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Gastrointestinal Bleeding Events and Statin Use: A Large Propensity Score-Matched Retrospective Cohort Study

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GASTROINTESTINAL BLEEDING EVENTS AND STATIN USE: A LARGE PROPENSITY SCORE-MATCHED RETROSPECTIVE COHORT STUDY

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Pharmacy
at the University of Kentucky

By

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2017

ABSTRACT OF THESIS

GASTROINTESTINAL BLEEDING EVENTS AND STATIN USE: A LARGE PROPENSITY SCORE-MATCHED RETROSPECTIVE COHORT STUDY

Literature is conflicting regarding the association between statin use and gastrointestinal (GI) bleeding. This study sought to determine whether there is an association between statin use and GI bleeding by comparing incidence of gastrointestinal events between statin users and an active comparator group.

Data was obtained from a large administrative claims database composed of subjects enrolled in a selection of insurance plans throughout the United States from 2009-2014. New statin users (exposed) and thyroid medication users (active comparator, unexposed) were followed from the baseline period (one year prior to medication initiation) until first event, discontinuation, or disenrollment. Subjects were matched using a propensity score based on demographics, comorbidities, healthcare utilization, and medication use. Odds of gastrointestinal events, including GIH, gastroduodenal (GD) ulcer, and gastritis/duodenitis were compared between groups.

The final analysis included 1,442,954 statin users matched using a 1:1 algorithm with replacement to thyroid medication users. Frequency of GIH in the unexposed group was 0.56±0.01% and frequency in the low, moderate, and high-intensity statin users group was 0.81±0.03%, 0.91±0.02%, and 0.90±0.05% respectively ($p<0.002$). Statin users had 1.81 times the rate of GIH compared to the active comparator group (HR 1.81; 95% confidence interval (CI) 1.76-1.86). Hazard ratios for GD ulcer and gastritis/duodenitis events were 1.13 (CI 0.618-2.05) and 1.19 (CI 0.796-1.80) respectively.

Practitioners should consider these trends when prescribing statins in patients at high-risk of bleeding. Additional research is needed to verify the association between statins and GIH.

KEYWORDS: gastrointestinal hemorrhage, statins, HMG-coA reductase inhibitors, propensity score matching, time-to-event analysis

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20 April 2017

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SECTION ONE: INTRODUCTION

Statin Use

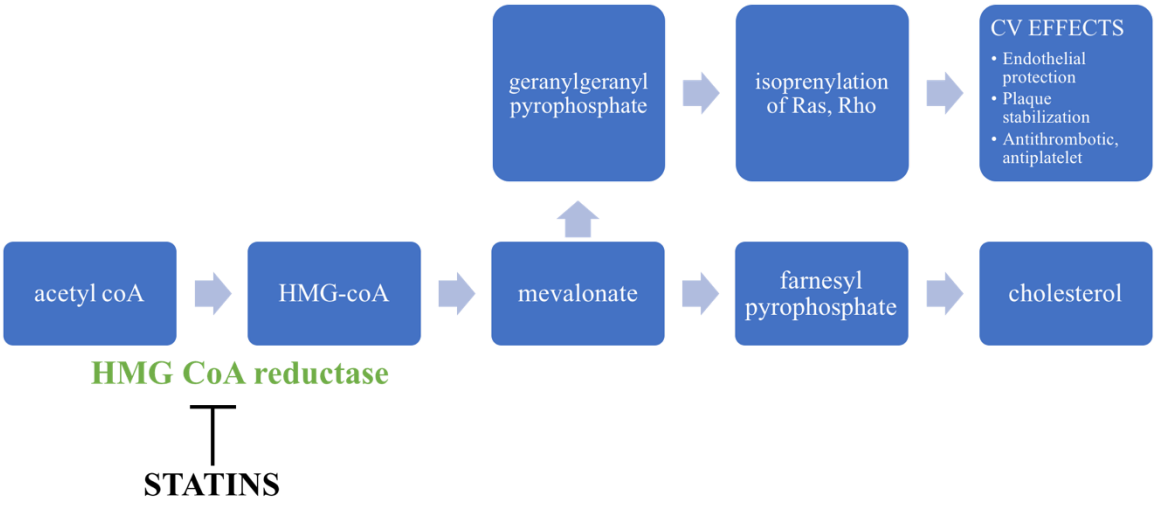
3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely utilized, with 28% of Americans having used a statin in the last 30 days. Among Americans with cardiovascular disease utilization is even higher, approximating 70% (based on data from 2012).[1] Both atorvastatin and simvastatin were in the top ten medicines by prescription, equating to nearly 154 million prescriptions per month in 2014.[2]

As with most commonly utilized medications, statins are generally considered safe and effective, with the most common adverse effects including mild diarrhea, limb and musculoskeletal pain, and elevated serum transaminases (2-20% incidence). Serious adverse effects such as rhabdomyolysis and liver damage have been reported to occur at <2% frequency.[3] In addition to these rare adverse effects, bleeding events such as epistaxis and hematuria have also been reported in post-marketing surveillance.

Statins are primarily used to treat hypercholesterolemia, due to their inhibition of HMG-coA reductase causing decreased cholesterol synthesis in the liver. Outside of lipid-lowering effects, statins also result in endothelial protection, plaque stabilization, and antithrombotic and antiplatelet effects in the cardiovascular system through reduced mevalonate production, which results in decreased activation of small GTP-ases Ras and Rho (see Figure 1.1). Due to these cardiovascular protective effects, statins are also indicated for both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Patients with ASCVD are often on other antiplatelet or anticoagulant medications due to common comorbidities such as myocardial infarction, stroke, and thromboses.

If statins exert a cardiovascular protective effect through the cholesterol synthesis pathway, then it is unlikely they would have additional bleeding adverse effects. However, there is evidence that suggests statins have anticoagulant and antiplatelet activity independent of their lipid-lowering effects. This may result in an increased risk of bleeding events, which is especially concerning given that a relatively high proportion of statin users are also on anticoagulants.

Figure 1.1-Statin Mechanism of Action



Proposed Mechanistic Explanations

Research into the effect of statins on both the coagulation and the platelet cascades suggests that statins may potentially have effects on blood clotting, and thus on bleeding events, outside of the cholesterol lowering pathway. Evidence suggests statins decrease tissue factor (TF) expression, modify various coagulation factors, and decrease the number and activation of platelets.

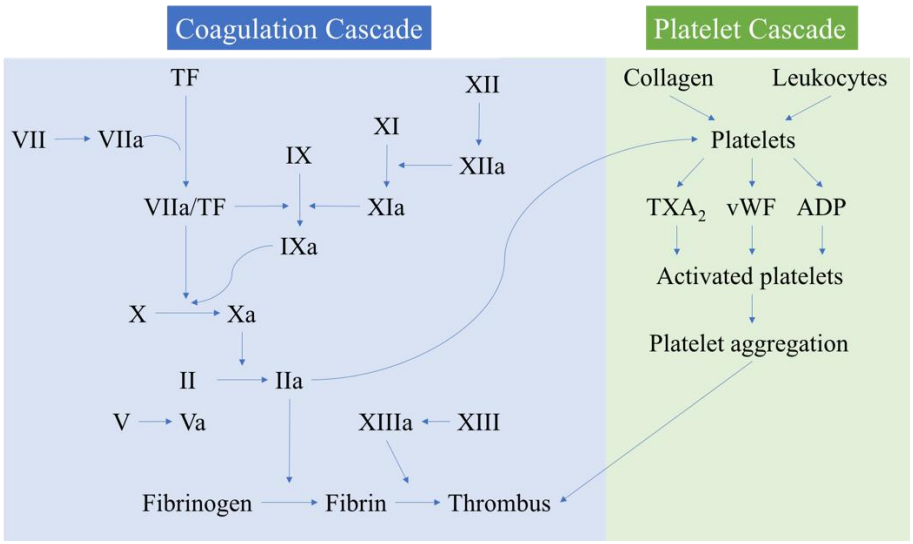
Tissue factor is a transmembrane receptor expressed on many cells that surround blood vessels.[4] Its binding with Factor VIIa is necessary to initiate the extrinsic pathway of the coagulation cascade (see Figure 1.2). Colli and colleagues found that lipophilic statins (fluvastatin and simvastatin) dose-dependently decreased TF expression by preventing an inducer from binding to the TF promoter. This effect was reversed by adding mevalonate, which suggests that the TF expression inhibition may be related to statins' effect on the cholesterol synthesis pathway.[5] Similar results were found in another study, wherein investigators demonstrated that cerivastatin also reduced TF expression.[6] Ferro et al. was able to verify that this statin-induced reduced TF expression does in fact decrease the rate of thrombin generation, and thus the rate of clot formation.[7] The inability to adequately form clots may result in a higher likelihood of bleeding.

In addition to their effect on tissue factor expression, there is also evidence to suggest statins affect other components of the coagulation cascade. Simvastatin has been shown

to decrease the rate of prothrombin (factor II) activation, factor Va generation, factor XIII activation, and fibrin formation from fibrinogen, as well as increase the rate of factor Va inactivation.[8] These changes result in the depression of thrombus formation, but there is also evidence that statins can increase the rate of thrombus degradation. Dangas et al. investigated the effect of statins on the thrombolytic pathway and found that pravastatin decreased the amount of plasminogen activator inhibitor-1 and the rate of thrombus formation regardless of changes in cholesterol level.[9]

The platelet cascade has also been implicated as a mechanism for statin-induced anti-thrombotic activity. Lovastatin has been shown to dose-dependently reduce platelet aggregation (mediated through both collagen and thrombin) and to dose-dependently induce platelet apoptosis.[10] Another study demonstrated that rosuvastatin impacted the platelet cascade in a dose-dependent manner by inhibiting platelet recruitment.[11] Further evidence of statins' effect on platelets involves a von Willebrand factor (vWF) cleaving protease, ADAMTS13, which is implicated as the main cause of thrombotic thrombocytopenia (TTP). Shen et al. found that simvastatin upregulated ADAMTS13 expression, leading to increased cleavage of vWF, and thus decreased platelet activation.[12]

Figure 1.2-Coagulation and Platelet Cascades



Existing Clinical Correlations

While there are numerous hypotheses for a possible mechanism for statin-induced bleeding events, studies investigating the clinical correlation of statin use and bleeding have not yielded consistent results. These studies have largely investigated either GI bleeds or intracerebral hemorrhages (ICH), as case studies have suggested possible risks in these areas. To date, some studies have found a decreased risk of bleeding associated with statin use, others suggest an increased risk of bleeding, while other researchers were unable to find any association at all (see Table 1.1).

Decreased Risk

Of the studies that found statin use was associated with a lower risk of bleeding, one nested case-control study of warfarin patients with atrial fibrillation found that statin use of one year or more was associated with a lower risk of GI bleeding. However, investigators did not find a similar association with recent statin use or statin use of any duration.[13] In a subgroup analysis of the OPUS-TIMI 16 trial, investigators found that statin users had lower rates of in-hospital GI bleeding than non-users.[14] Another study in rats found that simvastatin decreased both gastric acidity and the size of indomethacin-induced ulcers.[15] A retrospective analysis investigating the predictors of ICH found that statins were actually associated with a decreased ICH volume.[16]

Increased Risk

In contrast, there have also been studies that have reported an increased risk of bleeding associated with statin use. There have been reported cases of gastric ulceration,[17] thrombocytopenia (TCP),[10,18–22] thrombotic thrombocytopenic purpura (TTP),[23–25] and hemorrhagic cystitis[26] associated with recent initiation and continued use of statins, which have resolved after discontinuation. Varying levels of TCP (mild, moderate, and severe) possibly associated with statin use have been reported in the literature. When it happens, severe events are more commonly reported. Of the twelve case reports associating statins with bleeding, two reported TTP within 24 hours of beginning a new simvastatin therapy, which improved rapidly after drug discontinuation.[24,25] Five reports (two of TCP purpura, two of TCP, and one of

hemorrhagic cystitis) claimed that the adverse reaction took place within one week of statin initiation and again resolved quickly after discontinuation.[18–20,23,26] In one case, severe TCP occurred after switching from one atorvastatin manufacturer to a new generic manufacturer and hadn't occurred with previous simvastatin therapy. Again, this suggests that different statins may have different bleeding risks. Three reports posit a causal relationship between statin use, TCP, and gastric ulceration that occurred after a few months on statin therapy, but that resolved quickly upon switching to simvastatin (from atorvastatin) or discontinuing satin therapy.[17,21,27] Finally, one report claimed that a woman experienced TCP purpura after 3 years on a steady dose of simvastatin without any known drug interactions, which improved after 2 weeks of stopping the drug.[22] While the report makes a convincing argument that there are no other possible causes, the fact that the patient had been on therapy for so long makes it seem less likely that this report demonstrates a causal relationship. There are also incidental findings from randomized controlled trials that suggest statin users have higher rates of thrombocytopenia and hemorrhage than non-users.[28,29] Furthermore, two studies in rats showed larger indomethacin-induced gastric ulcers in simvastatin, atorvastatin, and rosuvastatin treated rats, which is contrary to the previously discussed study in rats.[30,31] Outside of GI bleeding and ulceration, there have been numerous studies suggesting an increased risk of ICH in statin users. These include a secondary analysis of the large SPARCL trial, a meta-analysis of seven randomized controlled trials, and two retrospective studies.[32–35] This finding that not all statins equally affect bleeding risk is not unique to this study. Some studies have suggested that in addition to a dose-dependent effect, there may also be a difference amongst statins based on lipophilicity (suggesting that the mechanism is gene-mediated), while others hypothesized a chemical structure relationship (finding more synthetic statins have a higher risk). There is also a study implicating certain ApoE genotypes as an important factor in the increased risk of ICH associated with statin use.[36]

No Association

While there have been studies that have found an increased risk of bleeding and studies that found a decreased risk of bleeding with statin use, other have investigated

the correlation and found no association. For example, one case-control study found no association between statin use (current, recent, or past) and upper GI bleeds, while another investigated patients treated with a thrombolytic and a statin and also found no correlation in the risk for subsequent bleeds.[37,38] A meta-analysis of 31 randomized controlled trials of statin therapy that reported ICH found that active statin therapy was not associated with a significant increase in ICH.[39] Interestingly, a recent retrospective study that initially found a protective effect of statins on major bleeds in those treated with anticoagulants later found that this protective effect disappeared when users were stratified by age and duration of statin use.[40] A second retrospective analysis, which was performed with propensity score matching, also found no association.[41]

Overall, investigations into the clinical correlation between statin use and gastrointestinal bleeding have given mixed results, and studies are mostly small and/or post-hoc.

Table 1.1-Summary of Clinical Correlations

Study Type	Population	Size (n)	Outcome	Author
Decreased Bleeding Risk				
Subgroup analysis	Acute coronary syndrome	10 288	Inpatient GI bleeds	Atar
Case-control	A. fib., on warfarin	79 207	Upper GI or ICH	Douketis
Chart review	ICH cases	139	ICH	Falcone
In vitro	Rats	18	Gastric ulcer size	Tariq
Increased Bleeding Risk				
Subgroup analysis	History of stroke or TIA	4 731	Hemorrhagic stroke	Huisa
RCT	Hypercholesterolemic patients	2 195	TCP	Miserez
RCT	Acute myocardial infarction	2 082	TCP, hemorrhage	Nikolsky
In vitro	Rats	48	Gastric ulcer size	Özbakis
Meta-analysis	High-dose statin users	31 099	ICH	Pandit
Chart review	IV thrombolytic users	1 446	ICH	Scheitz
Case-control	Warfarin users	353 489	GI bleeding	Schelleman
In vitro	Rats	150	Gastric ulcer size	Timoshin
Case-control	Hypercholesterolemic patients	558	ICH	Woo
No Bleeding Association				
Cohort	Statin users	6 342	GI hemorrhage	Badillo
Chart review	Alteplase-treated patients	119	ICH	Geng
Case-control	Serious upper GI bleed	3 652	GI bleed	Gulmez
Meta-analysis	Statin users	31 099	ICH	McKinney
Cohort	A. fib., on anticoagulants	8 188	Minor/major bleed	van Rein

A. fib = atrial fibrillation; GI = gastrointestinal; ICH = intracerebral hemorrhage; RCT = randomized controlled trial; TIA = transient ischemic stroke

Clinical Relevance

Upper GIHs are most often caused by an acidic peptic disease (such as gastric and duodenal ulcers, as well as gastritis), followed by variceal bleeding and erosive diseases. Diverticulosis and angiodysplasia are the most common causes of lower GIH.[42] However, if it is the case that statins are in some way associated with an increased risk of GI bleeding events, this could have a significant impact on the healthcare system. Studies estimate that the incidence of upper GIH is anywhere from 40 to 150 per 100 000 cases annually,[43] while lower GIH occurs around 20 to 30 per 100 000 cases annually.[44] Furthermore, a 2010 study found that patients who experienced upper GIH had higher healthcare utilization and costs in the subsequent 12 months compared to those who did not.[45] This finding remained significant even after excluding initial hospitalization costs, which were on average $11,228 for the upper GIH cohort compared to $3,652 for the general population cohort.

Furthermore, there is a significant proportion of statin users who are already at a higher risk of bleeding due to patients being concurrently treated with antiplatelets and anticoagulants. Finding that statins are associated with an increased risk of GI bleeding could lead clinicians to weigh the risk to benefit ratio of prescribing this class of medication in select groups of patients. The purpose of this study was to investigate whether statin use is associated with GI bleeding events by comparing GI bleeding event incidence between statin users (exposed) and an active comparator (unexposed) group.

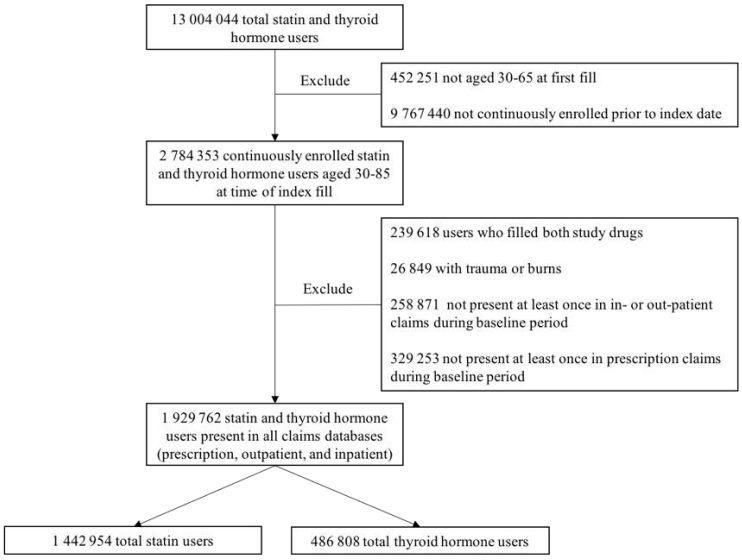
SECTION TWO: METHODS

Study Population

This study was a retrospective cohort analysis of subjects enrolled in health plans between 2009-2014 gathered from the Truven Health MarketScan® Research Database.[46] The database includes de-identified medical and prescription claims from nearly 350 private payers. Because this data is de-identified and anonymous, it does not meet the federal definition of "human subjects research" and thus is IRB exempt.[47]

Subjects aged 30-65 years at the time of first statin or thyroid hormone medication fill (index date) as documented by private insurers in the database were analyzed. To ensure the analysis included only new users and to avoid data contamination by users of both study medications, 12 months of continuous enrollment (allowing a 30-day gap in coverage) without a documented fill for either study medication was required (baseline period). Follow-up began on the index date and continued until first GI bleeding event (GIH, ulcer, gastritis, or duodenitis). Censoring occurred at treatment discontinuation (90 days after completion of the last study medication), disenrollment, or the end of the data, whichever came first. A flow diagram depicting subject selection is visualized in Figure 2.1-Subject Selection Process Data were retrieved using SAS Enterprise Guide software, Version 7.1 of the SAS System for Windows.[48]

Figure 2.1-Subject Selection Process



Exposure and Outcomes

This study employed an active comparator design. As such, two treatment groups were identified using GPI codes: statin users (exposed) and thyroid medication users (unexposed) (see Appendix C). Exposed individuals were defined as those with a prescription claim for a statin. Subjects were followed until first GI bleeding event (whether GIH, ulcer, gastritis, or duodenitis) and were censored at treatment discontinuation (defined as 90 days after the last supply of medication was exhausted) or disenrollment from the database.

The primary outcome in this study was GIH, although secondary outcomes of gastroduodenal ulcer and gastritis or duodenitis were also documented. GI bleeding events were identified from the first three diagnosis codes of both in- and outpatient visits documented in the database. These conditions were defined using AHRQ-CCS categories 153, 139, 140, 70, and 76 respectively. GIH was defined as bleeding in any segment of the GI tract from the esophagus to the rectum. GIH diagnosis codes included bleeds of any cause.

Outcome events were defined as an event that occurred between the index fill and 90 days after the last supply of medication was exhausted.

Confounders

Subject characteristics during the one year prior to treatment initiation (the baseline period) for the included subjects were identified from MarketScan. These variables were selected based on literature in the field, factors that might influence the propensity to be initiated on statin therapy, as well as factors that might influence the propensity to experience a GI bleeding event. In addition to age and sex, several possible confounders were included in the analysis.

Disease burden was determined using both the Charlson Comorbidity Index score and its individual components (AIDS, ulcer, congestive heart failure, cardiovascular disease, dementia, diabetes with and without complications, liver failure with and without complications, any malignancy, myocardial infarction, paralysis, renal failure, and rheumatologic diseases).[49] Health system utilization was measured using a categorization of in- and outpatient visits. Inpatient visits were categorized as 0, 1, or ≥ 2, while

outpatient visits were categorized as 0-1, 2-4, 5-6, or > 6. Prescription medication use during baseline was also measured by having one or more claims for the following medications, which were also used in a similar study[41]: angiotensin converting enzyme inhibitors, antiplatelets, antipsychotics, antithrombotics, aspirin, angiotensin receptor blockers, beta-blockers, bisphosphonates, calcium channel blockers, corticosteroids, diuretics, diuretics, oral hypoglycemics, proton pump inhibitors, sedatives, selective serotonin reuptake inhibitors, testosterone, and warfarin. Definitions for each comorbidity and prescription can be found in Appendix B and Appendix C.

Propensity Score Matching

In this study, a theory-driven approach was used to select which measured baseline covariates to include in the final propensity score model.[50–54] Of 38 measured baseline characteristics, 5 were associated only with exposure and thus were not included, and 12 were not found to be associated with either exposure or outcome and were also excluded (see Table 2.1). Liver disease and diabetes severities were combined into one measure each, as were malignancies and metastases.

Thus, the final propensity score was estimated using a logistic regression that included 18 baseline covariates: sex, age category, inpatient visits, outpatient visits, CCI score category, AIDS, any ulcer, congestive heart failure, cerebrovascular disease, diabetes, liver disease, cancer, renal failure, and use of bisphosphonates, blood thinners, corticosteroids, NSAIDs, or PPIs.

Balance in the matched cohort was assessed using standardized differences (or standardized mean difference, SMD). SMD is used to statistically test whether there is a difference between the two groups. This study defined imbalance between two groups as the absolute value of the standardized difference > 0.1, as is common in the literature.[55]

Table 2.1-Baseline Covariate Association with Exposure and Outcome

Associated only with exposure	Associated only with outcome	Associated both with exposure and outcome	Associated with neither exposure nor outcome
Myocardial infarction	Any ulcers	Age[56]	Dementia[56,57]
PVD[58]	Liver disease[59]	Sex[60]	Paralysis
Use of hypoglycemic	Malignancy[61]	Inpatient visits	Pulmonary disease
Use of non-statin LLA	Metastases	Outpatient visits	Rheumatic disease[58]
Use of antipsychotics[62]	Use of blood thinners	CCI score	Use of ACEi or ARBs[63]
	Use of corticosteroids	AIDS	Use of beta-blockers
	Use of NSAIDs[43,56,58]	CHF[64,65]	Use of CCBs
	Use of PPIs	Cerebrovascular disease[66,67]	Use of diuretics
		Diabetes[56]	Use of sedatives
		Renal failure[68–71]	Use of SSRIs
		Use of bisphosphonates[72]	Use of TCAs
			Use of testosterone

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CHF = congestive heart failure; LLA = lipid lowering agents; NSAID = non-steroidal anti-inflammatory drug; PPI = proton pump inhibitor; PVD = peripheral vascular disease

In this study, matching was completed with the user-created Stata command -psmatch2-[73] using 1:1 nearest-neighbor matching with replacement with a caliper of 0.25 the standard deviation of the propensity score. Replacement was used as is recommended in the literature when the unexposed group is significantly smaller than the exposed group.[74]

Event Analysis

Subjects were followed until first GI bleeding event and were censored at treatment discontinuation (defined as 90 days after the last supply of medication was exhausted) or disenrollment. The incidence rate per person-time at risk of GIH, ulcer, and gastritis/duodenitis was calculated using Poisson regression and was compared between exposed and unexposed groups, as well as within the exposed group at different doses. The number needed to harm was calculated both using incidence rate and cumulative incidence, and a comparison of both values was included in the analysis.

In addition, a Cox proportional hazard model was used to regress exposure status on outcome occurrence and determine hazard ratios for risk over time. Frequency weights and a robust variance estimator were used to account for the unexposed subjects used in multiple matched pairs, which violate the independent observation assumption in Cox regressions.

SECTION THREE: RESULTS

Propensity Score Model

The output of the logistic regression for propensity score estimation is found in Table 3.1. As can be seen in Figure 3.1, the propensity scores tend to be higher in the exposed group than the active comparator group. Figure 3.2 demonstrates that the distribution of propensity scores between the exposed and active comparator groups is identical after matching.

Table 3.1-Propensity Score Model

			No. obs = 1 929 762 *c-statistic = 0.7302*
	Odds Ratio	**95 % Confidence Interval**	
Sex, female	0.261	0.258	0.263
Age 30-39 yr			
40-49 yr	2.18	2.16	2.21
50-59 yr	3.30	3.27	3.34
≥ 60 yr	3.36	3.32	3.40
No Inpatient Visits			
1	1.12	1.11	1.13
> 1	1.17	1.15	1.18
0-1 Outpatient Visits			
2-4 Visits	0.849	0.841	0.856
5-6 Visits	0.711	0.700	0.721
> 6 Visits	0.611	0.602	0.619
CCI Score 0			
1	1.30	1.29	1.32
2	1.23	1.20	1.25
3	1.17	1.14	1.21
4	0.995	0.951	1.04
5	0.809	0.762	0.859
≥ 6	0.506	0.484	0.530
AIDS	3.30	2.98	3.64
Ulcers	0.814	0.773	0.858
Congestive heart failure	1.15	1.11	1.19
Cerebrovascular disease	2.10	2.05	2.15
Diabetes	1.90	1.88	1.93
Liver disease	0.452	0.427	0.478
Cancer	0.522	0.510	0.534
Renal disease	1.11	1.07	1.15
Bisphosphonates	1.23	1.20	1.26
Blood thinners	0.925	0.906	0.944
Corticosteroids	0.931	0.922	0.939
NSAIDs	1.15	1.14	1.16
PPIs	1.13	1.12	1.15
constant	2.42	2.39	2.45

AIDS = autoimmune deficiency syndrome; CCI = Charlson Comorbidity Index; NSAIDs = non-steroidal anti-inflammatory drugs; PPIs = proton pump inhibitors

Figure 3.1-Unmatched Cohort Propensity Score Distribution

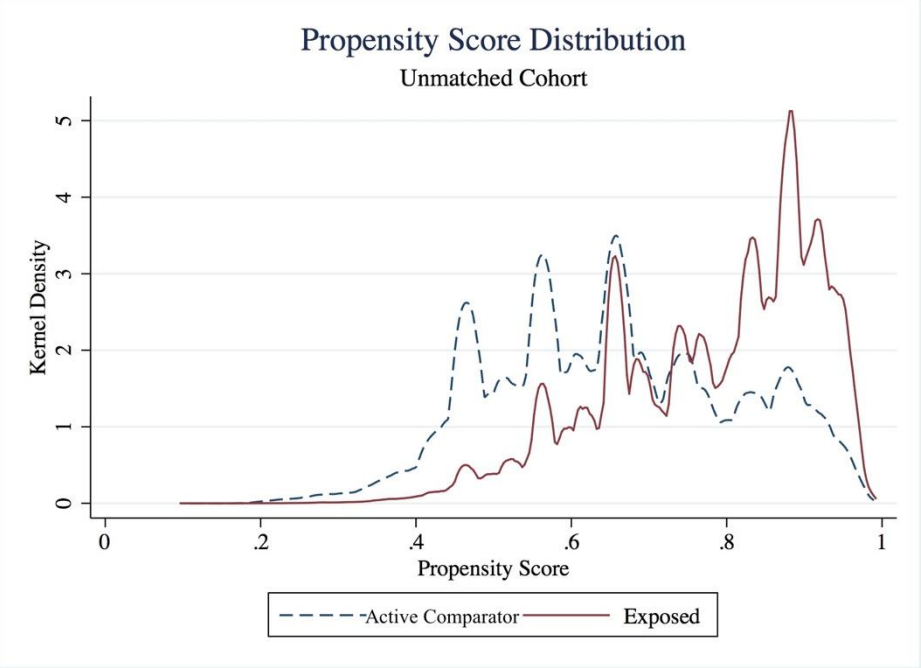
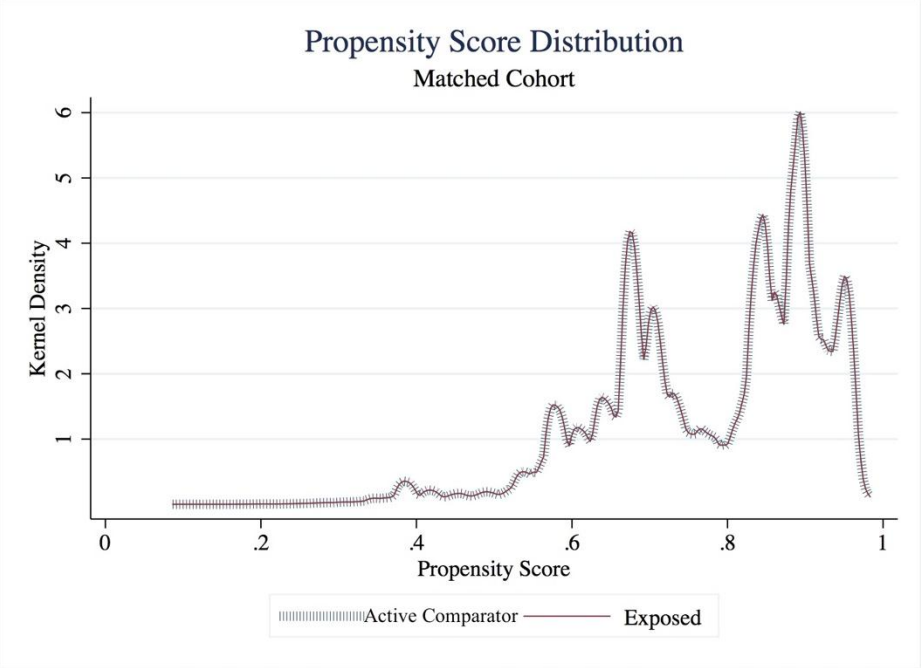


Figure 3.2-Matched Cohort Propensity Score Distribution



In this study, 21,552 active comparator subjects were matched to 1,442,954 exposed subjects because matching was done with replacement (see Table 3.2). As can be seen in Table 3.3, the matched cohort designed without replacement had significantly more bias than the one completed with replacement.

Table 3.2-Matching in Active Comparator Subjects

No. of Unexposed Subjects	Times Used to Match an Exposed Subject	Cumulative Percent of Active Comparator Subjects
10 702	1-6	49.66
6 633	7-25	80.43
2 057	26-60	89.98
1 078	61-140	94.98
865	141-860	98.99
217	> 860	100.00

Table 3.3-Matching Algorithm Comparison

	Active Comparator Cases Used	Exposed Cases Used	Mean Bias*	Median Bias
Unmatched	486 808	1 442 954	16.1%	11.0%
Matched without Replacement	486 808	486 808	6.2%	4.1%
Matched with Replacement	21 553	1 442 954	0.4%	0.3%

* Bias is defined as the standardized residual (difference in means divided by pooled standard deviation)

Baseline Characteristics

After all inclusion and exclusion criteria were applied, the full unmatched cohort consisted of 486,808 individuals in the active comparator group and 1,442,954 exposed individuals. Baseline characteristics for the unmatched cohort can be found in Table 3.4.

. These groups differ on most confounders included in the propensity score model. Active comparator individuals (thyroid hormone users) were more likely to be female and younger, have fewer inpatient but more outpatient visits, and have lower CCI scores. Significantly more statin users had diabetes and cerebrovascular disease (24.9% vs. 12.2% and 5.0% vs. 2.0, respectively), whereas significantly more thyroid hormone users had liver disease and cancer (0.48% vs. 0.27% and 8.2% vs. 4.1%, respectively). In the full unmatched cohort, 0.89% of statin users experienced a GIH, compared to 0.80% in the active comparator (standardized difference -0.01).

After matching on the propensity score, the exposed and active comparator groups were much more similar (see Table 3.5). Of note, statin users used the medication for an average of 279±325 days while active comparators used thyroid hormone for an average of 326±333 days. Statin users were followed for an average of 252±284 days, and active comparators were followed for an average of 331±301 days.

When comparing those who experienced the primary outcome to those who did not, significantly more subjects with the outcome took moderate intensity statins (see Appendix C for a definition of statin intensities), had more than six outpatient visits, and used blood thinners, corticosteroids, and PPIs. However, significantly fewer subjects who experienced the primary outcome had no inpatient visits, had none or one outpatient visit, and had a CCI score of 0 than those who did experience the outcome. Exact incidence by outcome group can be found in Appendix E.

Table 3.4-Unmatched Cohort Baseline Characteristics

	Active Comparator n=486 808	Exposed n=1 442 954	Standardized Difference
Female, n (%)	387 087 (79.52)	722 564 (50.08)	-0.648
Age Categories, n (%)			0.342
30-39 y.o.	92 713 (19.05)	108 562 (7.52)	
40-49 y.o.	132 623 (27.24)	345 783 (23.96)	
50-59 y.o.	172 734 (35.48)	642 961 (44.56)	
≥ 60 y.o.	88 738 (18.23)	345 648 (23.95)	
Inpatient Visits, n (%)			0.046
0	331 991 (68.20)	947 453 (65.66)	
1	101 535 (20.86)	328 123 (22.74)	
> 1	53 282 (10.95)	167 378 (11.60)	
Outpatient Visits, n (%)			-0.160
0-1	268 932 (55.24)	896 393 (62.12)	
2-4	130 495 (26.81)	358 511 (24.85)	
5-6	34 248 (7.04)	79 264 (5.49)	
> 6	53 133 (10.91)	108 786 (7.54)	
CCI, n (%)*			0.107
0	338 171 (69.47)	825 573 (57.21)	
1	82 053 (16.86)	402 794 (27.91)	
2	36 455 (7.49)	114 681 (7.95)	
3	14 806 (3.04)	61 719 (4.28)	
4	4 039 (0.83)	16 369 (1.13)	
5	2 181 (0.45)	8 050 (0.56)	
≥ 6	9 103 (1.87)	13 768 (0.95)	
Comorbidities, n (%)			
AIDS	573 (0.12)	3 998 (0.28)	0.036
Ulcer	2 296 (0.47)	6 540 (0.45)	-0.003
Congestive heart failure	5 124 (1.05)	25 114 (1.74)	0.059
Cerebrovascular disease	9 746 (2.00)	71 587 (4.96)	0.162
Diabetes	59 330 (12.19)	359 363 (24.90)	0.332
Liver disease	2 353 (0.48)	3 940 (0.27)	-0.034
Cancer	39 740 (8.16)	63 962 (4.43)	-0.154
Kidney disease	6 474 (1.33)	25 154 (1.74)	0.034
Medication Usage, n (%)**			
Bisphosphonates	10 311 (2.12)	28 316 (1.96)	-0.011
*Blood thinners****	13 775 (2.83)	60 506 (4.19)	0.074
Corticosteroids	93 180 (19.14)	243 557 (16.88)	-0.060
NSAIDs	111 443 (22.89)	345 828 (23.97)	0.025
PPIs	78 359 (16.10)	255 535 (17.71)	0.043

* As defined by Deyo et al. ** At least one prescription claim in baseline period, using GPI codes *** Includes aspirin, antiplatelets, antithrombotics, and warfarin

Table 3.5-Matched Cohort Baseline Characteristics

	Active Comparator n=1 442 954	Exposed n=1 442 954	Standardized Difference
Female, n (%)	722 274 (50.1)	722 562 (50.1)	0.000
Age Categories, n (%)			
30-39 y.o.	106 958 (7.4)	108 560 (7.5)	0.004
40-49 y.o.	342 710 (23.8)	345 783 (23.9)	0.005
50-59 y.o.	643 926 (44.6)	642 956 (44.6)	-0.001
≥ 60 y.o.	349 341 (24.2)	345 636 (24.0)	-0.006
Inpatient Visits, n (%)			
0	951 277 (65.9)	947 452 (65.7)	-0.006
1	327 073 (22.7)	328 118 (22.7)	0.002
> 1	164 585 (11.4)	167 365 (11.6)	0.006
Outpatient Visits, n (%)			
0-1	894 629 (62.0)	896 378 (62.1)	0.002
2-4	358 528 (24.9)	358 509 (24.9)	-0.000
5-6	79 003 (5.5)	79 264 (5.5)	0.001
> 6	110 775 (7.7)	108 784 (7.5)	-0.005
CCI, n (%)*			
0	827 883 (57.4)	825 573 (57.2)	-0.003
1	407 762 (28.3)	402 794 (27.9)	-0.008
2	111 549 (7.7)	114 675 (8.0)	0.008
3	60 339 (4.2)	61 718 (4.3)	0.005
4	14 922 (1.0)	16 369 (1.1)	0.010
5	7 432 (0.5)	8 050 (0.6)	0.006
≥ 6	13 048 (0.9)	13 756 (0.9)	0.005
Comorbidities, n (%)			
AIDS	3 112 (0.2)	3 988 (0.3)	0.012
Ulcer	5 429 (0.4)	6 540 (0.5)	0.012
Congestive heart failure	22 228 (1.5)	25 114 (1.7)	0.016
Cerebrovascular disease	65 980 (4.6)	71 570 (4.9)	0.018
Diabetes	363 274 (25.2)	359 346 (24.9)	-0.006
Liver disease	3 611 (0.3)	3 938 (0.3)	0.004
Cancer	65 291 (4.5)	63 960 (4.4)	0.004
Kidney disease	23 770 (1.7)	25 154 (1.7)	0.007
Medication Usage, n (%)**			
Bisphosphonates	28 164 (2.0)	28 314 (2.0)	0.001
*Blood thinners****	61 032 (4.2)	60 505 (4.2)	-0.002
Corticosteroids	242 186 (16.8)	243 552 (16.9)	0.003
NSAIDs	345 256 (23.9)	345 816 (23.9)	0.001
PPIs	258 341 (17.9)	255 529 (17.7)	-0.005

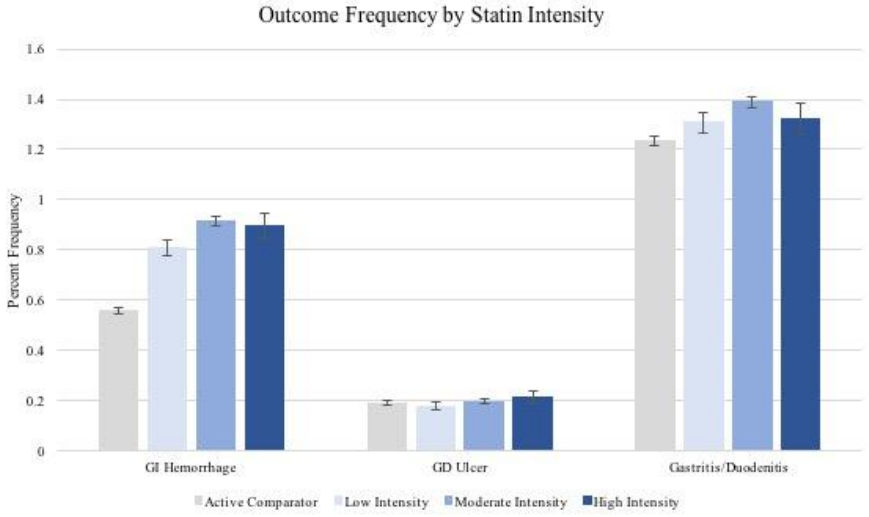
* As defined by Deyo et al. ** At least one prescription claim in baseline period, using GPI codes *** Includes aspirin, antiplatelets, antithrombotics, and warfarin

Event Analysis

Amongst those who experienced the primary outcome (GIH), the average duration of medication therapy for users was 505±448 days compared to 629±414 days for the active comparator group. Statin users who experienced the primary outcome did so after an average of 252±284 days of therapy, in comparison to 331±301 days of therapy for the active comparator group.

The frequency of GIH in low, moderate, and high intensity statin users was 0.81±0.03%, 0.91±0.02%, and 0.90±0.05% respectively (two sample t-test $p<0.002$; see Figure 3.3). For reference, a chart indicating which statin doses are included in each intensity can be found in Appendix C.

Figure 3.3-Outcome Frequency by Statin Intensity



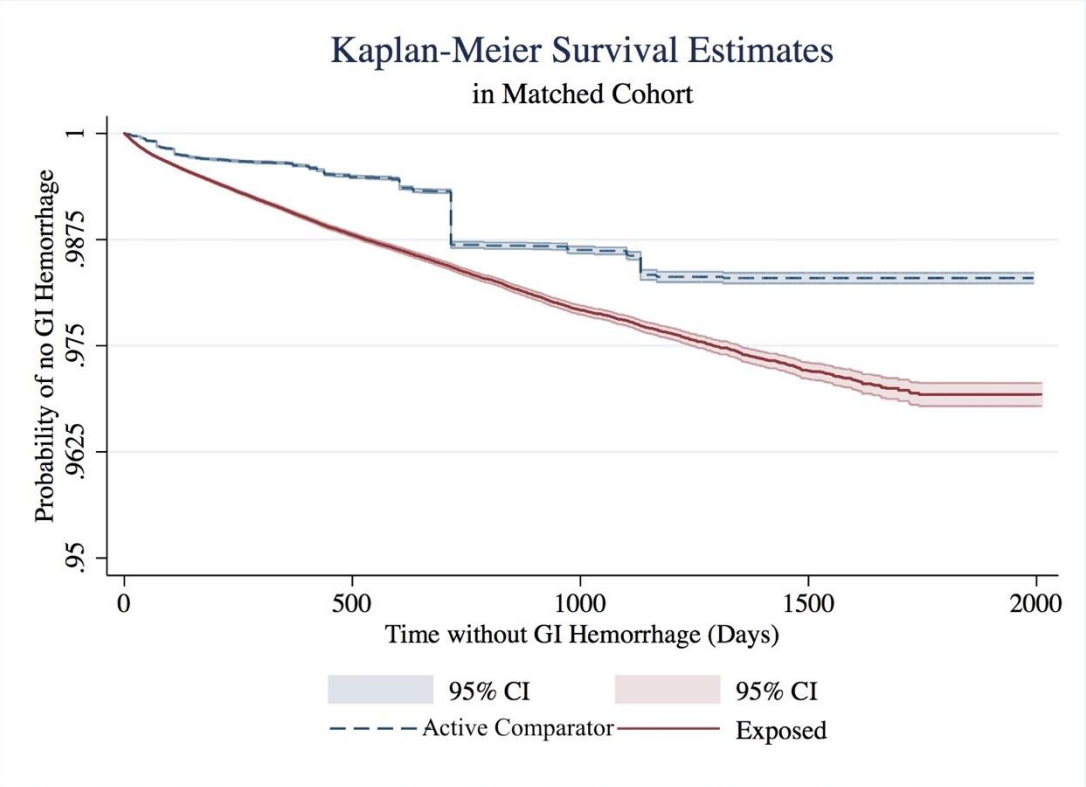
Comparing the rates of GIH between users and the active comparators, statin users had 1.81 times the rate of GIH compared to the active comparator group (HR 1.81; 95% CI 1.76-1.86; Table 3.6). Hazard ratios for secondary outcomes were not statistically significant. Of note, the Cox Proportional Hazards model met all assumptions, but because single subjects were used in multiple matched pairs, a robust variance estimator was used. Using the incidence rate, the number of patients needed to be treated with a statin to cause one GIH (number needed to harm; NNH) was 249. Using the cumulative incidence, NNH for the primary outcome was 298.

Table 3.6-Outcomes by Study Group

Outcome	Active Comparators		Statin Users		Hazard Ratio	95% CI	
	No. of subjects	Rate per 100 person-yr	No. of subjects	Rate per 100 person-yr			
GI Hemorrhage	8 009	0.490	12 866	0.891	1.81	1.05	3.10
GD Ulcer	2 749	0.167	2 802	0.193	1.13	0.618	2.05
Gastritis/Duodenitis	17 832	1.10	19 713	1.37	1.19	0.796	1.80

A time to event analysis is reflected in the Kaplan-Meier survival curve seen in Figure 3.4. Amongst subjects who experienced GIH, 12.25% experienced it within one month of therapy initiation, 54.89% within six months, 69.07% within 12 months, and 97.67% within three years. The maximum time to event amongst those who experienced the outcome was four years and nine months.

Figure 3.4-Matched Cohort Kaplan Meier Survival Estimates



SECTION FOUR: DISCUSSION

To our knowledge, this is the largest study that has investigated the association between statin use and gastrointestinal bleeding events. The rigorous study design, along with the robust analytic methods offer healthcare providers additional evidence to factor into their decisions when prescribing statins to patients at a high risk of bleeding.

Because there have been other retrospective cohort studies that have investigated this same question but have come to different conclusions, it is reasonable to discuss the rationale behind the study design choices that may have influenced these results.

Study Design

Any study using retrospective data analysis must include in its design methods to combat the inherent biases present. One of these biases occurs when comparing exposed to unexposed individuals using users and non-users of the study drug. Non-users are fundamentally different than users, predominantly in their health-seeking behaviors, though also in other areas such as use of chronic and preventive medications. This study utilizes an active comparator design, which is a well-validated method for reducing bias in retrospective cohort studies. Schneeweiss and colleagues have shown that increasing levels of restriction in observational studies brings study designs closer to that of a randomized controlled trial (RCT).[75] Based on a review of the literature, most studies utilizing active comparator designs use either topical anti-glaucoma medications or thyroid hormone substitution.[58]

The choice of following subjects for 90 days after treatment discontinuation was based on the available evidence associating bleeding with statins. A plausible mechanism may include clotting factor XIII inhibition, which has a half-life of 200 hours. Since on average, it takes five half-lives for a substance to disappear, complete inhibition of factor XIII would result in depletion after 41 days. Thus, it would be reasonable to conclude that if a patient has not taken a statin for 41 days that any effect would start to diminish. Increasing this interval to 90 days would allow for complete regeneration of factor XIII back to baseline.

Propensity Score Model

Another method this study used to reduce bias is propensity score matching (PSM). The propensity score balances the distribution of baseline covariates between the exposed and unexposed by estimating "the probability of treatment assignment conditional on observed baseline characteristics."[76] However, the specification of the propensity score model and the choice of algorithm used to match individuals are of utmost importance and can significantly change results. For this reason, it is important that both choices are thoughtfully made based on available literature.

Namely, the decision to match either with or without replacement is crucial to result interpretation. When matching without replacement is performed, an unexposed case is removed from the pool after it is used, which results in later matches having a larger difference in propensity score (leading to greater bias in the model). In matching with replacement, the closest unexposed individual is matched with an exposed individual, allowing the unexposed case to be used multiple times if it is the best match for many exposed cases. In the literature, matching with replacement is not commonly used. A meta-analysis of propensity score-matched medical studies completed in 2007 demonstrated that approximately 30% of studies stated that matching without replacement was used, but the rest did not state whether matching was done with or without replacement.[77] Dehejia and Wahba recommend that when the unexposed and exposed groups are significantly different, or the unexposed group is small relative to the exposed group, that matching with replacement results in better matches.[74] Based on these guidelines, this data is better suited to matching with replacement. Because the same untreated subject can be used in multiple matched pairs, however, it does require that the statistics account for this lack of independence in the pairs that have the same untreated individual.[77] For this reason, robust variance estimators were used to account for clustering within matched pairs. Even so, there is a concern about bias if the active comparator subjects selected to be matched are outliers and do not represent most subjects. In this study, 21,552 active comparator subjects were matched to 1,442,954 exposed subjects (see Table 3.2). This can be alarming, but is reassuring to note that nearly 90% of active comparator subjects were reused ≤ 60 times. Given that the exposed group is composed of roughly 1.5 million subjects, this is not a large proportion. The

maximum number of times one active comparator subject was reused to match an exposed subject was 62,339.

Because matching with replacement is not commonly reported in the literature and there are concerns of bias, the matching algorithm was run again without replacement to ensure the best model was employed. It has been shown that matching without replacement leads to more bias because the algorithm may be forced to use less optimal matched pairs,[74] but both models were run for completeness' sake. As can be seen in Table 3.3, the matched cohort designed without replacement had significantly more bias than the one completed with replacement. A comparison of both models is discussed in Appendix D. Importantly, both models reach the conclusion that there is a significant association between statin use and gastrointestinal hemorrhage.

To determine whether the model accurately represents the data, we can view it both graphically and statistically. Graphically, we can compare the distribution of propensity scores in the exposed and active comparator groups. Because the propensity score is a balancing score, we would want the two groups to be similar.

As can be seen in Figure 3.1, the propensity scores tend to be higher in the exposed group than the active comparator group. This is expected: since these are the subjects who *were* treated with statins, they have a higher probability of being treated. This distribution also demonstrates the importance of performing a match with replacement. As can be seen, there are significantly fewer active comparator subjects in the upper range of the propensity scores. Matching without replacement would mean that once these were used to match exposed subjects, later pairs would be worse matches.

To assess whether the algorithm resulted in "good" matches, it is possible to use a variety of statistical measures. In the past, t-tests and p-values have been used, but simply comparing means between variables isn't very useful, since units may be different. Thus, there has been a shift in the literature toward using the standardized mean difference (SMD), which compares means in a unit-less way independent of sample size. The SMD is also much less dependent on sample size, since it uses the standard deviation in its calculation. A value of zero means that the two exposure groups have equivalent effects. The values increase as the differences between exposed and active comparator groups increase.[78]

While there is no globally accepted method to interpret standardized difference, many studies use an absolute value > 0.1 as the definition of imbalance between two groups.[79] As seen in Table 3.4, the active comparator and exposed groups differ on nearly every measured baseline characteristic in the unmatched cohort. However, the matched cohort (seen in Table 3.5) has a much more even distribution between the exposure groups (no standardized differences > 0.02). These findings suggest that the matching algorithm was successful.

Event Analysis

The unmatched cohort's baseline characteristics were unsurprising, in that the active comparator group was generally healthier and younger than the user group. There was a statistically significant difference between the two groups in sex and age, as well as in diabetes and cancer incidence. However, the active comparator group was more similar to the user group than a non-user group would have been. As an example, in a recent propensity score-matched cohort study investigating the same matter, non-users differed significantly on age, sex, inpatient and outpatient encounters, as well as in their comorbidity scores.[41] This difference demonstrates the power of an active comparator group in removing unnecessary baseline bias between comparison groups.

After cohorts were matched using the propensity score, there were no statistically significant differences between groups on baseline characteristics. However, it should be noted that the user group duration of medication therapy was on average shorter than in the active comparator group. This might be explained by the fact that in general, statin users experience more adverse effects than thyroid hormone medication users which may have caused earlier therapy termination.

Subjects who experienced a GIH were different in some ways than those who did not, which is significant because initially both statin users and active comparators were well matched. Predictably, there were more blood thinner and corticosteroid users in amongst subjects who experienced the outcome, but there were also more PPI users. This is interesting because in general, PPIs are thought to be protective of many types of GI damage. This may be because those who experienced a GIH had first experienced an ulcer and were put on a PPI as a result. In fact, 0.96% of subjects who experienced a GIH

in the follow-up period previously had a gastroduodenal ulcer, compared to only 0.19% of subjects who did not experience a GIH. The fact that these subjects previously had GI damage may mean that they were at a higher risk, and may explain why more were taking PPI therapy.

Another interesting difference is that those who experienced the primary outcome used medication therapy for an average of approximately 8 months longer than those who did not experience the primary outcome, but were also followed for a longer period of time. This trend was consistent amongst statin users and active comparators. While this information may make the association between treatment and outcome less clear, the time to event analysis elucidates more details. The significant hazard ratio and the Kaplan-Meier survival curve demonstrate that at any particular time, 1.81 times as many subjects in the statin user group experience an outcome compared to the active comparator group. Over half of the subjects who did experience a GIH did so within six months of therapy initiation, suggesting that there is also a time-related effect. When calculating the NNH, using the incidence rate (which takes into account person-time) resulted in a lower number than using the cumulative incidence (which does not take into account time). This indicates that there is a temporal relation to the association between statin use and GIH. Although ulcers, gastritis, and duodenitis did not have statistically significant hazard ratios, the trend persisted even amongst these secondary outcomes. This time to event analysis helps to remove some of the bias that is associated with having differing follow-up times for each subject.

Looking at the difference in the primary outcome incidence amongst statin users, there is no statistically significant difference between the moderate- and high-intensity statin users, while low-intensity statin users have significantly fewer instances of the primary outcome than both moderate- and high-intensity users. These results are in line with previous *in vitro* studies that have found dose-dependent associations between statins and bleeding events. This finding may call into question current prescribing guidelines that recommend starting statin doses at the highest tolerable dose and adjusting based on adverse effects, such as the 2013 ACC/AHA Guideline on the both primary and secondary prevention of ASCVD.[80] Conversely, the most recently released United States Preventive Services Task Force (USPSTF) guidelines recommend initiating a low- or

moderate-intensity statin, suggesting that there is not sufficient evidence to determine which statin dosing strategies are the most clinically effective.[81] Given the ample evidence linking higher dose statins to more adverse effects, the addition of the information in this study would support starting at a lower statin intensity and titrating up to effect.

Strengths and Weaknesses

As discussed, previous studies have attempted to demonstrate an association between statin use and gastrointestinal bleeding events, but few have produced clinically meaningful results. In early 2015, a retrospective propensity-score matched cohort study investigated the possible association between upper GIH and statin use, finding neither an increased nor decreased risk of GIH in statin users. Although the sample size was limited, it was larger than any that had previously been studied to that point (6 342 statin users matched 6 342 non-users).[41] For this reason, it is reasonable to view the previously mentioned study as a benchmark on which to improve, which this study has strived to achieve.

Using propensity score matching to adjust for baseline differences in treatment exposure and an active comparator design to reduce health-seeking behavior bias, this study attempts to approximate a randomized controlled trial in design. The design of propensity score model was done rigorously, and in line with current recommendations in the literature. In contrast to other studies that include a wide variety of baseline covariates to estimate propensity scores without justification (such as the 2015 Badillo study)[41], this study includes only true and potential confounders (covariates related only to the outcome and those related both to exposure and outcome).

In addition, the study population represents a diverse group of individuals with claims from nearly 350 payers throughout the United States. Censoring mechanisms were chosen carefully to fulfill an analysis while treated instead of an intention to treat design. Instead of following subjects until first event or disenrollment, as done in previous studies, a censoring point 90 days after treatment discontinuation was chosen carefully based on mechanistic hypotheses. Furthermore, a strong biological plausibility for an association was established in this study through intensive background research.

While every attempt was made to reduce bias and produce robustly accurate results, certain limitations should be discussed. Foremost is the fact that propensity score modeling is very much an art, as much as a science. Particularly, the choice of covariates follow no rigorous guidelines, but rather are based on available literature in the field. Thus, a different estimation of propensity scores may produce drastically different results. While every attempt was made to create a model that considered all aspects that may impact propensity for statin treatment, there is nevertheless room for variation. Particularly, the PSM accounted for baseline use of blood thinners, which we defined as receipt of a prescription for an anticoagulant, antiplatelet, antithrombotic, or aspirin in the 12-months prior to the index date. However, most patients do not use third-party claims to pay for aspirin so its use would likely not appear in our model. Because statin users are more likely use aspirin than thyroid hormone medication users (due to confounding indications), there may be more statin users on blood thinners than accounted for in our model.

Moreover, this study did not consider the effect of subjects re-initiating therapy at a later date or switching therapy within the class. Subjects were considered as having discontinued therapy if a gap of more than 90 days occurred in the prescription claim database. Finally, it should be noted that the oldest subjects in this study were 65 years of age at treatment initiation, with the average age of 52.8 years old. Because more patients are being treated with statins for primary and secondary cardiovascular event prevention at greater ages, this study may not represent a clinically relevant population.

In the future, studies may consider adding more elderly patients into the analysis to make results more comparable to clinical prescribing habits. As an extension of this study, a time-varying analysis may be undertaken to account for an individual subject stopping and re-initiating therapy at a later date. It is clear from this data that many subjects had gastrointestinal bleeding events after censoring due to treatment discontinuation, and still more at multiple episodes of treatments with gaps interwoven. Using a more sophisticated analysis may be able to take into account these higher level usage patterns and more closely approximate a realistic hazard ratio.

Conclusions

In comparing the frequency of events amongst statin users, both moderate and high intensity statin users had higher a higher frequency of GIH than low intensity statin users. However, this trend did not persist in the secondary outcomes, nor was there a statistically significant difference in primary or secondary outcome frequency between moderate and high intensity statin users. This finding suggests that GI bleeding adverse effects may be associated with increased statin dosage, as has been suggested in the literature.

This study is the largest known retrospective study investigating the association between statin therapy and gastrointestinal hemorrhage. In a cohort of 2,885,870 propensity score-matched individuals aged 30-65 years, this study found that statin therapy statistically significantly increased the rate of GIH by 81%. Clinically, this effect size is surprising, but it should be noted that the benefits of statin therapy on cardiovascular health continue to outweigh the risk of gastrointestinal bleeding events in most patients.

In the paramount JUPITER study, the effect of statin therapy on the rate of cardiovascular events was investigated.[82] In this study, 17,802 healthy adults were randomized to rosuvastatin 20 mg or a placebo. Investigators found that the rate of major cardiovascular events was reduced by 43% in rosuvastatin users compared to the placebo group (HR 0.56; 95% CI 0.46-0.69). This is quite significant clinically, and clinicians would do well to note that based on the results of the JUPITER study, the number of patients needed to treat with a statin to prevent one major cardiovascular event is merely 25. This is in comparison to the results of this study, which demonstrate that nearly 250 subjects need to be treated before one experiences a GIH. While these are stark differences, it should be noted that JUPITER and this study are not directly comparable. While this study considered all instances of GIH, JUPITER considered only “major” instances. Presumably, if one were to restrict GIH events to only those that required hospitalization the number needed to harm would become even more alarming. Furthermore, only healthy patients were included in the JUPITER study, whereas this study strove to include patients with a variety of comorbidities to more accurately represent a clinically relevant population. When considering whether to prescribe a statin

for cardiovascular protection, the risk of GIH is small for the general population and statin benefits likely outweigh the risks.

In conclusion, this propensity score-matched cohort study demonstrated that a group of statin users had significantly higher rates of gastrointestinal hemorrhage than a similar group of thyroid hormone users. The results of this study may influence clinical decision making in a select group of patients who are at a higher baseline risk of bleeding. In patients who take anticoagulants or antiplatelets, or who have bleeding disorders, the risk of cardiovascular events should be weighed carefully with the risk of GIH from statins. While statins offer significant benefits in reducing cholesterol levels and cardiovascular disease, this new insight may guide clinicians in making treatment decisions for patients at higher baseline risks of bleeding.

APPENDIX A: THYROID HORMONE AND GASTROINTESTINAL BLEEDING

Because this study employs a design with thyroid hormone users as the active comparator, it was necessary to conduct a search of the literature to determine whether there was any association between thyroid hormones and GI bleeding that could bias the study. If there is some correlation between use of thyroid hormone and likelihood of GIH, using these subjects as active comparators in a study investigating GIH may not be the best method.

The thyroid gland is in the neck, just in front of the larynx. Its secreted hormone, T4, is the precursor to T3, which modifies gene transcription and thus protein synthesis in most tissues. Both T4 and T3 are well-known to affect nearly every organ and system in the body.

The three major targets of thyroid hormone are the bone, the heart, and metabolism regulation. Hypothyroidism has been associated with poor bone development in infancy, whereas hyperthyroidism is associated with osteoporosis in adults (as T3 stimulates osteocalcin).[83,84] In the heart, hypothyroidism causes bradycardia as T3 stimulates cardiac myocytes. In fact, thyroid hormones impact nearly every part of the cardiovascular system including hypertension and various cardiovascular diseases.[85] Both T3 and T4 can "enhance cardiac function, promoting weight loss and reducing serum cholesterol."[86] Although this is a potential confounder with our statin users, excluding all statin users who use thyroid hormones as well as thyroid hormone medication users who also use statins will ideally eliminate this bias. The weight loss component of thyroid hormone is due to its regulation of the metabolic rate, including its effects on glucose tolerance.[87] Thyroid hormones also have an important role in hematology. Important effects include stimulating red blood cell and hemoglobin production, so hypothyroidism can lead to both micro- and macrocytic anemia,[88] but other studies suggest that this isn't a clinically meaningful effect. However, a PubMed search for "thyroid AND bleed" provided only 19 results – none of which demonstrated a correlation between hyper- or hypothyroidism and risk of hemorrhage.[89]

A PubMed search was also completed for "thyroid*[Title] AND thrombocyto*[Title]" since thrombocytopenia is an important risk factor for GIH. Of the

38 results, 11 pointed to an association between immune thrombocytopenia (ITP) and auto-immune thyroid disease, such as Hashimoto's disorder. However, this association appears to be more related to an auto-immune disorder than the presence of hyper- or hypothyroidism because ITP is also associated with other auto-immune disorders unrelated to the thyroid gland.

Overall, while thyroid hormones are impactful on many body systems, it does not appear that there is sufficient evidence to suggest any meaningful clinical correlation between thyroid hormone substitution and GIH.

APPENDIX B : ICD-9 DIAGNOSIS CODES

Comorbidity	**ICD-9 Code**
Myocardial infarction	410.x, 412.x
Congestive heart failure	428.x
Peripheral vascular disease	443.9, 441.x 785.4, V43.4, Procedure 38.48
Cerebrovascular disease	430.x-438.x
Dementia	290.x
Chronic pulmonary disease	490.x-505.x, 506.4
Rheumatic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x
Peptic ulcer disease	531.x-534.x
Mild liver disease	571.2, 571.4-571.6
Diabetes without chronic complication	250.0-250.3, 250.7
Diabetes with chronic complication	250.4-250.6
Hemiplegia or paraplegia	344.1, 342.x
Renal disease	582.x, 583-583.7, 585.x, 586.x, 588.x
Any malignancy, except malignant neoplasm of the skin	140.x-172.x, 174.x-195.8, 200.x-208.x
Moderate or severe liver disease	456.0-456.21, 572.2-572.8
Metastatic solid tumor	196.x-199.1
AIDS/HIV	042.x-044.x

APPENDIX C: MEDICATIONS BY CLASS AND GPI CODES

Medication or Class	GPI Code
Angiotensin-converting enzyme inhibitor	3610x, 369915x, 369918x
Angiotensin receptor blocker	3615x, 369945x, 369930x, 369940x, 369965x
Antiplatelet	8515x
Antipsychotic	59x
Antithrombotic	8560x
Aspirin	6410001x
Beta-blocker	33x, 369920x
Bisphosphonate	300420x
Calcium channel blocker	34x, 369915x, 369945x, 369930x, 369968x
Corticosteroid	2210x
Diuretic	37x, 369920x, 369918x, 369945x, 369940x, 369968x, 369960x, 369990x
Hypoglycemic	27997x, 2720x
Non-statin lipid lowering agent	3910x, 3930x, 3950x, 3999x
Non-steroidal anti-inflammatory drug	6610x
Proton pump inhibitor	4927x, 499960x, 499930x
Sedative	6010x, 6020x
Selective serotonin reuptake inhibitor	5816x, 629950x
Statin	279930x, 3940x, 399940x, 409925x
Testosterone	2310x
Thyroid hormone	281x, 9664508400, 9664584700, 9680569110
Tricyclic antidepressant	5820x, 6040x, 629920x, 629940x
Warfarin	8320003020

Statin Intensity Chart

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins
atorvastatin 40 – 80 mg	atorvastatin 10 – 20 mg	simvastatin 10 mg
rosuvastatin 20 – 40 mg	rosuvastatin 5 – 10 mg	pravastatin 10 – 20 mg
	simvastatin 20 – 40 mg	lovastatin 20 mg
	pravastatin 40 – 80 mg	fluvastatin 20 – 40 mg
	lovastatin 40 mg	pitavastatin 1 mg
	fluvastatin 80 mg	
	pitavastatin 2 – 4 mg	

* Adapted from Stone et al., 2013

APPENDIX D: PROPENSITY SCORE MODEL AND MATCHING

The following is the distribution of propensity scores in the complete, unmatched cohort:

	Mean	Std. Dev.	Minimum	Maximum
Active Comparator	0.648	0.169	0.051	0.983
Exposed	0.781	0.136	0.044	0.985
Total	0.748	0.156	0.044	0.985

As shown, the region of common support (0.051 – 0.983) does not include all subjects, so the common support restriction must be used.

We initially ran the one-to-one nearest neighbor propensity score matching algorithm with replacement and without caliper and find that the maximum difference between propensity scores in matched pairs is 0.150. The literature suggests it should be a maximum of one-fourth the standard deviation of the propensity score in the unmatched cohort.[90] Thus, we will institute a caliper of 0.03989.

We run another one-to-one nearest neighbor propensity score matching algorithm with replacement on the logit of the propensity score instituting the common support requirement and a caliper of 0.03989. We exclude 19 exposed subjects who did not meet the common support requirement. The results are as follows:

ATT	Exposed	Active Comparator	S.E.
Unmatched	0.00892	0.00802	0.000154
Matched	0.00892	0.00555	0.000993

Because we matched with replacement, 21 552 unexposed subjects were matched to 1 442 935 exposed subjects. This resulted in 8 009 unexposed subjects (0.56%) with a GIH in the follow up period and 12 866 (0.89%) of the exposed subjects.

We also ran a one-to-one nearest neighbor propensity score matching algorithm without replacement, instituting the same caliper as the previous model. However, this did not result in a good match, as the average difference in propensity scores within a matched pair was 0.0256, compared to the previous algorithm which was 0.000005. We instituted a caliper of 0.001 with the following results:

ATT	Exposed	Active Comparator	S.E.
Unmatched	0.00892	0.00802	0.000154
Matched	0.00883	0.00826	0.000197

Because we matched without replacement and imposed a common support requirement, only 436 067 exposed subject were matched to 436 067 unexposed subjects. This resulted in 3 601 unexposed subjects (0.83%) with a GIH in the follow up period and 3 852 (0.88%) of the exposed subjects.

APPENDIX E : BASELINE CHARACTERISTICS BY OUTCOME GROUP

	No Outcome n=2 864 995	Outcome n = 20 875	Standardized Difference
Female, n (%)	1 435 196 (50.9)	9 640 (46.2)	0.111
Age Categories, n (%)			
30-39 y.o.	214 204 (7.5)	1 314 (6.3)	0.066
40-49 y.o.	684 512 (23.9)	3 981 (19.1)	0.166
50-59 y.o.	1 277 345 (44.6)	9 537 (45.7)	-0.031
≥ 60 y.o.	688 934 (24.05)	6 043 (28.95)	-0.157
Statin Intensity, n (%)			
Low	283 995 (9.9)	2 309 (11.1)	-0.053
Moderate	1 013 682 (35.4)	9 357 (44.8)	-0.274
High	132 392 (4.6)	1 200 (5.8)	-0.072
Inpatient Visits, n (%)			
0	1 886 689 (65.9)	12 040 (57.7)	0.239
1	649 261 (22.7)	5 930 (28.4)	-0.187
> 1	329 045 (11.5)	2 905 (13.9)	-0.103
Outpatient Visits, n (%)			
0-1	1 780 836 (62.2)	10 171 (48.7)	0.386
2-4	711 333 (24.8)	5 704 (27.3)	-0.080
5-6	156 937 (5.5)	1 330 (6.37)	-0.054
> 6	215 889 (7.5)	3 670 (17.6)	-0.434
CCI, n (%)*			
0	1 644 161 (57.4)	9 295 (44.5)	0.367
1	802 980 (28.0)	7 576 (36.3)	-0.251
2	224 327 (7.8)	1 897 (9.1)	-0.064
3	120 996 (4.20)	1 061 (5.1)	-0.058
4	30 865 (1.1)	426 (2.0)	-0.111
5	15 316 (0.5)	166 (0.8)	-0.045
≥ 6	26 350 (0.9)	454 (2.17)	-0.144
Comorbidities, n (%)			
AIDS	7 051 (0.3)	49 (0.2)	0.003
Ulcer	11 908 (0.4)	61 (0.3)	0.029
Congestive heart failure	46 585 (1.6)	757 (3.6)	-0.177
Cerebrovascular disease	136 140 (4.8)	1 410 (6.8)	-0.122
Diabetes	717 161 (25.0)	5 459 (26.2)	-0.036
Liver disease	7 422 (0.3)	127 (0.6)	-0.075
Cancer	128 045 (4.5)	1 206 (5.8)	-0.084
Kidney disease	48 300 (1.7)	624 (3.0)	-0.122
Medication Usage, n (%)**			
Bisphosphonates	55 996 (2.0)	482 (2.3)	-0.035
*Blood thinners****	119 936 (4.2)	1 601 (7.7)	-0.209
Corticosteroids	480 407 (16.8)	5 331 (25.5)	-0.305
NSAIDs	685 810 (23.9)	5 262 (25.2)	-0.042
PPIs	508 893 (17.8)	4 977 (23.8)	-0.212

* As defined by Deyo et al. ** At least one prescription claim in baseline period, using GPI codes *** Includes aspirin, antiplatelets, antithrombotics, and warfarin

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EDUCATION AND TRAINING

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Public Policy Analysis and Biological Sciences
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PROFESSIONAL LICENSURE AND CERTIFICATIONS

Pharmacist Intern License Number I11128 — 2013 – Present
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Cardiopulmonary Resuscitation and Basic Life Support — 2013 – Present
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HIPAA Training Certified — 2007 – Present
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PROFESSIONAL EXPERIENCE

Certified Pharmacy Technician — Lexington, Kentucky and Chicago, Illinois
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Pharmacist Intern — Lexington, Kentucky
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PUBLICATIONS AND PRESENTATIONS

Martinez AI, Moga DC, Freeman PR. (2016) "Association of Gastrointestinal Effects and Statin Use: A Large Propensity-Score Matched Retrospective Cohort Study" [Abstract]. *Journal of the American Pharmacists Association*. 56(3):e1-141

Martinez AI, Moga DC, Freeman PR. "Association of Gastrointestinal Effects and Statin Use: A Large Propensity Score-Matched Retrospective Cohort Study." Poster presented at: American Pharmacists Association Annual Meeting and Exposition; 2016 March 4 – 7; Baltimore, Maryland.

Elliott C, **Michnick AI**. "Impact of Glycemic Control Clinical Education in a Rural Medical Center." Poster presented at: LifePoint Health Executive Patient Safety Conference; 2015 June 24 – 26; Nashville, Tennessee.

Michnick AI. "Effectively Using Primary Research to Decrease Hospital Medication Error." Poster session presented at: Kentucky Society of Health-System Pharmacists Spring Conference; 2014 May 9; Lexington, Kentucky.

Michnick AI. (2014) Pharmacy Policy Issues: Effectively using pharmacists in interprofessional teams to reduce hospital medication errors. *The Kentucky Pharmacist*. 9:38-9.

PROFESSIONAL ACTIVITIES

Chapter Leader, IHI Open School University of Kentucky Chapter	April 2014 – May 2016
Pharmacy Student Representative, Patient Safety Student Interest Group	April 2013 – May 2016
Committee Head, Public Policy, Kentucky Society of Health-System Pharmacists	March 2014 - 2015
Member, American Pharmacists Association—Academy of Student Pharmacists	August 2013 – Present
Member, Kentucky Pharmacists Association	August 2013 – Present
Member, National Community Pharmacists Association	August 2013 – Present

HONORS AND AWARDS

Dean's List May 2016
University of Kentucky College of Pharmacy

1st Place Poster Presentation, Pharmacy Student Division March 2016
Rho Chi Alpha Xi Chapter at the University of Kentucky College of Pharmacy

National Patient Counseling Competition Local Chapter Winner February 2016
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