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# VENA CAVA FILTER UTILIZATION AND RETRIEVAL: A QUALITY OF CARE ISSUE

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# VENA CAVA FILTER UTILIZATION AND RETRIEVAL: A QUALITY OF CARE ISSUE

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DISSERTATION

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A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Pharmacy at the
University of Kentucky

By

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Lexington, Kentucky

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Lexington, Kentucky
2015

**Abstract of Dissertation**

Vena cava filters (VCFs) are mechanical devices implanted in the inferior vena cava to trap thrombi from travelling to the pulmonary circulation, resulting in pulmonary embolism. VCFs are available as permanent or non-permanent, retrievable devices and are generally indicated for use in patients unable to receive systemic anticoagulation or at exceedingly high risk for pulmonary embolism (PE). Retrievable devices allow for removal of the VCF once the contraindication to anticoagulation or high risk of PE has abated. Since the introduction of retrievable VCFs in the early 2000's, use of VCFs has increased three-fold, with >85% of all VCFs placed being retrievable. Complications due to indwelling VCFs are time-dependent and the FDA-recommended time periods for retrieval fall within 50-70 days post-implantation. However, retrieval rates are low. Generally around 30% of all VCFs are retrieved in eligible patients, with the remainder becoming permanent despite no indication for the VCF to remain in place. These studies sought to quantify the epidemiology of VCF use, and retrieval in Kentucky and nationally, and to inform future clinical interventions to increase retrieval rates. The following objectives were achieved: 1) describe treatment patterns for patients hospitalized with PE or other venous thromboembolism including VCF utilization and anticoagulation, 2) characterize patients who do and do not receive VCFs, 3) evaluate retrieval rates among subgroups of patients and identify factors associated with retrieval, and 4) evaluate a minimal intervention performed in the University of Kentucky hospital aimed at increasing VCF retrieval rates. Finally, a review of the literature was conducted to identify interventions that have increased retrieval rates at individual hospitals. All these data will be useful in developing a future institutional-level intervention to increase retrieval rates to better improve the quality of patient care.

**Key words:** vena cava filters, venous thromboembolism, pulmonary embolism, retrieval, quality of care

Joshua Brown
Student's Signature

November 22, 2016
Date

# VENA CAVA FILTER UTILIZATION AND RETRIEVAL: A QUALITY OF CARE ISSUE

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To Mom and Dad, for expecting nothing in return.

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*"A master in the art of living draws no sharp distinction between his work and his play; his labor and his leisure; his mind and his body; his education and recreation. He hardly knows which is which. He simply pursues his vision of excellence through whatever he is doing, and leaves others to determine whether he is working or playing. To himself, he always appears to be doing both."*

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## CHAPTER 1: INTRODUCTION TO VENA CAVA FILTERS

### *Venous thromboembolism epidemiology and treatment*

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) of the legs or pelvis and pulmonary embolism (PE). VTE incidence is estimated to be about 124 to 138 events per 100,000 person-years – equally divided between DVT alone and PE with or without DVT, with recurrence in approximately 30% of patients within 10 years.[1,2] VTE carries a high risk of mortality, with 30-day case-fatality rates of nearly 17% for PE and nearly 7% for DVT, a risk which increases with age.[2] The majority (~60%) of VTE is secondary to known major risk factors such as hospitalization, trauma, surgery, and cancer while also influenced by myriad of other clinical factors, treatment regimens, and acquired or inherited thrombophilia.[3]

Treatment of VTE is addressed by the American College of Chest Physicians (ACCP or CHEST) guidelines.[4] Updated as recently as 2016, the ACCP guidelines generally recommend systemic anticoagulation in the form of oral anticoagulants (OAC, warfarin, rivaroxaban, dabigatran, apixaban, edoxaban) or low-molecular weigh heparin (LMWH, tinzaparin, dalteparin, enoxaparin) for at least 3 months after VTE. Vena cava filters (VCFs) are devices usually implanted in the inferior vena cava to mechanically prevent thrombi migrating from the lower extremities to the pulmonary circulation (Figure 1.1). Designs of these device differ by manufacturer and model, but generally include an umbrella-like design to catch thrombi, barbed

arms that embed into the endothelium of the vena cava, and snare hooks to facilitate retrieval (Figure 1.2). ACCP recommendations are limited for VCFs in saying that they are considered only a last resort in patients with severe risk of PE and should never be used in patients that can use anticoagulants. As an introduction to VCFs, the utilization of and evidence supporting their use will be reviewed.

### *Vena cava filter utilization*

Despite strong, Grade 1B ("high evidence") recommendations by the ACCP guideline panel to not utilize VCFs but in the most severe cases, VCFs are still used in approximately 10% of all VTE cases and nearly 20% of all PE cases.[5,6] Overall utilization has steadily increased, especially with the introduction of retrievable, or optional, VCFs in 2003.[5,7,8] Use of VCFs is associated with patients deemed at high risk of recurrent VTE and/or high bleed risk including those with active cancer, advanced age, prior bleeding, trauma, surgery, and unstable patients.[5,7] Estimates of VCF placements in the U.S. have increased from ~3,000 devices per year during 1979 through 1984, up to 92,000 devices placed in 2006.[5] Utilization of VCFs may be excessive in the U.S., with utilization outpacing European nations by 25 to 40-fold.

### *Evidence for vena cava filters*

Prior to 2015, only one randomized controlled trial had evaluated the efficacy of VCFs for prevention of pulmonary embolism. The *Prévention du Risque d'Embolie*

*Pulmonaire par Interruption Cave* (PREPIC) study randomized patients with proximal DVT with or without PE to receive standard anticoagulant treatment with or without a VCF.[9] At this time, only permanent VCFs were available on the market. After eight years of follow-up, there was a significant protective effect of VCFs on pulmonary embolism (6.2% vs. 15.1%, *P*=0.008), a significant increase in DVTs associated with VCFs (35.7% vs. 27.5%, *P*=0.042), and no difference in mortality. In 2015, PREPIC2 data were released which updated the evidence for retrievable VCFs.[10] With a similar design applied to 399 patients, results at six months of follow-up showed a non-significant reduction in PE and other outcomes including DVT, major bleeding, and death. Overall, the PREPIC and PREPIC2 studies did not supply clear evidence for the use of VCFs, mainly due to the fact that the population studied is not considered the population in whom VCFs are usually indicated, i.e. those who have absolute or relative contraindications to anticoagulation. However, given that it would likely be difficult and unethical to conduct such a study, observational studies must fill in the evidence gap.

Observational studies have shown mixed results both in favor and against the utilization of VCFs in multiple patients groups. Stein *et al* showed an overall protective effect of VCFs for in-hospital mortality in stable, unstable, and elderly patients.[11,12] These studies are potentially biased given that the authors used National Inpatient Sample discharge data, which include no basis to establish temporality. Similarly, Isogai and colleagues associated VCFs with an overall protective effect for in-hospital mortality in a Japanese study of patients with

pulmonary embolism using propensity score techniques to reduce sample bias.[13] A pooled analysis of eight controlled studies evaluating prophylactic use of VCF filters (i.e. no VTE present) found a consistent protective benefit for PE and fatal PE with inconsistent findings for subsequent risk of DVT associated reduction in with VCF use.[14] This study found the number needed to treat to prevent one PE event ranged from 109 up to 962 patients in this setting.

A number of studies have also refuted the effectiveness claims of VCFs. Using data from California, VCFs were found to be used in patients with greater comorbidity, PE, bleeding, cancer, and prior stroke.[15] In adjusted analyses, VCF placement was not associated with a significant reduction in recurrent PE but was associated with higher risk of DVT – consistent with the findings of the PREPIC trial. Another study conducted in patients with cancer-associated VTE found that those patients with a VCF had higher mortality and recurrent VTE events compared to those treated with anticoagulation in propensity score weighted analyses.[16] Muriel *et al* evaluated survival effects of VCFs in patients with VTE and high bleeding risk.[17] Using a propensity-score matched sample, they found a non-significant reduction in all-cause death with VCF use (6.6% vs. 10.2%, $P$=0.12), a significant reduction in PE-related mortality (1.7% vs. 4.9%, $P$=0.03), and much higher risk for recurrent VTE with VCF placement (6.1% vs. 0.6%, $P$<0.001). Hemmila and colleagues investigated the survival benefit for prophylactic use of VCFs found that patients with a VCF in place had no impact on mortality and increased the risk of DVT.[18] The most recent study by White *et al* also used propensity score matched samples and found that

VCFs had a protective effect in for 30- and 90-day risk of death only in patients with active bleeding with no effect observed in patients with no contraindication to anticoagulation. [19]

Although there is a general lack of consensus in the evidence, [20] VCFs are widely accepted and utilized – again in roughly 10% of all VTE cases and to an equal degree for prophylactic indications. [5] Some physicians have even called for alarm given that VCFs have generally been approved by the U.S. Food and Drug Administration (FDA) using the 510(k) process, which has been condemned by the Institute on Medicine. [20] This process relies on existing information for a predicate device and allows for marketing of a new device with minimal data submission to the FDA, with few exceptions for prospective safety data collection or small trials to determine safety. [21] In this article subtitled, "How Could a Medical Device Be So Well Accepted Without Any Evidence of Efficacy?" the authors conclude that while RCTs will continue to lag behind in the information needed to guide clinical practice around VCFs, informed consent must be offered to patients so that the lack of evidence and growing evidence of harm can be considered by patients at the point of care. [20]

***Complication rates of vena cava filters***

In addition to the lack of evidence for efficacy, there are also complications related to VCF use that must be considered. Major complications can include the aforementioned increased risk of DVT, thrombosis in the inferior vena cava, device fracture and migration, and device perforation of the inferior vena cava and internal

organs. Complication rates appear to be on a device-by-device basis.[22] A study by Peterson and colleagues showed that roughly 1-in-5 patients with a VCF had a complication including: VCF thrombi (9.5%), DVT (4.7%), VCF penetration of the blood vessel (2.9%), and device migration (0.4%).[23] In the FDA's own Manufacturer and User Facility Device Experience (MAUDE) database between 2009-2012, 1,606 adverse events associated with VCFs were reported including 350 device fractures, 215 whole device migrations, 154 partial device embolizations, 197 VCF tilts, and 228 vena cava penetrations.[24] This, again, varied considerably across six individual types of filters included in the study and was mostly reported for retrievable VCFs.[24] Although PE may be prevented, the observed increased risk of DVT is not benign with up to 30% of patients developing post-thrombotic syndrome, which can have long-term effects on quality of life.[25-27]

Complications reported with VCFs are generally outside of 30 days post-implantation, i.e. they are associated with longer indwell times of retrievable VCFs.[28,29] In response to this concern, the FDA released an initial Safety Communication regarding retrieval of VCFs in 2010.[30] Citing a study which modeled the inflection point of the net clinical benefit of VCFs, the FDA formally recommended that VCFs be removed within 29 to 54 days after implantation or when clinically indicated, which can be interpreted as when the patient can be anticoagulated or is no longer at a substantial risk for PE.[31] The communication also detailed ongoing data collection through post-market surveillance and ongoing clinical study.[30]

### *Guidelines impacting use of vena cava filters*

Despite a lack of evidence and concern about complications, VCF utilization has been shown to continue to increase over the last several decades.[5] As mentioned, the ACCP guidelines, which are widely used for educating clinicians on treatment for VTE, are conservative in regards to VCF use and consider the device a "last resort." However, these guidelines are not the sole influence on medical practice surrounding VCF. Two specialties that interact with decision-making for VCFs include (vascular) interventional radiology and trauma who have created independent guidelines.

The American College of Radiology and Society of Interventional Radiology (SIR) guidelines cover the practice of interventional radiologists who are most often placing VCFs after patients are referred to their service from other specialties. The most recent 2011 guidelines are considered more liberal in VCF use compared to the ACCP guidelines, allowing and recommending VCF use for patients with VTE who are contraindicated to anticoagulation, prophylactically in those with trauma, bariatric surgery, or spinal cord injury and no VTE, as well as in patients with VTE treated with anticoagulation if there is recurrence or progression of the VTE, massive PE or massive clot burden, free-floating DVT, or in severe cardiopulmonary disease (Table 1.1).[32] To compare, ACCP guidelines recommend VCFs only when a contraindication to anticoagulation exists, specifically recommending against the other points made by the SIR guidelines and no recommendation for patients with recurrent VTE. It is logical to assume that those placing the devices will follow the

guidelines of their parent society. As a result, concordance with the ACCP guidelines is generally dismal with one study showing 41.3% of VCF placements following recommendations from ACCP.[33] This is contrasted with up to 95.7% concordance with SIR guidelines.

Trauma surgeons may also place VCFs in the acute care setting, relying on guidance from the Eastern Association for the Surgery of Trauma (EAST) guidelines.[34] Dealing with a special patient population that may include multiple bone fractures, severe blunt or penetrating trauma, as well as the need for multiple surgeries, the inherent risk of VTE is high. These patients make up the vast majority of prophylactic use of VCFs, which is approximately 50% of the VCF utilization.[28] The EAST guidelines make "Level III" recommendations meaning there is only retrospective, opinion, or case study data to support the claim. Nevertheless, they call for prophylactic use only in "very-high risk" trauma patients who have high bleeding risk, noting particularly older age along with hemorrhagic injuries or risk factors.[34] EAST guidelines also acknowledge prophylactic use as controversial, owning to the lack of evidence but also the lack of approved indication according to the product labeling. They further suggest that identification of the proper trauma patient group, via risk factor assessment, is needed so VCFs are allocated efficiently. These guidelines have not been updated since 2002.

The EAST and SIR guidelines have impacted the overall utilization of VCFs in the U.S. In a trend analysis, introduction of the EAST guidelines were associated with an

increase in VCF utilization of 138% while the SIR guidelines in 2006 were associated with an additional 122% increase.[35] The ACCP guidelines in 2008 and 2012 as well as decreased reimbursement from Medicare were also associated with a leveling off in utilization in that period.[35] Further, there was an increase in legal suits against some manufacturers throughout this period that may have added to the cooling off of the VCF market.

Comparisons of these guidelines vary given the different patient groups studied. However, one study conducted a cost effectiveness analysis in trauma patients, applying the guidelines as prophylactic (EAST, SIR) or non-prophylactic (ACCP) use of VCFs.[36] The authors found that for the overall trauma patient population, VCFs are more costly than no treatment and also result in in fewer quality-adjusted life-years. However, to the point of better identifying more appropriate subgroups for prophylactic treatment made earlier in the EAST guidelines, the authors found that VCFs were cost-effective if the risk of VTE was around 10% or greater (i.e. greater than double the risk than the general trauma population). Prophylactic VCF utilization was cost-effective only if the likelihood of complications associated with anticoagulation was at least 10-times the risk in the general trauma population. During the initial hospitalization, VCFs were cost-effective at an incremental cost-effectiveness ratio of nearly $400,000 per quality-adjusted life year, which would fail to reach the acceptable threshold by any normal cost-effectiveness considerations.[36]

***Variation in the utilization and retrieval of vena cava filters***

Multiple guidelines and limited evidence appears to have made a practice environment that varies from institution-to-institution and across state and geographical areas. White *et al* conducted a study of hospitals in California. Of the 263 hospitals included, variation in use of VCFs for active VTE ranged from 0% to nearly 40% with an overall mean use of 15% of all VTE cases. Of this variation, 18.5% was attributable to between hospital differences, with the rest attributed to patient factors or unmeasured characteristics. [37]

Using a trauma-specific database, Dossett *et al* observed what they referred to as "unwarranted national variation" in the use of prophylactic VCFs. [38] They observed variation in use of 0 to 13 prophylactic VCFs per 100 trauma patients. They also included a metric for "high-risk patients" in line with who would be considered high risk of VTE according to the EAST guidelines, with the goal of only utilizing VCFs in those patients at high risk. They found that median use was centralized around the EAST recommendations at 1.1 VCFs used per high-risk patient (i.e. patients who were not "high risk" received a VCF despite lack of need, indicating potential overuse by 50% of all trauma centers) but this ranged up to 206 VCFs used per high-risk patient in the most extreme case. Each study contributed some of the unobserved factors potentially contributing to this variation as "regional culture," hospital culture, and engrained physician practices. The Dossett study also notes that if high utilization of VCFs was clearly associated with improved outcomes, the push would be to increase utilization in centers found to be under-utilizing VCFs in

their study.[38] However, prophylactic VCF use remains controversial, off-label, and lacks clinical trial evidence to support this use.

Appropriateness of the use of VCFs is a moot point once placement has occurred. The shift in focus becomes the retrieval of the device once the indication for placement has abated, i.e. the patient is no longer at high risk for PE and/or the patient can initiate anticoagulation. Clinical studies like PREPIC2, even in a controlled environment with dedicated follow-up periods, retrieved roughly 80% of all VCFs placed after 3 months. In real-world clinical practice, however, this rate is closer to an estimated mean of 30%,[28] with some institutions reporting VCF retrieval as low as 8%.[39] Retrieval is pivotal to the safety of these devices, again because complication rates are correlated with longer indwell times.[28] Dismal retrieval rates are associated with poor patient follow-up and fractionated care given that the physicians placing the filters, mainly interventional radiologists, are not generally part of the follow-up plan.[40-42] Thus, the majority of patients are likely discharged without any plans for follow-up for VCF retrieval, making the device *de facto* permanent in these people. The previously mentioned FDA safety communication relays only that retrieval is a goal, not necessarily specifying the correct patient population or indications for which VCFs should be used.[30] Thus, VCFs are a medical device likely being overused given the paucity of data and one that is not consistently retrieved in a timely fashion, which is likely due to a lack of planning in *post hoc* patient care.

**Figure 1.1: Diagram of vena cava filter placement in the inferior vena cava to prevent clot movement from lower extremities.**

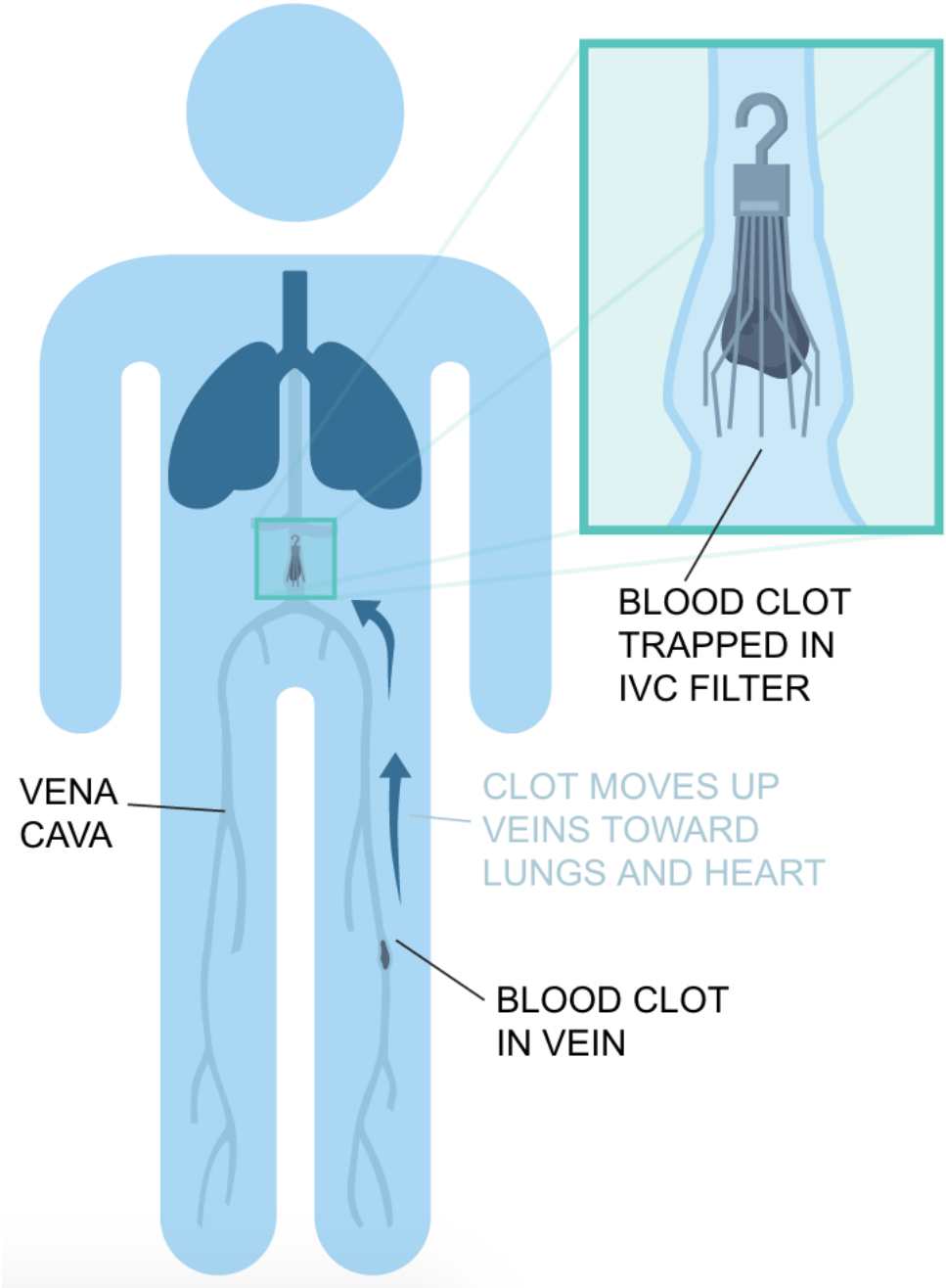
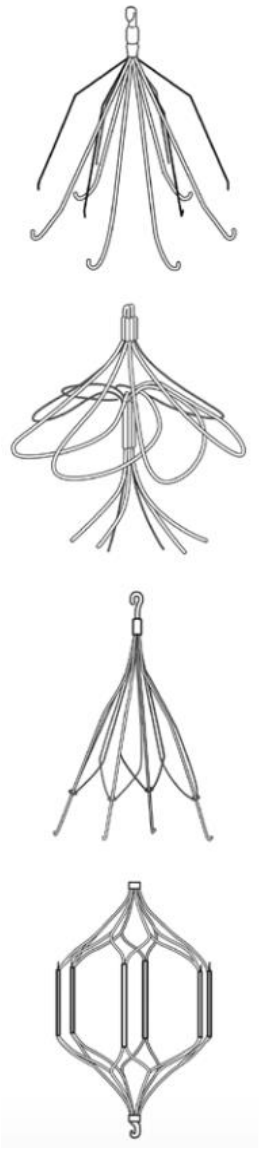


**Figure 1.2: Examples of four vena cava filter models showing filter sections, barbs, and retrieval hooks**



| Table 1.1: Comparison of guidelines impacting utilization of vena cava filters | | |
|---|---|---|
| **Scenario for VCF placement** | **ACCP Guidelines** | **SIR Guidelines** |
| VTE with anticoagulation | Recommends against VCFs | Recommends with progression, large clot burden, free-floating thrombi, or severe cardiopulmonary disease. |
| VTE with contraindication to anticoagulation | Recommends VCF | Recommends VCF |
| Recurrent VTE | No specific recommendation | Recommends VCF |
| Trauma (prophylaxis) | Recommends against VCF | Recommends consideration of VCF |
| Bariatric surgery (prophylaxis) | Recommends against VCF | No specific recommendation |
| Spinal cord injury (prophylaxis) | Recommends against VCF | Recommends VCF |

## HYPOTHESIS AND AIMS OF THIS DISSERTATION

I believe that the use of VCFs is highly variable and the outcomes poorly described. Understanding the epidemiology of VCF utilization can inform interventions to improve the quality of care for patients with VTE, ensuring that the correct patients receive VCFs and that post-implantation care is provided. The goal of this dissertation work is to describe and model the use and retrieval of VCFs. I will also be evaluate to efficacy and toxicity outcomes and provide some pilot work to address low retrieval rates as outlined in the Aims below.

### *Specific Aims*

Thus, I present these specific aims for this dissertation and address them in the next five chapters.

1) Assess utilization and variation in utilization of VCFs in acute care hospitals in Kentucky
2) Evaluate retrieval rates and factors associated with retrieval in a national cohort
3) Compare outcomes between patients treated with VCFs with and without anticoagulation, versus anticoagulation alone in a cancer patient subgroup at high risk of recurrent events
4) Evaluate an intervention to increase retrieval rates in the Interventional Radiology clinic at the University of Kentucky hospital
5) Perform a literature review of interventions to increase retrieval rates at other institutions to inform future efforts

## CHAPTER 2: HOSPITAL VARIATION AND PATIENT CHARACTERISTICS ASSOCIATED WITH VENA CAVA FILTER UTILIZATION IN ACUTE CARE HOSPITALS IN KENTUCKY

Study 2.1: Addresses VCF utilization in Kentucky hospitals by evaluating patient and hospital factors associated with use. This study has been published in the journal *Medical Care*.

Citation: Brown, Joshua D., and Jeffery C. Talbert. "Hospital Variation and Patient Characteristics Associated With Vena Cava Filter Utilization." *Medical Care* (2016). Ahead of print.

Study 2.2: Evaluates hospital-level variation in VCF utilization to observe whether it is explained by patient and hospital-level factors and to observe outliers along this continuum. This study has been published in the journal *JAMA Surgery* as a research letter and is formatted accordingly.

Citation: Brown, Joshua D., and Jeffery C. Talbert. "Variation in the Use of Vena Cava Filters for Venous Thromboembolism in Hospitals in Kentucky." *JAMA Surgery* (2016). doi:10.1001/jamasurg.2016.1004

## *Study 2.1: Hospital Variation and Patient Characteristics Associated With Vena Cava Filter Utilization*


### Abstract

**Introduction:** There is wide variation in the use of vena cava filter (VCFs).

**Objectives:** This study assessed the hospital and patient characteristics associated with VCF use in deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Methods:** Inpatient discharge data from all acute care hospitals with DVT/PE in Kentucky were used. Hierarchical logistic regression models were used to evaluate the relationships of study variables with VCF use.

**Results:** During the study period, 81,922 discharges for DVT/PE were observed and 10.5% of these received a VCF. This included 12,083 cases of PE+DVT, 18,571 cases of PE only, and 51,268 cases of DVT only. VCF use among these groups was 22.7%, 6.0%, and 7.8%, respectively. In adjusted analyses, VCF use was associated with increasing age, indicating that those over age 65 were twice as likely to receive a filter compared to the reference (21-25 year-old) group. Significant comorbidities associated with VCF use included cancer, liver disease, cerebrovascular disease, atrial fibrillation, anemia, and concurrent bleeding. Lower extremity, proximal DVTs, and patients receiving thrombolytic therapy or embolectomy, those having surgery, and those who were unstable or had trauma, were also more likely to receive a filter. Among cancer types, brain and metastatic tumors were significantly

associated with VCF use. Between-hospital variation after controlling for all covariates was 7.1%.

**Conclusion:** There was high variation in use of VCFs. Several high-risk subgroups were more likely to use VCFs including older adults and those with cancer and concurrent bleeding.

## Introduction

Increased utilization of vena cava filters (VCFs) for venous thromboembolism (VTE) has correlated with technical improvements in placement of VCFs as well as development of retrievable devices.[5] By 2006, roughly 9% of cases of deep vein thrombosis (DVT) and 12% of pulmonary embolism (PE) received a VCF and has continued to increase into 2012 with an estimated 259,000 VCFs placed in patients in the United States.[43,44]

This increase persists despite mixed recommendations and an overall lack of evidence for the use of VCFs.[20] American College of Chest Physicians guidelines recommend VCF use only if the patient has a contraindication to systemic anticoagulation as a last resort.[45] Conversely, The American College of Radiology and Society of Interventional Radiology guidelines support prophylactic VCF use for patients determined to be at high risk of developing DVT or PE.[46,47] These contrasting recommendations are important considering that in a study conducted at one academic medical center, nearly one-half of all VCFs placed were for prophylactic purposes and only a third of uses are associated with clear bleed-related contraindications to anticoagulation.[44] Another study corroborated these findings showing that up to 50% of VCFs used in trauma patients are "unwarranted."[48]

Given the potential for suboptimal use of VCFs and the wide variation in use between hospitals,[37] it is important to understand the hospital- and patient-level factors associated with utilization. Identifying these factors will assist in assessing the quality of care for patients presenting with DVT/PE and can also indicate subpopulations that may be of interest for future research. Thus, this study sought to characterize patients with VTE who received VCFs and to observe the amount of variation between hospitals. A cancer subgroup will also be analyzed with the same methodology due the high rates of VTE and potential of high bleeding risk in that population.

## Methods

*Data source*

State Inpatient Database (SID) data from Kentucky (years 2008-2014) were used. SID data are analogous to National Inpatient Sample (NIS) data but are state-specific and include all discharges instead of a probabilistic sample.[49] Data include patient demographic variables (age, gender, race, insurance, ZIP codes) and diagnosis and procedure fields. Data are de-identified and do not include unique patient identifiers, so no longitudinal tracking is possible. Thus, data represent discharges and may contain multiple records for the same person representing unique hospitalizations for that person. We use the terminology "patients" to distinguish

each unique hospitalization/discharge. The University of Kentucky Institutional Review Board approved of this study.

*Study variables*

The coding algorithms used are presented in the Appendix and are based on previously published coding algorithms.[15,37,50-52] All diagnoses for DVT PE were identified for those 21 and older from acute care hospitals. VCF use was identified by ICD-9-CM procedure code 38.7. Discharges from hospitals where no VCFs were placed over the entire 7-year period were excluded to avoid bias due to hospitals lacking the ability to perform the procedure. Variation in VCF use was described by the mean, median, interquartile range (IQR), and coefficient of variation.

Patients were classified as having DVT only, PE only, or having PE+DVT. Comorbidities identified included cancer, chronic obstructive pulmonary disease, cerebrovascular disease (CVD), atrial fibrillation (AFib), liver disease, hypertension, heart failure, hyperlipidemia, myocardial infarction, cellulitis, trauma, diabetes, infection, pneumonia, renal disease, bleeding, anemia, and sepsis/septic shock.[53] In addition, thrombolytic therapy and embolectomy/thrombectomy procedures were identified. Unstable patients were identified as those with shock or by use of a ventilator. Invasive surgical procedures were identified using a validated algorithm.[54] Discharge statuses of "deceased" or "transferred" were also recorded. Age was categorized by 5-year intervals. Race was categorized white, black, or other and insurance was classified as commercial, Medicaid, Medicare, or other/self-pay.

Individual hospitals were classified as being urban or rural, teaching or non-teaching, and categorized into quartiles by hospital bed size.

*Statistical analysis*

Comparisons were conducted between demographic and clinical characteristics using t-tests and chi-squared tests where appropriate using an *a priori*, two-sided significance level of 0.05. P-values are reported for comparisons between VCF users and non-users.

Based on previous studies the likelihood of receiving a VCF has a moderate association with the hospital where treatment occurs.[37] This is likely influenced at the institutional level by physician preferences and hospital policies and practices. To account for this natural clustering effect and its impact on treatment, hierarchical generalized linear modeling was used (henceforth: hierarchical logistic models) for the binary outcome of VCF use.[55] These models included random effects for each hospital and fixed effects for other covariates.[55,56] The first model included hospital random effects only. The second model included *level-1* fixed effects, which are patient demographic and clinical characteristics. *Level-2* effects, i.e., hospital characteristics, were included in a separate model alone and in the final full model, which included all random and *level-1* and *level-2* fixed effects. A cancer-only model was also estimated in the cancer subgroup with additional variables for cancer site (Table 2.4).

Odds ratios (ORs) and their 95% confidence intervals are presented for each variable from the final, full model. The intraclass correlation coefficient (ICC) was calculated for each model, which measures the variation explained by the hospital random effects. The p-value associated with the ICC corresponds to the comparison of between-hospital variance with $p<0.05$ showing significant differences. In addition, c-statistics were calculated as a measure of model discriminatory power between VCF users and non-users. Akaike (AIC) and Bayesian (BIC) information criterion were included to compare across models, which measure the fit of the models while penalizing for added parameters. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

A total of 70 acute care hospitals were included in the state. Of these, 11 hospitals placed no VCFs and were excluded (N=2,435 patients, 2.9% of total discharges). Among the remaining institutions (N=59), VCF use ranged from 0.4% to 15.2%, mean 7.2%, median 7.2%, IQR 4.1% to 10.1%, and coefficient of variation of 0.54.

During the period 2008 to 2014, there were 81,922 VTE-related hospital discharges and 10.5% of patients (N=7,786) received a VCF. The VCF group tended to have an older age distribution, and have more PE+DVT, cancer, cerebrovascular disease, atrial fibrillation, anemia, and trauma compared to those without VCFs (Table 2.1). The VCF group was also likely to be unstable, have proximal and lower DVTs, have bleeding, and receive thrombolysis.

The random effects only model resulted in an ICC of 12.0% ($p<0.001$) and c-statistic 0.62, showing that there was a significant difference between hospitals, which explained 12% of the overall variance in use (Table 2.2). Adding *level-1* patient-level covariates, the ICC was 12.7% ($p<0.001$) and the c-statistic was 0.81 showing no change in the explained variance for the random effects parameter and an overall strong discriminatory ability for the model. The full model included random effects with both *level-1* and *level-2* fixed effects. This model had an ICC of 7.1% ($p<0.001$) and c-statistic of 0.81. The cancer only model had an ICC of 3.5% ($p<0.001$) and c-statistic of 0.81.

The results of the full model (Table 2.3) showed that beginning at 46-50 years of age, the odds of receiving a VCF increased compared to the reference group (21-25 years-old). This trend continued with those over the age of 65 being roughly twice as likely to receive a VCF. VCFs were also associated with the commercial insurance category being more likely than those in the other/self-pay insurance category. Black race was also associated with lower odds of receiving VCFs compared to white race (OR=0.83 [0.75-0.92]).

Clinical characteristics were highly associated with VCF use. Compared to patients with DVT only, those with PE only (OR=3.84 [3.46-4.25]) and PE+DVT (OR=2.73 [2.57-2.90]) were much more likely to receive VCFs. Among DVTs, those with lower DVTs were more than six-fold more likely to receive a VCF compared to upper

extremity DVTs. Those with bleeding, cancer, liver disease, anemia, and atrial fibrillation were also more likely to receive VCFs.

Among those with cancer (N=13,104), 1,613 (12.3%) used VCFs. In the cancer-only model, estimates for demographic and clinical characteristics were similar to the primary model and are not shown. The most common cancers were lung (N=3,931, 30.0% of all cancers) and colorectal cancer (N=1,392, 10.6%). Of the twenty-two cancer sites identified, all but five had higher utilization of VCFs than in the average cohort (Table 2.4). The highest VCF use was associated with brain tumors (24.4%), cervical (17.0%), stomach and small intestine (16.3%), colorectal (16.2%), and bladder (15.6%). After controlling for all other variables, brain tumors (OR=2.31 [1.65-3.23]) remained the only significantly associated tumor site with VCF use while leukemia and breast cancers were negatively associated with use.

## Discussion

The primary findings suggest that while there is a wide variation in VCF utilization between institutions, most of that variation is controlled for by patient and hospital characteristics. In the final model, very little variation (~7%) in VCF use was attributed to differences between hospitals. This differs from an analogous study by White *et al*. using California SID data. Their results showed more variation (IQR 6.23%-18.14%) in VCF use and more variation (>12%) attributed to between hospital comparisons. This indicates that VCF utilization between hospitals varies

widely not only within a state, but also between states, as our coefficient of variation was smaller (0.54 vs. 0.65).

Among comorbid conditions considered, our results show strong associations with VCF use and cancer, cerebrovascular, atrial fibrillation, anemia, and concurrent bleeding. This suggests that consideration of baseline risk of thromboembolic and bleeding events is considered at the point of care. However, competing guideline statements make it difficult to assess the appropriateness of VCF use in subgroups at a high-risk of VTE, but not necessarily contraindicated to anticoagulation. The clearest indication for VCF use may be in those with concurrent bleeding in addition to the VTE already present. In this study, over 20% of patients with bleeding received a VCF and were 2.7 times more likely to receive a filter in adjusted analyses. VCF use was also associated with characteristics that potentially indicate severity including unstable patients, surgery, receipt of thrombolysis or embolectomy procedures, and trauma.

The association between cancer, VTE, and presence of multiple risk factors for bleeding prompted a more detailed look into individual cancers. Patients with cancer are at an exceedingly high risk of VTE compared to the general population.[57] Further, given the complexity of regimens, multiple drug-drug, and drug-disease interactions, and side effects of cancer treatments as well as many surgical procedures, it is possible that systemic anticoagulation is considered infeasible or is contraindicated for many cancer patients.[58] However, prior studies have shown that

anticoagulants are often used in addition to VCFs.[16,44] In this study, VCF use was highest for brain cancers, due to the high risk of intracranial bleeding, and with metastatic cancers. Surprisingly, lung cancers, which are often considered as a very high-risk group for cancer-associated VTE and highly prevalent in Kentucky,[59] were not associated with increased use.

The evidence for VCFs for PE/DVT is mixed, making conclusive arguments for its use difficult. In the PREPIC[9] and PREPIC2[10] randomized trials, no significant benefits were observed with VCFs with anticoagulation versus anticoagulation alone during short- and long-term follow-up. Observational studies show that VCFs are associated with improvements in short-term outcomes such as in-hospital mortality, 30-day mortality, and a reduction in subsequent PE events among all VTE patients and certain subgroups (trauma, unstable, and elderly).[11,13,14,60] Other studies have shown little or no benefit with VCFs, especially with longer follow-up.[15-18]

Retrievable filters have become widely used in the last decade. Sarosiek *et al*. evaluated the use of retrievable filters and subsequent complications at a single academic center.[44] Their main findings showed there was attempted retrieval in only 10% of VCFs. Of those retrieved, one-quarter were removed during the index hospitalization and the median time-to-retrieval was observed to be 122 days after placement. Their study further emphasized the lack of follow-up for patients receiving a VCF and a number of serious complications including filter fracture and migration. The authors emphasized the need for follow-up and proper retrieval of

devices to avoid complications associated with VCFs. This has been observed in other studies, as well, showing that utilization and retrieval rates as potential quality of care issues and deserve dedicated interventions to ensure quality outcomes for patients. [61-63]

It has also been suggested that use of VCFs, as well as their retrieval, is influenced by reimbursement rates. [44] Our findings seem to refute this strong assumption regarding use of VCFs, at least in a case-by-case (i.e. hospital) basis. Using the ICC to measure the impact of hospitals in the current study, the full model showed that only 7.1% of the variance in the model was explained by the discharge hospital. Our results suggest that there is not major variance between hospitals after controlling for patient and hospital characteristics and does not support the notion of pervasive overuse of VCFs in order to increase reimbursement.

Although our results suggest no institutional deviance in VCF use, there may still exist a general overuse of these devices, which is not definitively supported by current evidence and is further confounded given the lack of consensus in treatment guidelines. There is a great need for additional research in the effectiveness of VCFs in real-world practice, especially for subgroups at highest risk of complications (e.g. cancer and high bleeding risk). While randomized studies are not likely to be conducted to fill these knowledge gaps, well-conducted effectiveness studies using observational data should be used.

*Limitations*

Due to the nature of the data, detailed information on medication utilization is not possible with discharge data. This is important to distinguish those who would and would not use anticoagulants in place of, or concurrently with, VCFs as these groups may differ in clinical presentation and treatment course. Previous studies have shown that anticoagulants are often used with VCFs, likely proving that use persists without clear contraindications to anticoagulation therapy.[44] Further, as the data includes no unique patient-identifying variable, it is possible that multiple records for the same individual are included in the analyses. This would be due to multiple hospitalizations over the time period, including patients who transfer from one facility to another. To investigate the impact of transfers, we included an indicator for whether a patient transferred or not, as this may also indicate severity and influence whether a patient receives a VCF from that institution. At both a patient-level and institutional-level, transfer status and transfer rate were not significantly associated with VCF utilization. Finally, the data represent the patient population and medical practice within Kentucky and may have limited generalizability to other areas due to differences in comorbid conditions and practices between regions.

## Conclusion

In this study of VCF use in Kentucky, we found that much of the between hospital variation is explained by observed hospital and patient characteristics and little variation existed between hospitals after controlling for these factors. More research is needed to assess the effectiveness of VCFs, especially in high-risk subgroups such as cancer, elderly, high bleed risk, and trauma patients.

**Table 2.1: Comparison of patient characteristics between vena cava filter users and non-users**

| Characteristic | | No VCF N=74,136 | | VCF N=7,786 | | % Receiving VCF |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| **Age group** | 21-25 | 1,309 | 1.8% | 64 | 0.8% | 4.7% |
| | 26-30 | 1,958 | 2.6% | 109 | 1.4% | 5.3% |
| | 31-35 | 2,416 | 3.3% | 140 | 1.8% | 5.5% |
| | 36-40 | 3,092 | 4.2% | 205 | 2.6% | 6.2% |
| | 41-45 | 4,021 | 5.4% | 292 | 3.8% | 6.8% |
| | 46-50 | 5,225 | 7.1% | 416 | 5.3% | 7.4% |
| | 51-55 | 6,565 | 8.9% | 605 | 7.8% | 8.4% |
| | 56-60 | 7,148 | 9.6% | 716 | 9.2% | 9.1% |
| | 61-65 | 7,801 | 10.5% | 875 | 11.2% | 10.1% |
| | 66-70 | 7,780 | 10.5% | 963 | 12.4% | 11.0% |
| | 71-75 | 7,572 | 10.2% | 950 | 12.2% | 11.1% |
| | 76-80 | 7,188 | 9.7% | 941 | 12.1% | 11.6% |
| | 81+ | 12,061 | 16.3% | 1,510 | 19.4% | 11.1% |
| **Gender** | Female | 39,048 | 52.7% | 3,982 | 51.1% | 9.3% |
| | Male | 35,088 | 47.3% | 3,804 | 48.9% | 9.8% |
| **Race** | White | 65,860 | 88.8% | 7,068 | 90.8% | 9.7% |
| | Black | 6,746 | 9.1% | 540 | 6.9% | 7.4% |
| | Other | 1,530 | 2.1% | 178 | 2.3% | 10.4% |
| **Insurance** | Other/Self-pay | 10,187 | 13.7% | 949 | 12.2% | 8.5% |
| | Medicaid | 2,930 | 4.0% | 210 | 2.7% | 6.7% |
| | Medicare | 24,275 | 32.7% | 2,603 | 33.4% | 9.7% |
| | Commercial | 36,744 | 49.6% | 4,024 | 51.7% | 9.9% |
| **Clot type** | DVT only | 47,274 | 63.8% | 3,994 | 51.3% | 7.8% |
| | PE only | 17,466 | 23.6% | 1,105 | 14.2% | 6.0% |
| | PE with DVT | 9,396 | 12.7% | 2,687 | 34.5% | 22.2% |
| **Comorbidity** | Cancer | 11,491 | 15.5% | 1,613 | 20.7% | 12.3% |
| | Metastatic cancer | 6,087 | 8.2% | 959 | 12.3% | 13.6% |
| | Heart failure | 14,069 | 19.0% | 1,470 | 18.9% | 9.5% |
| | Liver disease | 3,224 | 4.3% | 420 | 5.4% | 11.5% |
| | Renal disease | 20,516 | 27.7% | 2,233 | 28.7% | 9.8% |
| | Diabetes | 20,656 | 27.9% | 2,111 | 27.1% | 9.3% |
| | Stroke | 4,893 | 6.6% | 798 | 10.2% | 14.0% |
| | Hypertension | 45,317 | 61.1% | 4,954 | 63.6% | 9.9% |
| | Hyperlipidemi | 23,826 | 32.1% | 2,603 | 33.4% | 9.8% |

**Table 2.1: Comparison of patient characteristics between vena cava filter users and non-users**

| | a | | | | | |
|---|---|---|---|---|---|---|
| | Atrial Fibrillation | 10,868 | 14.7% | 1,424 | 18.3% | 11.6% |
| | Cellulitis | 6,284 | 8.5% | 398 | 5.1% | 6.0% |
| | COPD | 23,630 | 31.9% | 2,528 | 32.5% | 9.7% |
| | Sepsis/Septic shock | 7,821 | 10.5% | 908 | 11.7% | 10.4% |
| | Infection/ Pneumonia | 25,051 | 33.8% | 2,712 | 34.8% | 9.8% |
| | Anemia | 24,874 | 33.6% | 3,538 | 45.4% | 12.5% |
| | Myocardial infarction | 6,700 | 9.0% | 793 | 10.2% | 10.6% |
| | Trauma | 3,143 | 4.2% | 558 | 7.2% | 15.1% |
| | Thrombolytic therapy | 1,571 | 2.1% | 546 | 7.0% | 25.8% |
| | Embolectomy | 249 | 0.3% | 68 | 0.9% | 21.5% |
| | Unstable/ ventilator | 3,455 | 4.7% | 567 | 7.3% | 14.1% |
| | Proximal DVT | 12,651 | 17.1% | 2,966 | 38.1% | 19.0% |
| | Lower DVT | 31,538 | 42.5% | 5,997 | 77.0% | 16.0% |
| | Bleeding | 4,612 | 6.2% | 1,173 | 15.1% | 20.3% |
| | Surgery | 14,340 | 19.3% | 2,177 | 28.0% | 13.2% |
| | Deceased | 4,200 | 5.7% | 436 | 5.6% | 9.4% |
| | Transfer | 1,907 | 2.6% | 155 | 2.0% | 7.5% |
| **Urban/rural status** | Rural | 19,096 | 25.8% | 1,692 | 21.7% | 8.1% |
| | Urban | 55,040 | 74.2% | 6,094 | 78.3% | 10.0% |
| **Teaching status** | Non-teaching | 36,792 | 49.6% | 3,210 | 41.2% | 8.0% |
| | Teaching | 37,344 | 50.4% | 4,576 | 58.8% | 10.9% |
| **Bed size** | ≤75 beds | 2,500 | 3.4% | 99 | 1.3% | 3.8% |
| | 76-135 beds | 6,216 | 8.4% | 331 | 4.3% | 5.1% |
| | 136-275 beds | 18,761 | 25.3% | 1,718 | 22.1% | 8.4% |
| | ≥276 beds | 46,659 | 62.9% | 5,638 | 72.4% | 10.8% |

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; VCF=vena cava filter; DVT=deep vein thrombosis; PE=pulmonary embolism; COPD=chronic obstructive pulmonary disease

**Table 2.2: Fit statistics of hierarchical logistic models predicting vena cava filter use**

| | **Model 1: Random effects only** | **Model 1 + *level 1* fixed effects** | **Model 1 + *level-2* fixed effects** | **Full model: Model 1 + *level 1* and *level-2* fixed effects [a]** | **Cancer model [b]** |
|---|---|---|---|---|---|
| **Intercept (SE)** | -2.70 (0.09) | -5.76 (0.18) | -3.38 (0.20) | -6.50 (0.26) | -7.10 (0.86) |
| **Hospital random effects, $\tau$ (SE)** | 0.45 (0.10) | 0.48 (0.11) | 0.22 (0.05) | 0.25 (0.06) | 0.12 (0.04) |
| **ICC[c]** | 12.0% | 12.7% | 6.4% | 7.1% | 3.5% |
| **C-statistic** | 0.62 | 0.81 | 0.62 | 0.81 | 0.81 |
| **AIC[d]** | 50326.46 | 42570.91 | 50301.07 | 42548.15 | -- |
| **BIC[d]** | 50330.61 | 42670.58 | 50315.61 | 42658.19 | -- |

[a] Level 1 fixed effects are patient level fixed effects including all demographic and clinical characteristics. Level-2 fixed effects are hospital characteristics .

[b] Cancer only model included only individuals with cancer and the individual sites of cancer (Table 4). Fit statistics are not included since it was not compared to other models.

[c] Intraclass correlation coefficient: The proportion of the model variance explained by the "hospital" parameter; e.g. 12.0% of the Model 1 variance is explained by the hospital where a person is discharged. Calculated by $\tau / \tau + 3.29$ for a binary logit model. All ICC values between hospitals were significant at $p<0.001$.

[d] Akaike information criterion and Bayesian information criterion fit statistics for comparison between models. Each measures the model fit but penalizes for additional parameters added to each model. Smaller values are preferred; thus, the full model is preferred over Model 1.

**Table 2.3: Hierarchical logistic regression results of patient characteristics associated with use of vena cava filters**

| Variable | | aOR | 95% CI | |
|---|---|---|---|---|
| **Age** | 21-25 | Ref. | Ref. | Ref. |
| | 26-30 | 1.12 | 0.80 | 1.56 |
| | 31-35 | 1.14 | 0.82 | 1.57 |
| | 36-40 | 1.25 | 0.92 | 1.70 |
| | 41-45 | 1.25 | 0.93 | 1.69 |
| | 46-50 | 1.38 | 1.04 | 1.84 |
| | 51-55 | 1.55 | 1.17 | 2.06 |
| | 56-60 | 1.57 | 1.19 | 2.08 |
| | 61-65 | 1.74 | 1.32 | 2.30 |
| | 66-70 | 2.00 | 1.51 | 2.65 |
| | 71-75 | 1.99 | 1.50 | 2.64 |
| | 76-80 | 2.11 | 1.59 | 2.79 |
| | 81+ | 2.18 | 1.65 | 2.88 |
| **Gender** | Female | Ref. | Ref. | Ref. |
| | Male | 1.05 | 1.00 | 1.10 |
| **Race** | White | Ref. | Ref. | Ref. |
| | Black | 0.83 | 0.75 | 0.92 |
| | Other | 1.13 | 0.95 | 1.35 |
| **Insurance** | Other/self-pay | Ref. | Ref. | Ref. |
| | Medicaid | 1.01 | 0.85 | 1.19 |
| | Medicare | 1.05 | 0.96 | 1.15 |
| | Commercial | 1.25 | 1.15 | 1.36 |
| **Clot type** | DVT only | Ref. | Ref. | Ref. |
| | PE only | 3.84 | 3.46 | 4.25 |
| | PE with DVT | 2.73 | 2.57 | 2.90 |
| **Comorbidities** | Cancer | 1.27 | 1.18 | 1.38 |
| | Metastatic cancer | 1.28 | 1.16 | 1.41 |
| | Heart failure | 1.01 | 0.94 | 1.08 |
| | Liver disease | 1.23 | 1.09 | 1.38 |
| | Renal disease | 0.94 | 0.88 | 1.00 |
| | Diabetes | 1.03 | 0.97 | 1.09 |
| | Stroke | 1.53 | 1.40 | 1.67 |
| | Hypertension | 1.02 | 0.96 | 1.08 |
| | Hyperlipidemia | 0.95 | 0.90 | 1.00 |
| | Atrial Fibrillation | 1.24 | 1.15 | 1.33 |
| | Cellulitis | 0.78 | 0.70 | 0.87 |
| | COPD | 1.03 | 0.98 | 1.09 |
| | Sepsis/Septic shock | 1.00 | 0.90 | 1.10 |
| | Infection/Pneumonia | 1.03 | 0.97 | 1.10 |

**Table 2.3: Hierarchical logistic regression results of patient characteristics associated with use of vena cava filters**

| | | | | |
|---|---|---|---|---|
| | Anemia | 1.58 | 1.50 | 1.67 |
| | Myocardial infarction | 0.99 | 0.91 | 1.08 |
| | Trauma | 1.62 | 1.46 | 1.81 |
| | Thrombolytic therapy | 2.32 | 2.06 | 2.61 |
| | Embolectomy | 1.51 | 1.11 | 2.05 |
| | Unstable/ventilator | 1.37 | 1.21 | 1.55 |
| | Proximal DVT | 1.54 | 1.45 | 1.63 |
| | Lower DVT | 6.49 | 5.92 | 7.11 |
| | Bleeding | 2.72 | 2.51 | 2.94 |
| | Surgery | 1.84 | 1.72 | 1.96 |
| **Discharged** | Deceased | 0.63 | 0.56 | 0.70 |
| | Transfer | 0.89 | 0.74 | 1.06 |
| **Metropolitan status** | Rural | Ref. | Ref. | Ref. |
| | Urban | 0.87 | 0.62 | 1.23 |
| **Teaching status** | Non-teaching | Ref. | Ref. | Ref. |
| | Teaching | 1.46 | 1.04 | 2.06 |
| **Bed size** | ≤75 beds | Ref. | Ref. | Ref. |
| | 76-135 beds | 1.41 | 0.85 | 2.32 |
| | 136-275 beds | 2.41 | 1.48 | 3.91 |
| | ≥276 beds | 3.06 | 1.77 | 5.29 |

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; VCF=vena cava filter; DVT=deep vein thrombosis; PE=pulmonary embolism; COPD=chronic obstructive pulmonary disease

**Table 2.4: Association between vena cava filter use and cancer site (N=13,104)**

| Cancer site | Total N | % Using VCF | aOR[a] | 95% CI | |
|---|---|---|---|---|---|
| **Oral** | 146 | 8.2% | 0.67 | 0.35 | 1.30 |
| **Skin** | 180 | 13.9% | 1.06 | 0.66 | 1.73 |
| **Bone/soft tissue** | 167 | 11.4% | 0.90 | 0.52 | 1.56 |
| **Stomach/small intestine** | 313 | 16.3% | 1.17 | 0.80 | 1.70 |
| **Colorectal** | 1,392 | 16.2% | 1.25 | 0.99 | 1.57 |
| **Liver** | 217 | 9.2% | 0.85 | 0.50 | 1.45 |
| **Pancreas** | 796 | 11.2% | 0.76 | 0.57 | 1.03 |
| **Lung/larynx/pleura** | 3,931 | 11.4% | 1.02 | 0.83 | 1.25 |
| **Breast** | 776 | 7.6% | 0.65 | 0.47 | 0.91 |
| **Uterus** | 312 | 15.1% | 1.02 | 0.69 | 1.49 |
| **Cervix** | 165 | 17.0% | 1.37 | 0.84 | 2.22 |
| **Ovarian** | 468 | 14.7% | 1.13 | 0.81 | 1.58 |
| **Prostate** | 613 | 14.2% | 0.98 | 0.72 | 1.32 |
| **Testicular** | 61 | 13.1% | 1.62 | 0.66 | 3.95 |
| **Bladder** | 360 | 15.6% | 1.12 | 0.79 | 1.58 |
| **Kidney** | 476 | 11.3% | 1.09 | 0.76 | 1.55 |
| **Brain** | 308 | 24.4% | 2.31 | 1.65 | 3.23 |
| **Thyroid** | 44 | 18.2% | 1.22 | 0.46 | 3.24 |
| **Myeloma** | 378 | 12.2% | 0.96 | 0.66 | 1.39 |
| **Leukemia** | 766 | 7.0% | 0.64 | 0.46 | 0.90 |
| **Lymphoma** | 293 | 7.2% | 0.76 | 0.46 | 1.26 |
| **Endocrine** | 121 | 14.0% | 0.92 | 0.31 | 2.75 |
| **Metastatic** | 7,046 | 13.6% | 1.13 | 1.00 | 1.29 |

[a]Cancer-specific regression model included all covariates from the primary model. Results for those variables were not meaningfully different and are excluded here for brevity.

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; VCF=vena cava filter

**Appendix Table 2.1: Coding algorithm for conditions and procedures**

| Disease/procedures | Code type | Codes |
|---|---|---|
| Inferior vena cava filter | ICD-9-CM Procedure | 38.7 |
| Pulmonary embolism | ICD-9-CM Diagnosis | 415.1x |
| Deep vein thrombosis | ICD-9-CM Diagnosis | 451.xx, 453.xx |
| Unstable | ICD-9-CM Diagnosis | 785.5, V46.1 |
| Cancer | ICD-9-CM Diagnosis | 140.xx-195.xx, 200.xx-208.xx |
| Metastatic cancer | ICD-9-CM Diagnosis | 196.xx-199.xx, 209.71, 209.74, 511.81, 789.51 |
| Heart failure | ICD-9-CM Diagnosis | 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 |
| Liver disease | ICD-9-CM Diagnosis | 570.xx-573.xx |
| Diabetes | ICD-9-CM Diagnosis | 250.xx |
| Renal disease | ICD-9-CM Diagnosis | 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 580.xx-588.xx, V42.0, V45.1, V56.x |
| Cerebrovascular disease | ICD-9-CM Diagnosis | 362.34, 430.xx-438.xx |
| Hypertension | ICD-9-CM Diagnosis | 401.xx-405.xx |
| Hyperlipidemia | ICD-9-CM Diagnosis | 272.xx |
| Atrial fibrillation | ICD-9-CM Diagnosis | 427.31 |
| Cellulitis | ICD-9-CM Diagnosis | 626.xx |
| Chronic obstructive pulmonary disease | ICD-9-CM Diagnosis | 416.8, 416.9, 490.xx-505.xx, 506.4, 508.1, 508.8 |
| Sepsis/septic shock | ICD-9-CM Diagnosis | 038.x, 995.91, 785.52 |
| Infection/pneumonia | ICD-9-CM Diagnosis | 001.x-139.x, 480.xx-488.xx |
| Anemia | ICD-9-CM Diagnosis | 280.xx-285.xx |
| Myocardial infarction | ICD-9-CM Diagnosis | 410.xx, 412.xx |
| Trauma | ICD-9-CM Diagnosis | 800.xx-829.xx, 850.xx-854.xx, 860.xx-897.xx, 925.xx-929.xx, 940.xx-957.xx |
| Bleeding | ICD-9-CM Diagnosis | 430.xx, 431.xx, 456.0, 456.20, 530.82, 531.xx-534.xx, 578.1, 530.7, 569.3, 578.0, 578.9, V12.71 |
| Thrombolysis | ICD-9-CM Procedure | 99.10 |

| Appendix Table 2.1: Coding algorithm for conditions and procedures | | |
|---|---|---|
| Embolectomy | ICD-9-CM Procedure | 38.00, 38.05, 38.07, 38.09, 38.08 |
| Surgery | ICD-9-CM Procedure | Surgery Flag definition for invasive surgeries[16] |

***Study 2.2: Variation in the Use of Vena Cava Filters for Venous Thromboembolism in Hospitals in Kentucky***

## Introduction

Use of vena cava filters (VCFs) has increased over the last decade without clear indication in many patients.[64,65] This increase in use has been suggested to be partially motivated by upcoding for increased reimbursement, given that placement of a VCF increases the reimbursement rate for venous thromboembolism by 250%.[65]

Wide variation in VCF utilization between institutions has been observed.[37] This variation may be influenced by many factors including the case-mix of patients, as well as institutional-level factors and physician preferences.[37] We analyzed the relationship of VCF use for venous thromboembolism (VTE) with institutional-level factors and patient variables to determine whether differences can be explained by observable factors rather than potential reimbursement upcoding.

## Methods

We used Kentucky inpatient discharge data from all acute care hospitals during 2008-2014. These data represent all discharges in the state and include up to twenty-five diagnosis and procedure fields as well as hospital variables.

Diagnoses for deep vein thrombosis (DVT) or pulmonary embolism (PE) were identified.[50] VCF use was identified by ICD-9-CM procedure code 38.7. Prophylactic VCF use without DVT or PE was excluded. Institution-level factors included bed size, teaching/non-teaching status, and urban status. Case-mix comorbidities included cancer, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, atrial fibrillation, liver disease, hypertension, heart failure, hyperlipidemia, myocardial infarction, cellulitis, trauma, diabetes, infection, renal disease, bleeding, anemia, and sepsis/septic shock based on previously published coding algorithms.[37,52,64] Case-mix variables were entered into the model as the proportion of patients with each condition at each hospital. The ratio of VTE events attributable to PEs versus DVTS at each hospital was included given that VCF use is more commonly used with PE. The proportion of patients dying or transferring and the percent receiving surgery, thrombolysis, or embolectomy was also included.[53]

A final linear model included the percent VCF utilization as the dependent variable and controlled for all covariates. Model assumptions were inspected including plots of the predicted values and the fitted model residuals. VCF use was plotted by year

and the overall trend from 2008 to 2014 was evaluated. All analyses were conducted using JMP Pro 12 (SAS Institute, Cary, NC). The University of Kentucky Institutional Review Board approved of this study.

## Results

Seventy hospitals were included in the analysis including 84,357 VTE-related discharges with 7,337 (8.7%) receiving VCFs. Overall use was 10% in 2008 and decreased to 7.5% by 2014 ($p<0.001$ for all trends; Figure 2.1). Hospital use ranged from 0% up to 15.2% with mean utilization of 6.1% (standard deviation 4.4%, median 6.7%, coefficient of variation 0.73). The variation between institutions was consistent throughout the time period. In adjusted analysis, VCF use was most strongly associated with case-mix, mainly the PE-to-DVT ratio. Other case-mix variables associated with increased VCF use were atrial fibrillation and cancer (Table 2.5). The model fit the data well, with $R^2=0.97$ and normally distributed residuals (Figure 2.2). Restricting the sample to hospitals with at least 50 PE/DVT discharges, similar results were observed with $R^2=0.99$. Table 2.6 compares patients at the University of Kentucky hospital, which had the highest overall utilization of VCFs at 15.2%. Overall, patients at the University of Kentucky hospital are worse off based on the comorbidities measured, which makes the utilization lay on the curve of the expected utilization produced by the model.

## Discussion

These results showed a wide distribution in the utilization of VCF for VTE in Kentucky that is explained almost completely by patient case-mix and institutional characteristics. Lack of residual variation between institutions after controlling for these variables suggests that there may not be substantive overuse of VCFs to increase reimbursement. However, there may still be a systematic overuse of VCFs given conflicting guidelines and lack of apparent indications for many patients in a prior study.[64] Additional work is needed to determine whether the rate of VCF use is appropriate.

**Acknowledgements**

Data were collected by the Kentucky Cabinet for Health and Family Services (KHA HCUP), Office of Health Policy and provided by the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust. The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Figure 2.1: Trend in vena cava filter (VCF) use during 2008-2014.** Tests for trend showed a 25% decrease in overall use (p<0.001), 33% decrease (p<0.001) for pulmonary embolism (PE) alone and with deep vein thrombosis (DVT), and a 19% (p<0.001) decrease for DVT alone.

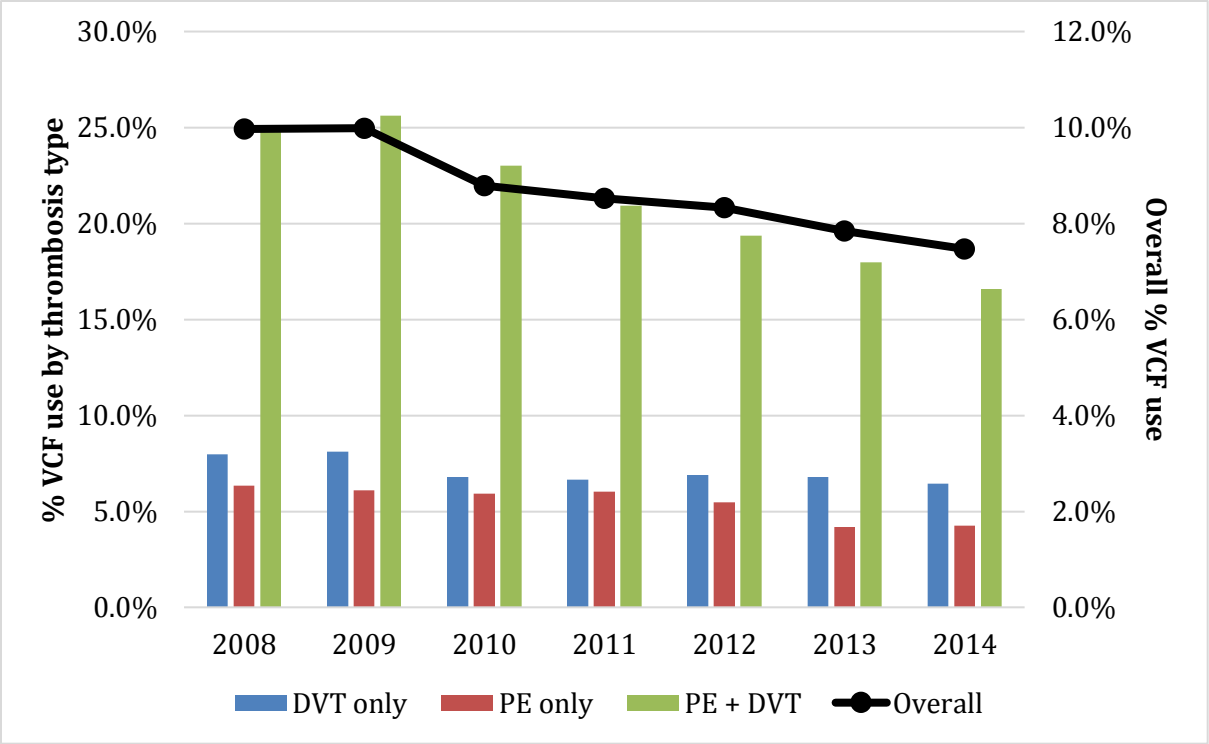
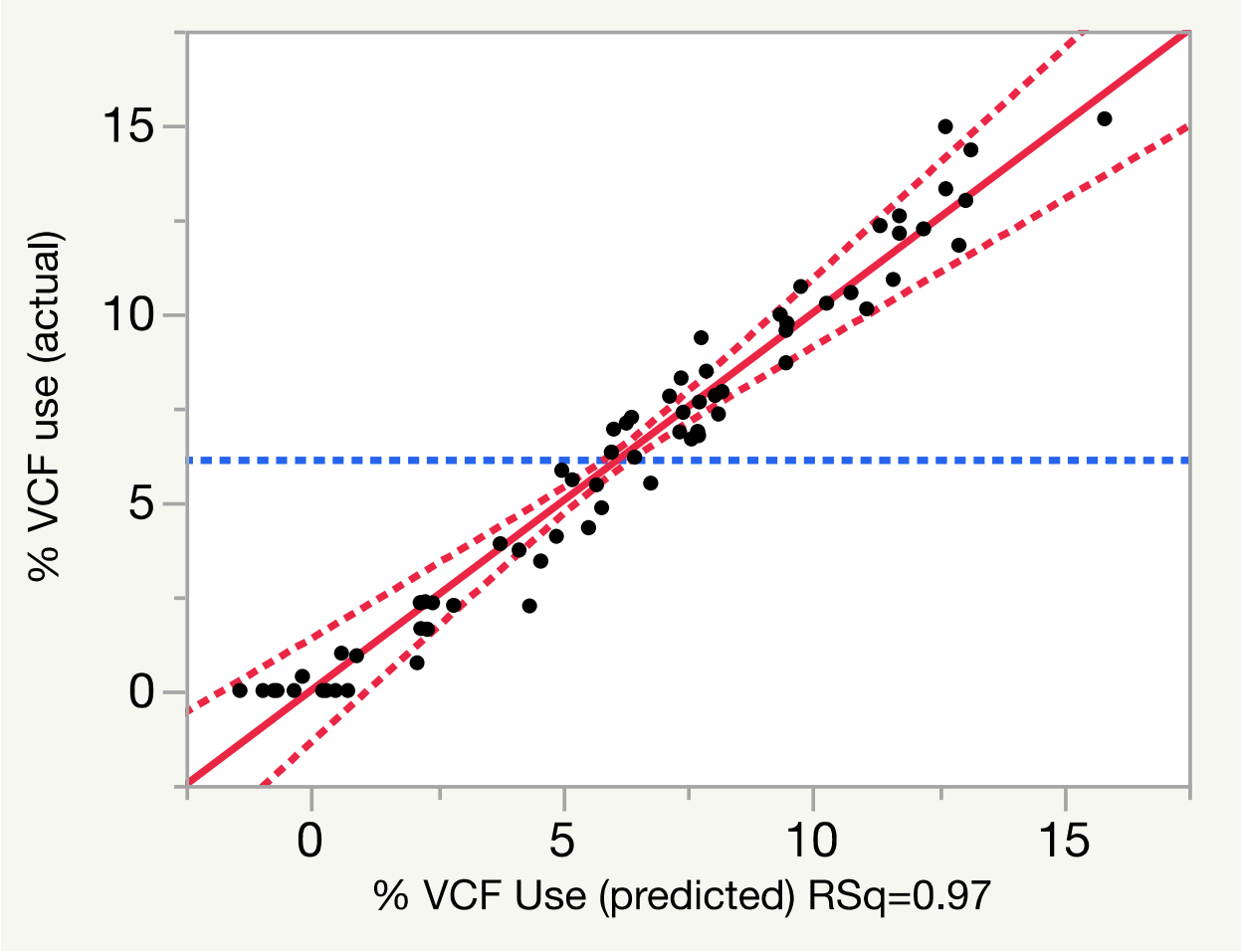


**Figure 2.2: Actual versus predicted VCF utilization of the full model.** The goodness of fit for the model produced $R^2$=0.97, showing a very strong fit to the data. Full model included all case-mix variables to control for differences in patient population between institutions. Red lines are the best-fit regression line and the 95% significance limits of the fitted model. Blue horizontal line represents the predicted mean from the model.



| Table 2.5: Scaled regression estimates of covariates predicting percent of PE/DVT patients receiving inferior vena cava filter | | | | |
|---|---|---|---|---|
| **Regression Term** | **Scaled Estimate[a]** | **p-value** | **Lower 95%** | **Upper 95%** |
| Intercept | 6.29 | <. 0001 | 5.87 | 6.71 |
| PE-to-DVT ratio | 7.96 | <. 0001 | 6.61 | 9.30 |
| Embolectomy | 2.80 | 0.001 | 1.22 | 4.37 |
| Cancer | 3.83 | 0.003 | 1.36 | 6.31 |
| Thrombolysis | -2.17 | 0.007 | -3.70 | -0.64 |
| Trauma | -2.00 | 0.032 | -3.82 | -0.18 |
| COPD | -1.75 | 0.043 | -3.44 | -0.06 |
| Bed size 76-135 | -0.73 | 0.046 | -1.44 | -0.01 |
| Atrial fibrillation | 1.28 | 0.048 | 0.12 | 2.69 |
| Bed size ≥276 | 1.08 | 0.050 | -0.07 | 2.24 |
| Cerebrovascular disease | 0.97 | 0.075 | -0.10 | 2.05 |
| Metropolitan area | -0.51 | 0.077 | -1.08 | 0.06 |
| Proximal DVT | -2.21 | 0.095 | -4.83 | 0.41 |
| Liver disease | -0.73 | 0.326 | -2.21 | 0.75 |
| Cellulitis | 0.69 | 0.399 | -0.94 | 2.31 |
| Renal disease | 0.69 | 0.412 | -1.00 | 2.39 |
| Rural area | 0.34 | 0.415 | -0.49 | 1.16 |
| Diabetes | 0.47 | 0.450 | -0.78 | 1.72 |
| Infection | 0.56 | 0.479 | -1.03 | 2.15 |
| Surgery | -0.89 | 0.483 | -3.43 | 1.65 |
| Heart failure | 0.36 | 0.529 | -0.79 | 1.51 |
| Micropolitan area | 0.17 | 0.564 | -0.44 | 0.79 |
| Bed size ≤75 | -0.27 | 0.600 | -1.29 | 0.75 |
| Transfer rate | 0.40 | 0.603 | -1.15 | 1.96 |
| Hypertension | 0.69 | 0.648 | -2.35 | 3.73 |

| **Table 2.5: Scaled regression estimates of covariates predicting percent of PE/DVT patients receiving inferior vena cava filter** | | | | |
|---|---|---|---|---|
| Myocardial infarction | -0.26 | 0.651 | -1.44 | 0.91 |
| Death | -0.24 | 0.666 | -1.36 | 0.88 |
| Unstable | 0.35 | 0.759 | -1.95 | 2.65 |
| Bed size 136-275 | -0.09 | 0.789 | -0.75 | 0.58 |
| Sepsis/septic shock | -0.24 | 0.794 | -2.08 | 1.60 |
| Concurrent bleeding | -0.12 | 0.827 | -1.27 | 1.02 |
| Non-teaching | -0.07 | 0.835 | -0.69 | 0.56 |
| Teaching | 0.07 | 0.835 | -0.56 | 0.69 |
| Metastatic cancer | -0.16 | 0.909 | -2.95 | 2.63 |
| Hyperlipidemia | -0.09 | 0.924 | -2.05 | 1.86 |
| Anemia | -0.01 | 0.990 | -1.50 | 1.48 |
| [a]Nominal variables are expanded to each category. Continuous variables are centered on the mean and scaled by the range/2. Estimates are ordered by significance in the model. | | | | |

**Table 2.6: Comparison of University of Kentucky hospital patients with patients in similar size hospitals by vena cava filter utilization and case-mix comorbidities**

| Characteristic | UKHC | Lexington hospital | Lexington hospital | Louisville teaching hospital | Paducah hospital |
|---|---|---|---|---|---|
| VCF utilization | ***15.2%*** | 13.0% | 12.1% | 7.8% | 5.5% |
| Bed size | 462 | 344 | 347 | 285 | 323 |
| Patient case-mix | | | | | |
| Cancer | ***26.4%*** | 14.4% | 16.1% | 13.8% | 13.3% |
| Metastatic | ***13.8%*** | 8.4% | 10.9% | 7.4% | 5.5% |
| Heart failure | 17.6% | 17.5% | 18.6% | 21.4% | 12.3% |
| Liver disease | ***8.9%*** | 4.3% | 4.3% | 4.2% | 1.3% |
| Renal disease | ***37.4%*** | 31.3% | 24.7% | 29.5% | 12.3% |
| Diabetes | 24.0% | 27.5% | 27.6% | 30.8% | 20.5% |
| Stroke | 9.7% | 7.0% | 8.0% | 7.1% | 2.7% |
| Hypertension | 54.1% | 58.9% | 65.4% | 66.5% | 45.2% |
| Hyperlipidemia | 22.9% | 30.3% | 42.9% | 40.3% | 12.1% |
| Atrial fibrillation | 13.1% | 19.1% | 18.2% | 17.7% | 9.3% |
| Cellulitis | 6.9% | 9.0% | 7.2% | 9.7% | 7.8% |
| COPD | 24.5% | 28.5% | 33.1% | 36.4% | 24.3% |
| Sepsis | ***19.0%*** | 12.2% | 7.4% | 11.8% | 2.3% |
| Infection | ***45.1%*** | 34.7% | 32.7% | 32.8% | 16.1% |
| Anemia | ***40.7%*** | 34.6% | 39.0% | 35.8% | 21.1% |
| Myocardial infarction | 13.3% | 9.1% | 9.9% | 13.6% | 2.7% |
| Trauma | ***11.2%*** | 3.0% | 2.9% | 3.8% | 2.5% |
| Thrombolysis | 3.7% | 8.7% | 4.5% | 2.6% | 0.4% |
| Embolectomy | 1.3% | 0.7% | 0.4% | 0.3% | 0.2% |

**Table 2.6: Comparison of University of Kentucky hospital patients with patients in similar size hospitals by vena cava filter utilization and case-mix comorbidities**

| | | | | | |
|---|---|---|---|---|---|
| Unstable | ***14.4%*** | 5.7% | 5.7% | 3.4% | 1.1% |
| Bleed | ***10.7%*** | 6.8% | 7.8% | 7.0% | 5.1% |
| Deceased on discharge | ***9.4%*** | 6.0% | 6.5% | 4.9% | 3.8% |

# CHAPTER 3: VENA CAVA FILTER RETRIEVAL RATES AND FACTORS ASSOCIATED WITH RETRIEVAL IN A NATIONAL COHORT


## Abstract

### Introduction

Retrieval of inferior vena cava filters (IVCFs) is important for the safety of these devices as complications increase with longer dwell times. This study sought to assess retrieval rates and patient demographic and clinical factors associated with retrieval in a national cohort.

### Methods

Patients receiving IVCFs were identified by procedural codes from the Truven MarketScan administrative claims database. The indication for placement was identified as pulmonary embolism (PE) with or without deep vein thrombosis (DVT), DVT only, or prophylactic. Patient demographic and clinical characteristics were included in proportional hazard regression models to find associations with early (90-day) and one-year retrieval.

**Results**

Of 54,766 patients receiving an IVCF, 36.9% had PE, 43.9% had DVT only, and 19.2% had no apparent VTE present. Over the one-year of follow-up, the cumulative incidence of IVCF retrieval was 18.4%, which differed based on indication, age, and several other key patient factors. Retrieval increased over time from a low of 14.0% in 2010 up to approximately 24% in 2014. In adjusted time-to-event models, increasing age, differing regions, and comorbidities associated with hyper- (e.g. prior stroke) or hypocoagulable (e.g. prior bleeding) states were associated with poorer retrieval. Those with and without retrieval, and those with early (≤90 day) and late (≥120 day) retrieval, did not differ in healthcare utilization of outpatient or inpatient visits prior to retrieval. Initiation of anticoagulation was poorly correlated with retrieval, with anticoagulation preceding retrieval by a median of 51 days and those without retrieval had a median of 278 days of exposure to anticoagulation.

**Conclusions**

IVCF retrieval has increase over time but remains suboptimal with only 1-in-5 being retrieved within one year. Improving retrieval rates can improve patient outcomes, prevent time-dependent complication rates, and improve clinic revenue with patient follow-up. Retrieval should be a priority for quality improvement initiatives at the institutional and national level.

## Introduction

Inferior vena cava filters (IVCFs) are used to mechanically prevent thrombi in the lower extremities from migrating to the pulmonary circulation. Generally, IVCFs are reserved for patients who have absolute or relative contraindications to systemic anticoagulation who are at a high risk of recurrent venous thromboembolism (VTE).[45-47] With the advent of retrievable IVCFs (rIVCFs), there has been a marked increase in overall use, especially in trauma and surgery patients.[5,6] The intuition behind retrievable devices calls for removal once the contraindications have subsided and patients can be initiated on anticoagulation.

In real-world settings, retrieval rates of rIVCFs are low, with reports ranging from 10-50% within individual institutions, with an estimated average near 30%.[28,66] Poor retrieval rates correspond to an increase in reported adverse events, as these temporary devices become *de facto* permanent.[28] Complications associated with VCFs include increased risk of deep vein thrombosis (DVT), inferior vena cava (IVC) thrombosis, IVC penetration, IVCF fracture, and IVCF embolization.[28,31,67,68] Given these trends, the U.S. Food and Drug Administration (FDA) has issued several safety communications highlighting the need to remove IVCFs once the risk of pulmonary embolism (PE) has subsided and anticoagulation is no longer contraindicated.[30]

Little is known regarding IVCF retrieval on a national scale given most studies have been conducted at single institutions.[31] Given the continued growth in IVCF use and

the variation that has been observed between institutions,[37,48,69-71] assessments of factors that drive retrieval rates on a national scale is needed to aid clinical decision-making.[72] This study utilized a large national database to assess IVCF retrieval and patient factors related to retrieval as well as differences in healthcare utilization. Further, we assessed the relationship between time to retrieval and time to initiation of anticoagulant therapy.

## Methods

*Data source*

This observational cohort study utilized the Truven Health Analytics MarketScan database. The MarketScan data are administrative healthcare claims data including medical diagnostic and procedural information and pharmacy fill records. The data include information for roughly 40 million unique individuals per year and is generally representative of those with commercial insurance and Medicare supplemental coverage. The University of Kentucky Institutional Review Board approved use of the data.

*Cohort identification*

All patients during the years 2010-2014 who had a IVCF placed were identified and assigned an index based using *Current Procedural Terminology* (CPT: 37191, 37620,

35940) and *International Classification of Diseases, 9th revision* (ICD-9: 38.7) procedural codes. The indication for VCF was identified by ICD-9 diagnosis codes as PE (415.1x) with or without DVT, DVT only (451.xx or 453.xx), or no apparent VTE (prophylactic).[50] For inclusion, patients were required to be 18 years or older and have a minimum of 6 months of pre-index time prior to IVCF placement.

*Cohort characteristics*

Demographic variables included age, sex, geographic region, and residence status. Age was divided into 18-34, 35-44, 45-54, 55-64, 65-74, and 75 and older categories. Geographic region included U.S. census regions (Northeast, North Central, South, West, and unknown) and residence status was divided into urban or rural based on metropolitan statistical area classifications. Patients' insurance status was classified as commercial or Medicare and whether or not they were enrolled in a fully or partially capitated insurance plan and if they had a primary care provider (PCP) assigned.

Certain concurrent conditions and procedures present during IVCF implantation were recorded. Concurrent bleeding, unstable condition, sepsis or septic shock, infection, anemia, trauma, and pregnancy were all recorded using ICD-9 diagnosis codes.[15,37] Patients receiving thrombolytic therapy, embolectomy procedures, or major surgery were identified using a combination of procedural codes.[53] Patients who died during the hospitalization during which the IVCF was placed were also

noted. Comorbid conditions observed in the pre-index period consisted of Charlson comorbidities and a summed Charlson Comorbidity Index (CCI). [52,73]

*Outcome events*

The primary outcome was IVCF retrieval identified by CPT (37193, 37203) and ICD-9 (38.7) procedure codes. Given the ICD-9 procedure code for placement and retrieval is the same, retrievals for those patients only having the ICD-9 procedure code present had to be on separate days to record a retrieval. However, since CPT codes and not ICD-9 codes are used for billing purposes, patients lacking the CPT codes were the exception with >95% of all patients having CPT codes recorded. Patients were followed forward from the index date (IVCF placement) until the IVCF was retrieved, they died, they were lost to follow-up, or the end of the study period. The 30, 60, 90, 180-day and one-year cumulative incidence of IVCF retrieval was estimated using Fine and Gray's method, accounting for death as a competing risk.[74] Time to IVCF retrieval was also reported.

*Time to anticoagulation initiation*

Anticoagulation initiation was assessed as the first filled prescription for an injectable (dalteparin, enoxaparin, tinzaparin, fondaparinux) or oral (warfarin, dabigatran, rivaroxaban, apixaban) anticoagulant. Time to anticoagulation and was compared with the time to retrieval and described for those who did not have retrieval during follow-up. Time for both events was calculated based on the date of discharge from a hospitalization, if the IVCF was placed during hospitalization, or

the day of IVCF placement if it was placed in an outpatient setting, given that prescription medications would not be observed during a hospitalization.

*Survival analysis*

To identify factors associated with IVCF retrieval, we developed a Cox proportional hazards regression model including patient demographic and clinical characteristics typically associated with either VTE, bleed risk, or IVCF use. Additionally, measures of comorbidity were included to scale individual's overall health. The proportionality assumption for all variables was evaluated for using Schoenfeld residuals as well as using time as an interaction term for each variable. Both methods showed that this assumption held true. Due to collinearity with age, insurance status of commercial or Medicare was excluded in the model. Two models were estimated predicting 90-day and one-year retrieval. Patients who had not had retrieval or had not died at the end of the 90-day or 365-day period were censored. Cause-specific hazard ratios (HR) and their 95% confidence intervals (CI) were estimated for the effect of each covariate on the retrieval rate with HR<1 indicating lower retrieval and HR>1 indicating higher retrieval.

*Case-control analysis*

To understand if there are differences in recurrent events, complications, and healthcare utilization during the post-implantation period, two *post hoc* nested case-control analyses were performed. Non-cancer patients who had a retrieval event were matched with up to three non-cancer controls who did not have a retrieval.

Likewise, patients who had retrieval within 90 days post-implantation ("early retrieval") were matched 1:1 (due to sample size) with controls who had retrieval ≥120 days post-implantation ("late retrieval"). Pairs were matched on variables found significant in the survival analysis as well as factors related to higher healthcare utilization including age, region, residence status, CCI score, and year of IVCF placement. Incidence density sampling without replacement was used for matching, allowing for controls who had at overlapping follow-up periods with cases. Controls were given the same length of time between IVCF placement as their respective cases to provide a consistent look-back period. Conditional logistic regression was used to assess the association between retrieval and non-retrieval as well as early versus late retrieval with complications (DVT, PE) and healthcare utilization (anticoagulation use, emergency room [ER] visits, hospitalizations, and outpatient visits) in the look-back period. VTEs coded on outpatient visits are assumed to be for the management of the initial VTE event while hospitalizations and emergency visits with VTEs as the primary diagnosis were assumed to be new VTE events, thus considered to be complications. For outpatient visits, the reference group was considered to be those who had less than the median number of visits compared to those who had equal or more median visits. For hospitalizations and emergency visits, those with none were used as the reference group for those with one and those with two or more. Utilization for IVC thrombosis and IVC injury were excluded due to low occurrence in the cohort. All analyses were conducted using SAS Enterprise Guide version 7.1 (Cary, NC).

## Results

*Patient characteristics*

During 2010-2014, 54,766 patients received an IVCF and met the eligibility requirements to be included in the study. Of these, 36.9% presented with a PE, 43.9% with DVT alone, and 19.2% had no apparent VTE present (Table 3.1). The mean (standard deviation, SD) age of the cohort was 65 (16), 51% were female, geographically diverse with nearly 85% residing in urban areas. Insurance details included 13.9% of the cohort having a PCP and 8.6% having insurance with full or partial capitated payments. A total of 1,628 (3.0%) of the cohort died during the initial hospitalization and were not included in subsequent analyses.

Concurrent with IVCF placement, 9.1% had active bleeding, 10.5% had trauma, 1.6% were unstable, nearly 17% had active infections, and nearly 19% had anemia (Table 3.1). Roughly one of every four patients had a major surgical procedure performed during the same hospitalization the IVCF was placed. The most common comorbid conditions in the cohort were hypertension (56.5%), hyperlipidemia (33.2%), cancer (30.4%), diabetes (24.9%), and chronic obstructive pulmonary disease (COPD, 23.6%).

Overall, 14.3% (N=7,619) of the cohort who survived the index hospitalization had the IVCF retrieved within one-year and 8% (N=4,228) died (Table 3.2). For those who had retrieval, the mean (SD) time-to-retrieval was 93 (78) days, with a median

of 71 days and interquartile range (IQR) of 35-130 days. Those with PE had the highest mean and median times-to-retrieval (101 and 81 days) compared to those with DVT only (91 and 68 days) and compared to those with no VTE (83 and 61 days).

Figure 3.1 shows the cumulative incidence of IVCF retrieval by the index indication and Table 3.3 shows the cumulative incidence for selected variables. At one-year, retrieval was highest for those with no VTE on index, reaching nearly 25% (23.9%-25.8%). Retrieval increased with each year of study, going from 14.0% (13.3%-14.7%) in 2010 up to 38.2% (19.4%-57.0%, skewed by low follow-up time) in 2014 ($P$ <0.001). Differences in retrieval between age groups were significant with younger age groups having higher retrieval. For example, those aged 18-34 had one-year retrieval of 42.8% (40.4%-45.2%) while retrieval in those 75 and older was just 5.4% (5.0%-5.8%, $P$ <0.001). Likewise, those without cancer had higher retrieval compared to those with cancer (20.8% vs. 11.7%, $P$ <0.001). Those with commercial insurance had much higher retrieval compared to those with Medicare. However, this effect was associated with age distribution between these two insurance groups, i.e. 98% of the Medicare insured were ≥65 years of age.

*Factors related to retrieval*

In fully adjusted analyses (Table 3.4), age remained significantly associated with IVCF retrieval at both 90-days and 365-days of follow-up, although the association was much stronger for the one-year model. Patients with no VTE were more likely to have retrieval compared to those with DVT only, and there was no difference in retrieval between those with PE compared to those with DVT. Geographic region was also significant, with those residing in the North Central (90-days and one-year) and West (one-year only) regions being more likely to have retrieval compared to those in the Northeast. Likewise, urban residence was associated with slightly higher retrieval compared to rural residence (90-days and one-year). At one-year, capitated payment insurance types were associated with lower retrieval.

Among concurrent conditions, infection and anemia were associated with lower retrieval at 90 days and one year while pregnancy was associated with higher retrieval at one-year of follow-up. Other comorbid conditions associated with lower one-year retrieval included myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, COPD, severe liver disease, paralysis, cancer, stroke, hypertension, and coronary heart disease.

Year of filter placement was modeled both as a covariate as well as used to stratify the analysis. In stratified analysis, no differences were observed between the covariates and their association with IVCF retrieval compared to the base model with year as a covariate. As a covariate, each year of IVCF placement was associated

with increased 90-day and one-year retrieval compared to year 2010. For the final year 2014, this corresponded to nearly a two-fold difference in retrieval rate compared to 2010 (HR=1.90, 95% CI 1.76-2.06).

*Time to anticoagulation*

During follow-up, the dataset had follow-up prescription information for 37,272 persons in the cohort. Among these, 23,510 (63.1%) initiated anticoagulation with median time to anticoagulation initiation of 17 (IQR 6-50) days. Initiation of anticoagulation differed significantly for those who eventually had retrieval (median 11, IQR 5-31 days) and those that did not have retrieval (median 17, IQR 6-50 days, $p<0.001$). Overall, time to anticoagulation and time to retrieval were poorly correlated, with anticoagulation preceding retrieval by a median of 51 (IQR 13-110) days. Figure 3.2 shows the correlation between the time to anticoagulation and the time to retrieval after hospitalization. As observed, anticoagulation occurs much earlier than retrieval (black line shows best fit of data). The red line shows the ideal best fit line assuming that anticoagulation would be started 4 weeks prior to retrieval so that anticoagulation can reach therapeutic levels and/or dissolution of any clots present in the IVCF. The area between the black and red lines represents excess exposure to IVCF indwell time beyond need, effectively exposing the individual to complications of IVCFs for a longer period. Those who were treated with anticoagulation had marginally longer time to retrieval than those who did not initiate anticoagulation. For those who never had retrieval, there was a median of

278 (IQR 98-350) days of anticoagulation treatment during the one-year follow-up period.

*Healthcare utilization*

Healthcare utilization in the time period between placement and retrieval was compared for those with retrieval versus those without and between those with an early retrieval (≤90 days) and late retrieval (≥120 days). Total and VTE-related outpatient visits for those with retrieval were significantly higher than those without (Table 3.5). Meanwhile, inpatient and emergency visits were more similar between groups. Outpatient, inpatient, and emergency visits were more similar between early and late retrieval groups (Table 3.5). In adjusted analyses, having more than the median number of total outpatient or VTE-related outpatient visits was associated with over twice the odds of having a retrieval versus not (Table 3.6). Having ≥2 hospitalizations, VTE-related and overall, was also associated with higher odds of retrieval. For early compared to late retrieval, having ≥2 hospitalizations of any kind was significantly associated with more early retrieval compared to late retrieval.

## Discussion

The increased utilization of IVCFs corresponded with new technology allowing for retrieval of these devices once the indication for placement has abated. This has led

to nearly 10% of all VTE events being treated with IVCF placement for secondary prevention and increased IVCF utilization for prophylactic indications. Safety studies and the one randomized trial of retrievable IVCFs have shown these devices to be generally safe with retrieval being completed within a short period after implantation. In PREPIC2, the only randomized trial for rIVCFs, the retrieval rate was >90% with a dedicated 3-month follow-up visit.[10] However, in real-world practice, estimates of the retrieval rates range much lower with an average of about one-third of all IVCFs eventually being retrieved.[28]

Eventual retrieval of IVCFs improves the safety profile of these devices as the incidence for complications generally increases with increasing indwell times. Patients with IVCFs are at risk for complications including IVC thrombosis, device fracture, device migration, and DVT – risks persisting as long as the IVCF remains in place. One study by Morales *et al*. evaluated the net clinical benefit of IVCFs taking into account the known reduction in the risk of PE along with the increased incidence of complications. This study found that there is an optimal net clinical benefit if an IVCF is retrieved within 29-54 days after placement in prophylactic indications. This estimate remained in favor of IVCF up to 180 days post-implantation, but data regarding complication rates beyond this time period are scarce, and does not address the net clinical benefit in patients with active VTE. This article was also referenced in a U.S. Food and Drug Administration (FDA) safety communication, which responded to multiple reports of complications with IVCFs and increasing publicity through litigation and media. The safety communication

also detailed ongoing safety data collection through clinical studies and post-marketing surveillance.

The current analysis is consistent with other reports regarding IVCF retrieval, with an overall retrieval of nearly 20% within 1-year. Considering that approximately 10% of all IVCFs placed are permanent devices, the effective retrieval rate was nearer 22%. Encouragingly, the retrieval rate has increased over time, from roughly every one out of every seven filters being retrieved in 2010 up to one out of every four retrieved in 2014 (extrapolated due to limited follow-up in 2014). This effect is explained by the increased attention IVCFs received over this time period including FDA safety alerts, as well as guideline updates which called for more conservative use of IVCFs. For those who did have their IVCF retrieved in our study, time to retrieval was within an acceptable range with mean and median times of 93 and 71 days post-implantation. However, retrieval was poorly correlated with anticoagulation initiation – an indicator that the IVCF is no longer indicated in that patient and should be removed as soon as possible.

Several patient-related factors were also associated with retrieval including demographic and clinical characteristics. Most notably, increasing age of the patient was associated with lower retrieval, likely contributed to perceived ongoing risk of PE or a desire to not treat older individuals with anticoagulation. Region of residence was also strongly associated with retrieval, which may indicate regional practice differences as well as differences in patient demography. Patients living in

an urban setting were more likely to have their filter retrieved as well, suggesting that patients being referred to a distant medical center for IVCF placement may have limited follow-up for retrieval. Among patient comorbidities, those considered pro-thrombotic (cancer, stroke, hyperlipidemia, MI) and related to bleeding (liver disease) were associated with lower retrieval. These disease states are intuitively associated with lower retrieval in that they reference underlying diseases which have high clot risk or high bleed risk and are more permanent than other transient contraindications to anticoagulation (e.g. surgery or trauma).

Other studies investigating factors associated with retrieval rates have focused on poor patient follow-up as the primary reason IVCFs are not removed. [40,75,76] However, patient follow-up in itself can be a multi-faceted factor associated with both institutional and patient related characteristics. To investigate this further in our data, we matched those who had retrieval to those who did not and assessed their healthcare utilization during follow-up, assuming that utilization of the healthcare system is a surrogate for patient follow-up. We observed a significant, but likely meaningless, difference in the number of outpatient visits overall and VTE-related visits for those without retrieval. While this may indicate poorer patient follow-up in the non-retrieval, the mean number of outpatient visits was 11.8 in the non-retrieval group, with 75% of this group having at least 1 outpatient visit. In comparing those with an early retrieval versus a late retrieval, we found that there were not any differences in the number of follow-up visits between these groups. Thus, opportunities exist to follow-up with patients regarding their IVCF, although it

remains alarming that a quarter of patients have no follow-up recorded after placement of an IVCF. Patient follow-up is generally left to the referring or primary physician, with some studies showing improved retrieval if the responsibility of follow-up is placed on the implanting physician instead. [40-42,75,76] Thus, it is likely not a question of the amount of follow-up, but more *who* is following up with the patient. This is supported further by the observation that patients who are hospitalized with new VTE events are more likely to have retrieval, possibly due to more specialists involved with their care (e.g. hematologists, etc.).

While there is inherent concern for patient safety associated with these low retrieval rates, clinical practices are also financially incentivized to increase retrieval of IVCFs. A study by d'Othée *et al.* showed that due to the increased cost between retrievable and permanent devices, retrievable devices are only cost-effective in interventional radiology clinics if at least 40% are eventually retrieved, driven by separate billable procedure codes for implantation and retrieval. [77] Even without the cost differential between permanent and retrievable devices, it is inherent that clinic revenue will be increased with improved patient follow-up, management, and retrieval. At least one study at a single institution evaluated the financial feasibility of implementing a quality improvement initiative within their clinical practice. [78] They had a staggered intervention and compared baseline retrieval rates to those achieved by issuing letters to patients and then to those achieved with prospective follow-up of patients. Overall, their retrieval rates increased from 8% to 40% with mailed letters and up to 52% with prospective

follow-up. Moreover, the interventions increased the revenue to the clinic by over $1,000 per IVCF placed via increased billing for retrieval and follow-up procedures. Thus, although improving IVCF retrieval requires a paradigm shift in patient management, retrieval will improve patient outcomes and provides financial incentive to the clinic. Further, this study demonstrates that even a low cost intervention such as mailing letters can have a large impact on retrieval rates, potentially utilizing few resources compared to the marginal improvement observed with more intensive follow-up.

*Limitations*

This study has limitations inherent to all studies utilizing administrative claims data.[79,80] Most notably, detailed clinical data are not available, including laboratory data, tumor staging, etc. which may have impacted the study results. Further, detailed information on the hospital or physician by whom the patient received care is not available. Wide variation in the utilization of IVCFs has been shown in prior studies and the general practice environment and physician practice patterns are likely to vary.[37,70] Procedural codes were utilized to identify IVCF placement; however, these codes are not specific to permanent or retrievable devices. As of 2006, retrievable devices made up about 85% of the IVCF market, which likely increased to over 90% since then.[22,25,81] Therefore, the retrieval estimates presented here are conservative. While we only followed patient up to one-year, there was a strong plateauing of the retrieval rate. With maximal follow-up, overall retrieval would have only reached roughly 25% compared to the 20% observed.

## Conclusion

In this national study of IVCF retrieval, less than one out of every four filters was retrieved within one-year. Retrieval rates differ based on patient characteristics but increased over the study time period (2010-2014). Retrieval of IVCFs once clinically indicated is required to optimize the net clinical benefit by removing the risk of complications associated with these devices.

**Table 3.1: Demographic and clinical characteristics of patients receiving vena cava filters by indication**

| | All | | Pulmonary Embolism | | Deep Vein Thrombosis | | No PE/DVT | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| | 54,766 | 100.0% | 20,202 | 36.9% | 24,060 | 43.9% | 10,504 | 19.2% |
| **Age Group** | | | | | | | | |
| **Mean (SD)** | 65 (16) | | 64 (15) | | 69 (16) | | 60 (17) | |
| **18-34** | 2,196 | 4.0% | 728 | 3.6% | 610 | 2.5% | 858 | 8.2% |
| **35-44** | 3,551 | 6.5% | 1,347 | 6.7% | 1,183 | 4.9% | 1,021 | 9.7% |
| **45-54** | 7,888 | 14.4% | 3,337 | 16.5% | 2,757 | 11.5% | 1,794 | 17.1% |
| **55-64** | 13,076 | 23.9% | 5,530 | 27.4% | 4,881 | 20.3% | 2,665 | 25.4% |
| **65-74** | 9,422 | 17.2% | 3,452 | 17.1% | 4,334 | 18.0% | 1,636 | 15.6% |
| **75 and older** | 17,846 | 32.6% | 5,492 | 27.2% | 10,038 | 41.7% | 2,316 | 22.0% |
| **Gender of Patient** | | | | | | | | |
| **Male** | 26,839 | 49.0% | 10,217 | 50.6% | 11,542 | 48.0% | 5,080 | 48.4% |
| **Female** | 27,927 | 51.0% | 9,985 | 49.4% | 12,518 | 52.0% | 5,424 | 51.6% |
| **Region** | | | | | | | | |
| **Northeast** | 11,526 | 21.0% | 4,154 | 20.6% | 5,191 | 21.6% | 2,181 | 20.8% |
| **North Central** | 15,678 | 28.6% | 5,752 | 28.5% | 7,142 | 29.7% | 2,784 | 26.5% |
| **South** | 18,448 | 33.7% | 6,666 | 33.0% | 7,882 | 32.8% | 3,900 | 37.1% |
| **West** | 7,891 | 14.4% | 3,158 | 15.6% | 3,361 | 14.0% | 1,372 | 13.1% |
| **Unknown** | 1,223 | 2.2% | 472 | 2.3% | 484 | 2.0% | 267 | 2.5% |
| **Residence** | | | | | | | | |
| **Rural** | 8,496 | 15.5% | 3,119 | 15.4% | 3,381 | 14.1% | 1,996 | 19.0% |
| **Urban** | 46,270 | 84.5% | 17,083 | 84.6% | 20,679 | 85.9% | 8,508 | 81.0% |
| **Concurrent conditions during hospitalization** | | | | | | | | |
| **Bleed** | 5,004 | 9.1% | 1,418 | 7.0% | 2,779 | 11.6% | 807 | 7.7% |
| **Unstable condition** | 870 | 1.6% | 243 | 1.2% | 464 | 1.9% | 163 | 1.6% |
| **Sepsis** | 2,351 | 4.3% | 619 | 3.1% | 1,360 | 5.7% | 372 | 3.5% |

**Table 3.1: Demographic and clinical characteristics of patients receiving vena cava filters by indication**

| | All | | Pulmonary Embolism | | Deep Vein Thrombosis | | No PE/DVT | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Infection** | 9,202 | 16.8% | 3,105 | 15.4% | 4,680 | 19.5% | 1,417 | 13.5% |
| **Anemia** | 10,195 | 18.6% | 3,193 | 15.8% | 5,433 | 22.6% | 1,569 | 14.9% |
| **Trauma** | 5,777 | 10.5% | 1,600 | 7.9% | 3,027 | 12.6% | 1,150 | 10.9% |
| **Thrombolytic therapy** | 841 | 1.5% | 452 | 2.2% | 316 | 1.3% | 73 | 0.7% |
| **Embolectomy procedure** | 367 | 0.7% | 176 | 0.9% | 149 | 0.6% | 42 | 0.4% |
| **Major surgery** | 13,371 | 24.4% | 5,249 | 26.0% | 5,836 | 24.3% | 2,286 | 21.8% |
| **Pregnant** | 441 | 0.8% | 148 | 0.7% | 221 | 0.9% | 72 | 0.7% |
| **Died during hospitalization** | 1,628 | 3.0% | 720 | 3.6% | 461 | 1.9% | 447 | 4.3% |
| **Comorbid conditions during pre-index look back** | | | | | | | | |
| **CCI score, mean (SD)** | 3.1 (3.3) | | 2.9 (3.3) | | 3.5 (3.4) | | 2.9 (3.3) | |
| **History of VTE** | 4,864 | 8.9% | 1,522 | 7.5% | 2,149 | 8.9% | 1,193 | 11.4% |
| **History of bleeding** | 8,483 | 15.5% | 2,587 | 12.8% | 4,577 | 19.0% | 1,319 | 12.6% |
| **MI** | 3,254 | 5.9% | 1,122 | 5.6% | 1,623 | 6.7% | 509 | 4.8% |
| **CHF** | 8,464 | 15.5% | 2,620 | 13.0% | 4,514 | 18.8% | 1,330 | 12.7% |
| **PVD** | 7,450 | 13.6% | 2,147 | 10.6% | 4,030 | 16.7% | 1,273 | 12.1% |
| **Dementia** | 2,366 | 4.3% | 621 | 3.1% | 1,518 | 6.3% | 227 | 2.2% |
| **COPD** | 12,925 | 23.6% | 4,872 | 24.1% | 5,735 | 23.8% | 2,318 | 22.1% |
| **Rheumatism** | 2,286 | 4.2% | 801 | 4.0% | 1,087 | 4.5% | 398 | 3.8% |
| **PUD** | 1,593 | 2.9% | 503 | 2.5% | 829 | 3.4% | 261 | 2.5% |
| **Mild liver disease** | 4,344 | 7.9% | 1,586 | 7.9% | 1,958 | 8.1% | 800 | 7.6% |

**Table 3.1: Demographic and clinical characteristics of patients receiving vena cava filters by indication**

| | All | | Pulmonary Embolism | | Deep Vein Thrombosis | | No PE/DVT | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Severe liver disease** | 549 | 1.0% | 135 | 0.7% | 315 | 1.3% | 99 | 0.9% |
| **Diabetes** | 13,623 | 24.9% | 4,483 | 22.2% | 6,322 | 26.3% | 2,818 | 26.8% |
| **Diabetes w/ complications** | 3,663 | 6.7% | 1,040 | 5.1% | 1,853 | 7.7% | 770 | 7.3% |
| **Paralysis** | 2,244 | 4.1% | 672 | 3.3% | 1,228 | 5.1% | 344 | 3.3% |
| **Renal disease** | 6,684 | 12.2% | 1,713 | 8.5% | 3,836 | 15.9% | 1,135 | 10.8% |
| **Cancer** | 16,672 | 30.4% | 6,251 | 30.9% | 7,856 | 32.7% | 2,565 | 24.4% |
| **Metastatic cancer** | 7,534 | 13.8% | 3,013 | 14.9% | 3,433 | 14.3% | 1,088 | 10.4% |
| **Stroke** | 9,744 | 17.8% | 2,957 | 14.6% | 5,240 | 21.8% | 1,547 | 14.7% |
| **Hypertension** | 30,918 | 56.5% | 10,719 | 53.1% | 14,541 | 60.4% | 5,658 | 53.9% |
| **CHD** | 11,125 | 20.3% | 3,604 | 17.8% | 5,597 | 23.3% | 1,924 | 18.3% |
| **Hyperlipidemia** | 18,195 | 33.2% | 6,676 | 33.0% | 8,047 | 33.4% | 3,472 | 33.1% |
| **Insurance Source** | | | | | | | | |
| **Commercial** | 26,350 | 48.1% | 10,821 | 53.6% | 9,281 | 38.6% | 6,248 | 59.5% |
| **Medicare** | 28,416 | 51.9% | 9,381 | 46.4% | 14,779 | 61.4% | 4,256 | 40.5% |
| **Insurance Details** | | | | | | | | |
| **Assigned Care Provider** | 7,586 | 13.9% | 2,910 | 14.4% | 3,116 | 13.0% | 1,560 | 14.9% |
| **Capitated Payment** | 4,718 | 8.6% | 1,821 | 9.0% | 1,969 | 8.2% | 928 | 8.8% |
| **Year of IVC filter placement** | | | | | | | | |
| **2010** | 11,784 | 21.5% | 4,250 | 21.0% | 5,239 | 21.8% | 2,295 | 21.8% |
| **2011** | 12,750 | 23.3% | 4,565 | 22.6% | 5,672 | 23.6% | 2,513 | 23.9% |

**Table 3.1: Demographic and clinical characteristics of patients receiving vena cava filters by indication**

| | All | | Pulmonary Embolism | | Deep Vein Thrombosis | | No PE/DVT | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **2012** | 12,210 | 22.3% | 4,369 | 21.6% | 5,393 | 22.4% | 2,448 | 23.3% |
| **2013** | 9,395 | 17.2% | 3,596 | 17.8% | 4,062 | 16.9% | 1,737 | 16.5% |
| **2014** | 8,627 | 15.8% | 3,422 | 16.9% | 3,694 | 15.4% | 1,511 | 14.4% |

Abbreviations: venous thromboembolism (VTE); myocardial infarction (MI); congestive heart failure (CHF); peripheral vascular disease (PVD); chronic pulmonary obstructive disease (COPD); peptic ulcer disease (PUD); coronary heart disease (CHD); inferior vena cava (IVC)

**Table 3.2: Outcomes of patients receiving vena cava filters at one-year of follow-up**

| **Outcome** | **Overall** | | **PE** | | **DVT** | | **No VTE** | |
|---|---|---|---|---|---|---|---|---|
| IVC filter retrieval | 7,619 | 14.3% | 2,884 | 14.8% | 2,686 | 11.4% | 2,049 | 20.4% |
| Died | 4,228 | 8.0% | 1,627 | 8.4% | 1,950 | 8.3% | 651 | 6.5% |
| Censored | 41,291 | 77.7% | 14,971 | 76.8% | 18,963 | 80.4% | 7,357 | 73.2% |
| Follow-up time | | | | | | | | |
| Mean (SD) | 202 (144) | | 202 (143) | | 202 (145) | | 200 (144) | |
| Median (IQR) | 186 (56-365) | | 188 (58-365) | | 187 (54-365) | | 176 (56-365) | |
| Time to retrieval | | | | | | | | |
| Mean (SD) | 93 (78) | | 101 (81) | | 91 (79) | | 83 (73) | |
| Median (IQR) | 71 (35-130) | | 81 (38-143) | | 68 (33-132) | | 61 (32-113) | |
| Time to death | | | | | | | | |
| Mean (SD) | 96 (91) | | 94 (91) | | 97 (91) | | 100 (90) | |
| Median (IQR) | 63 (26-142) | | 58 (24-140) | | 66 (26-144) | | 67 (32-141) | |

Abbreviations: pulmonary embolism (PE); deep vein thrombosis (DVT); venous thromboembolism (VTE); standard deviation (SD); interquartile range (IQR)

**Figure 3.1: Cumulative incidence of vena cava filter retrieval by indication over one-year of follow-up accounting for death as a competing risk**

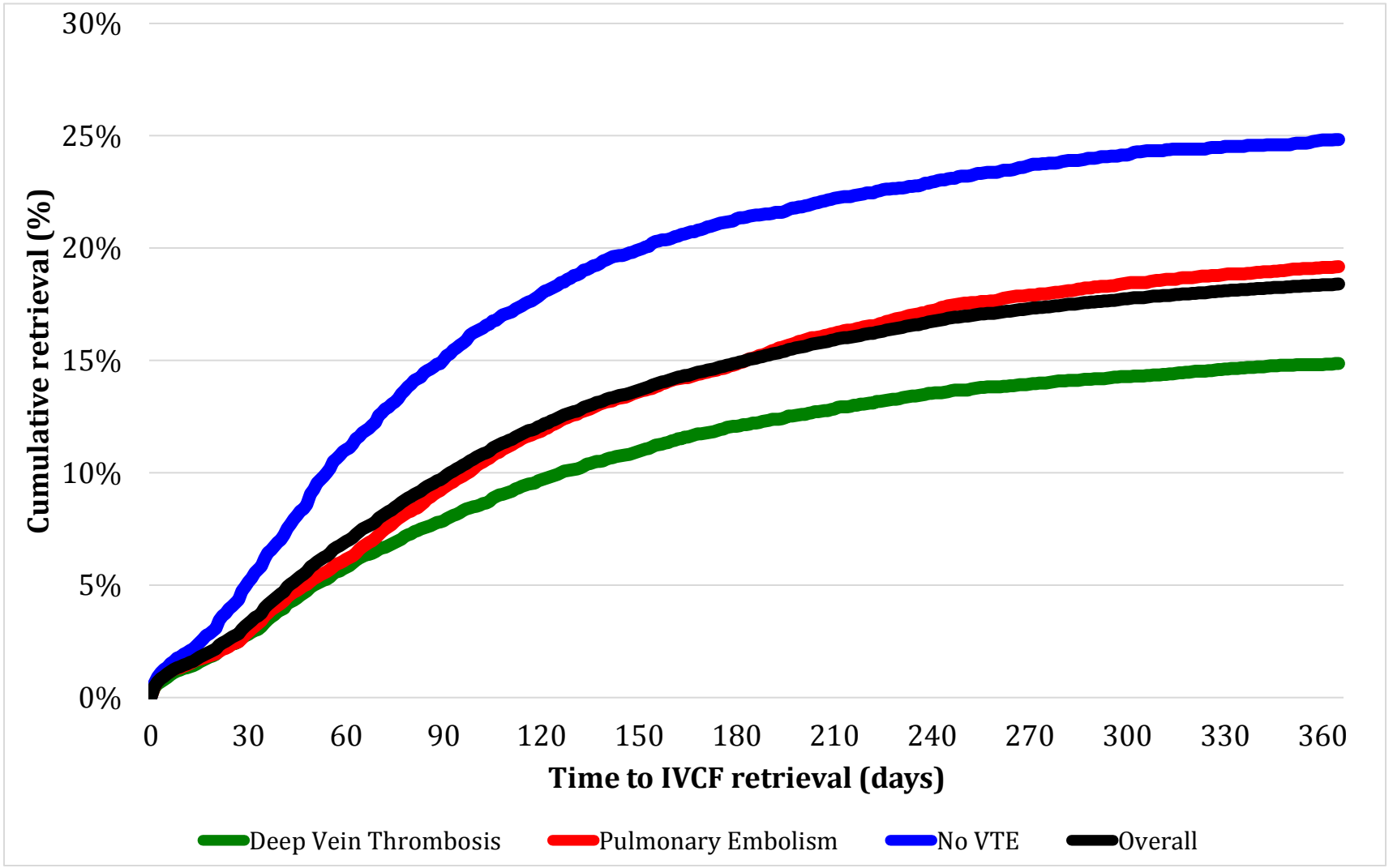


**Table 3.3: Cumulative incidence of vena cava filter retrieval at time intervals by key demographic and clinical factors**

| | | 30 days | 60 days | 90 days | 180 Days | 365 days |
|---|---|---|---|---|---|---|
| **Overall** | | 3.3% (3.1%-3.5%) | 6.9% (6.7%-7.2%) | 9.8% (9.5%-10.1%) | 14.9% (14.6%-15.2%) | 18.4% (18.0%-18.8%) |
| **Index VTE** | **No VTE** | 5.2% (4.7%-5.6%) | 11.0% (10.4%-11.7%) | 15.0% (14.3%-15.8%) | 21.3% (20.4%-22.2%) | 24.8% (23.9%-25.8%) |
| | **DVT** | 2.8% (2.6%-3.0%) | 5.8% (5.5%-6.1%) | 7.9% (7.5%-8.2%) | 12.1% (11.6%-12.6%) | 14.9% (14.3%-15.4%) |
| | **PE** | 2.9% (2.7%-3.1%) | 6.1% (5.8%-6.5%) | 9.3% (8.9%-9.8%) | 14.8% (14.3%-15.4%) | 19.2% (18.5%-19.8%) |
| **Year** | **2010** | 3.1% (2.8%-3.5%) | 6.0% (5.6%-6.5%) | 8.0% (7.5%-8.6%) | 11.3% (10.7%-11.9%) | 14.0% (13.3%-14.7%) |
| | **2011** | 3.0% (2.7%-3.3%) | 6.3% (5.9%-6.8%) | 8.8% (8.3%-9.3%) | 13.2% (12.6%-13.9%) | 16.1% (15.4%-16.8%) |
| | **2012** | 3.4% (3.1%-3.8%) | 7.5% (7.0%-8.0%) | 9.9% (9.4%-10.5%) | 15.6% (14.9%-16.3%) | 19.2% (18.4%-20.0%) |
| | **2013** | 3.3% (3.0%-3.7%) | 7.5% (7.0%-8.1%) | 11.2% (10.5%-11.9%) | 17.1% (16.3%-18.0%) | 21.6% (20.7%-22.6%) |
| | **2014** | 3.7% (3.3%-4.2%) | 7.7% (7.1%-8.3%) | 12.4% (11.6%-13.3%) | 20.5% (19.4%-21.6%) | 38.2% (19.4%-57.0%) |
| **Age** | **18-34** | 6.8% (5.8%-7.9%) | 15.2% (13.7%-16.8%) | 22.8% (21.0%-24.7%) | 34.9% (32.7%-37.1%) | 42.8% (40.4%-45.2%) |
| | **35-44** | 6.1% (5.3%-6.9%) | 13.9% (12.7%-15.1%) | 18.9% (17.6%-20.3%) | 28.4% (26.8%-30.0%) | 35.5% (33.7%-37.2%) |
| | **45-54** | 4.9% (4.5%-5.5%) | 11.4% (10.7%-12.2%) | 15.9% (15.0%-16.8%) | 23.7% (22.6%-24.7%) | 29.3% (28.1%-30.4%) |
| | **55-64** | 3.9% (3.5%-4.2%) | 8.0% (7.5%-8.5%) | 11.5% (10.9%-12.1%) | 17.8% (17.0%-18.5%) | 21.8% (21.0%-22.7%) |

**Table 3.3: Cumulative incidence of vena cava filter retrieval at time intervals by key demographic and clinical factors**

| | | 30 days | 60 days | 90 days | 180 Days | 365 days |
|---|---|---|---|---|---|---|
| | **65-74** | 2.7% (2.4%-3.1%) | 5.3% (4.8%-5.8%) | 7.4% (6.9%-8.0%) | 11.4% (10.7%-12.1%) | 14.1% (13.3%-15.0%) |
| | **75 and older** | 1.4% (1.2%-1.6%) | 2.4% (2.1%-2.6%) | 3.1% (2.8%-3.3%) | 4.5% (4.1%-4.8%) | 5.4% (5.0%-5.8%) |
| **Cancer** | **Yes** | 2.6% (2.3%-2.8%) | 4.5% (4.2%-4.9%) | 6.3% (5.9%-6.7%) | 9.1% (8.6%-9.7%) | 11.7% (11.1%-12.4%) |
| | **No** | 3.6% (3.4%-3.8%) | 7.9% (7.6%-8.2%) | 11.1% (10.8%-11.5%) | 17.0% (16.6%-17.5%) | 20.8% (20.4%-21.3%) |
| **Insurance source** | **Commercial** | 4.8% (4.5%-5.0%) | 10.5% (10.1%-10.9%) | 14.9% (14.5%-15.4%) | 22.6% (22.1%-23.2%) | 28.0% (27.4%-28.6%) |
| | **Medicare** | 1.9% (1.7%-2.0%) | 3.4% (3.2%-3.6%) | 4.6% (4.3%-4.9%) | 7.0% (6.6%-7.3%) | 8.6% (8.2%-8.9%) |

Abbreviations: venous thromboembolism (VTE); deep vein thrombosis (DVT); pulmonary embolism (PE)

**Figure 3.2: Plot of times to anticoagulation and vena cava filter retrieval.** Black line represents the fit of the data, red line represents the preferred line if anticoagulation was initiated 4 weeks prior to retrieval. Time is based on follow-up after the discharge date from the hospitalization where the IVCF was placed.

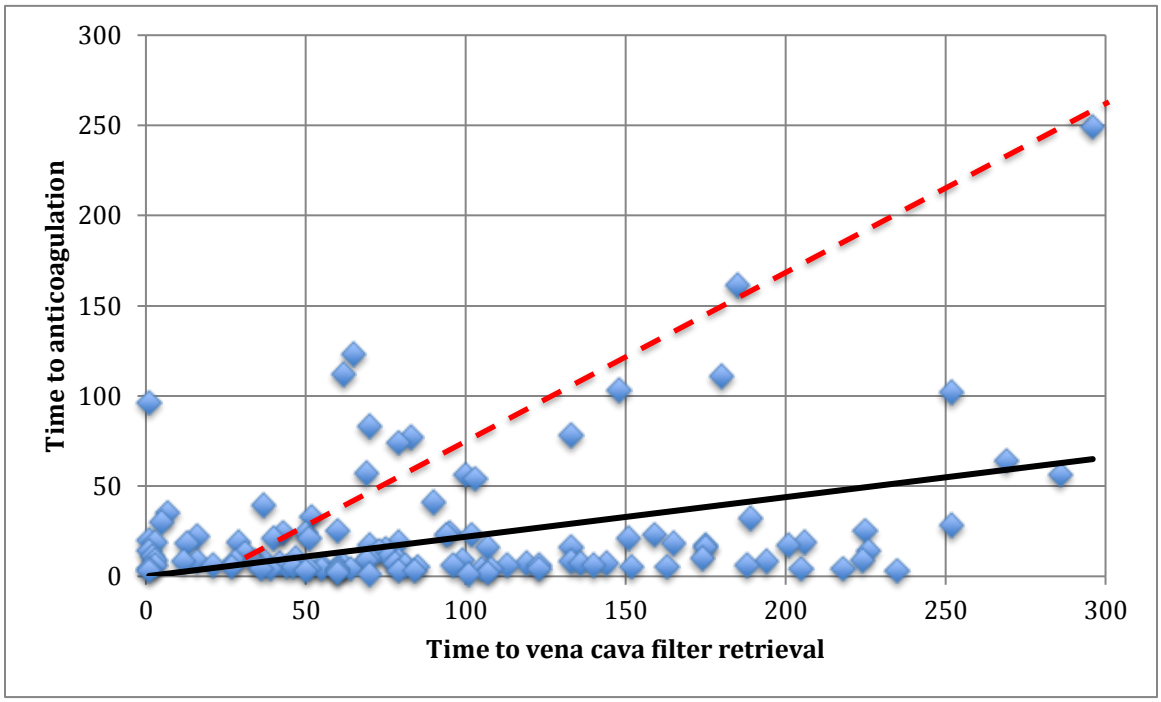


**Table 3.4: Regression results showing patient factors associated with 90-day (early) retrieval and 1-year retrieval**

| | *90-day retrieval* | | | *1-year retrieval* | | |
|---|---|---|---|---|---|---|
| | ***HR*** | ***95% CI*** | | ***HR*** | ***95% CI*** | |
| **Age** | | | | | | |
| **18-34** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **35-44** | 0.97 | 0.94 | 1.00 | 0.88 | 0.80 | 0.97 |
| **45-54** | 0.95 | 0.92 | 0.98 | 0.79 | 0.72 | 0.86 |
| **55-64** | 0.91 | 0.88 | 0.93 | 0.62 | 0.57 | 0.68 |
| **65-74** | 0.87 | 0.84 | 0.89 | 0.41 | 0.37 | 0.45 |
| **75 and older** | 0.82 | 0.80 | 0.84 | 0.17 | 0.15 | 0.19 |
| **Gender** | | | | | | |
| **Male** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **Female** | 1.01 | 1.01 | 1.02 | 1.04 | 0.99 | 1.09 |
| **Region** | | | | | | |
| **Northeast** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **North Central** | 1.03 | 1.02 | 1.04 | 1.29 | 1.20 | 1.38 |
| **South** | 0.99 | 0.98 | 1.00 | 0.89 | 0.83 | 0.95 |
| **West** | 1.10 | 1.09 | 1.12 | 1.89 | 1.76 | 2.04 |
| **Unknown** | 1.01 | 0.98 | 1.04 | 1.24 | 1.05 | 1.46 |
| **Residence** | | | | | | |
| **Rural** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **Urban** | 1.01 | 1.00 | 1.02 | 1.13 | 1.06 | 1.21 |
| **Index VTE** | | | | | | |
| **DVT only** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **No VTE** | 1.05 | 1.03 | 1.06 | 1.24 | 1.17 | 1.32 |
| **PE** | 0.99 | 0.98 | 1.00 | 0.99 | 0.93 | 1.04 |
| **Concurrent conditions during hospitalization** | | | | | | |
| **Bleed** | 1.00 | 0.99 | 1.02 | 1.10 | 0.93 | 1.29 |

**Table 3.4: Regression results showing patient factors associated with 90-day (early) retrieval and 1-year retrieval**

| | *90-day retrieval* | | | *1-year retrieval* | | |
|---|---|---|---|---|---|---|
| | ***HR*** | ***95% CI*** | | ***HR*** | ***95% CI*** | |
| **Unstable condition** | 0.98 | 0.96 | 1.00 | 0.80 | 0.60 | 1.06 |
| **Sepsis** | 1.00 | 0.98 | 1.01 | 0.92 | 0.76 | 1.12 |
| **Infection** | 0.98 | 0.97 | 0.99 | 0.84 | 0.76 | 0.91 |
| **Anemia** | 0.99 | 0.98 | 0.99 | 0.91 | 0.84 | 0.98 |
| **Trauma** | 0.99 | 0.98 | 1.00 | 1.00 | 0.92 | 1.09 |
| **Thrombolytic therapy** | 1.06 | 1.02 | 1.09 | 1.29 | 1.11 | 1.49 |
| **Embolectomy procedure** | 1.00 | 0.96 | 1.04 | 0.89 | 0.68 | 1.17 |
| **Major surgery** | 0.98 | 0.97 | 0.99 | 0.92 | 0.87 | 0.97 |
| **Pregnant** | 1.05 | 0.99 | 1.11 | 1.36 | 1.15 | 1.60 |
| **Comorbid conditions during pre-index look back** | | | | | | |
| **CCI score (per 1 unit)** | 1.00 | 0.99 | 1.01 | 0.97 | 0.90 | 1.05 |
| **History of VTE** | 1.03 | 1.02 | 1.04 | 1.17 | 1.08 | 1.26 |
| **History of bleeding** | 0.98 | 0.97 | 0.99 | 0.77 | 0.67 | 0.87 |
| **Myocardial infarction** | 0.99 | 0.98 | 1.00 | 0.82 | 0.71 | 0.96 |
| **Heart failure** | 0.98 | 0.97 | 0.99 | 0.67 | 0.60 | 0.74 |
| **Peripheral vascular disease** | 0.99 | 0.98 | 1.00 | 0.85 | 0.77 | 0.94 |
| **Dementia** | 0.97 | 0.96 | 0.98 | 0.31 | 0.22 | 0.43 |
| **COPD** | 0.99 | 0.98 | 1.00 | 0.88 | 0.83 | 0.94 |
| **Rheumatism** | 1.00 | 0.98 | 1.01 | 0.96 | 0.84 | 1.08 |
| **Peptic ulcer disease** | 1.02 | 1.00 | 1.04 | 1.16 | 0.95 | 1.41 |
| **Mild liver disease** | 1.00 | 0.98 | 1.01 | 1.00 | 0.91 | 1.11 |
| **Severe liver disease** | 0.99 | 0.98 | 1.00 | 0.86 | 0.81 | 0.92 |
| **Diabetes** | 0.99 | 0.98 | 1.00 | 0.96 | 0.85 | 1.09 |
| **Diabetes w/ complications** | 0.98 | 0.97 | 1.00 | 0.76 | 0.65 | 0.89 |
| **Paralysis** | 0.98 | 0.97 | 0.99 | 0.81 | 0.73 | 0.90 |

**Table 3.4: Regression results showing patient factors associated with 90-day (early) retrieval and 1-year retrieval**

| | *90-day retrieval* | | | *1-year retrieval* | | |
|---|---|---|---|---|---|---|
| | ***HR*** | ***95% CI*** | | ***HR*** | ***95% CI*** | |
| **Renal disease** | 0.99 | 0.98 | 1.00 | 0.94 | 0.87 | 1.00 |
| **Cancer** | 0.91 | 0.89 | 0.94 | 0.28 | 0.17 | 0.46 |
| **Metastatic cancer** | 0.92 | 0.90 | 0.93 | 0.43 | 0.38 | 0.49 |
| **Stroke** | 0.98 | 0.98 | 0.99 | 0.80 | 0.73 | 0.88 |
| **Hypertension** | 1.00 | 0.99 | 1.00 | 0.95 | 0.90 | 0.99 |
| **Coronary heart disease** | 1.00 | 0.99 | 1.00 | 0.87 | 0.80 | 0.94 |
| **Hyperlipidemia** | 1.02 | 1.01 | 1.03 | 1.23 | 1.17 | 1.30 |
| **Insurance Details** | | | | | | |
| **Assigned Care Provider** | 1.00 | 0.99 | 1.02 | 1.03 | 0.94 | 1.12 |
| **Capitated Payment** | 0.99 | 0.97 | 1.00 | 0.84 | 0.75 | 0.94 |
| **Year filter placed** | | | | | | |
| **2010** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **2011** | 1.01 | 1.00 | 1.02 | 1.19 | 1.11 | 1.28 |
| **2012** | 1.03 | 1.02 | 1.04 | 1.41 | 1.32 | 1.52 |
| **2013** | 1.04 | 1.03 | 1.05 | 1.63 | 1.51 | 1.75 |
| **2014** | 1.05 | 1.04 | 1.07 | 1.90 | 1.76 | 2.06 |

Abbreviations: venous thromboembolism (VTE); deep vein thrombosis (DVT); pulmonary embolism (PE); chronic obstructive pulmonary disease (COPD)

**Table 3.5: Comparison of utilization for matched patients based on retrieval status**

| | | No retrieval | Retrieval | | Late retrieval | Early retrieval |
|---|---|---|---|---|---|---|
| | N | 11,122 | 5,561 | | 1,297 | 1,297 |
| Outpatient visits | Mean (SD) | 11.8 (15.8) | 14.3 (16) | | 14.8 (10.6) | 15.4 (10.8) |
| | Median (IQR) | 6 (1-16) | 9 (2-20) | | 14 (7-20) | 14 (8-21) |
| Outpatient VTE visits | Mean (SD) | 6.4 (6.5) | 6.9 (6.4) | | 6.9 (5.2) | 7.2 (5.1) |
| | Median (IQR) | 4 (2-8) | 5 (2-10) | | 6 (2-10) | 6 (3-10) |
| Hospitalizations | Mean (SD) | 1.8 (1) | 1.8 (0.8) | | 1.8 (0.7) | 1.7 (0.8) |
| | Median (IQR) | 2 (1-2) | 2 (1-2) | | 2 (1-2) | 1 (1-2) |
| PE Hospitalizations | Mean (SD) | 1.3 (0.7) | 1.3 (0.5) | | 1.5 (0.7) | 1.2 (0.4) |
| | Median (IQR) | 1 (1-1) | 1 (1-2) | | 1 (1-2) | 1 (1-1) |
| DVT hospitalizations | Mean (SD) | 1.2 (0.5) | 1.2 (0.5) | | 1.3 (0.6) | 1.2 (0.4) |
| | Median (IQR) | 1 (1-1) | 1 (1-1) | | 1 (1-2) | 1 (1-1) |
| Emergency visits | Mean (SD) | 2 (1.9) | 1.7 (1.4) | | 1.7 (1.5) | 1.7 (1.3) |
| | Median (IQR) | 1 (1-2) | 1 (1-2) | | 1 (1-2) | 1 (1-2) |
| PE Emergency visits | Mean (SD) | 1.2 (0.4) | 1.3 (0.6) | | 1.2 (0.5) | 1.3 (0.8) |
| | Median (IQR) | 1 (1-1) | 1 (1-1) | | 1 (1-1) | 1 (1-1) |
| DVT Emergency visits | Mean (SD) | 1.2 (0.6) | 1.2 (0.5) | | 1.2 (0.4) | 1.2 (0.9) |
| | Median (IQR) | 1 (1-1) | 1 (1-1) | | 1 (1-1) | 1 (1-1) |

Abbreviations: pulmonary embolism (PE); deep vein thrombosis (DVT); venous thromboembolism (VTE); standard deviation (SD); interquartile range (IQR)

**Table 3.6: Adjusted analysis comparing the association of utilization with retrieval status**

| | Retrieval vs. no retrieval | | | Early (≤90 days) vs. Late (≥120 days) retrieval | | |
|---|---|---|---|---|---|---|
| | **Odds ratio** | **95% CL** | | **Odds ratio** | **95% CL** | |
| ≥ Median Outpatient visits (vs. <Median) | 2.32 | 2.05 | 2.62 | 0.87 | 0.73 | 1.04 |
| ≥ Median VTE outpatient visits (vs. <Median) | 2.18 | 1.98 | 2.39 | 1.10 | 0.90 | 1.33 |
| 1 hospitalization (vs. 0) | 1.08 | 0.97 | 1.20 | 0.96 | 0.75 | 1.22 |
| ≥2 hospitalizations (vs. 0) | 1.63 | 1.48 | 1.80 | 1.80 | 1.43 | 2.27 |
| 1 PE hospitalization (vs. 0) | 1.28 | 1.06 | 1.56 | 1.03 | 0.67 | 1.59 |
| ≥2 PE hospitalizations (vs. 0) | 1.70 | 1.25 | 2.31 | 5.37 | 2.33 | 12.37 |
| 1 DVT hospitalization (vs. 0) | 1.16 | 0.98 | 1.37 | 1.35 | 0.94 | 1.95 |
| ≥2 DVT hospitalizations (vs. 0) | 1.42 | 1.02 | 1.99 | 2.62 | 1.30 | 5.29 |
| 1 Emergency visit (vs. 0) | 0.95 | 0.85 | 1.06 | 0.81 | 0.64 | 1.02 |
| ≥2 Emergency visit (vs. 0) | 0.64 | 0.56 | 0.73 | 0.93 | 0.70 | 1.23 |
| 1 PE emergency visit (vs. 0) | 0.80 | 0.60 | 1.07 | 0.70 | 0.36 | 1.34 |
| ≥2 PE emergency visit (vs. 0) | 1.14 | 0.62 | 2.13 | 0.58 | 0.14 | 2.44 |
| 1 DVT emergency visit (vs. 0) | 0.66 | 0.53 | 0.84 | 0.84 | 0.51 | 1.39 |
| ≥2 DVT emergency visit (vs. 0) | 0.46 | 0.29 | 0.74 | 1.67 | 0.55 | 5.04 |

# CHAPTER 4: COMPETING RISKS ANALYSIS OF CANCER-ASSOCIATED RECURRENT THROMBOSIS, MAJOR BLEEDS, AND DEATH IN A GERIATRIC COHORT RECEIVING ANTICOAGULATION OR VENA CAVA FILTERS

This study details an outcomes study looking at the effectiveness of treatments, including vena cava filters, for cancer-associated VTE. It has been published in the *Journal of Health Economics and Outcomes Research*.

Citation: Joshua D. Brown, Kelley L. Ratermann, Jeffery C. Talbert, Val R. Adams. Competing Risks Analysis of Cancer-associated Recurrent Thrombosis, Major Bleeds, and Death in a Geriatric Cohort. *JHEOR* 2015;3(2):214-23

## Abstract

**Background:** Individuals with cancer are at an increased risk of venous thromboembolism (VTE). There is a continued increased of recurrent VTE after the initial event as well as increased bleed risk related to VTE treatment.

**Objectives:** This study sought to observe the incidence of recurrent VTE, major bleeding, and death in a geriatric oncology population during treatment for a cancer-associated VTE.

**Methods:** We utilized an insurance claims database of Medicare Advantage beneficiaries 65 and older. The index VTE was identified and individuals were followed up to 180 days to observe an outcome event. Treatment groups were classified among those receiving warfarin, low-molecular weight heparins (LMWH), vena cava (VC) filters with or without anticoagulation, or no treatment. Treatment groups were compared on baseline demographic and clinical characteristics and an inverse probability of treatment weight was used to balance these factors between the groups. A competing risks, time-to-event analysis was performed including treatment only models as well as adjusted models with additional covariates. Cause-specific hazards ratios (HR) and their 95% confidence intervals were reported.

**Results:** Treatment groups differed on baseline variables including age, comorbidities, and tumor sites. After balancing the treatment groups on baseline characteristics, those receiving LMWHs had no difference in recurrent VTE compared to warfarin but had less than half the risk of major bleeding (HR=0.48

[0.27-0.85]). Those receiving VC filters had increased risk of all outcome events relative to warfarin.

**Conclusions:** Patients over the age of 65 with cancer are at a high risk of experiencing recurrent VTE and major bleeding during treatment for a cancer-associated VTE. These results are consistent with United States guidelines which recommend LMWHs over warfarin for treatment and secondary prevention of VTE.

## Background

Compared to the general population, individuals with cancer are at 4 to 7 times the risk of developing a venous thromboembolism (VTE). [57,82-84] Malignancy induces a prothrombotic state which includes activation of the coagulation cascade and is further exacerbated by cancer treatment and surgery. [85] Additional risk factors for VTE in cancer include the site and stage of the tumor, older age, prior history of clots, and comorbidities. [86,87] Although at an already increased risk of death from cancer, VTE carries a substantial risk of mortality with clotting events accounting for up to 10% of all deaths in patients with cancer. [88-90] VTE events, including deep vein thrombosis (DVT) and pulmonary embolism (PE) account for significant lengths of stay and costs in this population with the mean hospital stay ranging from 11 days for DVT and up to 21 days for those with PE. [91]

In the United States (U.S.), prevention and treatment of VTE in patients with cancer is addressed in American Society of Clinical Oncology guidelines. [92] These guidelines recommend the use of low molecular weight heparins (LMWHs, dalteparin, enoxaparin, tinzaparin) for the initial and long term treatment of VTE for this population. Warfarin is recommended when LMWHs are contraindicated or limited in use because of cost or other factors including perceived intolerance. [93] In fact, LMWHs have been shown to outperform warfarin in randomized controlled trials and have further benefit in having weight based dosing, fewer drug and food interactions, little monitoring throughout treatment, and maintain positive patient

preference despite being an injectable.[88,94-97] However, real-world evidence shows that warfarin is used for a vast majority of cases.[98,99] In addition to anticoagulation therapy, vena cava (VC) filters are commonly utilized in the oncology patient population despite no survival benefit and excess risk compared to other treatment modalities.[100]

Individuals who have had a VTE remain at high risk of experiencing a recurrent VTE event and have high rates of bleeding.[91,101] Recurrent VTE has been reported as high as 21% and bleeding rates as high as 12.4% in cancer patients.[102] Risk factors related to recurrent VTE and adverse bleeding events include tumor site and histology, presence of metastases, age, and certain biomarker or laboratory findings as well as choice of anticoagulant therapy for acute treatment and long-term secondary prophylaxis.[103-106] To our knowledge, no studies have identified risk factors related to recurrent VTE, bleeding, and mortality related to geriatric patients experiencing a cancer-associated VTE and compared treatments on these outcomes. We sought to compare treatment selections on each of those three outcomes after an initial VTE event. Treatment will be observed for individuals treated with LMWHs, warfarin, VC filters, or who are untreated in a cohort of oncology patients in a large administrative claims database. Demographic and clinical variables associated with each of these three competing outcomes will also be explored.

## Materials and Methods

*Data source and cohort identification*

This retrospective cohort study used an extract from a large administrative claims database comprised of 1.4 million unique lives with Humana Medicare Advantage medical and pharmacy benefits from 2007 to 2009. The data included inpatient and outpatient medical encounters with procedural codes and diagnoses fields, filled prescription medication claims, and demographic and insurance coverage information linked at the individual level.

The data extract required that an individual have a diagnosis for a malignant neoplasm (104.xx-208.xx) and a DVT (451.xx, 453.xx) or a PE (415.1x) using ICD-9-CM codes for primary diagnosis fields. The earliest date of diagnosis with a DVT or PE was confirmed where at least one claim had a primary diagnosis of DVT or PE and a specific imaging study indicative of diagnostic procedures codes (Appendix).[107] Individuals were excluded if their initial VTE event occurred before their cancer diagnosis or if they were less than 65 years of age at cancer diagnosis. The remaining cohort was required to have at least 180 days of continuous medical and pharmacy coverage during the pre-index period. The 180-day pre-index period was used to assess clinical characteristics including comorbidities and cancer treatment patterns preceding the index event. Lastly, individuals receiving anticoagulant treatment during the 30 days preceding their index event were excluded to ensure

that temporality with diagnosis and treatment and to identify treatment naïve patients.

*Cohort characteristics*

Individual demographics and insurance coverage were determined during the pre-index period. Age was categorized 65-69, 70-74, and 75 or older. Race was categorized white, black, and other/unknown. Region was categorized by census regions including South, Midwest, West, and North. Insurance coverage was based on product type (fee-for-service, FFS; health maintenance organization, HMO; or preferred provider organization, PPO).

Tumor site was specified by ICD-9-CM codes including prostate, breast, lung, lymphoma, colon, kidney, pancreas, brain, liver, ovarian, and others. Claims data are limited so that tumor staging is not available. Metastases of the lymph nodes, respiratory, digestive, and other sites were identified using ICD-9-CM codes (195.xx-199.xx). Comorbidities were based on the Charlson Comorbidity Index using the ICD-9-CM coding algorithms by Quan *et al.* and recorded as a continuous weighted score and categorized by quartiles.[52] Other comorbidities and clinical characteristics were identified by ICD-9-CM codes available in Appendix 4A and were classified as binary variables.

Medications of interest were identified using Generic Product Identifier (GPI) codes or Healthcare Common Procedure Coding System (HCPCS) codes. Placement of VC

filters was identified by procedural codes in the medical claims. VTE treatment choice was determined within the 21 days preceding the index event and was recorded as the last outpatient anticoagulation used to allow for the possibility of bridge therapy or treatment changes. The timing of chemotherapy or radiation therapy was categorized based on its relative timing during the pre-index period to the clotting event as occurring within 30 days, between 31 and 90 days, 91-180 days, or unobserved during the pre-index period using a combination of procedural and medication codes within both the medical and pharmaceutical claims.

*Inverse probability of treatment weight*

A multinomial logistic regression model was estimated for treatment choice predicting the probability of each subject to receive warfarin, a LMWH, a VC filter, a VC filter and anticoagulation, or no treatment. All pre-index subject characteristics deemed by the clinical team to be potential predictors of treatment choice as well as related to the outcomes of interest were included. For each subject receiving a particular treatment, the inverse of the probability of receiving that treatment and the sample size within each treatment group was used to create a stabilized inverse probability of treatment weight (IPTW) for each subject. IPTW is a variant of propensity score methods that can be used to weight a regression analysis and has strengths in that no matching or stratification are required; thus, no reduction in sample size compared to other propensity score techniques.[108,109] Treatment group comparisons and the performance of the IPTW method were assessed using

standardized differences between the groups where a value of >0.10 is considered significant.

*Recurrent VTE, major bleeds, and mortality*

Subjects were followed from the index date for up to 180 days or until: 1) they experienced a recurrent VTE; 2) they experienced a major bleed; 3) they died; or 4) they were lost to follow-up due to end of the study period or end of eligibility. The earliest of these events was considered the event of interest. In the case where a death occurred on the same date as one of the other events, that outcome was noted as a death. Recurrent VTE were classified using the same coding algorithm as index event identification and required: a primary diagnosis of a DVT or PE with a specific diagnostic imaging study at least one day after the index event. This was done to help mitigate the chance of the initial event being recoded on a medical management claim as it is unlikely that additional imaging would be required for the index event. Major bleeding events were classified by an algorithm developed by Fang *et al.* considering a primary diagnosis of intracranial hemorrhage or a bleed requiring a hospitalization or emergency department visit. [110]

A competing risks, time-to-event analysis was performed taking into account the interdependence of the outcome events and producing a cumulative incidence function (CIF) for each outcome. This approach allowed for multivariable analyses with cause-specific coefficient estimates of the predictors for each outcome. Further, competing risks regression allows for the use of the IPTW detailed above so that

better direct comparisons could be made between treatment options. We computed the overall CIF for the cohort for each outcome as well as each outcome separately stratified by the treatment received. We fitted a competing risks regression model and included the baseline variables of interest that may still be predictive of outcome events even after IPTW weighting. Hazard ratios and 95% confidence intervals of these final variables are reported.

Data management and analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC) and the manuscript was drafted adhering to the STROBE Statement guidelines for reporting observational studies. The use of de-identified, Humana administrative claims database was approved by the University of Kentucky Institutional Review Board.

## Results

*Characteristics of treatment groups*

A total of 12,965 subjects met the inclusion and exclusion criteria. Nearly two-thirds of the index events were lower DVTs, 25.6% were PEs, and 8.7% were upper DVTs. Treatment groups, assessed in the acute treatment phase included: 30.4% treated with warfarin, 3.5% treated with LMWHs, 4.1% received a VC filter, 4.4% received a VC filter and anticoagulation, and 57.5% had no observed treatment. Distribution of the index event type was significant between treatment groups with most (82.3%) of the upper DVT index events untreated compared to 60% of lower DVTs and

42.6% of PEs (data not shown). Treatment groups differed significantly across multiple demographic characteristics including age categories, gender, race, region, plan type, and CCI score as well as comorbidities and tumor sites. Baseline demographic and clinical characteristic comparisons between the treatment groups are summarized in Table 4.1.

*IPTW weighting*

An IPTW was calculated for each individual based on the probability of receiving each treatment based on the covariates included in Table 4.1. The IPTW performed well when used to reweight the population to balance between the covariates. The standardized differences were compared and are shown in Appendix B relative to the warfarin group. Although the IPTW balanced well across all groups, some group-to-group comparisons included significant standardized differences (>0.10) showing the need for some further adjustment in outcome models.

*Outcome events*

During the 180-day follow-up period, there was a median follow-up of 87 days with a total of 3,323 person-years of follow-up time contributed by the cohort. Recurrent VTE had a median time-to-event of 4 days (IQR 1-21 days). Median time-to-event for death was 8 days (IQR 1-48 days) and for major bleeding the median was 14 days (IQR 2-57 days). There were a total of 1,661 recurrent VTEs (12.8% of total cohort; 500 recurrent VTEs per 1,000 person-years) consisting of 614 PEs. Major bleeds occurred in 6.1% (N=794) of the cohort (245 major bleeds per 1,000 person-

years) including 117 intracranial hemorrhages. Additionally, 3,690 individuals (28.5%) in the cohort died within the 180-day period (1,110 deaths per 1,000 person-years) while the remainder (N=6,820; 52.6%) of the cohort was censored or lost to follow-up before an event could be observed.

*Competing risks analysis*

Figure 4.1 graphs the CIF of each outcome by treatment group. The CIF curves differed significantly across treatment groups and overall group comparisons by Gray's method were significant at $p<0.001$. Three models were estimated including an unweighted, treatment-only model, a IPTW weighted treatment-only model, and an IPTW weighted model including covariates which were not balanced by the IPTW method or that were thought to potentially have residual impact on the outcomes of interest. Table 4.2 details the outcome-specific HRs and 95% CIs for each treatment group in the treatment-only models with warfarin as the referent treatment group. Some major differences are observed between the unweighted and weighted models further showing some bias in treatment group assignment. In the weighted analysis, those treated with LMWH had similar hazard of experiencing a recurrent VTE and over 50% reduced hazard of experiencing a major bleed (HR 0.48; 95% CI 0.27-0.85). Those receiving a VC filter or a VC filter with anticoagulation were much more likely than the warfarin group to have both recurrent VTE (80-94% increased hazard) and major bleeds (235-492% increased hazard). The untreated group had lower hazard of experiencing a recurrent VTE and no difference in the hazard of experiencing a major bleed. All treatment groups had higher hazards of death but

should be interpreted with caution as will be discussed in more detail in the Discussion section.

Further adjustment for the study covariates had marginal effects on the point estimates between the treatment groups. Table 4.3 includes the outcome-specific HRs and 95% CIs for the IPTW weighted model which included additional covariates other than treatment group. Those with an index PE event had an HR=1.83 (95% CI 1.64-2.03) for recurrent VTE compared to lower DVT index events. Individuals who had a history of prior bleeding events during the baseline period had over a 150% increased hazard of major bleed events as well as a 20% increase in recurrent VTE.

## Discussion

This study is the first study to our knowledge to assess the incidence of outcome events after an initial cancer-associated VTE in a geriatric oncology population. This population is of particular interest given the increased risk of treatment related complications as well as a high baseline risk of mortality from multiple causes.

Our findings are consistent with previous studies showing a high rate of recurrent VTE and major bleeding after an index VTE which differed across the treatment modality. [98,99,102,103,111] After balancing the treatment groups on baseline characteristics, we found no differences between warfarin and LMWHs and risk of recurrent VTE but showed that warfarin treated patients had more than twice the

hazard of a major bleed. Those receiving a filter had very large increases in all outcome events relative to both LMWH and warfarin. This generally confirms the recommendations made by U.S. clinical oncology practice guidelines which prefer LMWHs over warfarin and only recommend VC filters when other treatments are contraindicated. [58] VC filters have mixed results in randomized controlled trials [9,10] and observational studies [19] unless distinct population groups with high risk of VTE or high risk of bleeding are preferentially given this treatment over the general patient population.

LMWHs have been shown to have a large incremental cost-effectiveness ratio compared to warfarin [112] as well as perceived patient intolerance and higher pharmacy costs. [93] Nevertheless, oral anticoagulation with warfarin can be difficult in practice given the patient variability in dosing, diet limitations, and required monitoring as well as potential drug-drug interactions with chemotherapy, changes in body weight, altered liver or renal function, and unpredictable gastrointestinal absorption due to vomiting or mucositis. [58] These considerations will become more important as novel oral anticoagulants (NOACs; apixaban, rivaroxaban, dabigatran, edoxaban) are beginning to see use in this population and are currently being investigated for efficacy and safety for primary and secondary prophylaxis of cancer-associated VTE. [113-118]

There is likely significant bias in the choice of treatment for a given individual and is shown in our baseline comparisons. Using the IPTW in the regression analysis helps

to balance these differences in a way analogous to the randomization process of a randomized controlled trial. However, the IPTW is limited to the logistic regression model specification and may not capture all the bias that is present. We included several demographic and clinical characteristics which could drive the choice of treatment in this population. Important factors, which could not be controlled for given the nature of claims data, include tumor staging and histology as well as other important clinical history that may contribute to treatment choice or baseline risk of outcome events. However, our study is strengthened by a large sample size which includes some relatively rare cancers, such as multiple myeloma, brain, and renal cancers, that have lacked investigation in previous studies. [87,119]

Of particular interest throughout the conduct of this study is the untreated group which comprised the majority of the identified cohort. This finding is not unique to our study with a recent study of real-world data in another population in the U.S. reporting a treatment rate of 50%. [113,120,121] We hypothesize that this group could consist of several unique profiles of individuals. For one, a proportion of this group may include those that are unfit to receive any treatment given a poor prognosis related to the underlying cancer or the index event. There may also be cases which the index VTE event was considered asymptomatic or not a high priority for treatment based on unobservable patient factors. Further, there may have been some false positive misclassification of index events which met the coding criteria. However, as discussed below in the limitations, the sensitivity and specificity of the algorithm is expected to be >90% given the high risk of events in this population. [107]

It would further be expected that misclassification would not necessarily differ between treatment groups and would be evenly distributed among the treatment groups. While some groups have used treatment as confirmation of index VTE events, [122] the inclusion in our study would not impact the direct comparisons made between the other treatment groups and was considered a more thorough analysis.

Lastly, it is possible that other, non-guideline recommended treatments were used or that medications were purchased out-of-pocket or using another insurance benefit. Anywhere from 10-20% of warfarin prescription are purchased through low-cost generic programs in the United States and may contribute to exposure misclassification in this population. [123-125]

*Limitations*

Our study is subject to several limitations inherent to claims-based studies. [79,80] We relied on ICD-9-CM coding available in the claims to diagnose study subjects in addition to requiring the presence of specific imaging modalities to confirm index and recurrent VTE events. It is impossible to confirm a positive diagnosis using these data; however, claims-based coding algorithms for VTE have been shown to perform strongly especially when there is a high risk of VTE in the population [50,126]. In addition to this validated algorithm, we further required the presence of an imaging procedure specific for diagnosis of VTE events to indicate an event of interest which will have likely increased the specificity of our coding algorithm and insured that a recurrent VTE event was a new event and not management of the

previous index event. Further, we considered treatment group assignments based on the pattern of medication use or procedural codes within the first 10 days of the index events and held the treatment group assignment throughout the 180 days follow-up. Realistically, treatment, as well as other factors, may change drastically over the course of the study period. However, the majority of outcome events occurred during the first 30 days post-index where treatment choice and individual factors would generally remain stable. Future work should identify and account for important factors that may vary over time for inclusion in analytic models.

We used a competing risks framework given that the outcome events cannot be considered independent of each other, i.e. experiencing one may preclude experiencing another or one event may cause another. Failure to do so can overestimate survival for traditional Kaplan-Meier based analyses. [119] In this population especially, the competing risk of death is a contribution by many factors including the advanced age of the cohort, having cancer, as well as the risk of death from the other outcome events. [119] Given the nature of the data, we could not assign cause of death in this study. For example, if death was caused by a major bleed or recurrent VTE but not submitted for claims adjudication, the alternative outcome would not be observed. Thus, the findings related to the death should be interpreted with caution. Lastly, our results are from a commercially insured population of individuals with Medicare Advantage plans over the age of 65. Thus, our results may not be generalizable to the general geriatric population but do provide insight into

the burden of these outcome events in this population which makes of about 30% of those with Medicare insurance in the United States. [127]

## Conclusions

There is a high rate of recurrent VTE and major bleeding events within 180 days of a cancer-associated VTE. The risk of experiencing these outcomes varied across treatment groups showing no difference between warfarin and LMWHs for recurrent VTE but twice the risk of major bleeding with warfarin. Patients receiving VCFs with or without anticoagulation were at largely increased risk of all outcome events. These findings are consistent with U.S. clinical oncology practice guidelines which prefer LMWH over warfarin in both the acute and long-term treatment after a cancer-associated VTE and only recommend vena cava filters if other treatments are contraindicated.

**Table 4.1: Baseline demographic and clinical characteristics by treatment group**

| Characteristic N (%) | Warfarin | LMWH | VC Filter | VC Filter + Anticoag. | None |
|---|---|---|---|---|---|
| Total N=12,965 | 3,946 (30.4) | 458 (3.5) | 536 (4.1) | 574 (4.4) | 7,451 (57.5) |
| Age category* | | | | | |
| 65-69 | 1,038 (26.3) | 176 (38.4) | 124 (22.4) | 166 (28.8) | 2,119 (27.9) |
| 70-74 | 1,124 (28.4) | 124 (27.1) | 154 (27.9) | 158 (27.4) | 2,086 (27.5) |
| 75 and older | 1,793 (45.3) | 158 (34.5) | 275 (49.7) | 252 (43.8) | 3,392 (44.7) |
| Gender* | | | | | |
| Male | 1,833 (46.4) | 242 (52.8) | 222 (40.1) | 270 (46.9) | 3,917 (51.6) |
| Female | 2,122 (53.7) | 216 (47.2) | 331 (59.9) | 306 (53.1) | 3,680 (48.4) |
| Race* | | | | | |
| White | 2,614 (66.1) | 244 (53.3) | 185 (33.5) | 320 (55.6) | 4,491 (59.1) |
| Black | 338 (8.6) | 22 (4.8) | 40 (7.2) | 50 (8.7) | 589 (7.8) |
| Other | 1,003 (25.4) | 192 (41.9) | 328 (59.3) | 206 (35.8) | 2,517 (33.1) |
| Region* | | | | | |
| Midwest | 1,046 (26.5) | 117 (25.6) | 126 (22.8) | 138 (24.0) | 1,593 (21.0) |
| Northeast | 83 (2.1) | 14 (3.1) | 15 (2.7) | 20 (3.5) | 175 (2.3) |
| South | 2,421 (61.2) | 289 (63.1) | 368 (66.6) | 369 (64.1) | 5,144 (67.7) |
| West | 405 (10.2) | 38 (8.3) | 44 (8.0) | 49 (8.5) | 685 (9.0) |
| Plan type* | | | | | |
| FFS | 1,898 (48.0) | 214 (46.7) | 200 (36.2) | 219 (38.0) | 2,941 (38.7) |
| HMO | 1,547 (39.1) | 175 (28.2) | 285 (51.5) | 280 (48.6) | 3,615 (47.6) |
| PPO | 510 (12.9) | 69 (15.1) | 68 (12.3) | 77 (13.4) | 1,041 (13.7) |
| CCI Score* | | | | | |
| 0-1 | 1,079 (27.3) | 125 (27.3) | 63 (11.4) | 135 (23.4) | 1,821 (24.0) |
| 2-3 | 1,240 (31.4) | 171 (37.3) | 164 (29.7) | 173 (30.0) | 2,349 (30.9) |
| 4-5 | 843 (21.3) | 80 (17.5) | 143 (25.9) | 143 (24.8) | 1,593 (21.0) |
| 5+ | 793 (20.1) | 82 (17.9) | 183 (33.1) | 125 (21.7) | 1,834 (24.1) |
| Timing of cancer treatment before index event * | | | | | |
| Greater than 6 months | 3,181 (80.4) | 278 (60.7) | 404 (73.1) | 435 (75.5) | 6,547 (86.2) |
| 3-6 months | 103 (2.6) | 15 (3.3) | 21 (3.8) | 13 (2.3) | 172 (2.3) |
| 1-3 months | 158 (4.0) | 28 (6.1) | 36 (6.5) | 30 (5.2) | 234 (3.1) |
| Less than 1 month | 513 (13.0) | 137 (29.9) | 92 (16.6) | 98 (17.0) | 644 (8.5) |
| Initial event* | | | | | |
| Lower DVT | 2,484 (62.8) | 299 (65.3) | 291 (50.5) | 291 (50.5) | 5,212 (68.6) |
| Upper DVT | 150 (3.8) | 33 (7.2) | 12 (2.1) | 12 (2.1) | 943 (12.4) |
| PE | 1,321 (33.4) | 126 (27.5) | 273 (47.4) | 273 (47.4) | 1,442 (19.0) |
| **Comorbidities** | | | | | |
| Leukocytosis* | 181 (4.6) | 21 (4.6) | 55 (10.0) | 39 (6.8) | 421 (5.5) |
| Leukocytopenia* | 40 (1.0) | 14 (3.1) | 8 (1.5) | 5 (0.9) | 100 (1.3) |
| Thrombocytosis* | 65 (1.6) | 6 (1.3) | 17 (3.1) | 13 (2.3) | 173 (2.3) |
| Thrombocytopenia* | 177 (4.5) | 25 (5.5) | 37 (6.7) | 30 (5.2) | 450 (5.9) |
| Hypocoagulatory Disorder* | 244 (6.2) | 27 (5.9) | 28 (5.1) | 26 (4.5) | 297 (3.9) |
| Anemia* | 928 (23.5) | 143 (31.2) | 160 (28.9) | 135 (23.4) | 2,146 (28.3) |
| Liver disease* | 502 (12.7) | 93 (20.3) | 128 (23.2) | 91 (15.8) | 1,055 (13.9) |
| Renal disease* | 854 (21.6) | 90 (19.7) | 195 (35.3) | 144 (25.0) | 1,927 (25.4) |
| Hypertension* | 3,011 (76.1) | 336 (73.4) | 460 (83.2) | 450 (78.1) | 5,892 (77.6) |
| Prior bleed* | 413 (10.4) | 52 (11.4) | 154 (27.9) | 79 (13.7) | 990 (13.0) |
| Obese | 321 (8.1) | 37 (8.1) | 50 (9.0) | 60 (10.4) | 569 (7.5) |
| Myocardial infarction | 399 (10.1) | 50 (10.9) | 66 (11.9) | 65 (11.3) | 891 (11.7) |
| Congestive heart failure* | 954 (24.1) | 81 (17.7) | 144 (26.0) | 111 (19.3) | 1,679 (22.1) |
| Peripheral vascular disease* | 896 (22.7) | 99 (21.6) | 159 (28.8) | 141 (24.5) | 2,029 (26.7) |
| Cerebrovascular disease* | 731 (18.5) | 60 (13.1) | 174 (31.5) | 129 (22.4) | 1,431 (18.8) |
| Dementia* | 110 (2.8) | 6 (1.3) | 35 (6.3) | 17 (3.0) | 245 (3.2) |
| Chronic pulmonary disease* | 1,292 (32.7) | 144 (31.4) | 209 (37.8) | 191 (33.2) | 2,685 (35.3) |

**Table 4.1: Baseline demographic and clinical characteristics by treatment group**

| Characteristic N (%) | Warfarin | LMWH | VC Filter | VC Filter + Anticoag. | None |
|---|---|---|---|---|---|
| Rheumatic disease | 196 (5.0) | 24 (5.2) | 31 (5.6) | 27 (4.7) | 366 (4.8) |
| Peptic ulcer disease* | 96 (2.4) | 11 (2.4) | 38 (6.9) | 15 (2.6) | 256 (3.4) |
| Diabetes w/o complications* | 1,277 (32.3) | 153 (33.4) | 211 (38.2) | 193 (33.5) | 2,692 (35.4) |
| Diabetes w/ complications* | 436 (11.0) | 43 (9.4) | 78 (14.1) | 63 (10.9) | 1,091 (14.4) |
| Paraplegia/hemiplegia* | 103 (2.6) | 10 (2.2) | 56 (10.1) | 29 (5.0) | 207 (2.7) |
| Skin ulcers/cellulitis* | 534 (13.5) | 57 (12.5) | 95 (17.2) | 91 (15.8) | 1,186 (15.6) |
| **Tumor site** | | | | | |
| Oral | 67 (1.7) | 10 (2.2) | 14 (2.5) | 13 (2.3) | 153 (2.0) |
| Stomach* | 59 (1.5) | 12 (2.6) | 19 (3.4) | 13 (2.3) | 91 (1.2) |
| Colon* | 321 (8.1) | 54 (11.8) | 46 (8.3) | 61 (10.6) | 562 (7.4) |
| Liver* | 69 (1.7) | 17 (3.7) | 14 (2.5) | 10 (1.7) | 132 (1.7) |
| Pancreas* | 89 (2.3) | 42 (9.2) | 19 (3.4) | 16 (2.8) | 174 (2.3) |
| Lung* | 409 (10.3) | 89 (19.4) | 76 (13.7) | 80 (13.9) | 815 (10.7) |
| Breast | 469 (11.9) | 53 (11.6) | 49 (8.9) | 54 (9.4) | 846 (11.1) |
| Melanoma | 106 (2.7) | 6 (1.3) | 14 (2.5) | 16 (2.8) | 165 (2.2) |
| Uterine* | 73 (1.9) | 18 (3.9) | 14 (2.5) | 27 (4.7) | 120 (1.6) |
| Cervix* | 35 (0.9) | 8 (1.8) | 10 (1.8) | 12 (2.1) | 49 (0.6) |
| Ovarian* | 80 (2.0) | 24 (5.2) | 20 (3.6) | 18 (3.1) | 116 (1.5) |
| Prostate* | 701 (17.7) | 62 (13.5) | 124 (22.4) | 108 (18.8) | 1,177 (15.5) |
| Bladder* | 196 (5.0) | 25 (5.5) | 48 (8.7) | 31 (5.4) | 321 (4.2) |
| Kidney* | 110 (2.8) | 16 (3.5) | 28 (5.1) | 22 (3.8) | 230 (3.0) |
| Brain* | 58 (1.5) | 12 (2.6) | 50 (9.0) | 29 (5.0) | 108 (1.4) |
| Thyroid | 21 (0.5) | 1 (0.2) | 5 (0.9) | 5 (0.9) | 62 (0.8) |
| Lymphoma | 335 (8.5) | 52 (11.4) | 55 (10.0) | 47 (8.2) | 628 (8.3) |
| Myeloma | 86 (2.2) | 10 (2.2) | 15 (2.7) | 12 (2.1) | 127 (1.7) |
| Metastatic disease* | 692 (17.5) | 175 (38.2) | 157 (28.4) | 134 (23.3) | 1,160 (15.3) |

*Comparisons between groups significant at p<0.001
LMWH = low molecular weight heparin; VC = vena cava; FFS = fee-for-service; HMO = health maintenance organization; PPO = preferred provider organization; CCI = Charlson comorbidity index; DVT = deep vein thrombosis; PE = pulmonary embolism

**Table 4.2:Exposure treatment effect in unweighted and weighted (IPTW) competing risk models.**

| | | Unweighted | | | Weighted | | |
|---|---|---|---|---|---|---|---|
| | **Treatment** | **HR** | **95% CI** | | **HR** | **95% CI** | |
| **Recurrent VTE** | **Warfarin** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| | **LMWH** | 0.94 | 0.76 | 1.17 | 0.86 | 0.68 | 1.08 |
| | **Vena cava filter** | 1.41 | 1.14 | 1.74 | 1.79 | 1.48 | 2.17 |
| | **Vena cava filter and anticoagulation** | 1.90 | 1.62 | 2.23 | 1.94 | 1.65 | 2.28 |
| | **None** | 0.31 | 0.27 | 0.34 | 0.34 | 0.31 | 0.39 |
| **Major bleeding** | **Warfarin** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| | **LMWH** | 0.56 | 0.32 | 0.98 | 0.48 | 0.27 | 0.85 |
| | **Vena cava filter** | 5.49 | 4.27 | 7.06 | 5.92 | 4.66 | 7.53 |
| | **Vena cava filter and anticoagulation** | 3.18 | 2.45 | 4.15 | 3.35 | 2.59 | 4.32 |
| | **None** | 1.00 | 0.85 | 1.18 | 1.05 | 0.89 | 1.24 |
| **Death** | **Warfarin** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| | **LMWH** | 2.02 | 1.75 | 2.34 | 1.36 | 1.16 | 1.60 |
| | **Vena cava filter** | 5.03 | 4.44 | 5.69 | 3.41 | 2.98 | 3.91 |
| | **Vena cava filter and anticoagulation** | 2.39 | 2.08 | 2.75 | 1.91 | 1.66 | 2.19 |
| | **None** | 1.15 | 1.07 | 1.24 | 1.16 | 1.08 | 1.25 |

HR = hazard ratio; CI = confidence interval; LMWH = low molecular weight heparin

**Table 4.3: Event specific hazard ratios and 95% confidence intervals from IPTW competing risks analysis with all covariates included.**

| | Recurrent VTE | | | Major Bleed | | | Death | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | HR | 95% CI | | HR | 95% CI | |
| **Treatment** | | | | | | | | | |
| **Warfarin** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **LMWH** | 0.90 | 0.72 | 1.13 | 0.51 | 0.28 | 0.93 | 1.52 | 1.29 | 1.80 |
| **VC Filter** | 1.85 | 1.53 | 2.24 | 5.70 | 4.42 | 7.36 | 3.45 | 2.94 | 4.04 |
| **VC Filter + anticoagulation** | 2.01 | 1.71 | 2.37 | 3.47 | 2.68 | 4.50 | 1.80 | 1.53 | 2.12 |
| **None** | 0.34 | 0.30 | 0.38 | 1.12 | 0.94 | 1.32 | 1.34 | 1.24 | 1.44 |
| **Age category** | | | | | | | | | |
| **65-69** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **70-74** | 0.96 | 0.85 | 1.09 | 0.99 | 0.82 | 1.20 | 1.09 | 1.00 | 1.20 |
| **75 and older** | 0.80 | 0.71 | 0.90 | 1.00 | 0.83 | 1.20 | 1.30 | 1.19 | 1.41 |
| **Race** | | | | | | | | | |
| **White** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **Black** | 1.10 | 0.91 | 1.32 | 1.33 | 1.04 | 1.70 | 1.32 | 1.15 | 1.52 |
| **Other** | 1.04 | 0.68 | 1.60 | 0.98 | 0.51 | 1.86 | 0.97 | 0.68 | 1.38 |
| **CCI Score** | | | | | | | | | |
| **0-1** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **2-3** | 1.10 | 0.94 | 1.29 | 1.32 | 1.02 | 1.72 | 1.22 | 1.08 | 1.37 |
| **4-5** | 1.03 | 0.82 | 1.31 | 1.46 | 1.05 | 2.02 | 1.39 | 1.20 | 1.62 |
| **5+** | 1.23 | 0.86 | 1.77 | 1.30 | 0.83 | 2.03 | 1.48 | 1.19 | 1.83 |
| **Timing of cancer treatment before index event** | | | | | | | | | |
| **Greater than 6 months** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **3-6 months** | 0.73 | 0.49 | 1.07 | 0.97 | 0.61 | 1.57 | 1.27 | 1.06 | 1.52 |
| **1-3 months** | 0.82 | 0.59 | 1.12 | 0.93 | 0.62 | 1.39 | 1.32 | 1.14 | 1.53 |
| **Less than 1 month** | 0.87 | 0.71 | 1.06 | 0.94 | 0.70 | 1.26 | 1.27 | 1.15 | 1.40 |
| **Index event** | | | | | | | | | |
| **Lower DVT** | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| **Upper DVT** | 0.86 | 0.71 | 1.04 | 0.81 | 0.63 | 1.05 | 0.74 | 0.64 | 0.85 |
| **Pulmonary embolism** | 1.83 | 1.64 | 2.03 | 1.16 | 0.98 | 1.37 | 1.65 | 1.54 | 1.78 |
| **Comorbidities** | | | | | | | | | |
| **Leukocytosis** | 1.18 | 0.94 | 1.47 | 1.62 | 1.26 | 2.08 | 1.36 | 1.21 | 1.53 |
| **Leukocytopenia** | 0.95 | 0.58 | 1.57 | 1.39 | 0.80 | 2.43 | 1.10 | 0.86 | 1.40 |
| **Thrombocytosis** | 1.08 | 0.85 | 1.38 | 1.07 | 0.80 | 1.42 | 1.12 | 0.98 | 1.27 |
| **Thrombocytopenia** | 1.07 | 0.75 | 1.54 | 0.89 | 0.54 | 1.46 | 1.08 | 0.87 | 1.34 |
| **Hypocoagualotory disorder** | 0.97 | 0.44 | 2.13 | 0.66 | 0.22 | 2.05 | 2.05 | 1.40 | 3.00 |
| **Anemia** | 0.35 | 0.30 | 0.41 | 0.77 | 0.65 | 0.91 | 0.97 | 0.90 | 1.04 |

**Table 4.3: Event specific hazard ratios and 95% confidence intervals from IPTW competing risks analysis with all covariates included.**

| | Recurrent VTE | | | Major Bleed | | | Death | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | HR | 95% CI | | HR | 95% CI | |
| **Liver disease** | 1.09 | 0.92 | 1.28 | 0.96 | 0.77 | 1.19 | 1.15 | 1.06 | 1.26 |
| **Renal disease** | 1.14 | 0.98 | 1.33 | 1.22 | 1.01 | 1.48 | 1.24 | 1.14 | 1.36 |
| **Hypertension** | 1.15 | 1.00 | 1.32 | 0.94 | 0.76 | 1.16 | 0.85 | 0.77 | 0.93 |
| **Prior bleed** | 1.19 | 1.01 | 1.41 | 2.53 | 2.10 | 3.04 | 1.20 | 1.08 | 1.33 |
| **Obese** | 1.21 | 1.02 | 1.43 | 1.13 | 0.89 | 1.44 | 0.96 | 0.84 | 1.09 |
| **Myocardial infarction** | 0.90 | 0.75 | 1.08 | 1.11 | 0.90 | 1.36 | 0.93 | 0.84 | 1.04 |
| **Congestive heart failure** | 0.85 | 0.74 | 0.98 | 1.18 | 0.98 | 1.40 | 1.23 | 1.13 | 1.34 |
| **Peripheral vascular disease** | 1.02 | 0.90 | 1.16 | 1.01 | 0.85 | 1.20 | 0.92 | 0.85 | 1.00 |
| **Cerebrovascular disease** | 0.86 | 0.74 | 0.99 | 1.26 | 1.06 | 1.49 | 1.01 | 0.93 | 1.10 |
| **Dementia** | 0.85 | 0.62 | 1.19 | 0.68 | 0.43 | 1.07 | 1.38 | 1.17 | 1.63 |
| **Chronic pulmonary disease** | 1.02 | 0.90 | 1.15 | 1.05 | 0.89 | 1.24 | 1.22 | 1.13 | 1.32 |
| **Rheumatic disease** | 1.16 | 0.93 | 1.45 | 1.24 | 0.94 | 1.64 | 1.07 | 0.92 | 1.24 |
| **Peptic ulcer disease** | 0.83 | 0.58 | 1.18 | 0.96 | 0.70 | 1.32 | 1.01 | 0.83 | 1.22 |
| **Diabetes w/o complications** | 0.88 | 0.77 | 1.00 | 1.10 | 0.92 | 1.30 | 0.97 | 0.90 | 1.06 |
| **Diabetes w/ complications** | 0.89 | 0.72 | 1.10 | 1.03 | 0.81 | 1.31 | 1.00 | 0.88 | 1.12 |
| **Paraplegia/Hemiplegia** | 1.12 | 0.84 | 1.51 | 1.61 | 1.18 | 2.20 | 1.47 | 1.24 | 1.73 |
| **Skin ulcers/Cellulitis** | 0.85 | 0.74 | 0.98 | 0.89 | 0.72 | 1.10 | 1.00 | 0.90 | 1.10 |
| **Tumor site** | | | | | | | | | |
| **Oral** | 0.68 | 0.43 | 1.06 | 1.20 | 0.74 | 1.94 | 1.05 | 0.87 | 1.27 |
| **Stomach** | 1.66 | 1.14 | 2.42 | 0.57 | 0.25 | 1.29 | 1.39 | 1.15 | 1.69 |
| **Colon** | 0.99 | 0.81 | 1.20 | 1.17 | 0.90 | 1.52 | 1.07 | 0.96 | 1.19 |
| **Liver** | 0.74 | 0.45 | 1.21 | 0.48 | 0.21 | 1.08 | 1.09 | 0.91 | 1.29 |
| **Pancreas** | 0.67 | 0.43 | 1.04 | 1.09 | 0.66 | 1.81 | 1.64 | 1.41 | 1.89 |
| **Lung** | 0.72 | 0.59 | 0.88 | 1.14 | 0.87 | 1.49 | 1.27 | 1.16 | 1.40 |
| **Breast** | 1.02 | 0.87 | 1.20 | 0.98 | 0.75 | 1.28 | 0.88 | 0.78 | 0.99 |
| **Melanoma** | 0.86 | 0.61 | 1.23 | 0.99 | 0.60 | 1.63 | 0.88 | 0.73 | 1.07 |
| **Uterus** | 0.75 | 0.49 | 1.13 | 0.60 | 0.28 | 1.26 | 1.19 | 0.95 | 1.50 |
| **Cervix** | 1.03 | 0.56 | 1.88 | 1.47 | 0.64 | 3.37 | 1.29 | 0.94 | 1.77 |
| **Ovarian** | 0.89 | 0.57 | 1.39 | 1.10 | 0.55 | 2.19 | 1.24 | 1.02 | 1.51 |
| **Prostate** | 0.68 | 0.43 | 1.06 | 1.14 | 0.93 | 1.40 | 0.88 | 0.80 | 0.98 |
| **Testicular** | 1.66 | 1.14 | 2.42 | - | - | - | 1.02 | 0.70 | 1.47 |
| **Bladder** | 0.99 | 0.81 | 1.20 | 1.37 | 1.02 | 1.84 | 1.24 | 1.08 | 1.42 |
| **Kidney** | 0.74 | 0.45 | 1.21 | 1.10 | 0.75 | 1.62 | 1.04 | 0.88 | 1.22 |

**Table 4.3: Event specific hazard ratios and 95% confidence intervals from IPTW competing risks analysis with all covariates included.**

| | Recurrent VTE | | | Major Bleed | | | Death | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | | **HR** | **95% CI** | | **HR** | **95% CI** | |
| **Brain** | 0.67 | 0.43 | 1.04 | 0.81 | 0.46 | 1.43 | 1.32 | 1.10 | 1.60 |
| **Thyroid** | 0.72 | 0.59 | 0.88 | 2.17 | 1.19 | 3.98 | 0.80 | 0.50 | 1.26 |
| **Lymphoma** | 1.02 | 0.87 | 1.20 | 0.97 | 0.71 | 1.32 | 1.25 | 1.11 | 1.40 |
| **Myeloma** | 0.86 | 0.61 | 1.23 | 1.56 | 1.02 | 2.40 | 0.91 | 0.72 | 1.15 |
| **Metastatic disease** | 1.14 | 0.24 | 5.37 | 0.60 | 0.46 | 0.79 | 1.85 | 1.69 | 2.03 |

HR = hazard ratio; CI = confidence interval; LMWH = low molecular weight heparin; VTE = venous thromboembolism; DVT = deep vein thrombosis; VC = vena cava; CCI = Charlson comorbidity index; IPTW = inverse probability of treatment weight

**Figure 4.1a: Cumulative incidence functions of recurrent VTE** - Competing risks time-to-event analysis by treatment group over 180 days of follow-up. Cumulative incidence is the percent of the cohort experiencing each event. Cumulative incidence is unweighted and no demographic or clinical characteristics are controlled.

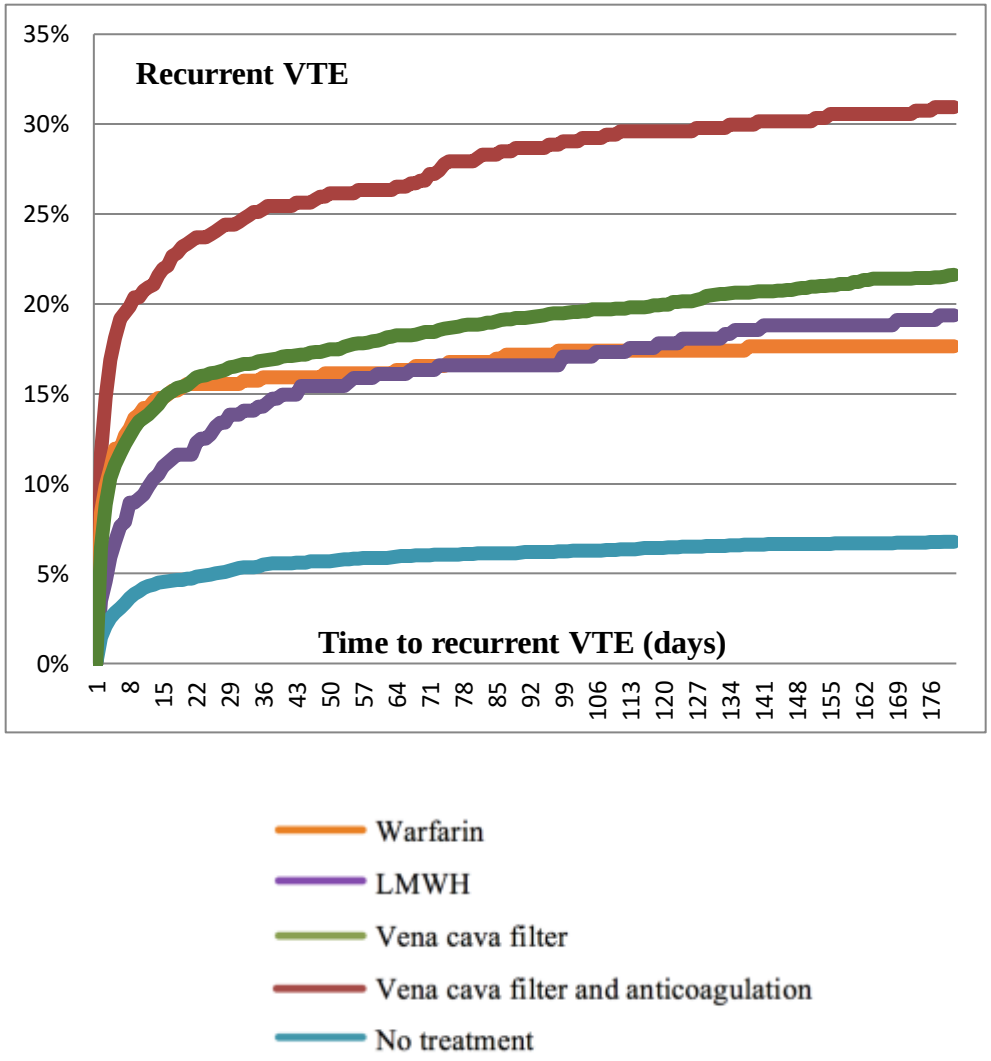


**Figure 4.1b: Cumulative incidence functions of major bleed** - Competing risks time-to-event analysis by treatment group over 180 days of follow-up. Cumulative incidence is the percent of the cohort experiencing each event. Cumulative incidence is unweighted and no demographic or clinical characteristics are controlled.

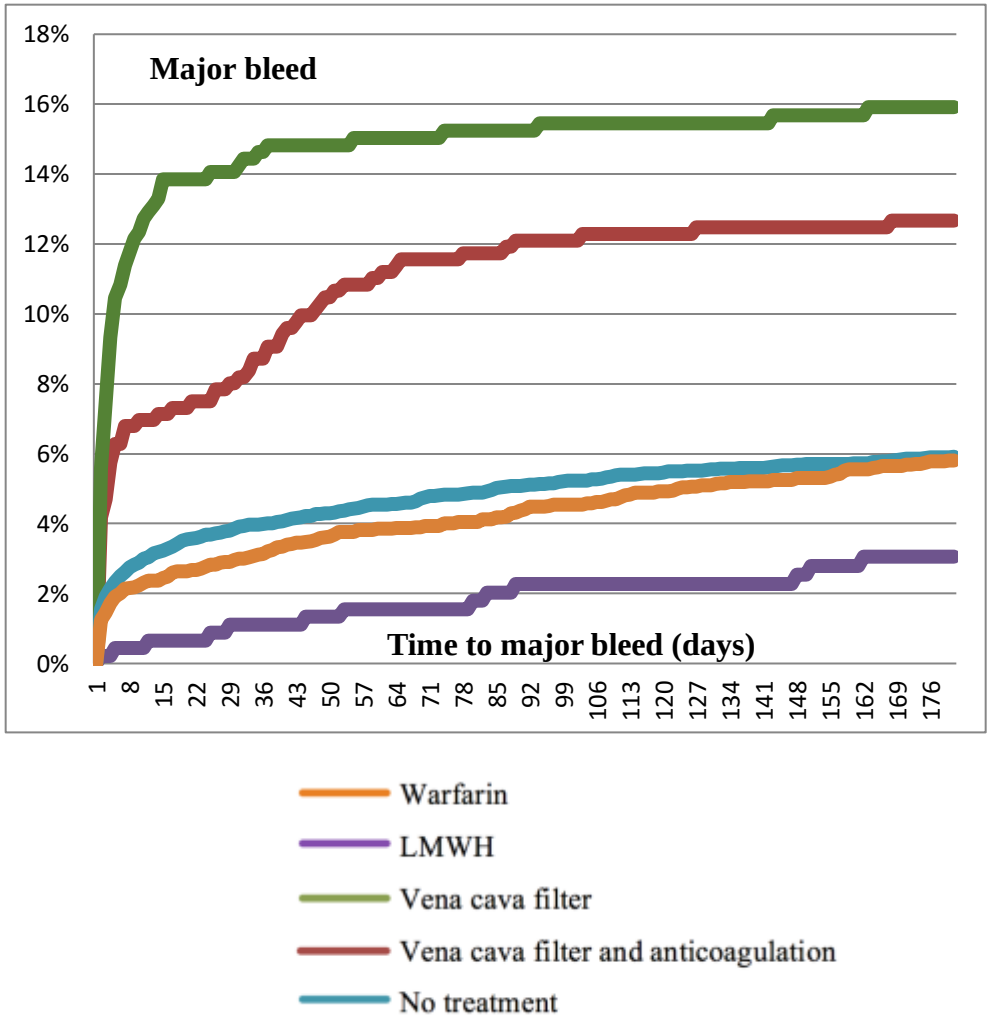
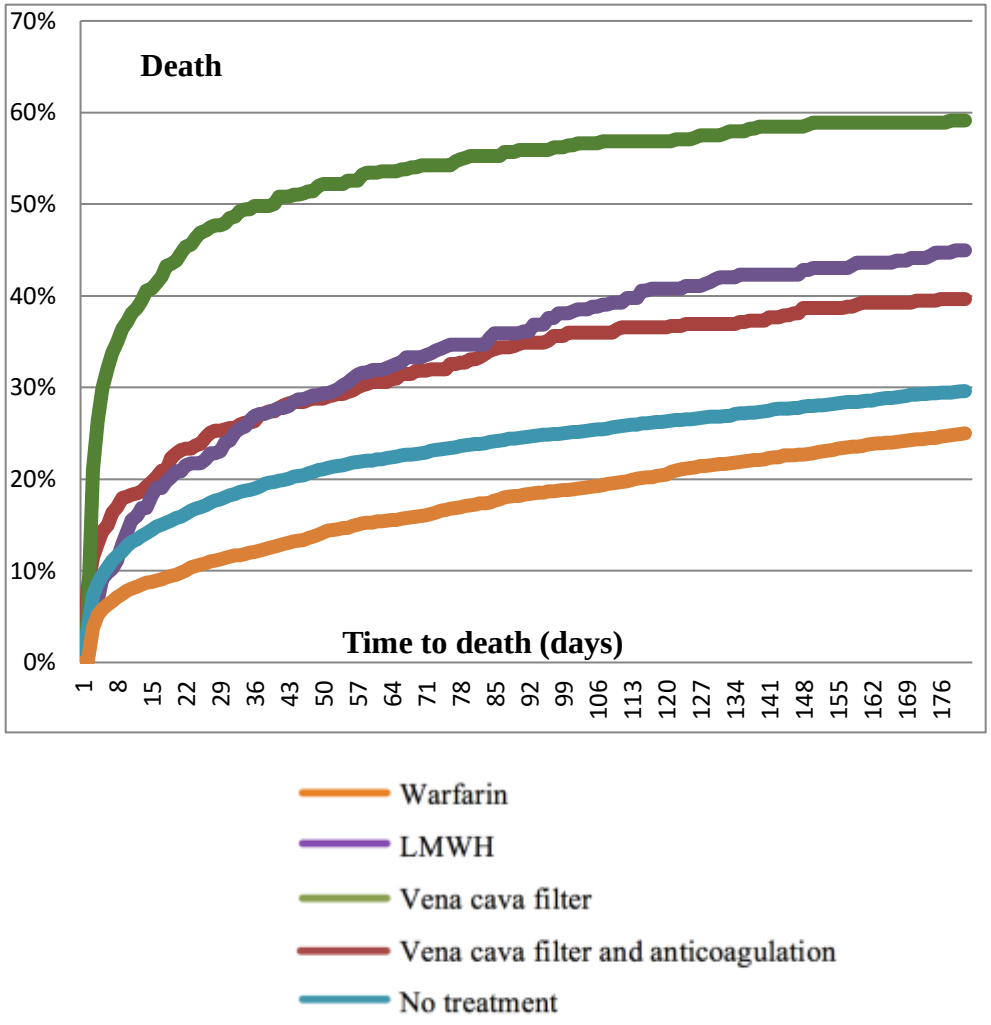


**Figure 4.1c: Cumulative incidence functions of death** - Competing risks time-to-event analysis by treatment group over 180 days of follow-up. Cumulative incidence is the percent of the cohort experiencing each event. Cumulative incidence is unweighted and no demographic or clinical characteristics are controlled.



| **Appendix Table 4A: Coding algorithms used for the analysis** | |
|---|---|
| Deep vein thrombosis | ICD-9-CM:<br>Lower DVT - 451.11, 451.19, 451.81, 453.4, 453.41, 453.42<br>Upper DVT - 451.2, 451.9, 453.1, 453.2, 453.8, 453.9 |
| Pulmonary embolism | ICD-9-CM: 415.1x |
| Imaging studies | |
| Echocardiography | CPT: 93306,93307,93308,93325,93312,93313,93314,93318, 93320,93321,93325,76881,76882,93970,93971,93975, 93976,75820,75822 |
| Chest X-Ray | CPT: 71020 |
| V/Q Scan | CPT: 78585 |
| CT scan/CT Angiography | CPT:71275, 21250, 71260, 71270, 73200, 73201, 73202, |
| MRI/MRI Angiography | 73700, 73701, 73702, 73206, 73706 |
| Ultrasound | CPT: 71555, 73218, 73220, 73718, 73720, 73225, 73725 75820, 75822, 76882, 93970, 93971, 93975, 93976 |
| Hypocoagulation defects | ICD-9-CM: 2860 2861 2862 2863 2864 2865 28652 28653 28659 2866 2867 2869 |
| Other coagulation defects or hemorrhage | ICD-9-CM: 2870 2871 2872 2878 2879 7827 |
| Thrombocytopenia | ICD-9-CM: 2873 2874 2875 |
| Low white cell count | ICD-9-CM: 2885 |
| High white cell count | ICD-9-CM:2886 |
| Hypercoagulation defects | ICD-9-CM:28981 28982 |
| Anemia | ICD-9-CM: 280-285 |

**Appendix 4B: Standardized differences relative to warfarin group**
(Significant value >0.10)

| | LMWH | Filter | Filter + Anticoagulation | None |
|---|---|---|---|---|
| Age (categorical) | 0.1070 | 0.0424 | 0.0661 | 0.0147 |
| Plan type | 0.1294 | 0.0967 | 0.0417 | 0.0019 |
| Region | 0.0849 | 0.0749 | 0.0323 | 0.0080 |
| Gender | 0.0784 | 0.0414 | 0.0162 | 0.0072 |
| Index event | 0.0323 | 0.1906 | 0.0618 | 0.0097 |
| Race | 0.1341 | 0.0577 | 0.0452 | 0.0101 |
| CCI (categorical) | 0.1088 | 0.1639 | 0.0630 | 0.0042 |
| Leukocytosis | 0.0471 | 0.0014 | 0.0689 | 0.0108 |
| Leukocytopenia | 0.0038 | 0.0087 | 0.0043 | 0.0063 |
| Thrombocytopenia | 0.0638 | 0.0175 | 0.0132 | 0.0113 |
| Thrombocytosis | 0.0072 | 0.0468 | 0.0379 | 0.0034 |
| Hypocoagulatory disorder | 0.0160 | 0.0724 | 0.0450 | 0.0046 |
| Anemia | 0.0349 | 0.0239 | 0.0609 | 0.0100 |
| Liver dysfunction | 0.0078 | 0.0325 | 0.0231 | 0.0047 |
| Renal dysfunction | 0.0635 | 0.0707 | 0.0271 | 0.0136 |
| Hypertension | 0.0357 | 0.0424 | 0.0634 | 0.0041 |
| Prior bleed | 0.0027 | 0.0360 | 0.0206 | 0.0023 |
| Obesity | 0.0030 | 0.0175 | 0.0046 | 0.0041 |
| Treatment timing | 0.0608 | 0.0706 | 0.0339 | 0.0051 |
| Tumor site | | | | |
| Oral | 0.0265 | 0.0173 | 0.0126 | 0.0050 |
| Stomach | 0.0227 | 0.0218 | 0.0068 | 0.0040 |
| Colon | 0.0260 | 0.0547 | 0.0175 | 0.0047 |
| Liver | 0.0053 | 0.0423 | 0.0004 | 0.0079 |
| Pancreas | 0.0198 | 0.0146 | 0.0335 | 0.0001 |
| Lung | 0.0304 | 0.0960 | 0.0346 | 0.0068 |
| Breast | 0.0092 | 0.0249 | 0.0117 | 0.0027 |
| Melanoma | 0.0420 | 0.0699 | 0.0460 | 0.0030 |
| Uterine | 0.0420 | 0.0699 | 0.0460 | 0.0030 |
| Cervix | 0.0003 | 0.0217 | 0.0037 | 0.0109 |
| Ovarian | 0.0226 | 0.0098 | 0.0220 | 0.0028 |
| Prostate | 0.0477 | 0.0554 | 0.0234 | 0.0088 |
| Bladder | 0.0016 | 0.0317 | 0.0126 | 0.0021 |
| Renal | 0.0635 | 0.0707 | 0.0271 | 0.0136 |
| Brain | 0.0503 | 0.0473 | 0.0014 | 0.0150 |
| Thyroid | 0.0950 | 0.0064 | 0.0074 | 0.0039 |
| Lymphoma | 0.0106 | 0.0777 | 0.0050 | 0.0015 |
| Myeloma | 0.0201 | 0.1132 | 0.0160 | 0.0023 |

| **Appendix 4B: Standardized differences relative to warfarin group** (Significant value >0.10) | | | | |
|---|---|---|---|---|
| Metastasis | 0.0166 | 0.0806 | 0.0685 | 0.0020 |
| Myocardial infarction | 0.0244 | 0.0653 | 0.0309 | 0.0050 |
| Congestive heart failure | 0.0531 | 0.0904 | 0.0288 | 0.0051 |
| Peripheral vascular disease | 0.0624 | 0.1103 | 0.0303 | 0.0023 |
| Cerebrovascular disease | 0.0109 | 0.0974 | 0.0285 | 0.0136 |
| Dementia | 0.0044 | 0.0586 | 0.0376 | 0.0085 |
| Chronic pulmonary disease | 0.0530 | 0.0432 | 0.0054 | 0.0006 |
| Rheumatic disease | 0.0453 | 0.1112 | 0.0202 | 0.0059 |
| Peptic ulcer disease | 0.0349 | 0.0039 | 0.0095 | 0.0064 |
| Diabetes w/o complications | 0.0022 | 0.0536 | 0.0579 | 0.0079 |
| Diabetes w/ complications | 0.0252 | 0.0517 | 0.0212 | 0.0004 |
| Paraplegia/hemiplegia | 0.0751 | 0.0258 | 0.0373 | 0.0102 |
| Depression | 0.0706 | 0.0236 | 0.0167 | 0.0013 |
| Skin ulcers/cellulitis | 0.0677 | 0.0894 | 0.0488 | 0.0012 |

# CHAPTER 5: EVALUATION OF A QUALITY IMPROVEMENT INTERVENTION TO INCREASE VENA CAVA FILTER RETRIEVAL AT THE UNIVERSITY OF KENTUCKY HOSPITAL

## Introduction

The recent attention into retrieval rates of inferior vena cava filters elicited several institutional interventions aimed at improving retrieval in the patient population. This has been spurred by reports of overall low retrieval rates as well as FDA safety communications calling for improved, as well as earlier retrieval of IVCFs.[28,30] In response to these communications, the University of Kentucky Healthcare (UKHC) Division of Vascular and Interventional Radiology (VIR) instituted a retrospective review of retrieval rates along with a prospective letter mailing intervention to increase retrieval in patients in whom an IVCF is no longer indicated. The design and impact of this intervention is described herein.

## Methods

As part of a clinical practice improvement initiative, a registry of all IVCFs placed at the UKHC hospital in Lexington, KY between October 2011 and February 2016 was created and housed within the Department of Radiology. A study coordinator

retrospectively collected all data to create the database. Patients from VIR, surgery, and cardiology services were included; however, detailed information was only available within the VIR service. Information collected included patient identifying information, referring physician, patient's primary care physician, filter indication and procedure details including date, and the retrieval date. There was no prospective follow-up or data collection implemented due to the inability to extend manpower.

Starting January 2014, all patients with IVCFs implanted by VIR and their primary care or referring physicians were followed-up with a one-time letter sent within 3 months by the implanting physician and study coordinator regarding the need for eventual IVCF retrieval. Contact information to the VIR clinic was provided and contact was encouraged by the primary care physician or patient. Other than the letters mailed, standard care was provided throughout the intervention period.

Patients were assumed to be eligible for retrieval until death was observed. The date of retrieval was noted, otherwise patients were censored at the beginning of the intervention period (for those in the pre-intervention group), or censored at the end of the data collection period (February 2016). Patients who died within 30 days of IVCF placement who did not already have retrieval were excluded from the cohort. Death was considered a competing event in the calculation of the cumulative incidence of retrieval using the method by Fine and Gray to allow for comparison between the pre- and post-intervention groups. The mean, standard deviation (SD),

median, and interquartile range (IQR) of the time-to-retrieval was also calculated and compared.

## Results

There were a total of 184 and 93 IVCFs placed at UKHC in the pre- and post-intervention periods. Of those, 10 and 3 patients were excluded from follow-up because they were deceased within 30 days after IVCF placement. Of the 90 patients in the intervention period, all patients were sent letters and 87 letters were sent to primary care providers (N=3 patients did not have a provider noted in the medical record).

Of those in the pre-intervention period, 7/174 (4%) had their IVCF retrieved while 7/90 (7.8%) of those in the post-intervention period were retrieved. In the time-to-event analysis, which accounted for death during follow-up, the observed retrieval rate at a total of 802 days of follow-up prior to the letter intervention was 4.4% (Figure 5.1). In the post-intervention period, the observed retrieval rate at 265 days of follow-up was 8.1% (Figure 5.1). At an equivalent follow-up period with a cumulative incidence estimate available (288 days), the pre-intervention group's estimated retrieval rate was <1%, giving a relative rate of retrieval of 12.8 between the two periods. Overall, the cumulative incidences between the two groups were significantly different (p=0.043). The time-to-retrieval in the pre-intervention period was a mean (SD) of 503 (207) days with a median (IQR) of 505 (301-742). In

the post-intervention period, time-to-retrieval was a mean (SD) of 119 (83) days and with median (IQR) of 128 (38-164) days (Table 5.1). Due to the intervention implemented, minimal financial impact to the clinic was expected and; thus, not evaluated.

## Discussion

The minimal intervention implemented in the VIR clinic at the UKHC hospital resulted in a significant increase in the IVCF retrievals. Overall, the magnitude of this impact was on the order of a relative rate of 12.8 when limiting the analysis to an equivalent follow-up time. Likewise, there was a decrease in the time-to-retrieval, showing that retrievals were occurring at earlier intervals. This can be expected to decrease the risk of complications reported with longer indwell times such as IVCF fracture, migration, and IVC thrombosis.

Despite the large relative change in IVCF retrieval, UKHC's observed rates of 4.4% and 8.1% represent some of the lowest reported retrieval rates in the literature. Only one other known institution has reported a similar rate of 8.5%.[64] Due to this low rate, that institution also implemented an intervention that increased their retrieval rate to over 50%.[39]

These low rates can be due to several factors. For one, UKHC is a level 1 trauma center serving a largely rural population, including the health disparate Appalachian

region, making follow-up difficult. The patient case-mix at UKHC is also known to be the worst in the state with higher comorbidity burdens along with the highest utilization of IVCFs.[70] More importantly, these retrieval rates are indicative of practice culture. However, it should not be inferred that UKHC is dramatically different from other institutions where retrieval rates have been reported to be much higher than that observed in our institution.[28] Rather, it is likely that a publication bias is present wherein institutions are not willing to discuss low retrieval due to concerns about how releasing these figures would change the perception of quality.

Although in context this minimal intervention can be perceived as successful, how it compares to other interventions is important for planning future improvements to the clinical workflow. This intervention included only mailed letters and retrospective collection of patient data. Other interventions instituted at other hospitals have generally included three facets: 1) patient and physician education regarding IVCFs; 2) a method of tracking patients (e.g. automated alerts through electronic medical records or active tracking); and 3) an individual who takes responsibility for the entire process.[128] Patient education has included pre-discharge education sessions as well as informed consent prior to implantation.[41,129] Physician education examples have included continuing medical education grand rounds, which have both increased retrieval along with reduced overall utilization of IVCFs.[130] Many studies also institute IVCF "registries" so that patients are catalogued continuously in a dedicated record developed specifically for the

population. [39] Further, the movement of responsibility for follow-up from the patient's referring or primary care physician to the implanting physician creates an environment of quality assurance and cross-communication between specialties. [41,42] The addition of these workflows and responsibilities has been shown to not increase workload significantly and has also been shown to increase clinic revenue because of increased patient follow-up and billable clinical visits. [78] All of these factors should be incorporated into a future intervention to further increase the retrieval rates at UKHC. Moreover, such an intervention should be expanded to incorporate inter-departmental collaboration and communication in all implanting and referring specialties, not only VIR.

## Conclusion

Utilizing a minimal letter mailing intervention, retrieval rates at our institution were increased approximately 12-fold with dramatic changes in the time-to-retrieval. However, given the post-intervention retrieval of only 8.5%, much more progress can be made to increase retrieval rates with a more thorough intervention. Lessons from other institutions that have implemented such interventions will be utilized to design a future intervention in order to transform the practice environment and ensure patient safety associated with IVCFs.

**Figure 5.1: Cumulative incidence plot of time to retrieval after vena cava filter placement**

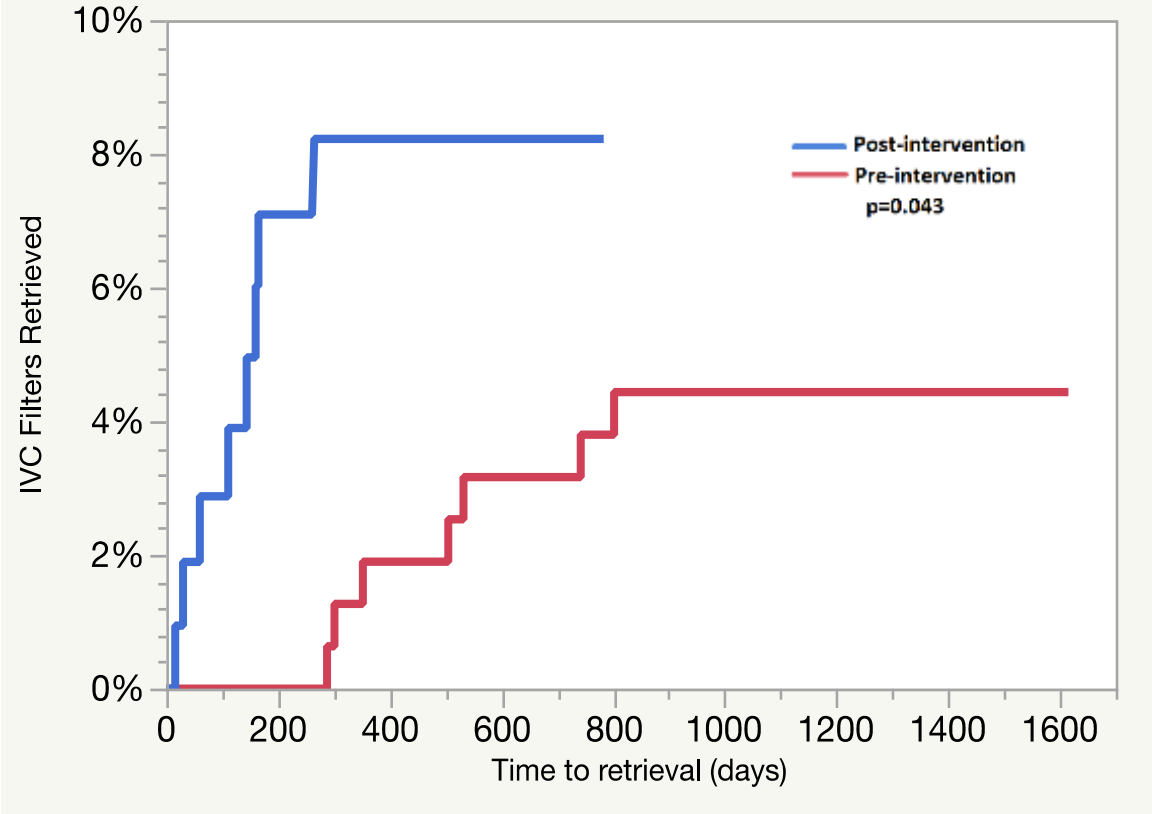


**Table 5.1: Time to retrieval comparison pre and post letter mailing intervention**

| | Pre-intervention (N=7) | Post-intervention (N=8) |
|---|---|---|
| Mean (SD) | 503 (207) days | 119 (83) days |
| Median (IQR) | 505 (301-742) days | 128 (38-164) days |

Standard deviation (SD); Interquartile range (IQR)

# CHAPTER 6: A LITERATURE REVIEW OF INTERVENTIONS TO IMPROVE RETRIEVAL RATES OF VENA CAVA FILTERS AND LESSONS LEARNED FOR FUTURE EFFORTS

## Introduction

In response to the observed poor retrieval rates at UKHC hospital and the small impact of the letter intervention, a literature review was undertaken to explore interventions instituted in other institutions. The overall goal was to define the key aspects of interventions and the overall impact an intervention could have on retrieval rates. A sub-aim of the review was to evaluate financial aspects of these interventions to understand the feasibility of interventions

## Methods

Abstract and full-text search terms including “vena cava filters”, “IVC filters”, and “inferior vena cava filters” were used in conjunction with “retrieval” in MEDLINE/PubMed, Google Scholar, and Cochrane databases. Published studies from January 2003 up to August 1, 2016 were included. Identified abstracts were screened by two independent reviewers, one health services researcher and one interventional radiology resident. Reviewers selected studies that indicated that an

intervention was implemented and compared to a control group or a pre-intervention period. Of those identified from abstract review only, full-text versions of the articles were acquired. Additional articles were discovered from identification in the references of collected manuscripts. Articles that did not meet the requirements of evaluating an intervention during full-text review were excluded.

After relevant studies were identified, the two reviewers independently read the manuscripts and extracted *a priori* defined data of interest including the study setting and year, type of institution and country of study, details of the intervention and the intervention staff, the comparison or control group, sample size, retrieval rates and indwell times, retrieval failures, complications, and loss to follow-up rates. All studies were included which reported both a pre-intervention and post-intervention comparison of retrieval rates. The only exclusion criteria of studies consisted of no pre-intervention measure being present to evaluate the impact of the intervention. Data were entered into a spreadsheet, which was consolidated and reviewed by an additional attending interventional radiologist reviewer for correctness. An *a priori* meta-analysis was planned. Based on the extracted information, the large heterogeneity in measurement definitions, interventions, and patient populations, no further analyses were deemed feasible. Ultimately, the goal was to make general recommendations for future interventions based on the findings from the reviewed studies. A brief narrative of each study is included.

## Results

A total of 288 abstracts were screen from all sources with 18 included for full text review. Of these, 5 studies were excluded as they either described an intervention with no control or comparison group (N=4) and one study was a review article itself. An additional 3 studies were identified from full-text review of other studies and underwent abstract screening and full-text review. One of these additional identified studies was excluded, as it did not include a comparison group or period. A total of 15 studies underwent detailed review and are described below. Summaries of the study characteristics and interventions implemented are provided in Table 6.1. Sample size, retrieval rates, and other study data are provided in Table 6.2 and 6.3.

Twelve of the 15 studies were conducted in the U.S., one each in Ireland, the United Kingdom, and New Zealand (Table 6.1). Of these, 13 were conducted in single, public institutions, primarily tertiary care centers, with 5 additionally indicated as level 1 trauma centers. The other two studies included an evaluation of a national military medical center, which tracked patients across multiple settings, and an evaluation of 14 urban hospitals linked within a single, integrated, regional healthcare system (Kaiser Permanente Northern California). Five of the studies included an intervention only in trauma patients for both prophylactic and secondary prevention efforts.

Absolute changes in retrieval rates ranged from 0% to nearly 70%. Relative changes ranged from 0% to over 2,200% changes in retrieval rates (Table 6.3). One study showed no change in their retrieval rate (45%) while showing a slight decrease in the average indwell time.[1] This study may have been limited by a small sample size (N=66 for pre- and post-intervention periods combined). The largest absolute and relative increase was from a pre-intervention retrieval rate of 3.1% to 73% an absolute change of 69.9% and a relative change of 2,254.8%. Ten out of the 15 studies reviewed at least doubled the baseline retrieval rate after the intervention was in place. All but two of the studies achieved post-intervention retrieval rates ≥50%.

Time-to-retrieval, or the indwell time for the IVCF, was reported for both the pre- and post-intervention periods in 11 studies. Of those, only 3 showed a decrease in the indwell time after the intervention. While some other studies showed increases in indwell times, most of the studies were limited in these comparisons due to sample size.

*Charlton-Ouw 2015*

This article details the implementation of planned retrievals at a single institution.[75] Charlton-Ouw and colleagues note that their institution is unique in that it has a large number of uninsured or underinsured persons (Houston, TX), thus, they also included a financial feasibility analysis due to this issue.

The authors report that they focus their analysis on trauma patients only and describe that they are in a level 1 trauma center with >6000 trauma admissions annually. Prospective enrollment into the retrieval program began in May 2011 with patients being referred to the program via electronic medical record, ordering system, or by telephone referral. The study involved collaboration between trauma/general surgery services and the interventional radiology department. After written consent , patients were followed-up by a clinic nurse or a study coordinator via mail, telephone, and e-mail. Determination of the need for IVCF retrieval was made by the study physicians (vascular surgeons) in consultation with the patient's primary healthcare providers. Patients not enrolled in the program were provided usual care.

The explicit goal of this program was to remove eligible filters within 6 months after placement, noting that this should be regardless of insurance status. They also note that an initial goal of retrieval prior to discharge failed due to difficulties in scheduling as well as ongoing indications for IVCFs. Patient were in the study until the filter was removed or until the filter was deemed permanent. Patients with filters that could not be removed or deemed permanent were followed yearly for an abdominal X-ray and initiated on daily aspirin.

For the cost analysis, commercial and Medicare insured individuals were grouped together while those with no insurance or Medicaid was grouped. Cost-to-charge ratios and payment-to-charge ratios were assessed for procedures. For patients

with no insurance or Medicaid, their costs were counted as losses to the hospital. Data analysis included univariate analyses to determine the effectiveness of the program.

Prior to the retrieval program, 64 trauma patients received an IVCF with only 2 being retrieved (3.1%). During the 2 years of the program, 247 trauma patients received IVCFs, 111 (45%) were enrolled into the retrieval program and 136 were followed in the standard of care arm. Those involved in the program had higher retrieval compared to those that were not: 73% vs. 18%, odds ratio 12.6 [6.6-24.3]. This retrieval rate represents *attempted* retrievals whereas the success rate of retrieval was 85%. The mean time to retrieval was 6.2 months (range 0.5-31.8 months). The financial analysis showed that overall, the hospital revenue from retrieval higher than the cost, which was a balance between payments received from those with insurance (60% of sample) making up for losses from those without insurance. This financial analysis is only generalizable to this individual hospitals practice, however. They describe the population as generally younger trauma patients that are uninsured, which makes follow-up and continuity of care a challenge. They recognize the need to make follow-up of patients dependent on the physicians and healthcare team rather than the patient. The opt-in feature of the program, via physician referral and patient agreement, creates the opportunity for some selection bias to be present in this study.

*Davies 2015*

This study was based in New Zealand through a partnership of Departments of Vascular Surgery and Interventional Radiology and the Venous Thromboembolism Clinic in a single institution.[40] The partnership developed a clinical pathway, i.e. a defined, streamlined clinical workflow for IVCF retrieval. IVCF placement between June 2010 and June 2012 were analyzed retrospectively as the control group with information collected including acute vs. elective, medical vs. surgical referrals, vascular surgeons vs. interventional radiologists performing the implant, etc. For the clinical pathway intervention, all placed IVCFs during July 2012 through June 2014 were included with retrievals documented through August 2014. All patients with IVCF placement were identified in a monthly report and entered into a dedicated IVCF database that was maintained by nurses in the Venous Thromboembolism Clinic. Patients with their IVCF *in situ* longer than 6 weeks were each discussed with the VTE consultant and the patient was subsequently followed-up in the clinic or via telephone consultation. If retrieval was warranted, an appointment was made or, if the filter was to remain in place, an additional follow-up consultation was scheduled. IVCFs were deemed permanent if the indication for placement was expected to extend for a long period or if retrieval was considered too risky. Statistical analyses included Kaplan-Meier survival plots including stratified analyses for key variables. They comment that patients were censored if they died, which was not incorporated in the statistical analysis.

In the control group, 39 patients had an IVCF placed. Of these, 15 underwent retrieval (14 successful) and 9 died. Time to retrieval was 97 (range 15-293) days.

Of those 24 with no retrieval, 5 were deemed permanent, 2 had scheduled retrievals, and 8 were lost to follow-up. The Kaplan-Meier estimate at 12 months was 63%. The authors note that there were differences between retrieval based on referring specialty (surgical 78% vs. medical 40%) and elective (85%) versus acute (55%) care settings.

In the post-intervention group, 56 patients had an IVCF placed with 29 retrievals, 12 deaths, and 7 deemed permanent. The Kaplan-Meier estimate at 12 months showed 100% retrieval. Similar results for differences between acute vs. elective and medical vs. surgical referrals were present. Pre-intervention the time-to-retrieval was 7.4 months and post-intervention it was 4.1 months (overlapping CIs) – suggesting an improvement in this metric as well. Overall, this study had much higher pre- and post-intervention retrieval rates than most other studies. This could be drive by hospital practices already established, but is also confounded due to the small sample size and the way in which patients were censored. Further, given the large proportion of patients who died in each period, the use of Kaplan-Meier methods will overestimate the retrieval rate since death is considered a censoring event instead of a competing risk, i.e. the retrieval rate is *credited* each time someone dies wherein they were still eligible for retrieval up to their death. The authors note the need for dedicated follow-up so that patients are not lost after implantation. They also note the need to place the burden of follow-up on either the implanting physician or a dedicated team aware of the IVCF status.

*Gasparis 2011*

This intervention was implemented in a tertiary care hospital in the United States.[129] The study presents results from the prospective intervention from January 2010 to January 2011. A specialized "DVT team" was developed including a vascular nurse practitioner (NP) and a physician. The NP followed-up with patients and managed the development of a dedicated database. Phone calls and letters were sent to patients and referring physicians suggesting the best retrieval. In addition, patients were educated prior to discharge regarding IVCF retrieval benefits and risks. A "rigorous" coordination system between the NP and referring physician was maintained, including accommodating patient and physician schedules and having dedicated room in the interventional procedural suite. IVCFs could be deemed permanent prior to insertion if (1) the patient could not be anticoagulated for a long period of time (e.g. due to fall risk, intracranial bleed, etc.), or (2) patients with short life span. IVCFs were made permanent if the patient refused retrieval, IVC thrombus was present, they had recurrent VTE, or patients had a short life span. Patients who died during follow-up were excluded. The comparison group's retrieval rate (18%) was reported from a prior study. Statistical analysis included basic Fisher's exact test with no survival analysis included.

During the 12-month period, 42 patients had an IVCF placed by vascular surgeons, with 40 being included in the analysis. Of these, 13 were placed as permanent. Most were placed for absolute contraindications to anticoagulation (58%), relative in 25%, and 17% were used prophylactically. An additional 5 IVCFs were converted to

permanent after placement – leaving 27 eligible for retrieval. Attempted retrieval was done in 22 of 27 patients with 86% success, giving a successful retrieval rate of 70% and 81% retrieval attempt rate. Post-intervention time-to-retrieval was 21 days (range 4-140 days) while pre-intervention time was not reported. They report a significant benefit of the intervention and note an added benefit that no patients were lost to follow-up.

*Inagaki 2015*

This study reports an intervention to increase IVCF retrieval implemented with Boston Medical Center during August 2012 to September 2014 and compared it retrospectively with data from September 2003 to July 2012.[39] Starting with the intervention, prospective data was collected for each patient including physician specialty, indication, filter type, retrieval, etc. IVCFs were placed by multiple departments included interventional radiology, vascular surgery, and cardiology. A multidisciplinary task force encompassing the implanting departments with trauma surgery and hematology was established and a new IVCF retrieval protocol was developed. The protocol included four facets: (1) patient educational pamphlets, (2) additional IVCF procedure form, (3) a centralized IVCF registry, and (4) a dedicated administrative coordinator. Patient education materials included descriptions of the risks, benefits, and process of implantation and retrieval and emphasized that most IVCFs should be removed once anticoagulation is tolerated. The procedure form documented the indication for placement and the estimated duration it would remain implanted with *permanent*, *immediate* (<1 month), *short-term* (1-6 months),

and *long-term* (≥6 months) filter placement. An additional form was completed at retrieval to document success and any reasons for failure. The administrative coordinator maintained the IVCF registry and also coordinated between departments to ensure patient follow-up through the process. They note that this coordinator took on these roles as part of the daily job duties with negligible effect. Patients were contacted by phone or mail, differing slightly between departments, using standardized guidelines to determine suitability for retrieval. Statistical analyses included chi-squared and ANOVA tests.

The clinical pathway was detailed in the article and is reproduced in Figure 6.1. The pathway included flow based on indication (VTE or prophylactic), accounted for time since implant, and if the patient was anticoagulated. In the comparison group, 1,088 IVCFs were placed with 784 (72%) being placed as retrievable devices, 47 (4%) of these died, and 17 (2%) were later deemed permanent. Of the 720 remaining eligible for retrieval, 99 (14%) had attempted retrieval; with 82 (83% ) successful; with median indwell time of 119 days (range 0-1882 days). In comparison, the post-intervention group included 151 IVCF placements, 32 (21%) were inserted as permanent, 14 (9%) of patients died, and 31 (21%) became permanent – leaving 74 (49%) eligible for retrieval. Retrieval attempts were performed in 49 (66%) of these with 40 (82%) being successful and median indwell time of 175 days (range 8-664). Reasons for failure were reported and included the IVCF being imbedded in most cases and abnormal positioning of the IVCF being second most common. Between the pre- and post-intervention periods, there was a

significant decrease in the proportion of prophylactic indications for IVCF placement (suggesting a potential Hawthorne effect or other practice changes during the time period), differences in the IVCF models used, and changes in the implanting service. Further, there were large differences in retrieval based on the classification of the retrieval: *immediate* IVCFs retrievals attempted in 92% of patients (successful in 83%) and median indwell time of 23 days; *short-term* IVCFs retrievals attempted in 62% of patients (successful in 82%) and median indwell of 164 days; and *long-term* IVCFs retrievals attempted in 50% (successful in 75%) and median indwell of 245 days – all significant differences.

*Irwin 2010*

This article discussed an intervention implemented in a level 1 trauma center in the United States between Q2 2007 and Q2 2008 with retrospective data back to 2003 for comparison. [76] The authors distinguish that when retrievable IVCFs became available in 2003, the trauma team attempted to coordinate retrieval with the interventional radiology department. They noted that the overwhelming issue was a lack of patient follow-up, problematic because many patients would be indicated for retrieval later. In response, a multidisciplinary team was formed consisting of trauma nurses and surgeons and nurses from several departments. The team met each morning (M-F) and reviewed patient needs and to coordinate care. The nurse for the interventional radiology department would then follow-up with scheduling. They note that this team secured communication between services and improved patient follow-up between departments.

Prior to implementation, 82 IVCFs were placed with 53 removed (65%) and 15 remaining in place without indication. After implementation of the team approach, of 33 IVCFs placed, 28 were removed (84%) and 3 remained in place without indication. The majority of IVCF placement in the trauma setting was for prophylactic indications over both time periods, and those with prophylactic indications had higher retrieval than those with active VTE (82% vs. 53%). They report multiple reasons for the 35 IVCFs that were not removed in the whole cohort including 8 transferred care to another facility, 3 lost to follow-up, 4 failed attempts at retrieval, 6 with contraindications to anticoagulation, 9 with IVC thrombosis, 2 with DVT while on anticoagulation, 3 who had need for multiple surgeries. Indwelling times were not reported but multiple filter repositioning procedures (N=30) were reported.

*Kalina 2012*

This study describes the impact of having a filter registry in a level 1 trauma center in the United States.[131] The filter registry was established in 2006 and its impact was evaluated using retrospective data. Information collected included Injury Severity Score, indications, etc. and was maintained by acute practice nurses (APN) working in trauma. The registry was updated every 2 weeks from inpatient charts. Patient cases were presented by the APNs to trauma physicians and APNs scheduled procedures or consultations accordingly. Outpatient follow-up was conducted with the in-house clinic by APNs as well. The filter registry was also reviewed monthly at

the trauma department so that implementation plans could be coordinated. Data analysis included basic statistical tests (Chi-square) and stepwise logistic to find independent factors associated with non-retrieval.

During the study period, 142 pre-registry and 165 post-registry IVCFs were placed. Significant differences existed in the length of stay, indications for placement, and the specific IVCFs utilized between the two periods. The reported retrieval rate in the pre-registry period was 15.5% (22 of 120) compared to 31.5% (52 of 113) in the post-registry period ($P<0.001$). The largest reason for non-retrieval was loss to follow-up, which was 21.1% and 27.6% in the two periods. In controlled analyses, IVC thrombosis, DVT, and loss to follow-up predicted non-retrieval.

*Ko 2009*

This study was based in a tertiary care hospital with a level-1 trauma center.[132] The author compared pre-intervention retrieval rates from 2004 to 2007 and implemented an intervention in August 2007. A physician assistant (PA) was given the duty to compile a prospective database of patients receiving an IVCF and subsequently coordinated the retrieval procedure to follow. Reasons for leaving the IVCF implanted were documented in the medical chart. Inpatients with IVCFs in place were highlighted on the rounding list daily and ongoing education of all trauma providers was given on the proper indications for IVCFs to re-enforce when they should be retrieved. Patients were electronically tracked with automated reminder e-mails sent to their admitting attending physician. Coordination between

hospital departments of vascular surgery, trauma, and interventional radiology was encouraged for inpatients and outpatients to increase retrieval. Basic statistical analyses (Chi-squared) were conducted.

In the pre-intervention period, 94 patients received IVCFs while 61 patients received the devices in the post-intervention period (an increase in utilization on a per trauma patient basis between the periods). Of the 94 patients in the pre-intervention period, 76 (80.9%) were deemed eligible for retrieval and retrieval was attempted in 32 (42.1%) of these with 28 (36.8%) being successful with an average indwell time of 24 days. In the post-intervention period, of the 37 (60.7%) were deemed eligible for retrieval and 35 (94.6%) of these underwent an attempted retrieval with 31 (83.8%) being successful at an average indwell time of 20 days. Except for the indwell time, each comparison (eligibility, attempt %, retrieval %) were statistically different. Reasons for non-eligibility were reported and differed between the two periods. In the pre-intervention period, 39 of 66 (59.1%) non-retrievals were due to "clinical oversight," i.e. loss to follow-up, and "medical reasons" (10, 15.2%). There were no cases of "physician preference" in the pre-intervention period. In the post-intervention group, "physician preference" was the most common reason, 11 of 30 (36.7%), representing a potential bias introduced by knowing that your practice is being evaluated, or differences between the prospective and retrospective data collection.

*Lee 2012*

This study was based in the UK and was inspired by a warning by the FDA-equivalent Medicines and Healthcare products Regulatory Agency (MHRA) regarding the complications related to IVCFs that remain indwelling. [133] The intervention design removed the responsibility of follow-up from the referring physician and placed it on the intervention radiology who performed the implantation. They used a pre-intervention comparison during May 2007 to April 2008 and implemented their intervention from May 2008 to April 2008. The radiologist-led approach to the follow-up of patients comprised of a log-sheet that generated standardized reports. These reports were faxed to the referring physician and suggested a retrieval date. In cases where retrieval was refused or not yet appropriate, additional reports were generated every 30 days. Statistical analyses included basic bivariate tests. Of the 28 IVCFs placed in the pre-intervention period, 14 (50%) retrievals were attempted (10 successful, 35.7%). Of the 14 not retrieved, 6 reasons for non-retrieval were undocumented while the other 8 were, leaving an effective retrieval rate of 14/20 (70%). In the post-intervention period, 29 IVCFs were inserted and 16 (55%) retrievals were attempted with 13 (44.8%) being successful. Of those not retrieved, only 1 was lost to follow-up, leaving an effective attempted retrieval rate of 16/17 (94.1%) (these figures were calculated and not reported in the original article). The authors note the importance of choosing a pre-specified time period to pursue retrieval (here 30 days) in that it is likely a clinically accepted interval and that retrieval rates beyond this time decrease dramatically (e.g. due to loss to follow-up and difficulty in retrieval) along with increased risk of complications.

*Logan 2016*

This report details an audit instituted at a tertiary care center in Ireland.[134] Audits of retrieval rates were conducted before and after the implementation of a coordinated management strategy for IVCF follow-up using The Royal College of Radiology's audit template. This audit template for IVCF states that 100% of retrievable IVCFs should have a retrieval attempt at all possible.

The intervention included a multidisciplinary team of interventional radiologists and hematologists. A framework was developed with a 3-point approach of (1) a specialist nurse keeping a registry, (2) hematology consultation if IVCFs are to remain *in situ* or for complex removals, and (3) beds in a day ward were made available. There was a 7-month lead-in period and then a 15-month evaluation period is presented from November 2013 to December 2014. This is compared to the retrospective period of January 2012 to March 2013.

Prior to the intervention, 33 patients received IVCFs largely for indications of planned surgeries or concurrent bleeding, low platelets, or active cancer. Thirty-three patients also received IVCFs in the intervention period, with a larger proportion receiving them for bleeding/low platelet indications along with a significant decrease in IVCF use for surgery indications. Between the two periods, more IVCFs were deemed permanent (12% vs. 39%) during the interventional period while the proportion removed was the same (15%). There was a noted

increase in documented retrieval plans (70% vs. 91%) between the two periods. There was also a reduction in average indwell time (61 vs. 44 days) and fewer patients were considered lost to follow-up (27% vs. 9%)

*Lucas 2012*

This study presented a unique patient population consisting of military trauma patients at a national military medical center. [135] The authors describe most of their patients coming from the theater of war, passing through medical facilities in Germany, then moving throughout the country in military, veteran, and civilian medical facilities – making tracking and follow-up of these patients difficult. An IVCF tracking system was implemented incorporating medical record review and communications between providers to increase retrieval rates in this population starting in January 2007, compared to the 2 years prior. The registry included all IVCF placements unless the patient died within 30 days of placement. Basic statistical testing between groups was utilized.

The control and registry groups comprised 20 and 93 patients, respectively. In the control period, 6 (30%) retrievals were attempted and successful while 65 (70%) attempted and 56 (605) successful retrievals were conducted in the registry period. The number lost to follow-up decreased from 65% to 5% between the two periods as well as the time to retrieval (210 to 84 days). The authors note a sub-analysis

within both periods showing that there was a non-significant difference between times to attempted retrieval for successful versus failed retrievals.

*Lynch 2011*

This report describes an intervention implemented in a tertiary care center in the United States. [41] A retrospective period (May 2002 to October 2005) and an interventional period (October 2005 to May 2010) were compared. At this facility, they note the need for proper patient selection and follow-up. Thus, they outline that patients only received a retrievable filter if their need for one would be temporary, otherwise a permanent device would be placed, a decision that was also part of the informed consent process with patients. Retrievable IVCFs made of 42% of the IVCFs placed. Starting in the interventional period, the responsibility of follow-up was placed on the implanting interventional radiologist instead of the referring physician, including initiated follow-up of patients who received IVCFs prior to the intervention implementation. Patients were tracked in a departmental quality assurance database (iSchedule) and a custom Access database. If an IVCF was not removed in 90 days, a medical record review was performed and patients were given a status of "declared permanent," "candidate for future removal," or "candidate for immediate removal." Patients eligible for future removal were reviewed again in 1-3 months. To follow-up, patients were contact via form letter that reviewed why the initial implant was done as well as the rationale for removal. If no response, additional letters (up to 3) were sent at 1-3 month intervals. Initially,

a phone call was given after failed communication but was abandoned due to workload for a final letter, and patients were declared lost to follow-up at that point.

Before the intervention, 154 IVCFs were placed and 973 were placed afterward (a large increase in overall utilization, 5.8/month increased to 17.5/month). Of those in the pre-period, 37 (24%) were removed compared to 574 (59%). Additionally, IVCFs placed in the pre-period that were prospectively contacted resulted in an additional 47 IVCF removals. Loss to follow-up remained similar during those time periods (18.2% vs. 16.2%). The time to retrieval increased dramatically from a mean/median of 103/91 days in the pre-period up to 307/224 days in the post-period. The proportion of those declared permanent also decreased from 25.3% to 16.7% between the periods. A large number also remained candidates for retrieval, (32% and 85 in pre- and post-periods), indicating that patient contact remained. Of all attempted retrievals reported, there were a low number of failures (9/667, 1.3%). Listed indications for permanence in 202 were need (101, 50%), death (72, 35.6%), and patient refusal (20, 9.9%). The authors note that the patient population resides in a generally rural and affluent area, which made follow-up easier than other settings. They also note the utility gained from an electronic medical record so that such an intervention can be implemented by a single individual.

*Minocha 2010*

The authors implemented an intervention starting in January 2009 and compared it to retrospective data from the 8 years prior at an urban tertiary care center.[42] A

dedicated IVCF clinic was established with a dedicated clinic database. The clinic staff included a nurse coordinator and interventional radiologist; tasks were added to their clinical responsibility. The nurse coordinator updated the prospective database with all patients receiving IVCFs by interventional radiology. Before placement, the interventional radiologist consulted with the referring physician to confirm the indication for IVCF placement, including the need for permanent versus optional devices. The IVCF clinic nurse and radiologist monitored the database and coordinated retrieval with the referring physician when indicated. Referring physicians were contacted 2-3 weeks after placement to discuss the possibility of removal otherwise, or if the device was to be made permanent. Retrieval procedures were initially scheduled after patient visits to the clinic. This was replaced by telephone calls, unless the case was complicated, due to the inefficiency of having multiple visits. Basic statistical analyses were used in addition to Kaplan-Meier survival analysis.

Each year, the proportion of optional IVCFs increased from 21% in 2001 to 64% in 2009. Of the 369 implanted in the pre-intervention period, 108 (29%) were retrieved compared to 60 of 100 placed (60%) in the post-intervention period. Between those two periods, there was a shift in the IVCFs utilized and no difference in the retrieval failure rate (6% vs. 5%). There was a general increase in the number of IVCFs placed per month over these two periods from a median of 3 during 2000-2008 up to a median of 10 per month in 2009. Of those IVCFs not retrieved in the post-intervention phase, 33/40 (82.5%) were deemed permanent. The median time

to retrieval, in which 50% of all IVCFs are placed, was 1.5 months via Kaplan-Meier estimation. Estimated retrieval at 3 months was near 80% according to the survival analysis. Only 2/100 patients experienced complications in the post-intervention period and only 1 was considered lost to follow-up.

*O'Keeffe 2011*

This study describes an intervention instituted at a level 1 trauma center in the United States.[136] At the time of IVCF placement, a fluorescent label was placed on each patient's chart along with an arm bracelet. Such patients were tracked by trauma nurse practitioners (NPs), which confirmed patient contact information prior to discharge. Three months after discharge, the NPs contacted patients to schedule pelvic and lower extremity venous duplex ultrasound. If no DVT were found along with no other contraindications, the NP would schedule IVCF retrieval with the radiology department. In cases of uncertainty, the attending trauma surgeon was consulted for final decision. Non-trauma patients receiving IVCFs received standard care. All IVCFs placed and included in the final analysis were for prophylactic indications only. The authors compared retrieval between trauma and non-trauma patients during the same time period using basic statistics as well as multivariable regression.

Among the trauma group, 91 patients received IVCFs and met criteria for inclusion. Of those, 14 were deemed ineligible for retrieval (3 deaths, 4 DVT present, 7 surgeon judgment). Of the 77 eligible for retrieval, 42 (54.5%) were removed. The

non-trauma group consisted of 76 patients and 45 were deemed ineligible for retrieval (10 deaths, 13 DVT present, 22 still indicated). Of the 31 eligible non-trauma patients, 6 (19.4%) were removed. Overall, the authors reported that there was a total retrieval of There was a difference in median age between the two group of over 20 years, large differences in gender, and shorter indwell times in the non-trauma group (median 14.5 vs. 48.5 days). Regression analysis found that trauma, younger age, and the specific trauma team (i.e. specific to one NP in particular) utilized predicted retrieval overall. Distance from hospital and insurance status were not significant. There is remaining concern over how balanced one can consider the trauma vs. non-trauma comparison, especially for wholly prophylactic indications.

*Sutphin 2015*

This article describes an intervention at a tertiary care hospital with a level-1 trauma center. [78] The article specifically mentions utilizing the DMAIC (Define, Measure, Analyze, Improve, Control) Methodology of Six Sigma as their process for implementation. To define the problem, they retrospectively analyzed retrieval at their institution and found that of all patients receiving IVCFs, 92% were lost to follow-up and 8% were retrieved. Two measures were determined to evaluate, mainly the retrieval rate achieved as well as the proportion of patients followed-up in the clinic. The authors created a process to increase these metrics including increased communication between referring and implanting physicians on how to schedule retrieval. A multidisciplinary team also met to outline issues related to this

workflow and categorized each issue into barriers associated with providers, patients, clinical, and systems and further divided into controllable or uncontrollable (Figure 6.1 reproduced). Key factors included provider knowledge and follow-up, patient knowledge and follow-up after the procedure, lack of a clinical database and a shortage of permanent filters for patients in whom they were indicated. New workflows were designed after recognizing these shortfalls. One workflow addressed patients with an IVCF already in place. A letter was sent to the primary physician to schedule a visit with a lower venous ultrasound study. Letters were repeated every two weeks up to three letters. The second workflow addressed prospective patients and included automatic scheduling of a clinic visit 4 weeks after IVCF placement as outpatient or 4-6 weeks after discharge as inpatient. The clinic visit included consulting and educating the patient about the potential retrieval. In addition, an IVCF database was maintained by a physician assistant, who also investigated non-compliant patient cases. Core monthly meetings and quarterly team meetings evaluated the intervention for adjustments. The cohort was divided into baseline (52 patients, pre-intervention), "letters" (43 patients retrospectively contacted), and prospective (45 patients, scheduled follow-up at placement) for evaluation. Deceased patients were excluded from eligibility, making up 15 (28.8%), 6 (14%), and 12 (26.7%) patients in each group. Basic statistical analyses were conducted.

The baseline group had a retrieval rate of 8% (4/51). This increased to 40% (17/43) in the letters group, and 52% (22/45). Between the groups, the average

time to retrieval was 64, 137, and 59 days, with no reported failures. In addition to the retrievals, ~20% of patients in the letters group and ~50% of those in the prospective group were followed-up in clinic. This increased the revenue per 100 IVCFs implanted from $2,249 in the baseline group, $10,518 in the letters group, and up to $17,022 in the prospective group – showing nearly eight-fold increase in revenue with prospective intervention. The financial analysis is unique among studies and the inclusion of an intervention for a retrospective group shows feasibility beyond only a prospective intervention.

*Wang 2016*

This unique study presents the systemic effect of multiple continuing medical education seminars on the practice patterns in an integrated healthcare system (Kaiser Permanente Northern California).[130] A system-wide IVCF tracking database was also implemented. Twelve in-hospital CME-approved grand rounds were given by a vascular and interventional radiologist specializing in IVCFs. These presentations were also broadcast to satellite clinics and 2 more medical facilities. The 14 facilities serve a combined 3.5 million members of the healthcare system. A new practice model for IVCFs was also introduced and included: (1) the radiology department assumed responsibility for follow-up; (2) a color-coded database alerts users when filters are approaching 9- or 12-week indwell times, the database was also capable of presenting dashboards to each facility if requested; (3) recommendation made to follow ACCP guidelines for IVCF use; (4) established collaboration with the anticoagulation clinic; (5) a monthly procedural code

generated list was made by each facility to double check no patient oversight; (6) a 9-12 week retrieval interval was generally recommended. Outcomes measured were IVCF utilization and retrieval as well as concordance with ACCP and SIR guideline recommendations for IVCF indications.

There was an 18.7% decrease in overall utilization of IVCFs, with changes ranging as low as decreases of 38.7% to increases in 16.7% at individual facilities. There was a significant correlation in the decrease in IVCF utilization and overall physician attendance. In the entire health system, this represented a net decrease in IVCF utilization of 22.2%. Prior to the intervention, 38.9% (111 attempts, 92 successful) of IVCFs were retrieved compared to 54.0% (127 attempts, 109 successful) in the post-intervention group (15.1% change). There was no significant change in indwell time (mean 10.2 vs. 10.8 weeks) or successful attempts (82.3% vs. 85.8%). There was a significant correlation in physician attendance and increased retrieval attempts. There were no differences in guideline concordance between the two periods, but overall compliance with ACCP guidelines was 75.9% (other institutions report 33.3% to 54% compliance with these conservative guidelines). The authors note that there are differences between West and East coast IVCF practices, and also differences between practices by patient payer status and the need for "defensive" medicine. They note these factors are decreased in a closed healthcare system like Kaiser Permanente.

Overall, differences in institutional characteristics, baseline practices, and interventional approach showed a broad range of impacts of these interventions. Absolute changes in retrieval rates ranged from 0% to nearly 70%. Relative changes ranged from 0% to over 2,200+% changes in retrieval rates (Table 6.3).

## Discussion

During this literature review, several key points were recognized and noted including: definition of retrieval (attempted vs. successful), inclusion and exclusion criteria implemented in each study, the statistical analyses utilized, and the potential of observed "Hawthorne" effects. Additionally, few studies reported on the financial aspects of the interventions and there was a large discussion about the responsibility of follow-up being shifted. Each is discussed below with case examples to illustrate how these points can impact how these interventions are evaluated.

*Definition of retrieval*

Studies differed on how they reported attempted versus successful retrievals although all studies used successful retrievals as the primary metric. Nearly all (13/15) reported the number of failed retrievals which ranged from none to nearly 30%; thus, the attempted retrieval rate can at least be calculated if it is not explicitly reported. Generally, retrieval failures can be expected to be 15% of all attempts,

although this can be variable depending on a combination of institutional, physician, and patient factors. In most of these studies, the differences in failed retrievals between pre- and post-intervention periods were not significantly different, although these comparisons were limited because of sample size. Further, if differences exist between the pre and post periods, in the failure rate, reporting and comparing these figures can be more important, more so if the intervention can be expected to impact failure rates in some way. Further, evaluation of these interventions must put in context the goal of the program. Follow-up is generally the goal in that if patients are followed-up with, then retrievals will naturally increase. Thus, both attempted and successful retrieval rates should be reported in such evaluations. Similarly, as the goal is often to retrieve earlier, comparison of indwell times between intervention periods is called for.

*Inclusion and exclusion criteria*

There was wide variation in the patient populations between studies (e.g. trauma, prophylactic, etc.) along with variation in the definition of eligible and included patients in each study. A clear definition of the patient population is paramount to evaluation and how these inclusion and exclusion criteria impact the assessment should be considered. More importantly, the same definition should be applied across pre- and post-intervention periods to allow an unbiased assessment of the program.

*Statistical analyses*

Most studies utilized "simple" statistical analyses in that they included only bivariate tests of significance, mostly chi-squared, Fisher's exact, or equivalent non-parametric or multiple groups tests. Two studies, Minocha and Davies utilized survival analysis in their studies. In each study, details about follow-up, censoring events, and competing events are limited. In Minocha's study, there were few patients lost to follow-up and it is not discernible how many died and were considered censored due to death. In the Davies study, they specify that patients were censored at death including 9/39 (23.1%) patients in the pre-intervention period and 12/56 (21.4%) patients in the post-intervention period.

The general assumption in Kaplan-Meier survival analyses is that censoring is uninformative, which can be interpreted as patients who are censored should not be different that patients that remain in the risk set. In the case of random censoring, e.g. true loss to follow-up, this assumption may generally hold. In the case of death as a censoring event, however, those that die are likely generally different. Thus, death is informative and should be considered a competing event, or a competing risk, and accounted for in estimates of the cumulative incidence of retrieval. [74] Ignoring competing risks will inflate the cumulative incidence as those who die are removed from the risk set (denominator) when the Kaplan-Meier product limit estimator is calculated. This essentially will bias the estimated retrieval rate from these methods; a bias that is on a magnitude determined by the actual death rate in the cohort. In the Davies study, more than 1 out of 5 patients died during follow-up,

a figure that indicates that the Kaplan-Meier estimates are tremendously biased. Davies and colleagues report a 12-month retrieval rate of 100% although 29 of 56 (51.7%) patients actually had retrieval.

To deal with this issue two approaches could be taken, which should likely be determined by the amount of detailed follow-up data included. For one, competing risks could be accounted for using estimation techniques like Fine and Gray's estimate of the cumulative incidence. This would require clear definitions of what constitutes loss to follow-up, censoring, and competing events. Further, studies should consider the impact of when follow-up begins. This is imperative where patients are assessed for ongoing indications for IVCFs and, intuitively, the follow-up for retrieval has not clinically been initiated. The other approach is more conservative and could involve calculating the retrieval rate in basic statistical analyses, i.e. like the majority of the studies in this review. Most important here is to develop a clear definition of who would be included in the denominator and to ensure that a set follow-up time is achieved, so not to punish the retrieval rate due to limited follow-up in those enrolled late into the study. For example, the base calculation of the 51.7% retrieval in the Davies study includes patients who had planned procedures and ongoing indications for retrieval. These patients should likely be excluded from any calculation of retrieval (including the survival analysis).

I may also be more prudent for studies to investigate retrieval rates within a defined time period, especially given the large interest in having shorter indwell times to

decrease device related complications.[30] Thus, we propose investigating retrieval rates with 90-180 days as an outcome versus longer periods. Such a calculation should consider the above recommendations of clear definitions of outcomes, as well. This will avoid potential biases related to follow-up and how eventually patients can be removed from the cohort.

*Hawthorne effect of intervention*

The classical dynamic explains how individuals behave differently when they are aware of ongoing evaluation. This could certainly be the case in most of these studies as those who implemented the interventions had their practice directly affected. Interesting questions can be posed to add to the understanding of the longevity of these policy changes.

However, there also remains the possibility that some pervasive effects could occur due to the ongoing evaluation. One example where this may have occurred is in the article by Logan *et al*. In this study, during the pre-intervention period, 12% of all patients eventually had their IVCFs deemed permanent. Based on the study definition of retrieval rate, this removed these patients from the denominator. In the post-intervention period, this proportion rose to 39% in the post-intervention period. While this could be influenced by several factors, a possible pervasive factor could have included physicians within the clinic becoming more likely to deem IVCFs as permanent, which would inflate the estimated retrieval rate due to the way this study defined this metric.

*Financial analyses*

Two studies, Sutphin *et al* and Charlton-Ouw *et al*, featured financial analyses in their evaluation of retrieval interventions. The Charlton-Ouw financial analysis was done to account for the known issue at this institution of patients being uninsured or having less generous insurance (i.e. Medicaid). [75] Thus, these patients represented potential losses for the IVCF clinic in the hospital, especially if follow-up was increased and more procedures performed. Their analysis showed that the charges from patients with insurance (commercial and Medicare) were enough to "cover" the uninsured group and still result in small revenue for the clinic. While similar considerations may be relevant at other institutions that treat large uninsured populations, this financial analysis is not generalizable.

The financial analysis by Sutphin provided a more generalizable analysis of the financial impact of such an intervention and provides a picture of how increased manpower and relatively simple interventions can be allotted to improve clinic revenue. Using the standardized metric of clinic revenue per 100 IVCFs placed, they show that the baseline revenue was $2,249/100 IVCFs in the baseline group, $10,518/100 IVCFs in the letters group, and up to $17,022/100 IVCFs in the prospective group. As described, the letters intervention with retrospective patients required little application of person-time to implement, i.e. letters were sent and patients or their primary provider could then follow-up. This is somewhat analogous to the simple letter campaign conducted within the UKHC IR clinic. Thus,

it is intuitive that clinic revenue will increase linearly with improvements in retrieval rates and Sutphin has shown it here.

Costs to the clinic are not only procedurally based. Retrievable IVCF equipment and devices are more costly than that of permanent IVCFs. In the context of few retrievals occurring, these devices become *de facto* permanent; thus, a permanent device could have been used in its place. A study by d'Othée and colleagues showed that when both types of devices are available, a minimum retrieval rate of 41% is needed for retrievable devices to be cost-effective compared to permanent devices. [77] All this shows that retrieval impacts costs in multiple ways. Dedication to good practice of retrieving devices can increase both procedural revenue and help recoup costs from increased device costs.

*Responsibility for patient follow-up*

Multiple studies in this review pointed at that the responsibility of patient follow-up was shifted from the patient's referring or primary physician to the physician who performed the implant or the clinic itself. Lynch's article discusses how he himself took on this responsibility to increase retrieval rates, which represents a paradigm shift in physician-to-physician and physician-to-patient communication in this setting, both prior to and after IVCF placement. [41] Minocha and colleagues implemented a similar practice with a dedicated interventional radiologist and nurse conducting follow-up. [42] Each of these studies also included the creation of an IVCF registry or database which assists these clinicians in implementing these plans.

Further, some studies also point out the importance of IVCF retrieval plans being included in discharge plans, enhancing the communication between providers. [81] In Logan's study, this was shown by tracking retrieval rates in those who had thorough documentation of the IVCF implant as well as plans for retrieval in the discharge notes. In the total population, the baseline retrieval rate was 45%, but increased to 91% in patients who had plans documented.

*Applicable guidelines*

In general, two guideline statements can be thought to cover the practice of implanting IVCFs and included the American College of Chest Physician (ACCP) guidelines on the management of VTE [4] and the Society for Interventional Radiology (SIR) guidelines for management of pulmonary embolism. [32] In medicine, the ACCP guidelines are generally considered "conservative" calling for use of IVCFs only if there are clear contraindications to anticoagulation. The ACCP guidelines do not call for prophylactic use. The SIR guidelines are more liberal allowing for prophylactic use in those who do not have an active VTE but are considered contraindicated or are high risk.

Only one study in this review evaluated these SIR and ACCP guidelines in their institution. The study by Wang *et al* of 14 medical centers included evaluation of the concordance of IVCF practices with these guidelines. [130] What they observed was that around 80% of all implantations were supported by ACCP guidelines and 20% were supported only by SIR guidelines. Thus, for this study, it seems the institutions

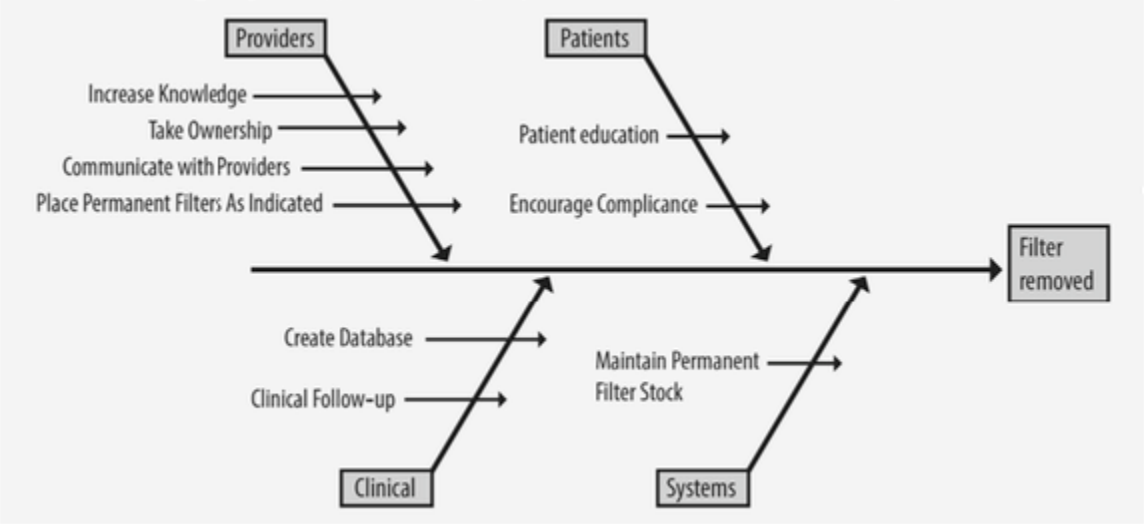
are practicing conservatively. However, this study was conducted within a self-contained health system where patients and physicians are insured and employed by the insurer (Kaiser Permanente) in fully owned medical centers. Because of this, the authors cite that factors that may lead to more liberal use, e.g. defensive medicine practices and need to increase reimbursement, are not present in this setting. To compare, a study not included in this review showed that in two hospitals in New York, compliance with ACCP guidelines was lower at 41.3% and reached 95.7% compliance with SIR guidelines.[33] The main discrepancy being prophylactic use of IVCFs.

## Conclusions

As has been shown, there is wide variation in practices of IVCF utilization and retrieval. This is due to a combination of physician preferences, practice environment, patients, and healthcare system qualities.[78] In the end, the general issue seems to be patient follow-up, which is a result of the aforementioned characteristics. To improve IVCF utilization, continuing medical education of accepted indications for use, indications for retrieval, and how these influence effectiveness and complications related to IVCFs is needed and has been shown to decrease utilization and increase retrieval. Patient education is also needed to ensure informed consent is provided to provide what is generally seen as a "low-value" healthcare service and to reinforce the concept of compliance with future

follow-up. A method of tracking these patients in combination with an individual or team of individuals who take clinical responsibility for this important quality of care issue is needed. [128]

**Figure 6.1: Action items for improvement of IVCF retrieval rates**




Reproduced from Sutphin (2015) [78] with permission

## Table 6.1: Characteristics of studies evaluating interventions to increase inferior vena cava retrieval rates

| Study citation | Study Year(s) | Setting | Intervention | Intervention staff | Implanting services | Control/Comparison group | Indications for insertion |
|---|---|---|---|---|---|---|---|
| Charlton-Ouw 2014 (USA) [75] | Pre: 4/2009-2011; Post: 5/2011-2013 | Level 1 trauma center | Mail, email, telephone follow-up with patients after EMR referral | Clinic nurse or study coordinator. Vascular surgery, trauma, IR physicians in multidisciplinary team. | IR: 23%; VS: 3%; trauma: 74% | Retrospective, pre-intervention | Trauma patients, prophylactic and secondary |
| Davies 2015 (NZ) [40] | Pre: 6/2010-6/2012; Post: 7/012-6/2014 | Tertiary center | Clinical coding registry and PACS review, monthly report. Phone and/or scheduled clinic follow-up. Clinical pathway developed. Focused on filters placed >6 weeks | VTE clinic nurses coordinated effort | IR, VS | Retrospective, pre-intervention | Med-surg patients |
| Gasparis 2011 (USA) [129] | Post: 1/2010-1/2011 | Tertiary center | NP coordinated with patients and referring physician for follow-up. Educated patients pre-discharge about IVCF benefits and risk. Dedicated time in suite. | Dedicated NP maintained database and follow up. Dedicated "DVT Team" with NP and physician. | VS | None: compared to baseline retrieval rate that was from previous study | Med-surg patients |
| Inagaki 2016 (USA) | Pre: 9/2003-7/2012; Post:8/2012-9/2014 | Tertiary center | Retrospective review followed by prospective retrieval program; EMR review. Task force, standardize retrieval process. 1) patient educational pamphlets, 2) procedure form, 3) centralized registry, dedicated coordinator | Multidisciplinary task force from VS, IR, cardiology, trauma, and hematology. Retrieval coordinator | VIR, VS, Cards | Retrospective, pre-intervention | Med-surg patients |
| Irwin 2010 (USA) | 1/2003-6/2008 | Level 1 trauma center | Team met each morning (M-F) to review patient care. Coordinated with IR staff to schedule retrievals. | Multidisciplinary task force of clinical nurses, executed by IR clinical nurse, led by trauma nurses in consultation with | VIR | Retrospective, pre-intervention | Trauma patients, prophylactic and secondary |

**Table 6.1: Characteristics of studies evaluating interventions to increase inferior vena cava retrieval rates**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | trauma surgeons | | | |
| Kalina 2012 (USA) | Pre: 1/2003-12/2005<br>Post: 1/2006-12/2009 | Level 1 trauma center | Filter registry. APNs managed data collection every 2 weeks, presented cases to trauma physicians, directly scheduled procedures. Registry reviewed monthly by department | Trauma surgeon, acute care nursing staff | Placement: trauma, VIR<br>Retrieval: VIR | Retrospective, pre-intervention | Trauma |
| Ko 2009 (USA) | Pre: 1/2004-2/2007<br>Post: 8/2007-7/2008 | Level 1 trauma center | Institutional protocol developed, automated email sent to ordering physician as reminder. Highlighted on rounding list for physicians. | PA, coordination between trauma, VS, IR | VS and IR. Mostly VS: 60% pre and 90% post | Retrospective, pre-intervention | Trauma patients: 1. very high risk; 2. contraindication to anticoag |
| Lee 2012 (UK) | Pre: 5/2007-4/2008<br>Post: 5/2008-4/2009 | Tertiary center | Proactive f/u organized by IR instead of referring physician. Clinical team contacted every 30 days by radiologist via fax to schedule retrieval. | IR | VIR | Retrospective, pre-intervention | Various |
| Logan 2016 (IRL) | Pre: 1/1/2012-3/31/2013<br>Post: 11/2013-12/2014 | Tertiary center | Nurse in charge of filter registry; consult with hematology to decide eligibility for retrieval; bed available for retrieval at short notice | Multidisciplinary team with interventional radiologists, hematologists, and nursing staff | VIR | Retrospective, pre-intervention | Various: major indications varied pre vs. post |
| Lucas 2012 (USA) | Pre: 12/2005-12/2006<br>Post: 1/2007-1/2011 | National Military Medical Center | Tracking system, medical record review and provider communication; Follow-up plans at the time of discharge | Administrative trauma coordinator in charge of tracking system, Multidisciplinary meeting and communication with providers | N/R | Retrospective, pre-intervention | Military combat trauma |
| Lynch 2011 (USA) | Baseline/retrospective: 5/2002-10/2005 | Tertiary center | Chart review and multiple f/u letter communications. IR was given responsibility | A single interventional radiologist | VIR | Retrospective, pre-intervention. Additional f/u with | SIR guideline indications: various |

**Table 6.1: Characteristics of studies evaluating interventions to increase inferior vena cava retrieval rates**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Post: 10/2005-5/2010 | | of follow-up. Informed consent included discussion of IVCFs. Registry maintained in iSchedule and Access database. Non-retrieval flagged if >90 days. Letters for f/u sent, up to 4 | | | past patients. | |
| Minocha 2010 (USA) | Pre: 1/2000-12/2008<br>Post: 1/2009-1/2010 | Tertiary center | Retrospective for pre-intervention pts and prospective for post-intervention pts. Dedicated registry. Contacted referring physician every 2-3 weeks until removed or deemed permanent. | Interventional radiologist and nurse coordinator - dedicated IVCF clinic | VIR | Pre: before IVC filter clinic<br>Post: after IVC filter clinic established in 1/2009 | SIR guideline |
| O'Keeffe 2011 (USA) | 1/1/2006-12/31/2006 | Level 1 trauma center | Prospective only: label, tracked by NP for f/u venous duplex US. F/u in 90 days for imaging and removal. | Multidisciplinary team with trauma surgeons, radiologists, and NPs, while NPs are in charge of aggressive patient follow up | N/R | Trauma (intervention): vs. Non-trauma (standard care): | Prophylactic use only in trauma and non-trauma groups |
| Sutphin 2015 (USA) | Baseline: 1/2012-8/2012<br>Letter (retro): 9/2012-4/2013<br>Prospective: 5/2013-12/2013 | Tertiary center | DMAIC methodology from Six Sigma. Retrospective letters to patients and physicians. Auto scheduling in 4-6 weeks. Correcting issues of physician, patients, clinical, and systems. Separate pathways for past and future patients. | Multidisciplinary team, IR physician/nurse, internal medicine nurse, and hospital quality facilitator | N/R | Baseline: no follow-up<br>"Letters": Patients receiving retrospective f/u. Post: Prospective f/u after full implementation | Various |
| Wang 2016 (USA) | Pre: 12/2011-03/2013<br>Post: 2/2013-5/2014 | 14 urban centers in northern CA (Kaiser | Gave 12 CME grand rounds. Deployed IVC clinic model and tracking system in IR clinics. 9/12 week dwell alerts, optional dashboards. | Board-certified VIR physician, clinical model coordinated IR with anticoagulation clinics at each | VIR - IR (57/59) or NIR (2/59) physicians | Pre- vs. post-intervention, each for one year period. Changes tracked at each institution and | Various |

**Table 6.1: Characteristics of studies evaluating interventions to increase inferior vena cava retrieval rates**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Permanente) | Recommended conservative ACCP guidelines. | institution | | overall. | |

## Table 6.2: Results from studies evaluating interventions to increase inferior vena cava filter retrieval rates

| Study citation | Comparison (N) | Intervention (N) | Comparison retrieval (%) | Intervention retrieval (%) | Comparison indwell time | Intervention indwell time | Failed retrievals | Complications | Loss to f/u |
|---|---|---|---|---|---|---|---|---|---|
| Charlton-Ouw 2014 (USA) | 64 | 111 | 3.1% | 73% | N/R | 6.2±4.0 months | 15% | 1.95% | 1 patient |
| Davies 2015 (NZ) | 39 | 56 | 63% | 100% | 7.4 months | 4.1 months | 3.2% | N/R | 0% |
| Gasparis 2011 (USA) | 14 | 40 | Retrieval: 18% | Attempt: 81%<br>Retrieval: 70% | N/R | 21 days (4 to 140) | 14% | 0% | None |
| Inagaki 2016 (USA) | 720 | 74 | Attempt: 14%<br>Retrieval: 11% | Attempt: 66%<br>Retrieval: 54% | 119 days | 130 days | Pre: 17%<br>Post: 18% | N/R | 34% lost to follow up |
| Irwin 2010 (USA) | 82 | 33 | 65% | 84% | unclear | unclear | 3.5% | N/R | 9.56% |
| Kalina 2012 (USA) | 120 | 113 | 15.5% | 31.5% | N/R | N/R | N/R | N/R | Pre: 21.1%<br>Post: 27.6% |
| Ko 2009 (USA) | 76 | 37 | Attempt: 42%<br>Retrieval: 37% | Attempt: 95%<br>Retrieval: 84% | 24±30 days | 20±15 days | Pre: 12.5%<br>Post: 11% | 0% | 0% |
| Lee 2012 (UK) | 28 | 29 | 50% | 55% | 10 days (median) | 16 days (median) | Pre: 28.6%<br>Post: 18.8% | 0% | Pre: 21%<br>Post: 3% |
| Logan 2016 (IRL) | 33 | 33 | 45%<br>(84% with retrieval plan) | 45%<br>(91% with retrieval plan) | 61 days<br>Failed: 94 days | 44 days<br>Failed: 92 days | Pre: 15%<br>Post: 9% | N/R | Pre: 27%<br>Post: 9% |
| Lucas 2012 (USA) | 20 | 93 | Attempt: 30%<br>Retrieval: 30% | Attempt: 70%<br>Retrieval:60% | 210±190 days | 84±101 days | Pre: 0<br>Post: 13.8% | N/R | Pre: 65%<br>Post: 5% |
| Lynch 2011 (USA) | 154 | 973 | 24% | 59% | Mean: 103 days<br>Median: 91 days | Mean: 307 days<br>Median: 224 days | 1.3% | N/R | Pre: 18.2%<br>Post: 16.2% |
| Minocha 2010 (USA) | 369 | 100 | 29% | 60% | N/R | Mean: 45 days | Pre: 6%<br>Post: 5% | 2% | Post: 2.5% |
| O'Keeffe 2011 (USA) | 31 | 77 | 19.4% | 54.5% | 14.5 days | 48.5 days | N/R | 1.2% | N/A |
| Sutphin 2015 (USA) | 36 | Letters: 25<br>Prospective:42 | 8% | Letters: 40%<br>Prospective: 52% | 64 days | Letters: 137 days<br>Prospective: 59 days | None | N/R | Unclear.<br>19% of letters and 49% of prospective patients not retrieved still had ongoing f/u |
| Wang 2016 (USA) | 285 | 235 | 38.9% | 54.0% | 71.4 days (10.2 weeks) | 75.6 days (10.8 weeks) | Pre: 17.7%<br>Post: 14.2% | 1.6% | 0% |

**Table 6.3: Impact of interventions to increase vena cava filter retrieval rates**

| Study | Pre-intervention retrieval rate | Post-intervention retrieval rate | Absolute change | Relative change |
|---|---|---|---|---|
| Charlton-Ouw 2014 (USA) | 3.1% | 73% | 69.9% | 2254.8% |
| Davies 2015 (NZ) | 63% | 100% | 37.0% | 58.7% |
| Gasparis 2011 (USA) | 18% | 70% | 52.0% | 288.9% |
| Inagaki 2016 (USA) | 14% | 66% | 52.0% | 371.4% |
| Irwin 2010 (USA) | 65% | 84% | 19.0% | 29.2% |
| Kalina 2012 (USA) | 15.5% | 31.5% | 16.0% | 103.2% |
| Ko 2009 (USA) | 42% | 95% | 53.0% | 126.2% |
| Lee 2012 (UK) | 50% | 55% | 5.0% | 10.0% |
| Logan 2016 (IRL) | 45% | 45% | 0.0% | 0.0% |
| Lucas 2012 (USA) | 30% | 70% | 40.0% | 133.3% |
| Lynch 2011 (USA) | 24% | 59% | 35.0% | 145.8% |
| Minocha 2010 (USA) | 29% | 60% | 31.0% | 106.9% |
| O'Keeffe 2011 (USA) | 19.4% | 54.5% | 35.1% | 180.9% |
| Sutphin 2015 (USA) | 8% | 52% | 44.0% | 550.0% |
| Wang 2016 (USA) | 38.9% | 54.0% | 15.1% | 38.8% |

## CHAPTER 7: CONCLUSIONS AND FUTURE DIRECTIONS

These studies have evaluated the utilization and retrieval of VCFs in both Kentucky and Nationally to put in context the quality of care surrounding this medical device. IVCFs are commonly utilized in the U.S. population with patient selection generally consisting of those with significant comorbidities that may affect their risk for VTE or bleed events. In these patients, and in a medical environment that encourages defensive medicine, IVCF use has increased to nearly 1-in-5 and 1-in-10 patients with PE and DVT. Further, IVCF use is in nearly equal quantities as prophylactic devices, an indication that is both refuted and supported by conflicting guidelines and remains, technically, off-label use, with little evidence for effectiveness. In fact, IVCF utilization has been used as one of several procedures to track low quality hospitals, physicians, and clinics as a procedure that has not be definitively shown to be effective. It is telling that when physicians are educated on the evidence behind these devices, the utilization decreases significantly and the retrieval increases significantly. [130]

In Kentucky, utilization was on par with national estimates, with similar findings in the epidemiology of use. Use is high in those with bleeding, cancer, or other conditions related to VTE or bleed risk. Interestingly, compared to another study in California, IVCF utilization between hospitals in Kentucky was less variable, and explained strongly by patients' clinical characteristics. The fact that use was less

variable shows that there is even more variability between states, regions, etc. in how these devices are used. Often, when variability on this scale is observed, there can be inferred a large quality of care issue. That is, when your propensity to receive a certain procedure is largely determined by where or by whom you receive care, the standard of care needs to be evaluated.

This is precisely the motivation for future work that have been driven by these studies as I transition from observational to interventional considerations. As Chapter 5 shows, quality of care at the University of Kentucky hospital VIR clinic is poor in terms of VCF retrieval and follow-up care. Chapter 6 was devoted to reviewing what other institutions have implemented to increase their own retrieval rates. Our aim was to glean a list of concepts from these interventions that are associated with success, i.e. increases in retrieval rates and decreases in the time-to-retrieval. Since that time, the initial planning of a quality of care intervention has begun, including a letter of intent to the translational research institute at the University. This intervention will acknowledge and look to improve upon the poor retrieval rates in the VIR clinic by incorporating learnings from the literature review including: 1) a prospective patient registry; 2) dedicated follow-up visits with the implanting VIR physician; 3) certified mail letters sent to patients and physicians. Using these interventions, we hypothesize that we can increase the retrieval rate in the VIR clinic to over 50%, shorten the time-to-retrieval, maximize anticoagulation and VTE therapy, as well as increase clinic revenue from additional patient visits and procedures. We hope that the intervention will be successful, most importantly,

but also that it will also pay for itself so that instituting it permanently can be broadly supported by the institution.

Lastly, future work also hopes to fill significant knowledge gaps regarding the optimal time for retrieval. The Morales study that informed the FDA safety communication synthesized the data and developed simulation models specified for a prophylactic indication.[31] Thus, as mentioned earlier, there is a general lack of knowledge regarding the optimal retrieval time in a patient with active VTE disease. Such information must account for confounding factors, patient age, VTE type, etc. and must be specialized to some distinct patient subgroups (e.g. cancer). Future work will expand on the Morales model by adding inputs that account for the risk of recurrent VTE (DVT or PE), VCF-related complications, and complications from anticoagulation. The establishment of a time-scale for retrieval and a deeper understanding of the net clinical benefit has the potential to influence the quality of care with VCFs, ensuring that the right device is used in the right patient at the right time.

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## Education

***2014 – present*** ***Ph.D. candidate Pharmaceutical Outcomes & Policy***
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University of Kentucky College of Pharmacy
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***2011 – 2014*** ***M.S. Pharmaceutical Evaluation & Policy***
University of Arkansas for Medical Science (UAMS)
College of Pharmacy – Little Rock, AR

***2010 – 2014*** ***Pharm.D. Doctor of Pharmacy***
UAMS - College of Pharmacy – Little Rock, AR
*With honors, with honors in research*

***2006 – 2010*** ***B.S. Biochemistry, Cum laude***
University of Arkansas – Fayetteville, AR

## Current Employment

***7/2014 – present*** ***Humana-Pfizer Post-Doctoral Fellow***
Comprehensive Health Insights, Humana Inc. –
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Supervisors: Margaret Pasquale, PhD; Jim Harnett,
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Institute for Pharmaceutical Outcomes & Policy – University of Kentucky College of Pharmacy – Lexington, KY
Supervisor: Jeffery Talbert, PhD

**Peer-reviewed Publications**

1. Brown JD, Hutchison LC, Martin BC. Comparing the Tools to Identify Potentially Inappropriate Medications in the Elderly and Future Research Directions. *Journal of Gerontology and Geriatrics Research*. 2016. DOI: 10.4172/2167-7182.1000321.
2. Brown JD, Shewale AR, Dherange P, Talbert JC. Treatment with anticoagulants for stroke prevention in atrial fibrillation is increasing but further improvements are needed. *Journal of the American College of Cardiology*. 2016 (Accepted).
3. Brown JD, Pauly NJ, Doshi PA, Talbert JC. Neonatal Abstinence Syndrome (NAS) rates increase despite efforts to combat the opioid abuse epidemic. *JAMA Pediatrics*. 2016. doi:10.1001/jamapediatrics.2016.2150.
4. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naïve non-valvular atrial fibrillation. *Journal of Managed Care and Specialty Pharmacy*. 2016 (In press).
5. Brown JD and Talbert JC. Hospital variation and patient characteristics associated with vena cava filter utilization. *Medical Care*. 2016 (In press). DOI: 0.1097/MLR.0000000000000599
6. Brown JD, Sheer RL, Null KD, Pasquale MK, Sato R. The relative burden of community-acquired pneumonia in seniors. *American Journal of Preventive Medicine*. 2016. doi:10.1016/j.amepre.2016.05.015
7. Brown JD. Low-cost generic drug programs in the United States: implications for payers and researchers. *Generics and Biosimilars Initiative Journal*. 2016. DOI: 10.5639/gabij.2016.0501.003

8. Brown JD, Shewale AR, Dherange P, Talbert JC. Comparison of oral anticoagulant utilization for atrial fibrillation in the elderly in the post-DOAC era: therapeutic substitution or increased treatment? *Drugs & Aging.* 2016. DOI: 10.1007/s40266-016-0369-y
9. Brown JD, Talbert JC. Explained variation in hospital utilization of vena cava filters in Kentucky. *JAMA Surgery*. 2016. DOI: 10.1001/jamasurg.2016.1004
10. Brown JD, Pauly NJ, Talbert JC. The Prevalence and Predictors of Low-Cost Generic Program Use in a Nationally Representative Uninsured Population. *Pharmacy*. 2016;4(1):14. DOI: 10.3390/pharmacy4010014.
11. Brown J, Adams V. Incidence and Risk Factors of Thromboembolism with Multiple Myeloma in the Presence of Death as a Competing Risk: An Empirical Comparison of Statistical Methodologies. *Healthcare*. 2016;4(1):16. DOI:10.3390/healthcare4010016.
12. Brown JD, Doshi PA, Talbert JC. Utilization of free medication samples in the United States in a nationally representative sample: 2009-2013. *Res Social Adm Pharm*. January 2016. DOI:10.1016/j.sapharm.2016.01.006.
13. Brown JD, Hutchison LC, Li C, Painter JT, Martin BC. Predictive Validity of the Beers and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) Criteria to Detect Adverse Drug Events, Hospitalizations, and Emergency Department Visits in the United States. *J Am Geriatr Soc*. 2016;64(1):22-30. doi:10.1111/jgs.13884.
14. Pauly NJ, Talbert JC, Brown JD. Low-Cost Generic Program Use By Medicare Beneficiaries: Implications For Medication Exposure Misclassification In Administrative Claims Data. *J Manag care Spec Pharm*. 2016;22(6):741-751. DOI:10.18553/jmcp.2016.22.6.741
15. Pauly NJ, Brown JD. Prevalence of Low-Cost Generic Program Use in a Nationally Representative Cohort of Privately Insured Adults. *J Manag care Spec Pharm*. 2015;21(12):1162-1170. doi:10.18553/jmcp.2015.21.12.1162.
16. Brown JD, Ratermann K, Talbert J, Adams V. Competing Risks Analysis of Cancer-associated Recurrent Thrombosis, Major Bleeds, and Death in a Geriatric Cohort. *JHEOR*. 2015;3(2):214-223.

17. Pauly NJ, Talbert JC, Brown JD. The Prevalence and Predictors of Low-Cost Generic Program Use in the Pediatric Population. *Drugs - Real World Outcomes*. 2015;2(4):411-419. doi:10.1007/s40801-015-0051-4.
18. Shewale AR, Borse MS, Brown JD, Li C. Mental health status of varenicline and bupropion users during a quit attempt compared to current smokers, other quitters, and non-smokers. *Drug Alcohol Depend*. 2015;154:132-138. doi:10.1016/j.drugalcdep.2015.06.028.
19. Brown J, Li C. Characteristics of online pharmacy users in a nationally representative sample. *J Am Pharm Assoc*. 2014;54(3):289-294. doi:10.1331/JAPhA.2014.13169.
20. Gupta PK, Brown J, Biju PG, et al. Development of high-throughput HILIC-MS/MS methodology for plasma citrulline determination in multiple species. *Anal Methods*. 2011;3(8):1759. doi:10.1039/c1ay05213f.

**Selected Poster and Podium Abstracts**

1. Brown JD, Talbert JC. Variation in the use of vena cava filters in Kentucky hospitals. International Conference for Pharmacoepidemiology, Dublin, IRL, August 23-27, 2016.
2. Brown JD, Adams VR, Moga DM. Transient impact of treatment exposures and one-year incidence of thrombosis in multiple myeloma: a case-time-control analysis. ISTH SSC Meeting, Montpellier, FR, May 22-25, 2016. *Podium and poster **Young Investigator Award ***Top Abstract Award ****Presidential Award
3. Brown J, Pauly N, Talbert J. The Prevalence and Predictors of Low-Cost Generic Program Use in the Pediatric Population. AMCP Annual Meeting, San Francisco, CA, April 19-22, 2016. *Gold Medal Abstract Award
4. Brown J, Sheer R, Null K, Pasquale M, Sato R. The relative burden of community-acquired pneumonia hospitalizations compared to other serious conditions in the older population. AMCP Annual Meeting, San Franciso, CA, April 19-22, 2016. *Silver Medal Abstract Award

5. Brown JD, Adams VR, Moga DM. Transient impact of treatment exposures and one-year incidence of thrombosis in multiple myeloma: a case-time-control analysis. ICPE Mid-Year Conference, Baltimore, MD, Apriil 10-12, 2016. *Podium **Abstract scholarship award
6. Brown J, MacLean E, Cisar L, Mardekian J, Harnett J. Treatment patterns and costs associated with axitinib and everolimus treatment for renal cell carcinoma: a commercial health claims analysis. American Society of Clinical Oncology (Accepted).
7. Pauly NJ, Brown JD. Low-Cost Generic Program Use By Medicare Beneficiaries: Implications For Medication Exposure Misclassification In Administrative Claims Data. International Conference for Pharmacoepidemiology (ICPE), Boston, MA, August 22-26, 2015
8. Pauly NJ, Brown JD. Use of low-cost generic programs in a nationally representative Medicare population and implications for quality initiatives. ISPOR International Meeting, Philadelphia, PA, May 16-20, 2015. AMCP Annual Meeting, San Francisco, CA. *Gold Medal Abstract Award
9. Pauly NJ, Brown JD. Prevalence of Low-Cost Generic Program Use in a Nationally Representative Cohort of Medicare Beneficiaries. ISPOR International Meeting, Philadelphia, PA, May 16-20, 2015.
10. Brown J, Ratermann K, Talbert J, Adams V. Risk of recurrent VTE or bleed in cancer patients: a time-to-event analysis. Hematology/Oncology Pharmacy Association Annual Conference, 2015, Austin, TX, March 25-28.
11. Brown J, Ratermann K, Talbert J, Adams V. Factors directing anticoagulation treatment in cancer patients with VTE. UHC Pharmacy Council Meeting, Anaheim, CA, December 5-6, 2014.

**Grants and research support**

- "Cancer-related venous thromboembolism: treatment choice, patterns, and outcomes."

- Role: Co-PI. Submitted in partnership with faculty mentors. Funded ($40,000) by the Hematology-Oncology Pharmacist Association (HOPA, 2016).

**Honors and awards**

- Gold medal abstract, Academy of Managed Care Pharmacy Annual Meeting (2016)
- Silver medal abstract, Academy of Managed Care Pharmacy Annual Meeting (2016)
- Best Graduate Student Poster, Rho Chi Research Day, University of Kentucky College of Pharmacy (2016)
- Young Investigator Award, International Society for Thrombosis and Haemostasis (2016)
- Milwaukee Presidential ISTH Scientific and Standardization Committee Award (2016)
- Top Abstract Award, ISTH Scientific and Standardization Committee Meeting (2016)
- Student Travel Award, ISPE Annual Conference (2016)
- Student Abstract Award, ISPE Mid-Year Meeting (2016)
- University of Kentucky Graduate Student Travel Award (2015, 2016)
- Student Travel Award for European Congress, International Society for Pharmacoeconomics and Outcomes Research European Congress (2014)
- Paul Ambrose Scholars Program (2013)
- AACP-Walmart Scholars Program (2013)
- Express Scripts Dual Degree Scholar (2012-14)