.20	1.26
Annual income $18,000-34,999[e]	1.17	1.01	<0.001	1.14	1.20
Annual income ≥$35,000[e]	0.92	1.01	<0.001	0.89	0.94
Income missing[e]	0.80	1.03	<0.001	0.76	0.84
Urban/suburban[f]	1.16	1.01	<0.001	1.14	1.18
Never smoker[g]	0.86	1.01	<0.001	0.84	0.88
Ever smoker[g]	1.05	1.03	0.08	0.99	1.11
Baseline microalbuminuria[h]	1.02	1.02	0.27	0.99	1.05
Microalbuminuria in follow-up[i]	0.93	1.01	<0.001	0.91	0.95
Macroalbuminuria in follow-up[i]	1.03	1.02	0.08	1.00	1.08
HbA1c	1.00	1.00	0.11	1.00	1.01
LDL	1.00	1.00	<0.001	1.00	1.00
Triglycerides	1.00	1.00	0.38	1.00	1.00
History of MI[j]	0.97	1.03	0.22	0.92	1.02
History of stroke[k]	1.16	1.04	<0.001	1.07	1.25
Family history of CVD[l]	1.08	1.05	0.11	0.98	1.20
CHF[m]	1.13	1.02	<0.001	1.08	1.18

Table 26 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Cardiac arrhythmias[n]	1.43	1.02	<0.001	1.37	1.49
Valvular disease[o]	1.28	1.06	<0.001	1.14	1.45
Pulmonary circulation disorders[p]	1.46	1.19	0.03	1.04	2.05
Peripheral vascular disorders[q]	1.18	1.02	<0.001	1.13	1.22
Hypertension[r]	0.98	1.01	<0.02	0.96	1.00
Paralysis[s]	1.67	1.09	<0.001	1.41	1.97
Other neurological disorders[t]	1.30	1.05	<0.001	1.18	1.43
Chronic pulmonary disease[u]	1.12	1.02	<0.001	1.09	1.16
Hypothyroidism[v]	1.01	1.02	0.55	0.97	1.06
Diabetes complicated[w]	1.20	1.01	<0.001	1.17	1.23
Liver disease[x]	1.22	1.03	<0.001	1.14	1.30
Peptic ulcer disease[y]	0.99	1.05	0.88	0.91	1.09
AIDS[z]	1.30	1.08	<0.001	1.13	1.49
Lymphoma[aa]	1.29	1.07	<0.001	1.12	1.48
Metastatic cancer[bb]	1.94	1.11	<0.001	1.59	2.36
Solid tumor without metastasis[cc]	1.15	1.02	<0.001	1.10	1.19
Rheumatoid arthritis / collagen vascular diseases[dd]	1.19	1.05	<0.01	1.08	1.31
Coagulopathy[ee]	1.39	1.05	<0.001	1.26	1.53
Obesity[ff]	1.04	1.01	<0.01	1.02	1.07
Weight loss[gg]	1.38	1.16	0.03	1.03	1.84
Fluid and electrolyte disorders[hh]	1.32	1.04	<0.001	1.23	1.42
Blood loss anemia[ii]	1.52	1.17	<0.01	1.12	2.07
Deficiency anemias[jj]	1.26	1.03	<0.001	1.20	1.33
Alcohol abuse[kk]	1.18	1.03	<0.001	1.11	1.25
Drug abuse[ll]	1.69	1.05	<0.001	1.53	1.87
Psychoses[mm]	1.54	1.03	<0.001	1.46	1.62
Depression[nn]	1.25	1.02	<0.001	1.22	1.29

Table 26 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Cohort 2004[oo]	0.97	1.02	0.12	0.93	1.01
Cohort 2005[oo]	0.94	1.02	<0.01	0.90	0.98
Cohort 2006[oo]	0.93	1.02	<0.001	0.90	0.97
/lnalpha	-0.85	0.01		-0.86	-0.83
alpha	0.43	0.004		0.42	0.44

Wald $\chi 2(62) = 8269.50$, $p<0.001$, log pseudolikelihood = -192329.35

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = Baseline macroalbuminuria, [i]Reference category = Normoalbuminuria in follow-up, [j] Reference category = No history of MI, [k] Reference category = No history of stroke, [l] Reference category = No family history of CVD, [m] Reference category = No CHF, [n] Reference category = No cardiac arrhythmias, [o] Reference category = No valvular disease, [p] Reference category = No pulmonary circulation disorders, [q] Reference category = No peripheral vascular disorders, [r] Reference category = Normotension, [s] Reference category = No paralysis, [t] Reference category = No other neurological disorders, [u] Reference category = No chronic pulmonary disease, [v] Reference category = No hypothyroidism, [w] Reference category = No diabetes complicated, [x] Reference category = No liver disease, [y] Reference category = No peptic ulcer disease, [z] Reference category = No AIDS, [aa] Reference category = No Lymphoma [bb] Reference category = No metastatic cancer, [cc] Reference category = No solid tumor without metastisis, [dd] Reference category = No rheumatoid arthritis/collagen vascular diseases, [ee] Reference category = No coagulopathy, [ff] Reference category = No obesity, [gg] Reference category = No weight loss, [hh] Reference category = No fluid and electrolyte disorders, [ii] Reference category = No blood loss anemia, [jj] Reference category = No deficiency anemias, [kk] Reference category = No alcohol abuse, [ll] Reference category = No drug abuse, [mm] Reference category = No psychoses, [nn] Reference category = No depression, [oo] Reference category = Cohort 2003

Table 27 displays the results of the negative binomial regression for variables predicting ED visits. Times (t+1), (t+2), and (t+3), the interaction between ARB monotherapy and time (t+4), age, annual income ≥$35,000, income missing, never smoker, and hypertension were associated with lower incidence rates of ED visits; ACEI monotherapy, annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, ever smoker, HbA1c, CHF, cardiac arrhythmias, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, metastatic cancer, solid tumor without metastasis, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression were associated with significantly higher incidence rates of ED visits ($p<0.017$ each). Of note, patients with fluid and electrolyte disorders were associated with 99% (70-133%) more ED visits, patients with deficiency anemias were associated with 59% (33-90%) more ED visits, and patients with drug abuse were associated with 81% (49-120%) more ED visits. The model resulted in a Wald $\chi 2(62) = 2987.43$, $p<0.001$, log pseudolikelihood = -27400.19.

Table 27: Negative Binomial Regression Analysis, ACEI or ARB versus Neither, for Variables Predicting ED Visits (N=55,530 person-years; N=34,060 patients)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.16	1.04	<0.001	1.07	1.25
ARB[a]	1.18	1.10	0.08	0.98	1.41
Time (t+1)[b]	0.79	1.06	<0.001	0.70	0.88
Time (t+2)[b]	0.79	1.07	<0.01	0.68	0.90
Time (t+3)[b]	0.66	1.11	<0.001	0.54	0.82
Time (t+4)[b]	0.41	1.55	0.04	0.17	0.97
ACEI*time (t+1)[c]	0.99	1.08	0.89	0.85	1.15
ACEI*time (t+2)[c]	0.93	1.10	0.43	0.77	1.12
ACEI*time (t+3)[c]	0.95	1.16	0.74	0.72	1.27
ACEI*time (t+4)[c]	0.67	2.01	0.56	0.17	2.63
ARB*time (t+1)[d]	0.99	1.17	0.34	0.63	1.17
ARB*time (t+2)[d]	1.04	1.20	0.83	0.73	1.48
ARB*time (t+3)[d]	1.28	1.33	0.38	0.74	2.22
ARB*time (t+4)[d]	0.00	2.03	<0.001	0.00	0.00
Age	0.97	1.00	<0.001	0.96	0.97
Annual income $6,000-17,999[e]	1.46	1.05	<0.001	1.33	1.61
Annual income $18,000-34,999[e]	1.20	1.05	<0.001	1.09	1.32
Annual income ≥$35,000[e]	0.66	1.06	<0.001	0.59	0.73
Income missing[e]	0.50	1.14	<0.001	0.39	0.65
Urban/suburban[f]	1.48	1.04	<0.001	1.37	1.60
Never smoker[g]	0.75	1.04	<0.001	0.69	0.81
Ever smoker[g]	1.30	1.10	<0.01	1.09	1.56
Baseline microalbuminuria[h]	0.99	1.06	0.86	0.88	1.11
Microalbuminuria in follow-up[i]	0.89	1.05	0.02	0.81	0.98
Macroalbuminuria in follow-up[i]	0.99	1.07	0.90	0.87	1.13
HbA1c	1.04	1.01	<0.01	1.01	1.06
LDL	1.00	1.00	0.30	1.00	1.00
Triglycerides	1.00	1.00	0.13	1.00	1.00
History of MI[j]	1.17	1.10	0.08	0.98	1.40
History of stroke[k]	1.28	1.15	0.08	0.97	1.70
Family history of CVD[l]	0.97	1.21	0.89	0.67	1.42
CHF[m]	1.37	1.08	<0.001	1.18	1.58
Cardiac arrhythmias[n]	1.35	1.10	<0.01	1.13	1.61

Table 27 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Valvular disease[o]	1.21	1.22	0.34	0.82	1.80
Pulmonary circulation disorders[p]	1.93	1.47	0.09	0.91	4.08
Peripheral vascular disorders[q]	1.38	1.07	<0.001	1.21	1.58
Hypertension[r]	0.89	1.04	<0.01	0.83	0.96
Paralysis[s]	2.17	1.26	<0.01	1.38	3.41
Other neurological disorders[t]	1.96	1.18	<0.001	1.43	2.70
Chronic pulmonary disease[u]	1.52	1.06	<0.001	1.37	1.69
Hypothyroidism[v]	0.92	1.09	0.33	0.79	1.08
Diabetes complicated[w]	1.27	1.04	<0.001	1.16	1.38
Liver disease[x]	1.62	1.11	<0.001	1.31	1.99
Peptic ulcer disease[y]	0.86	1.21	0.43	0.60	1.25
AIDS[z]	1.93	1.31	0.01	1.14	3.27
Lymphoma[aa]	1.90	1.32	0.02	1.10	3.26
Metastatic cancer[bb]	2.08	1.27	<0.01	1.30	3.33
Solid tumor without metastasis[cc]	1.34	1.07	<0.001	1.16	1.54
Rheumatoid arthritis / collagen vascular diseases[dd]	1.31	1.18	0.11	0.94	1.82
Coagulopathy[ee]	1.30	1.16	0.08	0.97	1.74
Obesity[ff]	1.00	1.05	0.93	0.91	1.09
Weight loss[gg]	2.97	1.60	0.02	1.18	7.49
Fluid and electrolyte disorders[hh]	1.99	1.09	<0.001	1.70	2.33
Blood loss anemia[ii]	2.94	1.34	<0.001	1.65	5.22
Deficiency anemias[jj]	1.59	1.10	<0.001	1.33	1.90
Alcohol abuse[kk]	1.21	1.08	0.02	1.03	1.42
Drug abuse[ll]	1.81	1.10	<0.001	1.49	2.20
Psychoses[mm]	1.42	1.08	<0.001	1.24	1.64
Depression[nn]	1.20	1.06	<0.01	1.08	1.33
Cohort 2004[oo]	0.89	1.08	0.11	0.77	1.03
Cohort 2005[oo]	0.85	1.08	0.03	0.73	0.98
Cohort 2006[oo]	0.94	1.08	0.39	0.81	1.09
/lnalpha	1.63	0.03		1.58	1.69
alpha	5.11	0.15		4.83	5.40

Wald $\chi 2(62) = 2987.43$, $p<0.001$, log pseudolikelihood = -27400.19

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = Baseline macroalbuminuria, [i]Reference category = Normoalbuminuria in follow-up, [j] Reference category = No history of MI, [k] Reference category = No history of stroke, [l] Reference category = No family history of CVD, [m] Reference category = No CHF, [n] Reference category = No cardiac arrhythmias, [o] Reference category = No valvular disease, [p] Reference category = No pulmonary circulation disorders, [q] Reference category = No peripheral vascular disorders, [r] Reference category = Normotension, [s] Reference category = No paralysis, [t] Reference category = No other neurological disorders, [u] Reference category = No chronic pulmonary disease, [v] Reference category = No hypothyroidism, [w] Reference category = No diabetes complicated, [x] Reference category = No liver disease, [y] Reference category = No peptic ulcer disease, [z] Reference category = No AIDS, [aa] Reference category = No Lymphoma [bb] Reference category = No metastatic cancer, [cc] Reference category = No solid tumor without metastisis, [dd] Reference category = No rheumatoid arthritis/collagen vascular diseases, [ee] Reference category = No coagulopathy, [ff] Reference category = No obesity, [gg] Reference category = No weight loss, [hh] Reference category = No fluid and electrolyte disorders, [ii] Reference category = No blood loss anemia, [jj] Reference category = No deficiency anemias, [kk] Reference category = No alcohol abuse, [ll] Reference category = No drug abuse, [mm] Reference category = No psychoses, [nn] Reference category = No depression, [oo] Reference category = Cohort 2003

The negative binomial regression for variables predicting hospitalization on the next page (Table 28) found times (t+1), (t+2), (t+3), and (t+4), the interaction between ACEI monotherapy and time (t+4), the interaction between ARB monotherapy and time (t+4), annual income ≥$35,000, income missing, never smoker, LDL, and hypertension were associated with lower incidence rates of hospitalization ($p<0.017$ each). ACEI monotherapy, annual income $6,000-17,999, annual income $18,000-34,999, ever smoker, HbA1c, history of MI, history of stroke, family history of CVD, CHF, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, metastatic cancer, solid tumor without metastasis, coagulopathy, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression were associated with higher incidence rates of hospitalization ($p<0.017$ each). Noteworthy conditions are peripheral vascular disorders (IRR=1.72, (1.52-1.95)), coagulopathy (IRR=2.20, (1.64-2.96)), fluid and electrolyte disorders (IRR=2.97, (2.57-3.43)), and deficiency anemias (IRR=1.99, (1.69-2.34)). The model resulted in a Wald $\chi 2(62) = 7101.79$, $p<0.001$, log pseudolikelihood = -21164.46.

Table 28: Negative Binomial Regression Analysis, ACEI or ARB versus Neither, for Variables Predicting Hospitalizations (N=55,530 person-years; N=34,060 patients)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.19	0.05	<0.001	1.08	1.30
ARB[a]	1.22	0.12	0.05	1.00	1.48
Time (t+1)[b]	0.77	0.06	<0.001	0.67	0.89
Time (t+2)[b]	0.79	0.06	<0.01	0.67	0.92
Time (t+3)[b]	0.59	0.07	<0.001	0.47	0.75
Time (t+4)[b]	0.11	0.06	<0.001	0.04	0.33
ACEI*time (t+1)[c]	1.11	0.10	0.25	0.93	1.33
ACEI*time (t+2)[c]	0.91	0.10	0.38	0.74	1.12
ACEI*time (t+3)[c]	1.05	0.18	0.77	0.75	1.47
ACEI*time (t+4)[c]	0.00	0.00	<0.001	0.00	0.00
ARB*time (t+1)[d]	0.97	0.17	0.86	0.68	1.37
ARB*time (t+2)[d]	0.86	0.19	0.48	0.55	1.32
ARB*time (t+3)[d]	0.92	0.32	0.81	0.46	1.83
ARB*time (t+4)[d]	0.00	0.00	<0.001	0.00	0.00
Age	0.98	0.00	<0.001	0.97	0.98
Annual income $6,000-17,999[e]	1.58	0.08	<0.001	1.43	1.74
Annual income $18,000-34,999[e]	1.39	0.08	<0.001	1.25	1.55
Annual income ≥$35,000[e]	0.74	0.04	<0.001	0.65	0.83
Income missing[e]	0.53	0.08	<0.001	0.40	0.71
Urban/suburban[f]	1.04	0.05	0.35	0.96	1.13
Never smoker[g]	0.56	0.03	<0.001	0.51	0.61
Ever smoker[g]	1.49	0.13	<0.001	1.24	1.77
Baseline microalbuminuria[h]	0.96	0.06	0.58	0.85	1.10
Microalbuminuria in follow-up[i]	0.92	0.06	0.16	0.81	1.04
Macroalbuminuria in follow-up[i]	1.05	0.09	0.58	0.89	1.23
HbA1c	1.02	0.01	<0.01	1.01	1.04
LDL	1.00	0.00	<0.001	1.00	1.00
Triglycerides	1.00	0.00	0.09	1.00	1.00
History of MI[j]	1.61	0.15	<0.001	1.35	1.94
History of stroke[k]	1.75	0.23	<0.001	1.36	2.25
Family history of CVD[l]	1.67	0.29	<0.01	1.18	2.35
CHF[m]	1.70	0.12	<0.001	1.48	1.95
Cardiac arrhythmias[n]	1.15	0.11	0.16	0.95	1.39

Table 28 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Valvular disease[o]	0.89	0.22	0.65	0.54	1.46
Pulmonary circulation disorders[p]	1.24	0.38	0.47	0.69	2.25
Peripheral vascular disorders[q]	1.72	0.11	<0.001	1.52	1.95
Hypertension[r]	0.81	0.03	<0.001	0.74	0.88
Paralysis[s]	2.95	0.55	<0.001	2.04	4.25
Other neurological disorders[t]	2.42	0.50	<0.001	1.61	3.63
Chronic pulmonary disease[u]	1.42	0.08	<0.001	1.27	1.57
Hypothyroidism[v]	1.03	0.09	0.72	0.87	1.22
Diabetes complicated[w]	1.53	0.08	<0.001	1.39	1.68
Liver disease[x]	1.80	0.19	<0.001	1.47	2.21
Peptic ulcer disease[y]	1.01	0.18	0.95	0.71	1.43
AIDS[z]	1.61	0.48	0.11	0.90	2.88
Lymphoma[aa]	1.71	0.42	0.03	1.05	2.78
Metastatic cancer[bb]	3.79	1.13	<0.001	2.12	6.78
Solid tumor without metastasis[cc]	1.42	0.10	<0.001	1.24	1.63
Rheumatoid arthritis / collagen vascular diseases[dd]	1.47	0.29	0.05	1.00	2.15
Coagulopathy[ee]	2.20	0.33	<0.001	1.64	2.96
Obesity[ff]	0.96	0.05	0.42	0.87	1.06
Weight loss[gg]	5.62	2.53	<0.001	2.33	13.59
Fluid and electrolyte disorders[hh]	2.97	0.22	<0.001	2.57	3.43
Blood loss anemia[ii]	2.44	0.76	<0.01	1.32	4.50
Deficiency anemias[jj]	1.99	0.17	<0.001	1.69	2.34
Alcohol abuse[kk]	1.59	0.13	<0.001	1.35	1.87
Drug abuse[ll]	2.22	0.24	<0.001	1.79	2.75
Psychoses[mm]	1.50	0.11	<0.001	1.31	1.72
Depression[nn]	1.30	0.07	<0.001	1.17	1.44
Cohort 2004[oo]	1.06	0.09	0.53	0.89	1.26
Cohort 2005[oo]	0.95	0.09	0.54	0.79	1.13
Cohort 2006[oo]	0.96	0.09	0.69	0.81	1.15
/lnalpha	1.66	0.04		1.59	1.73
alpha	5.28	0.19		4.91	5.67

Waldχ2(62) = 7101.79, p<0.001, log pseudolikelihood = -21164.46

[a] Reference category = neither, [b] Reference category = time (t), [c] Reference category =ACEI* time (t), [d] Reference category = ARB*time (t), [e] Reference category = Annual income <$6,000, [f] Reference category = rural, [g] Reference category = Current smoker, [h] Reference category = Baseline macroalbuminuria, [i]Reference category = Normoalbuminuria in follow-up, [j] Reference category = No history of MI, [k] Reference category = No history of stroke, [l] Reference category = No family history of CVD, [m] Reference category = No CHF, [n] Reference category = No cardiac arrhythmias, [o] Reference category = No valvular disease, [p] Reference category = No pulmonary circulation disorders, [q] Reference category = No peripheral vascular disorders, [r] Reference category = Normotension, [s] Reference category = No paralysis, [t] Reference category = No other neurological disorders, [u] Reference category = No chronic pulmonary disease, [v] Reference category = No hypothyroidism, [w] Reference category = No diabetes complicated, [x] Reference category = No liver disease, [y] Reference category = No peptic ulcer disease, [z] Reference category = No AIDS, [aa] Reference category = No Lymphoma [bb] Reference category = No metastatic cancer, [cc] Reference category = No solid tumor without metastisis, [dd] Reference category = No rheumatoid arthritis/collagen vascular diseases, [ee] Reference category = No coagulopathy, [ff] Reference category = No obesity, [gg] Reference category = No weight loss, [hh] Reference category = No fluid and electrolyte disorders, [ii] Reference category = No blood loss anemia, [jj] Reference category = No deficiency anemias, [kk] Reference category = No alcohol abuse, [ll] Reference category = No drug abuse, [mm] Reference category = No psychoses, [nn] Reference category = No depression, [oo] Reference category = Cohort 2003

ACEI Monotherapy versus ARB Monotherapy

The next section shows results of ACEI monotherapy compared to ARB monotherapy, a subgroup analysis of the overall sample. As such, patients receiving neither therapy were excluded from the following analyses. Table 29 displays the results of the logistic regression of ACEI monotherapy's effect, compared to ARB monotherapy, on the development of ESRD. Several patient characteristics were simultaneously entered in the model to control for their effects.

The majority of diagnostic tests are not available because it is assumed that robust errors take care of problems related to leverage, influence, large residuals, normality, and heteroscedasticity. The diagnostic tests for logistic regression are Pregibon's Link Test and Hosmer and Lemeshow goodness-of-fit. If each has a non-significant p-value it indicates a good model. Pregibon's Link Test tests for model misspecification. A significant Pregibon's Link Test indicates that there is at least one more predictor that would significantly contribute to the model. This is usually an interaction variable. The approach is to iteratively add interaction variables, keeping those that are significant and contribute to a higher p-value of the Pregibon's Link Test. Hosmer and Lemeshow is a Pearson chi-square derived from the observed and expected frequency contingency table; the closer the predicted and observed values the better the fit. A non-significant p-value means that the predicted and observed values do not significantly differ. In this model, the Pregibon's Link Test was nonsignificant (p=0.88). Similarly, the Hosmer and Lemeshow goodness-of-fit was nonsignificant (p=0.55; $\chi^2(8) = 6.85$).

Time (t+4), valvular disease, pulmonary circulation disorders, other neurological disorders, peptic ulcer disease, AIDS, lymphoma, metastatic cancer, rheumatoid

arthritis/collagen vascular diseases, coagulopathy, weight loss, and blood loss anemia were all dropped because they predicted failure perfectly, meaning that all of their observations had a value of zero for ESRD (i.e., none of the patients with these characteristics developed ESRD). The interaction between ACEI and time (t+4) was dropped due to multicollinearity.

LDL was associated with lower odds of ESRD development; time (t+2), diabetes complicated, liver disease, fluid and electrolyte disorders, and deficiency anemias were associated with higher odds of ESRD development ($p<0.05$ each). Patients with diabetes complicated had 160% (51-347%) higher odds of developing ESRD. The model resulted in Wald χ^2 (38) = 366.39, Log pseudolikelihood = -462.91, $p<0.001$ and explained 15.76% of the variation in ESRD development. The model also had a 0.83 probability of correctly classifying a randomly selected pair of cases from those who did and those who did not develop ESRD.

Table 29: Logistic Regression Analysis, ACEI versus ARB, for Variables Predicting ESRD (N = 38,655 person-years; N= 18,451 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	0.82	0.62	0.79	0.19	3.60
Time (t+1)[b]	3.47	2.45	0.08	0.87	13.87
Time (t+2)[b]	5.31	4.11	0.03	1.16	24.19
Time (t+3)[b]	1.94	1.61	0.43	0.38	9.90
ACEI*time (t+1)[c]	0.23	0.19	0.08	0.05	1.16
ACEI*time (t+2)[c]	0.24	0.22	0.11	0.04	1.38
ACEI*time (t+3)[c]	0.86	0.91	0.89	0.11	6.79
Age	0.99	0.02	0.32	0.96	1.01
Annual income $6,000-17,999[d]	1.42	0.51	0.32	0.71	2.85
Annual income $18,000-34,999[d]	1.47	0.51	0.27	0.74	2.90
Annual income ≥$35,000[d]	0.70	0.31	0.42	0.29	1.69
Income missing[d]	0.47	0.53	0.50	0.05	4.27
Urban/suburban[e]	0.83	0.23	0.50	0.47	1.44
Never smoker[f]	0.47	1.24	0.20	0.15	1.47
Ever smoker[f]	0.80	0.37	0.43	0.45	1.41
HbA1c	0.91	0.09	0.30	0.75	1.09
LDL	0.99	0.00	<0.01	0.98	1.00
Triglycerides	1.00	0.00	0.82	1.00	1.00
CHF[g]	1.79	0.69	0.13	0.84	3.83
Cardiac arrhythmias[h]	1.48	0.88	0.51	0.46	4.72
Peripheral vascular disorders[i]	1.79	0.80	0.19	0.75	4.28
Hypertension[j]	0.61	0.18	0.09	0.34	1.09
Paralysis[k]	4.91	4.93	0.11	0.69	35.16
Chronic pulmonary disease[l]	0.78	0.33	0.55	0.34	1.77
Hypothyroidism[m]	0.80	0.45	0.69	0.27	2.38
Diabetes complicated[n]	2.60	0.72	<0.01	1.51	4.47
Liver disease[o]	3.68	2.06	0.02	1.23	11.02
Solid tumor without metastasis[p]	1.59	0.68	0.28	0.69	3.69
Obesity[q]	0.49	0.21	0.09	0.22	1.13
Fluid and electrolyte disorders[r]	6.14	2.20	<0.001	3.04	12.41
Deficiency anemias[s]	5.79	2.21	<0.001	2.74	12.23
Alcohol abuse[t]	1.43	0.79	0.52	0.48	4.22

Table 29 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Drug abuse[u]	0.72	0.78	0.76	0.09	6.03
Psychoses[v]	0.81	0.46	0.71	0.27	2.43
Depression[w]	1.57	0.53	0.18	0.82	3.02
Cohort 2004[x]	0.57	0.26	0.23	0.23	1.41
Cohort 2005[x]	0.69	0.33	0.44	0.27	1.77
Cohort 2006[x]	0.44	0.24	0.14	0.15	1.30

McFadden's Pseudo $R^2 = 0.16$
Wald χ^2 (38) = 366.39, Log pseudolikelihood = -462.91, $p<0.001$
Area under the ROC curve = 0.83

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural , [f] Reference category = Current smoker, [g] Reference category = No CHF, [h] Reference category = No cardiac arrhythmias, [i] Reference category = No peripheral vascular disorders, [j] Reference category = Normotension, [k] Reference category = No paralysis, [l] Reference category = No chronic pulmonary disease, [m] Reference category = No hypothyroidism, [n] Reference category = No diabetes complicated, [o] Reference category = No liver disease, [p] Reference category = No solid tumor without metastasis, [q] Reference category = No obesity, [r] Reference category = No Fluid and electrolyte disorders, [s] Reference category = No deficiency anemias, [t] Reference category = No alcohol abuse, [u] Reference category = No drug abuse, [v] Reference category = No psychoses, [w] Reference category = No depression, [x] Reference category = Cohort 2003

The original model variables for logistic regression resulted in a significant Pregibon's Link Test (p=0.005). Age squared, income divided by 100,000, the interaction between HbA1c and LDL, the interaction between HbA1c and triglycerides, the interaction between LDL and triglycerides, the interaction between albuminuria and HbA1c, the interaction between albuminuria and triglycerides, the interaction between albuminuria and LDL, the interaction between age and triglycerides, the interaction between age and LDL, and the interaction between age and HbA1c were iteratively added to the model in an effort to have the model without a significant Pregibon's Link Test. Of the variables sequentially added, only those that had a significant p-value when added to the model and those that resulted in a larger p-value for Pregibon's Link Test were actually retained. Since it still resulted in a significant Pregibon's Link Test, indicating model misspecification, the Box-Tidwell transformation was attempted next. Box-Tidwell uses a maximum likelihood estimate to identify variable transformations to find better model fit. As none of the transformations would be interpretable, this approach was discarded. The final model is described on the next page. As previously mentioned, it still resulted in a significant Pregibon's Link Test (p=0.01), but did have a nonsignificant Hosmer and Lemeshow ($p = 0.43$; $\chi^2(8) = 8.09$). A nonsignificant Hosmer and Lemeshow indicates lack of a systematic pattern of bias.

Income missing was dropped due to multicollinearity. Age squared, never smoker, and ever smoker were associated with lower odds of IVDE occurrence; age, history of MI, history of stroke, CHF, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, fluid and electrolyte disorders, and deficiency anemias were associated with higher odds of IVDE occurrence ($p<0.05$ each).

In particular, patients who never smoked were associated with 64% (50-74%) lower odds of suffering an IVDE, patients with history of stroke were associated with 219% (117-368%) higher odds of an IVDE occurrence, patients with peripheral vascular disorders were associated with 197% (139-270%) higher odds of having an IVDE, and patients with fluid and electrolyte disorders were associated with 97% (31-197%) higher odds of acquiring an IVDE. The model resulted in a Wald $\chi^2(61) = 421.73$, Log pseudolikelihood = -4028.29, $p<0.001$ and explained 5.88% of the variation in IVDE occurrence. It also had a 0.68 probability of correctly classifying a randomly selected pair of cases from those who did and did not suffer an IVDE.

Table 30: Logistic Regression Analysis, ACEI versus ARB, for Variables Predicting IVDE (N = 29,400 person-years; N = 17,753 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.12	0.18	0.48	0.82	1.53
Time (t+1) [b]	1.07	0.19	0.72	0.75	1.52
Time (t+2) [b]	0.93	0.21	0.75	0.61	1.44
Time (t+3) [b]	1.00	0.26	0.99	0.61	1.65
Time (t+4) [b]	1.60	0.96	0.43	0.50	5.18
ACEI*time (t+1) [c]	0.76	0.16	0.19	0.51	1.14
ACEI*time (t+2) [c]	1.20	0.30	0.45	0.75	1.94
ACEI*time (t+3) [c]	0.89	0.28	0.71	0.48	1.66
Age	1.19	0.06	<0.001	1.08	1.31
Age squared	1.00	0.00	<0.01	1.00	1.00
Annual income $6,000-17,999[d]	1.03	0.12	0.83	0.81	1.29
Annual income $18,000-34,999[d]	1.21	0.14	0.10	0.97	1.53
Annual income ≥$35,000[d]	1.14	0.17	0.40	0.84	1.53
Annual income/100,000	0.84	0.08	0.08	0.69	1.02
Urban/suburban[e]	1.01	0.09	0.88	0.86	1.20
Never smoker[f]	0.36	0.46	<0.001	0.26	0.50
Ever smoker[f]	0.59	0.16	<0.001	0.49	0.70
Baseline microalbuminuria[g]	0.99	0.12	0.95	0.79	1.25
Microalbuminuria in follow-up[h]	0.61	0.18	0.09	0.35	1.07
Macroalbuminuria in follow-up[h]	0.51	0.29	0.23	0.17	1.53
HbA1c	0.87	0.07	0.09	0.74	1.02
Albuminuria*HbA1c	1.06	0.04	0.13	0.98	1.14
LDL	1.00	0.01	0.71	0.98	1.02
HbA1c*LDL	1.00	0.00	0.59	1.00	1.00
Triglycerides	1.00	0.00	0.41	1.00	1.00
LDL* triglycerides	1.00	0.00	0.06	1.00	1.00
Albuminuria* triglycerides	1.00	0.00	0.38	1.00	1.00
Age*LDL	1.00	0.00	0.22	1.00	1.00
History of MI[i]	2.30	0.38	<0.001	1.67	3.17
History of stroke[j]	3.19	0.63	<0.001	2.17	4.68
Family history of CVD[k]	1.25	0.41	0.50	0.66	2.37

Table 30 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
CHF[l]	1.42	0.22	0.02	1.05	1.91
Cardiac arrhythmias[m]	1.25	0.21	0.18	0.91	1.72
Valvular disease[n]	1.56	0.65	0.29	0.69	3.52
Pulmonary circulation disorders[o]	3.57	1.89	0.02	1.26	10.07
Peripheral vascular disorders[p]	2.97	0.33	<0.001	2.39	3.70
Hypertension[q]	1.03	0.10	0.80	0.84	1.25
Paralysis[r]	0.65	0.51	0.58	0.14	2.98
Other neurological disorders[s]	1.16	0.48	0.72	0.51	2.62
Chronic pulmonary disease[t]	1.39	0.16	<0.01	1.11	1.74
Hypothyroidism[u]	1.04	0.21	0.86	0.70	1.53
Diabetes complicated[v]	0.95	0.10	0.60	0.77	1.17
Liver disease[w]	0.86	0.27	0.64	0.47	1.59
Peptic ulcer disease[x]	0.65	0.29	0.33	0.27	1.55
AIDS[y]	2.28	2.17	0.39	0.35	14.77
Lymphoma[z]	0.82	0.62	0.79	0.19	3.58
Metastatic cancer[aa]	0.70	0.79	0.75	0.08	6.46
Solid tumor without metastasis[bb]	0.96	0.15	0.79	0.71	1.30
Rheumatoid arthritis/collagen vascular diseases[cc]	1.05	0.40	0.90	0.50	2.21
Coagulopathy[dd]	1.00	0.39	1.00	0.47	2.14
Obesity[ee]	1.12	0.11	0.24	0.92	1.37
Fluid and electrolyte disorders[ff]	1.97	0.41	<0.01	1.31	2.97
Blood loss anemia[gg]	1.80	1.31	0.42	0.43	7.51
Deficiency anemias[hh]	1.55	0.28	0.02	1.09	2.21
Alcohol abuse[ii]	1.03	0.22	0.90	0.67	1.57
Drug abuse[jj]	1.22	0.43	0.57	0.61	2.43
Psychoses[kk]	0.86	0.18	0.47	0.58	1.29
Depression[ll]	1.20	0.15	0.15	0.94	1.53
Cohort 2004[mm]	0.88	0.16	0.49	0.62	1.26
Cohort 2005[mm]	0.84	0.16	0.34	0.58	1.20
Cohort 2006[mm]	0.88	0.17	0.51	0.61	1.28

McFadden's Pseudo $R^2 = 0.06$
Wald $\chi^2(61) = 421.73$, Log pseudolikelihood = -4028.29, $p<0.001$

Area under the ROC curve = 0.68

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h] Reference category = Normoalbuminuria in follow-up, [i] Reference category No history of MI, [j] Reference category = No history of stroke, [k] Reference category = No family history of CVD, [l] Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] Reference category = No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No fluid and electrolyte disorders, [gg] Reference category = No blood loss anemias, [hh] Reference category = No deficiency anemias, [ii] Reference category = No alcohol abuse, [jj] Reference category = No drug abuse, [kk] Reference category = No psychoses, [ll] Reference category = No depression, [mm] Reference category = Cohort 2003

Table 31 displays the results of the logistic regression of ACEI monotherapy's effect, compared to ARB monotherapy on all-cause mortality. Several patient characteristics were simultaneously entered in the model to quantify their effects.

Again, because we have robust standard errors, there are limited available diagnostic tests. The model resulted in a nonsignificant Pregibon's Link Test (p=0.38). It also had a nonsignificant Hosmer and Lemeshow goodness-of-fit (p=0.08, $\chi^2(8) = 13.93$).

Never smoker, family history of CVD, valvular disease, pulmonary circulation disorders, paralysis, peptic ulcer disease, AIDS, metastatic cancer, rheumatoid arthritis/collagen vascular diseases, weight loss, and blood loss anemia were dropped from the model because observations with each of these characteristics did not experience all-cause mortality. The interaction between ACEI and time (t+4) was dropped due to multicollinearity. The interactions between ACEI monotherapy and times (t+1) and (t+2) were associated with lower odds of all-cause mortality ($p<0.05$ each). Higher odds of all-cause mortality were associated with times (t+1), (t+2), and (t+3), age, annual income $6,000-17,999, history of MI, CHF, peripheral vascular disorders, chronic pulmonary disease, lymphoma, and cohorts 2004, 2005, and 2006 ($p<0.05$ each). (Note the large odds ratios and robust standard errors for cohorts 2004, 2005, and 2006, a sort of warning to be heeded when interpreting results of a logistic regression.) Worth mentioning, patients with peripheral vascular disorders had OR=2.15, (1.27-3.63) whereas patients with chronic pulmonary disease had OR=1.95, (1.22-3.11). Because the Wald test for time (t+4) cannot be reported as it is dependent on the (robust) standard error for that variable and the Wald statistic for the model is dependent upon the Wald test for the

variable, there is no Wald statistic (or associated p-value) for the model. However, the model did explain 8.76% of the variance in all-cause mortality. It also had a 0.77 probability of correctly classifying a randomly selected pair of cases from those who did and did not die.

Table 31: Logistic Regression Analysis, ACEI versus ARB, for Variables Predicting All-cause Mortality (N= 28,386 person-years; N=17,121 patients)

	Odds Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	1.50	0.92	0.51	0.45	4.99
Time (t+1) [b]	4.77	2.99	0.01	1.39	16.29
Time (t+2) [b]	7.30	4.68	<0.01	2.08	25.66
Time (t+3) [b]	8.38	6.06	<0.01	2.03	34.58
Time (t+4) [b]	7.35×10^7	.	.	.	.
ACEI*time (t+1) [c]	0.22	0.16	0.03	0.06	0.88
ACEI*time (t+2) [c]	0.22	0.16	0.04	0.05	0.91
ACEI*time (t+3) [c]	0.41	0.34	0.28	0.08	2.10
Age	1.03	0.01	0.02	1.00	1.05
Annual income $6,000-17,999[d]	1.91	0.60	0.04	1.03	3.53
Annual income $18,000-34,999[d]	1.82	0.57	0.05	0.99	3.34
Annual income ≥$35,000[d]	1.66	0.53	0.12	0.88	3.10
Income missing[d]	0.77	0.58	0.73	0.17	3.40
Urban/suburban[e]	1.29	0.27	0.22	0.85	1.95
Ever smoker[f]	0.89	0.29	0.65	0.54	1.47
Baseline microalbuminuria[g]	0.94	0.32	0.82	0.52	1.67
Microalbuminuria in follow-up[h]	1.22	0.33	0.46	0.72	2.06
Macroalbuminuria in follow-up[h]	1.27	0.48	0.53	0.60	2.65
HbA1c	1.00	0.01	0.76	0.97	1.02
LDL	1.00	0.00	0.98	0.99	1.01
Triglycerides	1.00	0.00	0.68	1.00	1.00
History of MI[i]	2.37	0.92	0.03	1.11	5.06
History of stroke[j]	1.88	0.95	0.22	0.69	5.08
CHF[k]	2.09	0.65	0.02	1.13	3.84
Cardiac arrhythmias[l]	1.78	0.54	0.06	0.98	3.23
Peripheral vascular disorders[m]	2.15	0.58	<0.01	1.27	3.63
Hypertension[n]	0.67	0.14	0.06	0.44	1.02
Other neurological disorders[o]	0.95	0.97	0.96	0.13	7.01
Chronic pulmonary disease[p]	1.95	0.47	<0.01	1.22	3.11
Hypothyroidism[q]	1.67	0.57	0.13	0.86	3.24

Table 31 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Diabetes complicated[r]	1.03	0.26	0.90	0.63	1.69
Liver disease disease[s]	0.89	0.95	0.92	0.11	7.12
Lymphoma[t]	6.52	5.19	0.02	1.37	31.02
Solid tumor without metastasis[u]	1.44	0.45	0.24	0.78	2.65
Coagulopathy[v]	0.61	0.61	0.62	0.09	4.30
Obesity[w]	1.13	0.28	0.62	0.70	1.83
Fluid and electrolyte disorders[x]	0.94	0.70	0.93	0.22	4.06
Deficiency anemias[y]	0.86	0.46	0.78	0.30	2.48
Alcohol abuse[z]	1.75	0.87	0.26	0.67	4.61
Drug abuse[aa]	0.73	0.76	0.76	0.10	5.56
Psychoses[bb]	0.81	0.44	0.70	0.28	2.34
Depression[cc]	1.26	0.40	0.46	0.68	2.34
Cohort 2004[dd]	4.78×10^6	5.73×10^6	<0.001	4.57×10^5	5.01×10^7
Cohort 2005[dd]	5.89×10^6	6.98×10^6	<0.001	5.78×10^5	6.01×10^7
Cohort 2006[dd]	5.75×10^6	6.73×10^6	<0.001	5.79×10^5	5.70×10^7

McFadden's Pseudo $R^2 = 0.09$
Wald χ^2 (and its p-value) not reported, Log pseudolikelihood = -697.75
Area under the ROC curve = 0.77

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h] Reference category = Normoalbuminuria in follow-up, [i] Reference category No history of MI, [j] Reference category = No history of stroke, [k] Reference category = No CHF, [l] Reference category = No cardiac arrhythmias, [m] Reference category = No peripheral vascular disorders, [n] Reference category = Normotension, [o] Reference category = No other neurological disorders, [p] Reference category = No chronic pulmonary disease, [q] Reference category = No hypothyroidism, [r] Reference category = No diabetes complicated, [s] Reference category = No liver disease, [t] Reference category = No lymphoma, [u] Reference category = No solid tumor without metastasis, [v] Reference category = No coagulopathy, w Reference category = No obesity, [x] Reference category = No fluid and electrolyte disorders, [y] Reference category = No deficiency anemias, [z] Reference category = No alcohol abuse, [aa] Reference category = No drug abuse, [bb] Reference category = No psychoses, [cc] Reference category = No depression, [dd] Reference category = Cohort 2003

The negative binomial regression on the next page resulted in the interaction between ACEI and time (t+4) being dropped due to multicollinearity. Variables associated with lower incidence rates of outpatient visits were ACEI monotherapy, times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, income missing, never smoker, microalbuminuria in follow-up, LDL, and cohorts 2005 and 2006; variables associated with higher incidence rates of outpatient visits were the interaction between ACEI monotherapy and times (t+1), (t+2), and (t+3), annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, ever smoker, triglycerides, history of stroke, CHF, cardiac arrhythmias, valvular disease, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, obesity, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression ($p<0.05$ each). Closer inspection reveals patients with cardiac arrhythmias were associated with 45% (37-53%) more outpatient visits, patients with metastatic cancer were associated with 109% (60-172%) more outpatient visits, and patients with drug abuse were associated with 54% (36-75%) more outpatient visits. The model resulted in Wald $\chi^2(56) = 4943.70$, $p<0.001$, log pseudolikelihood = -106487.71.

Table 32: Negative Binomial Regression Analysis, ACEI versus ARB, for Variables Predicting Outpatient Visits (N=30,422 person-years; N=18,340 patients)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	0.96	0.02	0.02	0.92	0.99
Time (t+1)[b]	0.65	0.02	<0.001	0.62	0.69
Time (t+2)[b]	0.64	0.03	<0.001	0.59	0.69
Time (t+3)[b]	0.49	0.02	<0.001	0.45	0.53
Time (t+4)[b]	0.20	0.02	<0.001	0.17	0.25
ACEI*time (t+1)[c]	1.28	0.04	<0.001	1.21	1.35
ACEI*time (t+2)[c]	1.25	0.05	<0.001	1.15	1.36
ACEI*time (t+3)[c]	1.46	0.08	<0.001	1.32	1.61
Age	0.99	0.00	<0.001	0.99	0.99
Annual income $6,000-17,999[d]	1.20	0.02	<0.001	1.16	1.24
Annual income $18,000-34,999[d]	1.14	0.02	<0.001	1.10	1.19
Annual income ≥$35,000[d]	0.91	0.02	<0.001	0.88	0.94
Income missing[d]	0.77	0.02	<0.001	0.72	0.81
Urban/suburban[e]	1.18	0.02	<0.001	1.15	1.21
Never smoker[f]	0.88	0.01	<0.001	0.85	0.91
Ever smoker[f]	1.09	0.04	0.02	1.02	1.17
Baseline microalbuminuria[g]	0.99	0.02	0.56	0.95	1.03
Microalbuminuria in follow-up[h]	0.95	0.02	<0.01	0.92	0.98
Macroalbuminuria in follow-up[h]	0.97	0.02	0.22	0.93	1.02
HbA1c	1.00	0.00	0.06	1.00	1.01
LDL	1.00	0.00	<0.001	1.00	1.00
Triglycerides	1.00	0.00	0.05	1.00	1.00
History of MI[i]	0.99	0.03	0.65	0.92	1.05
History of stroke[j]	1.15	0.05	<0.01	1.05	1.25
Family history of CVD[k]	1.16	0.08	0.03	1.02	1.32
CHF[l]	1.17	0.03	<0.001	1.12	1.23
Cardiac arrhythmias[m]	1.45	0.04	<0.001	1.37	1.53
Valvular disease[n]	1.31	0.09	<0.001	1.15	1.49
Pulmonary circulation disorders[o]	1.23	0.14	0.07	0.98	1.53
Peripheral vascular disorder[p]	1.18	0.03	<0.001	1.12	1.23
Hypertension[q]	0.97	0.02	0.09	0.94	1.00

Table 32 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Paralysis[r]	1.31	0.16	0.03	1.03	1.67
Other neurological disorders[s]	1.21	0.08	<0.01	1.06	1.38
Chronic pulmonary disease[t]	1.11	0.02	<0.001	1.07	1.16
Hypothyroidism[u]	1.02	0.03	0.44	0.97	1.08
Diabetes complicated[v]	1.20	0.02	<0.001	1.16	1.24
Liver disease[w]	1.32	0.07	<0.001	1.20	1.47
Peptic ulcer disease[x]	0.96	0.06	0.51	0.86	1.08
AIDS[y]	1.41	0.16	<0.01	1.13	1.75
Lymphoma[z]	1.27	0.13	0.02	1.03	1.55
Metastatic cancer[aa]	2.09	0.28	<0.001	1.60	2.72
Solid tumor without metastasis[bb]	1.09	0.03	<0.001	1.04	1.14
Rheumatoid arthritis / collagen vascular diseases[cc]	1.12	0.08	0.12	0.97	1.29
Coagulopathy[dd]	1.39	0.07	<0.001	1.26	1.54
Obesity[ee]	1.04	0.02	0.02	1.01	1.07
Weight loss[ff]	1.14	0.20	0.47	0.80	1.61
Fluid and electrolyte disorders[gg]	1.30	0.06	<0.001	1.20	1.42
Blood loss anemia[hh]	1.28	0.15	0.03	1.02	1.61
Deficiency anemias[ii]	1.21	0.04	<0.001	1.14	1.30
Alcohol abuse[jj]	1.19	0.05	<0.001	1.10	1.28
Drug abuse[kk]	1.54	0.10	<0.001	1.36	1.75
Psychoses[ll]	1.51	0.05	<0.001	1.41	1.61
Depression[mm]	1.24	0.02	<0.001	1.19	1.28
Cohort 2004[nn]	0.95	0.03	0.06	0.90	1.00
Cohort 2005[nn]	0.93	0.03	<0.01	0.88	0.98
Cohort 2006[nn]	0.92	0.03	<0.01	0.87	0.97
/lnalpha	-0.91	0.01		-0.94	-0.88
alpha	0.40	0.01		0.39	0.41

Wald $\chi^2(56) = 4943.70$, $p<0.001$, log pseudolikelihood = -106487.71

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*time t, [d] Reference category = Annual income <$6000, [e] Reference category =

rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h] Reference category = Normoalbuminuria in follow-up, [i] Reference category No history of MI, [j] Reference category = No history of stroke, [k] Reference category = No family history of CVD, [l] Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] Reference category = No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = No fluid and electrolyte disorders, [hh] Reference category = No blood loss anemias, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

For the negative binomial regression model predicting ED visits (Table 33), times (t+1), (t+3), and (t+4), age, annual income ≥$35,000, income missing, never smoker, and hypertension were associated with lower incidence rates of ED visits ($p<0.05$ each). Annual income $6,000-17,999, urban/suburban living, ever smoker, history of MI, CHF, cardiac arrhythmias, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, metastatic cancer, solid tumor without metastasis, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression were associated with higher incidence rates of ED visits ($p<0.05$ each). More specifically, patients with annual income ≥$35,000 were associated with 35% (26-44%) fewer ED visits whereas patients with CHF were associated with 60% (34-91%) more ED visits, patients with chronic pulmonary disease were associated with 55% (35-78%) more ED visits, and patients with fluid and electrolyte disorders were associated with 98% (58-148%) more ED visits. The negative binomial regression for ED visits resulted in a Wald $\chi 2(56) = 1191.52$, $p<0.001$, log pseudolikelihood = -15420.78.

Table 33: Negative Binomial Regression Analysis, ACEI versus ARB, for Variables Predicting ED Visits (N=30,422 person-years; N=18,340 patients)

	Incidence Rate Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	0.99	0.09	0.88	0.83	1.18
Time (t+1)[b]	0.67	0.08	<0.001	0.53	0.84
Time (t+2)[b]	0.82	0.10	0.09	0.64	1.03
Time (t+3)[b]	0.59	0.10	<0.01	0.43	0.80
Time (t+4)[b]	0.06	0.06	<0.01	0.01	0.48
ACEI*time (t+1)[c]	1.15	0.15	0.26	0.90	1.48
ACEI*time (t+2)[c]	0.89	0.12	0.39	0.68	1.16
ACEI*time (t+3)[c]	1.07	0.22	0.73	0.72	1.60
Age	0.97	0.00	<0.001	0.96	0.97
Annual income $6,000-17,999[d]	1.40	0.09	<0.001	1.24	1.59
Annual income $18,000-34,999[d]	1.11	0.07	0.12	0.97	1.25
Annual income ≥$35,000[d]	0.65	0.05	<0.001	0.56	0.74
Income missing[d]	0.60	0.10	<0.01	0.44	0.82
Urban/suburban[e]	1.56	0.08	<0.001	1.41	1.72
Never smoker[f]	0.75	0.04	<0.001	0.68	0.83
Ever smoker[f]	1.36	0.16	0.01	1.07	1.72
Baseline microalbuminuria[g]	0.95	0.07	0.46	0.82	1.09
Microalbuminuria in follow-up[h]	0.96	0.06	0.53	0.85	1.09
Macroalbuminuria in follow-up[h]	1.05	0.09	0.59	0.88	1.24
HbA1c	1.02	0.01	0.10	1.00	1.03
LDL	1.00	0.00	0.64	1.00	1.00
Triglycerides	1.00	0.00	0.95	1.00	1.00
History of MI[i]	1.25	0.14	<0.05	1.00	1.56
History of stroke[j]	1.27	0.19	0.12	0.94	1.69
Family history of CVD[k]	0.97	0.24	0.89	0.59	1.58
CHF[l]	1.60	0.15	<0.001	1.34	1.91
Cardiac arrhythmias[m]	1.41	0.16	<0.01	1.13	1.75
Valvular disease[n]	1.19	0.29	0.49	0.73	1.92
Pulmonary circulation disorders[o]	2.20	1.18	0.14	0.77	6.27
Peripheral vascular disorder[p]	1.31	0.11	<0.01	1.11	1.54

Table 33 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Hypertension[q]	0.88	0.05	0.02	0.79	0.98
Paralysis[r]	2.73	0.89	<0.01	1.44	5.19
Other neurological disorders[s]	1.65	0.39	0.03	1.04	2.63
Chronic pulmonary disease[t]	1.55	0.11	<0.001	1.35	1.78
Hypothyroidism[u]	0.93	0.11	0.55	0.75	1.17
Diabetes complicated[v]	1.27	0.07	<0.001	1.14	1.41
Liver disease[w]	1.67	0.24	<0.001	1.26	2.22
Peptic ulcer disease[x]	0.80	0.21	0.39	0.47	1.34
AIDS[y]	0.41	0.31	0.24	0.09	1.81
Lymphoma[z]	2.18	0.97	0.08	0.91	5.22
Metastatic cancer[aa]	2.81	0.90	<0.01	1.51	5.26
Solid tumor without metastasis[bb]	1.38	0.14	<0.01	1.13	1.68
Rheumatoid arthritis / collagen vascular diseases[cc]	1.37	0.32	0.17	0.87	2.16
Coagulopathy[dd]	1.08	0.22	0.70	0.73	1.60
Obesity[ee]	1.00	0.05	0.98	0.90	1.11
Weight loss[ff]	3.44	1.95	0.03	1.13	10.45
Fluid and electrolyte disorders[gg]	1.98	0.23	<0.001	1.58	2.48
Blood loss anemia[hh]	2.69	1.12	0.02	1.19	6.09
Deficiency anemias[ii]	1.47	0.17	<0.01	1.18	1.85
Alcohol abuse[jj]	1.13	0.12	0.27	0.91	1.40
Drug abuse[kk]	1.72	0.25	<0.001	1.30	2.27
Psychoses[ll]	1.49	0.15	<0.001	1.23	1.81
Depression[mm]	1.26	0.09	<0.01	1.10	1.44
Cohort 2004[nn]	0.81	0.09	0.06	0.65	1.01
Cohort 2005[nn]	0.80	0.09	0.05	0.64	1.00
Cohort 2006[nn]	0.85	0.10	0.16	0.68	1.07
/lnalpha	1.58	0.04		1.51	1.65
alpha	4.84	0.17		4.51	5.20

Wald $\chi 2(56) = 1191.52$, $p<0.001$, log pseudolikelihood = -15420.78

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h] Reference category = Normoalbuminuria in follow-up, [i] Reference category No history of MI, [j] Reference category = No history of stroke, [k] Reference category = No family history of CVD, [l] Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] Reference category = No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = No fluid and electrolyte disorders, [hh] Reference category = No blood loss anemias, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

For the negative binomial regression predicting hospitalizations (Table 34), lower incidence rates of hospitalization were associated with times (t+1), (t+3), and (t+4), annual income ≥$35,000, age, income missing, never smoker, LDL, hypertension, and cohort 2005 ($p<0.05$ each). Higher incidence rates of hospitalization were associated with annual income $6,000-17,999, annual income $18,000-34,999, ever smoker, HbA1c, history of MI, history of stroke, family history of CVD, CHF, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, lymphoma, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, weight loss, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression ($p<0.05$ each). Of note, patients with history of MI were associated with 88% (52-133%) more hospitalizations, patients with CHF were associated with 71% (44-103%) more hospitalizations, patients with peripheral vascular disorders were associated with 70% (43-102%) more hospitalizations, and patients with fluid and electrolyte disorders were associated with 170% (121-229%) more hospitalizations. The negative binomial resulted in a Wald $\chi 2(56)=1524.66$, $p<0.001$, log pseudolikelihood = -12080.93.

Table 34: Negative Binomial Regression Model, ACEI versus ARB, for Variables Predicting Hospitalization (N = 30,422 person years; N= 18,340 patients)

	Incidence Rate Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	0.97	0.09	0.75	0.81	1.17
Time (t+1)[b]	0.74	0.09	0.01	0.58	0.94
Time (t+2)[b]	0.78	0.10	0.06	0.59	1.01
Time (t+3)[b]	0.48	0.09	<0.001	0.33	0.68
Time (t+4)[b]	0.15	0.08	<0.001	0.05	0.45
ACEI*time (t+1)[c]	1.12	0.16	0.43	0.85	1.47
ACEI*time (t+2)[c]	0.91	0.15	0.54	0.66	1.24
ACEI*time (t+3)[c]	1.00	0.24	0.99	0.63	1.58
Age	0.98	0.00	<0.001	0.97	0.98
Annual income $6,000-17,999[d]	1.56	0.10	<0.001	1.37	1.78
Annual income $18,000-34,999[d]	1.34	0.09	<0.001	1.17	1.53
Annual income ≥$35,000[d]	0.76	0.06	<0.001	0.66	0.89
Income missing[d]	0.60	0.12	<0.01	0.41	0.88
Urban/suburban[e]	1.00	0.05	0.98	0.90	1.11
Never smoker[f]	0.56	0.03	<0.001	0.50	0.62
Ever smoker[f]	1.52	0.18	<0.001	1.20	1.91
Baseline microalbuminuria[g]	0.93	0.08	0.42	0.79	1.10
Microalbuminuria in follow-up[h]	0.99	0.07	0.87	0.85	1.14
Macroalbuminuria in follow-up[h]	1.00	0.10	0.97	0.83	1.22
HbA1c	1.02	0.01	0.02	1.00	1.03
LDL	1.00	0.00	<0.001	0.99	1.00
Triglycerides	1.00	0.00	0.75	1.00	1.00
History of MI[i]	1.88	0.21	<0.001	1.52	2.33
History of stroke[j]	1.54	0.25	<0.01	1.12	2.12
Family history of CVD[k]	1.83	0.39	<0.01	1.21	2.78
CHF[l]	1.71	0.15	<0.001	1.44	2.03
Cardiac arrhythmias[m]	1.28	0.17	0.05	1.00	1.65
Valvular disease[n]	1.11	0.37	0.75	0.58	2.14
Pulmonary circulation disorders[o]	1.11	0.34	0.74	0.61	2.00

Table 34 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Peripheral vascular disorder[p]	1.70	0.15	<0.001	1.43	2.02
Hypertension[q]	0.74	0.04	<0.001	0.67	0.83
Paralysis[r]	2.04	0.61	0.02	1.13	3.68
Other neurological disorders[s]	2.60	0.91	<0.01	1.31	5.15
Chronic pulmonary disease[t]	1.42	0.10	<0.001	1.24	1.62
Hypothyroidism[u]	0.98	0.11	0.84	0.78	1.23
Diabetes complicated[v]	1.41	0.09	<0.001	1.26	1.59
Liver disease[w]	1.89	0.24	<0.001	1.46	2.43
Peptic ulcer disease[x]	0.96	0.24	0.86	0.59	1.56
AIDS[y]	0.64	0.26	0.28	0.29	1.42
Lymphoma[z]	2.55	0.87	<0.01	1.31	4.98
Metastatic cancer[aa]	2.37	1.13	0.07	0.93	6.04
Solid tumor without metastasis[bb]	1.35	0.13	<0.01	1.12	1.63
Rheumatoid arthritis / collagen vascular diseases[cc]	1.82	0.45	0.02	1.12	2.93
Coagulopathy[dd]	1.57	0.29	0.01	1.10	2.25
Obesity[ee]	1.03	0.06	0.65	0.92	1.15
Weight loss[ff]	3.05	0.89	<0.001	1.72	5.40
Fluid and electrolyte disorders[gg]	2.70	0.27	<0.001	2.21	3.29
Blood loss anemia[hh]	1.57	0.55	0.20	0.79	3.12
Deficiency anemias[ii]	1.91	0.23	<0.001	1.51	2.42
Alcohol abuse[jj]	1.58	0.18	<0.001	1.27	1.96
Drug abuse[kk]	1.95	0.29	<0.001	1.45	2.61
Psychoses[ll]	1.47	0.14	<0.001	1.22	1.77
Depression[mm]	1.27	0.08	<0.001	1.12	1.44
Cohort 2004[nn]	0.88	0.10	0.25	0.71	1.09
Cohort 2005[nn]	0.78	0.09	0.03	0.62	0.97
Cohort 2006[nn]	0.81	0.09	0.07	0.65	1.02
/lnalpha	1.56	0.05		1.47	1.65
alpha	4.76	0.23		4.34	5.23

Wald $\chi 2(56)=1524.66$, $p<0.001$, log pseudolikelihood = -12080.93

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h] Reference category = Normoalbuminuria in follow-up, [i] Reference category No history of MI, [j] Reference category = No history of stroke, [k] Reference category = No family history of CVD, [l] Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] Reference category = No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = No fluid and electrolyte disorders, [hh] Reference category = No blood loss anemias, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

ACEI Monotherapy versus ARB Monotherapy, PSA

The following Table shows the differences between groups before and after nearest-neighbor matching with propensity score obtained from the first-stage PSA along with percent reduction in bias achieved for ESRD, our primary question. The bias "is defined as the difference of the mean values of the treatment group and the (not matched/matched) non treatment group, divided by the square root of the average sample variance in the treatment group and the not matched non treatment group."[200] As can be seen with the percent reduction in bias in Table 35, comparing the difference in means of each variable between drug therapies, fourteen between group differences were significant before matching with propensity scores that are not with nearest-neighbor matching, seven between group differences became less significant with nearest-neighbor matching, one between group difference became more significant with nearest-neighbor matching, and one between group difference that was not significant before nearest-neighbor matching became significant with nearest-neighbor matching. (Note this tests all matched individuals between ACEI and ARB monotherapies.) Achieving balanced groups at baseline means we do not have a systematic mechanism to create error thus allowing our results to be interpreted as "causal" rather than "associated with." The subsequent table (Table 36) indicates the improved amount of explanation of treatment selection achieved with nearest-neighbor matching compared to not matching: about 2.5 times more explanation occurred with matching than not.

Table 35: Between Group Differences of Baseline Characteristics Before and After Matching on Propensity Score

Variable	**Sample**	**Mean, Treated (ACEI) Control (ARB)**	**% bias**	**% reduction |bias|**	**p**
Age	Unmatched	63.41 65.78	-22.70		<0.001
	Matched	63.30 65.47	-20.80	8.30	<0.001
Age squared	Unmatched	4133.60 4431.80	-22.00		<0.001
	Matched	4117.70 4392.20	-20.30	7.90	<0.001
Income/100,000	Unmatched	0.35 0.39	-5.20		<0.001
	Matched	0.37 0.39	-3.00	43.20	0.37
Rural versus urban/ suburban	Unmatched	0.70 0.72	-4.80		<0.01
	Matched	0.69 0.73	-10.60	-119.20	<0.001
Never smoker	Unmatched	0.03 0.04	-4.20		<0.01
	Matched	0.03 0.04	-2.60	36.40	0.70
Ever smoker	Unmatched	0.21 0.15	14.50		<0.001
	Matched	0.21 0.16	13.20	9.00	<0.001
HbA1c	Unmatched	7.35 7.30	1.10		0.41
	Matched	7.32 7.14	4.20	-280.00	<0.001
LDL	Unmatched	92.71 88.73	12.70		<0.001
	Matched	96.62 92.47	13.30	-4.10	<0.001

Table 35 (cont.)

Variable	Sample	Mean, Treated (ACEI) Control (ARB)	% bias	% reduction |bias|	p
Triglycerides	Unmatched	191.75 189.52	1.30		0.40
	Matched	193.27 191.07	1.30	1.20	0.12
History of MI	Unmatched	0.03 0.02	3.40		0.02
	Matched	0.03 0.02	3.60	-6.60	0.07
History of stroke	Unmatched	0.01 0.01	6.00		<0.001
	Matched	0.01 0.00	6.60	-8.90	0.08
Family history of CVD	Unmatched	0.00 0.02	-7.50		<0.001
	Matched	0.00 0.02	-7.00	6.90	0.03
CHF	Unmatched	0.05 0.08	-11.40		<0.001
	Matched	0.06 0.08	-10.40	9.00	<0.001
Cardiac arrhythmias	Unmatched	0.05 0.07	-5.80		<0.001
	Matched	0.05 0.06	-4.30	27.00	0.16
Valvular disease	Unmatched	0.00 0.01	-4.70		<0.001
	Matched	0.00 0.01	-4.80	-1.20	0.02
Pulmonary circulation disorders	Unmatched	0.00 0.00	-1.40		0.26
	Matched	0.00 0.00	2.20	-54.00	0.32

Table 35 (cont.)

Variable	Sample	Mean, Treated (ACEI) Control (ARB)	% bias	% reduction |bias|	p
Peripheral vascular disorders	Unmatched	0.06 0.07	-5.10		<0.001
	Matched	0.06 0.08	-5.90	-16.80	0.02
Hypertension	Unmatched	0.81 0.83	-6.80		<0.001
	Matched	0.81 0.84	-6.40	5.40	0.04
Paralysis	Unmatched	0.00 0.00	2.30		0.13
	Matched	0.00 0.00	2.80	-24.60	0.16
Other neurological disorders	Unmatched	0.00 0.00	0.60		0.66
	Matched	0.00 0.00	0.20	62.40	0.82
Chronic pulmonary disease	Unmatched	0.01 0.11	-4.60		<0.01
	Matched	0.10 0.10	-2.30	51.20	0.34
Hypothyroidism	Unmatched	0.04 0.05	-2.60		<0.05
	Matched	0.05 0.05	-0.20	92.40	0.41
Diabetes complicated	Unmatched	0.14 0.14	2.80		<0.05
	Matched	0.15 0.15	1.80	33.00	0.13
Liver disease	Unmatched	0.01 0.01	1.10		0.45
	Matched	0.01 0.01	0.30	69.80	0.75

Table 35 (cont.)

Variable	Sample	Mean, Treated (ACEI) Control (ARB)	% bias	% reduction |bias|	p
Peptic ulcer disease	Unmatched	0.01 0.02	-5.20		<0.001
	Matched	0.01 0.02	-6.50	-25.80	0.01
Lymphoma	Unmatched	0.00 0.00	1.90		0.19
	Matched	0.00 0.00	-2.70	-37.90	0.44
Metastatic cancer	Unmatched	0.00 0.00	1.50		0.32
	Matched	0.00 0.00	2.30	-49.30	0.32
Solid tumor without metastasis	Unmatched	0.06 0.07	-3.60		<0.01
	Matched	0.07 0.07	-2.90	19.30	0.48
Rheumatoid arthritis/collagen vascular diseases	Unmatched	0.00 0.00	0.10		0.93
	Matched	0.00 0.00	-1.50	-1216.50	0.56
Coagulopathy	Unmatched	0.01 0.02	-4.30		<0.01
	Matched	0.01 0.01	-1.00	76.70	0.72
Obesity	Unmatched	0.18 0.17	3.30		0.02
	Matched	0.19 0.18	2.50	24.60	0.40
Fluid and electrolyte disorders	Unmatched	0.02 0.02	1.20		0.38
	Matched	0.02 0.02	1.60	-33.90	0.26

Table 35 (cont.)

Variable	Sample	Mean, Treated (ACEI) Control (ARB)	% bias	% reduction |bias|	p
Blood loss anemia	Unmatched	0.00 0.00	-1.60		0.20
	Matched	0.00 0.00	-4.40	-181.50	0.48
Deficiency anemias	Unmatched	0.03 0.04	-2.80		0.03
	Matched	0.03 0.04	-4.30	-52.70	<0.05
Alcohol abuse	Unmatched	0.03 0.03	2.00		0.16
	Matched	0.03 0.02	4.30	-118.30	0.90
Drug abuse	Unmatched	0.01 0.01	6.80		<0.001
	Matched	0.01 0.01	8.60	-26.00	0.06
Psychoses	Unmatched	0.04 0.03	7.20		<0.001
	Matched	0.05 0.03	7.00	2.70	0.03
Depression	Unmatched	0.10 0.10	1.20		0.38
	Matched	0.10 0.10	2.10	-76.90	0.47
Allergic rhinitis	Unmatched	0.00 0.00	-4.00		<0.01
	Matched	0.00 0.00	-1.90	51.60	0.82
Cohort 2004	Unmatched	0.42 0.43	-2.10		0.12
	Matched	0.33 0.33	-0.10	97.30	0.70

Table 35 (cont.)

Variable	Sample	Mean, Treated (ACEI) Control (ARB)	% bias	% reduction |bias|	p
Cohort 2005	Unmatched	0.31 030	1.20		0.40
	Matched	0.32 0.32	-0.10	95.20	0.73
Cohort 2006	Unmatched	0.20 0.21	-1.50		0.27
	Matched	0.30 0.31	-0.80	46.40	0.74
Hypertension* peripheral vascular disorders	Unmatched	0.05 0.06	-3.20		0.02
	Matched	0.05 0.06	-2.90	6.90	0.17

*p-value for t-test, comparing between group differences before or after matching

Table 36: Differences in Explanation of Treatment Assignment, Unmatched versus Nearest-Neighbor Matched

Sample	**McFadden's Pseudo R^2**	**LR χ^2**	**p**
Unmatched	0.07	687.64	<0.001
Matched	0.17	687.78	<0.001

As mentioned in the Methods, PSA is comprised of two stages. The first stage is predicting treatment selection for each patient based on that patient's characteristics observable to the provider. Specifically, the first stage attempts to incorporate all things available to the provider at baseline in addition to the regular regression methods of including all variables that could impact the outcome. The result of this first stage logistic regression of treatment selection is a weight (inverse of the propensity score) that can be applied to each matched patient in the second stage.

The first stage is extremely flexible for model specification since predicting treatment selection is crucial to control it. Recommendations exist to change models until characteristics are balanced within each stratum. Accordingly, stratification informed us that additional variables (i.e., interactions and higher-order terms) were needed. After adding the interaction between hypertension and peripheral vascular disorders, age squared, and income/100,000, the only thing we were not able to balance within each stratum between groups was site, for which seven sites were not balanced in one of fourteen strata each. Without these additional variables, family history of cardiovascular disease was not balancing and we knew from univariate comparisons that those prescribed ARBs were more likely to have a family history of cardiovascular disease (Table 14). Obviously, this iterative process with feedback applies a more stringent criterion for propensity score balance between groups than weighted regression. Please see Figure 7 for overlap in common support (i.e., percent of ACEI and ARB patients within each stratum who have similar propensity scores). (Note Table 35 is different in that it shows if there was balance in each covariate across the sample as this

is the result of the first stage regression. However, even assessing balance this way we find 21 variables were balanced better with PSA.)

Figure 7: Overlap in Propensity Scores of ACEI and ARB Patients Obtained with Stratification

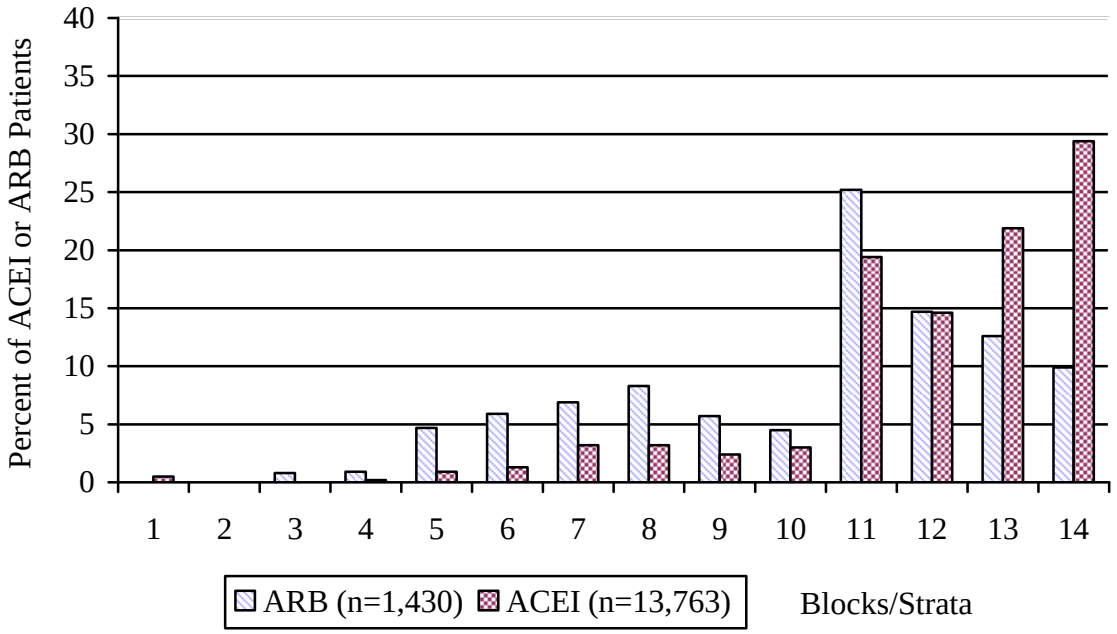


Table 37 found age, family history of CVD, CHF, peripheral vascular disorders, hypertension, and peptic ulcer disease had lower odds of explaining ACEI monotherapy selection ($p<0.05$ each). In other words, patients with these characteristics had significantly higher odds of receiving ARB monotherapy. In contrast, ever smoker, HbA1c, LDL, history of stroke, and the interaction between hypertension and peripheral vascular disorders had higher odds of receiving ACEI monotherapy ($p<0.05$ each).

Although results of Table 37 do not show each state and metropolitan area, these have been controlled for in analysis. Unlike previous regression results, this model does not have robust standard errors or clusters because we are only looking at baseline information for each patient. Despite this, STATA does not allow us to check for regression diagnostics, probably due to the fact that the literature recommends entering as many baseline observable characteristics as possible. However, this does mean this is the only regression model with likelihood ratio chi-square instead of a Wald chi-square as the model is based on log likelihoods rather than log pseudolikelihoods.

Table 37: Logistic Regression Analysis, for Variables Predicting ACEI or ARB Treatment Selection, a.k.a. First Stage PSA to Explain Treatment Selection (N=15,194 patients)

	Coefficient	Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Age	-0.06	0.03	0.04	-0.12	-0.01
Age squared	0.00	0.00	0.10	0.00	0.00
Income/100,000	0.00	0.04	0.95	-0.08	0.08
Urban/suburban[a]	-0.10	0.12	0.40	-0.33	0.13
Never smoker[b]	0.01	0.16	0.95	-0.30	0.33
Ever smoker[b]	0.29	0.08	<0.01	0.13	0.45
Baseline microalbuminuria[c]	0.14	0.07	0.06	-0.01	0.28
HbA1c	0.07	0.02	<0.01	0.02	0.12
LDL	0.00	0.00	<0.01	0.00	0.00
Triglycerides	0.00	0.00	0.47	0.00	0.00
History of MI[d]	0.19	0.19	0.32	-0.18	0.57
History of stroke[e]	0.84	0.35	0.02	0.15	1.53
Family history of CVD[f]	-0.78	0.26	<0.01	-1.29	-0.26
CHF[g]	-0.40	0.11	<0.001	-0.62	-0.18
Cardiac arrhythmias[h]	0.04	0.13	0.74	-0.20	0.29
Valvular disease[i]	-0.42	0.30	0.17	-1.01	0.17
Pulmonary circulation disorders[j]	1.07	1.05	0.30	-0.98	3.12
Peripheral vascular disorders[k]	-0.64	0.24	<0.01	-1.10	-0.18
Hypertension[l]	-0.23	0.08	<0.01	-0.39	-0.07
Paralysis[m]	0.67	0.74	0.37	-0.78	2.12
Other neurological disorders[n]	0.05	0.35	0.90	-0.63	0.72
Chronic pulmonary disease[o]	-0.09	0.10	0.38	-0.28	0.11
Hypothyroidism[p]	0.01	0.14	0.93	-0.26	0.28
Diabetes complicated[q]	0.08	0.09	0.34	-0.09	0.25
Liver disease[r]	-0.13	0.26	0.61	-0.65	0.38
Peptic ulcer disease[s]	-0.64	0.25	0.01	-1.13	-0.15
Lymphoma[t]	-0.19	0.46	0.68	-1.09	0.71
Metastatic cancer[u]	0.80	1.04	0.44	-1.24	2.84
Solid tumor without metastasis[v]	0.04	0.12	0.74	-0.19	0.26

Table 37 (cont.)

	Coefficient	Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Rheumatoid arthritis/ collagen vascular diseases[w]	-0.16	0.32	0.62	-0.79	0.47
Coagulopathy[x]	0.09	0.29	0.76	-0.48	0.66
Obesity[y]	-0.01	0.08	0.88	-0.16	0.14
Fluid and electrolyte disorders[z]	0.11	0.23	0.65	-0.35	0.56
Blood loss anemia[aa]	-0.80	0.69	0.25	-2.16	0.56
Deficiency anemias[bb]	-0.07	0.16	0.65	-0.38	0.24
Alcohol abuse[cc]	0.00	0.20	1.00	-0.39	0.39
Drug abuse[dd]	0.71	0.39	0.07	-0.05	1.46
Psychoses[ee]	0.31	0.17	0.07	-0.02	0.63
Depression[ff]	-0.06	0.10	0.55	-0.26	0.14
Allergic rhinitis[gg]	-0.38	0.36	0.29	-1.08	0.32
Cohort 2004[hh]	-0.05	0.16	0.74	-0.37	0.26
Cohort 2005[hh]	-0.07	0.16	0.69	-0.38	0.25
Cohort 2006[hh]	-0.10	0.16	0.55	-0.42	0.22
Hypertension*					
Peripheral vascular disorders	0.62	0.27	0.02	0.10	1.14

McFadden's Pseudo $R^2 = 0.08$
LR $\chi^2(300) = 742.44$, $p<0.001$, Log likelihood = -4,370.95

[a] Reference category = rural, [b] Reference category = Current smoker, [c] Reference category = Baseline macroalbuminuria, [d] Reference category = No history of MI, [e] Reference category = No history of stroke, [f] Reference category = No family history of CVD, [g] Reference category = No CHF, [h] Reference category = No cardiac arrhythmias, [i] Reference category = No valvular disease, [j] Reference category = No pulmonary circulation disorders, [k] Reference category = No peripheral vascular disorders, [l] Reference category = Normotension, [m] Reference category = No paralysis, [n] Reference category = No other neurological disorders, [o] Reference category = No chronic pulmonary disease, [p] Reference category = No hypothyroidism, [q] Reference category = No diabetes complicated, [r] Reference category = No liver disease, [s] Reference category = No peptic ulcer disease, [t] Reference category = No lymphoma, [u] Reference category = No metastatic cancer, [v] Reference category = No solid tumor without metastasis, [w] Reference category = No rheumatoid arthritis/collagen vascular diseases, [x] Reference category = No coagulopathy, [y] Reference category = No obesity, [z] Reference category = No fluid and electrolyte disorders, [aa] Reference category = No blood loss anemia, [bb] Reference category = No deficiency anemias, [cc] Reference category = No alcohol abuse, [dd] Reference category = No drug abuse, [ee] Reference category = No Psychoses, [ff] Reference

category = No depression, [gg] Reference category = No allergic rhinitis, [hh] Reference category = Cohort 2003

The following section presents the second stage weighted regressions, where each regression equation was weighted by the inverse of the propensity score obtained from the first stage PSA (Table 38). Second stage PSA balances observable patient characteristics at baseline by including those patients' characteristics that allow for any combination of observables to be observed in both treatments; therefore, the second stage weighted regressions were run in the context of common support = 1. There are 15,193 patients contributing 46,494 person-years who meet the common support of = 1 threshold.

Table 38 displays results for the logistic regression analysis weighted by inverse propensity scores of ACEI monotherapy's effect, compared to ARB monotherapy, on development of ESRD. Several patient characteristics were simultaneously entered in the model to control for their effects. Comparing the number of ACEI and ARB patients who merged with zipcode data and the number of patients who had common support, 72.77% of the sample matched.

The only diagnostic test assessed after model analysis was the Pregibon's Link Test, which was nonsignificant (p=0.59). We were unable to conduct the Hosmer and Lemeshow goodness-of-fit because the model was weighted. Similarly, we were unable to assess area under the ROC curve.

Time (t+4), the interaction between ACEI monotherapy and time (t+3), valvular disease, pulmonary circulation disorders, other neurological disorders, peptic ulcer disease, AIDS, lymphoma, metastatic cancer, rheumatoid arthritis/collagen vascular diseases, coagulopathy, weight loss, blood loss anemia, and drug abuse were dropped because each variable did not have an observation with a value of one for ESRD. The

interaction between ACEI monotherapy and time (t+4) was dropped due to multicollinearity. No variables were identified as having significantly lower odds of ESRD development. Times (t+1) and (t+2), diabetes complicated, liver disease, fluid and electrolyte disorders, and deficiency anemias had higher odds of ESRD development ($p<0.05$ each). Of particular importance, diabetes complicated had OR=2.66, (1.42-4.96). The model was significant [Wald $\chi^2(35) = 415.42$, $p<0.001$] and explained 15.84% of the variance in ESRD development.

Table 38: Second Stage PSA: Logistic Regression Weighted by Inverse Propensity Scores, ACEI versus ARB, for Variables Predicting ESRD (N=30,732 person-years; N=14,230 patients)

	Odds Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	1.12	1.03	0.90	0.19	6.72
Time (t+1) [b]	2.16	0.82	0.04	1.03	4.53
Time (t+2) [b]	4.13	1.57	<0.001	1.97	8.69
Time (t+3) [b]	2.04	1.31	0.27	0.58	7.21
ACEI*time (t+1) [c]	1.10	1.18	0.93	0.13	8.98
ACEI*time (t+2) [c]	2.57	2.67	0.36	0.34	19.65
Age	0.98	0.02	0.23	0.95	1.01
Annual income $6,000-17,999[d]	1.28	0.54	0.56	0.56	2.92
Annual income $18,000-34,999[d]	1.60	0.63	0.24	0.74	3.46
Annual income ≥$35,000[d]	0.60	0.33	0.36	0.20	1.78
Urban/suburban[e]	0.73	0.23	0.32	0.40	1.35
Never smoker[f]	0.45	1.50	0.23	0.12	1.64
Ever smoker[f]	1.02	0.32	0.94	0.54	1.96
HbA1c	0.93	0.11	0.51	0.74	1.16
LDL	0.99	0.00	0.13	0.98	1.00
Triglycerides	1.00	0.00	0.96	1.00	1.00
CHF[g]	1.54	0.76	0.38	0.59	4.03
Cardiac arrhythmias[h]	1.97	1.23	0.28	0.58	6.72
Peripheral vascular disorders[i]	2.48	1.21	0.06	0.95	6.48
Hypertension[j]	0.69	0.24	0.29	0.34	1.37
Paralysis[k]	6.04	5.80	0.06	0.92	39.68
Chronic pulmonary disease[l]	0.65	0.35	0.42	0.23	1.85
Hypothyroidism[m]	0.31	0.33	0.28	0.04	2.58
Diabetes complicated[n]	2.66	0.85	<0.01	1.42	4.96
Liver disease[o]	7.40	3.53	<0.001	2.91	18.87
Solid tumor without metastasis[p]	1.97	1.06	0.21	0.69	5.64
Obesity[q]	0.54	0.25	0.19	0.22	1.35
Fluid and electrolyte disorders[r]	7.71	3.14	<0.001	3.46	17.15
Deficiency anemias[s]	5.81	2.63	<0.001	2.40	14.09
Alcohol abuse[t]	1.51	0.99	0.53	0.42	5.44
Psychoses[u]	0.97	0.65	0.96	0.26	3.64
Depression[v]	1.10	0.48	0.82	0.47	2.59

Table 38 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Cohort 2004[w]	0.91	0.60	0.88	0.25	3.28
Cohort 2005[w]	1.30	0.83	0.68	0.37	4.55
Cohort 2006[w]	0.95	0.67	0.94	0.24	3.75

McFadden's Pseudo $R^2 = 0.16$
Wald $\chi^2(35) = 415.42$, $p<0.001$, Log pseudolikelihood = -337.18

[a] Reference category = ARB, [b] Reference category = Time (t), [c] Reference category = ACEI * time t, [d] Reference category = Annual income <$6,000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = No CHF, [h] Reference category = No cardiac arrhythmias, [I] Reference category = No peripheral vascular disorders, [j] Reference category = Normotension, [k] Reference category = No paralysis, [l]Reference category = No chronic pulmonary disease, [m] Reference category = No hypothyroidism, [n]Reference category = No diabetes complicated, [o] Reference category = No liver disease, [p] Reference category = No solid tumor without metastasis, [q] Reference category = No obesity, [r] Reference category = No fluid and electrolyte disorders, [s] Reference category = No deficiency anemias, [t] Reference category = No alcohol abuse, [u]Reference category = No psychoses, [v] Reference category = No depression, [w]Reference category = Cohort 2003

Table 39 presents the results for logistic regression of ACEI monotherapy's effect, compared to ARB monotherapy, on occurrence of IVDEs. Several patient characteristics were concurrently entered to quantify their effects. The original model resulted in a nonsignificant Pregibon's Link Test ($p=0.83$).

Weight loss was dropped because none of its observations had a value of one for IVDE. The interaction between ACEI and time (t+4) and income missing were dropped due to multicollinearity. Never smoker, ever smoker, and LDL had lower odds of IVDE occurrence ($p<0.05$ each). Age, history of MI, history of stroke, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, and fluid and electrolyte disorders had higher odds of IVDE occurrence ($p<0.05$ each). In particular, patients who never smoked had 64% (49-75%) lower odds of having an IVDE occurrence whereas patients with history of MI had 133% (65-233%) higher odds of suffering an IVDE, patients with history of stroke had 232% (119-395%) higher odds of acquiring an IVDE, and patients with peripheral vascular disorders had 229% (159-317%) higher odds of having an IVDE occurrence. The model was significant [Wald $\chi^2(54) = 372.64$, $p<0.001$] and explained 6.02% of IVDE occurrence.

Table 39: Second Stage PSA: Logistic Regression Weighted by Inverse Propensity Scores, for Variables Predicting IVDE (N=25,143 person-years; N=14,864 patients)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
ACEI[a]	1.01	0.20	0.97	0.68	1.49
Time (t+1) [b]	0.88	0.07	0.12	0.74	1.03
Time (t+2) [b]	1.10	0.11	0.37	0.90	1.35
Time (t+3) [b]	0.97	0.15	0.86	0.72	1.33
Time (t+4) [b]	1.55	1.12	0.55	0.37	6.43
ACEI*time (t+1) [c]	1.07	0.30	0.81	0.62	1.85
ACEI*time (t+2) [c]	0.77	0.35	0.57	0.32	1.88
ACEI*time (t+3) [c]	0.42	0.33	0.26	0.09	1.94
Age	1.01	0.00	0.04	1.00	1.02
Annual income $6,000-17,999[d]	1.04	0.15	0.76	0.79	1.37
Annual income $18,000-34,999[d]	1.24	0.16	0.09	0.97	1.58
Annual income ≥$35,000[d]	1.12	0.15	0.40	0.86	1.46
Urban/suburban[e]	0.98	0.09	0.79	0.82	1.17
Never smoker[f]	0.36	0.51	<0.001	0.25	0.51
Ever smoker[f]	0.58	0.19	<0.001	0.47	0.72
Baseline microalbuminuria[g]	1.01	0.12	0.93	0.80	1.28
Microalbuminuria in follow-up[h]	0.88	0.11	0.30	0.70	1.12
Macroalbuminuria in follow-up[h]	1.07	0.16	0.63	0.80	1.44
HbA1c	1.00	0.01	0.99	0.99	1.02
LDL	1.00	0.00	<0.001	0.99	1.00
Triglycerides	1.00	0.00	0.89	1.00	1.00
History of MI[i]	2.35	0.42	<0.001	1.65	3.33
History of stroke[j]	3.30	0.68	<0.001	2.19	4.95
Family history of CVD[k]	1.18	0.40	0.62	0.61	2.30
CHF[l]	1.25	0.22	0.20	0.89	1.76
Cardiac arrhythmias[m]	1.22	0.23	0.29	0.84	1.75
Valvular disease[n]	1.26	0.61	0.63	0.49	3.26
Pulmonary circulation disorders[o]	5.76	3.11	<0.001	2.00	16.60
Peripheral vascular disorders[p]	3.29	0.40	<0.001	2.59	4.17
Hypertension[q]	1.05	0.12	0.68	0.84	1.30
Paralysis[r]	0.73	0.58	0.69	0.15	3.47

Table 39 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Other neurological disorders[s]	1.32	0.59	0.54	0.54	3.19
Chronic pulmonary disease[t]	1.39	0.18	0.01	1.08	1.78
Hypothyroidism[u]	1.03	0.22	0.90	0.68	1.55
Diabetes complicated[v]	1.00	0.12	1.00	0.80	1.26
Liver disease[w]	0.81	0.29	0.57	0.41	1.64
Peptic ulcer disease[x]	0.79	0.36	0.61	0.32	1.93
AIDS[y]	2.78	2.57	0.27	0.45	17.04
Lymphoma[z]	1.06	0.80	0.94	0.24	4.69
Metastatic cancer[aa]	0.63	0.75	0.70	0.06	6.56
Solid tumor without metastasis[bb]	0.82	0.15	0.29	0.58	1.18
Rheumatoid arthritis/ collagen vascular diseases[cc]	0.97	0.43	0.95	0.41	2.31
Coagulopathy[dd]	0.91	0.34	0.80	0.44	1.88
Obesity[ee]	1.15	0.14	0.24	0.91	1.45
Fluid and electrolyte disorders[ff]	2.00	0.47	<0.001	1.27	3.17
Blood loss anemia[gg]	1.11	1.13	0.92	0.15	8.09
Deficiency anemias[hh]	1.41	0.29	0.10	0.94	2.12
Alcohol abuse[ii]	1.30	0.47	0.46	0.64	2.64
Drug abuse[jj]	1.12	0.44	0.77	0.52	2.44
Psychoses[kk]	1.05	0.32	0.86	0.58	1.90
Depression[ll]	1.05	0.16	0.73	0.78	1.42
Cohort 2004[mm]	0.89	0.18	0.57	0.60	1.32
Cohort 2005[mm]	0.82	0.17	0.33	0.55	1.22
Cohort 2006[mm]	0.86	0.18	0.46	0.58	1.28

McFadden's Pseudo R2 = 0.06
Wald $\chi^2(54) = 372.64$, $p<0.001$, Log pseudolikelihood = -3495.21

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural , [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h]Reference category = Normoalbuminuria in follow-up, [i] Reference category = No history of MI, [j]Reference category = No history of stroke, [k]Reference category = No family history of CVD, [l]Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No

peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No fluid and electrolyte disorders, [gg]Reference category = No blood loss anemia, [hh] Reference category = No deficiency anemias, [ii] Reference category = No alcohol abuse, [jj] Reference category = No drug abuse, [kk] Reference category = No psychoses, [ll] Reference category = No depression, [mm] Reference category = Cohort 2003

Table 40 displays the results of the logistic regression weighted by inverse propensity scores of ACEI monotherapy's effects, compared to ARB monotherapy, on all-cause mortality for those individuals in the region of common support. Several patient characteristics were concurrently entered to quantify their effects.

Again, because of the use of weights in this model the Hosmer and Lemeshow goodness-of-fit test was unable to be performed. The Pregibon's Link Test was significant (p=0.001), which resulted in an attempt of construction of another model. Age squared, income divided by 100,000, the interaction between HbA1c and LDL, the interaction between HbA1c and triglycerides, the interaction between LDL and triglycerides, the interaction between albuminuria and HbA1c, the interaction between albuminuria and triglycerides, the interaction between albuminuria and LDL, the interaction between age and triglycerides, the interaction between age and LDL, and the interaction between age and HbA1c were iteratively added to the original model for possible inclusion into the new model. Only the interaction between age and triglycerides was significant (p=0.01), but it did not increase the p-value for Pregibon's Link Test so the original model was retained for parsimony.

The interaction between ACEI monotherapy and time (t+3), never smoker, family history of CVD, valvular disease, pulmonary circulation disorders, paralysis, peptic ulcer disease, AIDS, metastatic cancer, rheumatoid arthritis/collagen vascular diseases, coagulopathy, weight loss, and blood loss anemia were dropped because none of the observations had a value of one for all-cause mortality. The interaction between ACEI monotherapy and time (t+4) as well as income missing were dropped due to multicollinearity. No variables were identified as having lower odds of all-cause

mortality. Higher odds of all-cause mortality were found for times (t+1), (t+2), and (t+3), age, annual income $6,000-17,999, annual income $18,000-34,999, annual income ≥$35,000, history of MI, CHF, peripheral vascular disorders, and cohorts 2004, 2005, and 2006 ($p<0.05$ each). (Note the large odds ratios and robust standard errors for cohorts 2004, 2005, and 2006, something to take into consideration of when interpreting results of a logistic regression.) Also worth mentioning, patients with history of MI had 185% (26-546%) higher odds of all-cause mortality while patients with peripheral vascular disorders had 144% (36-337%) higher odds of all-cause mortality. Because the Wald test for time (t+4) cannot be reported as it is dependent on the (robust) standard error for that variable and the Wald statistic for the model is dependent upon the Wald test for the variable, there is no Wald statistic (or associated p-value) for the model. However, the model explained 8.69% of the variance in all-cause mortality.

Table 40: Second Stage PSA: Logistic Regression Weighted by Inverse Propensity Scores, ACEI versus ARB, for Variables Predicting All-Cause Mortality (N=23,143 person-years; N=13,734 patients)

	Odds Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	0.86	0.56	0.81	0.24	3.07
Time (t+1) [b]	2.01	0.58	0.02	1.13	3.55
Time (t+2) [b]	3.71	1.18	<0.001	1.99	6.91
Time (t+3) [b]	7.44	3.13	<0.001	3.26	16.96
Time (t+4) [b]	$1.06x10^8$	.	.	.	.
ACEI*time (t+1) [c]	0.47	0.57	0.53	0.04	4.99
ACEI*time (t+2) [c]	0.90	0.93	0.92	0.12	6.88
Age	1.04	0.01	<0.01	1.01	1.06
Annual income $6,000-17,999[d]	2.23	0.89	0.04	1.02	4.88
Annual income $18,000-34,999[d]	2.44	0.93	0.02	1.15	5.15
Annual income ≥$35,000[d]	2.22	0.86	0.04	1.03	4.75
Urban/suburban[e]	1.28	0.30	0.30	0.80	2.04
Ever smoker[f]	0.81	0.37	0.49	0.45	1.47
Baseline microalbuminuria[g]	1.03	0.34	0.92	0.54	1.96
Microalbuminuria in follow-up[h]	1.60	0.57	0.19	0.79	3.21
Macroalbuminuria in follow-up[h]	1.89	0.85	0.15	0.79	4.56
HbA1c	1.01	0.01	0.09	1.00	1.02
LDL	1.00	0.00	0.51	1.00	1.01
Triglycerides	1.00	0.00	0.84	1.00	1.00
History of MI[i]	2.85	1.19	0.01	1.26	6.46
History of stroke[j]	2.04	1.20	0.23	0.64	6.47
CHF[k]	2.19	0.79	0.03	1.08	4.45
Cardiac arrhythmias[l]	1.47	0.55	0.30	0.71	3.05
Peripheral vascular disorders[m]	2.44	0.72	<0.01	1.36	4.37
Hypertension[n]	0.72	0.18	0.20	0.44	1.19
Other neurological disorders[o]	1.65	1.66	0.62	0.23	11.85
Chronic pulmonary disease[p]	1.64	0.48	0.09	0.92	2.93
Hypothyroidism[q]	1.48	0.61	0.34	0.66	3.31

Table 40 (cont.)

	Odds Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Diabetes complicated[r]	0.92	0.27	0.79	0.52	1.63
Liver disease[s]	1.98	2.07	0.52	0.25	15.42
Lymphoma[t]	2.20	2.40	0.47	0.26	18.60
Solid tumor without metastasis[u]	1.17	0.46	0.69	0.54	2.53
Obesity[v]	1.10	0.32	0.74	0.62	1.95
Fluid and electrolyte disorders[w]	0.64	0.66	0.66	0.08	4.86
Deficiency anemias[x]	0.93	0.57	0.90	0.28	3.10
Alcohol abuse[y]	1.01	0.63	0.99	0.29	3.46
Drug abuse[z]	1.32	1.28	0.78	0.19	8.92
Psychoses[aa]	0.51	0.38	0.36	0.12	2.17
Depression[bb]	1.48	0.50	0.25	0.76	2.87
Cohort 2004[cc]	5.09×10^6	5.87×10^6	<0.001	5.32×10^5	4.88×10^7
Cohort 2005 [cc]	7.14×10^6	7.92×10^6	<0.001	8.09×10^5	6.29×10^7
Cohort 2006 [cc]	8.44×10^6	9.57×10^6	<0.001	9.14×10^5	7.79×10^7

McFadden's Pseudo $R^2 = 0.09$
Wald $\chi^2(42)$ and its p-value were not reported, Log pseudolikelihood = -530.83

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural , [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h]Reference category = Normoalbuminuria in follow-up, [i] Reference category = No history of MI, [j]Reference category = No history of stroke, [k]No CHF, [l] Reference category = No cardiac arrhythmias, [m] Reference category = No peripheral vascular disorders, [n] Reference category = Normotension, [o] Reference category = No other neurological disorders, [p] No chronic pulmonary disease, [q] Reference category = No hypothyroidism, [r] Reference category = No diabetes complicated, [s] Reference category = No liver disease, [t] Reference category = No lymphoma, [u] Reference category = No solid tumor without metastasis, [v] Reference category = No obesity, [w] Reference category = No fluid and electrolyte disorders, [x] Reference category = No deficiency anemias, [y] Reference category = No alcohol abuse, [z] Reference category = No drug abuse, [aa] Reference category = No psychoses, [bb] Reference category = No depression, [cc] Reference category = Cohort 2003

Table 41 shows negative binomial regression weighted by inverse propensity scores for variables predicting outpatient visits among matched individuals. Lower incidence rates of outpatient visits were observed for times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, never smoker, microalbuminuria in follow-up, and LDL ($p<0.05$ each). Higher incidence rates of outpatient visits were found for annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, ever smoker, history of stroke, CHF, cardiac arrhythmias, valvular diseases, pulmonary circulation disorders, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, obesity, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression ($p<0.05$ each). In more detail, patients with cardiac arrthythmias had 45% (37-54%) more outpatient visits, patients with metastatic cancer had 139% (87-205%) more outpatient visits, patients with coagulopathy had 40% (25-55%) more outpatient visits, and patients with psychoses had 50% (39-62%) more outpatient visits. The model resulted in a Wald $\chi2(55) = 3789.42$, $p<0.001$, log pseudolikelihood = -855257.20.

Table 41: Second Stage PSA: Negative Binomial Regression Analysis Weighted by Inverse Propensity Scores, ACEI versus ARB, for Variables Predicting Outpatient Visits (N=25,160 person-years; N=14,871 patients)

	Incidence Rate Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	1.02	0.02	0.33	0.98	1.07
Time (t+1)[b]	0.80	0.01	<0.001	0.78	0.82
Time (t+2)[b]	0.76	0.01	<0.001	0.73	0.78
Time (t+3)[b]	0.59	0.02	<0.001	0.56	0.62
Time (t+4)[b]	0.20	0.03	<0.001	0.16	0.26
ACEI*time (t+1)[c]	1.03	0.05	0.51	0.94	1.13
ACEI*time (t+2)[c]	1.12	0.17	0.45	0.83	1.51
ACEI*time (t+3)[c]	1.15	0.13	0.24	0.91	1.44
ACEI*time (t+4)[c]	1.23	0.25	0.32	0.82	1.83
Age	0.99	0.00	<0.001	0.99	0.99
Annual income $6,000-17,999[d]	1.20	0.02	<0.001	1.16	1.25
Annual income $18,000-34,999[d]	1.14	0.02	<0.001	1.10	1.19
Annual income ≥$35,000[d]	0.91	0.02	<0.001	0.88	0.94
Urban/suburban[e]	1.17	0.02	<0.001	1.14	1.21
Never smoker[f]	0.89	0.02	<0.001	0.86	0.92
Ever smoker[f]	1.11	0.04	<0.01	1.03	1.20
Baseline microalbuminuria[g]	1.01	0.02	0.63	0.97	1.05
Microalbuminuria in follow-up[h]	0.94	0.02	0.01	0.90	0.99
Macroalbuminuria in follow-up[h]	0.99	0.03	0.72	0.94	1.05
HbA1c	1.01	0.00	0.06	1.00	1.01
LDL	1.00	0.00	<0.001	1.00	1.00
Triglycerides	1.00	0.00	0.09	1.00	1.00
History of MI[i]	0.97	0.04	0.49	0.91	1.05
History of stroke[j]	1.16	0.06	<0.01	1.06	1.28
Family history of CVD[k]	1.09	0.07	0.16	0.96	1.24
CHF[l]	1.18	0.03	<0.001	1.11	1.24
Cardiac arrhythmias[m]	1.45	0.04	<0.001	1.37	1.54
Valvular disease[n]	1.33	0.10	<0.001	1.14	1.54
Pulmonary circulation disorders[o]	1.35	0.19	0.03	1.03	1.77

Table 41 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Peripheral vascular disorder[p]	1.16	0.03	<0.001	1.10	1.23
Hypertension[q]	0.97	0.02	0.12	0.94	1.01
Paralysis[r]	1.35	0.15	<0.01	1.09	1.68
Other neurological disorders[s]	1.24	0.09	<0.01	1.07	1.43
Chronic pulmonary disease[t]	1.12	0.02	<0.001	1.07	1.17
Hypothyroidism[u]	1.01	0.03	0.82	0.95	1.07
Diabetes complicated[v]	1.19	0.02	<0.001	1.15	1.23
Liver disease[w]	1.30	0.07	<0.001	1.16	1.46
Peptic ulcer disease[x]	1.01	0.08	0.85	0.87	1.18
AIDS[y]	1.35	0.19	0.03	1.03	1.78
Lymphoma[z]	1.38	0.16	<0.01	1.10	1.72
Metastatic cancer[aa]	2.39	0.30	<0.001	1.87	3.05
Solid tumor without metastasis[bb]	1.11	0.03	<0.001	1.05	1.17
Rheumatoid arthritis/ collagen vascular diseases[cc]	1.05	0.09	0.56	0.89	1.23
Coagulopathy[dd]	1.40	0.08	<0.001	1.25	1.55
Obesity[ee]	1.03	0.02	<0.05	1.00	1.07
Weight loss[ff]	1.17	0.23	0.42	0.80	1.72
Fluid and electrolyte disorders[gg]	1.32	0.06	<0.001	1.20	1.45
Blood loss anemia[hh]	1.23	0.18	0.16	0.92	1.65
Deficiency anemias[ii]	1.21	0.04	<0.001	1.12	1.30
Alcohol abuse[jj]	1.19	0.05	<0.001	1.10	1.30
Drug abuse[kk]	1.44	0.08	<0.001	1.29	1.62
Psychoses[ll]	1.50	0.06	<0.001	1.39	1.62
Depression[mm]	1.21	0.03	<0.001	1.16	1.26
Cohort 2004[nn]	0.96	0.03	0.23	0.90	1.02
Cohort 2005[nn]	0.94	0.03	0.05	0.88	1.00
Cohort 2006[nn]	0.94	0.03	0.06	0.88	1.00
/lnalpha	-0.93	0.02		-0.96	-0.89
alpha	0.40	0.01		0.38	0.41

Wald $\chi 2(56) = 3789.42$, $p<0.001$, log pseudolikelihood = -855257.20

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h]Reference category = Normoalbuminuria in follow-up, [i] Reference category = No history of MI, [j]Reference category = No history of stroke, [k]Reference category = No family history of CVD, [l]Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = Fluid and electrolyte disorders, [hh] Reference category = No blood loss anemia, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

For the negative binomial regression weighted by inverse propensity scores among matched individuals predicting ED visits (Table 42), income missing was dropped due to multicolinearity. Lower incidence rates of ED visits were found for times (t+1) and (t+4), the interaction between ACEI monotherapy and time (t+4), age, annual income ≥$35,000 and never smoker while higher incidence rates of ED visits were found for annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, CHF, cardiac arrhythmias, peripheral vascular disorders, paralysis, chronic pulmonary disease, diabetes complicated, liver disease, metastatic cancer, solid tumor without metastasis, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression ($p<0.05$ each). Of note, patients with annual income $6,000-17,999 had 55% (36-78%) more ED visits, patients who lived in urban/suburban areas had 58% (41-77%) more ED visits, patients with chronic pulmonary disease had 52% (30-77%) more ED visits, and patients with fluid and electrolyte disorders had 111% (65-169%) more ED visits. The model resulted in a Wald $\chi2(56) = 2246.68$, $p<0.001$, log pseudolikelihood = -126635.08.

Table 42: Second Stage PSA: Negative Binomial Regression Analysis Weighted by Inverse Propensity Scores, ACEI versus ARB, for Variables Predicting ED visits (N=25,160 person-years; N=14,871 patients)

	Incidence Rate Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	1.08	0.14	0.55	0.84	1.40
Time (t+1)[b]	0.73	0.04	<0.001	0.65	0.81
Time (t+2)[b]	0.73	0.05	<0.001	0.64	0.83
Time (t+3)[b]	0.59	0.07	<0.001	0.47	0.74
Time (t+4)[b]	0.11	0.11	0.03	0.01	0.83
ACEI*time (t+1)[c]	0.82	0.19	0.39	0.53	1.28
ACEI*time (t+2)[c]	1.01	0.23	0.98	0.65	1.56
ACEI*time (t+3)[c]	2.04	0.87	0.09	0.89	4.71
ACEI*time (t+4)[c]	0.00	0.00	<0.001	0.00	0.00
Age	0.96	0.00	<0.001	0.96	0.97
Annual income $6,000-17,999[d]	1.55	0.11	<0.001	1.36	1.78
Annual income $18,000-34,999[d]	1.24	0.09	<0.01	1.07	1.43
Annual income ≥$35,000[d]	0.71	0.05	<0.001	0.61	0.82
Urban/suburban[e]	1.58	0.09	<0.001	1.41	1.77
Never smoker[f]	0.73	0.05	<0.001	0.64	0.83
Ever smoker[f]	1.25	0.16	0.08	0.97	1.62
Baseline microalbuminuria[g]	0.98	0.08	0.81	0.83	1.15
Microalbuminuria in follow-up[h]	1.01	0.07	0.88	0.88	1.16
Macroalbuminuria in follow-up[h]	1.12	0.11	0.27	0.92	1.35
HbA1c	1.02	0.01	0.12	1.00	1.04
LDL	1.00	0.00	0.54	1.00	1.00
Triglycerides	1.00	0.00	0.87	1.00	1.00
History of MI[i]	1.12	0.14	0.39	0.87	1.43
History of stroke[j]	1.15	0.20	0.42	0.82	1.61
Family history of CVD[k]	0.83	0.24	0.53	0.47	1.48
CHF[l]	1.52	0.16	<0.001	1.24	1.87
Cardiac arrhythmias[m]	1.43	0.18	<0.01	1.12	1.83
Valvular disease[n]	1.15	0.31	0.60	0.68	1.96
Pulmonary circulation disorders[o]	1.66	0.77	0.27	0.68	4.10

Table 42 (cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Peripheral vascular disorders[p]	1.34	0.12	<0.01	1.12	1.60
Hypertension[q]	0.91	0.06	0.11	0.81	1.02
Paralysis[r]	3.02	1.04	<0.01	1.54	5.92
Other neurological disorders[s]	1.74	0.45	0.03	1.05	2.90
Chronic pulmonary disease[t]	1.52	0.12	<0.001	1.30	1.77
Hypothyroidism[u]	0.89	0.11	0.34	0.69	1.13
Diabetes complicated[v]	1.24	0.08	<0.01	1.10	1.41
Liver disease[w]	1.71	0.29	<0.01	1.23	2.40
Peptic ulcer disease[x]	0.95	0.25	0.85	0.56	1.61
AIDS[y]	0.50	0.39	0.37	0.11	2.26
Lymphoma[z]	2.36	1.17	0.08	0.90	6.23
Metastatic cancer[aa]	2.51	0.95	0.02	1.19	5.28
Solid tumor without metastasis[bb]	1.47	0.17	<0.01	1.18	1.83
Rheumatoid arthritis / collagen vascular diseases[cc]	1.04	0.24	0.88	0.66	1.62
Coagulopathy[dd]	1.17	0.27	0.49	0.75	1.84
Obesity[ee]	0.98	0.06	0.68	0.87	1.10
Weight loss[ff]	3.49	1.94	0.03	1.17	10.39
Fluid and electrolyte disorders[gg]	2.11	0.26	<0.001	1.65	2.69
Blood loss anemia[hh]	2.32	0.98	<0.05	1.01	5.32
Deficiency anemias[ii]	1.54	0.19	<0.01	1.21	1.97
Alcohol abuse[jj]	1.08	0.14	0.54	0.84	1.40
Drug abuse[kk]	1.74	0.29	<0.01	1.25	2.41
Psychoses[ll]	1.50	0.17	<0.001	1.21	1.87
Depression[mm]	1.27	0.10	<0.01	1.09	1.49
Cohort 2004[nn]	0.87	0.11	0.29	0.67	1.12
Cohort 2005[nn]	0.84	0.11	0.19	0.65	1.09
Cohort 2006[nn]	0.94	0.12	0.64	0.73	1.22
/lnalpha	1.53	0.04		1.46	1.61
alpha	4.64	0.18		4.29	5.01

Wald $\chi 2(56) = 2246.68$, $p<0.001$, log pseudolikelihood = -126635.08

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category = rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h]Reference category = Normoalbuminuria in follow-up, [i] Reference category = No history of MI, [j]Reference category = No history of stroke, [k]Reference category = No family history of CVD, [l]Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = Fluid and electrolyte disorders, [hh] Reference category = No blood loss anemia, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

The negative binomial regression weighted by inverse propensity scores for variables predicting hospitalization among matched patients (Table 43), found times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, never smoker, LDL, and hypertension had significantly lower incidence rates of hospitalization ($p<0.05$ each). On the other hand, annual income $6,000-17,999, annual income $18,000-34,999, ever smoker, HbA1c, history of MI, history of stroke, CHF, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, weight loss, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression had higher incidence rates of hospitalization ($p<0.05$ each). In particular, patients with weight loss had 151% (79-251%) more hospitalizations, patients with fluid and electrolyte disorders had 172% (117-238%) more hospitalizations, and 93% (51-150%) more hospitalizations. The model resulted in a Wald $\chi2(56) = 2895.33$, $p<0.001$, log pseudolikelihood = -98569.52.

Table 43: Second Stage PSA: Negative Binomial Regression Analysis Weighted by Inverse Propensity Scores, ACEI versus ARB, for Variables Predicting Hospitalizations (N= 25,160 person-years; N=14,871 patients)

	Incidence Rate Ratio	**Robust Standard Error**	**p**	**95% CI Lower Bound**	**95% CI Upper Bound**
ACEI[a]	1.05	0.13	0.68	0.83	1.33
Time (t+1)[b]	0.78	0.05	<0.001	0.68	0.89
Time (t+2)[b]	0.73	0.06	<0.001	0.62	0.85
Time (t+3)[b]	0.43	0.06	<0.01	0.32	0.57
Time (t+4)[b]	0.14	0.11	0.02	0.03	0.69
ACEI*time (t+1)[c]	0.67	0.15	0.08	0.43	1.04
ACEI*time (t+2)[c]	0.94	0.31	0.86	0.50	1.79
ACEI*time (t+3)[c]	0.85	0.49	0.78	0.27	2.65
ACEI*time (t+4)[c]	0.00	0.00	<0.001	0.00	0.00
Age	0.98	0.00	<0.001	0.97	0.98
Annual income $6,000-17,999[d]	1.63	0.12	<0.001	1.41	1.89
Annual income $18,000-34,999[d]	1.36	0.10	<0.001	1.17	1.57
Annual income ≥$35,000[d]	0.77	0.07	<0.01	0.65	0.91
Urban/suburban[e]	1.00	0.06	0.96	0.90	1.12
Never smoker[f]	0.58	0.04	<0.001	0.52	0.66
Ever smoker[f]	1.68	0.21	<0.001	1.31	2.16
Baseline microalbuminuria[g]	0.98	0.09	0.87	0.82	1.18
Microalbuminuria in follow-up[h]	0.99	0.08	0.89	0.84	1.16
Macroalbuminuria in follow-up[h]	1.06	0.12	0.60	0.85	1.32
HbA1c	1.02	0.01	0.02	1.00	1.04
LDL	1.00	0.00	<0.001	0.99	1.00
Triglycerides	1.00	0.00	0.79	1.00	1.00
History of MI[i]	1.84	0.23	<0.001	1.44	2.35
History of stroke[j]	1.42	0.24	0.04	1.01	1.99
Family history of CVD[k]	1.33	0.28	0.18	0.88	2.00
CHF[l]	1.60	0.15	<0.001	1.33	1.92
Cardiac arrhythmias[m]	1.25	0.18	0.13	0.94	1.67
Valvular disease[n]	0.96	0.34	0.91	0.48	1.94
Pulmonary circulation disorders[o]	1.35	0.42	0.34	0.73	2.50
Peripheral vascular disorder[p]	1.77	0.16	<0.001	1.48	2.12

Table 43(cont.)

	Incidence Rate Ratio	Robust Standard Error	p	95% CI Lower Bound	95% CI Upper Bound
Hypertension[q]	0.76	0.05	<0.001	0.68	0.86
Paralysis[r]	2.36	0.75	<0.01	1.27	4.40
Other neurological disorders[s]	2.79	1.03	<0.01	1.35	5.76
Chronic pulmonary disease[t]	1.44	0.11	<0.001	1.24	1.68
Hypothyroidism[u]	0.98	0.12	0.89	0.77	1.26
Diabetes complicated[v]	1.37	0.09	<0.001	1.20	1.56
Liver disease[w]	1.88	0.29	<0.001	1.39	2.54
Peptic ulcer disease[x]	1.24	0.38	0.48	0.68	2.26
AIDS[y]	0.78	0.32	0.55	0.35	1.75
Lymphoma[z]	2.78	1.03	<0.01	1.34	5.75
Metastatic cancer[aa]	2.72	1.32	0.04	1.05	7.03
Solid tumor without metastasis[bb]	1.41	0.15	<0.01	1.15	1.73
Rheumatoid arthritis / collagen vascular diseases[cc]	1.53	0.41	0.11	0.90	2.60
Coagulopathy[dd]	1.56	0.32	0.03	1.05	2.32
Obesity[ee]	1.02	0.07	0.71	0.90	1.17
Weight loss[ff]	2.50	0.43	<0.001	1.79	3.51
Fluid and electrolyte disorders[gg]	2.71	0.31	<0.001	2.17	3.38
Blood loss anemia[hh]	1.47	0.60	0.34	0.66	3.25
Deficiency anemias[ii]	1.94	0.25	<0.001	1.51	2.50
Alcohol abuse[jj]	1.65	0.24	<0.01	1.24	2.20
Drug abuse[kk]	1.96	0.32	<0.001	1.41	2.70
Psychoses[ll]	1.48	0.17	<0.01	1.18	1.86
Depression[mm]	1.27	0.09	<0.01	1.10	1.46
Cohort 2004[nn]	0.97	0.12	0.80	0.76	1.23
Cohort 2005[nn]	0.83	0.10	0.12	0.65	1.05
Cohort 2006[nn]	0.90	0.11	0.42	0.71	1.16
/lnalpha	1.51	0.05		1.40	1.61
alpha	4.51	0.24		4.07	5.01

Wald $\chi 2(56) = 2895.33$, $p<0.001$, log pseudolikelihood = -98569.52

[a] Reference category = ARB, [b] Reference category = Time t, [c] Reference category = ACEI*Time t, [d] Reference category = Annual income <$6000, [e] Reference category =

rural, [f] Reference category = Current smoker, [g] Reference category = Baseline macroalbuminuria, [h]Reference category = Normoalbuminuria in follow-up, [i] Reference category = No history of MI, [j]Reference category = No history of stroke, [k]Reference category = No family history of CVD, [l]Reference category = No CHF, [m] Reference category = No cardiac arrhythmias, [n] Reference category = No valvular diseases, [o] Reference category = No pulmonary circulation disorders, [p] Reference category = No peripheral vascular disorders, [q] Reference category = Normotension, [r] Reference category = No paralysis, [s] Reference category = No other neurological disorders, [t] No chronic pulmonary disease, [u] Reference category = No hypothyroidism, [v] Reference category = No diabetes complicated, [w] Reference category = No liver disease, [x] Reference category = No peptic ulcer disease, [y] Reference category = No AIDS, [z] Reference category = No lymphoma, [aa] Reference category = No metastatic cancer, [bb] Reference category = No solid tumor without metastasis, [cc] Reference category = No rheumatoid arthritis/collagen vascular diseases, [dd] Reference category = No coagulopathy, [ee] Reference category = No obesity, [ff] Reference category = No weight loss, [gg] Reference category = Fluid and electrolyte disorders, [hh] Reference category = No blood loss anemia, [ii] Reference category = No deficiency anemias, [jj] Reference category = No alcohol abuse, [kk] Reference category = No drug abuse, [ll] Reference category = No psychoses, [mm] Reference category = No depression, [nn] Reference category = Cohort 2003

Comparisons of Non-PSA and PSA Regressions, ACEI Monotherapy versus ARB Monotherapy

As found in Table 37, variables were identified to be significant for selection of one monotherapy over another. Without propensity score adjustment, the lack of balance between the ACEI and ARB groups in age, HbA1c, LDL, and the interaction between hypertension and peripheral vascular disease, along with proportion of patients with history of stroke, family history of CVD, CHF, peripheral vascular disorders, hypertension, peptic ulcer disease, and ever smokers would have biased the results. This is demonstrated in the different results between the two models, in which change in direction of relationship of a covariate with outcome (i.e., protective factor became a risk factor after propensity score adjustment) occurred. Also, variables identified as not significant emerged as being significant or vice versa. Although many variables were common between the models, the differences mentioned above have important implications. The next paragraph focuses on these differences by outcome.

The unweighted logistic regression found LDL had lower odds of ESRD development, but after PSA, this disappeared and time (t+2) emerged with as having higher odds. The unweighted logistic regression found CHF and deficiency anemias had higher odds of IVDE while they became nonsignificant after propensity score adjustment; instead, LDL emerged as having a lower odds of IVDE. Despite the other outcomes being important, it is crucial to know what truly impacts all-cause mortality. The unweighted model found the interactions between ACEI monotherapy and times (t+1) and (t+2) had lower odds of all-cause mortality; these variables no longer remained significant after propensity score adjustment. Chronic pulmonary disease and lymphoma had higher odds of all-cause mortality, which also disappeared with the weighted model.

Lastly, although annual income $18,000-34,999 and annual income ≥$35,000 were not significant with the unweighted model, they emerged with higher odds of all-cause mortality in the second stage PSA. The unweighted model of outpatient visits found ACEI monotherapy and cohorts 2005 and 2006 had lower incidence rates whereas the interactions between ACEI monotherapy and times (t+1), (t+2), and (t+3), triglycerides and blood loss anemia had higher incidence rates; all became nonsignificant after propensity score adjustment. This adjustment also led to the discovery that pulmonary circulation disorders had a significantly higher incidence rate. In terms of ED visits, the unweighted model identified time (t+3) and hypertension as having lower incidence rates and ever smoker, history of MI, and other neurological disorders as having higher incidence rates; all disappeared in the weighted model. Also, the weighted model found annual income $18,000-34,999 had a higher incidence rate of ED visits, while the interaction between ACEI monotherapy and time (t+4) had a lower incidence rate; neither was not found in the unweighted model. Lastly, the unweighted model of hospitalizations identified time (t+2) and cohort 2005 as having lower incidence rates and family history of CVD and rheumatoid arthritis/collagen vascular diseases as having higher incidence rates; all three became nonsignificant after second stage PSA. Also after second stage PSA, metastatic cancer materialized with a higher incidence rate although this was nonsignificant with the unweighted model.

ATT Attained by PSA Techniques Other Than Weighted Regression

At first look, the average treatment effect on the treated (i.e., ACEI patients) bore the same results regardless of stratification or nearest-neighbor matching: all ATTs bore nonsignificant t-statistics (Appendix F, Tables 23 and 24). ESRD had similar ATT

values across methods. We see similar point estimates but a protective tendency for ACEI monotherapy with stratification while we see a protective tendency with ARB monotherapy with nearest-neighbor matching for IVDE occurrence. For all-cause mortality, point estimates were extremely similar across methods. Outpatient visits reveal differences in point estimates between the two methods. Although both show a nonsignificant protective effect with ACEI monotherapy, nearest-neighbor matching shows this effect to be about five-fold higher than that attained through stratification. ED visits exhibit relatively similar point estimates with either ATT estimation technique. Hospitalizations show a nonsignificant protective effect with ACEI monotherapy for nearest-neighbor matching and a nonsignificant protective effect with ARB monotherapy from stratification.

Validation of PSA: Sensitivity Analyses

Nearest-neighbor matching allowed the researchers to perform sensitivity analyses. Due to the fact that PSA can only balance observable characteristics, Mantel-Haenszel bounds and Rosenbaum bounds were defined for dichotomous and count variables, respectively, to assess the robustness of our findings in case there is an exogenous variable differentially affecting odds of treatment assignment. (Note no test exists that an unobserved variable is doing this.) The hypothetical situation of odds of differential treatment assignment is tested by changing gamma (the odds of differential treatment assignment) from one to two.[172,201,202] All sensitivity analyses were conducted using a weighted average across strata instead of separately assessing each stratum.

Mantel-Haenszel bounds found nonsignificant differences for ESRD and all-cause mortality between ACEI and ARB monotherapies holds true to the point that if an

unobserved variable exists, it would have to increase the odds of treatment assignment by more than 200% to change this conclusion. (Please see Appendix F, Tables' 25 and 27 p-value columns.) The nonsignificant between group differences for IVDE occurrence holds true in the potential presence of an unobserved variable until it increases the odds of treatment assignment by 115% to 120%. (Please see Appendix F, Table 26.)

Rosenbaum bounds reveal the nonsignificant differences in outpatient visits found by PSA only holds true in the presence of an unobserved variable if it affects odds of treatment assignment by between 105% and 110% (Please see Appendix F, Table 28). On the other hand, the PSA for ED visits showed patients receiving either monotherapy had similar ED visits, but this conclusion changes if an unobserved variable increased the odds of treatment assignment by less than 105% (Appendix F, Table 29). Finally, the result of no differences between monotherapies for hospitalizations remains true if an unobserved variable changed the odds of treatment assignment between 115% and 120% (Appendix F, Table 30).

CHAPTER 5: DISCUSSION

This chapter starts by reviewing the research problem and putting the problem in context of the diabetes epidemic. Then the chapter discusses the study results. Next, we discuss answers and implications to the research questions specific to this study. From there, the chapter delves into other issues pertinent to understanding the results of the study. In particular, the topics address compliance, VA as a closed system, and internal and external validity. Thereafter, we address limitations and close with a summary of conclusions and significance.

Background

The prevalence of diabetes has increased by 80% in the last ten years,[4] and projections estimate its prevalence to increase by more than 2.5 fold between the years 2000 and 2050.[5] The major modifiable contributor to this increase is obesity. Diabetes is already the leading health condition contributing to incident ESRD cases,[19] and the number of P2DM developing ESRD is expected only to increase as the number of P2DM increases despite a reduction in complications seen in the last decade as type 2 diabetes has such a steep rate of incidence.[203,204] Each of these complications has a high morbidity and mortality rate.

As albuminuria and hypertension are predictors of ESRD and CVD and because ACEIs and ARBs have been shown to reduce both albuminuria and hypertension, this study was designed to evaluate the effectiveness of ACEI or ARB monotherapy in reducing ESRD or CVD. Taking this one step further, it would be helpful for clinicians

to know the related complication all-cause mortality as well as be able to provide insight into differences in healthcare utilization between these monotherapies. As more Americans develop type 2 diabetes, there will be increased healthcare burden; therefore, information about any factors that reduce or increase healthcare utilization would be extremely valuable.

Current State of Diabetes in the VA Population

Our study provides insight regarding the current state of diabetes patients in the VA population. This itself is an important contribution as the study spans several years, is longitudinal, and analyzes a large patient population. We found that approximately 71% of the VA population had normoalbuminuria at baseline, 23% had microalbuminuria at baseline, and 6% had macroalbuminuria at baseline. This is comparable to a combined prevalence of microalbuminuria and macroalbuminuria of 26.5% in Americans with undiagnosed diabetes who are at least 40 years of age.[37] Our study demonstrated a 70.6% prevalence of hypertension at baseline, which is comparable to rates in two previous studies: one in American P2DM, which showed 73% were hypertensive and one in veteran patients with diabetes, which showed 67% had hypertension.[3,142] In terms of mean clinical parameters, patients in our study had a mean baseline HbA1c of 7.30% and mean baseline LDL of 94.56 mg/dL. This was similar to VA registry data, among veterans with diabetes, who had mean HbA1c values in fy2000 and fy2001 were 7.61% and 7.37%, respectively.[142] The same VA registry data showed veterans with diabetes had a mean LDL of 104 mg/dL in fy2000 and of 108 mg/dL in fy2001.[142]

Drug Therapy and Patient Characteristics

As expected, there were fewer between group differences for ACEI and ARB patients than either monotherapy compared to those receiving neither therapy (Tables 13 and 14). It appears that the patients receiving neither therapy may have been healthier. Specifically, the ACEI and ARB groups had over 80% of patients who were hypertensive while those receiving neither therapy had a hypertensive rate of about 60% (Table 14). The 20% difference in hypertensive status between patients receiving either monotherapy and those receiving neither therapy suggests that VA prescribers preferentially prescribed an ACEI or ARB based on hypertensive, rather than albuminuric, status. Nevertheless, the guidelines advise prescribing an ACEI or ARB to all P2DM with hypertension or all P2DM who have nephropathy (i.e., microalbuminuria or macroalbuminuria).[54,142] Alternately, it could suggest that patients with hypertension were more compliant to ACEI or ARB monotherapy compared to patients with normotension. This notion is due to the classification of patients into treatment groups based upon medication they have on-hand; patients were considered to have received ACEI or ARB monotherapy if they had at least a one-half years supply. Even though we were unable to assess this in our study, patients with normotension perhaps did not refill their prescription as frequently because of perceived lack of disease severity.

ACEI patients had a higher history of stroke (Table 16) while ARB patients were the oldest, had the highest percentage of never smokers, and had the highest percentage of CHF (Tables 15 and 16). (Notice these variables were all identified as factors influencing treatment selection of ACEI and ARB in the first stage PSA.)

Multivariate Analyses

ACEI or ARB Monotherapy versus neither

Unlike the comparisons between ACEI and ARB monotherapies, these analyses were conducted only by using traditional multivariate logistic regression and negative binomial regression techniques, as appropriate. The driving force behind this decision is the vast amount of published literature consistently showing benefit of ACEI or ARB monotherapy over neither therapy for nephropathy,[45-49,116,120] to the point that clinical guidelines published by the American Diabetes Association and the VA advocate their use in this patient population.[54,89,142] Still, it was believed that comparisons to patients receiving neither therapy were important for two main reasons. First, there is less published literature about monotherapy benefits in P2DM for cardio- and cerebro-vascular disease events and all-cause mortality. Second, many patients in our sample were found to have received less than 50% of a year's supply of ACEI or ARB monotherapy in a given year. Thus, not only should outcomes be compared across these three groups, but reasons for not adhering to the guidelines should also be discussed.

ACEI versus ARB Monotherapy

Propensity Score Analysis

The propensity score analysis (PSA) was successful for two main reasons. The first was the fact that it fulfilled the goal of undergoing this type of analysis: to achieve balance between groups on observable characteristics. The second goal was to have enough people on common support, meaning substantial overlap existed in propensity scores between patients on the two drug therapies.

With respect to the first reason, meeting the goal is key in arguing that the study controlled for treatment selection by having similar information a provider would have at the time of prescribing therapy and entering this information into a model. (Note we did not have information about blood pressure readings, race/ethnicity, antihypertensives, and antihyperlipidemics.) As can be seen in this study, treatment selection bias existed in the VA for these patients because we identified variables in the first stage PSA that had higher odds of one monotherapy over the other.

The first stage of PSA tries to balance each of the characteristics entered into the model across therapy groups. The flexibility in this stage of specifying different models is what allows for better estimation of treatment selection. Stratification balanced everything but seven sites in one of fourteen strata each. This means that for other than site, both groups were comparable at baseline. This is similar to the way patients are comparable at baseline in randomized clinical trials. Even in randomized clinical trials, not all observable variables may be balanced (failure of randomization).[205] If balance on observable variables cannot always be guaranteed through randomized clinical trials, the argument also exists that unobservable variables cannot always be balanced in randomized designs. Similar to randomized trials, our study cannot guarantee balance on unobservable variables. By achieving balanced groups at baseline in a similar way as randomized trials we can say we do not have a systematic mechanism to create error in our study.

Taking it one step further, Seeger et al. (2007) and Joffe et al. (1999) claim that PSA creates a better balance at baseline than randomization.[152,206] As a matter of statistical probability this is true. In a randomized clinical trial, 5% of covariates may not

be balanced due to chance alone. These variables would not generally be further adjusted. Particular to this study, out of 57 covariates, about 3 may not be statistically similar due to chance alone.

With respect to the second reason, common support refers to the overlap in those receiving ACEIs and those receiving ARBs who have similar propensity scores. In other words, a high proportion of patients should be matched on propensity scores. If there is not enough common support there is not enough information to generate accurate information about the counterfactual- what would have happened to a patient receiving one therapy if they instead received the other, based on their propensity score. The other implication of lack of common support is loss of generalizability. The current study was able to match 72.77% of patients

Intention-to-Treat Analysis

Since we used ITT for the same reasons it is used in randomized clinical trials, i.e., to maintain comparable between group characteristics established at baseline, we needed to assess the percentage of patients within each drug therapy at baseline who remained on the same drug therapy. The regression analyses comparing ACEI and ARB patients had substantially higher amounts of patients who stayed on the same therapy since neither patients were excluded: 99.14% and 99.73% of ACEI and ARB patients, respectively (data not shown).

Primary Constructs of Interest: Renal and Cardio- and Cerebro- Vascular Diseases

Relationship Between Drug Therapy and ESRD

In univariate analysis, we found that ACEI patients had a lower rate of ESRD development compared to ARB and neither patients (Table 17). We further explored albuminuria over time and by drug therapy. (See Appendix F, Tables 7-10).

Among those with baseline microalbuminuria, ACEI and ARB patients had similar improvement in albuminuria in years 1-5 despite a wider range of albuminuria values among ARB patients at year 1 (Appendix F, Tables 7 and 8). Neither patients, after their initial improvement between years 1 and 2, experienced worsening albuminuria between years 2 and 3 and years 2 and 4 (Appendix F, Table 8). These findings are important as about 78% of the sample had baseline microalbuminuria. Among patients with baseline macroalbuminuria, ACEI patients were the only group that not only had improving albuminuria at every year of follow-up compared to the first year, but also had better albuminuria in later years when compared to years two and three (Appendix F, Table 8).

Differences in ESRD Development, ACEI or ARB Monotherapy versus neither

As shown in Table 23, our primary interest, effectiveness of ACEI and ARB monotherapies, compared to neither therapy, found ACEI patients were associated with lower odds of developing ESRD. Age and LDL also were associated with lower odds of ESRD development ($p<0.017$ each; see Table 23). Time (t+2), annual income $18,000-34,999, CHF, diabetes complicated, fluid and electrolyte disorders, and deficiency anemias were associated with higher odds of ESRD development ($p<0.017$ each).

To our knowledge, this is the first study comparing ACEI monotherapy to neither/placebo among P2DM for ESRD and only the second study comparing ARB monotherapy to neither/placebo patients among P2DM for ESRD. It is the first comparing ARB monotherapy to neither/placebo for patients with majority baseline microalbuminuria. Although ARB monotherapy was not even found to have statistically significantly lower odds of ESRD development, the point estimate of the odds ratio, 0.50, shows promise of benefit. Based on the *a priori* power calculation for ESRD assuming equal size treatment groups, we were lower than the 80% power threshold as we had fewer patients in the ARB group than mentioned in Table 4.

Age makes sense as being associated with lower odds of ESRD development as it is associated with higher odds of all-cause mortality, a competing risk. It is also intuitive that LDL is associated with lower odds of ESRD. First, analysis of the RENAAL study found baseline LDL was not associated with development of ESRD.[207] Obviously, this in itself, does not give the complete picture. However, we captured LDL longitudinally and LDL levels can decrease as patients develop ESRD.[208]

It is interesting that patients who have three years of follow-up were associated with 2.76 higher odds of developing ESRD given that the mean follow-up is 2.17 years and the median follow-up is 2.00 years. In light of Brenner et al. finding significant beneficial effects of ARB monotherapy, compared to placebo, over 3.4 years in his baseline macroalbuminuric sample,[49] we may have also found a significant benefit for ARB monotherapy if we had longer average follow-up. We note annual income $18,000-34,999 was associated with a higher odds of ESRD (all other income levels had higher point estimate than <$6,000); the USRDS found approximately 25% of incident ESRD

cases in the U.S. had Medicaid coverage between 2002 and 2006.[209] CHF also makes sense as being associated with higher odds of ESRD development since renal and cardiac diseases are intricately woven together. Likewise, diabetes complicated and fluid and electrolyte disorders have rationale to be indicative of ESRD development. Diabetes complicated, defined by Elixhauser et al., includes any of the following: diabetes with renal manifestations, diabetes with ophthalmic manifestations, diabetes with neurological manifestations, diabetes with peripheral circulatory disorders, and diabetes with unspecified complications.[195] Similarly, fluid and electrolyte disorders is a collective of hypernatremia, hyponatremia, acidosis, alkalosis, volume depletion, fluid overload, hyperkalemia, hypokalemia, and fluid and electrolyte disorders not otherwise specified. Since fluid and electrolyte disorders can be a result of renal or cardiac dysfunction, perhaps the kidney already had some predisposition.[210] It is reasonable to say someone who has more clinically evident complications of diabetes at baseline or who has a fluid and electrolyte disorder at baseline would have higher odds (OR = 3.40 and OR = 4.19, respectively) of developing ESRD than someone who has not. Even if a patient has good glycemic control during the study, a patient may have had increasing levels of hyperglycermia over a long period of time, leading to diagnosis of type 2 diabetes. Deficiency anemias is intuitive as it encompasses iron deficiency anemias and anemia not otherwise specified, both of which have causes that are seemingly unrelated to ESRD or diabetes except for one: long-term treatment with NSAIDs.[211,212] This study did not capture the cause of deficiency anemias for each patient, but since other causes are cancer, esophageal varices, peptic ulcer disease, celiac disease, Crohn's disease, gastric bypass surgery, and antacid therapy there is no way to know if deficiency anemias was,

in fact, caused by long-term NSAID use in this sample. The researchers set out to look at this very covariate, but there were too many missing observations to retain the information.

When P2DM are newly-diagnosed healthcare providers should give ACEI or ARB therapy as recommended in treatment guidelines and encourage compliance with medication. The other factors found to be significant were nonmodifiable. Because this study showed ACEI monotherapy was associated with a lower odds of ESRD development at two years, albeit with limitations in using multivariate regression without propensity score adjustment, and found the three year time point to be a significant predictor, patients having longer treatment duration with at least 50% compliance would only be expected to reap larger benefits.

Difference in ESRD Development, ACEI versus ARB Monotherapy

There were no significant differences in ACEI and ARB monotherapies for ESRD development (Table 38). The only variable having lower odds of ESRD development was LDL, which was only found by unweighted logistic regression (Table 29). Time (t+2), diabetes complicated, liver disease, fluid and electrolyte disorders and deficiency anemias had higher odds of ESRD development in both models ($p<0.05$ each).

Similar to ACEI or ARB monotherapy versus neither therapy results of variables predicting ESRD, time (t+2), diabetes complicated, fluid and electrolyte disorders, and deficiency anemias had higher odds of ESRD development. Liver disease may have higher odds of ESRD development through two different mechanisms: first, cirrhosis could lead to expanded fluid volume, which could lead to ESRD; second, liver disease may predispose patients to ESRD because hepatorenal syndrome is a complication.[210,213]

This is the first study with comparable baseline characteristics between monotherapies to assess differences in ESRD development. The study shows no trends or significant differences between ACEI and ARB monotherapies for effects on ESRD development. Similarly, no trends or significant differences were seen for interactions between either monotherapy and time. Since propensity score adjustment is viewed as achieving similar balances in baseline characteristics as randomization, this is fairly strong evidence, yet is only one study in one population. Future research is needed to confirm results.

Relationship Between Drug Therapy and IVDE

ACEI and ARB patients suffered an IVDE more frequently in years 1-4 compared with neither patients (Table 18). Components analysis finds this pattern to be upheld the most for LVH, but is also seen for stroke and MI.

Differences in IVDE Occurrence, ACEI or ARB Monotherapy versus neither

Our primary research interest, whether ACEI or ARB monotherapy was associated with reducing IVDE occurrence, did not hold true; in fact, the difference was found in the opposite direction (Table 24). ACEI monotherapy, age, the interaction between LDL and triglycerides, history of MI, history of stroke, CHF, peripheral vascular disorders, chronic pulmonary disease, fluid and electrolyte disorders, and deficiency anemias were associated with higher odds of IVDE occurrence while age squared, never smoker, ever smoker, and LDL were associated with lower odds ($p<0.017$ each; Table 24).

As mentioned previously, the substantially higher mortality rate seen in neither patients compared to ACEI or ARB patients likely obscured benefits of monotherapies' other endpoints compared to neither patients assessed in this study. This makes it plausible that patients with ACEI monotherapy were associated with 1.54 higher odds of suffering an IVDE: more ACEI patients were alive to be at risk for having an IVDE.[20,214] Age, history of MI, history of stroke, CHF, peripheral vascular disorders, and fluid and electrolyte disorders are intuitively appealing to higher odds of IVDEs. Chronic pulmonary disease and deficiency anemias have been previously identified as risk factors for cardiovascular events: COPD may put patients at increased risk because of hypoxemia and inflammation[215,216] whereas anemia worsens cardiac function while simultaneously affecting renal function.[217] In fact, deficiency anemias was also associated with higher odds of ESRD development in the comparison of ACEI or ARB monotherapy to neither. Never smoker, ever smoker, and the interaction between LDL and triglycerides odds ratios make sense as there is a vast array of evidence that smoking and increased lipids lead to cardio- and cerebro- vascular disease events.[214] Age squared may be associated with a lower odds of IVDEs because death may be a competing risk of IVDEs. Similar to the mortality comment among neither patients, patients may die before suffering an IVDE.[218]

The modifiable factors are ACEI monotherapy, smoking, and lipid levels. In the context of results from all-cause mortality (Table 25), clinicians should prescribe ACEI monotherapy, again realizing this statistical method does not provide evidence of causality. This study adds evidence to already existing literature that healthcare professionals need to discourage smoking and encourage lower lipid levels.

Difference in IVDE Occurrence, ACEI versus ARB Monotherapy

No difference in effectiveness for reduction of IVDE was found between ACEI and ARB monotherapies (Table 39). Both the unweighted (Table 30) and weighted logistic regression models found never smoker and ever smoker had lower odds while age, history of MI, history of stroke, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, and fluid and electrolyte disorders had higher odds of IVDE occurrence ($p<0.05$ each). Also after propensity score adjustment, LDL had a lower odds of IVDE occurrence ($p<0.05$), despite it not being revealed in the unweighted model. Also after propensity score adjustment, CHF and deficiency anemias became nonsignificant although they were each identified as being associated with higher odds of IVDE occurrence.

We find it intuitively appealing that never smoker and ever smoker had lower odds of IVDE occurrence given the literature that smoking increases rates of MI and stroke. Similarly, history of MI, history of stroke, and peripheral vascular disorders are intuitive to having higher odds of IVDEs as history of MI,[20] history of stroke,[20] and peripheral vascular disorders[219] put patients at increased risk of MI and stroke. Pulmonary circulation disorders captures patients documented with chronic pulmonary heart disease, so this also makes sense.

Healthcare providers should prescribe ACEI or ARB monotherapy in P2DM as advocated in the guidelines[54,89,142,144,145,220] as the findings show evidence of comparable effectiveness in IVDE occurrence. Healthcare professionals should encourage prevention of MI, stroke, peripheral vascular disorders, chronic pulmonary disease, and fluid and

electrolyte disorders, so patients would be more likely to avoid downstream effects of increased IVDEs. One risk factor of these conditions is smoking. Cardio- and cerebro-vascular disease is cascading; previous research shows P2DM are at higher risk of cardio- and cerebro- vascular disease events than the general population.[91] P2DM with history of CVD are twice as likely as P2DM without such a history to suffer a recurrent MI or stroke.[20] Therefore, time needs to be spent educating and emphasizing to patients about these downstream effects, especially since approximately two-thirds of the diabetes population will die from cardio- or cerebro- vascular events.

Other Constructs: All-cause Mortality and Healthcare Utilization

Relationship Between Drug Therapy and All-cause Mortality

Every year, patients receiving neither therapy were dying at a rate several fold higher than ACEI or ARB patients ($p<0.001$ each; Table 18). In year 1, neither patients died at an 8-times higher rate than ACEI or ARB patients, which continued throughout follow-up (Table 18). All-cause mortality was comparable between ACEI and ARB patients at every year.

Differences in All-cause Mortality, ACEI or ARB Monotherapy versus neither

ACEI and ARB monotherapies were associated with 0.16 and 0.11 odds of all-cause mortality compared to neither therapy, respectively ($p<0.001$ each; Table 25). Also found, times (t+1) and (t+2), and income missing were associated with lower odds while the interaction between ACEI monotherapy and times (t+1), (t+2), and (t+3), age, urban/suburban living, HbA1c, CHF, peripheral vascular disorders, chronic pulmonary

disease, metastatic cancer, coagulopathy, fluid and electrolyte disorders, and cohorts 2004, 2005, and 2006 were associated with higher odds of all-cause mortality ($p<0.017$ each; Table 25).

Although multivariate logistic regression holds all other variables entered into the regression equation constant, it still does not ensure balance in baseline observable characteristics, thus this analysis most likely overestimated the benefit of ACEI and ARB monotherapy over neither therapy for all-cause mortality. Otherwise, with the mean and median follow-up of approximately 2 years in this study, it would be well-known publicly as well as found in previous studies, which it has not. Times (t+1) and (t+2) were associated with lower odds of all-cause mortality compared to time (t) even though univariate comparisons found similar or higher mortality rates at times (t+1) and (t+2) than time (t) within each drug therapy, suggesting some control over covariates (Table 19).

The interactions between ACEI monotherapy and times (t+1), (t+2), and (t+3) make sense because looking at the univariate comparisons we can see ACEI patients had a higher mortality rate at each of these timepoints compared to ACEI patients at time (t) (see Table 19). Age and HbA1c intuitively make sense as being associated with higher odds of all-cause mortality because age and HbA1c have a lot of supporting evidence of higher frequency of death. Also, Elixhauser et al. showed CHF, peripheral vascular disorders, chronic pulmonary disease, metastatic cancer, coagulopathy, and fluid and electrolyte disorders are associated with higher in-hospital mortality in the general population.[195]

To understand why cohorts 2004, 2005, and 2006, compared to cohort 2003, were associated with higher odds of all-cause mortality, we have to closely examine the results. Each of these variables has extremely large odds ratios and robust standard errors, signaling that there are a small number of patients with all-cause mortality in at least one cell of the 2x2 table for each of these cohorts compared to cohort 2003. Consequently, we have to use caution in interpreting the significance of these variables. Nevertheless, because of the associations of higher odds, additional *post hoc* analyses were conducted to further explore the relationship.

ANOVA followed by Tukey's Honestly Significant Differences pairwise comparisons found cohorts 2005 and 2006 each had more comorbidities than cohorts 2003 and 2004 (group means = 1.73, 1.75, 1.61, and 1.65, respectively). It is apparent from these numbers that the cohorts still do not "look" that different in terms of numbers of comorbidities. To shed a little more light on this perspective, Elixhauser et al. found 1.89 times as many people with three comorbidities had an in-hospital death (their only measure of mortality) than people with two comorbidities.[195] (Remember we excluded diabetes as a comorbidity since everyone in the sample has this condition whereas Elixhauser et al. studied the general population.) This only provides part of the picture so age and each of the mean baseline clinical parameters were also assessed between cohorts. However, age went in the opposite direction than expected and patients in cohort 2003 were significantly younger than cohorts 2004, 2005, and 2006 (adjusted p-value<0.004 each). None of the cohorts were significantly different than cohort 2003 for LDL or triglycerides while each cohort had higher mean baseline HbA1c than cohort 2003 (adjusted p-value<0.004 each). The only significant difference between cohorts,

when compared to cohort 2003, was for baseline albuminuria: cohort 2003 had fewer patients with macroalbuminuria than cohort 2004.

Modifiable significant factors were ACEI monotherapy, ARB monotherapy, and HbA1c. Due to observed associations, providers should write prescriptions for and encourage compliance with ACEI or ARB monotherapy. Providers should also educate patients about how to control HbA1c, prescribing medication when necessary and reinforcing compliance. Looking more upstream, healthcare professionals should counsel on preventable behaviors of chronic pulmonary disease and metastatic cancer as these comorbidities had higher odds of all-cause mortality (OR = 2.07 and OR = 9.29, respectively).

Difference in All-cause Mortality, ACEI versus ARB Monotherapy

No differences were found between monotherapies for all-cause mortality (Table 40). Lower odds of all-cause mortality were only found for the interactions between ACEI monotherapy and times (t+1) and (t+2); these variables were only found significant in the unweighted model. Chronic pulmonary disease, and lymphoma were associated with higher odds of all-cause mortality in the unweighted model while the second stage PSA found higher odds for annual income $18,000-34,999 and annual income ≥$35,000 ($p<0.05$ each). Both models found times (t+2) and (t+3), age, annual income $6,000-17,999, history of MI, CHF, peripheral vascular disorders, cohorts 2004, 2005, and 2006 were the only variables having higher odds of all-cause mortality ($p<0.05$ each; Tables 31 and 40).

Just as in the comparison of ACEI or ARB monotherapy to neither therapy for all-cause mortality, extremely large odds ratios and robust standard errors are present for

each of the cohorts, meaning that in each of the cohorts, compared to cohort 2003, there is at least one cell in the 2x2 table where there are only a small number of deaths. Still, we further explored the differences between cohorts to see if there are any other possible explanations. All cohorts, compared to cohort 2003, had higher mean baseline HbA1c (adjusted p-value<0.004 each). Also, cohorts 2005 and 2006 each had higher comorbidities compared to cohorts 2003 and 2004. These two differences could explain why members of cohorts 2004, 2005, and 2006 had higher odds of all-cause mortality compared to cohort 2003.

Times (t+1), (t+2), and (t+3) having higher odds of all-cause mortality make sense in relation to the univariate comparisons across time (Table 19). Age also is intuitive as people in general tend to die when they are older. It is extremely interesting that people with any income higher than the lowest of our categories are at higher odds of dying. History of MI also is rational as people with this history are about twice as likely to have a cardio- or cerebro- vascular event,[20] and we know that most P2DM die from these events.[3] In fact, history of MI and peripheral vascular disorders also had higher odds of IVDE occurrence in our sample. Additionally, CHF and peripheral vascular disorders are intuitive to having higher odds of all-cause mortality based on previous research by Elixhauser et al.[195]

This study provides evidence that there is no difference in ACEI and ARB monotherapy for all-cause mortality. Therefore, clinicians can view these medications as virtually identical for all-cause mortality. Clinicians also need to focus on preventive efforts so that MI, CHF, or peripheral vascular disorders do not develop.

Relationship Between Drug Therapy and Healthcare Utilization

ACEI patients had more outpatient visits, ED visits, and hospitalizations than neither patients (Table 20). Similarly, ARB patients had more outpatient visits and ED visits than neither patients (Table 20). When these groups were compared to neither patients, ACEI and ARB patients had higher rates of outpatient visits, ED visits, and hospitalizations for years 1-4 (Table 21). For healthcare utilization, we found only one significant difference between ACEI and ARB patients: overall, ACEI patients had more outpatient visits than ARB patients ($p<0.0083$; Table 20). When analyzed annually, no significant differences were seen between these two groups (Table 21).

Differences in Outpatient Visits, ACEI or ARB Monotherapy versus neither

ACEI and ARB monotherapies were associated with higher incidence rates of outpatient visits (1.19 and 1.25, respectively) compared to neither therapy ($p<0.001$ each; Table 26). In addition, the interactions between ACEI monotherapy and times (t+1), (t+2), (t+3), the interaction between ARB monotherapy and time (t+3), annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, history of stroke, CHF, cardiac arrhythmias, valvular disease, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression were associated with higher incidence rates of outpatient visits ($p<0.017$ each). Times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, income missing, never smoker, microalbuminuria in follow-up, LDL, hypertension, and cohorts

2005 and 2006 were associated with lower incidence rates of outpatient visits ($p<0.017$ each).

ACEI and ARB monotherapies could have been associated with higher incidence rates of outpatient visits because these patients could have been seeking help more frequently than patients receiving neither therapy because they are concerned with their health, and thus, are more compliant with their medications. As already mentioned, because neither patients are dying at a substantially higher rate than ACEI or ARB patients this is probably the main contributor. The interactions between ACEI monotherapy and times (t+1), (t+2), and (t+3) being associated with higher incidence rates of outpatient visits makes sense when taking Table 21 into consideration: univariate comparisons found significant difference between ACEI and neither therapies at each of these timepoints ($p<0.001$ each). Although not found statistically significant in univariate comparisons of ARB monotherapy and neither therapy at time (t+3), the mean number of outpatient visits is comparable to ACEI monotherapy, validating the finding of an association of higher incidence of outpatient visits for the interaction between ARB and time (t+3). Annual income $6,000-17,999 and annual income $18,000-34,999 could have higher incidence rates of outpatient visits because veterans may be more likely to afford transportation, public or private, to have outpatient visits compared to those with income <$6,000.[221] For a similar reason urban/suburban living may be associated with a higher incidence rate of outpatient visits: patients who live in cities will be more likely to have affordable public transportation; they are also more likely to be closer to a VA facility to obtain care.[222] The remaining significant predictors are comorbidities, so it is logical that patients with comorbidities, compared to patients without comorbidities, will

have more outpatient visits. This is especially true if patients with comorbidities are not dying earlier in the follow-up period, allowing more time for patients to attend outpatient clinics. There is no association between higher odds of all-cause mortality and cardiac arrhythmias, valvular disease, paralysis, other neurological disorders, diabetes complicated, liver disease, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, obesity, blood loss anemia, deficiency anemias, or psychoses, making this argument easy for these comorbidities (Tables 25 and 40). However, there is a relationship between higher odds of mortality for CHF, peripheral vascular disorders, chronic pulmonary disease, AIDS, lymphoma, metastatic cancer, coagulopathy, fluid and electrolyte disorders, alcohol abuse, drug abuse, and depression. Although it is outside the scope of this project to see when patients with each comorbidity die, making it unable to confirm this assumption, it does make sense. Preliminary evidence could be contrived from Table 14 as the comorbidities with increased odds of all-cause mortality make up maximally 29.58% of the sample while comorbidities without comprise maximally 50.27% of the sample. (Note the amount of overlap between comorbidities within the sample is unknown). With about equal proportions, it does provide more evidence that patients with the comorbidities identified as predictors of outpatient visits are not, in general, dying at earlier points in follow-up, allowing for accumulation of healthcare utilization, including outpatient visits.

Times (t+1), (t+2), (t+3), and (t+4) have face validity as univariate comparisons of outpatient visits over time displays fewer outpatient visits in each of these years from year 1 across all drug therapies. (Please see Table 22.) Age and people in cohorts 2005 and 2006 were probably associated with lower incidence rates of outpatient visits as they

were both associated with higher odds of all-cause mortality, a competing risk of outpatient visits (see Table 25).[218] Annual income ≥$35,000 makes sense as being associated with lower incidence rate of outpatient visits because higher income is associated with better health and better health could lead to fewer outpatient visits.[223,224] Those with missing income may have the same reason. The fact that never smokers had lower incidence rates of outpatient visits compared to current smokers is intuitively appealing because never smokers are believed to be generally healthier. The finding that patients with microalbuminuria in follow-up were associated with lower incidence rates than patients with normoalbuminuria in follow-up perhaps is due to differences in health perceptions. More specifically, patients with normoalbuminuria may attend outpatient clinics more often because they want to stay in good health. As evidence exists that a higher proportion of patients taking ACEI or ARB monotherapy regress to normoalbuminuria than placebo, and in the context that we defined patients as receiving ACEI or ARB monotherapy based on at least a 50% coverage in days supply with medication in a year, this conjecture also makes sense as people who are more compliant tend to be more concerned about their health. LDL could be protective if patients with higher LDL have higher LDL because they do not seek help as often as those with more controlled LDL. The same could be true for those with hypertension.

These findings should not be interpreted as evidence to not provide ACEI or ARB monotherapy, because, as mentioned above, it is probable that ACEI or ARB monotherapy was not associated with lower incidence rates of outpatient visits because patients receiving neither therapy were dying at a much faster rate in each year of follow-up, thereby allowing time for patients receiving either monotherapy to have higher

incidence rates of outpatient clinics than neither patients. Again, preventive medicine should be taking place before patients develop comorbidities. If providers advocated, and patients listened to and followed, preventive measures against acquiring comorbidities, there would be less strain on healthcare resources.

Difference in Outpatient Visits, ACEI versus ARB Monotherapy

ACEI and ARB monotherapies had similar incidence rates of outpatient visits in the weighted model (Table 41) although the unweighted model found ACEI monotherapy was associated with a lower incidence rate and the interactions between ACEI monotherapy and time (t+1), (t+2), and (t+3) were associated with higher incidence rates (Table 32). Times (t+1), (t+2), (t+3), and (t+4), age, annual income ≥$35,000, never smoker, microalbuminuria in follow-up, and LDL had significantly lower incidence rates of outpatient visits in unweighted and weighted negative binomial regression analyses ($p<0.05$ each). Higher incidence rates of outpatient visits were found for annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, ever smoker, history of stroke, CHF, cardiac arrhythmias, valvular disease, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, obesity, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression across models ($p<0.001$ each). Pulmonary circulation disorders also emerged as having a higher incidence rate of outpatient visits after second stage PSA.

Insight into why times (t+1), (t+2), (t+3), and (t+4) were protective factors of outpatient visits can be identified through univariate analysis of ESRD and mortality

within ACEI and ARB monotherapy across time. (Please see Table 20.) Among ACEI patients we see increasing rates of ESRD at times (t+1) and (t+2) compared to time (t). We also see increasing mortality rates at times (t+1), (t+2), and (t+3) compared to time (t). Turning to ARB patients we see an increasing trend in ESRD at time (t+3) compared to time (t) amounting to over a 12-fold difference. Although there is no statistical difference between subsequent years of follow-up, people who died in the previous year cannot seek outpatient care. The reason why ESRD is specifically addressed here is because there is literature that veterans with ESRD are more likely to receive care outside the VA.[225] This may also be why we see increasing age is protective against outpatient visits: people are Medicare-eligible so may be more likely to see providers outside the VA. Patients with annual income ≥$35,000 may have been otherwise employed, meaning Medicare Advantage's reduced payments could apply to these individuals; however, there were special enrollment periods for retired military personnel in which premiums were waived (although still had to pay copayments), which may nullify this reason.[226] An alternate hypothesis is that patients in this income group are healthier; previous literature has found patients with higher income have better health.[223,224] Never smoker seems reasonable to have a lower incidence rate of outpatient visits because, in theory, these patients are healthier than current smokers, reducing the need for outpatient visits. Similar to an argument made for LDL's lower incidence rate of hospitalization for ACEI or ARB monotherapy versus neither therapy, LDL and microalbuminuria in follow-up could have lower incidence rates of outpatient visits because they, in themselves, are probably not reasons for outpatient visits, but rather their complications.

Revisiting the higher incidence rates seen in income, veterans with annual income $6,000-17,999 and annual income $18,000-34,999 could have an easier time getting to the doctors' offices than those with annual income <$6,000 as those with the least amount of income probably could not afford a car and may even have a hard time paying for public transportation, if available.[221] Similarly, urban/suburban living promotes higher access to care, where rural areas may not even have a healthcare facility.[222] The remaining variables with significantly higher incidence rates of outpatient visits are comorbidities. Only three of these twenty-two comorbidities had increased odds of all-cause mortality (Tables 25 and 40), making the argument easy to make that patients with these comorbidities had the time to accumulate outpatient visits and that patients with comorbidities would be expected to have more outpatient visits than patients without comorbidities.

Differences in ED Visits, ACEI or ARB Monotherapy versus neither

Our primary interest, whether ACEI or ARB monotherapy was associated with reducing ED visits compared to neither therapy, was again not proven. Patients receiving ACEI monotherapy were associated with a significantly higher incidence rate of ED visits (1.16) compared to neither patients; ARB patients were associated with similar rates as neither patients (Table 27). The analysis also revealed annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, ever smoker, HbA1c, CHF, cardiac arrhythmias, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, AIDS, metastatic cancer, solid tumor without metastasis, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression were associated

with higher incidence rates of ED visits ($p<0.001$ each; Table 27). Times (t+1), (t+2), and (t+3), the interaction between ARB monotherapy and time (t+4), age, annual income ≥$35,000, income missing, never smoker, and hypertension were associated with lower incidence rates of ED visits ($p<0.017$ each).

As with outpatient visits, the fact that ACEI monotherapy was associated with a higher incidence rate of ED visits should not mean that providers conclude ACEI monotherapy is detrimental as it is associated with protection against all-cause mortality. Most variables identified as being associated with higher incidence rates of ED visits are nonmodifiable, but the fact that certain comorbidities associated with higher incidence rates of ED visits as well as outpatient visits (i.e., CHF, cardiac arrhythmias, peripheral vascular disorders, paralysis, chronic pulmonary disease, AIDS, metastatic cancer, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, and psychoses) means special attention should be given to patients to try to make sure that they limit behaviors that could result in these comorbidities, thus decreasing the burden on the healthcare system.

As found with outpatient visits, univariate analysis of ED visits across time decreased compared to time (t). (Please see Table 22.) This explains seeing incidence rate ratios less than one for times (t+1), (t+2), and (t+3). Unlike outpatient visits, there was not a significant difference between time (t+4) and time (t), most likely because there were few observations at time (t+4) and because of the fewer ED visits experienced by study participants compared to outpatient visits. The interaction between ARB monotherapy and time (t+4) being associated with a lower incidence rate of ED visits can be gleaned again from univariate comparisons seen in Tables 21 and 22. Although not

significantly different, looking at the rates themselves we see zero ED visits for ARB patients at time (t+4), the only intersection of drug therapy and time with a rate of zero for ED visits. Similar arguments can be made for age, annual income ≥$35,000, income missing, and never smoker as what was voiced for these associations with lower incidence rates of outpatient visits. Similar statements made for outpatient visits can be applied to rationalizing why ACEI monotherapy, annual income $6,000-17,999, annual income $18,000-34,999, urban/suburban living, and ever smoker as well as the comorbidities being associated with higher incidence rates of ED visits.

Difference in ED Visits, ACEI versus ARB Monotherapy

Patients receiving ACEI and ARB monotherapies had similar rates of ED visits (Table 42) although significantly lower incidence rates of ED visits were seen for age, times (t+1) and (t+4), annual income ≥$35,000, and never smoker across both models ($p<0.001$ each; Table 33). Significantly higher incidence rates of ED visits were observed for annual income $6,000-17,999, urban/suburban living, CHF, cardiac arrhythmias, peripheral vascular disorders, chronic pulmonary disease, paralysis, diabetes complicated, liver disease, metastatic cancer, solid tumor without metastasis, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression across both models ($p<0.05$ each). ACEI monotherapy and time (t+4) and annual income $18,000-34,999 emerged after propensity score adjustment as having a lower and a higher incidence rate, respectively.

Times (t+1) and (t+4) are rational to have lower incidence rates based on assessment of univariate analysis of ED visits over time. As mentioned previously, age could have a lower incidence rate of ED visits since patients with advanced age were

dying at a higher frequency (there is evidence in the weighted logistic regression comparison between ACEI and ARB monotherapy for all-cause mortality). Please see Table 40. Patients with annual income ≥$35,000 could have a higher incidence rate for the same two reasons used in outpatient visits: 1. a possibility that these patients were more likely to seek care outside the VA and 2. these patients may be healthier. Again, it is rational that never smokers have lower incidence rates of ED visits because they are presumed to be healthier than current smokers.

Veterans with annual income $6,000-17,999 may have higher odds of ED visits compared to those with income <$6,000 for the same reasons as they have higher odds of outpatient visits: these patients need a way to get to the ED and it costs a substantial amount of money to summon an ambulance. Urban/suburban living most likely has a higher incidence rate of ED visits, again because of patients' relative proximity to an ED.[222] The remaining variables with significantly higher incidence rates are comorbidities. Along the lines of previous arguments for patients with certain comorbidities having increased use of healthcare resources, patients with these comorbidities likely had higher incidence rates of ED visits than patients without these comorbidities as long as they were not at higher odds of all-cause mortality. Even if they were, as long as patients were not dying earlier in follow-up veterans would have had higher incidence rates of ED visits. Of the six comorbidities with higher incidence rates of ED visits, only CHF had a trend towards higher odds of all-cause mortality; none had a significantly higher odds of all-cause mortality. (Please see Table 40.)

Again, the clinical implication is that there are no significant differences between ACEI and ARB monotherapy for ED visits. Emphasis should be placed on prevention of comorbidities.

Differences in Hospitalizations, ACEI or ARB Monotherapy versus neither

Looking at Table 28, patients receiving ACEI monotherapy were associated with higher incidence rate of hospitalization (IRR=1.19). Other variables that were associated with higher incidence rates of hospitalization were annual income $6,000-17,999, annual income $18,000-34,999, ever smoker, HbA1c, history of MI, history of stroke, family history of CVD, CHF, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, metastatic cancer, solid tumor without metastasis, coagulopathy, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression ($p<0.001$ each). Alternately, times (t+1), (t+2), (t+3), and (t+4), the interaction between ACEI monotherapy and time (t+4), the interaction between ARB monotherapy and time (t+4), annual income ≥$35,000, income missing, never smoker, LDL, and hypertension were associated with lower incidence rates of hospitalization ($p<0.017$ each).

Since ACEI monotherapy, annual income $6,000-17,999 and annual income $18,000-34,999 were associated with higher incidence rates of hospitalization as they were for outpatient visits and ED visits, similar comments can be made as to the justification of why they were associated with higher incidence rates of hospitalization. The finding that ever smokers were associated with higher incidence rates of hospitalization may be a spurious finding. The remaining variables associated with

higher incidence rates of hospitalization were comorbidities. Since all comorbidities associated with higher incidence rates of hospitalization were identified as being associated with higher incidence rates of outpatient and/or ED visits except weight loss, a similar argument can be made as in those outcomes: as long as patients with these comorbidities are not dying earlier in follow-up, it is intuitively appealing that patients with these comorbidities would be hospitalized more frequently over the period of observation. Again looking at Table 25, this does not appear likely.

Similar to comparisons across time for all drug therapies for outpatient visits and ED visits, univariate comparisons demonstrated lower hospitalization rate for times (t+1), (t+2), (t+3), and (t+4) compared to time (t). (Please see Table 22). The interaction between ACEI monotherapy and time (t+4) and the interaction between ARB monotherapy and time (t+4) were probably due to the lower rates of hospitalization seen at time (t+4) compared to time (t) within each respective therapy. (Note it is significant for ACEI monotherapy, but not ARB despite ARB patients having a hospitalization rate of zero at time (t+4).) Age, annual income $\geq$\$35,000, income missing, and never smoker again appear as being inversely related to incidence rates as they did for outpatient visits and ED visits. LDL, HbA1c, and hypertension may be associated with lower incidence rates due to the fact that not many hospitalizations are, in and of themselves, directly due to either of these conditions, but rather complications from these conditions.[227]

As mentioned for the previous two types of healthcare utilization, just because ACEI monotherapy was associated with a higher incidence rate of hospitalization does not mean clinicians should not prescribe and enforce compliance with ACEI

monotherapy as patients receiving ACEI monotherapy were associated with lower odds of all-cause mortality than patients receiving neither therapy. Also as mentioned with outpatient visits and ED visits, the majority of variables associated with higher incidence rates of hospitalization are non-modifiable, making it imperative for healthcare providers to educate patients about the lifestyle choices that could lead to the comorbidities seen with increased hospitalization. The overwhelming majority of comorbidities associated with higher odds of hospitalization were also associated with higher odds of outpatient visits and/or ED visits. Lastly, we return to Elixhauser et al., who found all of the comorbidities identified in the present analysis as predicting hospitalization were found to increase length of stay (their marker of healthcare utilization) except for solid tumor without metastasis.[195]

Difference in Hospitalizations, ACEI versus ARB Monotherapy

There was no difference in incidence rates of hospitalization for patients on ACEI and ARB monotherapies (Tables 34 and 43). However, times (t+1), (t+3), and (t+4), age, annual income ≥$35,000, never smoker, LDL, and hypertension had significantly lower incidence rates while annual income $6,000-17,999, annual income $18,000-34,999, ever smoker, HbA1c, history of MI, history of stroke, CHF, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes complicated, liver disease, lymphoma, solid tumor without metastasis, coagulopathy, weight loss, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression had significantly higher incidence rates of hospitalization across unweighted and weighted negative binomial regression models ($p<0.05$ each). Time (t+2) had a

lower incidence rate of hospitalization and metastatic cancer had a higher incidence rate only after propensity score adjustment.

Times (t+1), (t+2), and (t+4) had lower rate of hospitalization among ACEI patients compared to time (t) in univariate comparisons across time. (Please see Table 22.) Although no statistical difference was found for decreased hospitalization rate between the time (t+3) and time (t) among ACEI patients or any of these three time periods among ARB patients in univariate comparisons, looking at the rates at each year, we do see a pattern a decreasing rates. For age, the same rationale applied to why age had a lower incidence rate of ED visits can be applied to hospitalizations: there was a higher odds of all-cause mortality (Table 31). Veterans with an annual income ≥$35,000 could have a lower incidence rate of hospitalization since income is positively related to health. Never smoker again emerged with a lower incidence rate of hospitalization, presumably because people who have never smoked are generally healthier than people who currently smoke. LDL, HbA1c, and hypertension, as mentioned in the ACEI or ARB monotherapy comparison with neither therapy for hospitalization, likely had lower incidence rates of hospitalization because they generally do not necessitate hospitalization; rather, their complications do.[227]

Veterans with annual income $6,000-17,999 and annual income $18,000-34,999 may have higher incidence rates of hospitalization because they have more means to pay for it than patients with income <$6,000. Ever smokers having higher incidence rates than current smokers is most likely due to a spurious finding. There was a trend toward higher odds of all-cause mortality for only two of the nine comorbidities with higher odds of hospitalization: CHF and peripheral vascular disorders, and none of the comorbidities

with higher incidence rates of hospitalization had significantly higher odds for all-cause mortality (Table 31). Thus, support is provided that patients with these comorbidities had the opportunity to be hospitalized in the follow-up period.

The first clinical implication that can be drawn from this information is that there is no difference in ACEI or ARB monotherapy in terms of hospitalization. Second, as has been mentioned before, healthcare professionals need to educate the public on actions, behaviors, and other lifestyle choices that can predispose patients to comorbidities in an effort to reduce healthcare utilization, including hospitalizations. In fact, numerous published articles exist across disease states documenting the benefits of such education;[228-233] furthermore, preventive services are recommended in clinical practice guidelines[234] and are now mandated to be reimbursed by private health plans.[235]

Summary of ACEI or ARB Monotherapy versus neither

ACEI monotherapy was associated with lower odds of ESRD development, higher odds of IVDE occurrence, lower odds of all-cause mortality, and higher incidence rates of outpatient visits, ED visits, and hospitalizations. The interaction between ACEI monotherapy and time (t+3) was associated with a higher odds of all-cause mortality and a higher incidence rate of outpatient visits while the interaction between ACEI monotherapy and time (t+4) was associated with a lower incidence rate of hospitalization. There were also associations between higher odds of all-cause mortality and higher incidence rates of outpatient visits for the interactions between ACEI monotherapy and times (t+1) and (t+2).

ARB monotherapy was associated with lower odds of all-cause mortality and a higher incidence rate of outpatient visits. The interaction between ARB monotherapy

and time (t+3) was associated with a higher incidence rate of outpatient visits while the interaction between ARB monotherapy and time (t+4) was associated with lower incidence rates of ED visits and hospitalizations.

Again we note the substantially higher mortality rate seen among neither patients likely biased results of our comparisons. There are plausible explanations of neither patients having a higher mortality rate while having fewer IVDEs, outpatient visits, ED visits, and hospitalizations compared to patients receiving either monotherapy despite, in general, appearing to be healthier. First, since death is a competing risk of healthcare utilization and other clinical events (like ESRD), it could be deduced that patients died before having these.[218] Second, even though death is a competing risk, patients receiving neither therapy and/or their providers could have been less vigilant about their health in general. Neither patients may have been prescribed ACEI or ARB monotherapy, but requested refills less than one-half the time even if providers were following the guidelines that all microalbuminuric and macroalbuminuric P2DM should have ACEI or ARB monotherapy regardless of hypertension status. Similarly, using another recommendation from the ADA and VA guidelines, that all patients should be tested annually for albuminuria, we found a higher percentage of missing data for patients receiving neither therapy than ACEI therapy; providers could be ordering these tests, but patients are not showing up at the lab. Third, ACEI and ARB monotherapies could afford more protection to P2DM who are sicker than the samples studied in previous research. Lastly, neither patients were more urban and had less income, indicating a possibility for worse living conditions. Although more urban, patients receiving neither therapy still may not have had the same access to care (i.e., transportation) due to their

decreased income.[221] In fact, previous nationwide research has shown that lower income is associated with poorer physical and mental health as well as less consumption of fruits and vegetables and less physical activity among patients with diabetes.[223,224] A recently-published study of veteran P2DM found increased physical activity was associated with lower risk of mortality.[236] Environmental factors and lifestyle choices were not captured in the current study.

We were surprised to find almost one-half of newly-diagnosed P2DM were receiving neither therapy. Three main reasons exist for not adhering to guideline recommendations for P2DM with microalbuminuria or macroalbuminuria: poor quality of care, patient refusal of treatment, and presence of contraindication or adverse reaction to therapy. (Personal communication, G. Murata. December 16, 2010). Assessing patient refusal of treatment and presence of contraindication or adverse reaction to therapy is beyond the scope of this project: no data are available in the VA datasets to indicate treatment refusal and, although ICD-9-CM codes would document hyperkalemia or azotemia, these codes were not collected for the study. However, we do have the ability to explore quality of care in the VA through *post hoc* analyses.

Since the guideline recommendation of annual albuminuria assessment[54,89,145,220] is most closely related to prescribing ACEI or ARB monotherapy to prevent albuminuria progression (i.e., both recommendations address the same clinical parameter), the percentage of missing albuminuria values were compared across the three treatment groups. Although similar proportions of missing values were found for ACEI and ARB patients, those receiving neither therapy had significantly more missing albuminuria values (23.51%, 24.99%, and 39.08%, respectively; $p<0.001$ each). We also assessed

differences in percentages of missing values for HbA1c, triglycerides, and LDL to further compare quality of care across drug therapies. Neither patients were found to consistently have significantly more missing values for these clinical parameters as well ($p<0.001$ each). It should also be noted that patients receiving neither therapy had HbA1c values between ACEI and ARB patients at year 1; HbA1c values at subsequent timepoints were comparable to ACEI and ARB groups for the rest of the study. Although patients receiving neither therapy had triglyceride values between ACEI and ARB patients at the two timepoints for which they were significantly different from monotherapy values, they had the highest LDL at baseline and years 2-4 ($p<0.0083$ each; Table 13 and Appendix F, Table 5).

Comparing these findings to previous studies of VA process and outcome measures, there are more missing values of albuminuria in each drug therapy compared to a cohort study including diabetes patients from six states in 1998 and 1999.[97] ACEI and ARB patients have similar frequencies of HbA1c testing as a random sample of diabetes patients from every VA in years 2004 and 2005.[96] Likewise, annual triglyceride and LDL had similar frequencies of testing in this study compared to the cohort study.[97] Given that some proportion of veterans also receive care outside the VA, it is essential to ensure continuity of care across healthcare organizations. In fact, this importance is now highlighted in a 2009 VHA Directive.[237]

Summary of ACEI versus ARB Monotherapy

Our study found no difference in ACEI and ARB monotherapies for all endpoints studied. The second stage PSA only found a difference between these monotherapies in terms of the interactions between ACEI monotherapy and time (t+4), in which a lower

incidence rate of ED visits was found. With respect to focusing educational preventive efforts on development of diseases identified as comorbidities with higher odds for clinical endpoints, our study found diabetes complications, liver disease, fluid and electrolyte disorders, and deficiency anemias caused ESRD; history of MI, history of stroke, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, and fluid and electrolyte disorders caused IVDEs; and history of MI, CHF, and peripheral vascular disorders caused all-cause mortality. Comorbidities causing consistently higher incidence rates of healthcare utilization were CHF, peripheral vascular disorders, paralysis, chronic pulmonary disease, diabetes complications, liver disease, metastatic cancer, solid tumor without metastasis, fluid and electrolyte disorders, deficiency anemias, drug abuse, psychoses, and depression. Patients should also be encouraged to not smoke as it caused fewer IVDEs and less healthcare utilization.

The two other PSA techniques (i.e., stratification and nearest-neighbor matching) looked at the average treatment effect on the treated (ACEI patients), and found the same results as revealed with the second stage regression, lending credence to our findings. Also, the results of the sensitivity analyses confirmed robustness of our findings in case an unobserved variable exists that increases the odds of treatment selection for ESRD and all-cause mortality by up to 100%. According to Aakvik (2001), "differing odds…by a factor of 2, or 100%, must be considered a very large number given that we have adjusted for many important characteristics."[238] Our findings are not as robust to possible unobserved variables affecting treatment selection for IVDE occurrence, outpatient visits, ED visits, and hospitalizations.

Outcome Rates in the Sample Compared to Previous Studies

Studies Comparing ACEI or ARB Monotherapy to Placebo

There are some interesting findings that are revealed when comparing this study to previous studies analyzing effects of monotherapy versus placebo. Again, none of the studies were conducted exclusively in the U.S.; in particular, four of seven studies included the continent of North America as part of their international studies. Two of the studies had majority or exclusive normoalbuminuric patients upon enrollment.[46,47] Two studies had healthier patients than ours as hypertensive or obese patients were excluded, limiting external validity.[47,48] Interestingly, another study may have had sicker patients with 69% having a history of CVD, although about two-thirds of patients had baseline normoalbuminuria.[46] Clearly, subjects in these previous studies are not representative of newly-diagnosed P2DM in the U.S. In general, these studies make for easier comparisons to our study than studies of ACEI and ARB monotherapy comparisons as studies comparing monotherapies to placebo have endpoints of progression from one albuminuria category to another, CVD, or mortality. There is one exception to this.[47]

Differences in patient characteristics between HOPE MICRO-HOPE and the current study explain the differences in event rates. Specifically, the majority of patients with normoalbuminuria at baseline in the former study explains our higher rate of macroalbuminuria progression.[46,71] An almost 8-fold higher amount of patients with history of CVD in HOPE MICRO-HOPE, each about twice as likely to have another CVD event than those without,[20] also contributed to the differences, especially in light of those with history of CVD having higher risks of MI than stroke.[20] Also important is that our patients were more hypertensive and albuminuric, which is each associated with higher rates of stroke than MI.[25,239] There is also evidence that gender, smoking status,

year, and racial/ethnic composition could affect rates of cardio- and cerebro- vascular events,[203,204,240-242] all in the direction we have seen between the studies. Taking into consideration the lower IVDE rate and shorter follow-up in the current study explains the lower mortality rate for ACEI patients with the current study, but this does not ring true for neither patients. Instead, we observed a higher rate despite there being significantly fewer documented comorbidities than our ACEI patients ($p<0.0083$). Perhaps this is due to more patients receiving neither therapy receiving non-VA care as well. Although we do not know the number of patients in each drug therapy receiving non-VA care, if conditions do not affect or require patient care or treatment, they would not be coded so would not be captured in the VA datasets.[243] Compared to Ahmad et al., univariate analysis of the current study patients who were microalbuminuric at baseline did not show as dramatic a difference between ACEI and neither patients as Ahmad's ACEI and placebo patients. Although the previous study had a higher HbA1c, they were less hypertensive, but we feel univariate analysis did not sufficiently control for covariates.

The current study had similar rates of macroalbuminuria progression for ARB patients as Parving's lower dose of ARB therapy.[45] The difference in hypertensive status among placebo and neither patients across studies explains the lower progression rate in the current study. The fact that we had similar rates of progression for ARB and neither patients is due to the fact that univariate analyses did not control for difference in health status. Hypertension, albuminuria, and HbA1c differences accounted for the higher ESRD, cardio- and cerebro- vascular disease, and mortality rates seen in the studies conducted by Brenner, Lewis, and Berl.[49,53,109] Comparisons between studies,

unfortunately, have not allowed us to explain similar mortality rates observed between neither and placebo patients for this study and the study conducted by Lewis.

Studies Comparing ACEI and ARB Monotherapy

As mentioned earlier, it is difficult to compare this study to previous studies looking at differences in effects between ACEI and ARB monotherapy in P2DM for the several reasons that make this study unique in its contribution to the field. The main reason behind this is the fact that all previous studies analyzed change in albuminuria as a continuous variable, and we did not. In general, subjects in previous studies were healthier than the general population of P2DM due to their strict exclusion criteria prohibiting certain comorbidities. Additionally, subjects behaved differently during follow-up than in the current study through two main reasons: 1. patients in other studies were given dietary and/or exercise advice[123,127,130,244] and 2. patients had treatment duration maximum of one year except for one study.[121]

In terms of cardio- and cerebro- vascular disease events reported, we can compare the present study to Barnett et al.'s, in which they report in their adverse events section that 11.5% of ACEI patients and 17.5% of ARB patients suffered from fatal and nonfatal heart failure, MI, or stroke over their 5 year follow-up.[121] The current study had an 8.07% incidence in ACEI patients while there was an 8.76% incidence in ARB patients Table 22). Our mean follow-up was 2.17 years; although we do not know the mean follow-up in the DETAIL study, we know 5 years of data were available for 67.2% of their patients resulting in longer follow-up than our study. Due to implications of capturing incident CHF through ICD-9 codes, (G. Murata, Personal Communication, 2007) different definitions of combining endpoints were used where the present study

excluded CHF and included LVH. Another reason for the difference in incidence rates seen for cardio- and cerebro- vascular disease events is that 48.84% of patients in the DETAIL study had a history of CVD while 8.88% of patients in the present study had documented CVD at baseline. (This was estimated by combining history of MI, history of stroke, and CHF in Table 16, but we are unaware of the amount of people who had documented LVH at baseline.) We know from Haffner et al. that P2DM who have a history of CVD are approximately twice as likely to have another event compared to those without a history.[20] Both studies had similar proportions of microalbuminuria and macroalbuminuria at baseline. The present study also had lower mean baseline HbA1c, LDL, and triglyceride values of 7.30%, 94.56mg/dL, and 189.96mg/dL compared to 8.4%, 136mg/dL, and 202mg/dL, respectively. We do not see as dramatic of a difference between treatment groups as the previous study.

In terms of all-cause mortality, the DETAIL study reported a 4.62% and 5.00% rate in ACEI and ARB groups, respectively. Our study found 1.01% and 1.04% mortality rates in ACEI and ARB patients, respectively. Similar arguments made for differences in cardio- and cerebro- vascular disease incidence rates between studies can be applied to the differences in mortality rates between studies. Specifically, we have a shorter follow-up period, fewer people with baseline CVD, and better mean values of clinical parameters at baseline. Since approximately 2/3 of P2DM die from CVD events[3] and patients in the current study had fewer CVD events, our study results make sense in light of Barnett et al.[121]

There are limited data that can be compared to previous studies due to the majority of these studies only assessing change in albuminuria, a surrogate endpoint.

However, our event rates appear reasonable for what can be compared. We find our patients had lower rates of cardio- and cerebro- vascular disease events and mortality than Barnett's due to 5.5 times as many patients having history of CVD in the previous study, higher HbA1c, LDL, and triglyceride values in the previous study, and a longer follow-up period in the previous study.

Other Issues to Consider in Context of Study Results

Compliance

The proportion of people who switched from ACEI or ARB monotherapy to neither therapy is a combination of two factors: prescribers not writing prescriptions and patients not refilling their prescriptions. In our study a patient needed to have enough medication on-hand for a minimum of 50% of the year to be classified as receiving ACEI or ARB therapy in that year. In fact, Table 12 shows good differentiation in days supply between ACEI or ARB therapy and neither therapy. A patient needs to have the medication on-hand to be able to ingest it since this is what determines clinical effectiveness.[245] Clearly, medications with longer half-lives will be more forgiving of a less compliant patient in terms of their effectiveness. In the case of this study, because two therapeutic classes of medications are being combined for analysis, large variation in half-lives exists among the individual drugs. For instance, captopril can be dosed three times daily while losartan can be dosed once daily.

Our definition of compliance may, at first, appear to be arbitrary. We had the knowledge that 80% is the convention of determining adherence because it was the threshold that still demonstrated effectiveness in antihypertensives[246] and the knowledge

that there is no standard for what defines adequate adherence[247] in addition to the fact that as dosing regimen complexity increases (i.e., number of prescribed medications, frequency of administration), compliance decreases.[248] As seen in Table 1, P2DM generally have many prescribed medications. We note there is also evidence that compliance is lower with long-term therapy than short-term among P2DM in clinical practice and that compliance is lower in clinical practice than research studies.[246,248-250] We point to two previous studies of ARB and/or ACEI monotherapy in P2DM: one had a 46.5% discontinuation rate of ARB monotherapy at 3.4 years while the other had a 32.8% discontinuation rate for patients using ACEI or ARB monotherapy at 5 years.[49,121] Furthermore, the HOPE MICRO-HOPE study showed a treatment effect at a 65% adherence level[46]. We also note that, among clinical trials of patients with chronic diseases, in which compliance is reported, it averages 43%-78%.[251-253]

It is important to assess the rate at which patients take medication to determine the effectiveness of these medications in clinical practice.[245] Since HOPE MICRO-HOPE showed treatment effect at 65% adherence, and in this study, monotherapy was defined as having minimally 50% of medication on-hand in a year, it is reasonable to expect to see treatment effect in this setting. Additionally, several VA cardiovascular disease or diabetes studies document lower adherence for non-White veterans compared to non-Hispanic white veterans.[254] Another finding from the investigation of racial disparities is that non-White veterans are less likely to receive care outside the VA.[254] These two findings are highlighted because of the lack of published literature in non-White P2DM: increasing the adherence level would likely lead to differential selection of non-Hispanic

whites to the monotherapies, and since were unable to obtain information on non-VA care, more non-VA care would not be captured.

Due to the definition of compliance and how our data were set up, if a patient died before month 6 of a given year, that patients was considered as receiving neither therapy among ACEI/ARB versus neither comparisons, which would inherently contribute to a higher mortality rate among those receiving neither therapy. Thus, a *post hoc* analysis was conducted in which all endpoints except mortality were re-run with multivariate regression excluding patients who died to see if results changed (see Appendix F, Table 31). Similar odds ratios and incidence rate ratios were obtained in this analysis as including all patients in our sample. Having said this, there are three statistically significant differences. First, ACEI monotherapy was previously associated with lower odds of ESRD compared to neither therapy, but no longer is. Second, ARB monotherapy was previously nonsignificant and now is associated with higher odds of IVDE compared to neither therapy. Third, ARB monotherapy was previously nonsignificant and now is associated with higher odds of ED visits compared to neither therapy. A direct interpretation of these results across the analyses is that the data suggest that patients who died were more likely to have ESRD, less likely to have IVDE, and less likely to have ED visits since the majority of deaths occurred in the neither group. Due to similar point estimates across both types of analysis, we can say there was no clinically significant difference in these analyses.

<u>The VA as a "Closed System" and VA-Medicare Dual Enrollees</u>

As of July 9, 2001, veterans who were exposed to Agent Orange and/or other herbicides were allowed to receive compensation for type 2 diabetes because it was

added to the list of conditions associated with Agent Orange and herbicide exposure.[255] This means that these veterans with this exposure have no financial incentive to go outside the VA Healthcare System because they have no copayments associated with outpatient medications or visits.[256] While all veterans are allowed to apply for compensation of VA healthcare benefits, those without a service-connected disability (including Agent Orange exposure) are placed on a sliding copayment scale based on income.[256] Lastly, patients with an annual household income and/or net worth below the VA threshold are also exempt from copayments.[257] Using Means Test data available and assuming all patients with missing data are above the threshold, we find 74.44% of our sample had no copays for all VA care and VA prescribed medications. For those veterans who were fortunate enough to not fall into these categories, and thus have copayments, receiving VA healthcare benefits comes without having to pay premiums. For instance, a majority of our sample could have applied for Medicare Part D to receive medications with copayments before reaching "the donut hole", but they also would have had to pay premiums to receive these medications, creating a financial disincentive. Furthermore, despite lack of a gold standard for assessing compliance, rates of prescription refills are accurate in a closed pharmacy system such as the VA as long they are followed longitudinally.[193,247,258,259] In fact, recent evidence shows that VA cardiovascular disease patients who were "ideal recipients" for ACEIs were more likely to receive these medications upon discharge compared to non-VA patients.[260]

Despite these arguments for why a small amount of outcomes and healthcare utilization was not captured in VA datasets, we acknowledge that undoubtedly, some services were provided outside the VA Health Care System. For instance, the 2001

National Survey of Veterans found that, among patients receiving VA care, roughly one-third only used VA for medical care while two-thirds used a combination of VA and non-VA care in the previous year.[261] We note this utilization rate was obtained before type 2 diabetes was declared to be associated with Agent Orange and herbicide exposure.[256] In terms of study implications, we can definitively say in light of this limitation that findings for all-cause mortality are robust to this circumstance: our method of capturing all-cause morality is independent of healthcare organization.[262]

In spite of this, expert opinion exists that patients use VA for certain conditions and non-VA for others before using VA for those conditions as well (Personal communication, G. Murata, December 16, 2010). Possible implications of this circumstance include the higher rate of ESRD development seen in this study (0.79% over 2 years) compared to UKPDS 64 (0.80% over 10 years) and the baseline prevalence of macroalbuminuria (8.00% versus 0.70% in UKPDS)[71] due to longer lead time than expected with newly-diagnosed diabetes patients. Also because of the use of non-VA services for certain conditions, ESRD development could be due to acute conditions not documented in VA ICD-9-CM codes for which ACEIs or ARBs are not effective. (Personal communication, G. Murata, December 16, 2010). Still, unless obtaining care outside the VA differentially affects the odds of selection of ACEI or ARB monotherapy beyond what is controlled with PSA, PSA findings should remain the same.

Internal and External Validity

As mentioned above, our common support was excellent, meaning we have internal validity because there was enough overlap between monotherapy propensity score distributions to provide unbiased estimates of effect. Additionally, the sensitivity

analyses of ESRD and all-cause mortality show even if an unobservable characteristic affects treatment selection, it would have to change the odds of choice by more than double, giving even more evidence of causality.

Also because our common support had substantial overlap, were able to estimate ATT with good precision[163] and to maintain generalizability to veteran P2DM because only approximately 27% of our patients were not able to be matched in PSA. Also in terms of generalizability, all of the states in the United States are represented as well as the District of Columbia and Puerto Rico. We would have a hard time extending this to women or younger individuals since these people were not included in the study. As the VA has achieved the 90th percentile in diabetes measures for quality of care, it may be difficult to extend these results to patients receiving care outside the VA. However, there are two alternate hypotheses. The first is that patients who have worse LDL and HbA1c may be more likely to show a difference in monotherapies as there may be more complications since these are risk factors. The second is that there may not be differences because of previous studies assessing patients with various blood pressure measurements, obesity, HbA1c, lipid profiles, and albuminuria status showed no difference in the surrogate marker in the short-term.

Limitations

Documentation

As with any database analysis, the conclusions of this study rely on the accuracy of the data. However, technical reports from the VA Health Economics Resource Center show agreement between electronic medical records and the national datasets to be about

99% for inpatient and outpatient records.[263,264] Additionally, capturing all-cause mortality with our methods has been found to capture approximately 97% of deaths in VA patients in- and out- side of the VA Health Care System.[262]

On that note, in an effort to control for history, inclusion of ICD-9 codes pertaining to history of MI or stroke were included. Once again, data inaccuracy may have lead to misclassification, especially for smoking status, family history of CVD, and LVH as it is noted that this is rarely coded, at least locally (Personal communication, G. Murata, January 8, 2008). In fact, "the very low rates for family history of CVD probably reflect the inadequacy of [the] data sources rather than the true genetic predisposition. After all, diabetes and vascular disease have strong familial tendencies." (Personal communication, G. Murata, December 16, 2010). We believe this also may have happened for documentation of obesity, cardiac disease, and ischemic stroke. Specifically, our documented prevalence of obesity is lower than the 62.4% found among P2DM in the U.S. and there is evidence that doctors underdiagnose obesity 25-50% of the time.[265-267] There is also evidence that cardiac disease can be under-reported in ICD-9 codes although this finding was reported in a different disease state.[268] Lastly, a study conducted at one VA medical center between 1995 and 1997 revealed 15-20% of inpatients with an ICD-9 code of stroke did not actually have one; this finding was mostly related to ICD-9-CM codes 433.X0 and 433.X1, which, of the patients with these codes, only 2% and 20%, respectively, had strokes.[269] Although using ICD-9 codes makes rates comparable to other studies relying on ICD-9 codes, it biases overall rates of baseline conditions as well as outcomes. Not only does use of ICD-9 codes probably miss some patients, but it also biases for disease severity. (Personal communication, G.

Murata, December 16, 2010). In particular, researchers who compared patients identified through two different methods, HbA1c ≥6.5% and problem lists versus ICD-9 codes for hospitalization and visits, found the former method identified patients with less severe disease. (Personal communication, G. Murata, December 16, 2010).

Also, we were not able to capture diagnoses at other healthcare organizations, and there is evidence that VA-Medicare dual enrollees seek care outside the VA. This may have influenced true prevalence rates of baseline characteristics and incidence rates of outcomes. However, because we do not expect misclassification to be different between ACEI and ARB patients, we can treat this data as missing completely at random.[270] Furthermore, unless care outside the VA differentially affects odds of treatment selection beyond what was found to be controlled with PSA, it should not impact PSA findings. Lastly, medications within each therapeutic class are assumed to have the same effects on progressive nephropathy, cardio- and cerebro- vascular disease events, and all-cause mortality. Having said this, no studies have been identified showing a difference between medications within the same therapeutic class, within diabetes or any other cardiovascular disease patients.

Limited Blood Pressure Information

In the VA administrative datasets we were only able to capture diagnosis of hypertension through ICD-9-CM codes, limiting blood pressure information to a dichotomous, rather than continuous, variable. Although the UKPDS 38 found no significant difference in renal failure or all-cause mortality for a 10 point difference in systolic blood pressure and a 5 point difference in diastolic blood pressure, the study revealed a 34% difference for their composite vascular disease endpoint (p=0.019).[25]

Additionally, JNC-7 states that for each 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure there is a doubling of risk of cardiovascular disease.[70]

Lack of Race/Ethnicity Data

Although we previously discussed the important disparities in terms of acquiring complications from type 2 diabetes and the differing risk of developing more severe complications in many races and ethnicities, we unfortunately had a lot of missing data for this variable which would result in a substantially reduced sample size. As found in the U.S. population, African American veterans are more likely to have renal disease and lower limb amputations.[254,271] Among cardiovascular disease studies, mixed results were found regarding racial disparities, including survival differences, between African Americans and non-Hispanic whites in the VA: 3 studies found African Americans had similar or less all-cause mortality while 2 other studies found African Americans had higher all-cause mortality.[254] Diabetes studies in the VA also had conflicting findings for racial disparities, but testing frequency as well as blood pressure, glycemia, and lipid control were generally worse for non-Whites than non-Hispanic whites.[254] Because the U.S. and VA populations are becoming more diverse we elected to keep individuals with missing data for analysis, especially in light of previous studies with majority non-Hispanic whites.

The current study still was able to obtain information pointing to higher risks in these races/ethnicities. For instance, African Americans, Mexican Americans, American Indians, and Native Hawaiians have higher risk of heart disease than Caucasians, mostly due to their higher rates of obesity and diabetes.[272] Similarly, African Americans have

higher risk of stroke than Caucasians, mostly because of higher rates of hypertension, diabetes, and obesity.[272] We were able to capture diagnosis of hypertension, diabetes, and obesity, hopefully accounting for most of these discrepancies although we note we were unable to extract the severity of hypertension and believe obesity was not reported as frequently as it should have been based on other estimates of obesity among P2DM.[265]

Lack of Lifestyle Information

Controllable risk factors for atherosclerosis include LDL, tobacco, hypertension, diabetes, obesity, and physical inactivity.[272] We captured LDL, previous and current tobacco use, hypertension, obesity, and diabetes information. Problems relating to hypertension and obesity information have already been described above. In this section we are focusing on physical activity and mentioning dietary consumption since it is related to LDL, hypertension, and obesity. Obviously, obesity and hypertension are also related to physical inactivity, especially in P2DM. Inappropriate nutrition and lack of physical activity increase the likelihood of acquiring long-term diabetes complications, in particular, heart disease.[273]

High cholesterol is a major risk factor for coronary artery disease, MI, and stroke due to atherosclerosis.[272] As LDL and platelets are deposited in the arterial walls leading to the heart and brain, an embolus becomes more likely.[272] If the embolus blocks a blood vessel leading to the heart, an MI results.[272] Alternately, if it blocks a blood vessel leading to the brain, a stroke can occur.

In a survey of veteran P2DM who were seen at a VA in Washington state between 2005 and 2006, 22% self-reported eating no fruits or vegetables per day in the last week, 64% reported eating between 1 and 4 fruits or vegetables per day in the last week, 42%

reported eating a diet rich in fats, and 33% admitted to not following their diabetic meal plan.[274] This same study found 9% did not engage in any physical activity while another 33% reported only light physical activity in the last week.[274]

Although we did not capture dietary consumption we do have LDL and triglyceride levels that are related to food choices. In fact, incorporation of food choices may have actually led to that information ultimately being dropped out of the regression models due to multicollinearity. Years ago there was hope that a better definition of diet for P2DMs would lead to better health outcomes. This included caloric restriction and percentage of types of foods consumed (i.e., carbohydrates versus proteins). There has been no consensus about what type of diet leads to better outcomes. For instance, the amount of protein consumed has not been found to be related to ESRD development or progressive renal impairment.[89]

Lack of Control over Unobservable Variables

Although every attempt was made to control for selection bias, PSA is not a perfect technique as it only controls observable variables. In theory, these observable patient characteristics are exactly what the provider would know when faced with the decision of which monotherapy to prescribe in these newly-diagnosed veteran P2DM. However; we did lose information on race and ethnicity; did not have information about lifestyle choices; were not aware of NSAID, antihypertensive, or antihyperlipidemic usage; did not have the exact blood pressure measurements; and were unable to capture care received outside the VA. Despite inability to control for unobservables, the sensitivity analyses revealed that we can be fairly confident in our results for ESRD and all-cause mortality. This means this study's estimates of effect for these clinical

outcomes are "causal" in nature. We cannot be as confident in the results pertaining to IVDE occurrence and healthcare utilization. The researchers remind the readers that those outcomes would only change if an exogenous variable exists that is changing odds of treatment assignment

Summary of Conclusions and Significance

Contribution to the Literature

Of the sixteen previously-published studies comparing ACEI and ARB monotherapies, only three controlled for albuminuria in their analyses.[121-123] Two of these three studies assessed the change in geometric mean albuminuria excretion rate while the third advised their patients to follow a special diet. This pattern was seen for the other studies as well. Looking at the sixteen studies as a whole, except for a safety endpoint in one study, the only outcome that has been assessed in ACEI and ARB monotherapy is related to change in albuminuria. This means that before this study there was a lack of information pertaining to clinical outcomes as albuminuria was a surrogate endpoint. This study is also the first to provide information about healthcare utilization when ACEI and ARB monotherapies are used in P2DM. Second, the previous studies had small sample sizes of relatively healthy individuals: 80% excluded patients with severe hypertension or enrolled patients who had a mean systolic blood pressure <140mmHg, 60% excluded patients with recent CVD or stroke, and 60% excluded patients with cancer. Third, no previous study has been conducted in the U.S., and there is extensive literature reporting the differences in complications and severity of type 2

diabetes across race/ethnicity groups. The U.S. population is generally more diverse than countries represented from previous studies; the VA also has a diverse population.

Additionally, as there are different rates of cardio- and cerebro- vascular disease across countries[20] as well as different patterns of healthcare utilization across countries,[275,276] this study is the most directly applicable to the U.S. population. Fourth, this is only the second study with treatment and/or follow-up lasting more than one year.[121] Fifth, this is only the second study that enrolled subjects diagnosed with type 2 diabetes within the year.[244] The previous study enrolled patients with baseline normoalbuminuria who were advised to follow a special diet and exercise; these people were not representative of newly-diagnosed P2DM as roughly one-quarter have microalbuminuria or macroalbuminuria upon diagnosis, and although P2DM may be counseled on a special diet or exercise, this is not communicated systematically in clinical practice. Furthermore, patients are more likely to adhere to instructions when being watched more closely (i.e., in a trial) according to the Hawthorne Effect. So, not only does this study supplement the published literature by providing the first comparisons of several clinically important outcomes, but this study is also most applicable to P2DM in the VA and U.S., populations that have been previously ignored, in terms of patient comorbidities, composition, and habits.

Particularly important findings relate to ACEI monotherapy being effective at reducing all-cause mortality compared to neither therapy. This could be added, at a lower grade of evidence, to the HOPE findings of ramipril reducing risk of all-cause mortality compared to placebo. Even more important, because of comparable baseline characteristics between treatment groups, are the head-to-head comparisons of ACEI and

ARB monotherapy, for which no significant differences were found for all endpoints. Until this study, it has just been assumed in clinical practice that these two therapeutic classes achieved comparable effects. However, previous notions in clinical practice have been subsequently dispelled by research,[277-279] which provided the impetus for this study. Thus, this study provides the first support for evidence-based medicine that can be practiced in P2DM; it also has particular focus on the U.S. population. Also of interest were comorbidities identified with increasing odds of clinical outcomes and/or incidence rates of healthcare utilization. Further research is needed in other populations to see if comorbidity findings hold true in other healthcare organizations.

Clinical Practice Guideline Implications

Due to the study contributions just cited, current guidelines should be updated, keeping in mind that PSA is a statistical technique used to mimic randomization. The first guideline, the ADA's Standards of Medical Care in Diabetes—2011, should update the section entitled, "Nephropathy Screening and Treatment," which states, "there are no adequate head-to-head comparisons of ACEIs and ARBs."[220] Our study findings for ESRD development using PSA can be added as Level of Evidence B (supportive evidence from well-conducted cohort studies). Later, these guidelines mention ACEIs reduce MI, stroke, and death in patients with diabetes, giving support for this medication class in microalbuminuric patients.[220] This study's findings of head-to-head comparisons using PSA relating to IVDE and all-cause mortality should be added, again with Level of Evidence B to further support ARBs' effects on these outcomes.

Turning to VA guidelines, VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus 2010 recommends use of an ACEI or ARB with kidney disease

(Strength of Recommendation A refers to preferential use of these therapeutic classes over other medication classes).[145] Similar to the ADA proposed update, we can say there are no differences in effectiveness between ACEIs and ARBs; this study provides Quality of Evidence II-2 (well-designed cohort), which provides moderate grade evidence directly linked to health outcomes for which no previous evidence exists for these head-to-head comparisons. This can also be incorporated into VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease in Primary Care 2007 recommendations of using ACEIs or ARBs to slow nephropathy progression in diabetes patients with microalbuminuria or macroalbuminuria.[89] In its section entitled, "Summary of Supporting Studies of ACEI/ARB Treatment," study findings of the head-to-head therapies with PSA can be added in terms of nephropathy progression; IVDEs, all-cause mortality, and healthcare utilization can be added as well. Cardiovascular disease and mortality risk are mentioned earlier in these guidelines for patients with chronic kidney disease, allowing this information to be relevant to the guideline. The VA/DoD Clinical Practice Guideline for Diagnosis and Management of Hypertension in the Primary Care Setting 2004 states, "ARBs appear to have similar short-term effects as ACEIs in patients with diabetes and nephropathy with fewer side effects. However there are no long-term outcome trials comparing an ACEI to an ARB to determine if these agents provide similar long-term benefits in patients with diabetes."[144] Our findings address this literature gap.

Focusing on identified comorbidities, the VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus 2010's[145] Screening Module S allows the opportunity for clinicians, while screening for diabetes based on its risk factors, to counsel on

interventions to prevent comorbidities that were found to increase odds ratios and/or incidence rate ratios in our study sample while simultaneously counseling on prevention of diabetes. Our study similarly affects the VA/DoD Clinical Practice Guideline for Diagnosis and Management of Hypertension in the Primary Care Setting 2004.[144] Since clinicians are advised to educate hypertensive patients about lifestyle modification in relation to other cardiovascular risk factors, communication regarding the significance of preventing some comorbidities identified as having increased odds of IVDE is already occurring. The remaining comorbidities identified as having increased healthcare utilization in this study should also be mentioned at this time since hypertension is a risk factor for diabetes. Obviously, these comorbidities would peak patient interest if implications on quality of life were stressed more than healthcare utilization.

Contribution to Public Policy

The federal government recognized the need for reducing nephropathy in patients with diabetes by declaring two objectives in Healthy People 2010.[10] This study provided information relating to Objective 4-7, which pertains to reducing the number of patients with incident cases of ESRD by 31%. In particular, ACEI monotherapy, compared to neither therapy, had a lower odds of ESRD development ($p<0.01$). Furthermore, patients with the comorbidities liver disease, fluid and electrolyte disorders, and deficiency anemias have 7.40, 7.71, and 5.81 higher odds of ESRD development, emphasizing the need for preventive measures of these comorbidities. According to Objective 4-8, there is a recognized need to increase the proportion of patients with diabetes and proteinuria who receive medical therapy to attenuate progression to chronic renal insufficiency. This study provides additional evidence of the importance of ACEI monotherapy and

simultaneously shows a substantial amount of patients not receiving ACEI or ARB monotherapy. Although it can be argued that patients not receiving therapy may be, in fact, receiving prescriptions at other healthcare organizations, this is unlikely given the high mortality rate in these patients and that minimally three-fourths of our sample would receive medications for free in the VA.

Healthy People 2010 also calls for a 10% reduction in CVD-related deaths and a 43% reduction in all-cause mortality.[10] As this is the only study comparing ACEI and ARB monotherapy for CVD endpoints and assessed treatment differences in all-cause mortality, this study provides evidence of a significant reduction in all-cause mortality for ACEI and ARB monotherapies compared to neither therapy ($p<0.001$ each) while also finding a nonsignificant difference between ACEI and ARB monotherapies. We also found a higher odds of IVDE occurrence for ACEI patients compared to neither patients while also finding no difference between ACEI and ARB monotherapies. Lastly, we found history of MI, history of stroke, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, and fluid and electrolyte disorders had higher odds of IVDE whereas history of MI, CHF, and peripheral vascular disorders had higher odds of all-cause mortality. This study provides the best evidence to date in addressing these endpoints for ACEI and ARB monotherapies in the U.S. population.

Contribution to the VA

Almost one-half of our sample received neither therapy meaning that it is essential for clinicians to prescribe, educate, and counsel patients on the importance of adhering to ACEI or ARB monotherapy. Findings of a recent study of cardiovascular patients who were “ideal candidates” for ACEIs were more likely to receive these in VA

than non-VA settings, underlining the importance of these activities. Since a proportion of the sample receives a combination of VA and non-VA care, continuity of care across healthcare organizations is a priority and must be ensured. This is emphasized in the 2011 ADA guidelines: "there is persistent variation in quality of diabetes care across practice settings…that indicates the potential for further improvements in diabetes care."[220]

The current study results are directly applicable to the VA as patients from all states plus the District of Columbia and Puerto Rico are represented. Additionally, for patients receiving ACEI or ARB monotherapy, about three-fourths were matched with PSA. This finding indicates clinicians have clinical equipoise for the majority of P2DM, making the results generalizable to veteran P2DM. Identification of lower odds of ESRD development associated with ACEI monotherapy compared to neither therapy ($p<0.01$) can confer a cost savings to the VA if prescribing of and counseling on implications of compliance with ACEI monotherapy was systematically increased. However, since ACEI and ARB monotherapies were associated with reduced all-cause mortality compared to neither therapy, our results also show ACEI or ARB monotherapy were associated with higher incidence rates of outpatient visits, ED visits, and hospitalizations compared to neither therapy. This means a higher burden on healthcare resources could ensue. Alternately, it could mean those who are more compliant with their medication are, in general, more vigilant about their health, so they are going to the doctor more often than those who are less vigilant, which could lead to less healthcare strain in the long run. Specific to comparisons of ACEI and ARB monotherapies, clinicians should prescribe what is on formulary, and if patients are intolerant to an ACEI, should not

hesitate to change patients over to an ARB. In fact, this is exactly what the VA guidelines advocate.[89,144,145]

Obviously, it is unethical to hold treatment that would otherwise help patients; because of this, healthcare providers are required to uphold the Hippocratic Oath. An appropriate way to offset healthcare resources would be on measures aimed at preventing comorbidities identified with higher odds of clinical outcomes and/or higher incidence rates of healthcare utilization. CHF, chronic pulmonary disease, diabetes complications, liver disease, solid tumor without metastasis, fluid and electrolyte disorders, deficiency anemias, drug abuse, psychoses, and depression had higher incidence rates of outpatient visits, ED visits, and hospitalizations. Although these comorbidities stem from several causes, each has at least one modifiable risk factor. For instance, smoking contributes to CHF, chronic pulmonary disease, and solid tumor without metastasis; exercise is associated with lower likelihood of diabetes complicated, drug abuse, and depression; and tattoos and intravenous drug use contribute to liver disease and psychoses. Of course, the veteran population is more at risk for drug abuse, psychoses, and depression purely due to exposure to combat situations when these patients were on active duty. Also, Agent Orange exposure can contribute to CHF, liver disease, and solid tumor without metastasis.[280] Exactly because these patients are already at higher risk emphasizes the importance of counseling on reducing and avoiding behaviors and attitudes that place these patients at higher risk of developing these comorbidities. VA guidelines already address preventing a substantial proportion of these comorbidities by advising clinicians to recommend lifestyle modification of risk factors contributing to these comorbidities in veterans at high risk for developing type 2 diabetes. This study

provides supplemental information by giving clinicians specific disease states in which to emphasize patient education efforts.

APPENDICES

APPENDIX A:

HRRC APPROVAL FORM

THE UNIVERSITY OF NEW MEXICO
HEALTH SCIENCES CENTER

Human Research Review Committee **MSC 08 4560 BMSB Room B71**
1 University of New Mexico~Albuquerque, NM 87131-0001
(505) 272-1129 Facsimile (505) 272-0803
http://hsc.unm.edu/som/research/hrrc/

04-Apr-2008

Khan, Nasreen
Pharmacy Practice

SUBJECT: HRRC Approval of New VA Research Protocol HRRC#: 08-094 Study Title: Comparison of Monotherapy with Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blocckers in Improving Health Outcomes among Veteran Patients with Type 2 Diabetes Type of Review: Expedited Review Approval Date: 01-Apr-2008 Expiration Date: 31-Mar-2009

Dear Dr. Khan:

The Human Research Review Committee (HRRC) has reviewed and approved* the above-mentioned research protocol including the following:

1. **HRRC Application received 031908**
2. **Protocol received 031908**

It is the responsibility of the Principal Investigator to ensure that all requirements of the VA are met and that documented VA approval has been obtained prior to study initiation (i.e., subject enrollment and/or data collection).

Consent decision: Waived the requirement for informed consent HIPAA Authorization Addendum waived

Medical Records are not to be flagged.

This study is approved to enroll only the number of subjects listed in the application, protocol and consent form(s). If the PI wants to enroll additional subjects, it is the responsibility of the PI to submit an Amendment/Change to the HRRC before the approved number of enrolled subjects is exceeded. If increased enrollment is requested, the application, protocol and/or consent form(s) must also be amended to include the new target.

Sincerely, Mark Holdsworth, Pharm.D., BCOP Executive Chair Human Research Review Committee

APPENDIX B:

TABLE OF IDENTIFIED STUDIES COMPARING ACEI OR ARB MONOTHERAPY TO PLACEBO IN P2DM

TABLE OF IDENTIFIED STUDIES COMPARING ACEI OR ARB MONOTHERAPY TO PLACEBO IN P2DM*

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference; Notes

ACEI (Ramipril 10mg daily); Placebo	Double-blind RCT for 4.5y. Study conducted in S. America, Europe, UK, N. America. N=3,577. ACEI, N=1,808. Placebo, N=1,769.	Normo or micro (micro=32%). Type 2DM=97.5%. Mean age=65.4y. Mean BMI=28.8kg/m^2. Mean BP=142/80mmHg. Mean duration with diabetes=11.4y. Current smoker=15%. Hx of CVD=69.0%.	Macro, severe renal dx, CHF, ejection fraction<0.4, uncontrolled HTN, MI or stroke within 4wk	• 8.4% of pts in placebo developed macro compared to 6.5% of pts in ACEI at 4.5y (p=0.027).
				  • NS diff for dialysis
				  • Sig diff for combined endpt of developing macro, dialysis, or laser therapy for retinopathy (17.6% for placebo vs. 15.1% for ACEI, p=0.036).
				• The combined outcome of MI, stroke, or cardiovascular death was reached in 19.8% of placebo pts compared to 15.3% of ACEI pts at 4.5y (p=0.0004).
				  • Sig diffs:
				  Placebo ACEI p-value
				  MI 12.9% 10.2% 0.01
				  Stroke 6.1% 4.2% 0.0074
				  CV death 9.7% 6.2% 0.0001
				• Total mortality was reached by 14.0% of placebo pts vs. 10.8% of ACEI pts (p=0.004).
				  • NS diffs for unstable angina, heart failure, worsening angina
				  • Sig diffs:
				  Placebo ACEI p-value
					Gerstein (HOPE)[46]. Stopped 6 mo early b/c found famipril was beneficial. Adherence rate=65% for ramipril (NR for placebo).

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference; Notes
				Revasc. 16.4% 14.0% 0.031 TIA 5.9% 4.4% 0.04	
ACEI (Enalapril 10mg daily); Placebo	Double-blind RCT for 6 y. Study conducted in Israel. N=156. ACEI, N=77. Placebo, N=79.	Normo. Mean age=54.9y. Mean duration of diabetes=5.8y. Mean BMI=24.7kg/m^2. Current smokers=15%. Mean BP NR. Mean HbA1c=9.2%	HTN; CA; autoimmune, hepatic, cardiovascular, or renal dx; BMI≥30kg/m^2.	At 6 y, mean UAER was 26.5mg/24h in placebo group and 15.8mg/24h in ACEI group (p=0.001)	Ravid[47] In sample size calculation assumed 15% of normotensive normoalbuminurics will develop microalbuminuria in 6y.
ACEI (Enalapril (dosing NR)); Placebo	Single-blind RCT. Study conducted in India. N=103. ACEI, N=52. Placebo, N=51.	Micro. Mean duration of diabetes=9.3y. Age range=43-55y. Mean HbA1c=8.0%. Mean BP=132/81 mmHg.	Obesity; hx or evidence of nondiabetic renal, systemic, cardiac, or hepatic dxs; GFR<90mL/min	• At 5 y, 23.5% of placebo pts and 7.7% of ACEI pts developed macro (p<0.001) • Annually, albuminuria decreased at a mean rate of 16.7% in the ACEI group while it increased at a mean rate of 12.3% in the Placebo group.	Ahmad[48]
ARB (Irbesartan 150mg daily); ARB (Irbesartan 300mg	Double-blind RCT for 2y. Study conducted in Europe, Australia, Canada, UK.	Micro. Mean BP=153/90mmHg. Mean age=58.0y. Mean BMI=30.1 kg/m^2. Mean duration with diabetes=9.7y.	Nondiabetic kidney dx, CA	14.9% of pts in the placebo group reached macro at 2y, compared to 9.7% for ARB 150mg (p=0.08) and 5.2% for ARB 300mg (p<0.001).	Parving[45]. At end of study, 56% of those in placebo group were taking antihypertensives. Adherence rate=81% for ARB

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference; Notes
daily); Placebo	N=590. ARB 150mg, N=195. ARB 300mg, N=194. Placebo, N=201.	Mean HbA1c= 7.1%. Hx of CVD=26.6%. Mean CrCl=109mL/min/1.73m^2. Mean TG=183.1mg/dL. Mean LDL=140.0mg/dL.			150mg and 89% for ARB 300mg (NR for Placebo). ARB negated nephropathy progression.
ARB (Losartan 50-100mg daily); Placebo	Double-blind RCT for 3.4y. Study conducted in Asia, Europe, Central America, N. America, S. America. N=1,513. ARB, N=751. Placebo, N=762.	Macro. Mean BP=153/82mmHg. Mean age=60y. Mean BMI=19.4 kg/m^2. Mean HbA1c= 8.4%. Current smokers= 18.3%. Mean LDL=142 mg/dL. Mean TG=219 mg/dL. Hx of MI=11.2%	Nondiabetic renal dx, MI or CABG within 4 wk, CVA or PTCA within 6mo, TIA within 1y, hx of heart failure	• 25.5% of pts in Placebo group reached ESRD at 3.4y, compared to 19.6% for ARB (p=0.002). • ARB had 35% reduction in mean albuminuria vs. placebo's 20% increase (p<0.001).	Brenner (RENAAL)[49]. Planned to have mean f/u of 4.5y, but stopped early b/c of new evidence that ACEIs may benefit pts with renal impairment in terms of CVD events (ACEIs were excluded in this study).
ARB (Irbesartan 300mg daily); CCB (Amlodipine 10mg daily); Plabebo	Double-blind RCT for 2.6y. Study conducted in N. America, S. America, Europe, Asia, Middle East,	Macro. Mean age=58.9y. Mean BMI=30.8kg/m^2. Mean BP=159/87mmHg. Insulin use=58.0%. Hx of CVD=28.7%. Mean HbA1c=8.2%	Normotension	• For the combined endpt of doubling SCr, development of ESRD, or death, 39.0% of placebo pts, 41.1% of CCB pts, and 32.6% of ARB pts reached this endpt. Compared to ARB pts, a sig higher proportion of placebo and CCB pts reached this endpt (p-values=0.02 and 0.006,	Lewis (IDNT (renal))[53]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference; Notes
	Australia. N=1,715. ARB, N=579. CCB, N=567. Placebo, N=569.			resp). • 14.2% of the ARB group, 18.3% of the CCB groups, and 17.8% of the placebo group developed ESRD (p-value>0.05) • NS diffs for death (incidence rates much closer than ESRD) • NS diffs for combined endpt of death from CVD, nonfatal MI, hosp for heart failure, permanent neurological defect from a cerebrovascular event, or lower limb amputation above the ankle	
ARB (Irbesartan 300mg daily); CCB (Amlodipine 10mg daily); Placebo	Double-blind RCT for 2.6y. Study conducted in N. America, S. America, Europe, Asia, Middle East, Australia. N=1,715. ARB, N=579. CCB, N=567. Placebo, N=569.	Macro. Mean age=58.9y. Mean BMI=30.8kg/m^2. Mean BP=159/87mmHg. Insulin use=58.0%. Hx of CVD=28.7%. Mean HbA1c=8.2%	Normotension	• Having a CVD event before renal failure, death, or censorship occurred in 32.5% of placebo pts, 28.3% of CCB pts, and 29.7% of ARB pts (p>0.2 for each comparison) • Developing CHF occurred in 13.8% of the ARB group, 19.9% of the placebo group, and 25.9% of the CCB group. Compared to the ARB group, the other groups had a sig higher rate (p=0.048 and p=0.004, resp)	Berl (IDNT (CVD))[109]

***=** 100% of subjects have type 2 diabetes unless otherwise stated; **ACEI=** angiotensin-converting enzyme inhibitor; **ARB=** angiotensin II type 1 receptor blocker; **BMI=** body mass index; **btwn=** between; **BP=** blood pressure; **CA=** cancer; **CABG=** coronary artery bypass graft; **CCB=** calcium channel blocker; **CHF=** congestive heart failure; **CrCl=** creatinine clearance; **CVA=** cerebrovascular accident; **CVD=** cardiovascular disease; **d=** days; **dx=** days; **endpt=** endpoint; **ESRD=** end-stage renal disease; **f/u=** follow-up; **h=** hours; **HbA1c=** glycosylated hemoglobin; **HTN=** hypertension; **hx=** history; **LDL=** low-density lipoprotein; **macro=** macroalbuminuria; **mo=** month; **normo=** normoalbuminuria; **NR=** not reported; **NS=** nonsignificant; **PTCA=** Percutaneous transluminal coronary angiography; **pts=** patients; **RCT=** randomized controlled trial; **revasc.=** revascularization; **SCr=** serum creatinine; **sig=** significant; **TG=** triglycerides; **TIA=** transient ischemic attack; **UAER=** urinary albumin excretion rate; **wk=** weeks; **y=** years

APPENDIX C:

TABLE OF IDENTIFIED STUDIES COMPARING ACEI OR ARB MONOTHERAPY TO ACTIVE CONTROLS IN P2DM

TABLE OF IDENTIFIED STUDIES COMPARING ACEI OR ARB MONOTHERAPY TO ACTIVE CONTROLS IN P2DM

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
ACEI (Captopril 50mg twice daily); BB (Atenolol 50-100mg daily)	Double-blind RCT for 9y. Study conducted in UK. N=758. ACEI, N=400. BB, N=358.	Normo (75.6%)/Micro (17.9%)/Macro (6.5%). Mean age=56.2y. Mean BMI=159/94mmHg. Receiving HTN drugs=35.5%. Current smokers=22.9%. Mean HbA1c=6.9%.	Normotension	• For albuminuria progression, 31% of ACEI group & 26% of BB group had micro at 9y (p=0.31) while 5% of ACEI group & 10% of BB group had macro at 9y (p=0.09). • Of 21 clinical endpts related to diabetes, none were sig btwn groups. Clinical endpts capture micro- & macro- vascular complications as well as death.	UKPDS 39[110] Adherence=80% for ACEI & 74% for BB.

ACEI (Fosinopril 20mg daily); CCB (Amlodipine 10mg daily)	Open-label RCT for 2.5y. Study conducted in Italy. N=380. ACEI, N=189. CCB, N=191.	Normo. Mean age=63.1y. Mean duration with diabetes =10.6y. Current smokers=5.8%. Mean BMI= 30.6kg/m2. Mean BP= 171/94mmHg. Mean HbA1c= 7.0%. Mean TG=156mg/dL.	Normotension ; hx of CVD, stroke, or other condition with a poor prognosis	• ACEI was sig better for:
				  • Any major vascular event (2.6% vs. 5.0%, p=0.030)
				  • Any major vascular event or any procedure (2.6% vs. 5.0%, p=0.030)
				  • Any death, vascular event, or procedure (3.6% vs. 6.3%, p=0.036)
					Tatti (FACET)[119] To control BP, amlodipine was given to 30.7% of fosinopril pts while fosinopril was given to 26.2% of amlodipine pts.

ACEI	Double-blind	Normo	Normotension	• Among those with BL normo or	Chan[116]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
(Enalapril 10-40mg daily); CCB (Nifedipine 20-40mg twice daily)	RCT for 1y. Study conducted in Europe. N=335. ACEI, N=168. CCB, N=167.	(42.2%)/Micro (33.3%)/Macro (24.5%). Mean age=58.0y. Mean BMI= 24.9kg/m^2. Mean BP=169/93 mmHg. Mean HbA1c=7.5%. Mean TG=1.99 mmol/L. Mean LDL=3.62mmol /L.	, hx of CVD	macro there were no between group diffs for progression of albuminuria (p=0.46 and p=0.086, resp) • Among those with BL micro, those on CCB were more likely to progress to macro than those on ACEI (p=0.046)	

ACEI (Cilaprazil 2.5mg daily); CCB (Amlodipine 5mg daily)	Double-blind RCT of 3y. Study conducted in Italy. N=44. ACEI, N=22. CCB, N=22.	Normo (59%)/Micro (41%). Mean age=54.3y. Mean duration with HTN=3.2y. Mean duration with diabetes= 5.4y. Mean TG=2.1mmol/L. Mean BMI= 29.9kg/m^2.	Endocrine HTN; heart failure class III or IV; hx of MI, LVH, or AV blockage of 2^{nd} or 3^{rd} degree; HbA1c>10% with variations>30 % in past 6mo; BMI> 35kg/m^2	• NS diffs btwn groups at 3y for reduction in UAER
				  • BL Normo (ACEI=33.0% vs. CCB=25.0%, p>0.05)
				  • BL Micro (ACEI=30.8% vs. CCB=26.5%, p>0.05)
					Velussi[111]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
			within last 6mo.		
ACEI (Lisinopril 10-20mg daily); CCB (Nifedipine 20-40mg twice daily)	Double-blind RCT for 1y. Study conducted in Europe. N=335. ACEI, N=168. CCB, N=167.	Micro. Mean age=58.5y. Mean BP= 163/98mmHg.	Normotension; autonomic neuropathy; renal artery stenosis; hematuria; malignant HTN; aortic/mitral valve obstruction; sig hepatic, hemapoietic, or endocrine dysfx; MI, unstable angina, TIA, or stroke within 3mo; CA; Psychiatric disorder; EtOH or drug abuse	• Median difference of UAER btwn groups at 6mo=20µg/min (p=0.0002) at 12mo=20µg/min (p=0.0006), favoring ACEI • NS diffs in BP reduction	Agardh[120]
ACEI (Enalapril 5-20mg daily);	Double-blind RCT for 98d followed by	Micro with mild HTN and diabetic	Nondiabetic renal dx, heart failure	• Short-term study: • ACEI group was better at controlling albuminuria change	Ruggenenti[112]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
CCB (Nitrendipine 10-40mg daily)	single-blind RCT for 1y. Study conducted in Italy. Double-blind: N=16. ACEI, N=8. CCB, N=8. Single-blind: N=14. ACEI, N=6. CCB, N=8.	glomerulopathy. Mean age= 52.5y. Mean BMI=29.5kg/m^2. Mean duration of HTN=3.6y. Mean duration of diabetes= 9.3y. Mean BP=156/97mmHg. Mean HbA1c =7.4%.	class III or IV, AV blockage of 2^{nd} or 3^{rd} degree, symptomatic coronary ischemic dx, liver or hematologic dx, CA, collagen vascular dx	(28.8 vs. 70.3, p<0.05) • Long-term study: • NS diffs for albuminuria change (p>0.05)	
ACEI (Lisinopril 10-20mg daily); BB (Atenolol 50-100mg daily)	Double-blind RCT for 12mo followed by single-blind RCT through 3.5y. Study conducted in Denmark. N=43. ACEI, N=21. BB, N=22.	Macro. Mean age=60.5y. Mean BMI= 33.1kg/m2. Mean duration of diabetes= 9.5y. Current smokers=54.5% Mean HbA1c=8.6%. Mean LDL= 3.7mmol/L. Mean TG= 2.1mmol/L	Nondiabetic renal dx	• ACEI was sig better for percent reduction in albuminuria than BB (55% vs. 15%, p=0.01) at 3.5y	Nielsen[113]
ACEI (Lisinopril	Blinding NR. Randomized	Macro. Mean age=62.1y.	Heart failure, poor diabetes	• ACEI was sig better for reduction in albuminuria than BB ((-1.65g/d vs. –	Bakris[114]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
(dosing NR)); CCB (Verapamil or Diltiazem (dosing NR)); BB (Atenolol (dosing NR))	trial for 6y. Study conducted in USA N=52. ACEI, N=18. CCB, N=18. BB, N=16.	Mean duration of diabetes= 13.7y. Mean duration of HTN=15.0y. Mean HbA1c= 10.7%. Mean BP=157/98mmHg.	or HTN control, CAD, severe claudication, orthostatic hypotension, psychiatric disorders, blindness	0.5g/d, p<0.01) • NS diffs btwn groups for reduction in albuminuria, ACEI vs. CCB (-1.65g/d vs. –1.95g/d, p>0.99)	
ACEI (Ramipril 5mg daily); CCB (Nitrendipine 10mg twice daily)	Blinding NR. Randomized trial for 2y. Study conducted in Italy. N=107. ACEI, N=54. CCB, N=53.	Macro. Mean age=56.3y. Mean duration with diabetes=8.3y. Mean weight=73.9kg. Mean BP=166/102mm/Hg. Mean HbA1c=7.1%	Cardiac or hepatic dysfx, ankle edema, albuminuria> 2g/d.	• NS diffs btwn groups for percentage change in UAER at 2y (-32.3% vs. –19.5%, p>0.05)	Fogari[115] Men only. Low protein, low sodium diet. 56 pts dropped out (NS diffs btwn groups). UAER decreased sig at 3mo for ACEI; took 1y for CCB. Changes in UAER not correlated with DBP, HbA1c, CrCL, or SCr changes.
ACEI (Enalapril (dosing	Double-blind RCT for 5.5y. Study	Stage of albuminuria NR. Mean	Normotension. MI or CVA within 6mo,	• ACEI was sig better for: • Nonfatal MI (2.1% vs. 9.4%, p=0.001)	Estacio (ABCD trial subanalysis of hypertensive pts)[118].

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
NR)); CCB (Nisoldipine (dosing NR))	conducted in USA. N=470. ACEI, N=235. CCB, N=235.	age=57.4y. Family hx of CAD=47%. Mean duration with diabetes= 8.6y. Mean HbA1c=11.6% Mean duration with HTN= 156/98mmHg. Current or former smokers =62%. Mean LDL=129mg/dL . Mean TG=291 mg/dL. Mean BMI=31.6kg/m^2.	CABG within 3mo, unstable angina within 6mo, class III or IV CHF	• Nonfatal & fatal MI (2.1% vs. 10.6%, p=0.001) • NS diffs for: • CVA (4.7% vs. 3.0%, p>0.05) • CHF (2.5% vs. 2.1%, p>0.05) • CVD death (4.3% vs. 2.1%, p>0.05) • All cause mortality (7.2% vs. 5.5%, p>0.05)	DSMB stopped trial early due to sig better rate in CVD events in ACEI group for hypertensives. Annual rate of 1 MI/y in ACEI group vs. 5 MIs/y in CCB group.
ARB (Valsartan 80-160mg daily); CCB (Amlodipine 5-10mg daily)	Double-blind RCT for 6mo. Study conducted in UK. N=332. ARB, N=169. CCB, N=163.	Micro. Normo- (35.0%) or hyper- (65.0%) tensive. Mean age=58.0y. Mean BMI=30.8 kg/m^2. Mean BP=147/85mm Hg.	Hx of MI, PTCA, or CVA within 3mo; severe neuropathy; hx of hypertensive encephalopathy; hepatic dx	• ARB was sig better for: • Reversal to normo (29.9% vs. 14.5%, p=0.001) • Decrease in UAER (44% vs 8%, p<0.001)	Viberti (MARVAL)[117] Study length set because max effect of RAAS inhibition is 6mo. Similar reduction in UAER for normo- and hyper- tensives.
ARB (Irbesartan 300mg	Double-blind RCT for 2.6y. Study	Macro. Mean age=58.9y. Mean	Normotension	• For the combined endpt of doubling SCr, development of ESRD, or death, 39.0% of placebo pts, 41.1% of CCB	Lewis (IDNT (renal))[53]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
daily); CCB (Amlodipine 10mg daily); Plabebo	conducted in N. America, S. America, Europe, Asia, Middle East, Australia. N=1,715. ARB, N=579. CCB, N=567. Placebo, N=569.	BMI=30.8kg/m^2. Mean BP=159/87mmHg. Insulin use=58.0%. Hx of CVD=28.7%. Mean HbA1c=8.2%		pts, and 32.6% of ARB pts reached this endpt. Compared to ARB pts, a sig higher proportion of placebo and CCB pts reached this endpt (p-values=0.02 and 0.006, resp). • 14.2% of the ARB group, 18.3% of the CCB groups, and 17.8% of the placebo group developed ESRD (p-value>0.05) • NS diffs for death (incidence rates much closer than ESRD) • NS diffs for combined endpt of death from CVD, nonfatal MI, hosp for heart failure, permanent neurological defect from a cerebrovascular event, or lower limb amputation above the ankle	
ARB (Irbesartan 300mg daily); CCB (Amlodipine 10mg daily); Placebo	Double-blind RCT for 2.6y. Study conducted in N. America, S. America, Europe, Asia, Middle East, Australia. N=1,715. ARB, N=579.	Macro. Mean age=58.9y. Mean BMI=30.8kg/m^2. Mean BP=159/87mmHg. Insulin use=58.0%. Hx of CVD=28.7%. Mean HbA1c=8.2%	Normotension	• Having a CVD event before renal failure, death, or censorship occurred in 32.5% of placebo pts, 28.3% of CCB pts, and 29.7% of ARB pts (p>0.2 for each comparison) • Developing CHF occurred in 13.8% of the ARB group, 19.9% of the placebo group, and 25.9% of the CCB group. Compared to the ARB group, the other groups had a sig higher rate (p=0.048 and	Berl (IDNT (CVD))[109]

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Results	Reference, Notes
	CCB, N=567. Placebo, N=569.			p=0.004, resp)	

ARB (Losartan (dosing NR)); BB (Atenolol (dosing NR)	Double-blind RCT for 4.7y. Study conducted in Europe, UK, USA. N=1,195. ARB, N=586. BB, N=609.	Stage of albuminuria NR. Mean age=67.4y. Mean BP=177/96mmHg. Mean BMI=30.0kg/m^2. Current smokers=13.6%. Any vascular event=35%.	Normotension, no signs of LVH	• ARB was sig better for:
				  • CVD mortality, stroke, or MI (39.2% vs. 53.6%, p=0.017)
				  • CVD mortality (13.6% vs. 21.8%, p=0.019)
				  • All cause mortality (22.5% vs. 37.2%, p=0.001)
				  • Hosp admission for heart failure (11.8% vs. 20.7%, p=0.013)
				• NS diffs for:
				  • Stroke (19.0% vs. 24.5%, p=0.190)
				  • MI (15.2% vs. 18.7%, p=0.318)
				  • Hosp admission for angina (11.1% vs. 11.1%, p=0.989)
				  • Revasc (23.5% vs. 26.6%, p=0.470)
					Lindholm (LIFE)[50]

ACEI= angiotensin-converting enzyme inhibitor; **ARB=** angiotensin II receptor type 1 blocker; **AV=** atrioventricular blockage; **BL=** baseline; **BMI=** body mass index; **BB=** beta-blocker; **BP=** blood pressure; **btwn=** between; **CA=** cancer; **CAD=** coronary artery disease; **CCB=** calcium channel blocker; **CHF=** congestive heart failure; **CrCl=** creatinine clearance; **CVA=** cerebrovascular accident; **CVD=** cardiovascular disease; **DBP=** diastolic blood pressure; **DSMB=** data and safety monitoring board; **dx=** disease; **endpts=** endpoints; **ESRD=** end-stage renal disease; **EtOH=** alcohol; **hosp=** hospitalization; **HTN=** hypertension; **hx=** history; **LDL=** low density lipoprotein; **LVH=** left ventricular hypertrophy; **macro=** macroalbuminuria; **MI=** myocardial infarction; **micro=**

microalbuminuria; **mo=** months; **normo=** normoalbuminuria; **NR=** not reported; **NS=** nonsignificant; **PTCA=** percutaneous transluminal coronary angioplasty; **pts=** patients; **RAAS=** renin angiotensin aldosterone system; **RCT=** randomized controlled trial; **revasc.=** revascularization; **SCr=** serum creatinine; **sig=** significant; **TG=** triglycerides; **TIA=** transient ischemic attack; **UAER=** urinary albumin excretion rate; **y=** years

APPENDIX D:

TABLE OF IDENTIFIED STUDIES COMPARING ACEI MONOTHERAPY TO ARB MONOTHERAPY IN P2DM

TABLE OF IDENTIFIED STUDIES COMPARING ACEI AND ARB MONOTHERAPY IN P2DM

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
ACEI (Enalapril 5mg daily); ARB (Losartan 50mg daily).	RCT of 12 mo treatment duration (blinding NR) in Turkey. Comparisons between enalapril monotherapy, losaratan monotherapy, and combo tx. N=34: N=12 ACEI, N=12 ARB, N=10 combo tx.	Micro. Mean age=55.6. CAD: 8.8%. Mean HbA1c=7.63%. Mean BP=124/77. Present or former smoking status. Mean BMI=29.0. Mean duration of DM=7.6y.	Alcoholism, thyroid disease, renal insufficiency not related to DM, chronic liver disease, insulin use, overt cancer, noncompliance	Mean (SD) UAER (mg/d) • ACEI 85.02 (31.25) • ARB 101.66 (41.19) • Combo 102.03 (32.77)	Mean (SD) UAER (mg/d) • ACEI 35.41 (19.59) • ARB 41.33 (21.08) • Combo 40.70 (29.52) % Δ • ACEI: 58 • ARB: 59 • Combo: 60	Tutuncu[51]. Sig decreases in albuminuria within each group (p<.0001, .0002, .0003, resp.). NS differences between groups. ARB group had 19.57% higher mean baseline UAER than ACEI, which was not controlled for in analyses. No drug-related AEs. Mean UAER for each group decreased throughout the study. Some patients in ea group reverted to normoalbuminuria.
At first, ACEI (Enalapril 5mg daily); ARB (Losartan 50mg daily). At wk 4, if sitting diastolic BP>85,	Double-blind RCT of 12 mo treatment duration in Canada. N=103. ACEI, N=51 ARB, N=52 at start of study. N=49 in each	Micro. & macro. (9.7% macro). Mean age=58.5. Mean duration of DM=11.15y. 96.1% NHW. Mean sitting BP=160/96.	UTI, CVA or MI within the year, current TIAs, unstable angina, history of heart failure,	Geometric mean UAER (mg/d, converted) • ACEI 106.4 • ARB 92.3	Geometric mean UAER (mg/d, converted) • ACEI 12wk: 73.0 28wk: 56.7 52wk: 48.2 • ARB 12wk: 79.3	Lacourciere[128]. Sig mean diff in UAER by wk 12, which was maintained for study duration. No sig diff btwn groups for Δ from baseline in log UAER after 12 & 28 wk. Also true for wk 52 after sig treatment*center interaction added. Fairly flat slope in UAER between wk 28 & 52.

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
enalapril doubled. At wk 8, if sitting diastolic BP>85 in either group, dose doubled. At wk 12, if sitting diastolic BP>85, HCTZ 12.5 titrated to 25. Thereafter, agents other than ACEI, ARB, CCB added for BP control.	group for ITT analysis.		drug/EtOH abuse, treatment with antiHTNs except ß-blockers or nitrates for treating stable angina, SBP>210		28wk: 53.0 52wk: 59.8	Mean(SD) dose of losartan= 86.3(22.5)mg. Mean (SD) dose of enalapril= 16.0(6.2)mg. Despite the baseline mean UAER to be 15.3% higher for ACEI than ARB, no statistical adjustment for this (ANOVA instead of ANCOVA). Sig diff @ baseline: sitting diastolic BP higher in losartan group, longer duration of diabetes in losartan group. As for UAER, no adjustment for these differences. Sig more cough in ACEI group (14% vs. 0%, p=.006), but no diffs btwn groups when all AEs combined. No deaths or CVD events.
ACEI (Captopril 25mg TID); ARB (Valsartan 80mg daily; valsartan 160mg daily);	Double-blind RCT of 12 mo treatment duration in Canada. N=122. ACEI, N=29 Each ARB	Micro & macro. Mean age=56.0. 89.1% NHW. 38.5% use antiHTNs. Mean sitting BP=136/83.	Noncompliance, sitting DBP>95, sitting SBP>160.	Geometric mean UAER (mg/d, converted) • ACEI 58.8 • ARB 80mg 86.4	Geometric mean UAER (mg/d, converted) • ACEI 43.3 • ARB 80mg 62.4	Muirhead[129]. NS baseline diffs in geometric mean UAER despite ARB 80 group was 46.9% higher and ARB 160 group was 42.3% higher than ACEI group. No adjustments for diffs. Analysis of ratio of

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
placebo.	dosage, N=31 Placebo, N=31 at start of study. N=27 for ARB 80, N=31 for ARB 160, N=29 for ACEI, N=28 for ITT analysis.			• ARB 160mg 83.7 • Placebo 91.15	• ARB 160mg 66.0 • Placebo 107.7	geometric mean at study end to baseline found ACEI and ARB 80 (but not 160) sig reduced UAER compared to placebo. The same analysis revealed NS differences in UAER reduction btwn ACEI and ARB 80 or 160. AEs: More incidence of cough and dizziness in ACEI group. No drug-related SAEs or deaths.
ACEI (Lisinopril 20mg daily); ARB (Candesartan 16mg daily).	Double-blind RCT for first 12 wk; for wk 12-24, the same patients received ACEI monotx, ARB monotx, or combo tx. Study conducted in Denmark, Finland, Israel, Australia. N=197. First	Micro. DBP 90-110 after 2-4 wk of placebo. Mean age=59.8. Mean BMI=30.3. Mean duration of HTN=8.6. Mean duration of DM=9.1. Mean BP = 1623/96. Mean HbA1c=7.6%. Mean SCr=85.4 umol/L. Mean CrCl=99.6ml/min	BMI≥40, systolic BP>200, CVD event in past 6 mo, SCr≥130 in women or 150 in men for 6 days, HbA1c>10 %	Geometric mean albumin: creatinine ratio (mg/mmol) • ACEI 6.6 • ARB 5.9	Wk 12: Adjusted mean reduction in geometric mean albumin: creatinine ratio (%, (CI)) from baseline • ACEI 46 (35-56), p<0.001 • ARB 30 (15-42), p<0.001 Wk 12: Adjusted mean	Mogensen (CALM)[122]. NS diff in baseline characteristics. Adjusted means in previous column=adjusted based on center, treatment, baseline value, weight, Δ in diastolic BP. The difference between treatments is the relative reduction, which has a trend favoring ACEI. Wk 24, compared to baseline: combo treatment had sig lower reduction in adjusted mean geometric albumin:creatinine ratio compared to ARB (34 (3-

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
	12 wk: ACEI, N=98, ARB, N=99. Wk 12-24: ACEI, N=64, ARB, N=66, combo, N=67.				difference between treatments (%, (CI)) 30 (1-70), p=0.058 Wk 24: Adjusted mean reduction in geometric mean albumin: creatinine ratio (%, (CI)) from baseline • ACEI 39 (20-54), p<0.001 • ARB 24 (0-43), p=0.05	55)), p=0.04 but NS compared to ACEI (18(-20-44)), p>0.20. There were no statistical analyses between ACEI and ARB comparing wk 24 to baseline for reduction n adjusted mean geometric albumin:creatinine ratio. AEs: 14 of 197 (7.1%) stopped treatment due to AEs. 5 due to dizziness or weakness (2 ACEI, 2 ARB, 1 combo tx). 3 due to cough (all on ACEI). NS Δs in lab values, including HbA1c, throughout study period.
ACEI (Enalapril 10mg daily); ARB (Telmisartan 40mg daily).	Double-blind RCT of 5 years treatment duration in Europe. N=250.	Micro & macro. Mean age=60.6. 98.4% NHW. Mean BMI=30.7. Mean BP=152/86. Median duration of HTN=6.7.	Other than CVD, a condition that would lead to premature death	No mention of raw numbers at baseline	No mention of raw numbers at study end. Geometric mean UAER ratio	Barnett (DETAIL)[121]. NS diff between baseline and study end not a surprise as patients were on ACEI ≥3 mo before enrollment. These are 2° outcomes; study may not be powered to detect a

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
	ACEI, N=130. ARB, N=120. Patients on ACEI≥3 mo. before enrollment.	Median duration of DM=8.0. 48.8% have hx of CVD. Mean LDL=137mg/dL. Mean HDL=48mg/dL. Mean TG=206mg/dL. Mean HbA1c=8.3%. Mean SCr=1.00 mg/dL. Mean GFR=92.9ml/min /1.73m^2.			<u>(end/baseline):</u> • ACEI .99 • ARB 1.03 <u>Geometric mean UAER ratio between groups (ARB/ACEI) (CI)</u> 1.04 (.71-1.51)	difference. Adjusted for differences in baseline mean (ANCOVA) when compared geometric mean reductions between baseline and study end. Last observation carried forward: 35 of 115 (30.4%) in ARB, 42 of 125 (33.6%) in ACEI. NS diffs in BP but ARB reduced BP 6.9 from baseline while ACEI reduced BP 2.9 from baseline (baseline had 1mmHg diff btwn groups). Also, BP not adjusted for in ANCOVA. Over 5 y, micro → macro in 17% of subjects not lost to f/u. AEs: 16.7% dropped out in ARB due to AEs; 23.1% dropped out in ACEI due to AEs. No statistical analysis performed for diffs in AEs btwn groups. CHF occurred in 7.5% of ARB & 5.4% of ACEI subjects. Combining fatal & nonfatal heart failure, MI & stroke, 17.5% of ARB and 11.5% of ACEI subjects

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
						had these AEs.
ACEI (Enalapril 10mg daily); ARB (Losartan 50mg daily); ACEI (Enalapril 20mg); ARB (Losartan 100mg daily); ACEI + ARB (Enalapril 10mg daily, Losartan 50mg daily).	Randomized crossover study (blindness NR) in Turkey. Each tx period = 3mo. Study had 6mo tx duration in total. N=22. 11 were randomized each to ACEI or ARB monotx in first 3mo. In mo 3-6, 5 in each group went to combo tx; the remaining 6 in each group stayed with monotx, but had their dosages doubled.	Macro. Mean age=54.7. Mean BP=151/93. Mean HbA1c=6.9%. At study start, advised to limit Na intake & BMI. Mean CrCl=65.3 ml/min/1.73m^2. At study start, advised to limit Na, AA, and caloric intake	None reported	Mean (SD) UAER (mg/d, converted) • ACEI 4790 (1280) • ARB 4840 (990)	Wk 12: Mean (SD) UAER (mg/d, converted) • ACEI 3170 (690) • ARB 3210 (710)	Cetinkaya[130]. Other than UAER, no mention of baseline characteristics per group or diffs in baseline characteristics btwn groups. No statistical adjustment for any differences btwn groups (t-test). At wk 12, 33.8% reduction in UAER for ACEI compared to baseline ($p<0.05$) & 33.7% reduction in UAER for ARB compared to baseline ($p<0.05$). NS diff btwn groups. At wk 24, 51% reduction in UAER for combo tx compared to baseline ($p<0.05$) and 37% reduction in UAER when mono tx doubled dosage compared to baseline($p<0.05$). AEs: NR.

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
ACEI (Perindopril 8mg daily); ARB (Irbesartan 300mg daily); ACEI + ARB (Perindopril 8mg daily, Irbesartan 300mg daily).	Randomized, open-label crossover study in Brazil. 3 treatment phases, each=16 wk. Subjects received ACEI mono, ARB mono, or combo tx in random order. Initial ACEI or ARB dosages titrated during first 2 wk. N=20.	Macro. Median age=54. 50% white, 40% black, 10% other. Median duration of HTN=10. Median duration of DM=11. Median BMI=30. 50% use insulin. 45% use oral hypoglycemics. All subjects received diuretics; hydralazine & clonidine sequentially added for BP control. At study start, advised to limit Na intake & eat 50%CHO, 30%fat, 20%AA. 5.3% smokers.	Malignant HTN, any condition other than diabetes leading to renal involvement, HbA1c≥9.0 %, recurrent UTI, severe PVD, stroke/MI in 6 mo, noncompliance	Geometric mean (95%CI) UAER (mg/d) • ACEI 829 (537-1280) • ARB 996 (686-1445) • Combo 966 (681-1369)	Geometric mean (95%CI) UAER (mg/d) • ACEI 545 (288-1029) • ARB 773 (478-1248) • Combo 644 (393-1085)	Matos[131]. Other than UAER, no mention of baseline characteristics per group or diffs in baseline characteristics btwn groups. No statistical adjustment for any differences btwn groups (t-test). Baseline mean UAER was 20.1% higher for ARB group vs. ACEI. Sig reduction in mean UAER for ACEI: 34% (53%-9%), p<0.05. NS reduction in mean UAER for ARB: 22% (45%-9% increase), p=0.17. Sig reduction in mean UAER for combo: 33% (49%-12%), p<0.02. NS diffs btwn groups: ACEI vs. ARB v. combo tx. Compliance: 95%-96% across txs AEs: no mention of deaths. 2 excluded b/c of PVD requiring hospitalization that led to missed visits. Sig reduction in hematocrit and sig increase in serum K for

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
						combo tx. 1 pt receiving ARB & another receiving combo tx dropped out for hyperkalemia. All hyperkalemic patients had GFR<60. 1 pt had increased BUN with ACEI. Uricemia decreased only during combo tx (5.9→ 5.3mg/dL, p<0.05). ARB and combo had similar increase in plasma rennin elevation; ACEI didn't. Aldosterone only decreased in combo tx (36% (53%-12%, p<0.02)).
ACEI (Ramipril 10mg daily); ARB (Candesartan 16mg daily); ACEI + ARB (Ramipril 5mg daily, Candesartan 8mg daily).	Double-blind crossover study in Korea. N=21. 3 treatment periods, each=16 wk. ACEI or ARB titrated biweekly.	Macro. Mean age=49y. 100% Korean. Mean BMI=21.0. Mean duration of diabetes=8y. Mean BP=134/80. Mean duration of ACEI or ARB before study= 11mo. Mean HbA1c=7.4%. Patients already on ≥5mg ACEI or	Absence of retinopathy, presence of nondiabetic renal dx, uncontrolled diabetes, morbid cardiac or vascular diseases, morbid malignancy	Mean (SD) UAER (mg/d, converted) • 4100 (1900)	Mean (SD) UAER (mg/d, converted) • ACEI 3500 (1800) • ARB 3300 (2000) • Combo 2900 (1400)	Song[132]. Including UAER, no mention of baseline characteristics per group or diffs in baseline characteristics btwn groups. ACEI, ARB, or combo tx led to sig reduction in UAER compared to baseline. Combo tx also led to sig reduction compared to each mono tx (p<0.05). No adjustments for diffs made (t-test btwn baseline & end). UAER sig correlated with

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
		≥8mg ARB.				duration of diabetes (r^2=.887) and systolic BP (r^2=.617) at baseline, but NS after tx. % Δ in UAER not sig correlated with mean systolic or diastolic BP, plasma creatinine, or CrCl. AEs: No stats done for diffs btwn groups. No mention of deaths or CVD. 1 (4.8%) and 2 (9.5%) in ARB and combo txs, resp, had hypotension. 1 (4.8%) in ARB had malaise/ fatigue. 1 (4.8%) and 2 (9.5%) had K>6.0mEq/L in ACEI and combo tx, resp. 1 pt (4.8%) in ACEI had Δ in SCr>30% (reversible w/d/c). 1 pt (4.8%) in ACEI had cough.
ACEI (Lisinopril 20mg daily); ARB (Telmisartan 80mg daily); ACEI + ARB (Lisinopril 20mg daily,	Randomized open-label crossover study of 52 wk duration in Turkey. First 24 wk, lisinopril vs. telmisartan.	Micro. Previously diagnosed with HTN. On ACEI monotherapy ≥ 6 mo. Patients advised to follow normocaloric diet (30kcal/kg) w/Na content	>65 y, BMI≥ 40 kg/m2, 2° diabetes, alcoholism, thyroid disease, SBP>200, any	<u>Week 0:</u> <u>Median (range) UAER (mg/d)</u> • ACEI 264 (150-300) • ARB 256 (140-300) <u>Week 24:</u>	<u>Mean (range) adjusted absolute reduction UAER (mg/d)</u> • ACEI 98 (80-124) • ARB 80 (74-105)	Sengul[123]. Mean adjusted reductions in previous column take treatment, baseline value, weight & Δ in DBP into account. Sig mean adjusted reductions in UAER within each group, wk 24 to baseline, p<0.001. Adjusted mean diffs btwn txs=18

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
Telmisartan 80mg daily).	Wk 24-52, same patients randomized to continue each mono tx or to be on combo tx. Throughout the study 12.5mg HCTZ QD added for BP control in some subjects. N=219.	~150mmol/d & protein content ~1.2g/kg. Mean age=56.6 y. Mean BMI=30.4kg/m2. Mean duration of DM=11.8 y. 36.6% smokers. Mean BP=151/89. Mean Scr=85.5. Mean CrCl=96.8 ml/min. Mean HbA1c=7.8%. Mean LDL=3.5mmol/L. Mean TG=2.1 mmol/L.	nondiabetic cause of 2° HTN (incl. Bilateral renal artery stenosis), UTI, persistent hematuria, chronic liver disease, overt cancer, CVD event in 6 mo, SCr≥ 150mmol/L, serum K ≥5.5mmol/L	Median (range) UAER (mg/d) • ACEI 166 (90-220) • ARB 176 (80-220) • Combo 175 (77-208)	No comparison, week 24 to week 52	(95%CI:0-37, p=0.12). No breakout of AEs except for increased cough noted in ACEI group.
ACEI (Lisinopril 10mg daily); ARB (Losartan 50mg daily); ACEI + ARB (Lisinopril 10mg daily, Losartan	Randomized trial of 12 mo tx duration in Turkey (blinding NR). N=34 @ start; N=26 @ end. ACEI, N=9. ARB, N=9. Combo,	Micro. Normotensive. Protein intake ≤0.8g/kg/d. Mean age=55.1y. Mean time since DM diagnosis=7.5y. Mean HbA1c=6.1%. Mean BP=120/78.	2° diabetes, chronic renal or hepatic failure, CHF, history of HTN (cannot be controlled	Mean (SD) UAER(mg/d) • ACEI 70.2 (32.9) • ARB 70.1 (16.2) • Combo 70.1 (31.9)	Mean (SD) UAER(mg/d) • ACEI 3mo:38.2 (18.7) 6mo: 24.0 (12.5) 9mo: 21.5 (5.8) 12mo: 21.9	Atmaca[127] . NS diffs btwn groups @ baseline, incl. UAER. Also only 0.1 absolute diff in UAER @ baseline. UAER sig reduced in ea group from baseline (p=0.001), but NS diffs btwn groups (p=0.587). Reversion to normo. in ea group for majority of subjects. 67.6%,

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
50mg daily).	N=8.	Mean BMI=27.8 kg/m². Mean TG=272mg/dL. Mean chol=249 mg/dL.	with antiHTNs), cancer, UTI, smoking history, HbA1c>7%		(13.8) • ARB 3mo: 45.3 (18.0) 6mo: 28.9 (9.1) 9mo: 27.3 (9.5) 12mo: 27.8 (14.8) • Combo 3mo: 48.1 (29.5) 6mo: 33.6 (24.2) 9mo: 37.7 (32.6) 12mo: 29.6 (24.3)	61.3% & 58.7% reduction in UAER for ACEI, ARB, combo, resp. Slope fairly flat after 6 mo (NS diff in reduction btwn 6 & 12 mo, p=1.000). Sig reduction in BP & BMI btwn baseline & study end w/in ea group but NS diffs btwn groups. AEs: 2 pts lost to f/u due to AEs (not told which group they were in). Although mentioned lost 4 pts to f/u in total, that would lead to N=30
ACEI (Quinapril 20mg daily); ARB (Losartan 50mg daily).	Randomized, single-blind (investigators blinded) crossover study in China. N=41. Ea tx period=4 wk.	Micro & macro. 61% Chinese, 34% Malays, 5% Indians. Mean age=52y. Mean duration of DM=8y. 73% were not on antiHTNs. Mean	SBP>180, DBP>105, TG>5mM, total chol>8mM, CAD, PVD, other serious chronic	Mean (SD) UAER(mg/g Cr) • ACEI 550 (170) • ARB 471 (153)	Mean (SD) UAER(mg/g Cr) • ACEI 501 (146) • ARB 378 (124)	Lim[125]. NS diff of 16.8% in UAER btwn groups at baseline. ARB sig reduced albumin:creatinine ratio compared to ACEI (p=.025). ARB reduction:93mg/g, ACEI reduction:49mg/g; ARB sig reduced albumin:creatinine ratio from

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
		BP=135/84. Patients were naïve to ACEI or ARB.	illness needing medication			baseline (p<.01) while ACEI had NS reduction. No statistical adjustments for covariates despite NS baseline diffs. AEs: sig increase in serum K (4.2→4.4mM, p=0.01) for ACEI.
ACEI (Perindopril 4mg daily); ARB (Candesartan 16mg daily).	Double-blind RCT in Italy. N=96. Tx period=4mo.	Normo. "Mildly hypertensive" (defined as 105<DBP>90). Dietary advice (50% CHO, 30% AA, 20% fat) and encouraged to exercise ≥30min X3-4 days/wk. Mean age=54y, Mean diabetes duration=3.5mo, mean BMI=27.0.	2° HTN, malignant HTN, unstable angina, MI in last 6 mo, liver or kidney abnormalities	Mean (SD) UAER(mg/24h) • ACEI 17 (10) • ARB 18 (11)	Mean (SD) UAER(mg/24h) • ACEI 6mo: 10.2 (7.4) 12mo: 9 (6.4) • ARB 6mo: 11.8 (7.2) 12mo: 10 (6.9)	Derosa[244]. NS diffs @ baseline. For reduction in albuminuria, no stat sig Δ in either group btwn baseline & 6 mo, but difference btwn baseline and 12 mo (p<0.05). NS diffs btwn groups for reduction in albuminuria. Sig diffs btwn groups for DBP, FPG, FPI, total chol, HDL, LDL. No statistical adjustments for covariates. No AEs were so severe for a subject to d/c therapy.
ACEI (Fosinopril 10mg daily); ARB (Losartan 50mg daily).	Open-label RCT in Turkey. N=33. Tx period=6mo.	Normo (54.5%) & micro (45.5%). Median age = 52.9y, median duration of diabetes =3y, 15% treated with	Macro, CrCl<100mL/min, previously on ACEIs or ARBs	Median (range) UAER(mg/24h) • ACEI 154 (44-300) • ARB 121 (32-264.5)	Median (SD) UAER(mg/24h) • ACEI 14 (10.6-46) • ARB 54.8 (8.6-	Kavgaci248. Unclear if sig diffs btwn groups in UAER @ baseline. Sig diffs btwn baseline & 6 mo for each tx, but NS diffs btwn trx for reduction in albuminuria. No statistical adjustments for

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
		insulin, SBP 140-180mmHg			261.0)	covariates. *Subgroup analysis:* In micro group, ARBs had NS increase in albuminuria from mo. 1 while ACEIs had continuous reduction in albuminuria. (Author notes similar to CALM, btwn wks 12 & 24 and to Parving's 150mg irbesartan group.) NS change in albuminuria from baseline for each therapy in normo group. *Other metabolic parameters:* stat sig reduction in FPG, TG for ARB group; stat sig reduction in total chol, TG for ACEI group.AEs: sig increase in transaminase for ACEI group.
ACEI (Lisinopril 10mg daily); ARB (Candesartan 8mg daily).	Double-blind RCT in the Netherlands. N=60. Tx period=12mo.	Normo, micro & macro. HTN. 100% NHW. Age=61 y, BP=150/93, BMI=28.9mg/k2, 19.6% smoke, total chol=5.3±1.0mm	UAER≥100 mg/24h, age>70y, hx of MI, angina pectoris, CABG, angioplasty, stroke,	Mean or median (range) UAER(mg/24h) • ACEI 13.2 (7.3-32.0) • ARB 12.3 (7.7-20.5)	Mean (SD) UAER(mg/24h) No mention of raw numbers for each tx.	Schram249. UAER was 2° endpoint. Authors note lack of power. NS baseline diffs for all characteristics, incl. reduction in albuminuria. Authors do not note whether baseline values are mean or median (may even be something else). NS diffs

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
		ol/L, LDL=3.2±0.9mmol/L, HDL=1.3mmol/L, TG=1.6mmol/L, CrCl=98mL/min,	CHF, cancer, SCr>140mmol/L, BMI>35kg/m2, EtOH &/or drug abuse			btwn groups for reduction in albuminuria (no p-value reported).Stat sig diffs for ea tx compared to baseline (p<.05). Authors note difference in UAER was30% dependent on the decrease in SBP (70% for ARB, 5% for ACEI). The study was a 2X2 factorial, so have effects of intensive vs. regular BP control interfering with albuminuria. AEs: NR.
ACEI (Enalapril 10mg daily); ARB (Valsartan 160mg daily (mean dosage=6.3mg and 109.1mg, resp.: only 25% and 36.4% achieved target dosage,	RCT (blinding NR) in Hong Kong. N=42. Tx period =12 mo.	(I inferred) normo, micro, macro. 100% Chinese. Mean age=61.0y, Mean duration of diabetes=9.6y, mean BMI=25.3 kg/m2, mean BP=143/77, mean FPG=8.5mmol/L, mean HbA1c=7.6%,	HTN>200/115mmHg, hx of MI, CVA, or uncontrolled CHF within previous 6 mo., plasma creatinine≥150mmol/L	<u>Mean (SD) albumin: creatinine ratio</u> • ACEI 7.1 (6.7) • ARB 3.7 (6.5) Mean (SD) UAER • ACEI 114.0 (7.6) • ARB 40.1(7.0)	<u>Mean (SD) albumin: creatinine ratio</u> • ACEI Wk 12: 123.7 (534.1) Wk 24: 95.5 (320.9) • ARB Wk 12: 69.5 (200.7) Wk 24: 51.6 (139.8) Mean (SD) UAER	Ko[281]. No control for baseline diffs in albuminuria even through huge diffs btwn tx groups @ baseline. P=0.073 for ACEI compared to ARB in terms of keeping patients @ normo, micro, or macro @ baseline within their respective albuminuric states. When stratified by ea albuminuric state, NS diffs btwn groups in terms of keeping patients within their respective albuminuric states. Investigators consider

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
resp.))					• ACEI Wk 12: 47.9 (154.6) Wk 24: 58.3 (195.3) • ARB Wk 12: 53.4 (198.8) Wk 24: 33.9 (92.6)	clinically relevant reduction in albuminuria = 10mg/day. AEs: 35% of subjects on ACEI complained of cough vs. none on ARB (p=.003).
ACEI (Enalapril 10mg daily); ARB (Candesartan 8mg daily).	Double-blind RCT in Italy. N=118. Tx period=24 wk.	Micro. Mild HTN. Mean age= 58.4y, 4.7% retinopathy, 10.8% heart disease	Arrhythmia, hemodynamically relevant valvular dx, AV blocks grade II & III, CHF, MI, stroke, coronary artery surgery or TIA in previous 3 mo., angina pectoris due to CAD	Mean (SD) albumin: creatinine ratio • ACEI 40.4 (88.3) • ARB 112.4 (451.7) Mean (SD) UAER (mg/day, converted) • ACEI 39.6 (86.0) • ARB 147.0 (697.2)	Mean (SD) albumin: creatinine ratio • ACEI 12.8 (7.4) • ARB 4.6 (6.6) Mean (SD) UAER (mg/day, converted) • ACEI 120.8 (13.5) • ARB 56.6 (9.5)	Rosei[124]. Albuminuria not mentioned as an endpoint: assume it is post hoc analysis. Baseline diffs in UAER btwn groups not controlled and are huge. "The comparison between groups, esp. when using non-parametric tests (Mann-Whitney test), showed stat sig diffs in favor of candesartan." I think this is hogwash: never an endpoint to begin with, did many tests to try to show a sig diff, and didn't control for baseline diffs in UEAR.

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
			needing tx other than nitrates, sympotomatic autonomic neuropathy, trophic lesions of lower limbs, proliferative retinopathy, renal artery stenosis, kidney transplant, SCr>1.6mg/dL, severe liver dysfx, serum Na≤130mmol/L, serum K≤3.6 or ≥5.5 mmol/L, past or current EtOH or drug abuse			

Δ= change; **2°=** secondary; **AA=** protein; **AEs=** adverse events; **antiHTNs=** antihypertensives; **BMI=** body mass index; **BP=** blood pressure; **btwn=** between; **CABG=** coronary artery bypass graft; **CAD=** coronary artery disease; **CCB=** calcium channel blocker; **CHF=** congestive heart failure; **CHO=**carbohydrates; **Chol=** cholesterol; **CI=** confidence interval; **Combo.=** combination therapy; **CrCl=** creatinine clearance; **CVA=** cerebrovascular accident; **DBP=** diastolic blood pressure; **diff=** different or differently; **diffs=** differences; **DM=** diabetes mellitus; **dx=** disease; **ea=** each; **EtOH=** alcohol; **FPG=** fasting plasma glucose; **FPI=** fasting plasma insulin; **f/u=** follow-up; **GFR=** glomerular filtration rate; **HCTZ=** hydrocholorothiazide; **HDL=** high-density lipoprotein; **HTN=** hypertension; **hx=** history (of); **incl=** including; **ITT=** intention-to-treat analysis; **K=** potassium; **LDL=** low-density lipoprotein cholesterol; **Macro.=** macroalbuminuria; **Micro.=** microalbuminuria; **mo=** month(s); **Na=** sodium; **NHW=** non-Hispanic White; **Normo.=** normoalbuminuria; **NormoHTN=** normotensive; **NR**= not reported; **NS=** nonsignificant; **PVD=** peripheral vascular disease; **RCT=** randomized clinical trial; **resp.=** respectively; **SCr=** serum creatinine; **SD=** standard deviation; **sig=** significant or significantly; **SBP=** systolic blood pressure; **TG=** triglycerides; **TIA=** transient ischemic attack; **TID=** three times daily; **tx=** treatment; **UAER**= urinary albumin excretion rate; **UTI=** urinary tract infection; **vs.=** versus; **wk=** week(s); **y=** year(s)

Geometric means reported when UAER was antilogged. Logged because of skewness in data. “Converted” when I converted the units to mg/d (multiply microgram/min to mg/day by multiplying by 1.44).

APPENDIX E:

TABLE OF IDENTIFIED STUDIES COMPARING ACEI AND ARB COMBINATION TO MONO- THERAPY IN P2DM

TABLE OF IDENTIFIED STUDIES COMPARING ACEI AND ARB COMBINATION TO MONO- THERAPY IN P2DM

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
ACEI (Lisinopril 20mg daily); ARB (candesartan 16mg daily); ACEI + ARB	Double-blind RCT for first 12 wk; for wk 12-24, the same patients received either ACEI alone, ARB alone, or combo. Study conducted in Denmark, Finland, Israel, Australia. N=197. First 12 wk: ACEI, N=98, ARB, N=99. Wk 12-24: ACEI, N=64, ARB, N=66, combo, N=67.	Micro. DBP 90-110 after 2-4 wk of placebo. Mean age=59.8. Mean BMI=30.3. Mean duration of HTN=8.6. Mean duration of DM=9.1. Mean BP = 162/96. Mean HbA1c=7.6%. Mean SCr=85.4 umol/L. Mean CrCl=99.6ml/min	BMI≥40, systolic BP>200, CVD event in past 6 mo, SCr≥130 in women or 150 in men for 6 days, HbA1c>10 %	Geometric mean albumin: creatinine ratio (mg/mmol) • ACEI 6.6 • ARB 5.9	Wk 12: Adjusted mean reduction in geometric mean albumin: creatinine ratio (%, (CI)) from baseline • ACEI 46 (35-56), p<.001 • ARB 30 (15-42), p<.001 Wk 12: Adjusted mean difference between treatments (%, (CI))	Mogensen (CALM)[122]. NS diff in baseline characteristics. Adjusted means in previous column=adjusted based on center, treatment, baseline value, weight, Δ in diastolic BP. The difference between treatments is the relative reduction, which has a trend favoring ACEI. Wk 24, compared to baseline: combo treatment had sig lower reduction in adjusted mean geometric albumin:creatinine ratio compared to ARB (34 (3-55)), p=0.04 but NS compared to ACEI (18(-20-44)), p>0.20. There were no statistical analyses between ACEI and ARB comparing wk 24 to baseline for reduction n adjusted mean geometric albumin:creatinine ratio. AEs: 14 of 197 (7.1%) stopped treatment due to AEs. 5 due to dizziness or weakness (2 ACEI, 2 ARB, 1 combo tx). 3 due to

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
					30 (1-70), p=.058 Wk 24: Adjusted mean reduction in geometric mean albumin: creatinine ratio (%, (CI)) from baseline • ACEI 39 (20-54), p<.001 • ARB 24 (0-43), p=.05	cough (all on ACEI). NS Δs in lab values, including HbA1c, throughout study period.
ACEI (Enalapril 5mg daily); ARB (Losartan 50mg daily); ACEI + ARB	RCT of 12 mo treatment duration (blinding NR) in Turkey. Comparisons between	Micro. Mean age=55.6. CAD: 8.8%. Mean HbA1c=7.63%. Mean BP=124/77. Present or former	Alcoholism, thyroid disease, renal insufficiency not related to DM,	Mean (SD) UAER (mg/d) • ACEI: 85.02 (31.25) • ARB: 101.66 (41.19)	Mean (SD) UAER (mg/d) • ACEI: 35.41 (19.59) • ARB:	Tutuncu[51]. Sig decreases in albuminuria within each group (p<.0001, .0002, .0003, resp.). NS differences between groups. ARB group had 19.57% higher mean baseline UAER than ACEI, which was not controlled

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
	enalapril monotherapy, losaratan monotherapy, and combo tx. N=34: N=12 ACEI, N=12 ARB, N=10 combo tx.	smoking status. Mean BMI=29.0. Mean duration of DM=7.6y.	chronic liver disease, insulin use, overt cancer, noncompliance	• ACEI + ARB: 102.03 (32.77)	41.33 (21.08) • ACEI + ARB: 40.70 (29.52) % Δ • ACEI: 58 • ARB: 59 • ACEI + ARB: 60	for in analyses. No drug-related AEs. Mean UAER for each group decreased throughout the study. Some patients in ea group reverted to normoalbuminuria.
ACEI (Lisinopril 20mg daily); ARB (Telmisartan 80mg daily); ARB + ACEI (Telmisartan 80mg daily, (Lisinopril 20mg daily); ACEI + ARB (Lisinopril 20mg daily, Telmisartan 80mg daily).	Randomized open-label crossover study of 52 week duration in Turkey. First 24 wk, lisinopril vs. telmisartan. Wk 24-52, same patients randomized to continue each monotx or to be on combo tx. Throughout	Micro. Previously diagnosed with HTN on ACEI monotherapy ≥ 6 mo. Patients advised to follow normocaloric diet (30kcal/kg) w/Na content ~150mmol/d & protein content ~1.2g/kg. Mean age=56.6 y. Mean BMI=30.4kg/m2. Mean duration of DM=11.8 y. 36.6% smokers.	>65 y, BMI≥ 40 kg/m2, 2° diabetes, alcoholism, thyroid disease, SBP>200, any nondiabetic cause of 2° HTN (incl. Bilateral renal artery stenosis), UTI, persistent	Week 24: Median (range) UAER (mg/d) • ACEI 166 (90-220) • ARB 176 (80-220) • ACEI + ARB: 175 (77-208)	Unadjusted mean (95% CI) reduction in UAER from baseline to 52 weeks: • ACEI: 107 (34-148) • ARB: 92 (42-124) • ARB + ACEI: 136 (24-172) • ACEI +	Sengul[123]. Mean adjusted reductions in previous column take treatment, baseline value, weight & Δ in DBP into account. Sig mean adjusted reductions in UAER within each group, wk 24 to wk 52, p<0.001. "From baseline to week 52, percentage reductions in AER with telmisartan, lisinopril, telmisartan plus lisinopril, and lisinopril plus telmisartan were 36.0, 40.5, 52.7, and 53.6%, respectively… "Subsequent treatment with lisinopril plus telmisartan for 28 weeks resulted in further

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
	the study 12.5mg HCTZ QD added for BP control in some subjects. N=219.	Mean BP=151/89. Mean Scr=85.5. Mean CrCl=96.8 ml/min. Mean HbA1c=7.8%. Mean LDL=3.5mmol/L. Mean TG=2.1 mmol/L.	hematuria, chronic liver disease, overt cancer, CVD event in 6 mo, SCr≥ 150mmol/L, serum K ≥5.5mmol/L		ARB: 139 (23-181)	significant reductions (P<0.001) in SBP, DBP, and AER." No breakout of AEs except for increased cough noted in ACEI group.
ACEI (Imidapril 10mg daily); ARB (Candesartan 8mg daily); ACEI + ARB (Imidapril 5mg, Candesartan 4mg daily).	Open-label before-and-after study of 27 Japanese P2DM + HTN already receiving imidapril or candesartan at baseline for >3mo. 3 mo f/u on ACEI+ARB. Combo therapy achieved with giving half the dose of ACEI	Micro., Macro. Mean age=62.4y. Mean baseline BP = 140/84mmHg, mean baseline HbA1c = 7.7%. Mean years since DM diagnosis= 14.0.	Other kidney disease, hepatic cirrhosis, malignancy, severe lung disease, inflammatory or infectious disease, ≥1000mg/g Cr, serum creatinine ≥1.5mg/dL	Geometric mean (range) albumin:creatinine ratio (mg/g), • ACEI or ARB: 79.4 (27.4-230)	Geometric mean (range) albumin:creatinine ratio (mg/g), • ACEI + ARB: 52.5 (17.1-161)	Fujisawa.[136] Combination therapy associated with a sig 34% mean reduction (95% CI = 14-49%) compared to each monotherapy. BP similar at baseline and after. Combination therapy found to be more effective at reducing albuminuria independent of BP or albuminuria at baseline.

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
	or ARB seen in monotx.					
ACEI (Enalapril 20mg daily, Lisinopril 20mg daily, or Captopril 100mg daily) + placebo; ACEI + ARB (Enalapril 20mg daily, Lisinopril 20mg daily, or Captopril 100mg daily, Candesartan 8mg daily).	Double-blind randomized crossover of 18 P2DM + HTN + diabetic retinopathy already receiving recommended doses of ACEI in Denmark. Each treatment period=2mo.	Macro. Mean baseline BP NR; mean BP, ACEI + placebo = 148/74mmHg; mean BP, ACEI + ARB = 138/71mmHg; mean HbA1c at end of second FU = 8.6%; NHW NR. Mean BMI=32.0 kg/m^2. Mean age=58y. Mean duration since DM diagnosed=13y.	Serum K > 4.6mmol/L, age >70y, EtOH or medicine abuse, systolic BP <100mmHg, GFR <25ml/min, pregnancy	N/A	Geometric mean (95% CI) albuminuria (mg/24h) • ACEI + Placebo: 1764 (1225-2540) • ACEI + ARB: 1334 (890-1998)	Rossing.[138] Combo tx led to a sig 24% mean reduction (2-58%, p=0.036) compared to ACEI + placebo. Large interindividual variability: 3 patients had no Δ in albuminuria.
ACEI (Enalapril 40mg daily, Lisinopril 40mg daily, or Captopril 150mg daily)	Double-blind randomized crossover of 20 P2DM + HTN already receiving maximum	Macro. Mean age=62y. Mean duration since DM diagnosed: 15y. Median # of antiHTNs in addition to those	Nondiabetic kidney or kidney tract disease, plasma K > 4.6mmol/L, GFR<25ml/	N/A	Geometric mean (IQR) albuminuria (mg/24h) • ACEI + Placebo: 706 (349-	Rossing.[139] Combo tx led to a 28% reduction (95% CI: 17-38%, p<0.001) compared to ACEI + placebo. Large interindividual variability; no significant changes in BP. Mean BP, ACEI + placebo =

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
+ placebo; ACEI + ARB (Enalapril 40mg daily, Lisinopril 40mg daily, or Captopril 150mg daily with Candesartan 16mg daily).	dosages of ACEI ≥ 2 mo in Denmark. Tx period=2 mo.	provided by study: 3. Mean baseline BP NR; 100% NHW. Mean BMI=31kg/m^2.	min		1219) • ACEI + ARB: 508 (228-909)	138/72mmHg; mean BP, ACEI + ARB = 135/70mmHg. No relationship btwn albuminuria change and 24h diastolic ABP or renin changes.
CCB (Amlodipine 5mg daily); ACEI (Temocapril 2mg daily); CCB + ARB (Amlodipine 5mg daily, Candesartan 4mg daily); ACEI + ARB (Temocapril 2mg daily , Candesartan 4mg daily).	RCT (blinding NR) of 17 P2DM + HTN in Japan. Two tx periods = 12 wk each. First 12 wk: CCB or ACEI. Second 12 wk: CCB + ARB or ACEI + ARB.	Macro. Mean age=52.7y. Mean BMI=23.2kg/m^2. Mean HbA1c = 7.7%. Mean baseline BP= 152.8/90.9mmHg, %NHW NR. Mean duration since DM diagnosed NR.	Serious diabetic complications, insulin use	Mean ±SD proteinuria (g/day) • CCB = 4.1±1.9 • ACEI = 3.5±1.7	Mean ±SD proteinuria (g/day) • CCB + ARB= 3.5±1.5 • ACEI + ARB=2.6 ±1.3	Kuriyama.[140] Compared to each monotherapy, addition of an ARB led to a sig reduction in proteinuria ($p<0.05$ and $p<0.01$ for CCB and ACEI, respectively). Analyses reported in terms of % Δ: • Compared to baseline, mean changes in daily proteinuria: • CCB: + 11% • ACEI: - 20% • CCB + ARB: -10% • ACEI + ARB: -43% (Combo tx with ACEI and ARB had an additional 23% reduction in daily

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
						proteinuria compared to ACEI monotherapy.) Maintained restricted caloric, salt, and protein intake.
ACEI (Ramipril 5-7.5mg daily); ACEI + placebo (Ramipril 5-7.5mg daily); ACEI + ARB (Ramipril 5-7.5mg daily, Candesartan 4-8mg daily).	Double-blind randomized crossover study including a subset of 18 P2DM without HTN in Korea. 8wk. run-in with ramipril, then two 16 wk. tx periods of candesartan or placebo.	Macro. Pts received ramipril ≥ 6mo. before study. Mean age = 42 y. % NHW NR. Mean baseline arterial pressure =92.3mmHg, mean baseline HbA1c NR. Mean BMI NR. Mean duration since DM diagnosed NR.	Vascular disease, cardiac disease, uncontrolled diabetes, malignancy	N/A	Mean (range) UAER (g/day) • ACEI: 4.1 (0.3) • ACEI + placebo: • 4.2 (0.3) • ACEI + ARB: 4.0 (0.2)	Song.[137] Results in adjacent column are in P2DM only. ACEI+ARB did not significantly reduce albuminuria compared to ACEI.
ACEI (Ramipril 10mg daily); ARB (Candesartan 16mg daily);	Double-blind randomized crossver study of 21 P2DM without HTN in Korea. 8	Macro. Pts received ACEI or ARB before. Mean age=49y. Mean BMI=21.9kg/m^2.	Age <18y; serum K >5.5mmol/L ;nondiabetic renal disease;	N/A	Mean (SD) albuminuria (g/day) • ACEI: 3.5 (1.8) • ARB:	Song.[132] The authors found a significant correlation btwn albuminuria, duration of diabetes, and systolic BP.

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
ACEI +ARB (Ramipril 5mg daily, Candesartan 8mg daily).	wk run-in with ramipril or candesartan, then three 16 wk tx periods (ea. monotx then combo). 8 wk washout btwn tx periods.	Mean BP=134/70mmHg. Mean HbA1c=7.4%. Mean duration since DM diagnosed=8y.	renal artery stenosis; type IV renal tubular acidosis; morbid cardiac, vascular disease or malignancy; uncontrolled diabetes; absence of retinopathy		3.3 (2.0) • ACEI + ARB: 2.9 (1.4) [p<0.05 compared to ea monotx]	
ACEI (Enalapril 10mg daily); ARB (Losartan 50mg daily); ACEI + ARB (Enalapril 10mg daily, Losartan 50mg daily).	Randomized crossover study (blinding NR) of 22 Turkish P2DM. Ea tx period lasted 12 wk.	Macro. Mean age=54.7y. Mean weight=68.2kg. Mean CrCl=65.3ml/min /1.73m^2. Mean BP=151/93mmHg. Mean HbA1c=6.9%. Mean duration since DM diagnosed NR.	NR	N/A	<u>Mean reduction in albuminuria (g/day)</u> • ACEI: 1.62 • ARB: 1.63 • ACEI + ARB: 2.36 [p<0.05 vs. ea monotx]	Cetinkaya.[130] Restriction of Na, protein, and calories. ACEI + ARB, compared to double the dose of either monotx (enalapril 20mg daily or losartan 50mg daily) resulted in a 51% reduction in albuminuria compared to a 37% reduction in albuminuria (p<0.05).

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
ACEI (Perindopril 8mg daily); ARB (Irbesartan 300mg daily); ACEI + ARB	Randomized open-label crossover study of 20 P2DM in Brazil; Ea tx period=16 wk.	Macro. Mean age=54y. 50% NHW. Duration since DM diagnosis: 11 y. 50% insulin users. Mean HbA1c=6.7%.	Age<40y, Malignant HTN, SBP≤140m mHg, HbA1c≥9%, severe peripheral vascular dx, stroke or MI within 6 mo, recurrent UTI, CrCl<40ml/ min/1.72m^2, serum K≥5.0mEq/ L, nondiabetic renal dx	Geometric mean (95%CI) UAER (mg/d) • ACEI 829 (537-1280) • ARB 996 (686-1445) • Combo 966 (681-1369)	Geometric mean (95%CI) UAER (mg/d) • ACEI 545 (288-1029) • ARB 773 (478-1248) • Combo 644 (393-1085)	Matos.[131] Other than UAER, no mention of baseline characteristics per group or diffs in baseline characteristics btwn groups. No statistical adjustment for any differences btwn groups (t-test). Baseline mean UAER was 20.1% higher for ARB group vs. ACEI. Sig reduction in mean UAER for ACEI: 34% (53%-9%), p<0.05. NS reduction in mean UAER for ARB: 22% (45%-9% increase), p=0.17. Sig reduction in mean UAER for combo: 33% (49%-12%), p<0.02. NS diffs btwn groups: ACEI vs. ARB v. combo tx. Compliance: 95%-96% across txs AEs: no mention of deaths. 2 excluded b/c of PVD requiring hospitalization that led to missed visits. Sig reduction in hematocrit and sig increase in serum K for combo tx. 1 pt receiving ARB & another receiving combo tx dropped out

Therapeutic strategies	Design; N	Patient characteristics	Exclusion criteria	Endpoint, baseline	Endpoint, results	Reference, Notes
						for hyperkalemia. All hyperkalemic patients had GFR<60. 1 pt had increased BUN with ACEI. Uricemia decreased only during combo tx (5.9→ 5.3mg/dL, p<0.05). ARB and combo had similar increase in plasma rennin elevation; ACEI didn't. Aldosterone only decreased in combo tx (36% (53%-12%, p<0.02)).

Δ= change; **ABP=** arterial blood pressure; **AER=** albumin excretion rate, to be used interchangeably with UAER; **AEs=** adverse events; **antiHTNs**= antihypertensives; **BMI=** body mass index; **BP=** blood pressure; **btwn=** between; **CAD=** coronary artery disease; **CCB=** calcium channel blocker; **CHF=** congestive heart failure; **CHO=**carbohydrates; **Chol=** cholesterol; **CI=** confidence interval; **Combo=** combination therapy; **CrCl=** creatinine clearance; **DBP=** diastolic blood pressure; **diff=** different or differently; **diffs=** differences; **DM=** diabetes mellitus; **dx=** disease; **ea=** each; **EtOH=** alcohol; **f/u=** follow-up; **GFR=** glomerular filtration rate; **HCTZ=** hydrocholorothiazide; **HDL=** high-density lipoprotein; **HTN=** hypertension; **hx=** history (of); **IQR**= interquartile range; **K=** potassium; **LDL=** low-density lipoprotein cholesterol; **Macro.=** macroalbuminuria; **Micro.=** microalbuminuria; **mo=** month(s); **monotx**= monotherapy; **N/A**= not applicable; **NHW=** non-Hispanic White; **NR=** not reported; **NS=** nonsignificant; **pts**= patients; **RCT=** randomized clinical trial; **resp.=** respectively; **SBP**= systolic blood pressure; **SCr=** serum creatinine; **SD=** standard deviation; **sig=** significant or significantly; **TG=** triglycerides; **tx=** treatment; **UAER**= urinary albumin excretion rate, to be used interchangeably with AER; **vs.=** versus; **wk=** week(s); **y=** year(s)

Geometric means reported when UAER was antilogged. Logged because of skewness in data. "Converted" when I converted the units to mg/d (multiply microgram/min to mg/day by multiplying by 1.44).

APPENDIX F:

ADDENDUM TO TABLES

Tables 1-4 detail how ICD-9-CM codes, DRGs, CPT-4 codes, and other data were incorporated in coding comorbidities, other covariates, original variables thought to affect treatment selection, and dependent variables. These tables also show once status of each of these variables were determined, how each of the variables were coded in the dataset.

Table 1. ICD-9-CM Codes and DRGs Denoting Elixhauser Comorbidities of Interest, Data Coding

Comorbidity*	**ICD-9-CM Codes**[a]	**DRGs**[b]	**Code in Dataset as:**
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-9	103-108, 110-112, 115-118, 120-127, 129, 132-133, 135-143	1 if fit criteria in footnote; else 0
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V53.3	103-108, 110-112, 115-118, 120-127, 129, 132-133, 135-143	1 if fit criteria in footnote; else 0
Valvular disease	093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3	103-108, 110-112, 115-118, 120-127, 129, 132-133, 135-143	1 if fit criteria in footnote; else 0
Pulmonary circulation disorders	416.0-416.9, 417.9	88, 103-108, 110-112, 115-118, 120-127, 129, 132-133, 135-143	1 if fit criteria in footnote; else 0
Peripheral vascular disorders	440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	130-131	1 if fit criteria in footnote; else 0
Hypertension, uncomplicated	401.1, 401.9	134	1 if fit criteria in footnote; else 0
Hypertension, complicated	402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99	103-108, 110-112, 115-118, 120-127, 129, 132-133-143, 302-305, 315-333	1 if fit criteria in footnote; else 0

Table 1 (cont.)

Comorbidity*	**ICD-9-CM Codes[a]**	**DRGs[b]**	**Code in Dataset as:**
Paralysis	342.0-342.12, 342.9-344.9	5, 14-17	1 if fit criteria in footnote; else 0
Other neurological disorders	331.9, 332.0, 333.4, 333.5, 334.0-335.9, 340.XX, 341.1-.9, 345.00-.11, 345.40-.51, 345.80-.91, 348.1, 348.3, 780.3, 784.3	1-34 or 35	1 if fit criteria in footnote; else 0
Chronic pulmonary disease	490-492.8, 493.00-.91, 494.XX, 495.0-505.XX, 506.4	88 or 96-98	1 if fit criteria in footnote; else 0
Hypothyroidism	243.XX-244.2, 244.8, 244.9	290 or 300-301	1 if fit criteria in footnote; else 0
Diabetes, complicated	250.40-.73, 250.90-.93	294 or 295	1 if fit criteria in footnote; else 0
Renal failure	403.11, 403.91, 404.12, 404.92, 585.XX, 586.XX, V42.0, V45.1, V56.0, V56.8	302 or 316-317	1 if fit criteria in footnote; else 0
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7	199-202 or 205-208	1 if fit criteria in footnote; else 0

Table 1 (cont.)

Comorbidity*	**ICD-9-CM Codes[a]**	**DRGs[b]**	**Code in Dataset as:**
Peptic ulcer disease	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71	174-177 or 178	1 if fit criteria in footnote; else 0
AIDS	042.XX-044.9	488, 489, or 490	1 if fit criteria in footnote; else 0
Lymphoma	200.XX-202.38, 202.50-203.01, 203.8-.81, 238.6, 273.3, V10.71, V10.72, V10.79	400-414, 473, or 492	1 if fit criteria in footnote; else 0
Metastatic cancer	196.XX-199.1	10, 11, 64, 82, 172, 173, 199, 203, 239, 257-260, 274, 275, 303, 318, 319, 338, 344, 346, 347, 354, 355, 357, 363, 366, 367, or 406-414	1 if fit criteria in footnote; else 0
Solid tumor without metastasis	140.XX-172.9, 174.XX-175.9, 179.XX-195.8, V10.00-.9	10, 11, 64, 82, 172, 173, 199, 203, 239, 257-260, 274, 275, 303, 318, 319, 338, 344, 346, 347, 354, 355, 357, 363, 366, 367, or 406-414	1 if fit criteria in footnote; else 0

Table 1 (cont.)

Comorbidity*	**ICD-9-CM Codes**[a]	**DRGs**[b]	**Code in Dataset as:**
Rheumatoid arthritis/collagen vascular diseases	701.0, 710.0-.9, 714.0-.9, 720.0-.9, 725.XX	240 or 241	1 if fit criteria in footnote; else 0
Coagulopathy	286.0-.9, 287.1, 287.3-.5	397	1 if fit criteria in footnote; else 0
Obesity	278.0	288 or 296-298	1 if fit criteria in footnote; else 0
Weight loss	260.XX-263.9	296, 297, or 298	1 if fit criteria in footnote; else 0
Fluid and electrolyte disorders	276.0-.9	296, 297, or 298	1 if fit criteria in footnote; else 0
Blood loss anemia	280.0	395 or 396	1 if fit criteria in footnote; else 0
Deficiency anemias	280.1-.9, 285.9	395 or 396	1 if fit criteria in footnote; else 0
Alcohol abuse	291.1, 291.2, 291.5, 291.8, 291.9, 303.90-.93, 305.00-.03, V113	433-436 or 437	1 if fit criteria in footnote; else 0
Drug abuse	292.0, 292.82-.89, 292.9, 304.00-.93, 305.20-.93	433-436 or 437	1 if fit criteria in footnote; else 0

Table 1 (cont.)

Comorbidity*	**ICD-9-CM Codes[a]**	**DRGs[b]**	**Code in Dataset as:**
Psychoses	295.00-298.9, 299.10-.11	430	1 if fit criteria in footnote; else 0
Depression	300.4, 301.12, 309.0, 309.1, 311.XX	426	1 if fit criteria in footnote; else 0

*This table is modified from Elixhauser et al.[195]

[a] ICD-9-CM codes had implied decimal points across VA datasets.

[B] The Elixhauser method, developed using only inpatient files, provides a DRG for inpatient files, meaning that the presence of any ICD-9 code without the presence of a DRG related to that indication defines that the condition as a comorbidity. Personal communication with Anne Elixhauser gave guidance to use her method in outpatient files, which means DRGs could not be used as a screen. Rather, ICD-9-CM codes were solely relied upon in determining comorbidities in outpatient files. For the dissertation, we went back three months from first date of health care utilization to examine inpatient and outpatient records for these ICD-9s and DRGs.

Table 2. ICD-9-CM Codes, CPT-4 Codes, Miscellaneous Data for Covariates of Interest, Data Coding

Covariate	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Age at baseline			Calculated from date of birth	Continuously: age in years
Gender			Gender	1=male, 0=female
Race/ethnicity			Value carried over from race/ethnicity information	1=Hispanic white, 2=Hispanic Black, 3=American Indian, 4=African American, 5=Asian, 6=White 7=Unknown Other=Missing
Income			Value carried over from INCOME, if ever documented	Continuously: annual household income in dollars
Means test			If ever documented, from MEANS	A=Below means test and no pharmacy copay I=Below means test with partial pharmacy copay C=Above means test threshold U=Means test required, but unknown result N=Means test no required

Table 2 (cont.)

Covariate	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Smoking	305.1 (current tobacco dependence), 491.0 (smoker's cough), V15.82 (history of tobacco use), 989.84 (toxic effect of tobacco)			3= If ICD-9 code 305.1 or 989.84 was ever documented 2=If ICD-9 code 491.0 was ever documented 1=If V15.82 was ever coded 0=None of these ICD=9 codes were ever documented
Family history of cardiovascular disease	V17.1, V17.3, V17.4			1=If any of the ICD-9 codes to the left were ever documented, else=0
History of stroke	438, V12.59			1=Either ICD-9 code documented at baseline (within 3 months of initial date of health care utilization), else=0
History of myocardial infarction	412.XX, 429.7X			1=Either ICD-9 code documented at baseline (within 3 months of initial date of health care utilization), else=0

Table 2 (cont.)

Covariate	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
New user of ACEI or ARB			Prescription information for dates of ACEI or ARB	1=If no prescription filled for ACEI or ARB within 6 months of initial date of health care utilization, else=0
Newly-diagnosed			Documented type 2 diabeets previous to first date of health care utilization for type 2 diabetes in study period	1=If type 2 diabetes not documented in the year previous to the first date of health care utilization for type 2 diabetes, else=0
Cohort			Based on year within study period in which first date of health care utilization for type 2 diabetes occurred	Cohort 2003=If first date occurred in FY 2003 Cohort 2004=If first date occurred in FY 2004 Cohort 2005=If first date occurred in FY 2005 Cohort 2006=If first date occurred in FY 2006
Time			Each year for which information on health care utilization was available after the index date	Time t = Year 1 Time (t+1) = Year 2 Time (t+2) = Year 3 Time (t+3) = Year 4 Time (t+4) = Year 5

Table 2 (cont.)

Covariate	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Urban/suburban versus rural living			Zip codes were converted to Rural Urban Commuting Area codes, categorization C	1=urban/suburban 0=rural
HbA1c			Value is obtained from RESULT field for test number 0017 from Lab Results files	Value was retained in natural units of %
LDL			Value is obtained from RESULT field for test number 0017 from Lab Results files	Value was retained in natural units of mg/dL
Triglycerides			Value is obtained from RESULT field for test number 0030 from Lab Results files	Value was retained in natural units of mg/dL
NSAID use			NSAID prescription dates and days supply	Proportion of months in a year with an NSAID 0=no prescription for an NSAID within the year

*ICD-9-CM codes had implied decimal points across VA datasets

Table 3. ICD-9-CM Codes, CPT-4 Codes, Miscellaneous Data for Variables Used for Control of Selection Bias, Data Coding

Variable	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Propensity Scores Analysis (variables indicating likelihood to cough)				
Allergic rhinitis	477.XX			If ICD-9 code is documented during the same visit an ACEI or ARB is first prescribed=1, else=0
GERD	530.11, 530.81			If ICD-9 code is documented during the same visit an ACEI or ARB is first prescribed=1, else=0
Postnasal drip	784.91			If ICD-9 code is documented during the same visit an ACEI or ARB is first prescribed=1, else=0
Treatment started in winter			Date the first prescription for an ACEI or ARB was written	If date of first prescription is during winter months=1, else=0

Table 3 (cont.)

Variable	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Smoking	305.1, 491.0, V15.82, 989.84			If smoking was ever documented, converted from categorical data 1-3 when used as covariate to 1. Is 0 if smoking was never documented, as was the case when smoking was used as a covariate.
Asthma, COPD, chronic bronchitis				1=If documented having chronic pulmonary disease in Elixhauser, else=0

*ICD-9-CM codes had implied decimal points across VA datasets.

Table 4. ICD-9-CM Codes, CPT-4 Codes, Miscellaneous Data for Dependent Variables of Interest, Data Coding

Variable	**ICD-9-CM Code(s)***	**CPT-4 Code(s)**	**Miscellaneous Data**	**Code in Dataset as:**
ESRD	585.6, V45.1, or V56.0, V56.8	36800, 36810, 36815, 90935, 90937, 90947, 90989, 90993; 50300, 50340, 50360, 50365, 90920, 90921, 90924, 90925, 90945, 90997, 90999		1 if fit criteria to left, else 0
Albuminuria; albumin:creatinine ratio			Value is obtained from RESULT field for test numbers 0032 and 0056, respectively, from Lab Results files	1. Value was retained in natural units of mg/dl and mg/g, respectively 2. Value was converted into categorical values denoting microalbuminuria, macroalbuminuria

Table 4 (cont.)

Variable	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Occurrence of incident MI	410.00-.02, 410.10-.12, 410.20-.22, 410.30-.32, 410.40-.42, 410.50-.52, 410.60-.62, 410.70-.72, 410.80-.82, 410.90-.92			1. Documented from any of the ICD-9 codes as the principal diagnosis in a year, else=0 2. Used as part of the composite endpoint of vascular disease. If this occurred ≥1 time in a year=1, else=0.
Left ventricular hypertrophy	429.3			1. 1 if fit criteria to left, else 0. Left ventricular hypertrophy happens once in a person's life, so once documented, all subsequent years=1. 2. Used as part of the composite endpoint of vascular disease. 1 if fit criteria to left, else 0.

Table 4 (cont.)

Variable	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Occurrence of incident ischemic stroke (lacunar, carotid circulation obstruction, vertebrobasilar occlusion) in a year	433, 433.0, 433.1, 433.2, 433.3, 434, 434.0, 434.1, 434.9, 434.91			1. Documented from any of the ICD-9 codes as the principal diagnosis in a year, else=0 2. Used as part of the composite endpoint of vascular disease. If this occurred ≥1 time in a year=1, else=0.
All-cause mortality			Date of death	1=If date of death documented, else=0
Number of hospitalizations				Number of times a patient was hospitalized in a given year. 0=if no documented inpatient data.
Number of ED visits		99281-8 in the outpatient visit data		Number of times a patient went to the ED in a given year. 0=if no documented ED visit data.

Table 4 (cont.)

Variable	ICD-9-CM Code(s)*	CPT-4 Code(s)	Miscellaneous Data	Code in Dataset as:
Number of outpatient visits		All visits in the outpatient visit data that do not have 99281-8		Number of times a patient was seen on an outpatient basis, but was not seen in the ED. 0=if no outpatient visit data documented without ED CPT-4 codes.

*ICD-9-CM codes had implied decimal point

Table 5 shows comparisons across drug therapies at each time point for continuous clinical parameters. Using results from the ANOVA and Kruskal-Wallis test we find ACEI patients had a higher mean value of HbA1c than ARB or neither patients at Year 1. During Year 2 each drug therapy had comparable HbA1c levels. ACEI patients had a comparable mean HbA1c as neither patients, but had a higher HbA1c value than ARB patients in Year 3. Years 4 and 5 showed no between group differences.

Drug therapy comparisons for LDL within each time period show those receiving neither therapy had the highest mean values of LDL while ARB patients had the lowest mean values and ACEI patients had values between the neither and ARB groups over Years 1, 2, and 3. At Year 4, ACEI and ARB had comparable LDL values, but each group had lower mean LDL than those in the neither group. Statistically, there were no differences in the fifth year of follow-up.

Triglyceride level comparisons between drug therapies show similar values in each group during Year 1. In Year 2, ACEI or ARB monotherapies each have higher values compared to neither patients. ACEI patients had a higher mean triglyceride value than those patients receiving neither therapy in Year 3; the mean triglyceride level for ARB patients was comparable to ACEI and neither patients. There were no differences in drug therapies for Years 4 and 5.

Table 5: Continuous Clinical Parameters by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
HbA1c	7.32*** (1.82)	7.28 (4.13)	7.28† (3.50)	7.24 (1.63)	7.01 (1.15)	7.30 (3.04)
LDL	96.19‡‡‡ (32.64)	91.02‖‖‖ (30.87)	89.60§§§ (30.59)	88.06 (28.49)	82.09 (30.04)	92.77 (31.59)
Triglycerides	197.70 (169.70)	189.60 (165.50)	186.90 (177.50)	174.60 (122.90)	173.80 (112.40)	191.60 (167.20)
ARB						
HbA1c	7.21 (3.24)	7.45 (7.00)	7.17 (3.81)	7.13 (1.34)	7.31 (1.71)	7.27 (4.754
LDL	91.66 (30.32)	88.16 (31.10)	86.52 (30.46)	84.72¶¶¶ (27.05)	96.13 (23.15)	89.01 (30.44)
Triglycerides	198.00$ (182.50)	184.60&&& (154.60)	177.90 (121.30)	176.20 (153.20)	178.90 (115.40)	188.20 (161.10)
Neither						
HbA1c	7.27 (1.66)	7.27 (3.45)	7.39 (4.33)	7.36 (4.32)	7.06 (1.29)	7.30 (3.14)
LDL	100.2 (34.79)	96.51 (33.84)	94.01 (34.05)	91.89 (42.33)	88.78 (32.80)	97.00 (35.37)
Triglycerides	193.00 (179.50)	187.30 (209.80)	183.00^^^ (160.10)	184.60 (222.40)	175.00 (139.60)	188.50 (189.60)

Notes: mean (standard deviation)

*** p<0.001, drug therapy group comparisons for Kruskal-Wallis test. Pairwise comparisons find two differences in rank means. Rank Mean difference = 1,265.91, critical value = 649.98, finds a significant difference between ACEI and ARB groups (rank mean = 19,256.85 and 17,990.94, respectively, p<0.001 at an adjusted p-value indicating significance = 0.0083). Rank Mean difference = 887.25, critical value = 274.29, finds a significant difference between ACEI and neither groups (rank mean = 19,256.85 and 18,369.60, respectively, p<0.0083 (adjusted p-value)).

[†]p<0.05, drug therapy group comparisons for Kruskal-Wallis test. Pairwise comparisons find one difference in rank means. Rank Mean difference = 421.43, critical value = 407.64, finds a significant difference between ACEI and ARB groups (rank mean = 8,203.52 and 7,782.10, respectively, p<0.0083 (adjusted p-value)).
[‡‡‡] p<0.001, drug therapy group comparisons for Kruskal-Wallis test within time t. Pairwise comparisons find three differences in rank means. Rank Mean difference = 1,469.30, critical value = 602.72, finds a significant difference between ACEI and ARB groups (rank mean = 16,507.80 and 15,038.49, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 2,549.73, critical value = 604.37, finds a significant difference between ARB and neither groups (rank mean = 15,038.49 and 17,588.22, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 1,080.42, critical value = 260.95, finds a significant difference between ACEI and neither groups (rank mean = 16,507.80 and 17,588.22, respectively, p<0.0083 (adjusted p-value)).
[‖‖‖]p<0.001, drug therapy group comparisons for Kruskal-Wallis test within time (t+1). Pairwise comparisons find three differences in rank means. Rank Mean difference = 772.99, critical value = 486.33, finds a significant difference between ACEI and ARB groups (rank mean = 11,490.06 and 10,717.07, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 1,895.53, critical value = 489.66, finds a significant difference between ARB and neither groups (rank mean = 10,717.07 and 12,612.59, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 1,122.53, critical value = 220.06, finds a significant difference between ACEI and neither groups (rank mean = 11,490.06 and 12,612.59, respectively, p<0.0083 (adjusted p-value)).
[§§§] p<0.001, drug therapy group comparisons for Kruskal-Wallis test within time (t+2). Pairwise comparisons find three differences in rank means. Rank Mean difference = 534.20, critical value = 383.12, finds a significant difference between ACEI and ARB groups (rank mean = 7,307.62 and 6,773.42, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 1,099.01, critical value = 383.85, finds a significant difference between ARB and neither groups (rank mean = 6,773.42 and 7,872.43, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 564.81, critical value = 174.60, finds a significant difference between ACEI and neither groups (rank mean = 7,307.62 and 7,872.43, respectively, p<0.0083 (adjusted p-value)).
[¶¶¶] p<0.001, drug therapy group comparisons for Kruskal-Wallis test within time (t+3). Pairwise comparisons find two differences in rank means. Rank Mean difference = 457.82, critical value = 282.95, finds a significant difference between ARB and neither groups (rank mean = 3,066.46 and 3,524.28, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 211.86, critical value = 119.47, finds a significant difference between ACEI and neither groups (rank mean = 3,312.41 and 3,524.28, respectively, p<0.0083 (adjusted p-value)).
[$] p<0.05, drug therapy group comparisons for ANOVA within time t. Tukey's Honestly Significant Difference finds no comparison is greater than the studentized range critical value (0.05, 3, 36793) = 3.32.
[&&&] p<0.001, drug therapy group comparisons for Kruskal-Wallis test within time (t+1). Pairwise comparisons find two differences in rank means. Rank Mean difference = 542.40, critical value = 509.40, finds a significant difference between ARB and neither groups (rank mean = 13,006.81 and 12,464.41, respectively, p<0.0083 (adjusted p-value)). Rank Mean difference = 668.42, critical value = 227.94, finds a significant

difference between ACEI and neither groups (rank mean = 13,132.83 and 12,464.41, respectively, $p<0.0083$ (adjusted p-value)).

^^^ $p<0.001$, drug therapy group comparisons for Kruskal-Wallis test within time (t+2). Pairwise comparisons find one differences in rank means. Rank Mean difference = 348.45, critical value = 178.89, finds a significant difference between ACEI and neither groups (rank mean = 8,095.72 and 7,747.28, respectively, $p<0.0083$ (adjusted p-value)).

Table 6 shows comparisons across time within each drug therapy for continuous clinical parameters. Among ACEI patients HbA1c values stayed constant over follow-up. In stark contrast, LDL values progressively decreased across years of follow-up. Triglyceride levels almost perfectly mirrored what was seen with LDL values: there was a constant decrease across years of follow-up until the fifth year.

Relating to ARB patients, we again saw similar values in HbA1c across time. Although the overall value for LDL showed change across time, no pairwise comparisons were significant. We also see comparable values in triglyceride across time within ARB patients.

For patients receiving neither therapy we saw a dip in HbA1c values in Year 2 that then returned and maintained at Year 1 values. Similar to what happened in ACEI patients, LDL values progressively decreased across years of follow-up. Triglyceride levels were comparable until the fifth year of follow-up, at which point they were lower than the first year.

Table 6: Continuous Clinical Parameters by Drug Therapy and Time Since Identification, Comparisons by Time Period

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
HbA1c	7.32 (1.82)	7.28 (4.13)	7.28 (3.50)	7.24 (1.63)	7.01 (1.15)	7.30 (3.04)
LDL***	96.19 (32.64)	91.02 (30.87)	89.60 (30.59)	88.06 (28.49)	82.09 (30.04)	92.77 (31.59)
Triglycerides†††	197.70 (169.70)	189.60 (165.50)	186.90 (177.50)	174.60 (122.90)	173.80 (112.40)	191.60 (167.20)
ARB						
HbA1c	7.21 (3.24)	7.45 (7.00)	7.17 (3.81)	7.13 (1.34)	7.31 (1.71)	7.27 (4.75)
LDL‡‡‡	91.66 (30.32)	88.16 (31.10)	86.52 (30.46)	84.72 (27.05)	96.13 (23.15)	89.01 (30.44)
Triglycerides‖	198.00 (182.50)	184.60 (154.60)	177.90 (121.30)	176.20 (153.20)	178.90 (115.40)	188.20 (161.10)
Neither						
HbA1c§§§	7.27 (1.66)	7.27 (3.45)	7.39[i] (4.33)	7.36 (4.32)	7.06 (1.29)	7.30 (3.14)
LDL¶¶¶	100.2 (34.79)	96.51 (33.84)	94.01 (34.05)	91.89 (42.33)	88.78 (32.80)	97.00 (35.37)
Triglycerides$$$	193.00 (179.50)	187.30 (209.80)	183.00 (160.10)	184.60 (222.40)	175.00 (139.60)	188.50 (189.60)

*** $p<0.001$, time comparisons for Kruskal-Wallis test within ACEI therapy. Pairwise comparisons find six differences in rank means. Rank Mean difference = 2,091.39, critical value = 373.91, finds a significant difference between first and second years of follow-up (rank mean = 20,656.75 and 18,565.36, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 2,657.85, critical value = 439.76, finds a significant difference between first and third years of follow-up (rank mean = 20,656.75 and 17,998.90, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 3,175.73, critical value = 658.43, finds a significant difference between first and fourth years of follow-up (rank mean = 20,656.75 and 17,481.02, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 5,531.87, critical value = 4,381.98, finds a significant difference between first and fifth years of follow-up (rank mean = 20,656.75 and 15,124.88, respectively, $p<0.0025$ (adjusted p-value)). Rank Mean difference = 566.46,

critical value = 464.12, finds a significant difference between second and third years of follow-up (rank mean = 18,565.36 and 17,998.90, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,084.34, critical value = 674.94, finds a significant difference between second and fourth years of follow-up (rank mean = 18,565.36 and 17,481.02, respectively, p<0.0025 (adjusted p-value)).

††† p<0.001, time comparisons for Kruskal-Wallis test within ACEI therapy. Pairwise comparisons find five significant differences in rank means. Rank Mean difference = 686.28, critical value = 384.85, finds a significant difference between first and second years of follow-up (rank mean = 21,087.10 and 20,400.82, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,047.81, critical value = 456.21, finds a significant difference between first and third years of follow-up (rank mean = 21,087.10 and 20,039.29, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,940.73, critical value = 686.71, finds a significant difference between first and fourth years of follow-up (rank mean = 21,087.10 and 19,146.37, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,254.44, critical value = 703.70, finds a significant difference between second and fourth years of follow-up (rank mean = 20,400.82 and 19,146.37, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 892.92, critical value = 745.13, finds a significant difference between third and fourth years of follow-up (rank mean = 20,039.29 and 19,146.37, respectively, p<0.0025 (adjusted p-value)).

‡‡ p<0.01, time comparisons for ANOVA. Tukey's Honestly Significant Difference finds no comparisons that are greater than the studentized range critical value (0.05, 5, 4057) = 3.859.

‖ p<0.05, time comparisons for Kruskal-Wallis test within ARB therapy. Pairwise comparisons find no significant difference in rank means.

§§§ p<0.001, time comparisons for Kruskal-Wallis test within neither therapy. Pairwise comparisons find three significant differences in rank means. Rank Mean difference = 429.41, critical value = 406.56, finds a significant difference between first and second years of follow-up (rank mean = 21,216.60 and 20,787.19, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 581.76, critical value = 503.51, finds a significant difference between second and third years of follow-up (rank mean = 20,787.19 and 21,368.96, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 803.82, critical value = 606.04, finds a significant difference between second and fourth years of follow-up (rank mean = 20,787.19 and 21,591.01, respectively, p<0.0025 (adjusted p-value)).

¶¶¶ p<0.001, time comparisons for Kruskal-Wallis test. Pairwise comparisons find nine significant differences in rank means. Rank Mean difference = 1,300.33, critical value 383.83, finds a significant difference between first and second years of follow-up (rank mean = 19,907.05 and 18,606.73, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,142.27, critical value = 438.14, finds a significant difference between first and third years of follow-up (rank mean = 19,907.05 and 17,764.78, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,838.67, critical value = 543.07, finds a significant difference between first and fourth years of follow-up (rank mean = 19,907.05 and 17,068.38, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 3,955.18, critical value = 1,418.73, finds a significant difference between first and fifth years of follow-up (rank mean = 19,907.05 and 15,951.87,

respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 841.95, critical value = 469.66, finds a significant difference between second and third years of follow-up (rank mean = 18,606.73 and 17,764.78, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,538.35, critical value = 568.80, finds a significant difference between second and fourth years of follow-up (rank mean = 18,606.73 and 17,068.38, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 2,654.85, critical value = 1,428.78, finds a significant difference between second and fifth years of follow-up (rank mean = 18,606.73 and 15,951.87, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 696.40, critical value = 606.77, finds a significant difference between third and fourth years of follow-up (rank mean = 17,764.78 and 17,068.38, respectively, p<0.0025 (adjusted p-value)). Rank Mean difference = 1,812.91, critical value = 1,444.32, finds a significant difference between third and fifth years of follow-up (rank mean = 17,764.78 and 15,951.87, respectively, p<0.0025 (adjusted p-value)).
[$$$] p<0.001, time comparisons for ANOVA. Tukey's Honestly Significant Difference finds one comparison that is greater than the studentized range critical value (0.05, 5, 40636) = 3.86. Triglycerides were lower at the fifth year of observation than the first (HSD test statistic = 4.23).

The next four tables show change in albuminuria over follow-up for a more direct comparison to previous studies based on patients' baseline albuminuria status. The first two show for those with microalbuminuria at baseline while the last two show for those with macroalbuminuria at baseline. At the first year of follow-up we see significant differences between all three treatment groups with those receiving neither therapy having the highest albuminuria. Also at this time we see a larger proportion of ARB patients across the spectrum of albuminuria than ACEI patients. The drug therapy groups have comparable values in Years 2 and 5. Those receiving neither therapy have higher albuminuria values than ACEI patients in Years 3 and 4. During years three and four we see significantly better albuminuria among ACEI patients compared to neither patients. There are significant changes across time in albuminuria for all three treatment groups through year four of observation.

For patients with macroalbuminuria at baseline, At Year 1, neither patients had higher levels of albuminuria than patients on ACEI or ARB monotherapies. Neither patients or ACEI patients have higher levels of albuminuria in Year 2 than ARB patients. Albuminuria levels for years three, four, and five are not significantly different between ACEI, ARB, and neither patients. In all groups we see regression to normoalbuminuria from baseline macroalbuminuria. Note there are few observations seen after year three within each treatment group.

Table 7: Albuminuria Changes for Baseline Microalbuminuric Patients by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Normoalbuminuria	0.07[a]	0.32	0.34	0.36	0.23	0.19
Microalbuminuria	0.92	0.59	0.55	0.49	0.59	0.76
Macroalbuminuria	0.02	0.01	0.13	0.15	0.18	0.06
ARB						
Normoalbuminuria	0.07[b]	0.28	0.36	0.35	0.67	0.19
Microalbuminuria	0.90	0.62	0.52	0.54	0.33	0.75
Macroalbuminuria	0.03	0.10	0.12	0.11	0.00	0.07
Neither						
Normoalbuminuria	0.05[c]	0.31	0.31	0.32	0.28	0.16
Microalbuminuria	0.93	0.59	0.56	0.55	0.60	0.78
Macroalbuminuria	0.02	0.10	0.13[d]	0.13[e]	0.13	0.06

Notes: values represent proportions

[a] $p<0.05$, ACEI versus ARB, for chi-square test. $X^2(2) = 7.04$.
[b] $p<0.001$, ARB versus neither, for chi-square test. $X^2(2) = 20.41$.
[c] $p<0.001$, ACEI versus neither, for chi-square test. $X^2(2) = 24.51$.
[d] $p<0.01$, ACEI versus neither, for chi-square test. $X^2(2) = 10.44$.
[e] $p<0.01$, ACEI versus neither, for chi-square test. $X^2(2) = 10.77$.

Table 8: Albuminuria Changes for Baseline Microalbuminuric Patients by Drug Therapy and Time Since Identification, Comparisons by Time

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Normoalbuminuria	0.07[a,b,c,d]	0.32[e,f]	0.34[g]	0.36	0.23	0.19
Microalbuminuria	0.92	0.59	0.55	0.49	0.59	0.76
Macroalbuminuria	0.02	0.10	0.12	0.15	0.18	0.06
ARB						
Normoalbuminuria	0.07[h,i,j,k]	0.28[l]	0.36	0.35	0.67	0.19
Microalbuminuria	0.90	0.62	0.52	0.54	0.33	0.75
Macroalbuminuria	0.03	0.10	0.12	0.11	0.00	0.07
Neither						
Normoalbuminuria	0.05[m,n,o,p]	0.31[q,r]	0.31	0.32	0.28	0.16
Microalbuminuria	0.93	0.59	0.56	0.55	0.60	0.78
Macroalbuminuria	0.02	0.10	0.13	0.13	0.13	0.06

Notes: values represent proportions

[a] $p<0.001$, albuminuria, time t and time (t+1) within ACEI for chi-square test. $X^2(2) = 3.10 \times 10^3$.
[b] $p<0.001$, albuminuria, time t and time (t+2) within ACEI for chi-square test. $X^2(2) = 2.90 \times 10^3$.
[c] $p<0.001$, albuminuria, time t and time (t+3) within ACEI for chi-square test. $X^2(2) = 2.10 \times 10^3$.
[d] $p<0.001$, albuminuria, time t and time (t+4) within ACEI for chi-square test. $X^2(2) = 40.30$.
[e] $p<0.001$, albuminuria, time (t+1) and time (t+2) within ACEI for chi-square test. $X^2(2) = 16.62$.
[f] $p<0.001$, albuminuria, time (t+1) and time (t+3) within ACEI for chi-square test. $X^2(2) = 55.19$.
[g] $p<0.001$, albuminuria, time (t+2) and time (t+3) within ACEI for chi-square test. $X^2(2) = 17.86$.

[h] $p<0.001$, albuminuria, time t and time (t+1) within ARB for chi-square test. $X^2(2) = 237.17$.
[I] $p<0.001$, albuminuria, time t and time (t+2) within ARB for chi-square test. $X^2(2) = 303.74$.
[j] $p<0.001$, albuminuria, time t and time (t+3) within ARB for chi-square test. $X^2(2) = 146.95$.
[k] $p<0.001$, albuminuria, time t and time (t+4) within ARB for chi-square test. $X^2(2) = 15.98$.
[l] $p<0.01$, albuminuria, time (t+1) and time (t+2) within ARB for chi-square test. $X^2(2) = 10.43$.
[m] $p<0.001$, albuminuria, time t and time (t+1) within neither for chi-square test. $X^2(2) = 3.50 \times 10^3$.
[n] $p<0.001$, albuminuria, time t and time (t+2) within neither for chi-square test. $X^2(2) = 3.10 \times 10^3$.
[o] $p<0.001$, albuminuria, time t and time (t+3) within neither for chi-square test. $X^2(2) = 2.40 \times 10^3$.
[p] $p<0.001$, albuminuria, time t and time (t+4) within neither for chi-square test. $X^2(2) = 334.78$.
[q] $p<0.001$, albuminuria, time (t+1) and time (t+2) within neither for chi-square test. $X^2(2) = 18.24$.
[r] $p<0.001$, albuminuria, time (t+1) and time (t+3) within neither for chi-square test. $X^2(2) = 14.64$.

Table 9: Albuminuria Changes for Baseline Macroalbuminuric Patients by Drug Therapy and Time Since Identification, Comparisons by Drug Therapy

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Normoalbuminuria	0.01	0.08[a]	0.10	0.15	0.00	0.05
Microalbuminuria	0.07	0.35	0.36	0.36	0.60	0.19
Macroalbuminuria	0.91	0.58	0.54	0.49	0.40	0.76
ARB						
Normoalbuminuria	0.01[b]	0.14[c]	0.13	0.13	0.00	0.07
Microalbuminuria	0.09	0.36	0.34	0.36	0.00	0.20
Macroalbuminuria	0.90	0.50	0.53	0.51	1.00	0.73
Neither						
Normoalbuminuria	0.01[d]	0.07	0.11	0.14	0.15	0.05
Microalbuminuria	0.06	0.34	0.33	0.36	0.42	0.17
Macroalbuminuria	0.94	0.58	0.57	0.50	0.44	0.78

Notes: values represent proportions

[a] $p<0.01$, ACEI versus ARB within time (t+1), for chi-square test. $X^2(2) = 10.41$.
[b] $p<0.05$, ARB versus neither within time t, for chi-square test. $X^2(2) = 7.20$.
[c] $p<0.01$, ARB versus neither within time (t+1), for chi-square test. $X^2(2) = 10.62$.
[d] $p<0.01$, ACEI versus neither within time t, for chi-square test. $X^2(2) = 14.96$.

Table 10: Albuminuria Changes for Baseline Macroalbuminuric Patients by Drug Therapy and Time Since Identification, Comparisons by Time

Variable	Time t	Time (t+1)	Time (t+2)	Time (t+3)	Time (t+4)	Total
ACEI						
Normoalbuminuria	0.01[a,b,c,d]	0.08[e,f]	0.10[g]	0.15	0.00	0.05
Microalbuminuria	0.07	0.35	0.36	0.36	0.60	0.19
Macroalbuminuria	0.91	0.58	0.54	0.49	0.40	0.76
ARB						
Normoalbuminuria	0.01[h,i,j]	0.14	0.13	0.13	0.00	0.07
Microalbuminuria	0.09	0.36	0.34	0.36	0.00	0.20
Macroalbuminuria	0.90	0.50	0.53	0.51	1.00	0.73
Neither						
Normoalbuminuria	0.01[k,l,m,n]	0.07[o]	0.11	0.14	0.15	0.05
Microalbuminuria	0.06	0.34	0.33	0.36	0.42	0.17
Macroalbuminuria	0.94	0.58	0.57	0.50	0.44	0.78

Notes: values represent proportions

[a] $p<0.001$, albuminuria, time t and time (t+1) within ACEI for chi-square test. $X^2(2) = 953.12$.
[b] $p<0.001$, albuminuria, time t and time (t+2) within ACEI for chi-square test. $X^2(2) = 858.93$.
[c] $p<0.001$, albuminuria, time t and time (t+3) within ACEI for chi-square test. $X^2(2) = 588.10$.
[d] $p<0.001$, albuminuria, time t and time (t+4) within ACEI for chi-square test. $X^2(2) = 39.68$.
[e] $p<0.05$, albuminuria, time (t+1) and time (t+2) within ACEI for chi-square test. $X^2(2) = 6.18$.
[f] $p<0.001$, albuminuria, time (t+1) and time (t+3) within ACEI for chi-square test. $X^2(2) = 24.06$.
[g] $p<0.05$, albuminuria, time (t+2) and time (t+3) within ACEI for chi-square test. $X^2(2) = 7.95$.

[h] p<0.001, albuminuria, time t and time (t+1) within ARB for chi-square test. $X^2(2) = 127.07$.
[I] p<0.001, albuminuria, time t and time (t+2) within ARB for chi-square test. $X^2(2) = 87.59$.
[j] p<0.001, albuminuria, time t and time (t+3) within ARB for chi-square test. $X^2(2) = 62.62$.
[k] p<0.001, albuminuria, time t and time (t+1) within neither for chi-square test. $X^2(2) = 937.91$.
[l] p<0.001, albuminuria, time t and time (t+2) within neither for chi-square test. $X^2(2) = 814.74$.
[m] p<0.001, albuminuria, time t and time (t+3) within neither for chi-square test. $X^2(2) = 800.24$.
[n] p<0.001, albuminuria, time t and time (t+4) within neither for chi-square test. $X^2(2) = 193.50$.
[o] p<0.001, albuminuria, time (t+1) and time (t+3) within neither for chi-square test. $X^2(2) = 19.72$.

Outpatient values have a mean of 10.52 and a standard deviation of 13.37, indicating overdispersion. With 14,962 of 124,296 patient-years (12.04%) without outpatient visits it is not abundantly clear that we have more zeroes than expected by chance.

Table 11 displays the diagnostic tests of the count variable regression models. The Poisson regression model resulted in a significant Hosmer and Lemeshow goodness-of-fit and Pregibon's Link Test ($p<0.001$ each). The next step was to run a negative binomial regression model which resulted in a significant Pregibon's Link Test ($p<0.001$) and overdispersion test (likelihood-ratio test of $\alpha=0$: chibar2(1) = 2.6e+05 Prob≥chibar2 < 0.001). A zero-inflated Poisson regression model was then run, which did not converge. The last model constructed was the zero-inflated negative binomial regression model. Looking at the results from the diagnostic tests of the Poisson, negative binomial, and zero-inflated negative binomial regressions, and knowing that the model with the lowest Akaike Information Criterion (AIC) is the best choice, we had another reason than the failed overdispersion test to rule out the Poisson model. This left the negative binomial and zero-inflated negative binomial regressions for comparison. Negative binomial regression had the best model fit because it had similar log pseudolikelihood and Bayesian Information Criterion (BIC) as the zero-inflated negative binomial, but it had fewer degrees of freedom.

Table 11: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for Outpatient Visits, ACEI or ARB versus Neither

Analytic Model	**Poisson**	**Nbreg[a]**	**ZIP[b]**	**ZINB[c]**
Hosmer and Lemeshow (p)	411,404.40 (<0.001)	Not available	Not applicable (model did not converge)	Not available
Pregibon's Link Test (p)	-0.09 (<0.001)	-0.08 (<0.001)	Not applicable (model did not converge)	Not available
Pearson's Correlation (p)	552,673.30 (<0.001)	Not available	Not applicable (model did not converge)	Not available
LL (null)[d]	Not applicable	-199,681.50	Not applicable (model did not converge)	-199,681.50
LL (model)[e]	-320,534.80	-192,329.40	Not applicable (model did not converge)	-192,402.90
df[f]	63	64	Not applicable (model did not converge)	103
AIC[g]	641,195.60	384,786.70	Not applicable (model did not converge)	385,011.80
BIC[h]	641,757.90	385,357.90	Not applicable (model did not converge)	385,931.00

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

The values of ED visits indicate overdispersion (mean = 0.18, standard deviation = 0.71). Additionally, 111,867 of 124,296 (90.00%) person-years indicate no record of an ED visit.

Table 12 presents the diagnostic tests for the count dependent variable regression models. We first ran a Poisson regression model which resulted in a nonsignificant Hosmer and Lemeshow goodness-of-fit and Pregibon's Link Test ($p<0.001$ each). As a next step we ran a negative binomial regression model which led to a significant Pregibon's Link Test ($p<0.001$) and overdispersion test (likelihood-ratio test of $\alpha = 0$: chibar2(1) = 1.1e+04 Prob≥chibar2 < 0.001. We then ran a zero-inflated Poisson regression model which did not converge. The last step was construction of the zero-inflated negative binomial regression model. As can be seen, the Poisson model had higher log pseudolikelihood, AIC, and BIC than the negative binomial or zero-inflated negative binomial. The negative binomial model has the best fit due to the similar AICs and BICs between it and the zero-inflated negative binomial and its fewer degrees of freedom.

Table 12: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for ED Visits, ACEI or ARB versus Neither

Analytic Model	Poisson	Nbreg[a]	ZIP[b]	ZINB[c]
Hosmer and Lemeshow (p)	49,945.00 (1.000)	Not available	Not applicable (model did not converge)	Not available
Pregibon's Link Test (p)	-0.09 (<0.001)	-0.14 (<0.001)	Not applicable (model did not converge)	Not available
Pearson's Correlation (p)	131,640.50 (<0.001)	Not available	Not applicable (model did not converge)	Not available
LL(null)[d]	Not applicable	-28,694.64	Not applicable (model did not converge)	-27,607.16
LL (model)[e]	-32,914.75	-27,400.19	Not applicable (model did not converge)	-27,208.56
df[f]	63	64	Not applicable (model did not converge)	103
AIC[g]	65,955.50	54,928.38	Not applicable (model did not converge)	54,623.12
BIC[h]	66,517.76	55,499.56	Not applicable (model did not converge)	55,542.36

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

Hospitalizations show overdispersion with a mean of 0.13 and standard deviation of 0.55. That, provided with 115,036 of 124,296 person-years (92.55%) showing no record of hospitalization, indicates we may need to look at a zero-inflated negative binomial regression model.

Table 13 presents the results for the diagnostic tests for the count dependent variable regression models. As has been the pattern, a Poisson regression model was first constructed, which resulted in a nonsignificant Hosmer and Lemeshow goodness-of-fit ($p=1.00$) and a significant Pregibon's Link Test ($p<0.001$). A negative binomial regression analysis was conducted, which resulted in a significant Pregibon's Link Test ($p<0.001$) and overdispersion test (likelihood-ratio test of $\alpha = 0$: chibar2(1) = 6525.74 Prob≥chibar2 < 0.001). As a next step, we ran a zero-inflated Poisson regression model which did not converge. Lastly, we ran a zero-inflated negative binomial regression. Lower log pseudolikelihood, AIC, and BIC are seen with the negative binomial compared to the Poisson model. Although all are also slightly lower with the zero-inflated negative binomial model than the negative binomial, the fewer degrees of freedom in the negative binomial model make this the model with the best fit.

Table 13: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for Hospitalizations, ACEI or ARB versus Neither

Analytic Model	Poisson	Nbreg[a]	ZIP[b]	ZINB[c]
Hosmer and Lemeshow (p)	37,198.10 (1.00)	Not available	Not applicable (model did not converge)	Not available
Pregibon's Link Test (p)	-0.08 (<0.001)	-0.10 (<0.001)	Not applicable (model did not converge)	Not available
Pearson's Correlation (p)	112,285.90 (<0.001)	Not available	Not applicable (model did not converge)	Not available
LL (null)[d]	Not applicable	-22,581.48	Not applicable (model did not converge)	-21,167.19
LL (model)[e]	-24,457.16	-21,164.46	Not applicable (model did not converge)	-20,823.50
df[f]	63	64	Not applicable (model did not converge)	103
AIC[g]	49,040.32	42,456.91	Not applicable (model did not converge)	41,852.99
BIC[h]	49,602.58	43,028.09	Not applicable (model did not converge)	42,772.24

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

Outpatient visits have a mean of 10.52 and a standard deviation of 13.37 (range 0 to 358), indicating overdispersion. During the observation period there were 14,962 person-years (12.04%) without an office visit, which is more than due to chance, so we run a zero-inflated negative binomial regression. (Note: we have information for these individuals because of at least one hospitalization and/or ED visit).

Table 14 displays results of the diagnostic tests for each of the count variable regression models of ACEI monotherapy's effects, compared to ARB monotherapy's, on outpatient visits. First, the Poisson regression model was run, which resulted in a significant Hosmer and Lemeshow goodness-of-fit and Pregibon's Link Test ($p<0.001$ each). Thus, a negative binomial regression model was constructed, which also resulted in significant Pregibon's Link Test ($p<0.001$) as well as a significant overdispersion test (likelihood-ratio test of $\alpha = 0$: chibar2(1) = 2.6e+05 Prob $\geq$ chibar2 < 0.001). The significant Pregibon's Link Test is indicative that we still have model misspecification. The significant overdispersion test tells us that the dispersion factor, α, is significantly different from zero, meaning the Poisson regression may not be a good choice since the Poisson is only equal to the negative binomial regression when $\alpha = 0$. We then tried a zero-inflated Poisson (for comparison's sake), but the model did not converge. Lastly, a zero-inflated negative binomial regression was performed. As the findings in the table show, the best model fit was for the negative binomial regression as it had lower AIC, BIC, and log pseudolikelihood compared to Poisson and it had similar AIC, BIC, and log pseudolikelihood compared to the zero-inflated binomial model, but fewer degrees of freedom.

Table 14: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for Outpatient Visits, ACEI versus ARB

Analytic Model	**Poisson**	**Nbreg[a]**	**ZIP[b]**	**ZINB[c]**
Hosmer and Lemeshow (p)	219,389.30 (<0.001)	Not available	Not applicable (model did not converge)	Not available
Pregibon's Link Test (p)	-0.10 (<0.001)	-0.09 (<0.001)	Not applicable (model did not converge)	Not available
Pearson's Correlation (p)	288,848.70 (<0.001)	Not available	Not applicable (model did not converge)	Not available
LL (null)[d]	Not applicable	-110,468.30	Not applicable (model did not converge)	-110,468.30
LL (model)[e]	-173,722.40	-106,487.70	Not applicable (model did not converge)	-106,487.70
df[f]	57	58	Not applicable (model did not converge)	98
AIC[g]	347,558.90	213,091.40	Not applicable (model did not converge)	213,171.40
BIC[h]	348,033.30	213,574.10	Not applicable (model did not converge)	213,987.10

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

For ED visits, we again see overdispersion with a mean of 0.18 and a standard deviation of 0.71 (range=0-32). Since we have 111,867 person-years (90.00%) of our sample without a visit to the ED, we needed to consider the zero-inflated negative binomial model.

Table 15 displays results of the diagnostic tests for each of the count variable regression models of ACEI monotherapy's effects, compared to ARB monotherapy's, on ED visits. First, a Poisson regression model was constructed, which resulted in a nonsignificant goodness-of-fit test, but significant Pregibon's Link Test ($p<0.001$). The next step involved a negative binomial regression model which resulted in a significant Pregibon's Link Test ($p<0.001$) and overdispersion test (likelihood-ratio test of $\alpha = 0$: chibar2(1) = 1.1e+04 Prob≥chibar2 < 0.001). Then a zero-inflated Poisson regression model was constructed and finally a zero-inflated negative binomial regression model was constructed. As Table 27 indicates, the Poisson model was quickly ruled out for good fit because it has the highest log pseudolikelihood, AIC, and BIC of the four models. The zero-inflated Poisson was next ruled out because, of the three remaining models, it had the highest log pseudolikelihood, AIC, and BIC, with more degrees of freedom than the negative binomial. This again left the negative binomial compared to the zero-inflated negative binomial. Although the zero-inflated model has lower log pseudolikelihood and AIC, it does have higher BIC and more degrees of freedom than the negative binomial, leaving the negative binomial with the best fit.

Table 15: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for ED Visits, ACEI versus ARB

Analytic Model	**Poisson**	**Nbreg[a]**	**ZIP[b]**	**ZINB[c]**
Hosmer and Lemeshow (p)	27,774.46 (1.00)	Not available	Not available	Not available
Pregibon's Link Test (p)	-0.08 (<0.001)	-0.14 (<0.001)	Not available	Not available
Pearson's Correlation (p)	68,951.36 (<0.001)	Not available	Not available	Not available
LL (null)[d]	Not applicable	-16,155.13	-16,041.63	-15,555.29
LL (model)[e]	-18,402.72	-15,420.78	-15,756.25	-15,304.59
df[f]	57	58	97	98
AIC[g]	36,919.45	30,957.57	31,706.5	30,805.19
BIC[h]	37,393.85	31,440.30	31,620.83	31,620.83

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

Hospitalization exhibits overdispersion with a mean of 0.13 and a standard deviation of 0.55 (range=0-16). It also has many zero values: 115,036 person-years (92.55%) do not have a hospitalization recorded.

Table 16 displays results of the diagnostic tests for each of the count variable regression models of ACEI monotherapy's effects, compared to ARB monotherapy's, on hospitalizations. A Poisson regression model was first run, which resulted in a nonsignificant Hosmer and Lemeshow goodness-of-fit, but significant Pregibon's Link Test ($p<0.001$ each) so we then ran a negative binomial regression model which resulted in a significant Pregibon's Link Test ($p<0.001$) and overdispersion test (likelihood ratio test of $\alpha = 0$:chibar2(1)=6532.85, prob≥chibar2 < 0.001). Systematically, a zero-inflated Poisson regression and zero-inflated negative binomial regression were performed next. Table 29 provides more evidence that the Poisson model had a poor fit; in fact, it had the poorest of the four models based on that it had the highest log pseudolikelihood, AIC, and BIC. The zero-inflated Poisson had higher AIC and BIC than the negative binomial whereas the negative binomial had higher log pseudolikelihood and lower degrees of freedom; therefore, the zero-inflated Poisson also had poor model fit. The zero-inflated negative binomial had lower log pseudolikelihood and AIC and higher BIC with more degrees of freedom, meaning the negative binomial model had the best fit.

Table 16: Model Fit Diagnostic Tests for Assessment of Count Dependent Variable Models for Hospitalizations, ACEI versus ARB

Analytic Model	**Poisson**	**Nbreg[a]**	**ZIP[b]**	**ZINB[c]**
Hosmer and Lemeshow (p)	37,211.70 (1.000)	Not available	Not available	Not available
Pregibon's Link Test (p)	-0.08 (<0.001)	-0.10 (<0.001)	Not available	Not available
Pearson's Correlation (p)	112,096.00 (<0.001)	Not available	Not available	Not available
LL (null)[d]	Not applicable	-12,862.65	-12,259.19	-12,098.96
LL (model)[e]	-13,763.78	-12,080.93	-12,040.23	-11,889.12
df[f]	57	58	97	98
AIC[g]	27,641.56	24,277.85	24,274.46	23,974.24
BIC[h]	28,115.96	24,760.58	25,081.78	24,789.88

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

Since diagnostic tests for multivariate unweighted regression comparing ACEI versus ARB monotherapy for each count variable was complete, the next step was to set up the data for propensity score analyses (PSA). The following tables show results of data setup for preparation of the first stage. First, we excluded patients who received neither therapy at baseline. Then, using zip code as a proxy for facility formulary and prescriber preference, we merged state and metropolitan area with our sample. Those individuals missing zip codes and their annual observations dropped out of future analysis giving us 20,876 patients with 120,900 person-years of observation (Tables 17 and 18). Table 19 shows the geographic diversity in the sample: patients in all states are represented as well as the District of Columbia and Puerto Rico. First-stage PSA includes those on- and off- support.

We verified two assumptions of the first-stage PSA were true for our study: 1) all propensity scores were between 0 and 1, and 2) we achieved enough overlap in our study, matching one ARB patient with one ACEI patient by obtaining a common support of 0.4 to 1.0 for each patient. This means ARB patients had similar propensities for treatment as ACEI patients. Lack of overlap would indicate lack of between group balance on observable characteristics at baseline.

Table 17: Merge Tabulation for Census and VA Zip Code

	Frequency	**Percent**
From VA data	3,396	2.35
From Census data	20,517	14.17
Both VA and Census data	120,900	83.49
Total	144,813	100.00

Table 18: Sample size on ACEI or ARB Monotherapy at Baseline after Zip Code Merge

Treatment	Frequency	Percent
ARB	1,929	9.24
ACEI	18,947	90.76
Total	20,876	100.00

Table 19: State and Territory Representation in Sample (N=63,808 person-years)

State/Territory	Frequency	Percent
Alabama	1,208	1.89
Alaska	67	0.11
Arizona	840	1.32
Arkansas	715	1.12
California	2,470	3.87
Colorado	440	0.69
Connecticut	286	0.45
Delaware	8	0.01
District of Columbia	14	0.02
Florida	3,990	6.25
Georgia	2,744	4.30
Hawaii	292	0.46
Idaho	357	0.56
Illinois	2,742	4.30
Indiana	2,003	3.14
Iowa	647	1.01
Kansas	1,112	1.74
Kentucky	1,311	2.05
Louisiana	805	1.26
Maine	378	0.59
Maryland	497	0.78
Massachusetts	524	0.82
Michigan	2,499	3.92
Minnesota	1,202	1.88
Mississippi	1,047	1.64
Missouri	2,746	4.30
Montana	228	0.36
Nebraska	322	0.50
Nevada	15	0.02
New Hampshire	357	0.56
New Jersey	455	0.71
New Mexico	228	0.36
New York	2,113	3.31
North Carolina	2,046	3.21
North Dakota	36	0.06
Ohio	3,356	5.26
Oklahoma	2,391	3.75
Oregon	630	0.99
Pennsylvania	3,897	6.11
Puerto Rico	78	0.12
Rhode Island	218	0.34
South Carolina	4,038	6.33

Table 19 (cont.)

State/Territory	Frequency	Percent
South Dakota	95	0.15
Tennessee	3,251	5.09
Texas	3,767	5.90
Utah	282	0.44
Vermont	137	0.21
Virginia	429	0.67
Washington	988	1.55
West Virginia	405	0.63
Wisconsin	1,240	1.94
Wyoming	164	0.26
Missing	1,698	2.66
Total	63,808	100.00

The values for outpatient visits show overdispersion is present with a mean of 11.84 and standard deviation of 13.56 (range = 0-358). Values of zero look like they have the possibility to not be more than due to chance with a frequency of 3,821 of 46,494 patient-years with common support = 1 (8.22%). We first ran a Poisson regression, which resulted in a significant Pregibon's Link Test ($p<0.001$), so we then ran a negative binomial regression which also had a significant Pregibon's Link Test ($p<0.001$). The next step was the zero-inflated Poisson regression, which did not converge, so we then ran a zero-inflated negative binomial regression.

Table 20 shows the results of the diagnostic tests for each of the regression models. The same patient characteristics were entered in one step into each of the models. Again, the Poisson model was found to have the worst fit with substantially higher log pseudolikelihood, AIC, and BIC than the other models. The zero-inflated negative binomial had a slightly lower log pseudolikelihood, AIC, and BIC than the negative binomial, but we didn't feel this was worth the 44 degrees of freedom.

Table 20: Diagnostic Model Fit for Outpatient Visits, PSA ACEI versus ARB

Analytic Model	Poisson	Nbreg[a]	ZIP[b]	ZINB[c]
Hosmer-Lemeshow (p)	1,755,631.00 (<0.001)	Not available	Not applicable (model did not converge)	Not available
Pregibon's Link Test (p)	-0.90 (<0.001)	-0.92 (<0.001)	Not applicable (model did not converge)	Not available
Pearson (p)	2,387,487.00 (<0.001)	Not available	Not applicable (model did not converge)	Not available
LL (null)[d]	Not applicable	-884,944.70	Not applicable (model did not converge)	-884,944.70
LL (model)[e]	-11,392,757.00	-854,280.80	Not applicable (model did not converge)	-853,881.00
df[f]	56	57	Not applicable (model did not converge)	101
AIC[g]	5,785,625.00	1,708,676.00	Not applicable (model did not converge)	1,707,964.00
BIC[h]	2,786,081.00	1,709,139.00	Not applicable (model did not converge)	1,708,785.00

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

As is expected, we have overdispersion with ED visits (mean = 0.19, standard deviation = 0.71. Much of this is due to the large numbers of person-years without a recorded ED visit: we have 41,424 of 46,494 person-years (89.10%) that do not show an ED visit. Poisson regression resulted in a significant goodness-of-fit ($p<0.001$) and a significant Pregibon's Link Test ($p<0.001$), so we then ran a negative binomial regression model which resulted in a significant Pregibon's Link Test ($p<0.001$). As a next step, we then ran a zero-inflated Poisson regression model since the Pregibon's Link Test for Poisson regression had a higher p-value than for the negative binomial regression. Table 21 shows the results of the diagnostic tests for each of the regression models. The Poisson and zero-inflated Poisson models had the highest and second-highest log pseudolikelihood, AIC, and BIC of the four models, respectively. The zero-inflated negative binomial had the lowest log pseudolikelihood, AIC, and BIC, but these seemed to be similar to the negative binomial model, which had fewer degrees of freedom.

Table 21: Model Fit Diagnostic Tests for ED Visits, PSA ACEI versus ARB

Analytic Model	Poisson	Nbreg[a]	ZIP[b]	ZINB[c]
Hosmer-Lemeshow (p)	227,339.00 (<0.001)	Not available	Not available	Not available
Pregibon's Link Test (p)	-0.09 (<0.001)	-0.12 (<0.001)	Not available	Not available
Pearson (p)	548,203.20 (<0.001)	Not available	Not available	Not available
LL (null)[d]	Not applicable	-133,045.40	-132,018.60	-127,954.70
LL (model)[e]	-151,183.50	-126,677.00	-129,485.30	-125,679.90
df[f]	56	57	100	101
AIC[g]	302,479.10	253,468.00	259,170.70	251,561.90
BIC[h]	302,934.50	253,931.60	259,984.00	252,383.30

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

Similar to ED visits, we have overdispersion (mean = 0.14, standard deviation = 0.56). We also have many values for which hospitalization is zero: 42,576 of 46,494 person-years (91.57%). Poisson regression model was first performed, which resulted in a significant goodness-of-fit test and Pregibon's Link Test ($p<0.001$ each). The next step was to perform a negative binomial regression analysis, which resulted in a significant Pregibon's Link Test ($p<0.001$). Thereafter, the researchers performed a zero-inflated Poisson regression. The last step was to run a zero-inflated negative binomial regression model, which did not converge. Table 22 shows results of the diagnostic tests for each of the regression models. As Table 22 reveals, the Poisson model had the highest log pseudolikelihood, AIC, and BIC, so it provided the worst model fit of the three models. The zero-inflated Poisson had lower log pseudolikelihood, AIC, and BIC than the negative binomial, but the values appear to be similar. As we did not want to waste 43 degrees of freedom, the negative binomial regression had the best fit.

Table 22: Model Fit Diagnostic Tests for Hospitalizations, PSA ACEI versus ARB

Analytic Model	Poisson	Nbreg[a]	ZIP[b]	ZINB[c]
Hosmer-Lemeshow (p)	167676.30 (<0.001)	Not available	Not available	Not applicable (model did not converge)
Pregibon's Link Test (p)	-0.07 (<0.001)	-0.09 (<0.001)	Not available	Not applicable (model did not converge)
Pearson (p)	472029.30 (<0.001)	Not available	Not available	Not applicable (model did not converge)
LL (null)[d]	Not applicable	-105031.80	-100230.70	Not applicable (model did not converge)
LL (model)[e]	-111760.90	-98578.89	-985175.05	Not applicable (model did not converge)
df[f]	56	57	100	Not applicable (model did not converge)
AIC[g]	223633.80	197271.80	196550.10	Not applicable (model did not converge)
BIC[h]	224089.20	197735.40	197363.40	Not applicable (model did not converge)

[a] Nbreg stands for negative binomial regression, [b] ZIP stands for zero-inflated Poisson, [c] ZINB stands for zero-inflated negative binomial, [d] LL (null) stands for log (pseudo)likelihood of the null model, [e] LL (model) stands for log (pseudo)likelihood of the full model, [f] df stands for degrees of freedom, [g] AIC stands for Akaike Information Criterion, [h] BIC stands for Bayesian Information Criterion

This section shows the results of average treatment effect on the treated (ATT) for each dependent variable. Please see Tables 23 and 24 for ATT for each outcome through matching with propensity score in each stratum (i.e., stratification) and then through nearest-neighbor matching.

Table 23: Average Treatment Effect on the Treated Patients in Our Sample, for Effect of ACEI Compared to ARB for Each Outcome, Stratification

	ACEI Patients (N)	**ARB Patients (N)**	**ATT**	**Standard Error**	**T-statistic**
ESRD	13,691	1,432	-0.00	0.001	-0.05
IVDE	13,691	1,432	-0.01	0.01	-0.87
All-cause mortality	13,691	1,432	0.001	0.001	0.61
Outpatient visits	13,691	1,432	-0.09	0.46	-0.19
ED visits	13,691	1,432	0.01	0.03	0.47
Hospitalizations	13,691	1,432	0.01	0.02	0.29

Table 24: Average Treatment Effect on the Treated Patients in Our Sample, for Effect of ACEI Compared to ARB for Each Outcome, Nearest-Neighbor Matching

	Sample	**Treated (ACEI)**	**Controls (ARB)**	**Difference**	**Standard Error**	**T-statistic**
ESRD	Unmatched	7.99×10^{-4}	1.40×10^{-3}	-5.98×10^{-4}	8.12×10^{-4}	-0.74
	ATT	6.99×10^{-4}	1.40×10^{-3}	-6.99×10^{-4}	12.10×10^{-4}	-0.58
IVDE	Unmatched	0.03	0.03	6.79×10^{-4}	0.01	0.13
	ATT	0.04	0.03	7.69×10^{-3}	0.01	1.08
All-Cause Mortality	Unmatched	0.002	0.002	0.000	0.001	0.10
	ATT	0.003	0.002	0.001	0.002	0.38
Outpatient visits	Unmatched	16.42	16.53	-0.10	0.38	-0.27
	ATT	16.06	16.53	-0.47	0.52	-0.89
ED visits	Unmatched	0.27	0.23	0.04	0.02	1.58
	ATT	0.26	0.23	0.03	0.03	1.12
Hospital-izations	Unmatched	0.19	0.18	0.01	0.02	0.62
	ATT	0.16	0.18	-0.01	0.02	-0.60

Note: S.E. for ATT does not take into account that the propensity score is estimated.

There is no direct test of the presence or absence of hidden bias from unobservable variables, but since PSA only includes observable variables, the sensitivity analysis that can be performed after nearest-neighbor matching gives a sense of robustness (or lack thereof) in determining true treatment effect for each dependent variable. All dependent variables assessed sensitivity of results to hidden bias by using a weighted average across all strata rather than assessing each stratum separately. The sensitivity analyses performed after nearest-neighbor matching yielded findings of interest in terms of robustness of this study's findings. Mantel-Haenszel bounds were conducted for dichotomous variables while Rosenbaum bounds were conducted for count dependent variables. Since it has been recommended to test gamma, the odds of differential treatment assignment, from one to two, these values defined our range.

Mantel-Haenszel bounds found nonsignificant differences for ESRD or all-cause mortality between ACEI and ARB monotherapies, as found in PSA results of this study, held true to the point that if an unobserved variable exists, it would have to increase the odds of treatment assignment by more than 200% to change the conclusion. (This can be seen by looking at the p-value columns.) Mantel-Haenszel bounds reveal that the nonsignificant between group differences of ATT for IVDE, based on nearest-neighbor matching, holds true in the potential presence of an unobserved variable until such variable increases the odds of treatment assignment by 115% to 120%.

Rosenbaum bounds reveal the nonsignificant differences in outpatient visits found by PSA only hold true if there is an unobserved variable affecting odds of treatment assignment by between 105% and 110%. Even more sensitive to possible unobservalbes affecting ttreatment assignment, the PSA for ED visits shows patients with ACEI or ARB

monotherapy had comparable ED visits only at gamma=1 (p-value=0.05), so this would only be certain if an unobserved variable increased the odds of treatment assignment by between 100% and 105%. Lastly, the PSA finding of no difference between ACEI and ARB monotherapies on hospitalizations would remain true if an unobserved variable existed and changed the odds of treatment assignment between 115% and 120%

Table 25: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for ESRD, Nearest-Neighbor Matching

Gamma	**Q_{MH}+**	**Q_{MH}-**	**p-value +**	**p-value -**
1	0.00	0.00	0.50	0.50
1.05	0.04	-0.04	0.48	0.52
1.1	0.08	-0.08	0.47	0.53
1.15	0.12	-0.12	0.45	0.55
1.2	0.16	-0.16	0.44	0.56
1.25	0.19	-0.19	0.42	0.58
1.3	0.23	-0.23	0.41	0.59
1.35	0.26	-0.26	0.40	0.60
1.4	0.29	-0.29	0.39	0.62
1.45	0.32	-0.32	0.37	0.63
1.5	0.35	-0.35	0.36	0.64
1.55	0.38	-0.38	0.35	0.65
1.6	0.41	-0.41	0.34	0.66
1.65	0.44	-0.44	0.33	0.67
1.7	0.47	-0.47	0.32	0.68
1.75	0.49	-0.49	0.31	0.69
1.8	0.52	-0.52	0.30	0.70
1.85	0.54	-0.54	0.29	0.71
1.9	0.57	-0.57	0.29	0.71
1.95	0.59	-0.59	0.28	0.72
2	0.61	-0.61	0.27	0.73

Gamma : odds of differential assignment due to unobserved factors
Q_{MH}+ : Mantel-Haenszel statistic (assumption: overestimation of treatment effect)
Q_{MH}- : Mantel-Haenszel statistic (assumption: underestimation of treatment effect)
p-value + : significance level (assumption: overestimation of treatment effect)
p-value - : significance level (assumption: underestimation of treatment effect)

Table 26: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for IVDE, Nearest-Neighbor Matching

Gamma	**Q_{MH}+**	**Q_{MH}-**	**p-value +**	**p-value -**
1	0.99	0.99	0.16	0.16
1.05	0.74	1.23	0.23	0.11
1.1	0.50	1.47	0.31	0.07
1.15	0.28	1.70	0.39	0.05
1.2	0.06	1.92	0.48	0.03
1.25	-0.06	2.13	0.52	0.02
1.3	0.14	2.33	0.44	0.01
1.35	0.33	2.52	0.37	<0.01
1.4	0.52	2.71	0.30	<0.01
1.45	0.70	2.90	0.24	<0.01
1.5	0.87	3.07	0.19	0.001
1.55	1.03	3.25	0.15	0.001
1.6	1.19	3.41	0.12	<0.001
1.65	1.35	3.58	0.09	<0.001
1.7	1.50	3.74	0.07	<0.001
1.75	1.65	3.89	0.05	<0.001
1.8	1.79	4.05	0.04	<0.001
1.85	1.93	4.19	0.03	<0.001
1.9	2.07	4.34	0.02	<0.001
1.95	2.20	4.48	0.01	<0.001
2	2.33	4.62	0.01	<0.001

Gamma : odds of differential assignment due to unobserved factors
Q_{MH}+ : Mantel-Haenszel statistic (assumption: overestimation of treatment effect)
Q_{MH}- : Mantel-Haenszel statistic (assumption: underestimation of treatment effect)
p-value + : significance level (assumption: overestimation of treatment effect)
p-value - : significance level (assumption: underestimation of treatment effect)

Table 27: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for All-Cause Mortality, Nearest-Neighbor Matching

Gamma	**Q_{MH}+**	**Q_{MH}-**	**p-value +**	**p-value -**
1	0.00	0.00	0.50	0.50
1.05	-0.06	0.06	0.53	0.47
1.1	-0.13	0.13	0.55	0.45
1.15	-0.19	0.19	0.57	0.43
1.2	-0.24	0.24	0.60	0.41
1.25	-0.30	0.30	0.62	0.38
1.3	-0.35	0.35	0.64	0.36
1.35	-0.37	0.40	0.64	0.35
1.4	-0.32	0.45	0.63	0.33
1.45	-0.28	0.50	0.61	0.31
1.5	-0.23	0.54	0.59	0.30
1.55	-0.19	0.58	0.58	0.28
1.6	-0.15	0.63	0.56	0.27
1.65	-0.11	0.67	0.55	0.25
1.7	-0.07	0.71	0.53	0.24
1.75	-0.04	0.75	0.52	0.23
1.8	-0.002	0.79	0.50	0.22
1.85	0.03	0.83	0.49	0.21
1.9	0.07	0.86	0.47	0.19
1.95	0.10	0.90	0.46	0.18
2	0.13	0.93	0.45	0.18

Gamma : odds of differential assignment due to unobserved factors
Q_{MH}+ : Mantel-Haenszel statistic (assumption: overestimation of treatment effect)
Q_{MH}- : Mantel-Haenszel statistic (assumption: underestimation of treatment effect)
p-value + : significance level (assumption: overestimation of treatment effect)
p-value - : significance level (assumption: underestimation of treatment effect)

Table 28: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for Outpatient Visits, Nearest-Neighbor Matching

Gamma	**sig+**	**sig-**	**t-hat+**	**t-hat-**	**CI+**	**CI-**
1	0.27	0.27	-1.30×10^{-6}	-1.30×10^{-6}	-1.00	0.50
1.05	0.08	0.57	-0.50	4.40×10^{-7}	-1.50	1.00
1.1	0.02	0.83	-1.00	0.50	-1.50	1.00
1.15	0.002	0.95	-1.00	0.50	-2.00	1.50
1.2	<0.001	0.99	-1.50	1.00	-2.00	1.50
1.25	<0.001	1.00	-1.50	1.00	-2.50	2.00
1.3	<0.001	1.00	-2.00	1.50	-2.50	2.00
1.35	<0.001	1.00	-2.00	1.50	-3.00	2.50
1.4	<0.001	1.00	-2.50	2.00	-3.00	2.50
1.45	<0.001	1.00	-2.50	2.00	-3.50	3.00
1.5	<0.001	1.00	-3.00	2.50	-3.50	3.00
1.55	<0.001	1.00	-3.00	2.50	-4.00	3.50
1.6	<0.001	1.00	-3.00	3.00	-4.00	3.50
1.65	<0.001	1.00	-3.50	3.00	-4.00	4.00
1.7	<0.001	1.00	-3.50	3.00	-4.50	4.00
1.75	<0.001	1.00	-4.00	3.50	-4.50	4.00
1.8	<0.001	1.00	-4.00	3.50	-5.00	4.50
1.85	<0.001	1.00	-4.00	3.50	-5.00	4.50
1.9	<0.001	1.00	-4.50	4.00	-5.00	4.50
1.95	<0.001	1.00	-4.50	4.00	-5.50	5.00
2	<0.001	1.00	-4.50	4.00	-5.50	5.00

gamma - log odds of differential assignment due to unobserved factors
sig+ - upper bound significance level
sig- - lower bound significance level
t-hat+ - upper bound Hodges-Lehmann point estimate
t-hat- - lower bound Hodges-Lehmann point estimate
CI+ - upper bound confidence interval (alpha = 0.95)
CI- - lower bound confidence interval (alpha = 0.95)

Table 29: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for ED Visits, Nearest-Neighbor Matching

Gamma	sig+	sig-	t-hat+	t-hat-	CI+	CI-
1	0.05	0.05	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.05	0.11	0.02	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.1	0.22	<0.01	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.15	0.36	0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.2	0.51	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.25	0.66	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.3	0.78	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.35	0.87	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.4	0.93	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.45	0.96	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.5	0.98	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.55	0.99	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.6	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.65	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.7	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.75	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.8	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.85	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
1.9	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}

Table 29 (cont.)

Gamma	**sig+**	**sig-**	**t-hat+**	**t-hat-**	**CI+**	**CI-**
1.95	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}
2	1.00	<0.001	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}	-2.60×10^{-7}

* gamma - log odds of differential assignment due to unobserved factors
sig+ - upper bound significance level
sig- - lower bound significance level
t-hat+ - upper bound Hodges-Lehmann point estimate
t-hat- - lower bound Hodges-Lehmann point estimate
CI+ - upper bound confidence interval (alpha = 0.95)
CI- - lower bound confidence interval (alpha = 0.95)

Table 30: Sensitivity Analysis Determining Affect of Potential Hidden Bias from Unobservable Characteristics on Treatment Effect for Hospitalizations, Nearest-Neighbor Matching

Gamma	Sig+	sig-	t-hat+	t-hat-	CI+	CI-
1	0.40	0.40	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.05	0.26	0.56	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.1	0.15	0.70	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.15	0.08	0.81	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.2	0.04	0.89	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.25	0.02	0.94	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.3	0.01	0.97	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.35	<0.01	0.99	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.4	0.001	0.99	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.45	0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.5	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.55	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.6	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.65	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.7	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.75	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.8	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.85	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
1.9	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}

Table 30 (cont.)

Gamma	Sig+	sig-	t-hat+	t-hat-	CI+	CI-
1.95	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}
2	<0.001	1.00	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}	-4.30 x 10^{-7}

gamma - log odds of differential assignment due to unobserved factors
sig+ - upper bound significance level
sig- - lower bound significance level
t-hat+ - upper bound Hodges-Lehmann point estimate
t-hat- - lower bound Hodges-Lehmann point estimate
CI+ - upper bound confidence interval (alpha = 0.95)
CII- - lower bound confidence interval (alpha = 0.95)

Table 31: Post hoc Multivariate Regression, ACEI or ARB versus Neither, for Variables Predicting ESRD, IVDE, Outpatient Visits, ED Visits, and Hospitalizations

	ACEI			ARB		
	OR[a]	RSE[b]	95% CI[c]	OR	RSE	95% CI
ESRD	0.51	0.19	0.25-1.04	0.36	0.37	0.05-2.64
IVDE	1.63	0.13	1.38-1.91	1.53	0.26	1.09-2.13
	IRR[d]	RSE	95% CI	IRR	RSE	95% CI
Outpatient visits	1.18	0.01	1.16-1.20	1.24	0.03	1.18-1.29
ED visits	1.19	0.05	1.09-1.30	1.22	0.12	1.01-1.47
Hospitalizations	1.32	0.07	1.20-1.46	1.41	0.15	1.14-1.74

[a]OR stands for odds ratio, [b]RSE stands for robust standard error, [c]95%CI stands for 95% confidence interval, [d]IRR stands for incidence rate ratio

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