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Incidence of and Risk Factors for Thromboembolic Events in Elderly Medicare Patients With Kidney Cancer

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Abstract

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MBMA, North Carolina State University, 1995

BS, Virginia Polytechnic Institute and State University, 1992

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

The incidence of venous and arterial thromboembolic events (VTEs/ATEs) varies greatly by cancer type and age, with increased risk in the elderly. Very little research has been reported specific to elderly kidney cancer patients. Retrospective cohort analyses of Medicare patients, 11,463 with and 11,463 without kidney cancer, between 2003 and 2010 were conducted to compare incidence rates of VTEs/ATEs in cancer patients with matched noncancer patients and to assess independent risk factors for VTEs in cancer patients. The advanced epidemiology triangle was the theoretical framework used to interpret the association between incident events and other factors. Using Cox proportional hazard regression, the first 2 research questions examined whether the incidence rates of VTEs/ATEs were higher in kidney cancer patients than noncancer patients; the third research question assessed which factors were associated with VTEs after kidney cancer diagnosis. In the year prior to index date, cancer patients had higher incidence rates of VTEs than noncancer patients; the incidence rate of myocardial infarction was higher in cancer patients than noncancer patients for patients with a history of cardiovascular disease. Elderly kidney cancer patients with transitional cell tumors had lower rates of pulmonary embolism and ischemic stroke compared to patients with clear cell tumors. Recent history of VTE and Charlson comorbidity score were strong predictors of VTE after cancer diagnosis. These results can lead to positive social change by helping healthcare providers to determine who may benefit from closer observation or prophylaxis to prevent or minimize morbidity from these thromboembolic events, thus improving health and quality of life for elderly kidney cancer patients.

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Dedication

I dedicate this dissertation to my family, especially my husband Mark, for all of their support.

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Chapter 1: Introduction to the Study

Introduction

Cancer patients are at increased risk of thromboembolic events, a group of serious conditions caused by a blockage of a vein or artery by a blood clot (Blom, Doggen, Osanto, & Rosendaal, 2005; Sallah, Wan, & Nguyen, 2002; Walker, Card, West, Crooks, & Grainge, 2013; White et al., 2005). Venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) in cancer patients can cause serious complications and reduce survival (Agnelli et al., 2006; Chew, Wun, Harvey, Zhou, & White, 2006; Sørensen, Mellemkjaer, Olsen, & Baron, 2000; Svoboda, Poprach, Dobes, Kiss, & Vyzula, 2012; Yeh & Bickford, 2009; Zhang et al., 2007). Cancer cells and tumors increase the risk for thromboembolic events through effects on blood vessels and blood flow, tissue necrosis, and cellular changes which promote clotting (Kuderer, Ortel, & Francis, 2009; Previtali, Bucciarelli, Passamonti, & Martinelli, 2011). Cancer-directed surgery also increases the risk of thromboembolic events, however the risk appears to vary by surgery type and the risk may be decreased through prophylactic therapy (Agnelli et al., 2006; Blom et al., 2006; Hall et al., 2009; Khorana et al., 2008; National Comprehensive Cancer Network [NCCN], 2015; Previtali et al., 2011; Sallah, Wan, & Nguyen, 2002). Surgery increases the risk for thromboembolic events through increased tissue factor expression and increased coagulation from immobilization and inactivity (Previtali et al., 2011). Chemotherapy and targeted therapies increase the risk for thromboembolic events by increasing tissue factor expression and reducing natural anticoagulant proteins in the bloodstream (Previtali et al., 2011).

Two of the factors which affect the incidence and risk of ATEs and VTEs in cancer patients are tumor type and patient age (Blom et al., 2006; Chew et al., 2006; Connelly-Frost, Shantakumar, Kobayashi, Li, & Li, 2013; Khorana & Connolly, 2009; NCCN, 2015; Piccirillo et al., 2008; Scappaticci et al., 2007; Walker et al., 2013). Age, gender, and calendar year adjusted incidence rates of VTEs per 1,000 person-years varied from 1.3 to 23 depending on the tumor site, with a rate of 4.7 for kidney cancer patients (Walker et al., 2013). Incidence rates of ATEs for kidney cancer patients were not identified in the literature, however an incidence proportion of 1.3% was reported based on clinical trial studies of patients treated with sunitinib or sorafenib chemotherapies for advanced or metastatic renal cell carcinoma (the most common type of kidney cancer) (Choueiri, Schutz, Je, Rosenberg, & Bellmunt, 2010). Kidney cancer is one of the 10 most common newly diagnosed cancers in U.S. men and women, with more than 60,000 new cases of kidney cancer diagnosed each year (American Cancer Society, 2015). In spite of the significant numbers of kidney cancer patients, information on VTEs and ATEs in kidney cancer patients is sparse.

The risk of VTEs in cancer patients also varies by other factors including cancer stage, receipt of chemotherapy, cardiovascular surgeries, history of a VTE or cardiovascular disease, and placement of a central venous catheter (Alcalay et al., 2006; Blom et al., 2005; Chew, Wun, Harvey, Zhou, & White, 2007; Connelly-Frost et al., 2013; Moore et al., 2011; Sallah, Wan, & Nguyen, 2002). Possible other risk factors are tumor histology and receipt of cancer-directed surgery (Alcalay et al., 2006; Blom, Osanto, & Rosendaal, 2004; Chew et al., 2007).

There is little published information about the incidence of ATEs and VTEs or the risk factors for VTEs in kidney cancer patients, even less so in elderly kidney cancer patients (Chew et al., 2006; Hall, Andersen, Krumholz, & Gross, 2009; Smith et al., 2014). Information specific to kidney cancer may aid patients and healthcare providers in assessing the likelihood of VTEs and ATEs in this population. Accurate risk assessments are important for determining if close patient observation or prophylactic treatments are warranted (NCCN, 2015; Walker et al., 2013).

Studies specific to elderly cancer patients are important because the elderly are a growing number of cancer patients and have age-related issues which impact care, morbidity and mortality (International Society of Geriatric Oncology, 2011; NCCN, 2015; Repetto et al., 2003). The probability of developing cancer increases with increasing age (American Cancer Society, 2015). Age has also been identified as a risk factor for VTEs in some cancer patients, but not consistently (Agnelli et al., 2006; Alcalay et al., 2006; Chew et al., 2006, 2007; Moore et al., 2011). As the United States population age distribution shifts towards greater proportions of elderly persons and life expectancy increases, the number of elderly cancer patients continues to increase and remains as a significant public health and medical issue (International Society of Geriatric Oncology, 2011; Repetto et al., 2003). Elderly patients are affected by issues which may impact their outcomes more so than younger patients including less participation or eligibility for clinical trials (which hinders knowledge of optimal treatments), patient and provider beliefs, functional status, comorbidities and risk of drug interactions, and cognitive functions (International Society of Geriatric Oncology, 2011;

NCCN, 2015; Repetto et al., 2003). A comprehensive study of the incidence of selected ATEs and VTEs and risk factors for these VTEs in elderly kidney cancer patients may improve understanding of the disease burden and risks in this at risk population.

This chapter begins with an overview of kidney cancer, including its epidemiology, histology groups, staging, and treatment, followed by a summary of published literature on VTEs and ATEs in elderly kidney cancer patients. This chapter also contains a statement of the research problem, the purpose of the study, and a listing of the descriptive analyses, research questions and their corresponding hypotheses. A description of the theoretical framework of the study, the nature of the study, and terms used in this study are presented. The next section assesses the study assumptions, scope, delimitations, and limitations. This chapter ends with the study significance and a summary of the chapter.

Background

Epidemiology of Kidney Cancer

It is estimated that over 60,000 people in the United States were newly diagnosed with kidney cancer in 2015 (American Cancer Society, 2015). Kidney cancer is the seventh most commonly diagnosed cancer in men and tenth most common in women (American Cancer Society, 2015). More than 90% of all kidney cancers in adults are renal cell carcinomas (RCC) (National Cancer Institute, 2010; Surveillance, Epidemiology, and End Results [SEER] Program, 2012). Renal cell carcinomas are malignant tumors that grow in the lining of kidney tubules (National Cancer Institute, 2013; SEER, 2012). Another 7% to 10% of kidney cancers are transitional cell cancers

which arise in the renal pelvis and have different histology, survival and staging than RCC (American Joint Committee on Cancer [AJCC], 2002; SEER, 2012). Established risk factors for kidney cancer include smoking tobacco, obesity, and hypertension (American Cancer Society, 2015; DeCastro & McKiernan, 2008; Ljungberg et al., 2011; National Cancer Institute, 2010; Weikert & Ljungberg, 2010). The risk of kidney cancer is also higher in patients with a family history of kidney cancer, end-stage renal disease (ESRD) or chronic renal failure, or mutations in the von Hippel-Lindau (VHL) gene (von Hippel Lindau syndrome), *c-met* proto-oncogene, *fumarate hydratase* gene, or *folliculin* tumor-suppressor gene (American Cancer Society, 2015; Ljungberg et al., 2011; National Cancer Institute, 2010; Weikert & Ljungberg, 2010). Evidence is inconsistent regarding an association between kidney cancer and occupational exposures to chemicals or carcinogenic metals (Ljungberg et al., 2011).

Kidney cancer predominantly affects the elderly and men. The median age of U.S. kidney cancer patients diagnosed from 2007 to 2011 is 64 years old for all patients, 63 years for men, 65 years for women, 64 for Whites, and 61 for Blacks (Howlader et al., 2014). During that same period, kidney cancer incidence rates for patients diagnosed at 65 years of age or older were 91.7 cases per 100,000 for men, 45.0 for women, 66.8 for Whites, and 73.8 for Blacks, respectively (Howlader et al., 2014). At each age group, the incidence rates for men were about two-fold the rate for women.

The age-standardized incidence rates of kidney cancer in the United States increased 2% to 3% between 1975 to 2008, followed by an annual percent change of approximately -1.0 from 2008 to 2011 (Howlader et al., 2014). More frequent use of

abdominal imaging over time is hypothesized to be part of the reason for the increase in incidence; however it does not fully explain the trend (American Cancer Society, 2013; Tyson et al., 2013).

Kidney cancer is a public health burden, especially in the elderly population (American Cancer Society, 2015; Howlader et al., 2014). Within the kidney cancer patient population, there are differences in incidence and survival by age, race, gender, and stage. Better understanding of the risks of VTEs and ATEs within these subpopulations is a start to improving patient care and adding to geriatric oncology knowledge.

Types of kidney cancer. The majority (90% or more) of kidney cancer tumors are RCC and the remainder are primarily transitional cell tumors of the renal pelvis (7% to 10%) (National Cancer Institute, 2010; SEER, 2012). Transitional cell tumors are a different histologic tumor type than RCC. Renal cell carcinoma is further divided into four main histology groups of clear cell, papillary, chromophobe, and other (Kovacs et al., 1997). In elderly kidney cancer patients, clear cell RCC is the most common group. Table 1 shows the definitions by ICD-O morphology code for each type of RCC and the proportions estimated in kidney cancer patients 60 years of age or older at diagnosis based on data from Keegan et al. (2012) and Olshan et al. (2013).

Table 1

Proportion of RCC Histology Groups in Elderly Kidney Cancer Patients

	ICD-O Histology Codes	Proportion in Kidney Cancer Patients aged 60 or older
Clear Cell	8310, 8312	79% - 82%
Papillary	8260	9% - 13%
Chromophobe	8317, 8270	4% - 5%
Other	All RCC codes except 8310, 8312, 8317, 8260, and 8270	3%- 5%

Note. Proportions of each histology type were based on data in Keegan et al. (2012) and Olshan et al. (2012).

Both studies of RCC patients used the SEER cancer registry data (Keegan et al., 2012; Olshan et al., 2013) but used different populations, different time periods and reported different age groups. Keegan et al. (2012) analyzed patients diagnosed with RCC between 2000 and 2005 in the SEER registries who underwent nephrectomy during the first course of treatment. The study by Olshan et al. (2013) included patients with clear cell, papillary or chromophobe RCC diagnosed in the SEER registry areas between 2000 and 2009.

The majority of kidney cancers are RCC (National Cancer Institute, 2010; SEER, 2012). Renal cell carcinoma can be further classified into four main histology groups (Kovacs et al., 1997). Histology group can impact patient prognosis (Keegan et al., 2012; Patard et al., 2005). As discussed further below, differences in incidence rates of VTEs by histology group has been noted in some tumors but not others (Alcalay et al., 2006; Blom et al., 2004; Chew et al., 2007, 2008). This study was the first known study to assess whether the incidence rates of VTEs and ATEs in kidney cancer patients differ by

histology group. It also assessed whether histology type is a risk factor for VTEs in kidney cancer patients.

Kidney cancer staging. Cancer staging is used to inform the healthcare provider about the extent of disease, as well as determine the type of treatment and patient prognosis (SEER, 2012). The main two staging systems used are the SEER summary stage and the staging system by the American Joint Committee on Cancer (AJCC) (SEER, 2012). Summary stage has five main groups which are (a) in situ, (b) localized, (c) regionalized, (d) distant, and (e) unknown (SEER, 2012). The main disadvantage of using the summary staging system is that the categories are very broad and may contain a wide variation of tumors (SEER, 2012). The AJCC staging system is a more detailed system defined by a combination of three components based on tumor size or invasiveness (T), whether tumor cells are present in regional lymph nodes (N), and whether the tumor has metastasized to distant sites (M) (AJCC, 2002; SEER, 2012). There are several editions of the AJCC cancer staging system, and the 6th edition was designed to use with cancer cases diagnosed from 2003 to 2009.

There are four stages for kidney cancer (excluding tumors of the renal pelvis) by the AJCC staging algorithm (a) Stage I, (b) Stage II, (c) Stage III, and (d) stage IV (AJCC, 2002). Stage I is defined by a tumor of 7 centimeters or less which is confined to the kidney, no regional lymph node metastases, and no distant metastases (AJCC, 2002). Stage II is defined by a tumor of greater than 7 centimeters which is confined to the kidney, no regional lymph node metastases, and no distant metastases (AJCC, 2002). Stage III is defined by a tumor with no distant metastases but which (a) extends beyond

the kidney into veins or fatty tissue around the kidney, or (b) had metastases in a single regional lymph node (AJCC, 2002). Stage IV is defined by extension of the tumor beyond the veins and fatty tissues around the kidney, metastases in more than one regional lymph node, or distant metastases (AJCC, 2002).

The AJCC staging system (sixth edition) of renal pelvis tumors is defined as follows. Stage I, II, and III tumors do not have any regional lymph node metastasis or distant metastasis (AJCC, 2002). These stages are distinguished by tumor extension. Stage I tumors have extended into the subepithelial connective tissue; Stage II tumors have extended the muscularis; and Stage III tumors have extended beyond the muscularis into peripelvic fat or the renal parenchyma (AJCC, 2002, p. 330). Stage IV tumors are defined by either (a) tumor extension into adjacent organs or into the perinephric fat, (b) any regional lymph node metastasis, or (c) distant metastasis (AJCC, 2002). AJCC stage instead summary stage was used to define stage in this study as the AJCC staging system is more detailed and clinically relevant.

VTEs and ATEs in elderly kidney cancer patients. The medical dictionary defines a thromboembolism as "the blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation" (MedlinePlus, 2014). According to the Centers for Disease Control and Prevention (CDC), the blockage or blood clot can occur in the vein (venous thromboembolism) or in an artery (arterial thromboembolism) (CDC, 2014). Two major types of VTEs are deep vein thrombosis (DVT) and pulmonary embolism (PE). Arterial thromboembolic events in arteries of the heart or brain include ischemic stroke, transient ischemic attack, heart attack, and other cardiovascular

complications (CDC, 2014; MedlinePlus, 2014). Venous and arterial thromboembolic events may result in patient death, organ damage, or other serious health conditions (CDC, 2014; MedlinePlus, 2014).

The risk factors for VTEs in cancer patients include age, cancer treatment (e.g., surgery, chemotherapy, immunotherapy), cancer site, history of VTE/ATE and cardiovascular conditions, comorbidities, cancer stage, histology group, major surgeries, hospitalizations, central venous catheter, and clinical factors (Blom et al., 2006; Connelly-Frost et al., 2013; Khorana & Connolly, 2009; NCCN, 2015). Comorbidities can be assessed individually or by a comorbidity index. The Charlson comorbidity index was originally developed to predict mortality in hospitalized patients due to comorbid conditions, and then adapted for predicting other adverse outcomes in hospitalized patients (Klabunde, Potosky, Legler, & Warren, 2000). The comorbidity index has been expanded and tested on inpatient and outpatient claims databases, and used for predicting other outcomes in patients including thromboembolic events (Doyle, et al., 2005; Klabunde, Legler, Warren, Baldwin, & Schrag, 2007; Smith et al., 2014).

Incidence rates of VTEs in kidney cancer patients were found in two published articles, with other articles reporting cumulative incidence (Agnelli et al., 2006; Blom et al., 2006; Chew et al., 2006; Walker et al., 2013). Only one of the articles presented incidence rates by age group, and the incidence rate for VTEs for kidney cancer patients age 60 years or older at diagnosis was 14 per 1,000 person-years (95% *CI* 10 - 18) (Walker et al., 2013). The studies varied in incidence measure reported and duration of follow-up after cancer diagnosis. Another study reported incidence rates of VTEs in

elderly RCC patients (Connelly-Frost et al., 2013). The study of RCC patients aged 65 years or older at diagnosis and who had Medicare coverage reported incidence rates per 1,000 person-years of 32.2 (95% *CI* 29.1-35.7) and 108.2 (95% *CI* 101.6-115.2) for DVT in the year prior and year after RCC diagnosis, respectively (Connelly-Frost et al., 2013). The incidence rates for pulmonary embolism were 8.0 (95% *CI* 6.5-9.8) and 30.0 (95% *CI* 26.6-33.7), for the same two respective periods relative to RCC diagnosis (Connelly-Frost et al., 2013). The incidence rates for the grouping of other VTEs were 23.7 (95% *CI* 21.1-26.7) and 49.0 (95% *CI* 44.6-53.7), in the year prior and year after RCC diagnosis respectively (Connelly-Frost et al., 2013). Incidence rates by RCC histology group were not reported by Connelly-Frost et al. (2013).

Incidence rates of ATEs were not found in the published literature, but cumulative incidence was found in cancer patients treated with chemotherapy. The incidence for myocardial infarction ranged from 0.2% to 2.9% depending on the treatment and patient population (Bayer HealthCare Pharmaceuticals, 2013; GlaxoSmithKline, 2014; Moore et al., 2011). Other studies reported incidence of ATEs as a group and the results ranged from 1.3% to 3.8% for chemotherapy-treated patients of all ages, varying by treatment and study population (Choueiri et al. 2010; Scappaticci et al., 2007). A pooled analysis of clinical trial data reported an incidence of ATEs in patients age 65 years or older as 2.5% in control patients and 7.1% in bevacizumab-treated patients (Scappaticci et al., 2007). In the patients 65 years or older, the incidence of ATE was 2.6% and 4.4% in controls and treated patients without a history of ATE, respectively, and 2.2% and 17.9% with a

history of ATE in the controls and bevacizumab-treated patients respectively (Scappaticci et al., 2007).

Summary

In summary, elderly kidney cancer patients are at increased risk of VTEs and ATEs which can increase mortality and cause other health problems (Blom et al., 2006; CDC, 2014; Connelly-Frost et al., 2013; Khorana & Connolly, 2009; MedlinePlus, 2014; NCCN, 2015). Incidence measures for VTEs in kidney cancer patients are available in the literature for VTEs but they are not consistent, and incidence of ATEs in kidney cancer patients is limited to clinical trial data from a specific subset of kidney cancer patients. The evidence of risk of VTEs and ATEs in elderly kidney patients is based mostly on studies of other tumor types and patients of all ages (Blom et al., 2005, 2006; Connelly-Frost et al., 2013; Sallah, Wan, & Nguyen, 2002; White et al., 2005).

I sought to address this gap in the knowledge of VTE and ATE incidence rates and the risk factors for VTEs specific to a recent cohort of elderly kidney cancer patients with Medicare coverage using population-based data. Having the information for this specific population on the incidence and risk factors for thromboembolic events can aid healthcare providers and patients in making informed decisions about the patients' risks for VTEs and ATEs, and thus improve both patient outcomes and patient care.

Problem Statement

Despite the risk of morbidity and mortality from VTEs and ATEs in cancer patients, in depth analyses of incidence rates and risk factors for these conditions have not been conducted in elderly kidney cancer patients. Incidence rates of VTEs and ATEs

in cancer patients vary widely by type of cancer and patient age, however very little published information is available specifically about elderly kidney cancer patients (Connelly-Frost et al., 2013; Hall et al., 2009; Walker et al., 2013).

Most studies of the risk factors for VTEs are based on studies of other cancers, multiple tumor types with small numbers of kidney cancer patients, or are not specific to the elderly (Chew et al., 2006; Hall et al., 2009). No studies were found for the risk factors for ATEs in elderly kidney cancer patients, with the only evidence reported from clinical trial data in a subset of patients on specific treatments (Choueiri et al., 2010). The problem is that incidence rates of VTEs and ATES for elderly kidney cancer patients (ages 65 years or older at diagnosis) are not readily available in the literature, much less incidence rates by histology group, patient, or other tumor characteristics. There is also a lack of evaluation of risk factors for VTEs in elderly kidney cancer patients.

Understanding the incidence of VTEs and ATEs in elderly kidney cancer patients can help health care providers assess the need for prophylactic treatments or additional observation. Information on whether there are differences for subpopulations within these patients may be of assistance for patient care as well.

Purpose of the Study

This was a quantitative, retrospective cohort study. The entire cohort consisted of elderly patients with Medicare coverage who resided in the SEER registry areas. The outcomes of interest were VTEs and ATEs, and the exposure status was determined as follows: patients diagnosed with incident kidney cancer from 2004 to 2009 were *exposed* and those who did not have a cancer diagnosis of any type at any point in the database

were *unexposed*. The study-specific aims were to (a) estimate the incidence rates of VTEs and ATEs that elderly kidney cancer patients with Medicare coverage have in the year prior to cancer diagnosis and in the year after diagnosis; (b) estimate the incidence proportions of VTEs and ATEs by discrete, mutually exclusive time periods after diagnosis; (c) compare the incidence rates of VTEs and ATEs occurring in the 12 months before diagnosis in cancer patients to a matched noncancer Medicare population during the same timeframe; (d) compare the incidence rates of VTEs and ATEs occurring in the follow-up period after diagnosis in cancer patients to a matched noncancer Medicare population during the same timeframe; and (e) assess the independent risk factors for each VTE and ATE in cancer patients after cancer diagnosis. The analyses for the first two aims and the last aim only used the exposed patients in the cohort (i.e., the kidney cancer patients). For the first aim, I estimated the incidence rates of VTEs and ATEs overall and according to factors including age group, gender, race, histology group, treatment, and year of diagnosis. For the third and fourth aims, I conducted a matched cohort study using all of the exposed patients and a random sample of the unexposed patients from the cohort. The unexposed patients (the noncancer patients) were matched to the exposed patients on age at index date, gender, race, SEER registry area, and duration of follow-up. The index dates for the exposed patients were the month and year of kidney cancer diagnosis. The index date for the unexposed patients was assigned the same as the corresponding exposed patient.

Descriptive Analyses, Research Questions, and Hypotheses

There are two parts to this study, one descriptive and the other analytic. The descriptive part of the study calculated the incidence rates, overall and by patient and tumor characteristics, of VTEs and ATEs in elderly kidney cancer patients in the follow-up period after index date. Also described was the timing of new events by presentation of the incidence proportions for VTEs and ATEs in discrete time intervals after index date. The analytic part of the study had two types of analyses. The first set of analyses used a matched cohort study to compare the incidence rates of VTEs and ATEs in the exposed patients (kidney cancer patients) to a matched noncancer comparison group in the year prior to the index date and compares the incidence rates in the follow-up period after the index date. The second analysis, conducted only in the exposed patients (elderly kidney cancer patients), was to quantify independent predictors of time to incident VTEs in this population.

Descriptive Analysis 1

The first descriptive analysis involved the calculation of the incidence rates of individual VTEs and of ATEs in elderly kidney cancer patients over the 12 months before index date (kidney cancer diagnosis) and in the follow-up period after index date. For each of the prespecified patient and tumor characteristics, the incidence rates of VTEs and ATEs are also presented by age group, race, gender, history of VTE/ATE, history of cardiovascular disease, AJCC stage, treatment by immunotherapy, treatment by nephrectomy, treatment by chemotherapy or targeted therapy, histology group, Charlson Comorbidity Index, SEER registry region, and year of diagnosis.

Descriptive Analysis 2

For this analysis, the proportion of elderly kidney cancer patients who experienced incident VTEs and incident ATEs in discrete, mutually exclusive time periods during follow-up (0 to 90 days, 91 to 180 days, 181 to 270 days, and 271 to 365 days) after index date were calculated. The incidence proportions were calculated for each VTE and ATE of interest.

Research Question 1

Research Question 1: How do the incidence rates of VTEs and ATEs in elderly exposed (kidney cancer) patients 12 months before index date compare to a matched unexposed (noncancer) Medicare population during the same 12-month timeframe?

H_A1: In the year prior to index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_01: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the year prior to the index date in the exposed patients and in the matched unexposed patients.

Research Question 2

Research Question 2: How do the incidence rates of VTEs and rates of ATEs in elderly exposed (kidney cancer) patients after index date compare to a matched unexposed (noncancer) Medicare population during the same timeframe?

H_A2: In the follow-up period after the index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

$H_0$2: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the period after index date in the exposed patients and in the matched unexposed patients.

Research Question 3

Research Question 3: In the follow-up period after kidney cancer diagnosis, what are the risk factors associated with time to newly diagnosed, individual VTE (DVT, PE, or OTE)?

H_A3: No factors are statistically significantly associated with the time to newly diagnosed VTEs in the period after kidney cancer diagnosis.

$H_0$3: Tumor histology and other factors are statistically significantly associated with the time to newly diagnosed VTEs after kidney cancer diagnosis.

For each question, a Cox proportional hazard model was used to identify independent predictors for each outcome. The outcome was time to the occurrence of the first VTE or ATE after kidney cancer diagnosis or duration of follow-up. The potential predictors included in the initial (full) model were age at diagnosis, race, gender, diabetes, atherosclerosis, varicose veins, cardiovascular surgery, central venous catheter, kidney disease, history of VTE, history of cardiovascular disease, AJCC stage, treatment type (immunotherapy, nephrectomy, chemotherapy), histology group, SEER registry region, and year of diagnosis. Independent variables which were statistically significant at the 0.05 level were retained in the final model. The final model included any variables identified as confounders or effect measure modifiers (EMMs). As incident ATEs were

expected to be rarer than incident VTEs, assessment of independent risk factors for ATEs in elderly kidney cancer patients was not included in this research question.

Theoretical Framework

A visual representation of the proposed theoretical framework is presented in Figure 1. This theoretical framework used the advanced epidemiology triangle to interpret the association between incident VTEs and ATEs with causative factors, environment and lifestyle factors, and population characteristics (Merrill, 2009). While the traditional epidemiology triangle is primarily used for modeling infectious disease transmission, the advanced epidemiology triangle is adapted for use with chronic diseases, injuries, and other conditions (Merrill, 2009). The factors which make up the traditional epidemiology triangle are host, agent, and environment, whereas the factors in the advanced triangle are population, causative factors, and environmental factors (Merrill, 2009). In the advanced model, environmental factors include behavioral, cultural, physiological and ecological elements (Merrill, 2009). The interaction of time with these factors is also taken into account.

The dependent variable, the outcomes, were incident ATEs and VTEs. The potentially confounding and effect measure modifying variables were identified from the literature and only variables which were included in this study were presented on the framework (Earp & Ennett, 1991). Patient factors and cancer-specific factors can directly impact the likelihood of a patient having a VTE, and indirectly through effects on which RCC treatments (e.g., chemotherapy and targeted therapies, nephrectomy, and immunotherapy) a patient receives, cardiovascular surgery or placement of a central

venous catheter. The patient factors (age, gender, SEER registry region of diagnosis/residence, and comorbidities) and cancer-specific factors (year of diagnosis, cancer stage, tumor histology, and cancer treatments) were selected based on previous studies of risk factors for VTEs and ATEs (Blom et al., 2006; Chew et al., 2006; Connelly-Frost et al., 2013; Geraci, Escalante, Freeman, & Goodwin, 2005; Khorana & Connolly, 2009; NCCN, 2015). Placement of a central venous catheter and cardiovascular surgery were selected based on studies that found them to be predictive factors for VTEs in cancer patients (Connelly-Frost et al., 2013; Khorana & Connolly, 2009). Additional detail on the theoretical framework was discussed in Chapter 2.

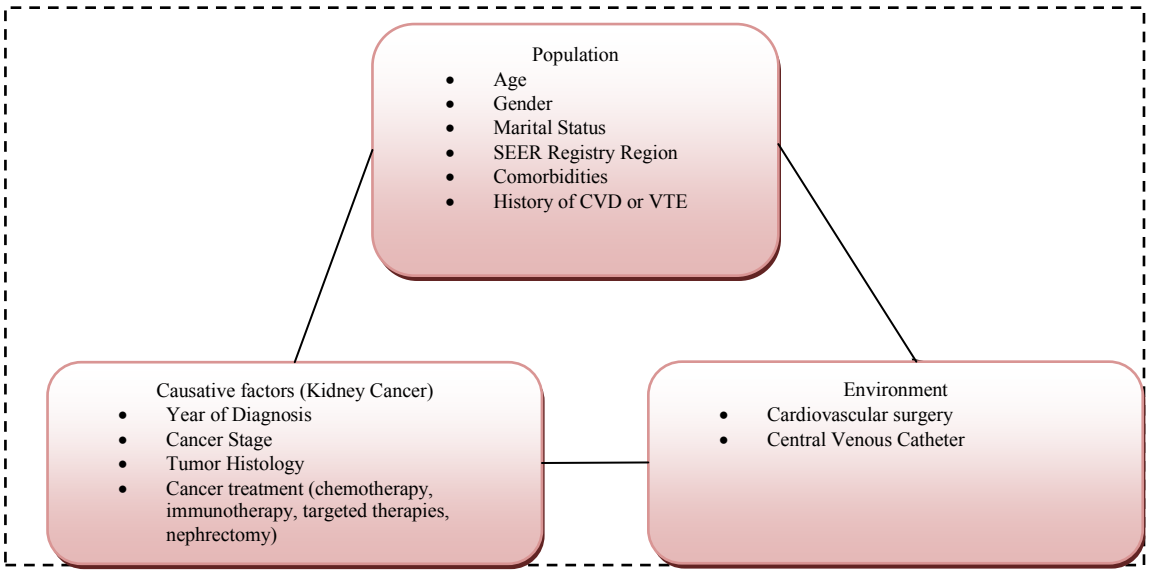

Figure 1. Theoretical model of the association between population, causative, and environmental factors related to thromboembolic events.

Nature of the Study

This study was a quantitative, retrospective cohort study. The cohort consisted of Medicare beneficiaries. The exposure was kidney cancer while the outcome was the occurrence of a venous or arterial thromboembolic event. The data source utilized was the linked SEER-Medicare database. The study population was patients diagnosed with kidney cancer between 2004 and 2009 (exposed) and, for Research Questions 1 and 2, a noncancer comparison group (unexposed) matched to the kidney cancer patients on gender, age, race, SEER registry region, and duration of follow-up after the index date. Each matched unexposed patient was assigned an index date of the month and year of the corresponding kidney cancer patient's diagnosis. The kidney cancer patients were restricted to patients 65 years of age or older, diagnosed between the years of 2004 and 2009, and whose kidney cancer was the patient's first malignancy. Age 66 years and 11

months was the effective minimum age as the patients in the cohort were be required to have two years of Medicare Part A and B coverage and no Medicare managed care plan participation prior to and including the month and year of the index date. Duration of follow-up was calculated as the number of months from index date until patient does not have both Parts A and B coverage, participates in a managed care plan, dies, or December 31, 2010. Follow-up time for the unexposed patient was truncated to the same amount of time as the corresponding kidney cancer patient.

In order to describe the risk of VTEs and ATEs in kidney cancer patients and in a noncancer comparison group, incidence rates and incidence proportions were calculated. Tables of the incidence rates overall and stratified by patient and tumor characteristics were generated. Cox proportional hazards regression analyses were used to model whether the incidence of VTEs and the incidence of ATEs are more likely in kidney cancer patients than the matched comparison group for each time period. Modeling the risk factors for each VTE in kidney cancer patients and estimating the relative risk of VTE after kidney cancer diagnosis used Cox proportional hazards regression analyses. Unadjusted Kaplan-Meier curves of time to VTE or ATE were generated overall and stratified by patient and tumor characteristics. Log rank tests were used to determine whether differences in the time-to-event curves are statistically significant. All analyses were conducted using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

This methodology is consistent with that used by Connelly-Frost et al. (2013) to estimate incidence of VTEs and ATEs in RCC patients, calculate relative risk estimates of VTEs and ATEs, compare the risk of VTEs and ATEs in RCC patients to a matched

noncancer comparison group. The incidence rate calculation is also consistent with Walker et al. (2013). Additionally models of relative risk and risk factors for VTEs and ATEs were assessed as an overall group and also using the CCI and histology group as potential risk factors, which provided results more easily comparable with other studies in other cancer types (Alcalay et al., 2006; Chew et al., 2007).

Definitions

Arterial thromboembolism: A thromboembolism which occurs in an artery (CDC, 2014; MedlinePlus, 2014). For this study, the ATEs to be examined are acute myocardial infarction and ischemic stroke.

Cancer-directed treatment: Treatment given with the purpose of destroying, removing, or controlling malignant or metastatic tumor cells. Palliative care and diagnostic tests are excluded (SEER, 2012).

Chemotherapy: Pharmaceutical drugs which kill cancer cells (National Cancer Institute, 2013).

Comorbidity: Any condition, acute or chronic, other than the disease of interest (Klabunde, Warren, & Legler, 2002).

Elderly: The elderly are defined as persons 65 years of age or older, as 65 has been considered the retirement age in the United States and it is the earliest age U.S. residents without ESRD or certain disabilities are eligible for the Medicare program (Centers for Medicare & Medicaid Services [CMS], 2013; Ohio State University Extension, 2004).

Exposed: The exposed population in the cohort consisted of patients with an incident diagnosis of kidney cancer between 2004 and 2009.

History of cardiovascular disease: A diagnosis code for a myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack in the 12 months before the period of interest (Connelly-Frost et al., 2013).

Immunotherapy: A type of biologic therapy which affects the immune system in order to treat diseases (National Cancer Institute, 2013). Types of immunotherapies include cytokines and monoclonal antibodies (National Cancer Institute, 2013).

Localized tumors: Tumors which are confined to the tissue or organ from which it originated (National Cancer Institute, 2013).

Metastasis: Cancer cells have spread to parts of the body outside the tissue or organ from which it originated (National Cancer Institute, 2013).

Nephrectomy: Surgery which removes part or the entire kidney (National Cancer Institute, 2010).

Palliative care: Treatments given to treat symptoms, treatment-related side effects, or otherwise improve patient quality of life (National Cancer Institute, 2013; SEER, 2012).

Pediatric: Related to children (National Cancer Institute, 2013). Children are considered any person of age 18 years or younger.

Resectable: A tumor which can be removed surgically (National Cancer Institute, 2013).

Stage (cancer): Cancer grouping based on the extent to which the cancer has spread from the tissue or organ from which it originated (SEER, 2012). Factors which go into staging include the primary tumor site, tumor size or thickness, extension or metastases beyond the primary site, and presence of metastases in regional lymph nodes (SEER, 2012).

Systemic therapy: Drugs which travel through the blood stream to affect cells in various parts of the body (National Cancer Institute, 2013).

Targeted therapy: Anticancer drugs which interrupt cancer cell growth and tumor spread. Different types of targeted therapies attack cells with different characteristics by targeting specific cellular molecules. (National Cancer Institute, 2013).

Thromboembolism: A blood vessel blockage caused by a portion of a blood clot which originated in another site (MedlinePlus, 2014).

Tumor: A mass caused by abnormal cell growth. Tumors are also known as neoplasms. (National Cancer Institute, 2013).

Unexposed: The exposed population in the cohort consisted of patients who did not have a cancer diagnosis in the SEER registry data at any time.

Venous thromboembolism: A thromboembolism which occurs in a vein (CDC, 2014; MedlinePlus, 2014). The VTEs to be examined in this study are deep venous thrombosis, pulmonary embolism, and other thromboembolic events.

Assumptions

The following assumptions were made for this study: (a) all clinically relevant diagnoses were captured in the diagnosis and procedure codes, (b) receipt of cancer-

directed treatments were processed by Medicare and thus captured in the data, (c) the date of cancer diagnosis was accurate, and (d) date of death was correctly identified. The first assumption is a limitation of administrative claims data (Klabunde, Warren, & Legler, 2002) which is discussed further in the limitations section below. The diagnoses of interest to this study (i.e., VTEs and ATEs) are serious conditions which should meet the criteria of being clinically relevant. The second assumption is specific to the SEER-Medicare database, as only claims processed by Medicare are included in the database (Applied Research Program, 2013). Nephrectomy, and intravenous immunotherapy and chemotherapy administered inpatient or outpatient settings which are covered by Medicare for kidney cancer patients should be captured. Studies have validated the SEER-Medicare data for assessing receipt of chemotherapy (Lund et al., 2013; Warren et al., 2002b). However, many of the targeted chemotherapy drugs for RCC approved in the past decade are given orally, do not have an IV equivalent, and thus may not be captured as they would be billed as prescription drugs. With the passage of the Medicare Modernization Act of 2003, prescription drug coverage (hereafter referred to as Part D) was an available option for Medicare participants beginning January 1, 2006 (CMS, 2013). Oral chemotherapy drugs may be captured in the HCPCS codes or in the prescription drug event file containing Part D data using National Drug Code (NDC) codes (Applied Research Program, 2013). The Part D data released with the SEER-Medicare data released in 2013 covers years 2007 to 2010 (Applied Research Program, 2013), which overlaps with half (2007 to 2009) of my study period. Part D is optional, so the data only includes claims for patients who have Part D coverage. Oral targeted

therapies are the primary therapy for Stage IV or advanced RCC (NCCN, 2015). Restricting to 2010 kidney cancer patients, 12% or less of Stage III patients age 60 years of age or older had chemotherapy in the first course of treatment (National Cancer Data Base, 2013). For Stage IV patients, 52% of patients age 60 to 69 years of age at diagnosis had chemotherapy in the first course of treatment and the proportion declined to 29% of patients 80 to 89 years of age, and 8% for patients 90 years of age or older (National Cancer Data Base, 2013). It was not possible to determine how many patients received oral drugs as part of the chemotherapy treatments. Treatments which are paid for by the patient during a prescription plan coverage gap are also not captured (CMS, n.d.).

SEER data is considered a high-quality cancer data source and there was approximately 90% agreement on the date of cancer diagnosis whether using the SEER data or Medicare claims data (Applied Research Program, 2013; SEER, 2013). The fourth assumption is necessary for correctly calculating duration of follow-up, and 96% of the dates of death have been validated in the Medicare enrollment file (Asper, 2012).

Scope and Delimitations

The population included elderly kidney cancer patients with Medicare (both parts A and B) coverage, who had no participation in Medicare Managed care plans in the two years prior to kidney cancer diagnosis or during follow-up, whose kidney cancer was their first diagnosed cancer, and who were 65 years of age or older at diagnosis. Continuous Medicare coverage with parts A and B and exclusion of patients in Managed Medicare plans prior to index date and during patient follow-up are required to reduce the likelihood of missing claims (e.g., treatments, comorbidities, and other information) for

the study patients (Asper & Mann, 2011). The proportion of Medicare enrollees participating in a managed care plan ranged from 13% to 25% between 1998 and 2010 (Asper & Mann, 2011). Although people may be eligible for Medicare coverage starting at age 65 (excluding people with coverage at earlier ages due to disability or end-stage renal disease), so that there are two years of data including the month of index date for each patient prior to kidney cancer diagnosis (index date) the study population needs to be at least 66 years and 11 months of age to be eligible. Patients at risk for a VTE or ATE during each period (the year prior to diagnosis/ index date or the year after diagnosis/index date) were defined as patients who did not have a diagnosis for the VTE or ATE in the year prior to the period of interest. Thus, a second year prior to the diagnosis/index date was necessary for identifying incident events in the first year prior to that date.

Duration of follow-up was calculated from the month after the index date until loss of Parts A and B of Medicare coverage, participation in a Medicare managed care plan, death, or December 31, 2010. Patients who died or were lost to follow-up in the same month of index date (i.e., duration of follow-up is zero full months) were excluded. Thus, the study population had at least 1 month of follow-up. No other minimum amount of follow-up was required so as not to introduce survival bias into the study. Additionally, follow-up for matched unexposed patients were truncated at the same duration as the corresponding kidney cancer patient.

Patients with other cancers diagnosed in the same month as or prior to the kidney cancer diagnosis were excluded also. This was so that the pharmaceutical and surgical

therapies captured were for treatment of the kidney cancer and not another cancer type. Additionally, restricting to patients without other cancers helped ensure that the study findings in the exposed patients were due to the exposure (kidney cancer) and not other exposures. Thus, the results of this study are generalizable to elderly Medicare patients newly diagnosed with kidney cancer, which have both parts A and B of Medicare coverage, and who do not participate in a managed care plan.

Limitations

Some potential limitations arise from the use of SEER-Medicare, an administrative claim database. Administrative claims are designed for billing and reimbursement purposes, thus reimbursement rates may influence which diagnoses and procedures are listed and how they are listed (Klabunde, Warren, & Legler, 2002). Another limitation is that the claims file may not contain all of the diagnosis or procedure codes from a health care interaction. Only claims processed through Medicare are captured. Care which took place at Veterans Administration, was billed to an insurance program other than Medicare, or was paid for out-of-pocket are being captured in the database (Applied Research Program, 2013). The Medicare claims databases have a predefined number of variables to capture the diagnosis or procedure codes; for example the outpatient claims dataset had 10 diagnosis codes variables prior to 2010, but 25 variables for 2010 and later (Applied Research Program, 2013). As such, some conditions may be underreported because there are not enough positions for them to be included in the file. Conditions which exist but are not considered clinically relevant may not be

listed as a diagnosis code (Klabunde et al., 2002). This is a limitation with any administrative claim database.

Another limitation of using administrative claims is that severity of comorbidity is difficult or impossible to measure (Geraci et al., 2005). Lab data are not contained in the database, thus serum levels of bilirubin (high levels are a contraindication for temsirolimus) cannot be ascertained. Severity of condition could not be assessed in this study, and presence or absence of VTE, comorbidity and procedures were reported based on ICD-9-CM diagnosis codes, ICD-9-CM procedure codes, or HCPCS procedure codes.

However, SEER-Medicare database also has advantages over use of other data sources. One such benefit is the generalizability of the database because the source population is large and population-based. In addition, several validation studies have been conducted using the database to assess its usefulness and appropriateness for various purposes including identification of chemotherapy (Lund et al., 2013; Warren et al., 2002b) and comorbidities (Klabunde et al., 2000; Klabunde et al., 2002).

Significance

This project was significant for several reasons. First, it quantified the rates of VTEs and ATEs and the risk of VTEs in a group of kidney cancer patients for whom there is not a lot of information (elderly patients with Medicare coverage) and assessed whether the incidence rates of thromboembolic events differed from the rates in a matched, noncancer comparison group. Information on incident conditions post-diagnosis can aid in interpreting clinical trial or post-marketing drug safety profiles and identify areas where standards of care for patients can be improved (FDA, 2011).

Secondly, the assessment of the association between time to incident VTEs and ATEs and potential independent risk factors can aid in the understanding of patient risk for VTEs and ATEs among elderly kidney cancer patients with Medicare coverage. New contributions of this study are the assessment of histology group as a potential risk factor and use of AJCC stage instead of summary stage. Histology group had not been assessed as a risk factor for VTEs or ATEs in kidney cancer patients, however it was found as a risk factor for VTEs in patients with other tumor types (Blom et al., 2004; Chew et al., 2007, 2008). The results of this study contributed to positive social change by quantifying the incidence and risk of VTEs and ATEs for this population. Increased understanding of the patient risk for VTEs and ATEs may improve patient care and prognosis. The understanding may help inform healthcare providers as to which patients may benefit from additional observation or prophylactic treatments to prevent thromboembolic events.

Summary

VTEs and ATEs are serious conditions for which elderly cancer patients are at higher risk than the general population (Connelly-Frost et al., 2013; Khorana & Connolly, 2009; NCCN, 2015). Although the risk of VTE and ATE varies by cancer type, information on the risk and risk factors in elderly kidney cancer patients is sparse (Blom et al., 2006; Connelly-Frost et al., 2013). Therefore, tumor type-specific assessment of the risks and outcomes in the patient population can help health-care providers and patients make treatment decisions and understand potential outcomes. This retrospective cohort study sought to address gaps in the literature by calculating incidence rates in an

elderly kidney cancer population, comparing incidence rates in kidney cancer patients to a matched, noncancer comparison group, and assessing risk factors for incident VTEs and ATEs in elderly kidney cancer patients. Chapter 2 presents the literature search methodology and a review of the literature for incidence rates of VTEs and ATEs and risk factors for VTEs in elderly kidney cancer patients. The chapter concludes with a summary of the literature and discussion of the contribution of the current study.

Chapter 2: Literature Review

Introduction

This review of the literature provides background information on the incidence and risk of ATEs and VTEs in elderly kidney cancer patients. Most of the publications citing the increased risk for thromboembolism events in cancer patients are based on multiple cancers (which included approximately 0% to 3% kidney cancers), assessed outcomes as a grouping instead of individual thromboembolic events, and included adult patients of all ages without results presented stratified by elderly and nonelderly (Agnelli et al., 2006; Blom et al., 2006; Hall et al., 2009; Khorana et al., 2008; Sallah et al., 2002). Other studies which included kidney cancer patients included patients diagnosed more than a decade ago (e.g., 2003 or earlier) or focused on specific groups of patients such as clinical trial participants who received a specific treatments (Connelly-Frost et al., 2013; Hurwitz et al., 2011; Svoboda, Poprach, Dobes, Kiss, & Vyzula, 2012). The problem is that evidence on ATEs and VTEs in elderly kidney cancer patients is not available from a recent population-based data source which reflects the incidence rates of ATEs and VTEs in this population or assesses the risk factors for the conditions in this population (Connelly-Frost et al., 2013; Khorana, Kuderer, Culakova, Lyman, & Francis, 2008). Thus this quantitative study analyzed kidney cancer patients diagnosed between 2004 and 2009 and a matched, noncancer cohort during the same period in order to ascertain the incidence of ATEs and VTEs before and after kidney cancer diagnosis, compare the incidence rates in kidney cancer patients to a comparable group of noncancer patients, and assess independent risk factors for VTEs in elderly kidney cancer patients.

Only one study was found which published incidence rates of VTEs and assessed risk factors for VTEs in elderly RCC cancer patients diagnosed between 1991 and 2003 (Connelly-Frost et al., 2013). Other studies reported incidence rates or cumulative incidence of VTEs in kidney cancer patients of all ages (Blom et al., 2006; Chew et al., 2006; Walker et al., 2013). No similar study of ATEs in kidney cancer patients was identified in the published literature.

This chapter details the strategy utilized in search engines to identify the current literature reviewed for this study. The next section discusses in depth the theoretical framework of this study that was introduced in chapter one. The published literature on ATEs and VTEs in elderly kidney cancer patients was exhaustively reviewed in regards to study methodology and variables. The chapter ends with a summary of the published literature and transition to the methods chapter.

Literature Search Strategy

Searches for peer-reviewed literature were conducted in the Scopus electronic multidisciplinary database. The Scopus database contains abstracts and citations from more than 20,000 peer-reviewed journals, 6 million conference papers, and articles-in-press from almost 4,000 journals (Elsevier, 2014). The search criteria and numbers of articles found during the search on September 29, 2015 are found in Table 2. The asterisk directs Scopus to search for words containing the characters prior to asterisk plus any variation of characters which appear in place of the asterisk. The Scopus search was restricted to results in journal articles, English language, and published between January 2003 and September 2015. A total of 355 abstracts were reviewed to identify relevant

articles. Reviews were included in the initial search and the reference lists of all studies pulled were searched for additional relevant articles, including those with information on other cancer types. In addition, the title and abstracts of publications which cited the articles selected for review in this chapter were also examined for locating additional relevant articles. Searches of the primary authors' other publications also yielded articles including in this literature review. Case studies and studies focusing on pediatric populations were excluded.

Table 2

Scopus Search Criteria and Results

	Search Terms	Articles found
Row 1	("kidney cancer" or "renal cell carcinoma") and ("pulmonary embolism" or "deep venous thrombosis" or "venous thromboemb*" or "thromboemb*")	279
Row 2	("kidney cancer" or "renal cell carcinoma") and ("myocardial infarction" or "stroke")	92
Row 3	#1 or #2	355
Row 4	Articles included in the literature review	58

Theoretical Framework

The theoretical framework for the study of factors related to ATEs and VTEs in elderly kidney cancer patients was the advanced epidemiologic triangle, which is applicable to diseases and conditions other than infectious diseases (Merrill, 2009). This epidemiologic triangle consists of three components –population, causative factors, and environmental factors, and also incorporates time (Merrill, 2009). The advanced

epidemiologic triangle does not assume a single cause or etiology, and allows for the modeling the complex nature of conditions (Merrill, 2009).

The outcome, ATE or VTE, in elderly kidney cancer patients is influenced by several factors, some directly and others indirectly. The population factors are increasing age, gender, marital status, region of residence or diagnosis, number of comorbidities, and history of cardiovascular or thromboembolic events. These characteristics have been shown to be risk factors for VTEs (Alcalay et al., 2006; Chew et al., 2007; Connelly-Frost et al., 2013; Hall et al., 2009; Walker et al., 2013). The causative factor or exposure of interest in this study is kidney cancer. The factors which may affect development of a VTE or ATE are year of diagnosis, cancer stage, and cancer treatment. Cancer treatments include receipt of chemotherapy or immunotherapy, receipt of targeted therapies, or undergoing a cancer-directed surgery (e.g., nephrectomy). Whether tumor histology group is a risk factor for thromboembolic events in kidney cancer patients has not been assessed. However, in some cancer types, histology has been an independent risk factor for thromboembolic events (Alcalay et al., 2006; Chew et al., 2007). Major cardiac or vascular surgery and placement of a central venous catheter are grouped with the environmental risk factors for thromboembolic events (Alcalay et al., 2006; Khorana & Connolly, 2009; NCCN, 2015).

Thus the framework for this study was constructed from patient and tumor characteristics, kidney cancer treatments, and whether the patient had the insertion of a central venous catheter or underwent a major cardiac or vascular surgery. Studies of risk factors for ATEs and VTEs in cancer patients using the SEER-Medicare database

included these factors in their initial or final multivariate models (Connelly-Frost et al., 2013; Doyle et al., 2005; Hall et al., 2009). The Connelly-Frost et al. (2013) article, the only one which analyzed any kidney cancer patients, found that atherosclerosis, presence of a central venous catheter, diabetes, high-risk surgery, history of CVD, and kidney disease were effect measure modifiers of the risk of VTEs in RCC patients compared to the matched, noncancer cohort. Male gender; diagnoses of atherosclerosis, diabetes, hypercholesterolemia, kidney disease, varicose veins, history of cancer diagnosis, history of VTE; receipt of chemotherapy or immunotherapy treatment; placement of a central venous catheter; undergoing high-risk surgery; and cancer stage were statistically significant predictors of new VTEs (DVT, pulmonary embolism or other thromboembolic events) in the 12 months after RCC diagnosis (Connelly-Frost et al., 2013). Other studies which examined risk factors of VTEs using other data sources found some of these factors as independent predictors in multivariate models (Agnelli et al., 2006; Alcalay et al., 2006; Blom et al., 2004; Chew et al., 2008; Khorana et al., 2008; Moore et al., 2011; Scappaticci et al., 2007). Where available they also included clinical data, which was not available in the SEER-Medicare data (Agnelli et al., 2006; Blom et al., 2004; Khorana et al., 2008; Moore et al., 2011).

Smith et al. (2014) used a subset of these factors to estimate the risk of VTEs in a kidney cancer population compared to a noncancer population matched on age, sex, and comorbidity score. After adjusting for the matching and year of cancer diagnosis, they found that the risk of VTEs after cancer diagnosis was higher than the risk in a noncancer population after adjusted for matching and year of cancer diagnosis (Smith et al., 2014).

The increased risk persisted even after stratifying by comorbidity score, time since cancer diagnosis, whether or not the cancer was metastatic, and presence of surgery within 3 months of VTE (Smith et al., 2014). These factors, measureable in the SEER-Medicare database, are discussed in further detail below.

The advantage of this framework was that it is comprehensive yet flexible enough to assess risk factors for VTEs in the population of interest. The weakness of the framework was that it can only include measurable information available in the study data and therefore does not include clinical information or other variables which were identified as risk factors in other studies.

Incidence of Venous Thromboembolic Events

Methods

The studies of incidence rates of VTEs for kidney cancer have analyzed different populations with some variations of methods (Agnelli et al., 2006; Blom et al., 2006; Chew et al., 2006; Connelly-Frost et al., 2013; Walker et al., 2013). The Walker et al. (2013) study analyzed patients registered with a general practitioner in the United Kingdom, diagnosed with a cancer in the national cancer registry database between 1997 and 2006, were 18 or older at time of cancer diagnosis, were included in the UK Clinical Practice Research Datalink (CPRD) database linked to the Hospital Episode Statistics data, had no history of VTE prior to the first cancer diagnosis, and the cancer diagnosis occurred during a registration period but after the first year of registration at a practice (p. 1405). Cancer diagnoses were based on cancer registry data and only the first cancer was selected for analyses (Walker et al., 2013). Duration of follow-up for the incidence rates

was calculated as time from cancer diagnosis until diagnosis of a VTE, death, exit from a practice which was linked to CPRD, or December 31, 2010. The median follow-up time was 2 years with an interquartile range of 0.3 to 5.7 years for all cancer patients (Walker et al., 2013). Statistics on follow-up time were not presented separately by cancer type, so the corresponding information for the kidney cancer patients was not reported. Chew et al. (2006) also analyzed cancer registry data; however it was linked to state hospital discharge data. Connelly-Frost et al. (2013) reported incidence rates of VTEs in a subset of kidney cancer patients using the SEER-Medicare database which is cancer registry data linked to the Medicare claims database. The Medicare claims database includes patient information from inpatient, outpatient, long-term, short-term, hospice and other stays (Applied Research Program, 2013). Similarly, Blom et al. (2006) analyzed cancer registry data linked to another data source, anticoagulation clinic data. However, the study population for the Agnelli et al. (2006) study was selected prospectively from patients undergoing cancer-directed surgery in Italian surgical departments. The main strength of using cancer registry data is that it is a population-based data source. Linkages with data sources where patients with VTEs are likely to be treated (e.g., hospitalization data, anticoagulation clinics) increase the likelihood of capturing VTEs, however some incidents may not be captured if the patient died prior to hospitalization or anticoagulation treatment (Blom et al., 2006).

Unlike Walker et al. (2013), other studies restricted the maximum amount of follow-up post cancer diagnosis. Chew et al. (2006) presented incidence rates and cumulative incidence of VTEs in the first two years after cancer diagnosis, whereas

Chavez-MacGregor et al. (2011), Connelly-Frost et al. (2013) and Shantakumar, Connelly-Frost, Kobayashi, Allis, and Li (2015) restricted to a maximum of one year. Studies reporting cumulative incidence of VTEs in kidney cancer patients used follow-up of six months or less with follow-up starting at time of cancer diagnosis or date of cancer-directed surgery (Agnelli et al., 2006; Blom et al., 2006). Researchers have consistently shown that VTEs after cancer diagnosis more frequently occur closer to the date of the cancer diagnosis and are less common as time increases (Chavez-MacGregor et al., 2011; Chew et al., 2006; Connelly-Frost et al., 2013; Walker et al., 2013). Thus, while restriction of the duration of follow-up is reasonable, variations in reported incidence measures may be due to differences in duration of follow-up time used. Another difference in reported incidence measures may be due to the exclusion of patients with prior VTEs. Walker et al. (2013) and Chew et al. (2006) excluded patients with prior VTEs from analyses. Agnelli et al., (2006), Blom et al. (2006), and Connelly-Frost et al. (2013) did not exclude patients with prior VTEs allowing for estimation of incidence measures or risk by history of VTE. As history of VTE was shown to increase the risk of a future VTE, the incidence measures from these studies are expected to be higher than those from studies where patients with a prior VTE were excluded (Agnelli et al., 2006; Blom et al., 2006; Connelly-Frost et al., 2013).

Three studies examined the incidence of VTEs in cancer patients in the period prior to cancer diagnosis (Connelly-Frost et al., 2013; Shantakumar et al., 2015; White et al., 2005). White et al. (2005) presented the number of VTE events in the 12 months prior to the cancer diagnosis and the standardized incidence ratio comparing the observed

counts to the expected counts in the general California population. The study population consisted of all patients age 18 or older with a cancer diagnosed between 1993 and 1995 or 1997 and 1999 which was recorded in the California Cancer Registry (White et al., 2005). Connelly-Frost et al. (2013) presented incidence rates in the 12 months prior to RCC diagnosis for DVT, pulmonary embolism and OTE separately. Shantakumar et al. (2015) presented incidence rates in the 12 months prior to soft tissue sarcoma diagnosis for DVT, pulmonary embolism and OTE separately. Both Connelly-Frost et al. (2013) and Shantakumar et al. (2015) used SEER-Medicare database and included patients 65 years of age or older at cancer diagnosis who had continuous coverage by Medicare Parts A and B without participation in a managed care plan for at least 24 months prior to the cancer diagnosis. Only the White et al. (2005) study excluded patients with a VTE diagnosed more than 1 year prior to cancer diagnosis from the incidence calculations.

For this study, incidence rates were calculated prior to and after cancer diagnosis. Incidence rates were calculated using 12 months in the period prior to cancer diagnosis for kidney cancer patients and index date for the matched noncancer patients. For the period after cancer diagnosis/index date, incidence rates were presented for the entire follow-up period.

Incidence

Table 3 summarizes the incidence rates by cancer type, patient age, and stage for several solid tumor types. Few studies contributed information for the same cell (e.g., reporting 60 years and older versus reporting 65 years and older) and one study (Connelly-Frost et al., 2013) reported incidence rates separately for each type of VTE

(DVT, pulmonary embolism, and OTE) for elderly patients diagnosed with RCC, a subset of kidney cancer. Connelly-Frost et al. (2013) did not report an overall incidence rate for any type of VTE, while most other articles reported overall incidence rates without separating the rates by type of VTE.

Of the four studies which reported the incidence of VTEs in kidney cancer patients, only one provided incidence rates for older patients (Agnelli et al., 2006; Blom et al., 2006; Chew et al., 2006; Walker et al., 2013). The incidence rate for patients diagnosed at age 60 or older at diagnosis was 14 per 1,000 person-years (95% *CI* 10 – 18) (Walker et al., 2013). Although other studies of multiple cancer types have reported differences in the incidence of VTEs for younger and older patients, Walker et al. (2013) found that the incidence rate for kidney cancer patients diagnosed at ages 18 to 60 (12 per 1,000 person-years, 95% *CI* 8.1-19) was similar to the rate for the older patients (Chew, Wun, Harvey, Zhou, & White, 2007; Hall et al., 2009). Walker et al. (2013) reported that although the overall incidence rate for VTEs in all cancer patients 60 or older was higher than the rate for younger cancer patients, that pattern did not hold for all individual cancer types and for some types the pattern was reversed (Walker et al., 2013).

Timing relative to cancer diagnosis, stage at diagnosis, and time since cancer diagnosis appeared to effect differences in incidence rates. Chew et al. (2006) reported first and second year incidence rates for VTEs after a kidney cancer diagnosis by summary staging. The first year incidence rates were higher than the second year, and incidence rates increased with later stage (Chew et al., 2006). The incidence rates for VTEs in the first year after cancer diagnosis were 12, 37, and 60 per 1,000 person-years

for localized, regional, and distant metastatic stage, respectively (Chew et al., 2006). The rates in the second year were approximately a quarter of the rates for the first year for each stage (Chew et al., 2006). Other studies also consistently found that the incidence rates or proportions of VTEs in kidney cancer patients or cancer patients with other tumor types were highest in the periods directly after the date of cancer diagnosis, then decreased for later periods from the date of cancer diagnosis (Chew et al., 2008; Connelly-Frost et al., 2013; Moore et al., 2011; Walker et al., 2013). Studies of other tumor types also reported higher incidence rates in patients diagnosed with later stages of cancer (Alcalay et al., 2006; Chew et al., 2007, 2008; Connelly-Frost et al., 2013; Moore et al., 2011).

Studies of breast, lung, and colorectal cancer patients have been inconsistent as to whether incidence rates of VTEs differ by histology group (Alcalay et al., 2006; Blom et al., 2004; Chew et al., 2007, 2008). A study of colorectal cancer patients found statistically significant differences in the 2-year cumulative incidence of VTEs by histology group (Alcalay et al., 2006). Incidence rates also appear to vary by histology group in lung cancer patients as well. The incidence rates in patients with squamous cell carcinoma was 21.2 per 1,000 person-years (95% *CI* 10.1-36.2) as compared to 66.7 per 1,000 person-years (95% *CI* 36.2-106.2) in patients with adenocarcinoma lung cancers (Blom et al., 2004). The increased risk persisted even after adjusting for age, gender, and cancer treatment. The incidence rates of VTEs also appeared to differ by histology group in lung cancer patients in a study by Chew et al. (2008), however no statistical testing was done to compare the incidence rates by histology type nor were confidence intervals

for the incidence rates reported. However, a study of breast cancer patients reported little difference between incidence rates by histology group (Chew et al., 2007). No studies were identified which calculated incidence rates of VTEs in kidney cancer patients by histology group.

Table 3

Incidence Rates of VTEs by Cancer Type and Age

	All Ages	Less than 60 years of age	60 years or older/ 65 years or older	All ages, localized stage	All ages, advanced stage	65 years or older, advanced stage	References
Pancreatic	98	127	89	-	-	-	Walker et al., 2013
	-	-	-	42	200	-	Chew et al., 2006
	-	-	-	-	-	174	Hall et al., 2009
Lung	44	48	42	-	-	-	Walker et al., 2013
	44	-	-	-	-	-	Blom et al., 2004
	-	-	-	11	50	-	Chew et al., 2006
	-	-	-	-	-	60	Hall et al., 2009
Breast	9	5	12	-	-	-	Walker et al., 2013
	12	-	-	8	68	-	Chew et al., 2007
	-	-	-	5	28	-	Chew et al., 2006
	-	-	-	-	-	50	Hall et al., 2009
Colorectal	17	16	17	-	-	-	Walker et al., 2013
	-	-	-	9	43	-	Chew et al., 2006
	-	-	-	-	-	50	Hall et al., 2009
Prostate	9	7	9	-	-	-	Walker et al., 2013
	-	-	-	8	9	-	Chew et al., 2006
	-	-	-	-	-	14	Hall et al., 2009
Kidney	13	12	14	-	-	-	Walker et al., 2013
	13	-	-	-	-	-	Blom et al., 2006
	25	-	-	-	-	-	Agnelli et al., 2006
	-	-	-	12	60	-	Chew et al., 2006
RCC	-	-	108	-	-	229	Connelly-Frost et al., 2013
Noncancer cohort	3.0	1.0	4.3	-	-	-	Walker et al., 2013

Note. Rates are per 1,000 person-years and based on the first year after cancer diagnosis, except for rates from Blom et al. (2006) and Chew et al. (2007) which are based on the first six months after cancer diagnosis.

Of the studies identified which contained incidence of VTEs in kidney cancer patients, only one reported rates in older patients, one stratified by cancer stage, and the

others reported cumulative incidence. Differing patient populations and methods makes comparison across studies challenging. The increased incidence of VTEs in the period just after kidney cancer diagnosis is consistent with findings in other cancer types, however the incidence of VTEs may not follow the pattern of higher incidence in older patients and whether there are any differences by histology group has not been assessed.

Risk Factors for Venous Thromboembolic Events

Methods

Most studies used the Cox proportional hazards model to analyze the time to the first VTE after cancer diagnosis and generate hazard ratios for risk factors (Alcalay et al., 2006; Blom et al., 2004; Chew et al., 2006, 2007, 2008; Connelly-Frost et al., 2013; Hall et al., 2009; Walker et al., 2013). The hazard ratio estimates the incidence rate ratio as long as the Cox proportional hazards assumption holds true (Hoffman et al., 2008; Spruance, Reid, Grace, & Samore, 2004). Less commonly, odds ratios from multivariate logistic regression analyses were presented based on an outcome of occurrence of a VTE during follow-up (Agnelli et al., 2006; Blom et al., 2005; Khorana et al., 2008; Moore et al., 2011). One study used logistic regression and generated odds ratios for identifying risk factors (Chavez-MacGregor et al., 2011).

The main strength of using the hazard ratio over using the odds ratio as the epidemiologic measure includes the ability to account for varying patient follow-up time. This is important as survival time differs greatly by one potential risk factor, stage, and forcing a minimum amount of follow-up/survival time could bias the study towards

including only the patients with lower stage or who are healthier (American Cancer Society, 2014).

Cox proportional hazards model were used to compare the incidence rates of VTEs during the 12 months prior to the index date between exposed patients and matched unexposed patients (Research Question 1) and for the period after index date (Research Question 2).

Tumor Type

Several studies have reported differences in the risk of VTEs in cancer patients by tumor type (Blom et al., 2005; Hall et al., 2009; Walker et al., 2013; White et al., 2005). A study comparing the incidence of VTEs in California cancer patients diagnosed between 1993 and 1995 or 1997 and 1999 to the incidence rates in the total California population reported standardized incidence ratios (*SIR*s) ranging from 0.6 to 4.2 depending on tumor type (White et al., 2005). The standardized incidence ratio for VTE in kidney cancer patients was 2.5 (95% *CI* 1.5-3.9), the standardized incidence ratio for acute myelogenous leukemia patients was 4.2 (95% *CI* 2.4-6.8), and for melanoma the standardized incidence ratio was 0.6 (95% *CI* 0.2-1.1) (White et al., 2005). Similarly, a study of cancer patients in the Netherlands reported adjusted odds ratios of 1.6 to 28.0 for VTEs depending on the type of cancer (Blom et al., 2005). The adjusted odds ratio for VTE in kidney cancer patients was 6.2 (95% *CI* 0.8-46.5), but patients with a hematologic cancer had an adjusted odds ratio of 28.0 (95% *CI* 4.0-199.7) (Blom et al., 2005). Venous thromboembolic events occurred at a higher rate in breast cancer patients (*HR* = 4.86, 95% *CI* 2.93-8.08), female pancreatic cancer patients (*HR* = 21.57, 95% *CI*

12.21-38.09), and male pancreatic cancer patients (*HR* = 17.68, 95% *CI* 9.48-32.95) compared to prostate cancer patients (Hall et al., 2009). Cancer is comprised of several heterogeneous diseases which vary in presentation, characteristics, risk factors, and treatments (National Cancer Institute, 2013). Differences in the risks of VTE by tumor type indicate that findings based on one tumor type may not necessarily hold true in other tumor types. Thus, there is a need for assessment of the risk factors for VTEs by specific tumor type. My goal in conducting this study is to add to the evidence for or against the association between previously identified risk factors and the occurrence of VTEs in kidney cancer patients.

Age at Diagnosis

Similar to the inconsistent findings regarding differences in incidence rates by age group, study results have not been consistent as to whether age is an independent risk factor for VTEs in cancer patients after adjusting for other factors. Additionally, the majority of evidence was based on studies of multiple tumor types combined or individual tumor types other than kidney cancer.

One study which assessed the association between age and incidence of VTE in the year after kidney cancer diagnosis found no significant risk with increasing age after adjusting for race, gender, and stage (*HR* = 1.0, 95% *CI* 0.8-1.1) (Chew et al., 2006). Chew et al. (2006) analyzed patients diagnosed between 1993 and 1995 in California and excluded any patient with a hospitalization for VTE between 1991 and the cancer diagnosis. In a study of elderly RCC patients Connelly-Frost et al. (2013) similarly found no association between age at diagnosis and development of VTE after cancer diagnosis.

Some studies of combined tumor types reported that the risk of VTEs in cancer patients increases with age. In one study, the risk increased 19% (*OR* = 1.19, 95% *CI* 1.02-1.39) for each 10-year increase in age at diagnosis after adjusting for gender, race, presence of a CVC, stage and performance status (Moore et al., 2011). A study of cancer patients of all ages and multiple types undergoing cancer-directed surgery found a 2.6-fold risk of VTEs in patients age 60 or older compared to patients under 60 (*OR* = 2.6, 95% *CI* 1.2-5.7) (Agnelli et al., 2006).

Studies of the association between age and risk of VTE within specific tumor types have shown inconsistent results. Researchers focusing on breast cancer and colorectal cancer patients reported increasing risk of VTE in older age groups compared to patients less than 45 years old or 50 years old or younger at diagnosis (Alcalay et al., 2006; Chew et al., 2007). In a study of breast cancer patients 66 years or older at diagnosis, researchers also reported increasing risk of VTEs with increasing age at diagnosis (Chavez-MacGregor et al., 2011). Another study of patients with ovarian serous or clear cell carcinoma reported that age of 60 years or older increased the risk compared to patients less than 60 years of age (Matsuo et al., 2015). In contrast, a study of lung cancer patients found that age at diagnosis after age 44 was protective against the development of VTE after cancer diagnosis in non-small cell lung cancer (Chew et al., 2008). The adjusted hazard ratios for increasing age groups in patients diagnosed with small cell lung cancer were also less than 1.0; however they did not reach statistical significance (Chew et al., 2008). Age was also not associated with development of VTE after adjusting for tumor type, gender, and receipt of chemotherapy in a study of elderly

late stage breast, lung, colon, prostate and pancreatic cancer patients (Hall et al., 2009). A study of chemotherapy-associated VTE in cancer patients of multiple tumor types also did not find an association with age after adjusting for other risk factors (Khorana, Kuderer, Culakova, Lyman, & Francis, 2008). Other studies in multiple tumor types adjusted for age in the multivariate models assessing risk factors for VTEs without indicating whether age was evaluated as an independent risk factor (Blom et al., 2004, 2005, 2006).

Given the inconsistent results in the literature, there is a need to assess whether there are differences in the risk of VTE by age group within the elderly kidney cancer population independent of other risk factors. The prevalence of comorbidities varies by age group and patterns of other risk factors, such as receipt of cancer treatment, are different in elderly patients as compared to younger cancer patients (NCCN, 2015; Piccirillo et al., 2008). Thus the identification of risk factors in elderly kidney cancer patients as the risk factors may be different than those in younger kidney cancer patients was a focus of this study.

Tumor Stage of Disease

Most studies reported that tumors with distant metastases have higher risks of VTEs than patients with tumors without distant metastases. The risk in one study of patients in the Netherlands reported an adjusted odds ratio of 58.0 (95% *CI* 9.7-346.7) for patients with metastatic tumors compared to noncancer patients, and adjusted odds ratio of 19.8 (95% *CI* 2.6-149.1) compared to patients with nonmetastatic tumors (Blom et al., 2005). A study of cancer patients treated with surgery also reported increased risk with

advanced and metastatic tumors compared to early stage tumors (*OR* = 2.7, 95% *CI* 1.4-5.2) (Agnelli et al., 2006). In elderly Medicare enrollees with breast cancer, patients diagnosed with Stage IV cancer were at 1.5 to two-fold risk of venous thromboembolic events compared to patients with Stage I tumors at diagnosis (Chavez-MacGregor et al., 2011). A study of advanced and metastatic breast, colon, lung, and pancreatic cancers reported that the risk of VTEs was higher in metastatic (Stage IV) tumors compared to advanced (Stage III) tumors (*HR* = 1.75, 95% *CI* 1.44-2.12) (Hall et al., 2009). These studies included none or few (less than 4%) of kidney cancer patients (Agnelli et al., 2006; Blom et al., 2005; Hall et al., 2009). However, a study of elderly RCC patients also reported higher rates of VTEs in patients with regional or distant summary stage compared to localized stage (Connelly-Frost et al., 2013).

Tumor stage at diagnosis was assessed as a potential risk factor for development of VTEs in elderly kidney cancer patients. Tumor stage in this study was defined by AJCC staging which is more clinically relevant for treatment and prognosis than stage defined by summary staging.

Histology

Two studies of lung cancer patients reported statistically significant increases in the risk for VTEs in patients with adenocarcinoma compared to patients with squamous cell carcinoma (Blom et al., 2004; Chew et al., 2008). Chew et al. (2008) also reported increased risk for patients with carcinoma not otherwise specified compared to squamous cell carcinoma lung cancer. Conversely studies of breast cancer patients and colorectal cancer patients found no statistically significant difference in the risk of VTEs by

histologic subtype (Alcalay et al., 2006; Chew et al., 2007). A study of ovarian cancer patients, reported that risk for VTEs was increased in patients with advanced stage ovarian clear cell carcinoma compared to advanced serous ovarian carcinoma (Matsuo et al., 2015). Neither early stage serous ovarian carcinoma nor early stage ovarian clear cell carcinoma increased the risk compared to advanced serious ovarian carcinoma (Matsuo et al., 2015). No study was found comparing the risk of VTEs in kidney cancer patients by histology group. Kidney cancer histology groups differ from the groups in other tumor types, thus it cannot be inferred from the findings of other tumor types as to whether there is any difference in risk by kidney cancer histology group. This study was the first study (known to date) in which incidence rates of VTEs by histology group in elderly kidney cancer patients were calculated. The risk of developing incident VTEs by histology groups was also assessed. The histology analyses were unique contributions of this study to the literature and further informed healthcare providers regarding the risks of VTEs in kidney cancer patients.

History of VTE

Previous VTE (*OR* = 6.0, 95% *CI* 2.1-16.8), was a significant risk factor for VTEs in cancer patients undergoing cancer-directed surgical treatment (Agnelli et al., 2006). Similarly, in a study of elderly RCC patients, previous VTE prior to cancer diagnosis increased the risk for DVT (*HR* = 5.4, 95% *CI* 4.4-6.4), pulmonary embolism (*HR* = 20.1, 95% *CI* 13.8-29.2), and OTE (*HR* = 7.6, 95% *CI* 5.9-9.9) (Connelly-Frost et al., 2013). Some researchers have chosen to exclude patients with a prior VTE from the analysis (Chew et al., 2006; Walker et al., 2013). However, such a restriction may exclude some

of the patients at highest risk of developing VTEs after cancer diagnosis (Connelly-Frost et al., 2013). Therefore, information about the history of VTE as a potential risk factor for development of a subsequent VTE after cancer diagnosis was needed.

Cancer Treatments

The main treatments for RCC are nephrectomy, chemotherapy, and immunotherapy (Kirkali, 2009; NCCN, 2015). All three of these treatments may be risk factors for VTEs to varying levels. The evidence for increased risk after cancer-directed surgery is mostly based on studies which included few to no kidney cancers and did not analyze specific surgical types (Agnelli et al., 2006; Blom et al., 2006; Hall et al., 2009).

Nephrectomy. Connelly-Frost et al. (2013) reported incidence rates of VTEs among RCC patients for DVT, pulmonary embolism and OTE by nephrectomy. Radical and partial nephrectomies were not distinguished, and the incidence rates for each VTE were higher in the patients who did not undergo nephrectomy (Connelly-Frost et al., 2013). The unadjusted incidence rates per 1,000 person years for DVT, pulmonary embolism and OTE were 95.5, 28.1, and 47.6 for patients who had a nephrectomy, respectively (Connelly-Frost et al., 2013). For the patients who did not have a nephrectomy, the incidence rates for the three VTEs were 148.6, 35.9, and 53.3, respectively (Connelly-Frost et al., 2013). Nephrectomy was not an independent predictor of individual VTEs in the study; however high risk cardiac or vascular surgeries in the year after RCC diagnosis appeared to reduce the risk of VTE after adjusting for age and race (Connelly-Frost et al., 2013). The authors hypothesize that the decreased risk may have been due to prophylaxis and monitoring for VTE after surgery, as the clinical

guidelines recommend risk assessment for VTE among cancer patients (Connelly-Frost et al., 2013; NCCN, 2015). Similarly, if patients who underwent a nephrectomy received thromboembolism prophylaxis, this may have accounted for the lowered incidence rates and finding that nephrectomy did not have a statistically significant impact on risk of VTE. Additionally, the patients who were at higher risk of VTE may have been poor candidates for surgical treatment.

Hall et al. (2009) reported higher risk of VTE associated with cancer-directed surgery in the year after a diagnosis of advanced lung, breast, colon, prostate or pancreas cancer in elderly patients (*RR* = 4.0, 95% *CI* 3.49-4.57). However, receipt of surgery was not a significant risk factor in the multivariate cox proportional hazards model (Hall et al., 2009). A study of Dutch cancer patients also reported no significant increase in risk of VTE in patients with cancer-directed surgery as the first course of treatment (adjusted *RR* = 1.0; 95% *CI* 0.8–1.2) (Blom et al., 2006). This study included patients of multiple tumor types and ages, and the risk of VTE by specific tumor type or surgery type was not reported (Blom et al., 2006).

Agnelli et al. (2006) studied 2,373 cancer patients undergoing cancer-directed surgeries in Italy, of which 79 (3.3%) had kidney cancer. It was reported that 71% to 87% of the patients received in-patient antithrombotic prophylaxis and approximately 30% of patients received prophylaxis treatments at discharge (Agnelli et al., 2006). The incidence of VTE (DVT or pulmonary embolism) was higher in general surgery and gynecologic surgery patients (2% to 2.8%) than in patients who underwent urologic surgery (0.87%)

(Agnelli et al., 2006). Because all of the patients had surgery, incidence of VTEs could not be compared to the incidence in patients without surgery.

Nephrectomy was defined dichotomously (i.e., receipt of nephrectomy or lack thereof) instead of being defined by type of nephrectomy (e.g., no nephrectomy, partial nephrectomy, or radical nephrectomy). Prophylaxis therapy for VTEs was not well captured in the SEER-Medicare data and so was not assessed.

Chemotherapy. The approved chemotherapy treatments for kidney cancer are targeted therapies, specifically the following tyrosine kinase inhibitors (TKIs): bevacizumab, everolimus, pazopanib, sorafenib, sunitinib, temsirolimus, axitinib, and erlotinib (Monsuez et al., 2010; NCCN, 2015). Bevacizumab is also a monoclonal antibody, while the other medications listed above are small molecule TKIs (Monsuez et al., 2010). A meta-analyses and pooled studies of the association of treatment with bevacizumab and the risk of VTEs in cancer patients reported conflicting results. One, which included a study of RCC patients, reported an increased risk of VTE in patients treated with bevacizumab plus chemotherapy (*RR* = 1.29, 95% *CI* 1.03-1.63) compared to patients treated with chemotherapy without bevacizumab (Nalluri, Chu, Keresztes, Zhu, & Wu, 2008). Two pooled studies found no statistically significant increase in the risk of VTE in patients who were treated with chemotherapy plus bevacizumab, however neither of those studies included RCC patients (Hurwitz et al., 2011; Scappaticci et al., 2007). Of note, of the 15 studies included in the meta-analyses, the largest relative risk in a single study was the analysis of RCC patients and that study was only one of two studies which had statistically significant elevated risks (Nalluri et al., 2008). This study provided the

estimation of risk for VTEs from chemotherapy for RCC patients as well as transitional cell kidney cancer patients and risk for each histology group in all kidney cancer patients.

Evidence for an association between one of these newer treatments, bevacizumab, and risk of VTE from meta-analyses or pooled studies is inconsistent (Hurwitz et al., 2011; Nalluri, Chu, Keresztes, Zhu, & Wu, 2008; Scappaticci et al., 2007). The cardiovascular risks of small molecule TKIs are primarily associated with ATEs, and no associations were found with VTEs (Qi et al., 2013; Sonpavde et al., 2013; Svoboda, Poprach, Dobes, Kiss, & Vyzula, 2012; Yeh & Bickford, 2009). However, similar to bevacizumab, the meta-analyses evidence for VTEs was based on trial data, included many tumor types, and patients of all ages.

Receipt of chemotherapy increased the risk of VTEs in one study of elderly breast cancer patients (Chavez-MacGregor et al., 2011). A different study of specific chemotherapies (cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and any chemotherapy not otherwise specified) in elderly breast cancer patients reported that none of the chemotherapy types nor receipt of any chemotherapy were statistically significant with an increase in myocardial infarction and had wide confidence intervals, after adjusting for age, race, stage, year of breast cancer diagnosis, preexisting heart disease, and comorbidity score (Doyle et al., 2005). The study had 31,748 women in the study, 5,575 of which received any chemotherapy, however the authors did not report the number of patients with myocardial infarction (Doyle et al., 2005). Thus, it is difficult to know whether the lack of association between myocardial infarction and chemotherapy was due to no true association or small numbers in the model.

A study of Dutch patients diagnosed with any cancer type reported a two-fold relative risk of VTE in patients treated with chemotherapy for patients without metastases (*RR* = 2.0, 95% *CI* 1.6-2.7) and for patients with metastatic tumors (*RR* = 2.3, 95% *CI* 1.7-3.1) (Blom et al., 2006). A study of VTEs in lung cancer patients also reported two-fold elevated risks in patients with chemotherapy (*OR* = 2.9, 95% *CI* 1.8-4.0) (Blom et al., 2004). Similarly, a study of advanced or metastatic breast, colon, lung and pancreatic cancer reported higher risk of VTEs in patients treated with chemotherapy (*HR* = 1.31, 95% *CI* 1.10-1.57) (Hall et al., 2009).

Although there are several types of immunotherapy used to treat cancers, the main immunotherapies used to treat RCC are two cytokines, interleukin-2 (IL-2) and interferon alfa (NCCN, 2015). Neither IL-2 nor interferon alfa are listed as risk factors in the clinical guidelines for VTE in cancer patients (NCCN, 2015). However, there is some evidence for cardiovascular toxicity for both drugs. Cardiovascular disorders due to treatment with interferon alfa are rare, however the evidence is based on studies limited by small sample sizes, were not in RCC or kidney cancer patients, or were conducted more than a decade ago (Sleijfer, Bannink, Van Gool, Kruit, & Stoter, 2005). Cardiovascular toxicity is more common with IL-2, possibly due in part to its adverse effect of vascular leak syndrome (Clark et al., 2013; Siegel & Puri, 1991). Based on the toxicity profile of IL-2, it has not been widely used in elderly cancer patients (Clark et al., 2013). However, a recent study of 22 elderly metastatic cancer patients reported less toxicity for most adverse events compared to patients under age 65 years (Clark et al., 2013). The main limitation of the study was the small sample size (Clark et al., 2013). In

addition, it was not possible to assess the impact of bias introduced if the older patients treated with IL-2 were healthier than the treated younger patients.

This study assessed receipt of chemotherapy and receipt of immunotherapy dichotomously, without attempting to identify individual chemotherapy and immunotherapy drugs or drug classes, as that level of detail was outside the scope of this study.

Other Factors

The study of elderly RCC patients by Connelly-Frost et al. (2013) reported that CVC and cardiac or vascular surgeries which occurred more than 30 days before the event were independent risk factors protective for DVT, pulmonary embolism, and OTE in RCC patients after the cancer diagnosis. The authors hypothesize that the decreased risk observed may have been due to prophylactic treatment given to these patients because of the association between surgery and CVC and VTE risk (Connelly-Frost et al., 2013; NCCN, 2015). Additionally, the reduced risk from cardiovascular surgeries and CVD may have also been due to selection bias as elderly patients undergo geriatric assessments as an additional screening when determining how to treat the patient's cancer (NCCN, 2015). The study by Alcalay et al. (2006) of colorectal cancer patients also reported lower incidence of VTEs in patients who undergone a major abdominal surgery compared to those who never had (*HR* = 0.4, 95% *CI* 0.3-0.4). This study also was unable to assess use of prophylactic therapy (Alcalay et al., 2006). Similarly, a study of breast cancer patients age 18 or older reported lower incidence risk of VTE in patients who underwent breast-related surgery (*HR* = 0.6, 95% *CI* 0.5-0.7) (Chew et al., 2007).

Conversely, the study by Chavez-MacGregor et al. (2011) in breast cancer patients reported placement of a CVC within the first year after the cancer diagnosis increased the risk of VTEs. CVC was not assessed as a potential risk factor in the Alcalay et al. (2006) or Chew et al. (2007) studies.

A study of cancer patients aged 19 or older at diagnosis and treated with cisplatin at the Memorial Sloan-Kettering Cancer Center in 2008 reported that a central venous catheter increased the risk of a thromboembolic event, even after adjusting for age, gender, race, Karnofsky performance status, cancer stage, and risk group (*OR* = 1.61, 95% *CI* 1.10-2.36) (Moore et al., 2011). Surgery was also assessed as a risk factor, but was not statistically significant in univariate analyses. However, the timing of the surgery variable was within two months of starting cisplatin treatment and the types of surgery included in the variable were not described (Moore et al., 2011). This study included 932 cancer patients of multiple cancer types. Ten percent of the study population was classified as "other" cancer types, which may have included kidney cancer (Moore et al., 2011). The number and proportion of kidney cancer patients could not be determined from the publication.

A study of elderly breast, colon, lung, prostate, and pancreas cancer patients with Stage III or IV cancers found an increased incidence of VTEs in patients who had cancer-directed surgeries ($p < 0.01$), however the risk was not statistically significant in the multivariate analysis (Hall et al., 2009). The risk of VTE varied widely by cancer type, was increased in Stage IV cancers (*HR* = 1.75, 95% *CI* 1.44-2.12) compared to Stage III patients, and receipt of chemotherapy (*HR* = 1.31, 95% *CI* 1.10-1.57) (Hall et al., 2009).

A study of the risk of heart diseases, including myocardial infarction, in elderly breast cancer patients reported that neither breast cancer surgery nor histologic subtype were associated with the broad category of heart disease in this population after adjusting for other factors (Doyle et al., 2005). CVC and other surgical procedures were not assessed in the Doyle et al. (2005) study. This study included binary variables indicating insertion of a CVC and receipt of a high risk surgery as potential risk factors for development of VTEs.

Incidence of Arterial Thromboembolic Events

Incidence rates of ATEs in kidney cancer patients were not found in the published literature, but cumulative incidence was found in RCC patients treated with chemotherapy. According to prescribing information, the incidence of myocardial infarction in clinical trials of Nexavar-treated patients with late-stage RCC was 2.9% (Bayer HealthCare Pharmaceuticals, 2013). Similarly, clinical trials of Votrient-treated patients with late-stage RCC reported 2% incidence of myocardial infarction or ischemia (GlaxoSmithKline, 2014). However this information is from clinical trial data, may not have been published, is not population-based, and is often limited by small sample size.

A meta-analysis of clinical trials which reported on the incidence of ATEs (defined as myocardial infarction, arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, or myocardial ischemia) in RCC patients was restricted to advanced or metastatic patients who received specific targeted therapies as treatment (Choueiri et al., 2010). The incidence of ATEs in these RCC patients was 1.8% (Choueiri et al., 2010). Another meta-analysis of clinical trial data reported an incidence of ATEs in

RCC patients of 2.0% (95% *CI* = 1.5–2.7%) (Qi et al., 2014). There was some overlap in the studies used by Choueiri et al. (2010) and Qi et al. (2014).

A pooled analysis of clinical trial data, but which included no kidney cancer patients, reported an incidence of ATEs as 2.5% in control patients and 7.1% in bevacizumab-treated patients 65 years of age or older (Scappaticci et al., 2007). In the patients 65 years of age or older, the incidence of ATE was 2.6% and 4.4% in patients without a history of ATE and 2.2% and 17.9% with a history of ATE, in the controls and bevacizumab-treated patients respectively (Scappaticci et al., 2007). The definition of ATEs used by Scappaticci et al. (2007) included the same events as Choueiri et al. (2010) but also included angina pectoris. Neither Scappaticci et al. (2007), Choueiri et al. (2010), nor Qi et al. (2014) reported incidence for individual ATE events.

A meta-analysis of patients with various cancers who participated in randomized clinical trials of anti-EGFR agents reported an incidence of arterial thromboembolic events of 4.5% in the patients the cituximab or erlotinib versus 3.4% in the comparison group (Petrelli, Cabiddu, Borgonovo, & Barni, 2012). One of the studies was of RCC patients, however the sample size was only 104 patients total with only 1 ATE event. Myocardial infarction was included in the definition of ATEs, but ischemic stroke was not.

One study of cancer patients treated with cisplatin-based chemotherapy reported incidence of 0.2% for myocardial infarction and 2% for any arterial events (Moore et al., 2011). This study analyzed 932 cancer patients aged 19 to 87 years of age treated in 2008, and it was unclear if any kidney cancer patients were included (Moore et al., 2011).

A study reported an incidence rate for ischemic stroke of 21.80 per 1,000 p-y in the lung cancer group and 15.10 per 1,000 p-y in the noncancer comparison group (Chen, Muo, Lee, Yu, & Sung, 2011). The patients were 20 or older at lung cancer diagnosis, diagnosed between 1999 and 2007, and matched by age, sex, and month of lung cancer diagnosis to a noncancer comparison group (Chen et al., 2011). All patients were beneficiaries of the Taiwan National Health Insurance.

A study of Dutch lung cancer patients of all ages reported incidence rates of 4.5 and 3.8 per 1,000 p-y for myocardial infarction and ischemic stroke in the first six months after cancer diagnosis (van Herk-Sukel et al., 2013). For 6 months after lung cancer diagnosis until the end of follow-up, the incidence rate for myocardial infarction and ischemic stroke were 1.9 and 1.8, respectively (van Herk-Sukel et al., 2013). There were no statistically significant differences in incidence rates for the lung cancer patients compared to a noncancer comparison group for myocardial infarction or ischemic stroke. However because there were less than 15 of either myocardial infarction or ischemic stroke events in those periods, there may not have been sufficient power to distinguish any differences.

The 1-year cumulative incidence of ischemic stroke in cohorts of elderly cancer patients and matched cohorts of noncancer patients vary by cancer type. The cumulative incidence for breast cancer patients and the noncancer cohort were 3.6% and 3.6% respectively (Navi et al., 2015). The incidences for prostate cancer and its comparison cohort were similar to those for the breast cancer cohorts, 3.3% and 3.3%. However, the

incidence rates were higher for colorectal cancer, 5.8% and 4.3%, and for lung cancer, 7.3% and 4.1% (Navi et al., 2015).

A study of Dutch patients of all ages who had been hospitalized for breast cancer reported incidence rates of 1.6, 1.6, and 1.8 per 1,000 p-y for myocardial infarction in the first six months after breast cancer hospitalization, 6 to 12 months after, and 12 months to end of follow-up (van Herk-Sukel et al., 2011). For ischemic stroke, the incidence rates for the same periods were 1.5, 1.8, and 1.6 (van Herk-Sukel et al., 2011). The number of events was small (less than 10) in each period in the first 12 months after the breast cancer hospitalization, but increased in the rest of the follow-up period. Similar to the lung cancer study, after adjusting the incidence rates were not statistically significantly different from a noncancer comparison group (van Herk-Sukel et al., 2011).

No report of incidence (rates or cumulative) of ATEs myocardial infarction, or ischemic stroke in the broader kidney cancer population was identified. This study was the first (known to date) to calculate incidence rates for ATEs in elderly kidney cancer patients utilizing a large, population-based data source, and which presented the incidence rates stratified by patient and tumor characteristics. Incidence rates for ATEs were presented overall as well as for individual ATEs (myocardial infarction and ischemic stroke). Although ATEs were rarer than VTEs, the incidence and risk of ATEs were of interest particularly for understanding the background rate of these conditions and interpreting clinical trial or post-marketing drug safety profiles (FDA, 2011).

Risk Factors for Myocardial Infarction and Ischemic Stroke

Myocardial infarction and ischemic stroke may be higher in cancer patients than noncancer patients, although the risk may vary by cancer type. The standardized incidence ratio for ischemic stroke in Swedish kidney cancer patients was 1.1 (95% *CI* 1.1 – 1.2) (Zoller, Ji, Sundquist, & Sundquist, 2012). The standardized incidence ratios for other cancers in this population ranged from 0.7 to 1.6, with an overall standardized incidence ratio of 1.2 (95% *CI* 1.2 – 1.2) (Zoller et al., 2012). Another study of Swedish breast cancer patients reported an increased risk of ischemic stroke in breast cancer patients aged 55 to 69 (*RR* = 1.1, 95% *CI* 1.0–1.3) and breast cancer patients 70 years or older (*RR* = 1.1, 95% *CI* 1.0–1.2) compared to the expected numbers of events in the general population of those age groups (Nilsson et al., 2005).

A study of Taiwanese cervical cancer patients who underwent radiotherapy had higher risks of myocardial infarction and ischemic stroke than a comparison group of appendectomy patients. The adjusted hazard ratios for myocardial infarction and ischemic stroke in cancer patients compared to the comparison group were 1.58 and 1.52, both with p-values of 0.01 or less (Tsai et al., 2013). A study of Taiwanese head and neck cancer patients reported higher risk of stroke compared to noncancer patients (adjusted *HR* = 1.5, 95% *CI* 1.4 – 1.7) (Chu et al., 2011).

Two articles were identified which assessed risk factors for myocardial infarction or ischemic stroke in lung and breast cancer patients (van Herk-Sukel et al., 2011, 2013). Both studies were conducted in Dutch cancer patients of all ages. The risk factors for myocardial infarction after breast cancer hospitalization increased with age 50 and older

compared to 49 and younger, prior use of antihypertensive drugs, and a hospitalization of 11 or more days within the first six months after breast cancer hospitalization (van Herk-Sukel et al., 2011). The risk factors for ischemic stroke was age of 70 or older compared with patients 49 or younger at diagnosis, prior use of platelet aggregation inhibitor drugs, prior use of antihypertensive drugs, and prior use of antidiabetic drugs (van Herk-Sukel et al., 2011).

The risk factors for myocardial infarction or ischemic stroke in lung cancer patients in the period starting sex months after the cancer diagnosis to the end of the follow-up period were age of 65 years or older, prior hospitalization for the condition, prior drug use of antithrombotic drugs, cardiovascular drugs, or antidiabetic drugs (van Herk-Sukel et al., 2013). Female gender was protective for both conditions (van Herk-Sukel et al., 2013).

In a study of lung cancer patients in Taiwan, the risk factors for any type of stroke (other than traumatic stroke) were age, male gender, blue collar or other work compared to white collar work, history of hypertension, history of diabetes, history of coronary heart disease, history of atrial fibrillation, and history of coronary obstructive pulmonary disorder (Chen et al., 2011). Decreasing urbanization was identified as protective against stroke (Chen et al., 2011). These findings were based on the unadjusted hazard ratios as adjusted model results were not presented.

Studies of risk factors for ischemic stroke comparing cancer patients and noncancer patients have reported similar prevalence of several risk factors in the two groups. Two studies reported lower prevalence of atrial fibrillation in cancer patients who

had a stroke than in noncancer stroke patients (Karlinska, Gromadzka, Karlinski, & Czlonkowska, 2015; Kim & Lee, 2014). No differences in the prevalence of diabetes or smoking status were found (Karlinska et al., 2015; Kim & Lee, 2014). The Karlinska et al. (2015) article found a lower prevalence of previous stroke in cancer patients, but no difference in the prevalence of hypertension, or congestive heart failure. Kim and Lee (2015) reported lower prevalence of hypertension, ischemic heart disease, hyperlipidemia, and family history of stroke in cancer patients compared to the noncancer patients. There was no difference in the prevalence of previous stroke in the cancer and noncancer patients (Kim & Lee, 2014). Although both studies included patients with various kinds of cancers, neither Karlinska et al. (2015) nor Kim and Lee (2014) had more than five kidney cancer patients in their studies.

The published literature regarding risk factors for myocardial infarction or ischemic stroke in cancer patients was limited to a couple of tumor types. Age, co-medications, and comorbidities increased the risk of the outcomes. In comparison with noncancer patients, the prevalence of risk factors for ATEs was similar for smoking and diabetes, but lower for atrial fibrillation. Whether the prevalence of other risk factors differed between cancer and noncancer patients depended on the study population and methodology. Research on the risk factors for ATEs in kidney cancer patients was not found, and so this study will make a contribution to the literature by providing information in this area.

Summary and Conclusions

This literature review summarized what was known about the incidence of VTEs and ATEs in kidney cancer patients and the assessed risk factors for VTEs. Incidence rates for VTEs in kidney cancer patients are approximately 13 – 14 per 1,000 person-years overall, but are higher for more distant stage (Chew et al., 2006; Walker et al., 2013). No significant differences in the rates of VTEs in kidney cancer were observed for older patients compared to younger patients (Chew et al., 2006; Walker et al., 2013). Studies of other tumor types have been inconsistent as to whether there are differences in rates or risk of VTEs by age at cancer diagnosis (Alcalay et al., 2006; Chew et al., 2007, 2008; Hall et al., 2009; Khorana et al., 2008). While studies have consistently shown that the risk of VTE varies significantly by tumor type, there are very few studies conducted specifically in kidney cancer patients (Blom et al., 2005; Hall et al., 2009; Walker et al., 2013; White et al., 2005). Thus, it is unclear whether VTE risk factors identified in other tumor types are risk factors for VTEs in kidney cancer patients as well. In addition, incidence and risk of VTEs and ATEs is noticeably absent for kidney cancer histology groups. Venous thromboembolic events in cancer patients have been more studied than ATEs for all tumor types including kidney cancer. This study provided incidence rates for VTEs and ATEs in elderly kidney cancer patients, described incidence rates by histology group, and assessed independent risk factors for VTEs in this population including histology group.

Chapter 3 provides more detail on the study population criteria, calculation of incidence rates, and the Cox proportional hazards models which were conducted for the

descriptive analyses and to answer the research questions. Each variable and how it was constructed are provided. Threats to validity and ethical concerns are discussed as related to this study.

Chapter 3: Research Method

Introduction

The previous chapters described the importance of VTEs and ATEs in elderly cancer patients, summarized the literature, and highlighted the gaps in knowledge. The problem was that incidence rates of VTEs and ATES for elderly kidney cancer patients (ages 65 years or older at diagnosis) are not readily available in the literature, much less incidence rates by histology group, and other patient and tumor characteristics. Analysis of risk factors for VTEs in elderly kidney cancer patients was also needed.

This chapter described the rationale and methodology for using a quantitative, retrospective cohort study design. The study population, inclusion and exclusion criteria, the data set characteristics and procedures for accessing the data set, operational constructs, the data analysis plan, threats to validity, and ethical procedures were thoroughly discussed.

Research Design and Rationale

The dependent variables were diagnoses of VTE or ATE, depending on the analysis or research question. For Research Question 1, the outcome was the calculation of incidence rates for diagnosis of the first incident VTE/ATE in the year prior to kidney cancer diagnosis or index date. Hazard ratios were calculated to estimate the incidence rate ratios of VTE/ATEs comparing the exposed to unexposed groups. For Research Question 2, the dependent variable was the calculated hazard ratio approximating the incidence rate ratios of the incidence rate of VTE/ATE in the exposed and the incidence

rate of VTE/ATE in the unexposed. Only the first incident event was counted for all analyses.

The exposed and unexposed patients were matched on age (in years) at kidney cancer diagnosis (exposed) or index date (unexposed), gender, race, SEER registry area, and duration of follow-up. For matching, duration of follow-up for the unexposed was required to be equal to or greater than the duration of follow-up for the exposed. However, for the analyses, the duration of follow-up for the unexposed was truncated to the same value as the corresponding kidney cancer patient. Patients from the exposed and unexposed cohorts were matched in order to reduce the likelihood that the differences in the incidence rate ratios are due to age, gender, or any of the other matching factors, as estimating any difference in rate ratios due to exposure status is the objective.

The analysis for Research Question 3 included kidney cancer patients only. The dependent variable was the time in years from kidney cancer diagnosis to occurrence of the first VTE or duration of follow-up. Individual dependent variables were created for each VTE and for any VTE. The potential predictors included in the initial (full) model were age at diagnosis, race, gender, diabetes, atherosclerosis, varicose veins, cardiovascular surgery, central venous catheter, kidney disease, history of VTE, history of cardiovascular disease, AJCC stage, treatment type (immunotherapy, nephrectomy, chemotherapy), histology group, SEER registry region, Charlson comorbidity score, and year of diagnosis.

This study was a quantitative, retrospective cohort study. A cohort study was the appropriate study design for assessing incidence rates and incidence proportions for the

descriptive analyses and research questions (Aschengrau & Seage, 2008; Rothman, 1986). The resource constraint from the use of a retrospective cohort design using secondary data for this research study was that only the data on outcomes and independent variables included in the dataset were available. Thus measurement of some risk factors for incident VTEs and ATEs were not in the dataset, and were not included in this study. The use of the study design was consistent with other studies which add to the understanding of incident VTEs and ATEs in cancer patients (Connelly-Frost et al., 2013; Walker et al., 2013).

Data Source

The SEER-Medicare database is a linkage of the SEER cancer registry data with Medicare claims data, creating a population-based resource for cancer-related analyses (Warren et al., 2002a). Also available with the SEER-Medicare database is Medicare enrollment and claims data for a sample of noncancer patients. The noncancer patients are selected from a 5% random sample of Medicare beneficiaries who reside in the same SEER registry areas and who are not in the SEER cancer registry database (Applied Research Program, 2013; Warren et al., 2002a). The noncancer patient cohort was used in this research study as the unexposed comparison group.

The SEER data contains newly diagnosed cancers in the SEER registry areas, some of which began collecting data in 1973. As of 2013, there were 18 registry areas which covered approximately 27% of the entire U.S. population (SEER, 2013). The SEER data are of high quality and annually meet quality criteria of the North American Association of Central Cancer Registries (Warren et al., 2002a).

Medicare is a government program to insure the elderly in the United States, although persons with disabilities or end-stage renal disease may qualify for Medicare coverage before 65 years of age. The Medicare data include claims plus demographic and entitlement information from the Medicare master enrollment file (Applied Research Program, 2013; Warren et al., 2002a).

The two databases were first linked in 1991 and updated in subsequent years, with current plans to update the linkage every two years (Applied Research Program, 2013; Warren et al., 2002a). Social security number, sex, name, and date of birth are used to link the databases (Warren et al., 2002a), however personal identifiers such as social security number and name are not included in the final database for release to researchers. Generalizability of the database has been assessed as well. On characteristics such as age and sex, the database population is similar to the U.S. elderly population (Warren et al., 2002a). However, the database differs from the U.S. elderly population in race, residence in an urban (versus rural) location, participation in a Medicare managed care plan, and cancer mortality rate (Warren et al., 2002a).

Although the linked SEER-Medicare database is a high-quality, population based resource for researchers, it has several limitations. Limitations identified include no information about services which are not covered by Medicare or which are paid for out of pocket, incomplete claims for persons enrolled in Medicare managed care plans, and the general limitations which affect any administrative claims databases (Warren et al., 2002a). However, the database can be used for various types of studies along the entire continuum of care for cancer patients (Applied Research Program, 2013). Study topics

published include cancer screening, treatment patterns and outcomes, hospice and other resource utilization, health economic studies, healthcare disparities, and survival analyses (Applied Research Program, 2013; Warren et al., 2002a).

Study Population

The exposed cohort consisted of patients in the SEER-Medicare database diagnosed with kidney cancer at age 65 years or older, diagnosed between the years of 2004 and 2009, and whose kidney cancer was their first primary cancer. Patient follow-up was from the month of kidney cancer diagnosis until death, participation in a managed care plan, coverage by only Part A or B of Medicare, or December 31, 2010. For this study, the estimated number of kidney cancer patients was 12,240. This estimate was calculated by summing the number of kidney cancer patients in the SEER-Medicare database between 2004 and 2009 (Applied Research Program, 2013) and multiplying by 69% to estimate the number of patients remaining after applying the study inclusion and exclusion criteria. The percentage remaining after applying inclusion and exclusion criteria was based on the proportion remaining after applying the same criteria for the Connelly-Frost et al. (2013) study.

The patient criteria applied for the counts from the Applied Research Program (2013) were: (a) patients 65 years of age or older at diagnosis, (b) kidney cancer was the first diagnosed cancer (sequence number 00 or 01), and (c) patients had Medicare Part A and B coverage and were not participating in a Medicare managed care program during the month of diagnosis.

A comparison cohort of noncancer patients were individually matched, without replacement, to the kidney cancer patients by age at index date, sex, SEER registry region, and duration of follow-up. The index date of the matched noncancer patient was assigned as the month and year of diagnosis of its corresponding kidney cancer patient. The unexposed patients were also required to have two years of continuous enrollment in Medicare parts A and B prior to the index date with no participation in a managed care program during that time. Each unexposed patient were required to have at least as much follow-up as their corresponding exposed patient, however the follow-up for the unexposed was truncated to the same month as the corresponding cancer patient. With 659,639 noncancer patients in the potential comparison group, the majority of exposed patients were matched to an unexposed patient.

Sampling Strategy

The sampling strategy for the exposed cohort was to include all kidney cancer patients who met the inclusion and exclusion criteria and were matched to a corresponding unexposed patient. Cancer patients who developed multiple primary cancers before or at the time of the initial kidney cancer diagnosis were excluded. Inclusion criteria required all patients to have at least two years of continuous enrollment in Medicare parts A and B prior to the index date and at least one month of survival after the index date. Patients who participated in a managed Medicare plan in the two years prior to the index date were excluded. The same inclusion and exclusion criteria were applied to matched patients using the index date.

Power calculations were not generated for the descriptive analyses. For Research Question 1, the required sample size to achieve power of 0.8 ranged from 848 to 3594, depending on the unknown true values of the overall response probability, covariate standard deviation, and odds ratios for specific VTE or ATE. The assumptions used were alpha level 0.05, covariate odds ratio of 1.2, and odds ratio for test predictor of 1.5 to 1.75. The ranges for the covariate odds ratio and test predictors were based on the values reported by Connelly-Frost (2013).

For the second and third research questions, power calculations were generated to compare two survival curves using the log-rank test. Using the assumptions that both survival curves are exponential, a year (12 months) of follow-up time, and a two-sided test at alpha level 0.05, a sample size of 1,044 per group is needed to achieve power of 0.8 and a sample size of 1,194 per group is needed to achieve power of 0.85. All power calculations were generated using SAS 9.3 software.

Variable Definitions and Operationalization

Variables to identify the kidney cancer patients, variables related to the kidney cancer diagnosis, patient characteristics and Medicare coverage or managed Medicare plans were contained in or constructed from information in the SEER-Medicare Patient Entitlement and Diagnosis Summary File. The Patient Entitlement and Diagnosis Summary File contains cancer information at diagnosis and during first course of treatment from the SEER program. The Medicare claims files were used to identify cancer treatments, diagnoses of venous and arterial thromboembolic events, and the medical conditions which are potential confounders or effect measure modifiers.

The Medicare Entitlement files contain monthly indicators of participation in Part A, Part B, or managed care plans. To determine eligibility, a patient must have had coverage by Parts A and B of Medicare for 24 months prior to index date and no participation in HMO during that time. Thus, each of the 24 variables for the period prior to index date indicating Medicare coverage must have a value of 3, Parts A and B coverage. Each of the 24 variables for the period prior to index date indicating managed care participation must have a value of 0 indicating no participation to be eligible. Duration of follow-up was calculated as the number of months after the index date until the variable indicating coverage does not have a value of 3, the variable indicating managed care participation has a value other than 0, the patient dies (using month and year of death), or December 2010.

The index date for patients was defined as follows. For kidney cancer patients, the index date was first day of the month and year of the first kidney cancer diagnosis. For the matched, noncancer comparison group, the index date was the same as the index date of the corresponding kidney cancer patient it is matched to. One of the matching criteria was the comparator patient must meet the same Medicare coverage and managed care criteria in the month of the index date.

Age at index date was calculated as the number of years between year of birth and year of index date. Age was grouped into the following categories: 65-69, 70-74, 75-79, 80-84, and 85 or older.

Race was provided by the Medicare Entitlement information and was categorized as White, Black and other race. Because there were less than 10 patients in each cohort with unknown race, those patients were included with the other race group.

Gender was categorized as male or female, and was provided in the Medicare Entitlement file.

SEER registry area of diagnosis or residence was categorized using the United States Census Region groupings for analysis of geographic region. The regions were Northeast, Midwest, South and West. The states which make up each region are listed in Appendix B.

For analyses of Research Questions 1 and 2, the unexposed patients (the noncancer patients) were matched to the exposed patients on age at index date, gender, race, SEER registry area, and duration of follow-up. The matched, unexposed patients were assigned the same index date as the corresponding exposed patient, and thus were required to meet the same criteria of Part A and B Medicare coverage with no managed care participation prior to the same index date.

Kidney cancer was defined using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) coding site for the kidney (C64.9), excluding histology codes 9590-9989. Only malignant tumors were included.

The types of kidney cancer, transitional cell and RCC, were defined by ICD-O-3 codes as well. Transitional cell kidney cancer was defined as kidney cancers with histology codes 8050-8130 (inclusive). RCC was defined as kidney cancers excluding histology codes 8050-8130 (inclusive). The types of RCC were defined as Clear Cell

(ICD-O-3 histology codes 8310 or 8312); Papillary (ICD-O-3 histology code 8260); Chromophobe (ICD-O-3 histology codes 8317, 8270) and Other RCC (ICD-O-3 histology codes excluding 8050-8130 inclusive, 8310, 8312, 8317, 8260, and 8270).

For VTEs, each condition (deep vein thrombosis, pulmonary embolism, or other thromboembolic events) were coded dichotomously, indicating whether or not a diagnosis of the condition was recorded. The codes used to define these conditions are located in Appendix B. A derived variable for any VTE was coded dichotomously.

Similarly, for ATEs, each condition (myocardial infarction or ischemic stroke) were coded dichotomously, indicating whether or not a diagnosis of the condition was recorded. For ischemic stroke, diagnoses were only included if they occurred during a hospitalization. This is because outpatient claims with a diagnosis of ischemic stroke may be for rehabilitation or other follow-up care and not actually indicate the incident stroke event. The codes used to define these conditions are located in Appendix B. A derived variable for any ATE was coded dichotomously.

Cancer treatments were coded as follows. Any chemotherapy was coded dichotomously, indicating whether or not a cancer patient received chemotherapy. The procedure and NDC codes used to identify chemotherapy are located in Appendix B. Any immunotherapy was coded dichotomously, indicating whether or not a cancer patient received immunotherapy. The procedure and NDC codes used to identify immunotherapy are located in Appendix B. Nephrectomy was coded dichotomously, indicating whether or not a procedure code for nephrectomy was coded. The procedure codes to identify nephrectomy are in Appendix B.

The following conditions were defined dichotomously, with a value of 1 indicating whether or not the condition was reported in the claims data: diabetes, atherosclerosis, varicose veins, high risk cardiovascular surgeries, placement of a CVC, and kidney disease. The diagnosis and procedure codes to define each of these conditions are located in Appendix B. High risk surgeries and placement of a CVC events were restricted to those events which occurred more than 30 days prior to the outcome.

A weighted score was calculated from the conditions in the adapted Charlson comorbidity index. The score was analyzed as 0, 1, 2, and 3 or greater. See Appendix C for the index conditions and the ICD-9-CM diagnosis and procedure codes used to define the score. See Appendix D for the program to calculate the score.

Data Analysis Plan

SAS 9.3 was used to perform all analyses. Analyses for each research question and hypotheses are described below. Univariate and bivariate frequencies and descriptive statistics were generated for variables to identify outliers and unusual values.

Descriptive Analysis 1

The first analysis involved the calculation of the incidence rates of individual VTEs and of ATEs in elderly kidney cancer patients over the 12 months before and in the follow-up period after cancer diagnosis. Incidence rates were calculated as the number of incident events in the study period divided by the sum total of person-time at risk during the period. No statistical tests were performed. For each of the prespecified patient and tumor characteristics, the incidence rates of VTEs and ATEs were presented by age group, race, gender, history of VTE/ATE, history of cardiovascular disease, AJCC stage,

treatment by immunotherapy, treatment by nephrectomy, treatment by chemotherapy or targeted therapy, histology group, Charlson Comorbidity Index, SEER registry region, and year of diagnosis.

Descriptive Analysis 2

For this analysis, the proportion of elderly kidney cancer patients who experienced incident VTEs and incident ATEs in discrete, mutually exclusive time periods during follow-up (0 to 90 days, 91 to 180 days, 181 to 270 days, and 271 to 365 days) after cancer diagnosis were calculated. Incidence proportions were calculated as the number of incident events in the time period divided by the number of patients still at risk for an incident VTE or ATE during the period. No statistical tests were performed.

Research Question 1

Research Question 1: How do the incidence rates of VTEs and ATEs in elderly exposed (kidney cancer) patients 12 months before index date compare to a matched unexposed (noncancer) Medicare population during the same 12-month timeframe?

H_A1: In the year prior to index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_01: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the year prior to the index date in the exposed patients and in the matched unexposed patients.

Hazard ratios were calculated to compare the incidence rates of VTEs and ATEs in cancer patients to the matched noncancer cohort in the period after diagnosis (index

date). Adjustment was made for the matching of the cohorts using the STRATA statement in the PHREG procedure of SAS.

Research Question 2

Research Question 2: How do the incidence rates of VTEs and rates of ATEs in elderly exposed (kidney cancer) patients after index date compare to a matched unexposed (noncancer) Medicare population during the same timeframe?

H_A2: In the follow-up period after the index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_02: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the period after index date in the exposed patients and in the matched unexposed patients.

Hazard ratios were calculated to compare the incidence rates of VTEs and ATEs in cancer patients to the matched noncancer cohort in the period after diagnosis (index date). Adjustment was made for the matching of the cohorts using the STRATA statement in the PHREG procedure of SAS.

Research Question 3

Research Question 3: In the follow-up period after kidney cancer diagnosis, what are the risk factors associated with time to newly diagnosed, individual VTE (DVT, PE, or OTE)?

H_A3: No factors are statistically significantly associated with the time to newly diagnosed VTEs in the period after kidney cancer diagnosis.

$H_0$3: Tumor histology and other factors are statistically significantly associated with the time to newly diagnosed VTEs after kidney cancer diagnosis.

For each question, a Cox proportional hazard model was used to identify independent predictors for each outcome. The outcome was time to the occurrence of the first VTE or ATE after kidney cancer diagnosis or duration of follow-up. The potential predictors to be included in the initial (full) model were age at diagnosis, race, gender, diabetes, atherosclerosis, varicose veins, cardiovascular surgery, central venous catheter, kidney disease, history of VTE, history of cardiovascular disease, AJCC stage, treatment type (immunotherapy, nephrectomy, chemotherapy), histology group, SEER registry region, and year of diagnosis. Exploration of the data and these variables prior to modeling included production of a correlation matrix to identify any highly correlated variables. Highly correlated variables were those with an absolute value of the correlation coefficient greater than or equal to 0.7 (Taylor, 1990). If two variables were highly correlated, then only one variable of the pair were included in the model to avoid redundancy.

Potential effect measure modifiers were identified by testing the equality of survivorship over strata for each variable. If a variable had a p-value for the log rank test less than 0.05, then this variable were characterized as a potential effect measure modifier (Szklo & Nieto, 2006). Potential confounders were identified as those variables which were a) associated with exposure and b) associated with outcome among the unexposed. Mediating variables are variables which are on the causal pathway between the independent and dependent variables (Creswell, 2009). None of the variables for the

model were considered mediating variables. The initial full model contained all potential effect measure modifiers and confounders. The proportional hazards assumption was tested for each variable. If the proportional hazards assumption did not hold true for any variable, stratification of the model by this variable was used to account for the violation. For those variables for which the proportional hazards assumption held, the final test for effect measure modifiers were conducted by determining whether the p-value for interaction term was less than 0.05 in the full model. Next the final confounders for the model were identified as those variables for which there is a 15% change in the hazard ratio estimate for the adjusted versus unadjusted model.

Alternative models were run using a Deyo-Romano adaptation of the Charlson Comorbidity Index (CCI) instead of the individual variables (diabetes, cardiovascular surgery, kidney disease, and history of cardiovascular disease), as the CCI includes these procedures and diagnoses in addition to others (see Appendix C).

Survival curves were generated for incidence of VTEs and ATEs stratified by patient and tumor characteristics, using the log-rank test to distinguish statistically significant differences in curves at the 0.05 level.

Threats to Validity

The main threat to validity was unmeasured factors, such as smoking and patient platelet counts, which may impact the incidence or risk of VTEs or ATEs. Other threats to validity were minimized by the use of previously defined constructs for comorbidity classification, exposure and independent variable definitions. Bias may also have been introduced if any of the covariates in the model were mediator variables. Inclusion of

mediator variables in the model will introduce bias if (a) confounders of the mediator-outcome relationship are not adjusted for in the model, (b) the mediator-outcome confounders are affected by exposure, or (c) there is an interaction effect between the exposure and the mediator variables (Richiardi, Bellocco, & Zugna, 2013). None of the variables in this study were considered mediator variables but were adjusted for as confounders or effect measure modifiers.

Ethical Procedures

Accessing the Data

In order to access the SEER-Medicare database, several steps were completed. The first step was to submit an application for review. The application contained the completed application form which included a description of the study project and a signed data use agreement (Applied Research Program, 2013). The data was only available for purchase after the application has been approved. The proposal for the original study using SEER-Medicare data was submitted and approved in 2006. The request to update the study with additional cancer sites, years of data, and outcomes was approved January 2013. As this project does not require restricted variables which may compromise patient or provider confidentiality, the request form for these variables was not necessary.

The data was accessed through a pharmaceutical company. The SEER-Medicare account manager at the company was listed as the Principal Investigator and signatory on the data use agreement, although the use of the data was restricted to my analysis as the data may only be used for the project approved in the application (Applied Research

Program, 2013). The study proposal for the research questions and hypotheses were approved prior to purchase of the data. Note that IRB approval was not required as the original proposal was approved prior to the inclusion of IRB approval as an application component. However, IRB approval of this study was requested through Walden University prior to start of any data analysis. The Walden University IRB approval number for this study is 07-23-15-0083161.

The National Cancer Institute has taken multiple steps to protect patient and provider confidentiality in the SEER-Medicare database and it is considered a limited-data set per the Health Insurance Portability and Accountability Act (HIPAA) regulations (Applied Research Program, 2013). The database uses encrypted identifiers for patients, providers and hospitals; and does not provide variables such as patient zip code unless justification is provided that the data are absolutely necessary for the research project. Additional conditions to protect the data confidentiality and usage are required as part of the data use agreement, including suppression of cell sizes less than 11 in tables.

The data was uploaded to a departmental LINUX server and stored securely and centrally. No duplications were made. Access to this server was restricted solely to qualified data analysts via a secure connection on a validated environment. Access to source data directories and files were further protected by means of an electronic gateway system which ensured that the data were accessible only to authorized users who understood and agreed to comply with contractual obligations specific to the data source. All work with the dataset was carried out by authorized personnel of the Worldwide Epidemiology Department via the secured company network, and no data was stored on

computer hard drives at any time. I was required to comply with existing policies and procedures to ensure proper computer security and appropriate data access, storage, use, and confidentiality. The data will be destroyed after five years, unless other arrangements are made, as stipulated in the data use agreement.

Summary

This study aimed to address deficiencies in the published literature regarding the incidence of VTEs and ATEs and the risk factors for VTEs in elderly kidney cancer patients with Medicare coverage. Overall and stratified incidence rates and incidence proportions were calculated for descriptive analyses 1 and 2. Rate ratios and 95% confidence intervals were calculated for each VTE and ATE for the three research questions, accounting for matching (for Research Questions 1 and 2) and differing duration of follow-up for study population in the year after index date (Research Questions 2 and 3). Cox proportional hazard models were used to identify statistically significant predictors for each VTE to answer Research Question 3. The study used the SEER-Medicare database which is a large, population-based data source consisting of cancer registry data linked with Medicare claims data. Strengths of this study included use of a large study population size (11,463 cancer patients and 11,463 matched noncancer patients). Limitations included lack of lab data and limitations inherent in the use of administrative claims databases. The contribution of this study was to improve the knowledge surrounding the risks associated with these potentially serious events in elderly kidney cancer patients.

The following chapter presents the data analyses conducted to address the descriptive analyses and research questions. Baseline descriptive and demographic characteristics of the study population are presented in tabular form. The results for the descriptive analyses and Research Questions 1 and 2 were reported and interpreted. For Research Question 3, each step of testing and decision making for the potential confounders and effect measure modifiers were presented along with the rationale for including or excluding each variable from the final model. The chapter concludes with a summary of the study results.

Chapter 4: Results

Introduction and Purpose of the Study

The purpose of this retrospective cohort study was to describe the incidence rates of venous and arterial thromboembolic events in elderly kidney cancer patients and compare the incidence rates in cancer patients with matched noncancer elderly patients. In addition, the risk factors for venous thromboembolic events in elderly kidney cancer patients were assessed. The three research questions and associated hypotheses are listed below.

Research Question 1

Research Question 1: How do the incidence rates of VTEs and ATEs in elderly exposed (kidney cancer) patients 12 months before index date compare to a matched unexposed (noncancer) Medicare population during the same 12-month timeframe?

H_A1: In the year prior to index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_01: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the year prior to the index date in the exposed patients and in the matched unexposed patients.

Research Question 2

Research Question 2: How do the incidence rates of VTEs and rates of ATEs in elderly exposed (kidney cancer) patients after index date compare to a matched unexposed (noncancer) Medicare population during the same timeframe?

H_A2: In the follow-up period after the index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

$H_0 2$: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the period after index date in the exposed patients and in the matched unexposed patients.

Research Question 3

Research Question 3: In the follow-up period after kidney cancer diagnosis, what are the risk factors associated with time to newly diagnosed, individual VTE (DVT, PE, or OTE)?

H_A3: No factors are statistically significantly associated with the time to newly diagnosed VTEs in the period after kidney cancer diagnosis.

$H_0 3$: Tumor histology and other factors are statistically significantly associated with the time to newly diagnosed VTEs after kidney cancer diagnosis.

This chapter describes the process of identifying the data eligible for the study, the data analyses processes including variable selection and modeling, and the analyses results. The study results for each of the descriptive analyses and research questions are thoroughly discussed.

Data Collection

All kidney cancer tumors diagnosed 1973 to 2009 were identified in the SEER-Medicare database. Kidney cancer was defined by ICD-O-3 coding with malignant behavior. During this period, 64,659 kidney cancer tumors were identified in 53,804

patients. After restricting to the first kidney cancer for each patient, 43,784 patients had a kidney cancer diagnosed between 2004 and 2009. The number of kidney cancer patients excluded for each criteria are listed in Table 4. The distinct number of cancer patients excluded for having any of the exclusion criteria was 32,319. The number in the exposed cohort eligible for this study was 11,465. After matching the exposed cohort to the unexposed, noncancer patients on age, sex, race, SEER registry region and duration of follow-up; the final numbers of eligible patients for this study were 11,463 in the exposed cohort and 11,463 in the unexposed cohort. The two exposed cohort members who were not matched were male; one was 66 to 69 years of age and one was 85 or older at diagnosis; and both were of unknown or other (neither White nor Black) race.

The excluded patients were much more likely to be younger (median age of 67 years with a range of 18 to 107 years) compared to the patients eligible for the study (median age of 76 years with a range of 66 to 108 years). This was not unexpected as the age, minimum duration of Medicare coverage, and reason for initial Medicare entitlement criteria in effect excludes patients less than 66 years and 11 months old. The excluded patients were more likely to be diagnosed in the later years of the study period, be male, nonwhite, and reside in the West.

Table 4

Exposed Cohort Exclusion Criteria and Patient Counts

Exclusion Criteria	Number of Patients Excluded
Prior cancer in the SEER research data	10,254
Invalid date of death	21
Age less than 65 at date of kidney cancer diagnosis	12,569
Original reason for Medicare entitlement was disability or ESRD	10,313
Less than 24 months of Medicare coverage (A & B) before index date	14,820
Medicare managed care plan participation within 24 months before index date	8,093
Less than 1 month follow-up after index date	19,623

Note. Exclusion criteria were not mutually exclusive.

After matching by gender, age, region, race, and minimum duration of follow-up, there were 11,463 patients in each cohort. Because the age-matching was done by matching the year of birth and year of index date, not including month of birth, the proportions in each age group differ slightly in spite of the matching. For example, a patient in the unexposed cohort had the same year of birth and year of index date as his/her corresponding exposed cohort member, but was born in a different month. Thus, when I calculated age at index date using month of birth, year of birth, month of index date and year of index date, the matched patient had an age which was 1 year greater or younger than the corresponding exposed patient.

The kidney cancers in the exposed cohort were mostly renal cell carcinoma (97.6%). The histology types were clear cell carcinoma (75.7%), with 8.5% papillary tumors, 3.6% chromophobe, 9.7% other RCC types, and 2.4% Transitional cell tumors. Approximately half of the kidney cancers were Stage I, with 7.4% Stage II, 14.5% Stage

III, 18.1% Stage IV, and 10.3% unstaged or stage unknown. The majority of the cancer patients were treated with a nephrectomy (66.8%), however less than 11 of the unexposed cohort had nephrectomies as well. This was not surprising in the cancer patients as nephrectomy is a primary treatment especially for patients with Stage I, II, and III kidney cancer (NCCN, 2015). Nephrectomies in these noncancer patients were most likely due to other conditions. Chemotherapy was used to treat 20.6% of the cancer patients and immunotherapy was recorded for 4.2% of the cancer patients (Table 5).

Table 5
Descriptive Characteristics of Study Population

	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
Total study participants	11,463 (100)	11,463 (100)
Age at index date		
66-69	1,932 (16.85)	1,939 (16.92)
70-74	3,131 (27.31)	3,139 (27.38)
75-79	2,885 (25.17)	2,867 (25.01)
80-84	2,042 (17.81)	2,073 (18.08)
85+	1,473 (12.85)	1,445 (12.61)
Gender		
Male	6,331 (55.23)	6,331 (55.23)
Female	5,132 (44.77)	5,132 (44.77)
Race		
White	9,788 (85.39)	9,788 (85.39)
Black	892 (7.78)	892 (7.78
Other or unknown	783 (6.83)	783 (6.83)
Year of Index		
2004	1,845 (16.10)	1,845 (16.10)
2005	1,956 (17.06)	1,956 (17.06)
2006	1,940 (16.92)	1,940 (16.92)
2007	2,002 (17.46)	2,002 (17.46)
2008	1,896 (16.54)	1,896 (16.54)
2009	1,824 (15.91)	1,824 (15.91)
Geographic Region		
Midwest	1,451 (12.66)	1,451 (12.66)
Northeast	2,388 (20.83)	2,388 (20.83)
South	3,102 (27.06)	3,102 (27.06)
West	4,522 (39.45)	4,522 (39.45)
Cancer Stage		
Stage I	-	5,700 (49.73)
Stage II	-	848 (7.40)
Stage III	-	1,658 (14.46)
Stage IV	-	2,078 (18.13)
Stage Unknown	-	1,179 (10.29)

(continued)

	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
Cancer Histology Group		
Chromophobe	-	413 (3.60)
Clear Cell	-	8,678 (75.70)
Other RCC	-	1,117 (9.74)
Papillary	-	977 (8.52)
Transitional cell tumor	-	278 (2.43)
Cancer treated with chemotherapy		
No	-	9,102 (79.40)
Yes	-	2,361 (20.60)
Cancer treated with immunotherapy		
No	-	10,986 (95.84)
Yes	-	477 (4.16)
Nephrectomy after index date		
No	- (> 99.9)	3,810 (33.24)
Yes	< 11 (< 0.1)	7,653 (66.76)

Note. Numbers less than 11 have been suppressed.
Note. RCC = renal cell carcinoma.

For each outcome, the number of patients with the outcome was higher in the exposed cohort than in the unexposed cohort (Table 6). For each outcome and cohort, the number of patients with the outcome was higher in the period after index date as compared to the year prior to the index date (Table 6).

Table 6
Frequency of Outcomes Within Study Population

	Year prior to index date		Follow-up period after index date	
	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
Any VTE				
No	11,192 (97.64)	11,069 (96.56)	11,022 (96.15)	10,061 (87.77)
Yes	271 (2.36)	394 (3.44)	441 (3.85)	1,402 (12.23)
DVT				
No	11,316 (98.72)	11,217 (97.85)	11,174 (97.48)	10,491 (91.52)
Yes	147 (1.28)	246 (2.15)	289 (2.52)	972 (8.48)
PE				
No	11,408 (99.52)	11,373 (99.21)	11,363 (99.13)	11,077 (96.63)
Yes	55 (0.48)	90 (0.79)	100 (0.87)	386 (3.37)
Other VTE				
No	11,365 (99.15)	11,334 (98.87)	11,336 (98.89)	11,085 (96.70)
Yes	98 (0.85)	129 (1.13)	127 (1.11)	378 (3.30)
Any ATE				
No	11,172 (97.46)	11,109 (96.91)	10,838 (94.55)	10,380 (90.55)
Yes	291 (2.54)	354 (3.09)	625 (5.45)	1,083 (9.45)
MI				
No	11,310 (98.67)	11,271 (98.33)	11,172 (97.46)	10,848 (94.63)
Yes	153 (1.33)	192 (1.67)	291 (2.54)	615 (5.37)
IS				
No	11,318 (98.74)	11,290 (98.49)	11,093 (96.77)	10,915 (95.22)
Yes	145 (1.26)	173 (1.51)	370 (3.23)	548 (4.78)

Note. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

The following table presents the frequency of each covariate in both cohorts for the year prior to index date and for the follow-up period after index date.

Table 7
Frequency of Covariates Within Study Population

	Year prior to index date		Follow-up period after index date	
	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
Charlson Score				
0	5,688 (49.62)	4,446 (38.79)	4,754 (41.47)	2,373 (20.70)
1	2,843 (24.80)	3,037 (26.49)	2,732 (23.83)	2,098 (18.30)
2 to 3	2,182 (19.04)	2,794 (24.37)	2,700 (23.55)	3,849 (33.58)
4+	750 (6.54)	1,186 (10.35)	1,277 (11.14)	3,143 (27.42)
Type 1 Diabetes				
No	10,964 (95.65)	10,711 (93.44)	10,776 (94.01)	10,307 (89.92)
Yes	499 (4.35)	752 (6.56)	687 (5.99)	1,156 (10.08)
Type 2 Diabetes				
No	8,702 (75.91)	7,839 (68.39)	8,230 (71.80)	7,008 (61.14)
Yes	2,761 (24.09)	3,624 (31.61)	3,233 (28.20)	4,455 (38.86)
Atherosclerosis				
No	10,539 (91.94)	10,147 (88.52)	10,094 (88.06)	9,225 (80.48)
Yes	924 (8.06)	1,316 (11.48)	1,369 (11.94)	2,238 (19.52)
Varicose Veins				
No	11,349 (99.01)	11,353 (99.04)	11,264 (98.26)	11,256 (98.19)
Yes	114 (0.99)	110 (0.96)	199 (1.74)	207 (1.81)
Kidney Disease				
No	10,736 (93.66)	9,813 (85.61)	10,063 (87.79)	6,200 (54.09)
Yes	727 (6.34)	1,650 (14.39)	1,400 (12.21)	5,263 (45.91)
History of CVD [a]				
No	9,799 (85.48)	9,526 (83.10)	9,521 (83.06)	8,914 (77.76)
Yes	1,664 (14.52)	1,937 (16.90)	1,942 (16.94)	2,549 (22.24)
History of VTE [a]				
No	11,247 (98.12)	11,225 (97.92)	11,192 (97.64)	11,069 (96.56)
Yes	216 (1.88)	238 (2.08)	271 (2.36)	394 (3.44)
History of DVT [a]				
No	11,358 (99.08)	11,324 (98.79)	11,316 (98.72)	11,217 (97.85)
Yes	105 (0.92)	139 (1.21)	147 (1.28)	246 (2.15)
History of PE [a]				
No	11,419 (99.62)	11,429 (99.70)	11,408 (99.52)	11,373 (99.21)
Yes	44 (0.38)	34 (0.30)	55 (0.48)	90 (0.79)
History of Other VTE [a]				
No	11,374 (99.22)	11,368 (99.17)	11,365 (99.15)	11,334 (98.87)
Yes	89 (0.78)	95 (0.83)	98 (0.85)	129 (1.13)
History of Any ATE [a]				
No	11,213 (97.82)	11,228 (97.95)	11,172 (98.74)	11,109 (96.91)
Yes	250 (2.18)	235 (2.05)	291 (2.54)	354 (3.09)

(continued)

	Year prior to index date		Follow-up period after index date	
	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
History of MI [a]				
No	11,340 (98.93)	11,335 (98.88)	11,310 (98.67)	11,271 (98.33)
Yes	123 (1.07)	128 (1.12)	153 (1.33)	192 (1.67)
History of IS [a]				
No	11,326 (98.80)	11,349 (99.01)	11,318 (98.74)	11,290 (98.49)
Yes	137 (1.20)	114 (0.99)	145 (1.26)	173 (1.51)
High-risk Surgery prior to VTE[a]				
No	- (> 97.0)	378 (95.94)	416 (94.33)	1,264 (90.16)
Yes	< 11 (< 3.0)	16 (4.06)	25 (5.67)	138 (9.84)
CVC prior to VTE[b]				
No	- (> 97.0)	383 (97.21)	425 (96.37)	1,229 (87.66)
Yes	< 11 (< 3.0)	11 (2.79)	16 (3.63)	173 (12.34)
High-risk Surgery prior to DVT[b]				
No	- (> 96.0)	230 (93.50)	271 (93.77)	856 (88.07)
Yes	< 11 (< 4.0)	16 (6.50)	18 (6.23)	116 (11.93)
CVC prior to DVT[b]				
No	- (> 96.0)	235 (95.53)	277 (95.85)	826 (84.98)
Yes	< 11 (< 4.0)	11 (4.47)	12 (4.15)	146 (15.02)
High-risk Surgery prior to PE[b]				
No	- (> 80.0)	- (> 88.0)	- (> 89.0)	339 (87.82)
Yes	< 11 (< 20.0)	< 11 (< 12.0)	< 11 (< 11.0)	47 (12.18)
CVC prior to PE[b]				
No	- (> 80.0)	- (> 88.0)	- (> 89.0)	329 (85.23)
Yes	< 11 (< 20.0)	< 11 (< 12.0)	< 11 (< 11.0)	57 (14.77)
High-risk Surgery prior to Other VTE[b]				
No	- (> 88.0)	- (> 91.0)	- (> 91.0)	333 (88.10)
Yes	< 11 (< 12.0)	< 11 (< 9.0)	< 11 (< 9.0)	45 (11.90)
CVC prior to Other VTE[b]				
No	- (> 88.0)	- (> 91.0)	- (> 91.0)	331 (87.57)
Yes	< 11 (< 12.0)	< 11 (< 9.0)	< 11 (< 9.0)	47 (12.43)
High-risk Surgery prior to Any ATE[b]				
No	279 (95.88)	339 (95.76)	565 (90.40)	936 (86.43)
Yes	12 (4.12)	15 (4.24)	60 (9.60)	147 (13.57)
CVC prior to Any ATE[b]				
No	- (> 96.0)	- (> 96.0)	607 (97.12)	936 (86.43)
Yes	< 11 (< 4.0)	< 11 (< 4.0)	18 (2.88)	147 (13.57)

(continued)

	Year prior to index date		Follow-up period after index date	
	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)	Noncancer patients *n* (%)	Kidney cancer patients *n* (%)
High-risk Surgery prior to MI[b]				
No	- (> 92.0)	- (> 94.0)	264 (90.72)	514 (83.58)
Yes	< 11 (< 8.0)	< 11 (< 6.0)	27 (9.28)	101 (16.42)
CVC prior to MI[b]				
No	- (> 92.0)	- (> 94.0)	- (> 96.0)	513 (83.41)
Yes	< 11 (< 8.0)	< 11 (< 6.0)	< 11 (< 4.0)	102 (16.59)
High-risk Surgery prior to IS[b]				
No	- (> 92.0)	- (> 92.0)	325 (87.84)	459 (83.76)
Yes	< 11 (< 8.0)	< 11 (< 8.0)	45 (12.16)	89 (16.24)
CVC prior to IS[b]				
No	- (> 92.0)	- (> 92.0)	358 (96.76)	473 (86.31)
Yes	< 11 (< 8.0)	< 11 (< 8.0)	12 (3.24)	75 (13.69)

Note. Any ATE = any arterial thromboembolic event (MI or IS); CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

[a] History is within the 12 months prior to the start of the period of interest.

[b] High-risk surgery and central venous catheter were more than 30 days before outcome. Proportion is out of patients with the outcome.

Results

Descriptive Analysis 1

The purpose of descriptive analysis 1 was to describe the incidence rates of thromboembolic events in the kidney cancer cohort in the year prior to kidney cancer diagnosis (Tables 8 to 14) and in the follow-up period after cancer diagnosis (Tables 15 to 21). The incidence rates were described overall and stratified by demographic, cancer, and other patient characteristics.

The year prior to kidney cancer diagnosis. The incidence rate for any VTE in the year prior to kidney cancer diagnosis was 35.05 per 1,000 person-years for all patients (Table 8). Although not a consistent trend, the incidence rates increased with increasing

age at kidney cancer diagnosis, with the highest rate in the patients 85 or older. Incidence rates also varied by race with Black patients having incidence rates almost twice that of the White patients. Females had a higher incidence rate than males, 39.88 as compared to 31.16 per 1,000 p-y, respectively. The incidence rates for any VTE were similar across geographic regions and year of diagnosis. Within RCC, the incidence rates were similar and lower than the incidence rate for transitional cell tumors. However, the incidence rate or 52.30 for transitional cell tumors was based on a small number of events (n = 14) and had a wide confidence interval (95% *CI* 28.60-87.76). The incidence rate ranged from 30.04 to 36.54 for patients with Stage I to IV tumors, but was 56.11 for patients with unstaged or unknown stage tumors (Table 8). A history of any VTE was a major characteristic driving up the incidence rates overall, with a rate of 1,481 per 1,000 p-y compared to a rate of 20.67 per 1,000 p-y in patients without a history of any VTE in the prior year. The incidence rates increased with increasing Charlson score.

Table 8

Incidence Rates per 1,000 p-y for Any VTE in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	394	11,239.8	35.05	31.68-38.69
Age at Diagnosis	66-69	54	1,911.92	28.24	21.22-36.85
	70-74	98	3,087.67	31.74	25.77-38.68
	75-79	101	2,806.75	35.98	29.31-43.72
	80-84	69	2,031.17	33.97	26.43-42.99
	85+	72	1,402.25	51.35	40.18-64.66
Race	Black	53	862.25	61.47	46.04-80.40
	Other/Unknown	22	769.50	28.59	17.92-43.29
	White	319	9,608.00	33.20	29.66-37.05
Gender	Female	200	5,014.75	39.88	34.55-45.81
	Male	194	6,225.00	31.16	26.93-35.87
Geographic Region	Midwest	51	1,424.25	35.81	26.66-47.08
	Northeast	92	2,335.83	39.39	31.75-48.30
	South	104	3,041.67	34.19	27.94-41.43
	West	147	4,438.00	33.12	27.99-38.93
Year of Diagnosis	2004	67	1,812.17	36.97	28.65-46.95
	2005	64	1,918.92	33.35	25.69-42.59
	2006	59	1,910.00	30.89	23.51-39.85
	2007	76	1,956.42	38.85	30.61-48.62
	2008	60	1,859.17	32.27	24.63-41.54
	2009	68	1,783.08	38.14	29.61-48.35
Histology Group	Chromophobe	12	406.92	29.49	15.24-51.51
	Clear Cell	296	8,512.58	34.77	30.92-38.97
	Other RCC	41	1,092.58	37.53	26.93-50.91
	Papillary	31	960.00	32.29	21.94-45.84
	Transitional cell tumor	14	267.67	52.30	28.60-87.76

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	182	5,589.17	32.56	28.00-37.65
	Stage II	25	832.25	30.04	19.44-44.34
	Stage III	58	1,631.75	35.54	26.99-45.95
	Stage IV	65	2,046.00	31.77	24.52-40.49
	Stage Unknown	64	1,140.58	56.11	43.21-71.65
History of Condition	No	230	11,129.1	20.67	18.08-23.52
	Yes	164	110.67	1,481.93	1,263.80-1,726.89
History of CVD	No	282	9,374.50	30.08	26.67-33.81
	Yes	112	1,865.25	60.05	49.44-72.25
CVC[a]	No	383	11,232.6	34.10	30.77 - 37.69
	Yes	11	7.17	1,534.88	766.21 – 2,746.33
High-risk Surgery[a]	No	378	11,230.0	33.66	30.35 - 37.23
	Yes	16	9.75	1,641.03	937.99 – 2,664.92
Charlson Score	0	95	4,396.75	21.61	17.48-26.41
	1	77	2,993.67	25.72	20.30-32.15
	2 to 3	139	2,708.67	51.32	43.14-60.59
	4+	83	1,140.67	72.76	57.96-90.20

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); RCC = renal cell carcinoma; VTE = venous thromboembolic event.
[a] More than 30 days before the outcome.

The incidence rate for DVT in the year prior to kidney cancer diagnosis was 21.71 per 1,000 p-y (Table 9). The pattern of rates was similar to the pattern in Table 8 for race, geographic region, year of diagnosis, stage, history of condition, history of CVD, and Charlson score. The incidence rates were similar for females 23.10 (95% *CI* 19.10-27.68) and males, 20.59 (95% *CI* 17.19-24.47). There were very small numbers with DVT in the Chromophobe and transitional cell tumors, leading to very wide confidence intervals which included in the incidence rates of the other histology groups.

Table 9
Incidence Rates per 1,000 p-y for DVT in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	246	11,329.6	21.71	19.08-24.60
Age at Diagnosis	66-69	35	1,920.92	18.22	12.69-25.34
	70-74	62	3,108.58	19.94	15.29-25.57
	75-79	59	2,835.58	20.81	15.84-26.84
	80-84	39	2,049.00	19.03	13.53-26.02
	85+	51	1,415.50	36.03	26.83-47.37
Race	Black	38	870.67	43.64	30.89-59.91
	Other/Unknown	14	774.25	18.08	9.89-30.34
	White	194	9,684.67	20.03	17.31-23.06
Gender	Female	117	5,065.42	23.10	19.10-27.68
	Male	129	6,264.17	20.59	17.19-24.47
Geographic Region	Midwest	34	1,434.67	23.70	16.41-33.12
	Northeast	58	2,357.25	24.60	18.68-31.81
	South	68	3,062.00	22.21	17.25-28.15
	West	86	4,475.67	19.22	15.37-23.73
Year of Diagnosis	2004	40	1,825.50	21.91	15.65-29.84
	2005	47	1,930.08	24.35	17.89-32.38
	2006	31	1,924.67	16.11	10.94-22.86
	2007	44	1,974.58	22.28	16.19-29.91
	2008	37	1,877.83	19.70	13.87-27.16
	2009	47	1,796.92	26.16	19.22-34.78
Histology Group	Chromophobe	< 11	-	14.61	5.36-31.79
	Clear Cell	191	8,575.33	22.27	19.23-25.67
	Other RCC	24	1,102.42	21.77	13.95-32.39
	Papillary	17	969.00	17.54	10.22-28.09
	Transitional cell tumor	< 11	-	29.40	12.69-57.94

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	120	5,630.50	21.31	17.67-25.48
	Stage II	17	839.00	20.26	11.80-32.44
	Stage III	33	1,643.00	20.09	13.83-28.21
	Stage IV	41	2,056.17	19.94	14.31-27.05
	Stage Unknown	35	1,160.92	30.15	21.00-41.93
History of Condition	No	159	11,259.5	14.12	12.01-16.49
	Yes	87	70.08	1,241.38	994.29-1,531.24
History of CVD	No	168	9,440.50	17.80	15.21-20.70
	Yes	78	1,889.08	41.29	32.64-51.53
CVC[a]	No	235	11,322.4	20.76	18.19 - 23.59
	Yes	11	7.17	1,534.88	766.21 – 2,746.33
High-risk Surgery[a]	No	230	11,318.9	20.32	17.78 - 23.12
	Yes	16	10.67	1,500.00	857.38 – 2,435.91
Charlson Score	0	53	4,420.50	11.99	8.98-15.68
	1	37	3,016.00	12.27	8.64-16.91
	2 to 3	90	2,742.17	32.82	26.39-40.34
	4+	66	1,150.92	57.35	44.35-72.96

Note. Numbers less than 11 and the associated person-years have been suppressed.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); DVT = deep vein thrombosis; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for pulmonary embolism in the year prior to kidney cancer diagnosis was 7.88 per 1,000 p-y (Table 10). There were a small number of patients with the outcome in many categories making patterns and differences between groups difficult to distinguish. Blacks and females had incidence rates approximately twice that of their reference groups. In the two histology groups with 11 or more patients with pulmonary embolism, clear cell carcinoma and other RCC, the incidence rates were similar - 7.98 (95% *CI* 6.21 – 10.10) and 9.91 (95% *CI* 4.95 – 17.73), respectively. Incidence rates were much higher in the patients with a history of pulmonary embolism or a history of CVD.

Table 10

Incidence Rates per 1,000 p-y for PE in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	90	11,417.2	7.88	6.34-9.69
Age at Diagnosis	66-69	19	1,931.17	9.84	5.92-15.36
	70-74	17	3,130.33	5.43	3.16-8.70
	75-79	22	2,854.58	7.71	4.83-11.67
	80-84	16	2,063.58	7.75	4.43-12.59
	85+	16	1,437.50	11.13	6.36-18.08
Race	Black	-	-	15.85	8.67-26.60
	Other/Unknown	< 11	-	5.12	1.40-13.11
	White	72	9,752.92	7.38	5.78-9.30
Gender	Female	56	5,102.00	10.98	8.29-14.25
	Male	34	6,315.17	5.38	3.73-7.52
Geographic Region	Midwest	< 11	-	4.84	1.94-9.96
	Northeast	-	-	8.84	5.47-13.52
	South	-	-	7.11	4.46-10.77
	West	40	4,502.33	8.88	6.35-12.10
Year of Diagnosis	2004	14	1,838.67	7.61	4.16-12.78
	2005	-	-	5.64	2.82-10.10
	2006	< 11	-	5.16	2.48-9.49
	2007	17	1,994.25	8.52	4.97-13.65
	2008	19	1,884.67	10.08	6.07-15.74
	2009	19	1,813.75	10.48	6.31-16.36
Histology Group	Chromophobe	< 11	-	4.85	0.59-17.51
	Clear Cell	69	8,644.75	7.98	6.21-10.10
	Other RCC	11	1,109.83	9.91	4.95-17.73
	Papillary	< 11	-	7.19	2.89-14.82
	Transitional cell tumor	< 11	-	3.61	0.09-20.11

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	53	5,668.50	9.35	7.00-12.23
	Stage II	< 11	-	5.92	1.92-13.81
	Stage III	< 11	-	5.43	2.48-10.31
	Stage IV	< 11	-	4.34	1.98-8.23
	Stage Unknown	14	1,171.33	11.95	6.53-20.05
History of Condition	No	63	11,402.4	5.53	4.25-7.07
	Yes	27	14.75	1,830.51	1,206.32-2,663.29
History of CVD	No	66	9,494.75	6.95	5.38-8.84
	Yes	24	1,922.42	12.48	8.00-18.58
CVC[a]	No	-	-	7.71	6.18 - 9.50
	Yes	< 11	-	1,500.00	181.66 – 5,418.52
High-risk Surgery[a]	No	-	-	7.62	6.10 - 9.40
	Yes	< 11	-	1,440.00	296.96 – 4,208.29
Charlson Score	0	18	4,437.58	4.06	2.40-6.41
	1	23	3,024.00	7.61	4.82-11.41
	2 to 3	32	2,778.25	11.52	7.88-16.26
	4+	17	1,177.33	14.44	8.41-23.12

Note. Numbers less than 11 and the associated person-years have been suppressed.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); PE = pulmonary embolism; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

More kidney cancer patients had a diagnosis of other VTE than pulmonary embolism, still some of the subgroups had very small counts (Table 11). The incidence rate of other VTE was 11.33 per 1,000 p-y. The incidence rate for patients 66 to 69 at diagnosis was 7.25, with higher rates for older patients at diagnosis, but there was no apparent trend at the older ages. There were small numbers in nonwhite patients but the rates appear similar for each group. Similarly, there were small numbers of patients with the outcome for the chromophobe and transitional cell tumor patients. The incidence rates for the other histology groups were similar. Incidence rates were higher in females than

males, patients with history of other VTE or history of CVD, and increased with increasing Charlson score. No clear patterns were visible for geographic region or year of diagnosis.

Table 11
Incidence Rates per 1,000 p-y for Other VTE in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	129	11,385.9	11.33	9.46-13.46
Age at Diagnosis	66-69	14	1,930.92	7.25	3.96-12.17
	70-74	39	3,118.33	12.51	8.89-17.10
	75-79	37	2,841.83	13.02	9.17-17.95
	80-84	22	2,060.58	10.68	6.69-16.16
	85+	17	1,434.25	11.85	6.90-18.98
Race	Black	< 11	-	10.14	4.63-19.24
	Other/Unknown	< 11	-	9.00	3.62-18.53
	White	113	9,719.83	11.63	9.58-13.98
Gender	Female	69	5,090.67	13.55	10.55-17.15
	Male	60	6,295.25	9.53	7.27-12.27
Geographic Region	Midwest	16	1,440.58	11.11	6.35-18.04
	Northeast	35	2,369.00	14.77	10.29-20.55
	South	31	3,084.50	10.05	6.83-14.27
	West	47	4,491.83	10.46	7.69-13.91
Year of Diagnosis	2004	27	1,832.33	14.74	9.71-21.44
	2005	19	1,944.50	9.77	5.88-15.26
	2006	24	1,925.17	12.47	7.99-18.55
	2007	27	1,985.25	13.60	8.96-19.79
	2008	18	1,884.08	9.55	5.66-15.10
	2009	14	1,814.58	7.72	4.22-12.94
Histology Group	Chromophobe	< 11	-	14.66	5.38-31.91
	Clear Cell	91	8,623.50	10.55	8.50-12.96
	Other RCC	14	1,108.50	12.63	6.90-21.19
	Papillary	11	970.92	11.33	5.66-20.27
	Transitional cell tumor	< 11	-	25.57	10.28-52.69

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	50	5,668.92	8.82	6.55-11.63
	Stage II	< 11	-	8.31	3.34-17.12
	Stage III	24	1,645.25	14.59	9.35-21.70
	Stage IV	25	2,066.25	12.10	7.83-17.86
	Stage Unknown	-	-	19.78	12.54-29.68
History of Condition	No	61	11,339.7	5.38	4.11-6.91
	Yes	68	46.25	1,470.27	1,141.72-1,863.92
History of CVD	No	100	9,467.25	10.56	8.59-12.85
	Yes	29	1,918.67	15.11	10.12-21.71
CVC[a]	No	-	-	11.16	9.30 - 13.27
	Yes	< 11	-	1,263.16	152.97 – 4,562.96
High-risk Surgery[a]	No	-	-	10.81	8.98 - 12.89
	Yes	< 11	-	1,674.42	614.48 – 3,644.50
Charlson Score	0	35	4,425.25	7.91	5.51-11.00
	1	30	3,019.92	9.93	6.70-14.18
	2 to 3	47	2,762.42	17.01	12.50-22.63
	4+	17	1,178.33	14.43	8.40-23.10

Note. Numbers less than 11 and the associated person-years have been suppressed. Cells with numbers greater than 11 are also suppressed so that the counts for other cells cannot be derived.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); Other VTE = other venous thromboembolic event; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for any ATE (myocardial infarction or ischemic stroke) in the year prior to kidney cancer diagnosis was 31.32 per 1,000 person-years (Table 12). With wide confidence intervals, there was no clear trend due to age, year of diagnosis, or stage. However, patients with unknown stage appeared to have higher incidence rates of any ATE than patients whose tumors were staged at diagnosis. The incidence rates were similar for Black and White patients, but lower for those with other or unknown race. The rate for males was higher than the incidence rate for females. Incidence rates were lowest in the West, but similar in the Midwest, Northeast and South. The incidence rates

increased with increasing Charlson score, with history of any ATE, history of CVD, recent placement of a CVC, and recent high-risk surgery. The incidence rates for the four RCC histology groups (range 25.92 to 41.02) and these rates were not different than the rate for transitional cell tumors, 29.15. However, the confidence intervals for the incidence rates for all of the histology groups were very wide.

Table 12
Incidence Rates per 1,000 p-y for Any ATE in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	354	11,303.5	31.32	28.14 - 34.76
Age at Diagnosis	66-69	40	1,921.25	20.82	14.87 - 28.35
	70-74	83	3,104.33	26.74	21.30 - 33.14
	75-79	104	2,818.75	36.90	30.15 - 44.71
	80-84	68	2,041.08	33.32	25.87 - 42.24
	85+	59	1,418.08	41.61	31.67 - 53.67
Race	Black	31	879.33	35.25	23.95 - 50.04
	Other/Unknown	19	775.83	24.49	14.74 - 38.24
	White	304	9,648.33	31.51	28.07 - 35.26
Gender	Female	141	5,066.42	27.83	23.43 - 32.82
	Male	213	6,237.08	34.15	29.72 - 39.06
Geographic Region	Midwest	60	1,425.83	42.08	32.11 - 54.17
	Northeast	83	2,351.00	35.30	28.12 - 43.76
	South	99	3,056.75	32.39	26.32 - 39.43
	West	112	4,469.92	25.06	20.63 - 30.15
Year of Diagnosis	2004	54	1,819.17	29.68	22.30 - 38.73
	2005	61	1,925.58	31.68	24.23 - 40.69
	2006	61	1,912.75	31.89	24.39 - 40.97
	2007	53	1,975.83	26.82	20.09 - 35.09
	2008	63	1,871.50	33.66	25.87 - 43.07
	2009	62	1,798.67	34.47	26.43 - 44.19
Histology Group	Chromophobe	-	-	26.96	13.46 - 48.23
	Clear Cell	265	8,559.67	30.96	27.34 - 34.92
	Other RCC	45	1,097.00	41.02	29.92 - 54.89
	Papillary	25	964.33	25.92	16.78 - 38.27
	Transitional cell tumor	< 11	-	29.15	12.59 - 57.44

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	178	5,624.42	31.65	27.17 - 36.65
	Stage II	23	836.92	27.48	17.42 - 41.24
	Stage III	42	1,639.17	25.62	18.47 - 34.63
	Stage IV	55	2,052.00	26.80	20.19 - 34.89
	Stage Unknown	56	1,151.00	48.65	36.75 - 63.18
History of Condition	No	309	1,1097.4	27.84	24.83 - 31.13
	Yes	45	206.08	218.36	159.27 - 292.18
History of CVD	No	249	9,791.08	25.43	22.37 - 28.79
	Yes	105	1,512.42	69.43	56.78 - 84.04
CVC[a]	No	-	-	30.54	27.40 - 33.94
	Yes	< 11	-	1,421.05	649.80 -2,697.60
High-risk Surgery[a]	No	339	11,293.9	30.02	26.91 - 33.39
	Yes	15	9.58	1,565.22	876.04 – 2,581.59
Charlson Score	0	57	5,246.42	10.86	8.23 - 14.08
	1	85	3,147.00	27.01	21.57 - 33.40
	2 to 3	141	2,268.42	62.16	52.32 - 73.31
	4+	71	641.67	110.65	86.42 - 139.57

Note. Numbers less than 11 and the associated person-years have been suppressed. Cells with numbers greater than 11 are also suppressed so that the counts for other cells cannot be derived.
Note. Any ATE = any arterial thromboembolic event (MI or IS); CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; MI = myocardial infarction; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for myocardial infarction in the year prior to kidney cancer diagnosis was 16.88 per 1,000 person-years (Table 13). The incidence rates were higher for patients 70 years or older at diagnosis than patients 66 to 69 years of age. The incidence rates were similar for Black and White patients, but less for those with other or unknown race. The incidence rates were higher for males than females. There was no clear trend in rates for geographic region, year of diagnosis, or histology group. The incidence rates increased with increasing Charlson score, with history of myocardial

infarction and with history of CVD. The rates were similar for the RCC histology groups, but the confidence intervals were very wide. The numbers of patients with myocardial infarction were less than 11 for the chromophobe and transitional cell tumor patients.

Table 13
Incidence Rates per 1,000 p-y for MI in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	192	11,373.8	16.88	14.58-19.44
Age at Diagnosis	66-69	18	1,931.08	9.32	5.52-14.73
	70-74	52	3,117.92	16.68	12.46-21.87
	75-79	50	2,842.83	17.59	13.05-23.19
	80-84	40	2,052.42	19.49	13.92-26.54
	85+	32	1,429.58	22.38	15.31-31.60
Race	Black	-	-	15.79	8.63-26.49
	Other/Unknown	< 11	-	12.83	6.15-23.60
	White	168	9,707.83	17.31	14.79-20.13
Gender	Female	72	5,095.58	14.13	11.06-17.79
	Male	120	6,278.25	19.11	15.85-22.86
Geographic Region	Midwest	24	1,441.67	16.65	10.67-24.77
	Northeast	48	2,364.67	20.30	14.97-26.91
	South	53	3,078.25	17.22	12.90-22.52
	West	67	4,489.25	14.92	11.57-18.95
Year of Diagnosis	2004	33	1,827.42	18.06	12.43-25.36
	2005	28	1,940.25	14.43	9.59-20.86
	2006	33	1,923.75	17.15	11.81-24.09
	2007	27	1,988.50	13.58	8.95-19.76
	2008	36	1,883.58	19.11	13.39-26.46
	2009	35	1,810.33	19.33	13.47-26.89
Histology Group	Chromophobe	< 11	-	19.53	8.43-38.49
	Clear Cell	144	8,614.33	16.72	14.10-19.68
	Other RCC	20	1,105.25	18.10	11.05-27.95
	Papillary	14	969.67	14.44	7.89-24.22
	Transitional cell tumor	< 11	-	21.82	8.01-47.49

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	101	5,656.33	17.86	14.54-21.70
	Stage II	13	840.17	15.47	8.24-26.46
	Stage III	19	1,649.58	11.52	6.93-17.99
	Stage IV	23	2,067.92	11.12	7.05-16.69
	Stage Unknown	36	1,159.83	31.04	21.74-42.97
History of Condition	No	159	11,267.5	14.11	12.00-16.48
	Yes	33	106.33	310.34	213.63-435.84
History of CVD	No	110	9,478.75	11.60	9.54-13.99
	Yes	82	1,895.08	43.27	34.41-53.71
CVC[a]	No	-	-	75.32	70.28 - 80.64
	Yes	< 11	-	1,523.81	657.87 – 3,002.51
High-risk Surgery[a]	No	809	10,970.1	73.75	68.75 - 79.01
	Yes	26	14.42	1,803.47	1,178.09 – 2,642.50
Charlson Score	0	12	4,439.75	2.70	1.40-4.72
	1	35	3,018.92	11.59	8.08-16.12
	2 to 3	75	2,762.17	27.15	21.36-34.04
	4+	70	1,153.00	60.71	47.33-76.70

Note. Numbers less than 11 and the associated person-years have been suppressed. Cells with numbers greater than 11 are also suppressed so that the counts for other cells cannot be derived.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); MI = myocardial infarction; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for ischemic stroke in the year prior to kidney cancer diagnosis was 15.19per 1,000 person-years (Table 14). There was no clear trend in incidence rates for age at diagnosis, gender, year of diagnosis, or stage at diagnosis. The incidence rates increased with increasing Charlson comorbidity score and were higher in patients with history of ischemic stroke, history of CVD, recent placement of CVC, and recent high-risk surgery. Incidence rates appeared higher for regions other than the West and for the Other RCC histology group, however there were very wide confidence intervals.

Table 14
Incidence Rates per 1,000 p-y for IS in the Year Prior to Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	173	11,389.9	15.19	13.01 - 17.63
Age at Diagnosis	66-69	23	1,928.83	11.92	7.56 - 17.89
	70-74	34	3,124.33	10.88	7.54 - 15.21
	75-79	56	2,842.75	19.70	14.88 - 25.58
	80-84	30	2,061.08	14.56	9.82 - 20.78
	85+	30	1,432.92	20.94	14.13 - 29.89
Race	Black	-	-	19.21	11.19 - 30.76
	Other/Unknown	< 11	-	11.55	5.28 - 21.92
	White	147	9,725.75	15.11	12.77 - 17.76
Gender	Female	73	5,101.08	14.31	11.22 - 17.99
	Male	100	6,288.83	15.90	12.94 - 19.34
Geographic Region	Midwest	38	1,434.50	26.49	18.75 - 36.36
	Northeast	38	2,373.83	16.01	11.33 - 21.97
	South	49	3,079.83	15.91	11.77 - 21.03
	West	48	4,501.75	10.66	7.86 - 14.14
Year of Diagnosis	2004	22	1,836.67	11.98	7.51 - 18.14
	2005	33	1,941.33	17.00	11.70 - 23.87
	2006	30	1,928.42	15.56	10.50 - 22.21
	2007	27	1,989.08	13.57	8.95 - 19.75
	2008	34	1,882.08	18.07	12.51 - 25.24
	2009	27	1,812.33	14.90	9.82 - 21.68
Histology Group	Chromophobe	< 11	-	7.29	1.50 - 21.31
	Clear Cell	129	8,621.08	14.96	12.49 - 17.78
	Other RCC	26	1,108.67	23.45	15.32 - 34.36
	Papillary	13	971.25	13.38	7.13 - 22.89
	Transitional cell tumor	< 11	-	7.21	0.87 - 26.04

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	81	5,667.33	14.29	11.35 - 17.76
	Stage II	< 11	-	11.84	5.68 - 21.77
	Stage III	25	1,647.08	15.18	9.82 - 22.41
	Stage IV	34	2,061.25	16.49	11.42 - 23.05
	Stage Unknown	-	-	19.67	12.47 - 29.51
History of Condition	No	-	-	14.54	12.40 - 16.94
	Yes	< 11	-	83.46	38.16 - 158.44
History of CVD	No	135	9,839.83	13.72	11.50 - 16.24
	Yes	38	1,550.08	24.51	17.35 - 33.65
CVC[a]	No	-	-	14.93	12.77 - 17.35
	Yes	< 11	-	1,800.00	371.20 – 5,260.36
High-risk Surgery[a]	No	-	-	14.49	12.37 - 16.88
	Yes	< 11	-	1,811.32	782.00 – 3,569.02
Charlson Score	0	35	5,258.33	6.66	4.64 - 9.26
	1	44	3,167.75	13.89	10.09 - 18.65
	2 to 3	65	2,302.33	28.23	21.79 - 35.98
	4+	29	661.50	43.84	29.36 - 62.96

Note. Numbers less than 11 and the associated person-years have been suppressed. Cells with numbers greater than 11 are also suppressed so that the counts for other cells cannot be derived.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The follow-up period after kidney cancer diagnosis. In the follow-up period after cancer diagnosis, the incidence rate for any VTE was 53.00 per 1,000 p-y (Table 15). The incidence rates increased with increasing age, year of diagnosis, stage at diagnosis, and increasing Charlson score. The rates were higher in patients who were Black, female, treated with chemotherapy, treated with immunotherapy, history of any VTE, and history of CVD. Patients treated with nephrectomy had lower incidence rates than patients without nephrectomy, however this may be due to nephrectomy being a

treatment indicated for lower stage tumors. Lower stage tumors had lower incidence rates than higher staged tumors. The incidence rates were highest in the Northeast and South, followed by the Midwest and West region. Incidence rates also differed by histology group. The incidence rates were highest in the patients with other RCC (76.03, 95% *CI* 63.52-90.17), followed by transitional cell tumors (64.37, 95% *CI* 43.74-91.37), clear cell tumors (53.13, 95% *CI* 50.02-56.39), papillary (43.88, 95% *CI* 36.17- 52.76), and chromophobe (33.39, 95% *CI* 24.07-45.14). However, some of the histology groups have very wide confidence intervals and so some groups may not be different at a statistically significant level.

Table 15
Incidence Rates per 1,000 p-y for Any VTE After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	1,402	26,452.7	53.00	50.26 -55.85
Age at Diagnosis	66-69	224	5,148.58	43.51	38.00 -49.59
	70-74	394	7,965.67	49.46	44.70 -54.60
	75-79	364	6,979.50	52.15	46.93 -57.80
	80-84	255	4,247.00	60.04	52.90 -67.88
	85+	165	2,112.00	78.13	66.66 -91.00
Race	Black	138	1,813.33	76.10	63.94 -89.91
	Other/Unknown	78	1,799.25	43.35	34.27 -54.10
	White	1,186	22,840.2	51.93	49.01 -54.97
Gender	Female	676	11,840.2	57.09	52.87 -61.56
	Male	726	14,612.5	49.68	46.13 -53.43
Geographic Region	Midwest	175	3,354.25	52.17	44.73 -60.50
	Northeast	346	5,881.83	58.83	52.79 -65.36
	South	379	6,860.00	55.25	49.82 -61.10
	West	502	10,356.7	48.47	44.32 -52.90
Year of Diagnosis	2004	266	6,239.17	42.63	37.66 -48.08
	2005	254	5,703.83	44.53	39.22 -50.36
	2006	249	5,076.58	49.05	43.15 -55.53
	2007	233	4,366.42	53.36	46.73 -60.67
	2008	213	3,112.92	68.42	59.54 -78.26
	2009	187	1,953.83	95.71	82.48 -110.45
Histology Group	Chromophobe	42	1,257.75	33.39	24.07 -45.14
	Clear Cell	1,084	20,402.3	53.13	50.02 -56.39
	Other RCC	132	1,736.08	76.03	63.62 -90.17
	Papillary	113	2,575.08	43.88	36.17 -52.76
	Transitional cell tumor	31	481.58	64.37	43.74 -91.37

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	550	16,442.3	33.45	30.71 -36.37
	Stage II	88	2,364.33	37.22	29.85 -45.86
	Stage III	328	3,802.75	86.25	77.17 -96.11
	Stage IV	301	1,709.17	176.11	156.77 -197.17
	Stage Unknown	135	2,134.25	63.25	53.03 -74.87
Chemotherapy	No	977	21,267.8	45.94	43.10 -48.91
	Yes	425	5,185.00	81.97	74.36 -90.14
Immunotherapy	No	1,303	25,332.5	51.44	48.68 -54.31
	Yes	99	1,120.25	88.37	71.83 -107.59
Nephrectomy	No	400	5,147.08	77.71	70.28 -85.72
	Yes	1,002	21,305.7	47.03	44.16 -50.03
History of Condition	No	1,119	26,177.2	42.75	40.28 -45.33
	Yes	283	275.50	1,027.22	911.02 -1,154.14
History of CVD	No	1,045	21,328.6	49.00	46.07 -52.06
	Yes	357	5,124.17	69.67	62.63 -77.29
CVC[a]	No	1,229	26,147.7	47.00	44.41 - 49.71
	Yes	173	305.08	567.06	485.71 - 658.14
High-risk Surgery[a]	No	1,264	26,193.1	48.26	45.63 - 50.99
	Yes	138	259.67	531.45	446.48 - 627.88
Charlson Score	0	193	4,777.17	40.40	34.90 -46.52
	1	210	4,435.75	47.34	41.16 -54.20
	2 to 3	458	9,258.92	49.47	45.04 -54.21
	4+	541	7,980.92	67.79	62.19 -73.75

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); RCC = renal cell carcinoma; VTE = venous thromboembolic event.
[a] More than 30 days before the outcome.

The incidence rate for DVT in the follow-up period after kidney cancer diagnosis was 35.56 per 1,000 p-y (Table 16). The incidence rates followed similar patterns as for any VTE. Unlike in the period prior to cancer diagnosis (Table 9), incidence increased with stage and year of diagnosis.

Table 16

Incidence Rates per 1,000 p-y for DVT After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	972	27,336.6	35.56	33.36 -37.86
Age at Diagnosis	66-69	144	5,313.08	27.10	22.86 -31.91
	70-74	277	8,223.42	33.68	29.83 -37.89
	75-79	236	7,265.50	32.48	28.47 -36.90
	80-84	197	4,348.33	45.30	39.20 -52.09
	85+	118	2,186.25	53.97	44.68 -64.64
Race	Black	106	1,882.25	56.32	46.11 -68.11
	Other/Unknown	47	1,869.50	25.14	18.47 -33.43
	White	819	23,584.8	34.73	32.39 -37.19
Gender	Female	463	12,306.0	37.62	34.27 -41.21
	Male	509	15,030.6	33.86	30.99 -36.94
Geographic Region	Midwest	128	3,463.00	36.96	30.84 -43.95
	Northeast	248	6,097.83	40.67	35.77 -46.06
	South	262	7,093.25	36.94	32.60 -41.69
	West	334	10,682.5	31.27	28.00 -34.81
Year of Diagnosis	2004	181	6,482.50	27.92	24.00 -32.30
	2005	196	5,846.83	33.52	28.99 -38.56
	2006	172	5,282.67	32.56	27.88 -37.81
	2007	161	4,506.83	35.72	30.42 -41.69
	2008	142	3,210.17	44.23	37.26 -52.14
	2009	120	2,007.58	59.77	49.56 -71.47
Histology Group	Chromophobe	27	1,308.17	20.64	13.60 -30.03
	Clear Cell	750	21,059.0	35.61	33.11 -38.26
	Other RCC	90	1,794.50	50.15	40.33 -61.65
	Papillary	80	2,681.00	29.84	23.66 -37.14
	Transitional cell tumor	25	493.92	50.62	32.76 -74.72

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	374	16,879.8	22.16	19.97 -24.52
	Stage II	64	2,414.08	26.51	20.42 -33.85
	Stage III	224	4,048.00	55.34	48.33 -63.08
	Stage IV	220	1,770.83	124.24	108.36 -141.78
	Stage Unknown	90	2,223.92	40.47	32.54 -49.74
Chemotherapy	No	666	21,907.9	30.40	28.13 -32.80
	Yes	306	5,428.67	56.37	50.23 -63.05
Immunotherapy	No	909	26,121.1	34.80	32.57 -37.14
	Yes	63	1,215.50	51.83	39.83 -66.31
Nephrectomy	No	295	5,262.67	56.06	49.84 -62.83
	Yes	677	22,073.9	30.67	28.40 -33.07
History of Condition	No	803	27,165.9	29.56	27.55 -31.68
	Yes	169	170.67	990.23	846.57 -1,151.30
History of CVD	No	703	22,032.9	31.91	29.59 -34.36
	Yes	269	5,303.67	50.72	44.84 -57.16
CVC[a]	No	826	2,7074.4	30.51	28.46 - 32.66
	Yes	146	262.17	556.90	470.23 - 654.91
High-risk Surgery[a]	No	856	27,127.7	31.55	29.48 - 33.74
	Yes	116	208.83	555.47	458.99 - 666.23
Charlson Score	0	122	4,908.50	24.85	20.64 -29.68
	1	132	4,571.75	28.87	24.16 -34.24
	2 to 3	314	9,551.00	32.88	29.34 -36.72
	4+	404	8,305.33	48.64	44.02 -53.63

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); DVT = deep vein thrombosis; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for pulmonary embolism in the follow-up period after kidney cancer diagnosis was 13.58 per 1,000 p-y (Table 17). There was no consistent trend in incidence rates by age at diagnosis or geographic region. Incidence rates increased with increasing year of diagnosis, stage at diagnosis, and Charlson score. The rates were

higher in Black patients, females, patients treated with chemotherapy or immunotherapy, history of pulmonary embolism, and history of CVD. Patients treated with nephrectomy had lower rates of pulmonary embolism. Less than 11 patients with chromophobe or transitional cell tumors had pulmonary embolism and so the incidence rates had very wide confidence intervals. The incidence rates for the other histology groups ranged from 13.77 to 19.26, with overlapping confidence intervals.

Unlike the year prior to cancer diagnosis (Table 10), the incidence rates for pulmonary embolism in females (14.88, 95% *CI* 12.84-17.15) was only slightly larger than the incidence rate for males (12.52, 95% *CI* 10.83-14.40) in the period after cancer diagnosis (Table 17).

Table 17
Incidence Rates per 1,000 p-y for PE After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	386	28,421.4	13.58	12.26 -15.01
Age at Diagnosis	66-69	84	5,425.33	15.48	12.35 -19.17
	70-74	114	8,554.08	13.33	10.99 -16.01
	75-79	96	7,514.08	12.78	10.35 -15.60
	80-84	48	4,634.33	10.36	7.64 -13.73
	85+	44	2,293.58	19.18	13.94 -25.75
Race	Black	34	2,024.92	16.79	11.63 -23.46
	Other/Unknown	16	1,926.08	8.31	4.75 -13.49
	White	336	24,470.4	13.73	12.30 -15.28
Gender	Female	190	12,768.9	14.88	12.84 -17.15
	Male	196	15,652.5	12.52	10.83 -14.40
Geographic Region	Midwest	52	3,599.50	14.45	10.79 -18.94
	Northeast	92	6,384.08	14.41	11.62 -17.67
	South	94	7,396.50	12.71	10.27 -15.55
	West	148	11,041.3	13.40	11.33 -15.75
Year of Diagnosis	2004	63	6,759.33	9.32	7.16 -11.92
	2005	61	6,166.33	9.89	7.57 -12.71
	2006	83	5,471.83	15.17	12.08 -18.80
	2007	56	4,670.17	11.99	9.06 -15.57
	2008	67	3,288.83	20.37	15.79 -25.87
	2009	56	2,064.92	27.12	20.49 -35.22
Histology Group	Chromophobe	< 11	-	5.17	2.08 -10.64
	Clear Cell	302	21,932.6	13.77	12.26 -15.41
	Other RCC	36	1,868.75	19.26	13.49 -26.67
	Papillary	38	2,749.25	13.82	9.78 -18.97
	Transitional cell tumor	< 11	-	5.81	1.20 -16.99

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	163	17,349.6	9.40	8.01 -10.95
	Stage II	30	2,489.00	12.05	8.13 -17.21
	Stage III	67	4,364.83	15.35	11.90 -19.49
	Stage IV	98	1,876.33	52.23	42.40 -63.65
	Stage Unknown	28	2,341.67	11.96	7.95 -17.28
Chemotherapy	No	253	22,681.8	11.15	9.82 -12.62
	Yes	133	5,739.58	23.17	19.40 -27.46
Immunotherapy	No	357	27,151.0	13.15	11.82 -14.59
	Yes	29	1,270.42	22.83	15.29 -32.78
Nephrectomy	No	112	5,469.00	20.48	16.86 -24.64
	Yes	274	22,952.4	11.94	10.57 -13.44
History of Condition	No	325	28,346.2	11.47	10.25 -12.78
	Yes	61	75.25	810.63	620.07 -1,041.29
History of CVD	No	289	22,785.3	12.68	11.26 -14.23
	Yes	97	5,636.08	17.21	13.96 -21.00
CVC[a]	No	329	28,326.7	11.61	10.39 - 12.94
	Yes	57	94.75	601.58	455.63 - 779.42
High-risk Surgery[a]	No	339	28,338.7	11.96	10.72 - 13.31
	Yes	47	82.75	567.98	417.33 - 755.29
Charlson Score	0	47	4,989.75	9.42	6.92 -12.53
	1	56	4,682.00	11.96	9.03 -15.53
	2 to 3	128	9,893.42	12.94	10.79 -15.38
	4+	155	8,856.25	17.50	14.85 -20.48

Note. Numbers less than 11 and the associated person-years have been suppressed.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); PE = pulmonary embolism; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rates for other VTE in the period after kidney cancer diagnosis was 13.35 per 1,000 p-y (Table 18). There was no clear trend in incidence rates for age at diagnosis, race, gender, treatment with nephrectomy, history of CVD, or Charlson score; however, some of the groups had very wide confidence intervals. The incidence rates were higher in patients diagnosed in 2008 or 2009 than in earlier years, diagnosed with

other RCC, diagnosed with Stage III or IV kidney cancer, treated with chemotherapy or immunotherapy, and patients with history of other VTE.

Table 18
Incidence Rates per 1,000 p-y for Other VTE After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	378	28,321.7	13.35	12.03 -14.76
Age at Diagnosis	66-69	58	5,461.00	10.62	8.06 -13.73
	70-74	106	8,495.67	12.48	10.22 -15.09
	75-79	117	7,480.17	15.64	12.94 -18.75
	80-84	58	4,611.67	12.58	9.55 -16.26
	85+	39	2,273.25	17.16	12.20 -23.45
Race	Black	27	2,039.83	13.24	8.72 -19.26
	Other/Unknown	26	1,886.42	13.78	9.00 -20.19
	White	325	24,395.5	13.32	11.91 -14.85
Gender	Female	179	12,755.5	14.03	12.05 -16.25
	Male	199	15,566.3	12.78	11.07 -14.69
Geographic Region	Midwest	32	3,661.58	8.74	5.98 -12.34
	Northeast	105	6,326.33	16.60	13.57 -20.09
	South	100	7,355.17	13.60	11.06 -16.54
	West	141	10,978.7	12.84	10.81 -15.15
Year of Diagnosis	2004	76	6,677.08	11.38	8.97 -14.25
	2005	61	6,182.00	9.87	7.55 -12.68
	2006	70	5,454.75	12.83	10.00 -16.21
	2007	61	4,654.67	13.11	10.02 -16.83
	2008	62	3,294.92	18.82	14.43 -24.12
	2009	48	2,058.33	23.32	17.19 -30.92
Histology Group	Chromophobe	< 15	-	9.74	5.19 -16.66
	Clear Cell	297	21,862.8	13.58	12.08 -15.22
	Other RCC	33	1,853.92	17.80	12.25 -25.00
	Papillary	29	2,761.33	10.50	7.03 -15.08
	Transitional cell tumor	< 11	-	11.79	4.33 -25.66

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	131	17,407.8	7.53	6.29 -8.93
	Stage II	19	2,491.42	7.63	4.59 -11.91
	Stage III	123	4,223.50	29.12	24.20 -34.75
	Stage IV	59	1,899.42	31.06	23.65 -40.07
	Stage Unknown	46	2,299.67	20.00	14.64 -26.68
Chemotherapy	No	263	22,640.4	11.62	10.25 -13.11
	Yes	115	5,681.33	20.24	16.71 -24.30
Immunotherapy	No	342	27,085.6	12.63	11.32 -14.04
	Yes	36	1,236.17	29.12	20.40 -40.32
Nephrectomy	No	81	5,481.67	14.78	11.73 -18.37
	Yes	297	22,840.1	13.00	11.57 -14.57
History of Condition	No	297	28,178.1	10.54	9.38 -11.81
	Yes	81	143.67	563.81	447.74 -700.76
History of CVD	No	306	22,664.0	13.50	12.03 -15.10
	Yes	72	5,657.75	12.73	9.96 -16.03
CVC[a]	No	331	28,241.1	11.72	10.49 - 13.05
	Yes	47	80.67	582.64	428.11 - 774.79
High-risk Surgery[a]	No	333	28,239.4	11.79	10.56 - 13.13
	Yes	45	82.33	546.56	398.66 - 731.34
Charlson Score	0	57	4,957.83	11.50	8.71 -14.90
	1	66	4,676.50	14.11	10.92 -17.96
	2 to 3	131	9,808.17	13.36	11.17 -15.85
	4+	124	8,879.25	13.97	11.62 -16.65

Note. Numbers less than 11 and the associated person-years have been suppressed. Additional cells were suppressed where necessary so that the number in an individual cell with counts less than 11 could not be determined.
Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); Other VTE = other venous thromboembolic event; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for any ATE in the period after kidney cancer diagnosis was 39.68 per 1,000 p-y (Table 19). Incidence rates increased with increasing age at diagnosis and increasing Charlson score. Incidence rates were higher in Black patients, patients

diagnosed outside of the West geographic region, diagnosed with Stage IV or unknown stage, with other RCC, not treated with nephrectomy, with history of any ATE, history of CVD, placement of CVC, and high-risk surgery. There was no clear difference in rates across gender, year of diagnosis, treatment by chemotherapy or treatment by immunotherapy.

Table 19
Incidence Rates per 1,000 p-y for Any ATE After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	1,083	27,290.4	39.68	37.36 - 42.12
Age at Diagnosis	66-69	151	5,277.75	28.61	24.23 - 33.56
	70-74	272	8,267.58	32.90	29.11 - 37.05
	75-79	309	7,164.67	43.13	38.45 - 48.22
	80-84	209	4,381.58	47.70	41.45 - 54.62
	85+	142	2,198.83	64.58	54.39 - 76.12
Race	Black	108	1,944.50	55.54	45.56 - 67.06
	Other/Unknown	58	1,865.42	31.09	23.61 - 40.19
	White	917	23,480.5	39.05	36.57 - 41.67
Gender	Female	482	12,337.2	39.07	35.66 - 42.72
	Male	601	14,953.3	40.19	37.04 - 43.54
Geographic Region	Midwest	150	3,484.08	43.05	36.44 - 50.52
	Northeast	263	6,054.25	43.44	38.35 - 49.02
	South	306	7,055.83	43.37	38.64 - 48.51
	West	364	10,696.3	34.03	30.62 - 37.71
Year of Diagnosis	2004	231	6,364.50	36.30	31.77 - 41.29
	2005	235	5,839.00	40.25	35.27 - 45.73
	2006	203	5,297.08	38.32	33.23 - 43.97
	2007	161	4,545.58	35.42	30.16 - 41.33
	2008	148	3,225.25	45.89	38.79 - 53.90
	2009	105	2,019.00	52.01	42.54 - 62.96
Histology Group	Chromophobe	44	1,305.67	33.70	24.49 - 45.24
	Clear Cell	840	20,989.0	40.02	37.36 - 42.82
	Other RCC	92	1,801.83	51.06	41.16 - 62.62
	Papillary	88	2,702.50	32.56	26.12 - 40.12
	Transitional cell tumor	19	491.42	38.66	23.28 - 60.38

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	581	16,625.3	34.95	32.16 - 37.91
	Stage II	92	2,395.67	38.40	30.96 - 47.10
	Stage III	160	4,203.92	38.06	32.39 - 44.44
	Stage IV	122	1,866.58	65.36	54.28 - 78.04
	Stage Unknown	128	2,199.00	58.21	48.56 - 69.21
Chemotherapy	No	871	21,709.5	40.12	37.50 - 42.88
	Yes	212	5,580.92	37.99	33.04 - 43.46
Immunotherapy	No	1,040	26,059.9	39.91	37.52 - 42.41
	Yes	43	1,230.50	34.95	25.29 - 47.07
Nephrectomy	No	317	5,263.17	60.23	53.78 - 67.24
	Yes	766	22,027.3	34.78	32.36 - 37.33
History of Condition	No	968	26,741.0	36.20	33.95 - 38.55
	Yes	115	549.42	209.31	172.81 - 251.25
History of CVD	No	750	23,176.8	32.36	30.09 - 34.76
	Yes	333	4,113.58	80.95	72.49 - 90.13
CVC[a]	No	936	26,932.4	34.75	32.56 - 37.05
	Yes	147	358.00	410.61	346.92 - 482.62
High-risk Surgery[a]	No	936	26,937.5	34.75	32.56 - 37.05
	Yes	147	352.92	416.53	351.92 - 489.57
Charlson Score	0	90	5,727.17	15.71	12.64 - 19.32
	1	145	5,055.58	28.68	24.20 - 33.75
	2 to 3	374	9,852.00	37.96	34.21 - 42.01
	4+	474	6,655.67	71.22	64.95 - 77.93

Note. Any ATE = any arterial thromboembolic event (MI or IS); CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; MI = myocardial infarction; RCC = renal cell carcinoma.

[a] More than 30 days before the outcome.

The incidence rates for myocardial infarction in the period after kidney cancer diagnosis was 21.91 per 1,000 p-y (Table 20). The incidence rates increased with increasing age at diagnosis and Charlson score. The patterns for the incidence rates were similar for the rates for any ATE (Table 19), except the highest incidence rates by

histology group was for patients with Transitional cell tumors. The confidence intervals for incidence rates by histology groups were very wide except for clear cell tumor which was the most frequently type of histology diagnosed. The incidence rates for myocardial infarction were higher than for pulmonary embolism and other VTE, which was unexpected based on the assertion in the published literature at ATEs were rarer than VTEs.

Table 20
Incidence Rates per 1,000 p-y for MI After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	615	28,065.1	21.91	20.22 -23.72
Age at Diagnosis	66-69	95	5,381.50	17.65	14.28 -21.58
	70-74	150	8,478.75	17.69	14.97 -20.76
	75-79	168	7,426.00	22.62	19.33 -26.31
	80-84	122	4,516.25	27.01	22.43 -32.25
	85+	80	2,262.58	35.36	28.04 -44.01
Race	Black	63	1,999.25	31.51	24.21 -40.32
	Other/Unknown	32	1,900.75	16.84	11.52 -23.77
	White	520	24,165.1	21.52	19.71 -23.45
Gender	Female	256	12,713.5	20.14	17.74 -22.76
	Male	359	15,351.6	23.39	21.03 -25.93
Geographic Region	Midwest	88	3,575.42	24.61	19.74 -30.32
	Northeast	157	6,246.17	25.14	21.36 -29.39
	South	157	7,305.25	21.49	18.26 -25.13
	West	213	10,938.3	19.47	16.95 -22.27
Year of Diagnosis	2004	135	6,589.17	20.49	17.18 -24.25
	2005	126	6,055.75	20.81	17.33 -24.77
	2006	115	5,454.67	21.08	17.41 -25.31
	2007	93	4,627.08	20.10	16.22 -24.62
	2008	85	3,286.08	25.87	20.66 -31.98
	2009	61	2,052.33	29.72	22.74 -38.18
Histology Group	Chromophobe	25	1,332.25	18.77	12.14 -27.70
	Clear Cell	469	21,633.4	21.68	19.76 -23.73
	Other RCC	53	1,841.92	28.77	21.55 -37.64
	Papillary	51	2,760.83	18.47	13.75 -24.29
	Transitional cell tumor	17	496.67	34.23	19.94 -54.80

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	324	17,129.4	18.91	16.91 -21.09
	Stage II	58	2,447.25	23.70	18.00 -30.64
	Stage III	88	4,324.33	20.35	16.32 -25.07
	Stage IV	67	1,899.92	35.26	27.33 -44.78
	Stage Unknown	78	2,264.17	34.45	27.23 -42.99
Chemotherapy	No	502	22,325.9	22.49	20.56 -24.54
	Yes	113	5,739.17	19.69	16.23 -23.67
Immunotherapy	No	589	26,799.7	21.98	20.24 -23.83
	Yes	26	1,265.33	20.55	13.42 -30.11
Nephrectomy	No	180	5,398.17	33.34	28.65 -38.59
	Yes	435	22,666.9	19.19	17.43 -21.08
History of Condition	No	543	27,773.2	19.55	17.94 -21.27
	Yes	72	291.92	246.65	192.99 -310.61
History of CVD	No	373	22,666.0	16.46	14.83 -18.21
	Yes	242	5,399.08	44.82	39.35 -50.84
CVC[a]	No	1,349	25,498.4	52.91	50.12 - 55.81
	Yes	205	349.42	586.69	509.12 - 672.74
High-risk Surgery[a]	No	1,370	25,491.0	53.74	50.94 - 56.67
	Yes	184	356.83	515.65	443.83 - 595.78
Charlson Score	0	24	5,029.42	4.77	3.06 -7.10
	1	62	4,690.08	13.22	10.14 -16.95
	2 to 3	155	9,868.92	15.71	13.33 -18.38
	4+	374	8,476.67	44.12	39.76 -48.83

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); MI = myocardial infarction; RCC = renal cell carcinoma.
[a] More than 30 days before the outcome.

The incidence rate for ischemic stroke in the period after kidney cancer diagnosis was 19.39 per 1,000 p-y (Table 21). The incidence rates by histology group were 15.59, 19.95, 24.11, and 16.60 for Chromophobe, Clear cell, Other RCC, and Papillary, respectively. With wide confidence intervals, the differences in incidence rates may not

be statistically significant. The incidence rates increased with increasing age at diagnosis and increasing Charlson comorbidity score.

Table 21
Incidence Rates per 1,000 p-y for IS After Kidney Cancer Diagnosis

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
TOTAL	TOTAL	548	28,256.5	19.39	17.80 - 21.09
Age at Diagnosis	66-69	71	5,451.00	13.03	10.17 - 16.43
	70-74	144	8,521.33	16.90	14.25 - 19.90
	75-79	165	7,435.75	22.19	18.93 - 25.85
	80-84	97	4,573.75	21.21	17.20 - 25.87
	85+	71	2,274.67	31.21	24.38 - 39.37
Race	Black	55	2,039.58	26.97	20.31 - 35.10
	Other/Unknown	28	1,909.50	14.66	9.74 - 21.19
	White	465	24,307.4	19.13	17.43 - 20.95
Gender	Female	260	12,735.5	20.42	18.01 - 23.05
	Male	288	15,521.0	18.56	16.47 - 20.83
Geographic Region	Midwest	72	3,620.50	19.89	15.56 - 25.04
	Northeast	127	6,340.67	20.03	16.70 - 23.83
	South	171	7,290.08	23.46	20.07 - 27.25
	West	178	11,005.3	16.17	13.89 - 18.73
Year of Diagnosis	2004	115	6,663.75	17.26	14.25 - 20.72
	2005	131	6,058.92	21.62	18.08 - 25.66
	2006	104	5,473.75	19.00	15.52 - 23.02
	2007	75	4,678.75	16.03	12.61 - 20.09
	2008	72	3,314.92	21.72	16.99 - 27.35
	2009	51	2,066.42	24.68	18.38 - 32.45
Histology Group	Chromophobe	-	-	15.59	9.65 - 23.83
	Clear Cell	434	21,756.8	19.95	18.12 - 21.92
	Other RCC	45	1,866.25	24.11	17.59 - 32.26
	Papillary	46	2,771.08	16.60	12.15 - 22.14
	Transitional cell tumor	< 11	-	3.88	0.47 - 14.02

(continued)

	Level	*n*	Person-Years	Incidence Rate	95% *CI*
Stage at Diagnosis	Stage I	306	17,188.9	17.80	15.86 - 19.91
	Stage II	36	2,481.83	14.51	10.16 - 20.08
	Stage III	86	4,357.83	19.73	15.79 - 24.37
	Stage IV	58	1,913.33	30.31	23.02 - 39.19
	Stage Unknown	62	2,314.58	26.79	20.54 - 34.34
Chemotherapy	No	428	22,504.8	19.02	17.26 - 20.91
	Yes	120	5,751.75	20.86	17.30 - 24.95
Immunotherapy	No	525	26,975.9	19.46	17.83 - 21.20
	Yes	23	1,280.58	17.96	11.39 - 26.95
Nephrectomy	No	158	5,434.83	29.07	24.72 - 33.97
	Yes	390	22,821.7	17.09	15.43 - 18.87
History of Condition	No	515	27,958.4	18.42	16.86 - 20.08
	Yes	33	298.08	110.71	76.21 - 155.47
History of CVD	No	390	23,816.9	16.37	14.79 - 18.08
	Yes	158	4,439.58	35.59	30.26 - 41.59
CVC[a]	No	473	28,073.9	16.85	15.36 - 18.44
	Yes	75	182.58	410.77	323.10 - 514.91
High-risk Surgery[a]	No	459	28,024.1	16.38	14.91 - 17.95
	Yes	89	232.42	382.93	307.53 - 471.23
Charlson Score	0	53	5,770.08	9.19	6.88 - 12.01
	1	87	5,142.42	16.92	13.55 - 20.87
	2 to 3	201	10,105.8	19.89	17.23 - 22.84
	4+	207	7,238.17	28.60	24.83 - 32.77

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; RCC = renal cell carcinoma.

[a] More than 30 days before the outcome.

The incidence rates of thromboembolic events were higher in the period after cancer diagnosis than in the period before diagnosis for each outcome. Consistently, incidence rates increased with history of the condition, history of CVD, and increasing Charlson score. Ischemic stroke was the most common ATE and typically drove the

patterns seen for the any ATE tables. The incidence rates of ATEs were higher than expected, however appears to be due to the inclusion of ischemic stroke. The incidence rate for ischemic stroke of 60.12 per 1,000 p-y was higher than the incidence rate for any of the venous thromboembolic events.

Descriptive Analysis 2

The purpose of descriptive analysis 2 was to describe the incidence proportions of thromboembolic events in the kidney cancer cohort in discrete periods after kidney cancer diagnosis. Tables 21 to 23 contain the results for each outcome with incidence proportions within 90 days, 91 to 180 days, 181 to 270 days, and 271 to 365 days after the cancer diagnosis. The incidence proportions in the entire follow-up period were also provided.

Within the first year after cancer diagnosis, the highest incidence proportions of VTEs and ATEs occurred in the first 90 days (Tables 22 to 24). The trend was that the incidence proportions decreased in later time periods for all outcomes except other VTE and ATEs (any, myocardial infarction, or ischemic stroke); however there were wide, overlapping confidence intervals and so the incidence proportions may not have been different at a statistically significant level. The highest incidence proportions occurred in the entire follow-up period.

Table 22

Incidence Proportions for Any VTE and DVT After Kidney Cancer Diagnosis

	Any VTE		DVT	
Period	Incidence Proportion	95% *CI*	Incidence Proportion	95% *CI*
0 - 90 days	6.38%	5.94% - 6.84%	4.29%	3.93% - 4.68%
91 - 180 days	1.37%	1.15% - 1.62%	0.90%	0.72% - 1.10%
181 - 270 days	0.98%	0.79% - 1.21%	0.78%	0.61% - 0.99%
271 - 365 days	0.82%	0.64% - 1.04%	0.50%	0.36% - 0.67%
Entire Follow-up Period	12.2%	11.6% - 12.8%	8.48%	7.98% - 9.00%

Note. DVT = deep vein thrombosis; VTE = venous thromboembolic event.

Table 23

Incidence Proportions for PE and Other VTEs After Kidney Cancer Diagnosis

	PE		Other VTE	
Period	Incidence Proportion	95% *CI*	Incidence Proportion	95% *CI*
0 - 90 days	1.64%	1.42% - 1.89%	1.57%	1.35% - 1.81%
91 - 180 days	0.41%	0.29% - 0.55%	0.44%	0.32% - 0.59%
181 - 270 days	0.30%	0.20% - 0.43%	0.19%	0.11% - 0.30%
271 - 365 days	0.20%	0.12% - 0.32%	0.27%	0.17% - 0.40%
Entire Follow-up Period	3.37%	3.04% - 3.71%	3.30%	2.98% - 3.64%

Note. Other VTE = other venous thromboembolic event; PE = pulmonary embolism.

Table 24
Incidence Proportions for ATEs After Kidney Cancer Diagnosis

	Any ATE		MI		IS	
Period	IP	95% *CI*	IP	95% *CI*	IP	95% *CI*
0 - 90 days	3.19%	2.88% - 3.53%	1.82%	1.59% - 2.09%	1.47%	1.26% - 1.71%
91 - 180 days	0.90%	0.72% - 1.10%	0.58%	0.45% - 0.75%	0.36%	0.25% - 0.49%
181 - 270 days	0.67%	0.51% - 0.86%	0.34%	0.23% - 0.48%	0.36%	0.25% -0.50%
271 - 365 days	0.78%	0.61% - 0.99%	0.41%	0.28% - 0.56%	0.40%	0.28% - 0.56%
Entire Follow-up Period	9.45%	8.92% - 10.0%	5.37%	4.96% - 5.79%	4.78%	4.40% - 5.19%

Note. Any ATE = any arterial thromboembolic event (MI or IS); IS = ischemic stroke; MI = myocardial infarction.

Research Question 1

Research Question 1: How do the incidence rates of VTEs and ATEs in elderly exposed (kidney cancer) patients 12 months before index date compare to a matched unexposed (noncancer) Medicare population during the same 12-month timeframe?

H_A1: In the year prior to index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_01: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the year prior to the index date in the exposed patients and in the matched unexposed patients.

The purpose of Research Question 1 was to compare the incidence rates in the exposed to unexposed cohorts in the year prior to index date. The incidence rate ratios were estimated by the hazard ratio and all models were adjusted for the matching factors. Adjusted models were run twice, first using kidney disease and diabetes as potential confounders and effect measure modifiers; second, using the Charlson score as a potential confounder. Kidney disease and diabetes are two conditions which are

components of the Charlson comorbidity score. Using backward selection, variables were retained in the model if they had a p-value of less than 0.05. The hazard ratios were stratified by variables whose interaction terms with gender had a p-value less than 0.05 in the full model.

The incidence rate for any VTE was higher in the exposed cohort than in the unexposed cohort in the crude and adjusted models (Table 25). The crude hazard ratio comparing the incidence rate in the exposed to the unexposed was 1.44 (95% *CI* 1.23 – 1.69). After adjusting for other factors, the hazard ratio increased. Using the first method, the hazard ratio was 1.65 (95% *CI* 1.30 - 2.09) after adjusting by atherosclerosis, varicose veins, placement of central venous catheter more than 30 days prior to the outcome, kidney disease and history of VTE. Using the Charlson comorbidity score instead of kidney disease and diabetes variables in the full model, the adjusted hazard ratio was 1.81 (95% *CI* 1.42 – 2.28) and the adjusting factors were Charlson score, varicose veins, central venous catheter and history of VTE.

The incidence rate for DVT was higher in the exposed cohort than the unexposed cohort in the year prior to index date (Table 25). The crude hazard ratio was 1.69 (95% *CI* 1.38 – 2.08), but decreased slightly after adjusting for confounders. The confounders in the first adjusted model were atherosclerosis, varicose veins, kidney disease and history of CVD and the hazard ratio was 1.50 (95% *CI* 1.19-1.89). The model adjusted by the Charlson score yielded a hazard ratio of 1.57 (95% *CI* 1.24 – 1.98) and was adjusted by atherosclerosis and varicose veins. After adjusting for the Charlson score, history of CVD was no longer a confounder for the relationship.

The incidence rate for pulmonary embolism in the year prior to index date was higher in the exposed cohort than the unexposed cohort for all models (Table 25). The crude hazard ratio (*HR* = 1.62, 95% *CI* 1.16 – 2.27) was between the two adjusted hazard ratios.

Unlike any VTE, DVT, and pulmonary embolism, the incidence rate for other VTEs in the year prior to index date was not consistently higher for the exposed than the unexposed at a statistically significant level (Table 25). The crude hazard ratio was 1.32 (95% *CI* 1.01 - 1.71). However, in the first model the history of CVD was an EMM and the incidence rate ratio was greater than one in the population without history of CVD (*HR* = 1.41, 95% *CI* 1.02 – 1.96). The hazard ratio for patients with a history of CVD was 0.83 (95% *CI* 0.38 – 1.80) and was not statistically significant at the 0.05 level. The hazard ratio for the model adjusted by the Charlson score was greater than 1 (*HR* = 1.23, 95% *CI* 0.93 – 1.62), but it was also not statistically significant at the 0.05 level.

Table 25

Incidence Rate Ratios for Venous Thromboembolic Events in the Year Prior to Index Date (N = 22,926)

	Crude *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)	Adjusted *HR* (95% *CI*)
Any VTE (*n* = 394 events in cancer cohort; *n* = 271 events in noncancer cohort)			
Cancer vs. noncancer	1.44 (1.23 - 1.69)***	1.65 (1.30 - 2.09)[b]***	1.81 (1.42 - 2.28)[c]***
DVT (*n* = 246 events in cancer cohort; *n* = 147 events in noncancer cohort)			
Cancer vs. noncancer	1.69 (1.38 - 2.08)***	1.50 (1.19 -1.89) [d]***	1.57 (1.24 - 1.98)[e]***
PE (*n* = 90 events in cancer cohort; *n* = 55 events in noncancer cohort)			
Cancer vs. noncancer	1.62 (1.16 - 2.27)**	1.52 (1.07 - 2.18)[f]*	1.84 (1.24 - 2.74)[g]**
Other VTE (*n* = 129 events in cancer cohort; *n* = 98 events in noncancer cohort)			
Cancer vs. noncancer	1.32 (1.01 - 1.71)*		1.23 (0.93 - 1.62)[i]
Without history of CVD		1.41 (1.02 - 1.96)[h]*	
With history of CVD		0.83 (0.38 - 1.80)[h]	

Note. CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); DVT = deep vein thrombosis; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

[a] *Model adjusted only for matching*

[b] *Model adjusted for matching and atherosclerosis, varicose veins, central venous catheter, kidney disease, and history of VTE. Placement of central venous catheter was more than 30 days before outcome.*

[c] *Model adjusted for matching and Charlson Comorbidity Score, varicose veins, central venous catheter, and history of VTE. Placement of central venous catheter was more than 30 days before outcome.*

[d] *Model adjusted for matching and atherosclerosis, varicose veins, kidney disease and history of CVD.*

[e] *Model adjusted for matching and Charlson Comorbidity Score, atherosclerosis, and varicose veins.*

[f] *Model adjusted for matching, type 2 diabetes and kidney disease.*

[g] *Model adjusted for matching and Charlson Comorbidity Score.*

[h] *Model adjusted for matching and type 2 diabetes and varicose veins. Stratified by history of CVD.*

[i] *Model adjusted for matching and Charlson Comorbidity Score and varicose veins.*

** $p < .05$. ** $p < .01$. *** $p < .001$.*

The incidence rate ratio was greater than 1.0 comparing the exposed to unexposed cohorts for any ATE in the year prior to index date, but only for the crude model (Table 26). After adjusting for other factors including type 2 diabetes, kidney disease, Charlson Comorbidity Score, atherosclerosis, varicose veins, high-risk surgery, history of CVD, and history of ATE, there was no statistically significant difference in the incidence rates of any ATE for cancer patients and noncancer patients.

The incidence rate ratio for myocardial infarction in the year prior to index date differed by history of CVD (Table 26). Although the hazard ratio was greater than 1 for the crude model (*HR* = 1.26, 95% *CI* 1.20 – 1.56), the hazard ratio was not significantly different than 1.0 for the model adjusted by the Charlson score (*HR* = 1.18, 95% *CI* 0.88

– 1.59). In patients without a history of CVD, the hazard ratio was greater than 1 (*HR* = 1.46, 95% *CI* 1.05 – 2.05). The hazard ratio was less than 1.0 for patients with a history of CVD (*HR* = 0.48, 95% *CI* 0.24 – 0.97).

Elderly kidney cancer patients did not have a higher incidence rate of ischemic stroke than the matched, noncancer comparison group. Although the hazard ratios were greater than 1.0, for neither the crude nor adjusted models were the results statistically different from 1.0 (Table 26). The crude hazard ratio was 1.20, but after adjusting for other risk factors the hazard ratio decreased to 1.04 to 1.09 for the two multivariate models.

Table 26

Incidence Rate Ratios for Arterial Thromboembolic Events in the Year Prior to Index Date (N = 22,926)

	Crude *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)	Adjusted *HR* (95% *CI*)
Any ATE (*n* = 354 events in cancer cohort; *n* = 291 events in noncancer cohort)			
Cancer vs. noncancer	1.23 (1.05 - 1.43)*	1.11 (0.92 - 1.34) [b]	1.14 (0.93 - 1.39) [c]
MI (*n* = 192 events in cancer cohort; *n* = 153 events in noncancer cohort)			
Cancer vs. noncancer	1.26 (1.02 - 1.56)*		1.18 (0.88 - 1.59)[e]
Without history of CVD		1.46 (1.05 - 2.04)[d]**	
With history of CVD		0.48 (0.24 - 0.97) [d]**	
IS (*n* = 173 events in cancer cohort; *n* = 145 events in noncancer cohort)			
Cancer vs. noncancer	1.20 (0.96 - 1.50)	1.04 (0.81 - 1.34)[f]	1.09 (0.84 - 1.42)[g]

Note. Any ATE = any arterial thromboembolic event (MI or IS); CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); MI = myocardial infarction; IS = ischemic stroke.

[a] *Model adjusted only for matching*

[b] *Model adjusted for matching and type 2 diabetes, atherosclerosis, high-risk surgery, kidney disease, history of CVD, and history of ATE. High-risk surgery was more than 30 days before outcome.*

[c] *Model adjusted for matching and Charlson Comorbidity Score, atherosclerosis, high-risk surgery and history of ATE. High-risk surgery was more than 30 days before outcome.*

[d] *Model adjusted for matching and type 2 diabetes and kidney disease. Stratified by history of CVD.*

[e] *Model adjusted for matching and Charlson Comorbidity Score and history of MI .*

[f] *Model adjusted for matching and type 1 diabetes, atherosclerosis, history of ischemic stroke, and kidney disease. High-risk surgery was more than 30 days before outcome.*

[g] *Model adjusted for matching and Charlson Comorbidity Score, atherosclerosis, and history of IS.*

** $p < .05$. ** $p < .01$. *** $p < .001$.*

For most outcomes, the incidence rate of thromboembolic events was higher in the exposed cohort than the unexposed cohort in the year prior to index date. For other VTEs, any ATE, myocardial infarction, and ischemic stroke, history of CVD was an EMM with the incidence rate of events higher in the exposed cohort for patients without a history of CVD. In patients with a history of CVD, the incidence rate was lower in the exposed cohort or not statistically significantly different than the unexposed cohort.

Thus, the null hypothesis was rejected for any VTE, DVT and pulmonary embolism after adjusting for other factors in the model. The null hypothesis could not be rejected for other VTEs and myocardial infarction in patients with a history of CVD when the models did not adjust for the Charlson comorbidity score. The null hypothesis

could also not be rejected for other VTEs, any ATE, myocardial infarction, and ischemic stroke after adjusting by the Charlson comorbidity score.

Research Question 2

Research Question 2: How do the incidence rates of VTEs and rates of ATEs in elderly exposed (kidney cancer) patients after index date compare to a matched unexposed (noncancer) Medicare population during the same timeframe?

H_A2: In the follow-up period after the index date, the incidence rates of VTEs or of ATEs are statistically significantly greater in the exposed patients than in the unexposed patients.

H_02: There is no statistically significant difference in the incidence rates of VTEs or ATEs in the period after index date in the exposed patients and in the matched unexposed patients. The purpose of Research Question 2 was to compare the incidence rates in the exposed to unexposed cohorts in the follow-up period after index date. The methodology was the same as for Research Question 1.

The incidence rate for any VTE was higher in the exposed cohort than the unexposed cohort in the follow-up period (Table 27). In the first model, Type 2 diabetes and kidney disease were EMMs. The rate was more than five times higher in the exposed population than the unexposed population in patients who had neither type 2 diabetes nor kidney disease (5.42, 95% *CI* 4.18 – 7.02). The incidence rate was twice as high in the exposed population in patients with type 2 diabetes only or kidney disease only. The incidence rate was not statistically significantly different for the exposed to the unexposed cohort in patients with both type 2 diabetes and kidney disease (1.15, 95% *CI*

0.78 – 1.68). In the second model, the incidence rate was more than three times as high in the exposed population (*HR* = 3.44, 95% *CI* 2.97 – 3.99) and no factors were EMMs.

The incidence rate for DVT in the exposed cohort was higher than in the unexposed cohort in the follow-up period after index date (Table 27). In the first model, atherosclerosis and kidney disease were EMMs. The incidence rate ratios were higher in the exposed cohort for patients without both disease and for patients with only atherosclerosis or kidney disease. The hazard ratio was 0.88 (95% *CI* 0.53 – 1.49) for patients with both atherosclerosis and kidney disease. In the second model, atherosclerosis was an EMM. The incidence rate ratio estimates were greater than 1.0 in patients without atherosclerosis (*HR* = 3.56, 95% *CI* 2.88 – 4.41) and in patients with atherosclerosis (*HR* = 1.75, 95% *CI* 1.13 – 2.72).

The incidence rate ratio for pulmonary embolism was approximately three times higher in the exposed cohort than the unexposed cohort in the follow-up period (Table 27). Both adjusted models yielded similar hazard ratios. The first model hazard ratio was 2.95 (95% *CI* 2.31 – 3.77) and the second model adjusted hazard ratio was 3.28 (95% *CI* 2.60 – 4.14). Both models were adjusted by atherosclerosis, with the first model also adjusted by kidney disease and the second model also adjusted by the Charlson score.

The incidence rate ratio for other VTEs differed by type 2 diabetes and kidney disease in the first model (Table 27). In patients without diabetes and kidney disease, the hazard ratio was 4.31 (95% *CI* 2.89 – 6.43); in patients with kidney disease the hazard ratio was 1.80 (95% *CI* 0.90 – 3.57); in patients with type 2 diabetes the hazard ratio was 2.08 (95% *CI* 1.19 – 3.64); and in patients with both type 2 diabetes and kidney disease,

the hazard ratio was 0.87 (95% *CI* 0.47 – 1.61). In the second model, there were no EMMs and the incidence rate ratio in the exposed cohort was 2.6 times that of the unexposed cohort after adjusting for Charlson score, varicose veins, and placement of central venous catheter more than 30 days prior to VTE (*HR* = 2.66, 95% *CI* 2.11 – 3.36).

Table 27

Incidence Rate Ratios for Venous Thromboembolic Events in Follow-up Period After Index Date (N = 22,926)

	Crude *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)	Adjusted *HR* (95% *CI*)
Any VTE			
(*n* = 1,402 events in cancer cohort; *n* = 441 events in noncancer cohort)			
Cancer vs. noncancer	3.41 (3.05 - 3.81)***		3.44 (2.97 - 3.99)[c]***
Without type 2 diabetes or kidney disease.		5.42 (4.18 - 7.02)[b]***	
Without type 2 diabetes, with kidney disease.		2.19 (1.48 - 3.23)[b] ***	
With type 2 diabetes, without kidney disease.		2.84 (2.00 - 4.04)[b] ***	
With type 2 diabetes and kidney disease.		1.15 (0.78 - 1.68)[b]	
DVT			
(*n* = 972 events in cancer cohort; *n* = 289 events in noncancer cohort)			
Cancer vs. noncancer	3.55 (3.10 - 4.06) ***		
Without atherosclerosis or kidney disease.		4.45 (3.37 - 5.89)[d]***	
Without atherosclerosis, with kidney disease.		1.57 (1.04 - 2.38)[d] *	
With atherosclerosis, without kidney disease.		2.51 (1.48 - 4.23)[d] **	
With atherosclerosis and kidney disease.		0.88 (0.53 - 1.49)[d]	
Without atherosclerosis			3.56 (2.88 - 4.41)[e]**
With atherosclerosis			1.75 (1.13 - 2.72)[e]**
PE			
(*n* = 386 events in cancer cohort; *n* = 100 events in noncancer cohort)			
Cancer vs. noncancer	3.88 (3.11 - 4.84) ***	2.95 (2.31 - 3.77)[f]***	3.28 (2.60 - 4.14)[g]***
Other VTE			
(*n* = 378 events in cancer cohort; *n* = 127 events in noncancer cohort)			
Cancer vs. noncancer	3.07 (2.50 - 3.76) ***		2.66 (2.11 - 3.36)[i]***
Without type 2 diabetes or kidney disease.		4.31 (2.89 - 6.43)[h]**	
Without type 2 diabetes, with kidney disease.		1.80 (0.90 - 3.57)[h]	
With type 2 diabetes, without kidney disease.		2.08 (1.19 - 3.64)[h]**	
With type 2 diabetes and kidney disease.		0.87 (0.47 - 1.61)[h]	

Note. DVT = deep vein thrombosis; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

[a] *Model adjusted only for matching.*

[b] *Model adjusted for matching and type 1 diabetes, atherosclerosis, varicose veins, high-risk surgery, central venous catheter, and history of VTE. Stratified by type 2 diabetes and kidney disease. High-risk surgery was more than 30 days before outcome.*

[c] *Model adjusted for matching and Charlson Comorbidity Score, varicose veins, high-risk surgery, central venous catheter, and history of VTE. High-risk surgery was more than 30 days before outcome.*

[d] *Model adjusted for matching and. Stratified by atherosclerosis and kidney disease.*

[e] *Model adjusted for matching and Charlson Comorbidity Score, varicose veins, high-risk surgery, central venous catheter, and history of DVT. Stratified by atherosclerosis. High-risk surgery and central venous catheter were more than 30 days before outcome.*

[f] *Model adjusted for matching and atherosclerosis and kidney disease.*

[g] *Model adjusted for matching and Charlson Comorbidity Score and atherosclerosis.*

[h] *Model adjusted for matching and varicose veins and central venous catheter. Stratified by type 2 diabetes and kidney disease. Placement of central venous catheter was more than 30 days before outcome.*

[i] *Model adjusted for matching and Charlson Comorbidity Score, varicose veins, and central venous catheter. Placement of central venous catheter was more than 30 days before outcome.*

** $p < .05$. ** $p < .01$. *** $p < .001$.*

The incidence rate ratio for any ATE comparing the exposed to unexposed cohort was 1.81 (95% *CI* 1.64 – 2.01) for the crude model (Table 28). After adjusting for other factors, the incidence rate was higher for the exposed cohort in patients without atherosclerosis and without kidney disease for the first model; and in patients without atherosclerosis for the second model. Conversely, the incidence rate for any ATE was

lower for the exposed cohort in patients who had both atherosclerosis and kidney disease (*HR* = 0.59, 95% *CI* 0.40 - 0.86).

The incidence rate ratios for myocardial infarction in the follow-up period differed in the exposed and unexposed cohorts by history of myocardial infarction (Table 28). In the first model, presence of atherosclerosis also impacted the incidence rate ratio. In patients without atherosclerosis or history of myocardial infarction, the exposed cohort had higher incidence rates of myocardial infarction (*HR* = 1.42, 95% *CI* 1.10 – 1.84). In patients with history of myocardial infarction or atherosclerosis, the incidence rate was lower in the unexposed cohort than the exposed cohort. In the second model, patients in the exposed cohort with a history of myocardial infarction had a higher incidence rate than the unexposed cohort without a history of myocardial infarction (*HR* = 1.35, 95% *CI* 1.11 – 1.65). Patients in the exposed cohort with history of had a much lower incidence rate than patients in the unexposed cohort (*HR* = 0.05, 95% *CI* 0.00 – 0.72).

The incidence rate ratio for ischemic stroke in the follow-up period comparing the exposed to unexposed differed by presence of kidney disease in the first model, and by the presence of atherosclerosis in the second model which also adjusted by the Charlson comorbidity score (Table 28). In the first model, the incidence rates for ischemic stroke were higher for the exposed cohort in patients without kidney disease, but lower for the exposed cohort in patients with kidney disease. The second model results were similar in that the incidence rate was lower for the exposed cohort in patients with atherosclerosis. The incidence rate ratio was not statistically different from 1.0 for patients without atherosclerosis.

Table 28

Incidence Rate Ratios for Arterial Thromboembolic Events in Follow-up Period After Index Date (N = 22,926)

	Crude *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)	Adjusted *HR* (95% *CI*)
Any ATE			
(*n* = 1,083 events in cancer cohort; *n* = 625 events in noncancer cohort)			
Cancer vs. noncancer	1.81 (1.64 - 2.01)***		
Without atherosclerosis and without kidney disease		1.47 (1.21 - 1.79) [b]*	
Without atherosclerosis, with kidney disease		0.96 (0.71 - 1.31) [b]	
With atherosclerosis, without kidney disease		0.89 (0.61 - 1.30) [b]	
With atherosclerosis and kidney disease		0.59 (0.40 - 0.86) [b]*	
Without atherosclerosis			1.27 (1.08 - 1.49) [c]*
With atherosclerosis			0.77 (0.55 - 1.08) [c]
MI			
(*n* = 615 events in cancer cohort; *n* = 291 events in noncancer cohort)			
Cancer vs. noncancer	2.17 (1.89 - 2.51)***		
Without atherosclerosis or history of MI.		1.42 (1.10 - 1.84) [d]*	
Without atherosclerosis, with history of MI.		0.03 (0.00 - 0.44) [d]**	
With atherosclerosis, without history of MI.		0.80 (0.50 - 1.27) [d]	
With atherosclerosis and history of MI.		0.02 (0.00 - 0.25) [d]**	
Without history of MI			1.35 (1.11 - 1.65) [e]**
With history of MI			0.05 (0.00 - 0.72) [e]**
IS			
(*n* = 548 events in cancer cohort; *n* = 370 events in noncancer cohort)			
Cancer vs. noncancer	1.47 (1.29 - 1.68)***		
Without kidney disease		1.34 (1.06 - 1.70) [f]*	
With kidney disease		0.52 (0.35 - 0.78) [f]***	
Without atherosclerosis			1.04 (0.84 - 1.29) [g]
With atherosclerosis			0.55 (0.34 - 0.90) [g]*

Note. Any ATE = any arterial thromboembolic event (MI or IS); CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; MI = myocardial infarction.

[a] *Model adjusted only for matching*

[b] *Model adjusted for matching and type 2 diabetes, high-risk surgery, central venous catheter, kidney disease, history of ATE and history of CVD. Stratified by atherosclerosis and kidney disease. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

[c] *Model adjusted for matching and Charlson Comorbidity Score, high-risk surgery, central venous catheter, and history of ATE. Stratified by atherosclerosis. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

[d] *Model adjusted for matching, Type 2 diabetes, high-risk surgery, central venous catheter, kidney disease, and history of CVD. Stratified by atherosclerosis and history of MI. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

[e] *Model adjusted for matching and Charlson Comorbidity Score, high-risk surgery and central venous catheter. Stratified by history of MI. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

[f] *Model adjusted for matching and type 2 diabetes, atherosclerosis, high-risk surgery, central venous catheter, and history of IS. Stratified by kidney disease. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

[g] *Model adjusted for matching and Charlson Comorbidity Score, high-risk surgery, central venous catheter, and history of IS. Stratified by atherosclerosis. Central venous catheter and high-risk surgery were more than 30 days before outcome.*

** $p < .05$. ** $p < .01$. *** $p < .001$.*

In the follow-up period after index date, the incidence rate was higher in the exposed cohort than the unexposed cohort for thromboembolic events. The null hypothesis was rejected for any VTE, DVT, pulmonary embolism, and other VTEs after adjusting for the Charlson comorbidity score. In the models stratified by EMMs, the

higher incidence rates in the exposed cohort were mostly limited to the patients without the EMM condition (e.g., type 2 diabetes, kidney disease, or atherosclerosis). The null hypothesis was rejected for any ATE in patients without atherosclerosis and without kidney disease in the first model, and in patients without atherosclerosis in the second model which adjusted for Charlson comorbidity score. The null hypothesis was rejected for myocardial infarction in patients after adjusting for the Charlson comorbidity score, and rejected for ischemic stroke in patients without atherosclerosis after adjusting for the Charlson comorbidity score. The null hypothesis could not be rejected for any ATE in patients with atherosclerosis or kidney disease but not both; for myocardial infarction in patients with atherosclerosis but without a history of myocardial infarction; and for ischemic stroke in patients without atherosclerosis after adjusting for the Charlson comorbidity score. In outcomes where both models contained EMMs or no models contained EMMS, the two models yielded similar results.

Research Question 3

Research Question 3: In the follow-up period after kidney cancer diagnosis, what are the risk factors associated with time to newly diagnosed, individual VTE (DVT, PE, or OTE)?

H_A3: No factors are statistically significantly associated with the time to newly diagnosed VTEs in the period after kidney cancer diagnosis.

H_03: Tumor histology and other factors are statistically significantly associated with the time to newly diagnosed VTEs after kidney cancer diagnosis.

The purpose of Research Question 3 was to identify risk factors for venous thromboembolic events in the exposed cohort in the follow-up period after kidney cancer diagnosis. A Cox proportional hazard model was used for each outcome to identify factors associated with time to event at the 0.05 significance level. Backward selection was used to determine which variables were kept in the model. In both models, histology group was kept in regardless of statistical significance.

The risk factors associated with incidence of any VTE in the follow-up period were the oldest age group at diagnosis (80 years or older); Black race; Northeast region; Stage III, IV or unknown; history of any VTE; placement of CVC more than 30 days prior to VTE; varicose veins; treatment by chemotherapy; and being male without high-risk surgery more than 30 days prior to VTE (Table 29). In the first model transitional cell tumor, kidney disease and type 1 diabetes were also identified as risk factors. In the second model Charlson score of 2 or greater, year of diagnosis, and history of CVD were also identified as risk factors for any VTE in this population.

Table 29

Risk Factors Associated With Incidence of Any VTE in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	1.06 (0.89, 1.25)	1.06 (0.90, 1.26)
	75-79	1.11 (0.93, 1.32)	1.14 (0.95, 1.35)
	80-84	1.22 (1.01, 1.47)*	1.26 (1.04, 1.53)*
	85+	1.26 (1.01, 1.56)*	1.32 (1.06, 1.64)*
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	0.92 (0.77, 1.09)	0.93 (0.78, 1.10)
	Papillary	1.08 (0.88, 1.32)	1.08 (0.88, 1.32)
	Transitional cell tumor	0.67 (0.46, 0.97)*	0.70 (0.48, 1.02)
Charlson Score	0	-	(Ref)
	1	-	1.20 (0.98, 1.46)
	2 to 3	-	1.26 (1.06, 1.50)*
	4+	-	1.49 (1.24, 1.80)***
Race	White	(Ref)	(Ref)
	Black	1.23 (1.02, 1.48)*	1.22 (1.01, 1.47)*
	Other/Unknown	0.79 (0.62, 1.02)	0.77 (0.60, 0.99)*
Geographic Region	West	(Ref)	(Ref)
	Midwest	1.02 (0.85, 1.23)	1.01 (0.84, 1.21)
	Northeast	1.20 (1.04, 1.39)*	1.20 (1.04, 1.39)*
	South	1.06 (0.92, 1.23)	1.06 (0.92, 1.22)
Year of Diagnosis		-	1.04 (1.00, 1.08)*
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	1.09 (0.87, 1.38)	1.11 (0.89, 1.40)
	Stage III	2.26 (1.95, 2.61)***	2.26 (1.96, 2.61)***
	Stage IV	2.62 (2.24, 3.07)***	2.65 (2.26, 3.11)***
	Stage Unknown	1.24 (1.01, 1.52)*	1.28 (1.04, 1.57)*
History of Condition	No	(Ref)	(Ref)
	Yes	14.08(12.13,16.35)***	14.12(12.19,16.52)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
History of CVD	No	(Ref)	(Ref)
	Yes	-	0.79 (0.69, 0.92)**
CVC[c]	No	(Ref)	(Ref)
	Yes	4.34 (3.40, 5.54)***	4.45 (3.49, 5.68)***
Varicose veins	No	(Ref)	(Ref)
	Yes	1.92 (1.45, 2.53)***	1.87 (1.41, 2.47)***
Kidney Disease	No	(Ref)	(Ref)
	Yes	1.33 (1.19, 1.50)***	-
Chemotherapy	No	(Ref)	(Ref)
	Yes	1.33 (1.17, 1.52)***	1.33 (1.17, 1.51)***
Type 1 Diabetes	No	(Ref)	(Ref)
	Yes	0.80 (0.67, 0.95)*	-
Gender	Female	(Ref)	(Ref)
	Male without high-risk surgery	0.82 (0.73, 0.92)*	0.82 (0.73, 0.92)*
	Male with high-risk surgery	1.29 (0.86, 1.92)	1.32 (0.88, 1.96)

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); RCC = renal cell carcinoma; VTE = venous thromboembolic event.

[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).

[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.

[c] More than 30 days before the outcome.

** $p < .05$. ** $p < .01$. *** $p < .001$.*

The risk factors associated with incidence of DVT in the follow-up period were other or unknown race; Stage III, IV, or unknown stage; history of DVT; high risk surgery; placement of central venous catheter; varicose veins; and treatment by chemotherapy (Table 30). In the first model, type I diabetes, kidney disease, and female gender were also identified as risk factors. In the second model, Charlson score and Northeast region were also risk factors.

Table 30

Risk Factors Associated With Incidence of DVT in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	1.18 (0.96, 1.46)	1.17 (0.95, 1.45)
	75-79	1.15 (0.92, 1.42)	1.14 (0.92, 1.41)
	80-84	1.55 (1.24, 1.94)***	1.54 (1.23, 1.93)***
	85+	1.44 (1.11, 1.87)**	1.46 (1.12, 1.89)**
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	1.00 (0.81, 1.22)	0.99 (0.81, 1.22)
	Papillary	1.16 (0.91, 1.47)	1.16 (0.91, 1.48)
	Transitional cell tumor	0.87 (0.57, 1.33)	0.91 (0.60, 1.39)
Charlson Score	0	(Ref)	(Ref)
	1	-	1.22 (0.95, 1.57)
	2 to 3	-	1.32 (1.06, 1.63)*
	4+	-	1.54 (1.24, 1.91)***
Race	White	(Ref)	(Ref)
	Black	1.24 (1.00, 1.54)	1.23 (0.98, 1.53)
	Other/Unknown	0.63 (0.46, 0.85)**	0.63 (0.46, 0.86)**
Geographic Region	West	(Ref)	(Ref)
	Midwest	-	0.93 (0.75, 1.16)
	Northeast	-	1.20 (1.01, 1.43)*
	South	-	1.01 (0.85, 1.20)
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	1.19 (0.90, 1.56)	1.22 (0.93, 1.60)
	Stage III	2.25 (1.89, 2.68)***	2.27 (1.91, 2.71)***
	Stage IV	2.74 (2.28, 3.31)***	2.83 (2.34, 3.42)***
	Stage Unknown	1.43 (1.12, 1.82)**	1.41 (1.11, 1.80)**
History of Condition	No	(Ref)	(Ref)
	Yes	22.36(18.48,27.05)***	21.41(17.66,25.95)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	4.11 (3.03, 5.57)***	4.00 (2.95, 5.43)***
Type 1 Diabetes	No	(Ref)	(Ref)
	Yes	0.78 (0.63, 0.96)*	-
CVC[c]	No	(Ref)	(Ref)
	Yes	6.26 (4.73, 8.30)***	6.30 (4.76, 8.33)***
Varicose veins	No	(Ref)	(Ref)
	Yes	1.87 (1.35, 2.60)***	1.75 (1.26, 2.42)***
Kidney Disease	No	(Ref)	(Ref)
	Yes	1.44 (1.25, 1.66)***	-
Chemotherapy	No	(Ref)	(Ref)
	Yes	1.31 (1.13, 1.52)***	1.33 (1.14, 1.54)***
Gender	Female	(Ref)	(Ref)
	Male	0.83 (0.73, 0.95)**	0.85 (0.75, 0.98)*

Note. CVC= central venous catheter; DVT = deep vein thrombosis; RCC = renal cell carcinoma.
[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).
[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.
[c] More than 30 days before the outcome.
** $p < .05$. ** $p < .01$. *** $p < .001$.*

The risk factors for incidence of pulmonary embolism in the follow-up period were age; papillary and transition cell tumor histology; Stage III or IV; history of pulmonary embolism; high-risk surgery more than 30 days prior to event; placement of central venous catheter more than 30 days prior to event; treatment by chemotherapy or nephrectomy; and gender (Table 31). Type 1 diabetes and kidney disease were also associated with pulmonary embolism in the first model, whereas the Charlson score was associated with pulmonary embolism in the second model.

Table 31

Risk Factors Associated With Incidence of PE in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	0.89 (0.66, 1.19)	0.86 (0.64, 1.16)
	75-79	0.67 (0.49, 0.92)*	0.67 (0.49, 0.91)*
	80-84	0.63 (0.43, 0.91)*	0.62 (0.43, 0.90)*
	85+	0.83 (0.56, 1.23)	0.84 (0.56, 1.25)
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	0.95 (0.68, 1.32)	0.96 (0.69, 1.33)
	Papillary	1.50 (1.06, 2.14)*	1.53 (1.08, 2.18)*
	Transitional cell tumor	0.28 (0.09, 0.90)*	0.30 (0.09, 0.96)*
Charlson Score	0	(Ref)	(Ref)
	1	-	1.28 (0.86, 1.90)
	2 to 3	-	1.51 (1.07, 2.12)*
	4+	-	1.68 (1.19, 2.38)**
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	0.98 (0.64, 1.49)	0.98 (0.64, 1.50)
	Stage III	1.53 (1.13, 2.06)**	1.52 (1.12, 2.05)**
	Stage IV	2.43 (1.80, 3.28)***	2.50 (1.85, 3.38)***
	Stage Unknown	0.75 (0.47, 1.18)	0.78 (0.50, 1.23)
History of Condition	No	(Ref)	(Ref)
	Yes	38.08(27.19,53.32)***	34.65(24.76,48.51)***
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	5.14 (3.04, 8.70)***	5.42 (3.18, 9.23)***
CVC[c]	No	(Ref)	(Ref)
	Yes	9.04 (5.52, 14.80)***	8.42 (5.13, 13.82)***
Type 1 Diabetes	No	(Ref)	(Ref)
	Yes	0.70 (0.50, 1.00)*	-
Kidney Disease	No	(Ref)	(Ref)
	Yes	1.61 (1.29, 2.00)***	-

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Chemotherapy	No	(Ref)	(Ref)
	Yes	1.56 (1.23, 1.96)***	1.57 (1.24, 1.98)***
Nephrectomy	No	(Ref)	(Ref)
	Yes	0.71 (0.54, 0.94)*	0.75 (0.57, 0.99)*
Gender	Female	(Ref)	(Ref)
	Male	0.75 (0.60, 0.93)**	0.75 (0.61, 0.93)**

Note. CVC = central venous catheter; PE = pulmonary embolism; RCC = renal cell carcinoma.
[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).
[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.
[c] More than 30 days before the outcome.
** $p < .05$. ** $p < .01$. *** $p < .001$.*

The risk factors associated with other VTE in the follow-up period were age at diagnosis; Northeast region; year of diagnosis; Stage III, IV, and unknown Stage; history of other VTE; history of CVD; high-risk surgery; and central venous catheter (Table 32). In the first model, treatment by chemotherapy was also a risk factor and a diagnosis of varicose veins was an EMM. Histology group was not a statistically significant risk factor in either model. Charlson score was also not associated with other VTE in the second model.

Table 32

Risk Factors Associated With Incidence of Other VTE in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	1.05 (0.75, 1.47)	1.02 (0.73, 1.43)
	75-79	1.41 (1.01, 1.96)*	1.41 (1.02, 1.96)*
	80-84	0.97 (0.66, 1.44)	0.86 (0.59, 1.27)
	85+	1.42 (0.92, 2.19)	1.36 (0.89, 2.09)
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	0.93 (0.67, 1.30)	0.94 (0.67, 1.30)
	Papillary	0.98 (0.66, 1.46)	0.98 (0.66, 1.45)
	Transitional cell tumor	0.58 (0.26, 1.33)	0.61 (0.27, 1.39)
Charlson Score	0	(Ref)	(Ref)
	1	-	0.97 (0.67, 1.42)
	2 to 3	-	1.19 (0.86, 1.63)
	4+	-	1.22 (0.87, 1.73)
Geographic Region	West	(Ref)	(Ref)
	Midwest	0.77 (0.52, 1.14)	0.81 (0.54, 1.19)
	Northeast	1.40 (1.07, 1.83)*	1.47 (1.12, 1.91)**
	South	1.16 (0.89, 1.51)	1.20 (0.92, 1.56)
Year of Diagnosis		1.07 (1.00, 1.15)*	1.09 (1.02, 1.17)*
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	0.92 (0.57, 1.50)	0.94 (0.57, 1.52)
	Stage III	3.12 (2.42, 4.04)***	3.13 (2.42, 4.04)***
	Stage IV	1.66 (1.18, 2.34)**	1.57 (1.11, 2.22)*
	Stage Unknown	1.62 (1.11, 2.36)*	1.73 (1.20, 2.50)**
History of Condition	No	(Ref)	(Ref)
	Yes	28.94 (21.46, 39.04)***	26.33 (19.62, 35.33)***
History of CVD	No	(Ref)	(Ref)
	Yes	0.63 (0.48, 0.84)**	0.62 (0.46, 0.83)**
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	12.41 (7.29, 21.14)***	10.26 (6.06, 17.36)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
CVC[c]	No	(Ref)	(Ref)
	Yes	3.82 (2.29, 6.38)***	3.88 (2.31, 6.52)***
Chemotherapy	No	(Ref)	(Ref)
	Yes	1.31 (1.02, 1.67)*	1.26 (0.99, 1.62)
Gender	Female	(Ref)	(Ref)
	Male without varicose veins	0.97 (0.78, 1.20)	-
	Male with varicose veins	0.13 (0.04, 0.38)***	-

Note. CVC= central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); Other VTE = other venous thromboembolic event; RCC = renal cell carcinoma.

[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).

[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.

[c] More than 30 days before the outcome.

** $p < .05$. ** $p < .01$. *** $p < .001$.*

The null hypotheses could not be rejected for any of the venous thromboembolic events as at least one factor was associated with the occurrence of a new event after kidney cancer diagnosis. With regards to histology group, the null hypothesis was not rejected for any VTE, except when the model was adjusted by the Charlson comorbidity score. It was also not rejected for pulmonary embolism in either model. The null hypothesis would have been rejected for DVT and other VTEs if only considering histology.

Post-hoc analyses. Because the number of patients with ATEs was larger than expected, models to assess the risk factors associated with these outcomes were produced in the post-hoc analyses. The risk factors associated with any ATE were age of 75 or older at diagnosis, geographic region (Northeast or South versus West), year of diagnosis, history of any ATE, history of CVD, high-risk surgery, placement of CVC,

atherosclerosis, chemotherapy and nephrectomy (Table 33). Receipt of chemotherapy or nephrectomy were associated with a decreased risk of ATE. In the first model, type 1 diabetes and kidney disease were also risk factors for any ATE. In the second model, the risk increased with Charlson comorbidity score (*HR* = 1.97 for a score of 1, *HR* = 3.01 for a score of 2 -3, *HR* = 4.50 for a score of 4 or greater).

Table 33
Risk Factors Associated With Incidence of Any ATE in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	1.05 (0.86 - 1.29)	1.04 (0.85 - 1.28)
	75-79	1.30 (1.06 - 1.58)*	1.27 (1.04 - 1.55)*
	80-84	1.36 (1.10 - 1.69)**	1.32 (1.06 - 1.63)*
	85+	1.53 (1.20 - 1.96)***	1.50 (1.17 - 1.91)**
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	1.00 (0.83 - 1.21)	1.00 (0.83 - 1.20)
	Papillary	0.99 (0.79 - 1.24)	0.99 (0.79 - 1.24)
	Transitional cell tumor	0.75 (0.47 - 1.21)	0.78 (0.48 - 1.26)
Charlson Score	0	(Ref)	(Ref)
	1	-	1.97 (1.43 - 2.72)***
	2 to 3	-	3.01 (2.26 - 4.00)***
	4+	-	4.50 (3.39 - 5.99)***
Geographic Region	West	(Ref)	(Ref)
	Midwest	1.25 (1.03 - 1.52)*	1.19 (0.98 - 1.44)
	Northeast	1.22 (1.04 - 1.44)*	1.20 (1.02 - 1.41)*
	South	1.30 (1.11 - 1.51)**	1.25 (1.07 - 1.45)**
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	1.18 (0.94 - 1.48)	1.18 (0.94 - 1.48)
	Stage III	1.09 (0.91 - 1.30)	1.10 (0.92 - 1.32)
	Stage IV	1.38 (1.11 - 1.71)**	1.44 (1.16 - 1.78)***
	Stage Unknown	1.08 (0.88 - 1.33)	1.10 (0.90 - 1.36)
Year of Diagnosis	(continuous)	1.05 (1.01 - 1.09)*	1.05 (1.01 - 1.09)*
History of Condition	No	(Ref)	(Ref)
	Yes	2.93 (2.31 - 3.71)***	2.99 (2.43 - 3.68)***
History of CVD	No	(Ref)	(Ref)
	Yes	1.30 (1.11 - 1.52)**	-
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	3.97 (3.06 - 5.14)***	3.70 (2.85 - 4.81)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
CVC[c]	No	(Ref)	(Ref)
	Yes	4.31 (3.32 - 5.60)***	4.38 (3.37 - 5.69)***
Type 1 Diabetes	No	(Ref)	(Ref)
	Yes	1.45 (1.24 - 1.71)***	-
Kidney Disease	No	(Ref)	(Ref)
	Yes	1.65 (1.44 - 1.89)***	-
Atherosclerosis	No	(Ref)	(Ref)
	Yes	1.40 (1.23 - 1.60)***	1.26 (1.10 - 1.45)***
Chemotherapy	No	(Ref)	(Ref)
	Yes	0.84 (0.72 - 0.98)*	0.81 (0.70 - 0.95)**
Nephrectomy	No	(Ref)	(Ref)
	Yes	0.76 (0.65 - 0.89)***	0.75 (0.64 - 0.88)***

Note. Any ATE = any arterial thromboembolic event (MI or IS); CVC= central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; MI = myocardial infarction; RCC = renal cell carcinoma.

[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).

[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.

[c] More than 30 days before the outcome.

** $p < .05$. ** $p < .01$. *** $p < .001$.*

The risk factors associated with myocardial infarction were region (Midwest or Northeast where West was the reference), year of diagnosis, stage IV (versus stage I) at diagnosis, history of myocardial infarction, high-risk surgery and placement of CVD (Table 34). Chemotherapy and nephrectomy were protective against myocardial infarction with hazard ratios ranging from 0.75 to 0.77. In the first model, history of CVD, Type 1 diabetes, atherosclerosis, and kidney disease were associated with greater rates of myocardial infarction. In the second model, the hazard ratio increased with increasing Charlson score.

Table 34

Risk Factors Associated With Incidence of MI in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	0.98 (0.76, 1.28)	0.97 (0.75, 1.26)
	75-79	1.01 (0.78, 1.31)	1.01 (0.78, 1.30)
	80-84	1.23 (0.93, 1.62)	1.20 (0.91, 1.58)
	85+	1.36 (0.99, 1.88)	1.35 (0.98, 1.86)
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	1.06 (0.83, 1.36)	1.05 (0.82, 1.35)
	Papillary	1.05 (0.78, 1.41)	1.06 (0.79, 1.42)
	Transitional cell tumor	1.03 (0.60, 1.75)	1.04 (0.61, 1.78)
Charlson Score	0	(Ref)	(Ref)
	1	-	2.63 (1.64, 4.22)***
	2 to 3	-	3.35 (2.18, 5.16)***
	4+	-	6.95 (4.56, 10.59)***
Geographic Region	West	(Ref)	(Ref)
	Midwest	1.40 (1.09, 1.81)**	1.33 (1.03, 1.71)*
	Northeast	1.24 (1.00, 1.54*	1.26 (1.02, 1.55)*
	South	1.17 (0.95, 1.44)	1.12 (0.91, 1.38)
Year of Diagnosis		1.08 (1.02, 1.14)**	1.08 (1.02, 1.14)**
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	1.34 (1.01, 1.80)*	1.31 (0.98, 1.74)
	Stage III	1.07 (0.84, 1.37)	1.08 (0.85, 1.37)
	Stage IV	1.48 (1.11, 1.98)**	1.50 (1.12, 1.99)**
	Stage Unknown	1.13 (0.86, 1.48)	1.14 (0.87, 1.50)
History of Condition	No	(Ref)	(Ref)
	Yes	4.80 (3.55, 6.48)***	5.01 (3.81, 6.60)***
History of CVD	No	(Ref)	(Ref)
	Yes	1.36 (1.12, 1.64)**	-
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	4.99 (3.50, 7.11)***	4.69 (3.27, 6.74)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
CVC[c]	No	(Ref)	(Ref)
	Yes	4.87 (3.40, 6.96)***	5.23 (3.64, 7.51)***
Diabetes Type 1	No	(Ref)	(Ref)
	Yes	1.54 (1.25, 1.89)***	-
Atherosclerosis	No	(Ref)	(Ref)
	Yes	1.24 (1.03, 1.49)*	-
Kidney Disease	No	(Ref)	(Ref)
	Yes	2.30 (1.89, 2.80)***	-
Chemotherapy	No	(Ref)	(Ref)
	Yes	0.77 (0.62, 0.95)*	0.76 (0.61, 0.94)*
Nephrectomy	No	(Ref)	(Ref)
	Yes	0.75 (0.61, 0.93)**	0.76 (0.62, 0.94)*

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); MI = myocardial infarction; RCC = renal cell carcinoma.

[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).

[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.

[c] More than 30 days before the outcome.

** $p < .05$. ** $p < .01$. *** $p < .001$.*

Age at diagnosis 75 years or older, history of ischemic stroke, history of CVD, atherosclerosis, CVC, high-risk surgery and diagnoses in the South region were associated with greater risk of ischemic stroke after kidney cancer diagnosis (Table 35). ischemic stroke occurred less frequently in patients with transitional cell tumors compared to patients with clear cell tumors (*HR* = 0.22 for model 1; *HR* = 0.21 in model 2). The risk of ischemic stroke was also lower in patients who had a nephrectomy compared to patients who did not. In the first model, males with Type 1 were at greater risk of ischemic stroke. In the second model, the risk increased with increasing Charlson score and with Stage IV cancer at diagnosis (compared to Stage I).

Table 35

Risk Factors Associated With Incidence of IS in Follow-up Period After Kidney Cancer Diagnosis (N = 11,463)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
Age at Diagnosis	66-69	(Ref)	(Ref)
	70-74	1.04 (0.78 - 1.39)	1.05 (0.78 - 1.40)
	75-79	1.38 (1.04 - 1.83)*	1.34 (1.01 - 1.78)*
	80-84	1.41 (1.04 - 1.93)*	1.33 (0.98 - 1.82)
	85+	1.68 (1.19 - 2.37)**	1.61 (1.14 - 2.27)**
Histology Group	Clear Cell	(Ref)	(Ref)
	Chromophobe/Other RCC	1.01 (0.78 - 1.31)	1.00 (0.76 - 1.30)
	Papillary	0.97 (0.71 - 1.32)	1.01 (0.74 - 1.38)
	Transitional cell tumor	0.22 (0.05 - 0.87)*	0.21 (0.05 - 0.85)*
Charlson Score	0	(Ref)	(Ref)
	1	-	1.61 (1.04 - 2.49)*
	2 to 3	-	2.83 (1.95 - 4.11)***
	4+	-	3.02 (2.07 - 4.41)***
Geographic Region	West	(Ref)	(Ref)
	Midwest	1.10 (0.84 - 1.46)	1.07 (0.81 - 1.41)
	Northeast	1.05 (0.83 - 1.33)	1.04 (0.82 - 1.31)
	South	1.52 (1.23 - 1.88)***	1.49 (1.20 - 1.84)***
Stage at Diagnosis	Stage I	(Ref)	(Ref)
	Stage II	-	0.96 (0.67 - 1.36)
	Stage III	-	1.17 (0.91 - 1.50)
	Stage IV	-	1.38 (1.02 - 1.87)*
	Stage Unknown	-	1.14 (0.85 - 1.53)
History of Condition	No	(Ref)	(Ref)
	Yes	2.23 (1.48 - 3.36)***	2.44 (1.67 - 3.58)***
History of CVD	No	(Ref)	(Ref)
	Yes	1.29 (1.04 - 1.59)*	-
High-risk surgery[c]	No	(Ref)	(Ref)
	Yes	8.08 (5.34 - 12.21)***	7.82 (5.18 - 11.80)***

(continued)

	Level	Adjusted *HR* (95% *CI*)[a]	Adjusted *HR* (95% *CI*)[b]
CVC[c]	No	(Ref)	(Ref)
	Yes	4.30 (2.76 - 6.70)***	4.05 (2.61 - 6.29)***
Atherosclerosis	No	(Ref)	(Ref)
	Yes	1.57 (1.31 - 1.90)***	1.45 (1.20 - 1.75)***
Type 1 Diabetes	No	(Ref)	(Ref)
	Yes	1.38 (1.10 - 1.74)**	-
Nephrectomy	No	(Ref)	(Ref)
	Yes	0.74 (0.60 - 0.90)**	0.72 (0.58 - 0.90)**

Note. CVC = central venous catheter; CVD = cardiovascular disease (myocardial infarction, ischemic stroke, new onset congestive heart failure, angina or transient ischemic attack); IS = ischemic stroke; RCC = renal cell carcinoma.

[a] Model assessing kidney disease, Type 1 and Type 2 diabetes as a potential confounder or effect measure modifier (EMM).

[b] Model assessing Charlson score as a potential confounder or effect measure modifier (EMM). Kidney disease and diabetes were components of the Charlson score and were not assessed in the model.

[c] Central venous catheter and high-risk surgery were more than 30 days before outcome.

** $p < .05$. ** $p < .01$. *** $p < .001$.*

Summary

After applying inclusion criteria, exclusion criteria, and matching the exposed kidney cancer cohort to the unexposed noncancer cohort, 11,463 patients in each cohort were included in this study. The first descriptive analysis objectives were to describe the incidence rates of venous and arterial thromboembolic events in the exposed cohort. Tables 8 to 14 described the incidence rates of VTEs and ATEs in the year prior to kidney cancer diagnosis in the exposed cohort. The incidence rates varied greatly across type of thromboembolic event. For VTEs, the lowest incidence rate occurred for pulmonary embolism (7.88 per 1,000 p-y) and the highest rate occurred for DVT (21.71 per 1,000 p-y). The incidence rate for any VTE (pulmonary embolism, DVT, or other VTEs) was 35.05 per 1,000 p-y. The incidence rate for myocardial infarction was 16.88

per 1,000 p-y while the rate for ischemic stroke was 76.02 per 1,000 p-y. The incidence rate for any ATE (myocardial infarction or ischemic stroke) was 31,32 per 1,000 p-y. The incidence rates varied across strata and outcome, however consistently the incidence rates were higher in patients who had a history of the condition in the year prior to the period start and increased with increasing Charlson score.

The second objective of the first descriptive analysis was to describe the incidence rates of thromboembolic events in the follow-up period after kidney cancer diagnosis. Tables 15 to 21 describe the incidence rates in this period overall and by patient characteristics and covariates. For any VTE, DVT, and PVT the incidence rates after kidney cancer diagnosis were higher than the rates in the year prior to kidney cancer diagnosis. The incidence rates for other VTE and for myocardial infarction were slightly higher in the follow-up period than in the year prior to kidney cancer diagnosis. The incidence rate for ischemic stroke was lower in the year prior to kidney cancer diagnosis (15.19 per 1,000 p-y) than in the period after kidney cancer diagnosis (19.39 per 1,000 p-y). Similar to the period prior to kidney cancer diagnosis, for each outcome the incidence rate was much higher in patients with a history of the condition in the year prior and increased with increasing Charlson score.

The objective of the second descriptive analysis was to describe the incidence proportions of thromboembolic events in discrete periods after kidney cancer diagnosis. Table 22 to 24 show the incidence rates within 90 days, 91 to 181 days, 181 to 270 days, 271 to 365 days, and for the entire follow-up period. Within the first year after the incidence proportions were highest in the first three months after kidney cancer diagnosis

and decreased in later periods. The incidence proportions were highest for the entire follow-up period.

The first research question modeled the incidence rate ratios for thromboembolic events in the exposed cohort compared to the unexposed cohort in the year prior to index date. Tables 25 and 26 show the results for the crude and adjusted models. For every thromboembolic event except ischemic stroke, the crude hazard ratio was significantly greater than 1.0 at the 0.05 level. After adjusting the models, the incidence rate ratios were greater than 1.0 for any VTE, DVT, and pulmonary embolism. For other VTEs, the incidence rate was higher in the exposed cohort than the unexposed cohort in patients without a history of CVD (*HR* = 1.41, 95% *CI* 1.02 – 1.96) after adjusting for matching, type 2 diabetes and a diagnosis of varicose veins. For any arterial thromboembolic events and ischemic stroke, the adjusted hazard ratios were not statistically different from 1.0.

The second research question modeled the incidence rate ratios for thromboembolic events in the exposed cohort compared to the unexposed cohort in the follow-up period after the index date. Tables 27 and 28 show the results for the crude and adjusted models. The crude incidence rates for venous thromboembolic events in the exposed cohort were three times the incidence rates in the unexposed cohort (Table 27). After adjusting the models, for most patients the incidence rates for VTEs in the exposed cohort were 57% to 542% greater than the rates in the unexposed cohort. For arterial thromboembolic events, the crude hazard ratios ranged from 1.47 to 2.17 and were statistically significant at the 0.05 level (Table 28). After adjusting, the incidence rate ratio for the exposed cohort was only statistically different from 1.0 for any ATE for

patients without atherosclerosis and without kidney disease (*HR* = 1.47, 95% *CI* 1.21 – 1.79); and without atherosclerosis (*HR* = 1.27, 95% *CI* 1.08 – 1.49) in the second model adjusted for the Charlson score and other factors. For myocardial infarction, the adjusted incidence rate ratio was greater than 1.0 in patients without atherosclerosis and without history of myocardial infarction (*HR* = 1.42, 95% *CI* 1.10 – 1.84) in the first model; in the second model, the incidence rate ratio was greater than 1.0 in patients without history of myocardial infarction (*HR* = 1.35, 95% *CI* 1.11 – 1.65). In patients with a history of myocardial infarction, the incidence rate ratio was 0.05 or less in both models (Table 28). For ischemic stroke, the adjusted incidence rate ratio was statistically greater than 1.0 in patients without kidney disease in the first model (*HR* = 1.34, 95% *CI* 1.06-1.70). The incidence rate ratio was 0.52 for patients with kidney disease. In the second model, patients with atherosclerosis had an adjusted hazard ratio of 0.55 (95% *CI* 0.34 – 0.90) which was statistically significant at the 0.05 level (Table 28).

Research question 3 assessed potential risk factors for venous thromboembolic events in kidney cancer patients after kidney cancer diagnosis. Histology group was only statistically significantly associated with incidence of pulmonary embolism (Table 31). Placement of a CVC, Stage III, and Stage IV tumors at diagnosis were risk factors for any VTE, DVT, pulmonary embolism, and other VTEs. Other characteristics were not consistent risk factors across the types of venous thromboembolic events.

Due to sufficient numbers of patients with myocardial infarction and ischemic stroke, the risk factors for these arterial thromboembolic events were also assessed (Tables 33 to 35). Increasing Charlson score, history of condition, placement of CVC,

high-risk surgery, and Stage IV tumors at diagnosis were risk factors for any ATE, myocardial infarction, and ischemic stroke. Nephrectomy appeared protective against the arterial outcomes.

The incidence rates and risk factors for venous and arterial thromboembolic events differed by each type of event as well as demographic and patient characteristics in kidney cancer patients. In the year prior to index date, the incidence rates were higher for the exposed cohort than the unexposed cohort for any VTE, DVT, and pulmonary embolism. For other VTEs and myocardial infarction the incidence rates for the outcomes were higher in the exposed cohort than the unexposed cohort in patients without a history of CVD. In the follow-up period after index date, the incidence rates were higher in the exposed cohort than the unexposed cohort for all of the venous thromboembolic events; but the relationship was less consistent for the arterial thromboembolic events. In chapter 5, I discuss the interpretations of the findings, the limitations of the study, recommendations for future study, and the implications for positive social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to describe the incidence rates of venous and arterial thromboembolic events in elderly kidney cancer patients; describe incidence proportions of thromboembolic events in elderly kidney cancer patients in the period following cancer diagnosis; compare the incidence rates of thromboembolic events in elderly kidney cancer patients to matched noncancer patients in the year prior to index date and in the follow-up period after index date; and assess risk factors for venous thromboembolic events in elderly kidney cancer patients after cancer diagnosis. Because there were sufficient number of patients with myocardial infarction and ischemic stroke, risk factors for those arterial thromboembolic events in elderly kidney cancer patients were also assessed as post-hoc analyses. I conducted a retrospective cohort study using linked cancer registry and administrative claims data in elderly patients with Medicare coverage to achieve the study objectives. Use of the linked database provided population-based data containing cancer-specific information including histology type and stage along with demographic, treatment, outcome, and potential confounder information.

The incidence rates of VTEs and ATEs differed by patient and tumor characteristics in the period before and period after kidney cancer diagnosis. In the period after cancer diagnosis, the incidence rates for most thromboembolic events were higher than in the year prior to the cancer diagnosis. Within the first year after cancer diagnosis, the incidence proportions were highest in the first three months for each thromboembolic

event (Tables 22 to 24). It was hypothesized that the incidence rates of VTEs and ATEs in the kidney cancer patients would be higher than rates in the noncancer patients. In the year prior to the index date, the null hypothesis could not be rejected for any VTE, DVT, or pulmonary embolism. The incidence rates for these outcomes were higher in kidney cancer patients than in the noncancer patients in the year prior to the index date. In the period after the index date, the null hypothesis could also not be rejected for any VTE, DVT, or pulmonary embolism. For these outcomes, the incidence rates were higher in the kidney cancer patients than in the noncancer patients in the follow-up period after the index date. Several factors were identified which affected the risk of VTEs or ATEs after kidney cancer diagnosis. This chapter interprets the findings for each of the descriptive analyses and research questions, describes the study limitations, and provides recommendations for further research. The implications for positive social change are discussed and the study conclusion stated.

Interpretation of the Findings

Descriptive Analysis 1

The year prior to kidney cancer diagnosis. The incidence rates of DVT, pulmonary embolism, and other VTEs in the year prior to kidney cancer diagnosis were 21.7, 7.9 and 11.3 per 1,000 p-y, respectively (Tables 9 to 11). These rates are much lower than the rates for RCC patients reported by Connelly-Frost et al. (2013) of 32.2, 8.0, and 23.7 per 1,000 p-y in their analysis of RCC patients diagnosed between 1991 and 2003. Walker et al. (2013) reported that the incidence rates for venous thromboembolic events in cancer patients have been increasing since 1997. Since the patients in this study

were diagnosed with kidney cancer in later years than patients in the Connelly-Frost et al. (2013) study, it would have been expected for the incidence rates to be higher than previously reported, not lower. The inclusion of other kidney cancer histology groups does not explain the difference in rates. One possible reason for the lower incidence rates is that possible invalid diagnoses or rule-out diagnoses were removed from the analysis data prior to identifying the outcomes and comorbid conditions. Diagnoses were included if they were on inpatient claims, or there were at least two different physician or outpatient claims that were more than 30 days apart. The program to do this was publically available from the SEER-Medicare web site (http://healthcaredelivery.cancer.gov/seermedicare/program/comorbidity.html). Connelly-Frost et al. (2013) did not apply these exclusions to the claims data. If those exclusions had not been applied, the incidence rates for DVT, pulmonary embolism, and other VTEs were 39.1, 11.5, and 19.2 per 1,000 p-y, respectively. Those rates are more similar to those reported by Connelly-Frost et al. (2013) in the 12 months prior to the cancer diagnosis.

The incidence rates for any ATE (myocardial infarction or ischemic stroke), myocardial infarction, and ischemic stroke in the year prior to cancer diagnosis were 31.3, 16.9, and 15.2 per 1,000 p-y (Tables 12 to 14). The incidence rates for these conditions in kidney cancer patients prior to the cancer diagnosis were not identified in the published literature. For Medicare beneficiaries, the incidence rates of hospitalization for acute myocardial infarction decreased from 10.2 per 1,000 p-y in 2004 to 8.7 per 1,000 p-y in 2007 (Chen et al., 2010). The incidence rate of 16.9 per 1,000 p-y for

myocardial infarction from this study is higher than the incidence rate for acute myocardial infarction in Medicare patients in general, which is not surprising as the definition of myocardial infarction used for this study was not restricted to only acute events.

The incidence rate for ischemic stroke in cancer patients in this study (15.2 per 1,000 p-y) was higher than the rate of ischemic stroke in the general Medicare population. The annual incidence rate for ischemic stroke in Medicare beneficiaries in 2008 was 11.5 per 1,000 (Casper, Nwaise, Crost, & Nilasena, 2008).

The follow-up period after kidney cancer diagnosis. The incidence rate of DVT in the follow-up period after kidney cancer diagnosis, 53.0 per 1,000 person-years (Table 15), was higher than the rate of any VTE (14.0 per 1,000 person-years) reported by Walker et al. (2013) but less than the rate for DVT of 108.2 per 1,000 person-years reported by Connelly-Frost et al. (2013). Part of the reason for the discrepancy was differences in methodologies used including not excluding patients with a history of the condition, use of entire follow-up period even if longer than 12 months, and removing potential rule-out diagnoses prior to calculating the incidence rates. Walker et al. (2013) excluded patients with a VTE prior to cancer; however, the incidence rate in patients without a history of any VTE was 42.75 (Table 15) which is still much higher than the rate reported by Walker et al. (2013). One difference is that only 12 months prior to the study period of interest were included for identifying history of VTE, whereas Walker et al. (2013) excluded patients if they had a VTE any time prior to the first cancer diagnosis. The difference in the period prior to cancer diagnosis which was assessed for history of

VTE may be a contributing factor for the differences in reported incidence rates. Another factor may be this study population included American patients whereas Walker et al. (2013) reported rates in patients in the United Kingdom. Walker et al. (2013) reported an incidence rate of 4.3 per 1,000 p-y for VTEs in the noncancer cohort age 60 or older. The incidence rates for VTEs in a U.S. population by age group ranged from 1.69 to 8.49 per 1,000 p-y for females, and 1.63 to 9.84 per 1,000 p-y for males (Silverstein et al., 1998). Both Walker et al. (2013) and I allowed for follow-up periods of longer than 12 months. Connelly-Frost et al. (2013) included patients with a history of VTE prior to cancer diagnosis but restricted follow-up to 12 months. Without the rule-out diagnosis exclusion applied, the incidence rates for DVT, pulmonary embolism, and other VTEs in the follow-up period after cancer diagnosis were 66.5, 21.7, and 27.7, respectively as compared to 108.2, 30.0, and 49.0 as reported by Connelly-Frost et al. (2013). The combination of the removal of the rule-out diagnoses and the longer follow-up period is the probable reason for the lower incidence rates in this study as compared with Connelly-Frost et al. (2013).

The incidence rates of any ATE, myocardial infarction, and ischemic stroke were 39.7, 21.9, and 19.4 per 1,000 p-y, respectively (Table 19 to Table 21). These incidence rates were higher than expected based on the literature found, however that may be due to differences in the real world population included in this study and clinical trial populations. Arterial events were rare in clinical trial patients of chemotherapy-treated RCC patients (Bayer HealthCare Pharmaceuticals, 2013; Choueiri et al., 2010; GlaxoSmithKline, 2014; Qi et al., 2014). Ischemic stroke was not included in the

definition of ATE for several studies (Choueiri et al., 2010; Petrelli et al., 2012). The number of clinical trial participants was small compared to this population-based study, include stricter inclusion and exclusion criteria for the study participants, and were not restricted solely to elderly patients with Medicare coverage.

Descriptive Analysis 2

The incidence proportions of venous thromboembolic events were higher in the period closest to cancer diagnosis then decreased in later periods. These findings were consistent with other published studies (Chew et al., 2008; Connelly-Frost et al., 2013; Moore et al., 2011; Walker et al., 2013). None of these studies reported the incidence proportions for the entire follow-up period so that could not be compared. Incidence proportions of arterial thromboembolic events in cancer patients were not identified in the published literature.

Research Question 1

The incidence rate ratios estimates for DVT and pulmonary embolism in the year prior to the index date were not dissimilar from the relative risks presented by Connelly-Frost et al. (2013). Connelly-Frost et al. (2013) reported a relative risk of 1.6 (95% *CI* 1.3 – 1.9) for DVT, while the two models in this study estimated the incidence rate ratio to be 1.50 to 1.57 (Table 25). Connelly-Frost et al. (2013) reported a relative risk of 1.8 (95% *CI* 1.3 – 2.6) for pulmonary embolism; the estimates from this study were 1.5 and 1.8 (Table 25). I did not find a statistically significant difference in the incidence rate ratios for other VTEs after adjusting for other factors (Table 28), however Connelly-Frost et al. (2013) reported a relative risk of 1.5 (95% *CI* 1.2 – 1.8). Both studies reported the

incidence rate ratios for other VTEs stratified by history of CVD. The incidence rate ratio was higher in cancer patients than the noncancer patients for patients without a history of CVD. Connelly-Frost et al. (2013) reported 1.7 (95% *CI* 1.3 – 2.1) and this analysis resulted in an incidence rate ratio of 1.4 (95% *CI* 1.0 – 2.0) (Table 25). Neither study found a significant difference in the incidence rates for the patients with a history of CVD (*HR* = 0.8, 95% *CI* 0.4 – 1.8 from this study; *OR* = 1.0, 95% *CI* 0.7 – 1.4 from Connelly-Frost et al., 2013).

The incidence rate ratios estimated in this study for venous thromboembolic events were in the same direction, but lower than the standardized incidence ratio reported for kidney cancer patients diagnosed in California. White et al. (2005) reported a standardized incidence ratio of 2.5 (95% *CI* 1.5 – 3.9) for the year prior to cancer diagnosis. The difference in the estimates may be due to the differences in the populations as the White et al. (2005) study analyzed adults aged 18 or older diagnosed with cancer in California prior to 2000. The participants in this study were 66 years or older at first cancer diagnosis, more geographically distributed and diagnosed in later years. Another difference is in the measures used by the two studies. While White et al. (2005) calculated a standardized incidence ratio, I calculated hazard ratios to estimate incidence rate ratios.

No studies were found in the published literature of the incidence rate ratios of myocardial infarction or ischemic stroke comparing kidney cancer cohort to a noncancer cohort in the year prior to the index date. After adjusting for other factors, the incidence rates of any ATE and ischemic stroke were not statistically significantly different

between the two cohorts. For myocardial infarction the incidence rates were higher in the kidney cancer cohort than the noncancer cohort in the patients without a history of CVD. Conversely, in patients with a history of CVD the first model (which assessed diabetes and kidney disease instead of the Charlson score as potential confounders and effect measure modifiers) found that the incidence rates were lower in the kidney cancer patients. The second model, which adjusted by the Charlson score, produced a hazard ratio of 1.18; however it was not statistically significant at the 0.05 level. This is consistent with the findings of lung cancer patients in the Netherlands who did not have a statistically significant increased incidence of myocardial infarction or ischemic stroke in the year prior to cancer diagnosis (van Herk-Sukel et al., 2013). While the incidence rates of ATEs may be higher in cancer patients than in the general Medicare population, it does not appear that kidney tumors are the reason for the higher rates. Other factors in the cancer population such as comorbidity score are more likely the drivers for the incidence rates of ATEs in this population.

Research Question 2

The incidence rate ratios for venous thromboembolic events in the follow-up period after index date were higher in the kidney cancer cohort than the noncancer cohort (Table 27). Blom et al. (2005) also reported a higher risk of VTE after kidney cancer diagnosis compared to noncancer patients (adjusted *OR* = 6.2, 95% *CI* 0.8 – 46.5), even though it was not statistically significant at the 0.05 level. Connelly-Frost et al. (2013) reported higher incidence rate ratios in the cancer cohort than the noncancer cohort for DVT (*HR* = 3.6), pulmonary embolism (*HR* = 4.3), and other VTE (*HR* = 2.4). I found

higher incidence rates of DVT in the cancer cohort than noncancer cohort in patients without atherosclerosis (*HR* = 3.6, 95% *CI* 2.9 – 4.4) and with atherosclerosis (*HR* = 1.8, 95% *CI* 1.1 – 2.7) (Table 27). The first model in this study included higher incidence rates in the cancer cohort except for those with both atherosclerosis and kidney disease (Table 27). Although Connelly-Frost et al. (2013) restricted their maximum duration of follow-up to 12 months, their study similarly reported higher incidence rates for DVT in the cancer cohort stratified by atherosclerosis (*HR* = 2.0, 95% *CI* 1.5 – 2.6 for patients with atherosclerosis; *HR* = 4.1, 95% *CI* 3.5 – 4.9 for patients without atherosclerosis) (Connelly-Frost et al., 2013).

The incidence rate ratio for pulmonary embolism was approximately three fold higher in the kidney cancer patients than the noncancer cohort (Table 27). Connelly-Frost et al. (2013) reported a hazard ratio of 4.3 (95% *CI* 3.2 – 5.7) for pulmonary embolism in the year after index date. The incidence rate ratio for other VTE was higher for the cancer cohort as well. The second model yielded an adjusted hazard ratio of 2.7 (95% *CI* 2.1 – 3.4) (Table 27). The hazard ratio for other VTE reported by Connelly-Frost et al. (2013) was very similar (*HR* = 2.4, 95% *CI* 2.0 – 2.8). The first model reported higher incidence rates in the cancer cohort for patients without type 2 diabetes and without kidney disease (*HR* = 4.3, 95% *CI* 2.9 – 6.4). There was a two-fold increase for patients with only one of kidney disease or type 2 diabetes, but the result was only statistically significant for patients without kidney disease (Table 27).

In the follow-up period after the kidney cancer diagnosis, the results for arterial thromboembolic events were inconsistent as to whether they were higher for the cancer

cohort. For any ATE, the first adjusted model yielded an adjusted hazard ratio of 1.5 for patients without atherosclerosis and without kidney disease (Table 28). For patients with both atherosclerosis and kidney disease, the adjusted hazard ratio was 0.6. The second model similarly reported an adjusted hazard ratio greater than 1.0 for patients without atherosclerosis (*HR* = 1.3), but a lower hazard ratio of 0.77 for patients with atherosclerosis. For myocardial infarction, the incidence rate for the cancer cohort was higher than the noncancer cohort for patients without a history of atherosclerosis or history of myocardial infarction (the first model) or patients without a history of myocardial infarction (second model). For ischemic stroke, the incidence rates were higher in the cancer cohort in patients who did not have kidney disease; incidence rates were lower in the cancer cohort in patients with kidney disease. After adjusting for the comorbidity score and other factors, the incidence rates of ischemic stroke were similar for the cancer and noncancer cohorts in patients without atherosclerosis (Table 28). For patients with atherosclerosis, the incidence rate for ischemic stroke was lower in the cancer cohort after adjusting for the Charlson comorbidity score and other factors (*HR* = 0.6) (Table 28). The incidence rates for ATEs in cancer patients were higher than noncancer patients in the absence of atherosclerosis and kidney disease. In patients with atherosclerosis and kidney disease, the incidence rates of ATEs in cancer patients were half or less than the rates in noncancer patients. Cancer patients with more chronic conditions have greater healthcare utilization, including more primary care or specialist visits and hospitalizations, than cancer patients with less chronic conditions (Legler, Bradley, & Carlson, 2011; Yu, Ravelo, Wagner, & Barnett, 2004; Zulman et al., 2015).

Timing may also be a factor in whether or not the incidence rates were higher in cancer patients compared to noncancer patients. The hazard ratios for myocardial infarction and for ischemic stroke comparing lung cancer to noncancer patients were 1.0 or greater in the first six months after cancer diagnosis, but less than 1.0 for more than six months after diagnosis (van Herk-Sukel et al., 2011).

Research Question 3

Age was a risk factor for some venous thromboembolic events in the follow-up period after kidney cancer diagnosis. Age of 80 or older increased the risk of any VTE and DVT in kidney cancer patients compared to ages 66 to 69 at diagnosis (Tables 29 to 30). For other VTEs, only age of 75 to 79 increased the risk of the event while age 80 or older at diagnosis was not a statistically significant predictor (Table 32). For pulmonary embolism, the risk of event decreased with increasing age at diagnosis (Table 31). Chew et al. (2006) nor Connelly-Frost et al. (2013) found age to be a statistically significant predictor for venous thromboembolic events in kidney cancer or elderly RCC patients. The differences in the study populations and duration of follow-up after cancer diagnosis may be the reasons some association with age was reported from this analyses but Chew et al. (2006) did not find the same association. Where age was assessed by 5-year age increments in this study and the population was elderly patients, the population studied by Chew et al. (2006) included patients of all ages and was younger (median age of 64 years). Chew et al. (2006) also looked for an association of venous thromboembolic events in the 12 months after cancer diagnosis with 10-year age increments. I did not restrict follow-up after cancer diagnosis to a maximum of 12 months. Connelly-Frost et

al. (2013) also assessed age as a risk factor in the 12 months after cancer diagnosis. I and Connelly-Frost et al. (2013) used the same 5-year age increments; however this study reported very different incidence rates due to the differences in duration of follow-up and use of the algorithm to remove potential rule-out diagnoses as discussed earlier. The percent changes in incidence rates from the 66 to 69 year olds to the 85 years or older in the Connelly-Frost et al. (2013) study were 38%, 2%, and 58% for DVT, pulmonary embolism, and other VTEs respectively. The percent changes for the incidence rates in this study were 99%, 24%, and 62%. So I may have found some association with age even though Connelly-Frost et al. (2006) did not due to the differences in the observed incidence rates and the pattern of rates by age group. Age was also not a risk factor for pulmonary embolism in lung cancer patients in the first six months after lung cancer diagnosis (van Herk-Sukel et al., 2013). However, age of 65 years or older at diagnosis was associated with higher risk of myocardial infarction and ischemic stroke in lung cancer patients compared to lung cancer patients less than 65 years old (van Herk-Sukel et al., 2013).

Research on the risk of venous thromboembolism by histology group in kidney cancer patients was not found in the published literature. Histology was not a statistically significant risk factor for DVT or other VTEs in elderly kidney cancer patients (Tables 30 and 32). The risk of any VTE was lower in transitional cell tumors compared to patients with clear cell tumors (Table 29). The hazard ratio from the second model (0.70) was very similar to the hazard ratio from the first model (0.67), however it was not statistically significant at the 0.05 level. Transitional cell tumors also appeared protective

against pulmonary embolism as well, with hazard ratios of 0.28 to 0.30. The risk of pulmonary embolism was increased in patients with papillary tumors as compared to clear cell tumors (Table 31). This is the first known study to examine this relationship in kidney cancer patients. This is the first evidence of any difference in risk of venous and thromboembolic events by histology type in kidney cancer patients. In other tumors, any difference in risk of thromboembolic events by histology type is inconsistent (Alcalay et al., 2006; Blom et al., 2004; Chew et al., 2007, 2008; Matsuo et al., 2015; van Herk-Sukel et al., 2013). The findings from this study of elderly kidney cancer patients suggests that the thromboembolism preventive measures or care for these patients do not need to differ based on histology type.

Compared to patients with Stage I tumors at diagnosis, patients diagnosed with Stage III or IV were at higher risk of any VTE, DVT, pulmonary embolism, and other VTEs (Tables 29 to 32). Unknown and unstaged tumors also increased the risk for any VTE, DVT and other VTEs, but not pulmonary embolism. Connelly-Frost et al. (2013) also found that later stage (regional or distant) tumors increased the risk of venous thromboembolism compared to localized tumors in elderly RCC patients. Other studies also reported higher risk of venous thromboembolic events in patients with metastatic or Stage IV tumors of other cancer types (Agnelli et al, 2006; Blom et al., 2005; Chavez-MacGregor et al., 2011; Hall et al., 2009).

History of the event in the 12 months prior to kidney cancer diagnosis was a significant risk factor for all types of venous thromboembolic events. The hazard ratios ranged from 14.08 for any VTE (first model, Table 29) to 38.08 for pulmonary embolism

(first model, Table 31). These estimates consistent with the findings but higher than reported by previous studies (Agnelli et al., 2006; Connelly-Frost et al., 2013). Conversely, history of cardiovascular disease decreased the risk of any VTE and of other VTEs (Tables 29 and 32). As discussed below for the post hoc analysis, history of CVD increased the risk for any ATE, myocardial infarction and ischemic stroke (Tables 33 to 35). One hypothesis as to why history of CVD would decrease the risk of VTEs is that those patients were more likely to die before having a venous event. Alternatively, the patients with a history of CVD may have been given medical therapy or therapeutic lifestyle changes as secondary prevention of coronary artery disease. These secondary prevention techniques include smoking cessation, physical activity regimens, dietary modification, weight management and pharmacologic treatments (Hall & Lorenc, 2010). These techniques may improve patient health and reduce the risk of not only coronary artery disease but also thromboembolic events. However, assessing that hypothesis is beyond the scope and capabilities of this study methodology. Additionally, as cardiac surgeries is one type of surgical procedure which can increase the risk of thromboembolic events, the healthcare provider may be more likely to give cardiac surgery patients prophylactic therapy or keep the patients under closer observation for thromboembolic events.

Nephrectomy decreased the risk of pulmonary embolism, but was not a risk factor for the other venous thromboembolic events (Table 31). Connelly-Frost et al. (2013) did not find nephrectomy to be a risk factor for any venous thromboembolic event, but the incidence rates were lower in patients who had a nephrectomy. Researchers of other

tumor types also reported that cancer-directed surgery was not associated with venous thromboembolic events after adjusting for other factors (Blom et al., 2006; Hall et al., 2009). I also found that nephrectomy was protective against any ATE, myocardial infarction, and ischemic stroke. One researcher reported that cancer-directed surgery in lung cancer patients was not associated with myocardial infarction or ischemic stroke (van Herk-Sukel et al., 2013). However, cancer-directed surgeries for different tumor types vary in body system affected, in type of surgery, and invasiveness. Thus, even though the findings from this study are consistent with findings in other tumor types, the comparison of findings across tumor types may not be appropriate.

Chemotherapy however increased in the risk of all types of venous thromboembolic events in this study (Tables 29 to 32). This is consistent with the finding by Connelly-Frost et al. (2013) for DVT and other VTEs, but the Connelly-Frost et al. (2013) study did not find chemotherapy to be a risk factor for pulmonary embolism. The difference in findings may be due to different chemotherapy treatments used to treat RCC and kidney cancer patients prior to 2004. Chemotherapy was protective against any ATE and myocardial infarction. A study of lung cancer patients found no association between receipt of chemotherapy and myocardial infarction or ischemic stroke (van Herk-Sukel et al., 2013). Doyle et al. (2005) also did not find an association between receipt of chemotherapy and myocardial infarction in a study of elderly breast cancer patients.

High-risk cardiac and vascular surgeries were not risk factors for DVT, but greatly increased the risk for pulmonary embolism and for other VTEs (Tables 30 to 32). High-risk surgery was a risk factor for any VTE in males compared to females, but the

result was not statistically significant (Table 29). Compared to females, men without high-risk surgery were at lower risk of any VTE (Table 29). Placement of a central venous catheter before an event significantly increased the risk of all venous thromboembolic events by 3.8 to 9-fold (Tables 29 to 32). These findings are the opposite of those reported by Connelly-Frost et al. (2013) where high-risk surgery or CVC before an event was a protective factor. The Chavez-MacGregor et al. (2011) study reported higher risk of VTEs in the year after breast cancer diagnosis with placement of a CVC. It is unclear why I found results the opposite of the Connelly-Frost et al. (2013) study. However, similar to other findings of this study which contradicted the results of the Connelly-Frost et al. (2013) study, the answer may lie in the difference in the follow-up period and the removal of the potential rule-out diagnoses.

A Charlson score of two or greater, compared to a Charlson score of zero, was a risk factor for any VTE, DVT, and pulmonary embolism (Tables 29 to 31). For these events, in the first model which assessed diabetes and kidney disease instead, kidney disease increased the risk of the event however type 1 diabetes decreased the risk. Type 2 diabetes was not a statistically significant risk factor for any of the venous thromboembolic events. The increased risk of DVT due to kidney disease is consistent with Connelly-Frost et al. (2013); however the risk of DVT was higher in patients without kidney disease. The risk of pulmonary embolism and other VTEs was not increased in patients with kidney disease (Connelly-Frost et al., 2013).

I reported differences in the risks of any VTE and DVT by race and differences of thromboembolic event risks (other than pulmonary embolism) by geographic region.

Neither race, year of diagnosis, nor geographic region was reported to be statistically significant predictors of venous thromboembolic events in the study by Connelly-Frost et al. (2013). Several researchers adjusted for race and did not report the risk for events by racial groups (Chew et al., 2006; Doyle et al., 2005; Moore et al., 2011).

A diagnosis of varicose veins was a risk factor for DVT in the Connelly-Frost et al. (2013) study and in this study (Table 30). A varicose veins diagnosis was also a risk factor in this study for any VTE (Table 29). Similar to Connelly-Frost et al. (2013), male gender was protective against DVT and pulmonary embolism (Tables 30 to 31). One model in this study also found that male gender was protective against other VTEs, however only in male patients with a diagnosis of varicose veins (Table 32). When an association is found, the presence of varicose veins and male gender are generally found to increase the risk of thromboembolic events in cancer patients compared to patients without varicose veins and female gender, respectively (Khorana & Connolly, 2009; Konigsbrugge et al., 2013). However, I and Connelly-Frost et al. (2013) reported opposite findings for an association with gender. The unexpected finding of lower risk of any VTE in males with varicose veins may be an artifact of the study population or the model. Further research will be needed to determine whether the result can be replicated.

Post-hoc Analysis

As the number of any ATE, myocardial infarction, and ischemic stroke were higher than expected, the risk factors for these events were also assessed. Kidney cancer patients with age at diagnosis of 70 or older were at higher risk of any ischemic stroke than patients aged 66 to 69 at diagnosis (Table 35). Patients in age groups 75 and older

were at increased risk for any ATE (myocardial infarction or ischemic stroke) (Table 33). Increased risk for ischemic stroke in the older cancer patients is consistent with studies in other cancer types (Chen et al., 2011; van Herk-Sukel et al., 2011, 2013). Although I did not find age to be a statistically significant risk factor for myocardial infarction, another researcher and colleagues reported increased risk for myocardial infarction in older cancer patients (van Herk-Sukel et al., 2011, 2013).

Patients with transitional cell tumors were at decreased risk for ischemic stroke compared to patients with clear cell tumors (Table 35). Histology group was not at risk factor for myocardial infarction or any ATE. van Herk-Sukel et al. (2013) found that the subtype of lung cancer did not increase the risk for myocardial infarction or ischemic stroke. However, the histology types were specific to lung cancer and are not generalizable to the histology groupings for kidney cancer.

Patients with a history of the arterial event were at greater risk for any ATE, myocardial infarction and ischemic stroke (Tables 33 to 35). This finding is consistent with the findings in lung cancer patients as reported by van Herk-Sukel et al. (2013). A history of CVD was also still an independent risk factor for these arterial events after adjusting for history of the event and other factors.

Patients with Stage IV tumors at diagnosis, Charlson score of one or greater, had a diagnosis of atherosclerosis, a diagnosis of kidney disease, or who had a CVC inserted were also at higher risk for any ATE, myocardial infarction, and ischemic stroke (Tables 33 to 35). Geographic region other than the West was a risk factor for myocardial infarction and any ATE. Patients in the Midwest and Northeast were at higher risk for

myocardial infarction (Table 34). Patients in the Northeast were also at higher risk for any ATE (Table 33). Males were at higher risk than females for any ATE and ischemic stroke if they also had a diagnosis of diabetes or high-risk surgery (Tables 33 and 35). Nephrectomy was protective against myocardial infarction or any ATE in kidney cancer patients (Tables 33 to 34). Chemotherapy was protective against myocardial infarction as well (Table 34).

Theoretical Framework

The advanced epidemiologic triangle as described by Merrill (2009) was the theoretical framework used to interpret the association between incident VTEs and ATEs with causative factors, environment and lifestyle factors, and population characteristics. In this study, the causative factors were kidney cancer, cancer stage and cancer treatments. The environment and lifestyle factors were high-risk surgeries and placement of central venous catheter. The population characteristics were age, region of diagnosis, race, Charlson comorbidity score and individual comorbidities. Time is also considered in the advanced epidemiologic triangle.

The first research question examined the incidence rate ratios of thromboembolic events in cancer patients compared to noncancer patients in the year prior to the index date. In the advanced epidemiologic triangle used for this study, being diagnosed with kidney cancer was a causative factor. Because this time period is prior to diagnosis, the framework seemed to suggest that there should not be any difference in incidence rates of thromboembolic events in the cancer patients and noncancer patients. However, the patients who will be diagnosed with cancer most likely had cancer in this period but it

was not diagnosed yet. Kidney cancer can be asymptomatic and there are no routine screening tests specific for kidney cancer (American Cancer Society, 2014). Thus, the framework is still applicable during this period and the findings of increased incidence of any VTE, DVD, and pulmonary embolism in the cancer cohort are not inconsistent with the framework (Table 25).

The second research question examined the incidence rate ratios of thromboembolic events in the follow-up period after the index date. The incidence rates of events were higher in the cancer patients than the noncancer patients (Tables 27 and 28). This finding is consistent with the theoretical framework as kidney cancer diagnosis and cancer characteristics were characterized as causative factors. The incidence rate ratios differed by the diagnosis of other comorbidities, and the environmental and other population characteristics were statistically significant confounders in most of the models.

The third research question was analyzed in the cancer patient cohort only. Other than the cancer itself, the causative factors included cancer stage and treatments. Stage, particularly late stage, and chemotherapy were associated with increased risk of venous thromboembolic events (Tables 29 to 32). Nephrectomy, another cancer treatment, was associated with a decreased risk of pulmonary embolism (Table 31). The population characteristics and environment and lifestyle factors including older age, comorbidities, geographic region, race, and history of other conditions also impacted the risk of venous thromboembolic events.

In each research question, the effect of cancer diagnosis differed by type of thromboembolic event, comorbidities (i.e., population factors), high-risk surgery and placement of central venous catheter (i.e., environment and lifestyle factors). The differences in findings across the three research questions suggest that within the framework the relationships of the factors to the events may be different for venous and arterial events. Before the index date, the incidence rates of most venous thromboembolic events were higher in cancer patients than noncancer patients, but that was not the case for ischemic stroke. After the index date, the incidence rates of venous thromboembolic events were higher in the kidney cancer patients, while they were higher in arterial thromboembolic events but only in patients without certain comorbidities (Tables 25 to 28). Within the kidney cancer patient cohort receipt of chemotherapy increased the risk of venous thromboembolic events, whereas it was protective for myocardial infarction and not statistically significant for ischemic stroke (Tables 29 to 35). Future frameworks developed for studies of venous and arterial thromboembolic events in cancer patients may benefit from developing two frameworks which model differences in the relationships of factors such as chemotherapy and outcome.

Limitations of the Study

The main limitation of this study as discussed in chapters 1 and 3 are that there are potential confounders and other factors which we cannot measure such as smoking status, platelet counts, lab values of other conditions, or severity of conditions. That data is simply not available in the administrative claims database utilized for this study. The advantages of using the SEER-Medicare database are that it is population-based, has a

large sample size, and contains high-quality and detailed cancer data. For the objectives of this study, these advantages outweigh the limitations of the unmeasured factors. Another limitation is that the study is limited to the diagnoses and procedures indicated in the claims data. Conditions, procedures, and medications which were not submitted and reimbursed by Medicare were missed. Although rule-out diagnoses were removed as much as possible, it is still possible that some rule-out diagnoses or diagnoses which were follow-up visits were included in the study data. Conversely, some legitimate diagnoses and procedures may have been removed during the data cleaning process. Other studies of thromboembolic events in cancer patients which use administrative claims databases have similar limitations.

Recommendations

I reported incidence rates, incidence proportions and risk factors for venous and arterial thromboembolic events in elderly kidney cancer patients and incidence rate ratios for the events comparing the cancer cohort to a matched noncancer cohort. New contributions to the research include incidence rates stratified by histology type, assessment of histology group as a risk factor for thromboembolic events, incidence rates and proportions for myocardial infarction and ischemic stroke, and assessment of risk factors for arterial thromboembolic events in kidney cancer patients. Future studies should include assessment of kidney cancer histology type as a risk factor for venous and arterial thromboembolic events in other populations and age groups. Given the incidence rates of myocardial infarction and ischemic stroke were as high as incidence rates of venous thromboembolic events and these outcomes can impact patient quality of life and

patient prognosis; more studies are needed of myocardial infarction and ischemic stroke in cancer patients of all cancer types including kidney cancer.

Differences in cancer stage at diagnosis, healthcare utilization, and cancer survival have been shown in studies of different cancer types within the United States (Farkas, Greenbaum, Singhal, & Cosgrove, 2012; Niu, Roche, Pawlish,& Henry, 2013; Ward et al., 2008). Thus the findings from this study, which used a Medicare population who did not participate in a managed care plan, may not apply to the elderly who have different insurance coverage or are uninsured. It would be beneficial to determine whether these findings and relationships would be found in kidney cancer patients with other insurance coverage and in different age groups. If the associations between factors and thromboembolic events are different for patients with payers other than Medicare, who have a Medicare managed-care plan, or who are nonelderly; then applying the evidence generated by this study could lead to sub-optimal care and risk assessment for these other patient groups.

The difference in risk by age group across thromboembolic event type was unexpected, and in future studies, risk factors for venous thromboembolic events should be assessed for any VTE as well as each VTE individually. By conducting studies which just report findings for the group of thromboembolic events, differences in trends and risk factors may be missed or incorrectly generalized to each individual event.

In general, the models performed similarly when using the Charlson score versus using kidney disease and diabetes variables individually. Future studies may reasonably

use the Charlson score instead of running separate models which include the selected conditions which are components of the Charlson comorbidity score.

Implications for Positive Social Change

The findings from study have several implications for positive social change. Better understanding of the factors which affect the risk of venous and arterial thromboembolic events can inform patients and healthcare providers. This information can aid healthcare providers in determining which patients may benefit from closer observation or prophylaxis to prevent or minimize morbidity from these events. The risk of arterial thromboembolic events was not previously researched in kidney cancer patients and so the findings from this study provide additional information to patients, healthcare providers, and other researchers. I also contributed research on incidence rates by histology type in kidney cancer patients and whether histology type impacted the risk of venous and arterial thromboembolic events. Based on the findings of this study, healthcare providers have no reason to believe the risks of venous and arterial thromboembolic events differ by histology group within RCC patients with Clear cell, Chromophobe, Papillary or other RCC. For the outcomes other than pulmonary embolism and ischemic stroke, there was no difference in incidence of thromboembolic events in kidney cancer patients with RCC or transitional cell tumors. Thus healthcare providers would not need any change in observation, prophylaxis, or treatment in this regard based on histologic type of RCC. Similarly the lower risk of VTEs in patients with transitional cell tumors compared to patients with clear cell tumors indicates that no additional care would be needed for this group, beyond the usual thromboembolic risk assessment and

care for elderly kidney cancer patients. The increased risk of pulmonary embolism in patients with papillary histology may warrant additional consideration by the healthcare provider during the risk assessment for thromboembolic events.

Conclusion

This population-based, retrospective cohort study of elderly Medicare beneficiaries with and without kidney cancer provided new and useful information on the incidence and risk factors for venous and arterial thromboembolic events. Incidence rates of myocardial infarction were calculated, and were as high as the incidence rates of the venous thromboembolic events. I confirmed that incidence rates of thromboembolic events are higher in kidney cancer patients in the follow-up period after cancer diagnosis than in the year prior to diagnosis. Similar to other studies the incidence proportions in the first year after cancer diagnosis were highest in the first three months. Prior to the index date, the incidence rates of venous thromboembolic events were higher in the cancer (exposed) cohort than the noncancer comparator cohort. For any ATE and ischemic stroke, there were no statistically significant differences in incidence rates between the two cohorts. In the follow-up period after index date, the incidence rates of most thromboembolic events were different in the cancer cohort than in the noncancer cohort when the patients were stratified by kidney disease, type 2 diabetes, or atherosclerosis. Unexpectedly, the incidence rate ratios were greater than 1.0 for patients without kidney disease, type 2 diabetes, or atherosclerosis. More research is needed to understand why the presence of these comorbidities would differentially impact the incidence rates of thromboembolic events in cancer and noncancer patients. This study

was the first study (to my knowledge) in which the relationship of histology groups of kidney cancer and thromboembolic events were assessed and to report that kidney cancer patients with transitional cell tumors appear to be at lower risk for pulmonary embolism and ischemic stroke compared to patients diagnosed with clear cell tumors. A better understanding of the risk factors for thromboembolic events in elderly kidney cancer patients may inform patients and healthcare providers, in turn proving beneficial for patient care.

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Appendix A: Abbreviations

	Definition
AJCC	American Joint Committee on Cancer
AMI	Acute Myocardial Infarction
ATE	Arterial Thromboembolic Event
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CVC	Central Venous Catheter
CVD	Cardiovascular Disease
DVT	Deep Venous Thrombosis
EMM	Effect Measure Modifier
FDA	United States Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-O	International Classification of Diseases for Oncology
IL-2	Interleukin-2
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
IS	Ischemic Stroke
mTOR	Mammalian Target Of Rapamycin
MeSH	Medical Subject Headings
MHSA	Mental Health and Substance Abuse
MVT	Motor Vehicle Traffic
NCCN	National Comprehensive Cancer Network
NDC	National Drug Code
NEC	Not Elsewhere Classified
OR	Odds Ratio
OS	Overall Survival
OTE	Other Thromboembolic Event
PE	Pulmonary Embolism
PFS	Progression-free Survival
OS	Overall Survival
PH	Proportional Hazard
RCC	Renal Cell Carcinoma
RR	Relative Risk
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic Status
US	United States
VEGF	Vascular Endothelial Growth Factor
VHL	von Hippel-Lindau
VTE	Venous Thromboembolic Event

Appendix B. Operational Definitions

	Coding Definitions
Kidney cancer	ICD-O-3 site code C64.9, excluding histology codes for hematopoietic cancers (9590-9989), with malignant behavior.
Transitional cell tumors of the kidney	ICD-O-3 site code C64.9 and histology codes 8050-8130 (inclusive), with malignant behavior.
RCC	ICD-O-3 site code C64.9, excluding histology codes 8050-8130 (inclusive) and histology codes for hematopoietic cancers (9590-9989), with malignant behavior.
RCC Histology	Clear Cell: ICD-O-3 and histology codes 8310, 8312 Papillary: ICD-O-3 site code C64.9 and histology code 8260 Chromophobe: ICD-O-3 site code C64.9 and histology codes 8317, 8270 Other: ICD-O-3 site code C64.9, excluding histology codes 8050-8130 (inclusive) and 8310, 8312, 8317, and 8270
Age at diagnosis (index date)	The integer number of years between the year of birth and the year of diagnosis (index date).
Race	Use the race variable from the Medicare entitlement file. Exclude patients with unknown race. The race categories were combined into three race groups - White, Black, and other races.
Geographic region	This variable was categorized into the four United States Census regions of Northeast, Midwest, South and West. The states which make up the Northeast region are Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island, New Jersey, New York, Pennsylvania; the states in the Midwest region are North Dakota, South Dakota, Nebraska, Kansas, Missouri, Iowa, Minnesota, Wisconsin, Illinois, Michigan, Indiana, Ohio; the states in the South region are Maryland, Delaware, West Virginia, Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Arkansas, Louisiana, Oklahoma, Texas, and District of Columbia; the states in the West region are Washington, Idaho, Montana, Wyoming, Oregon, California, Nevada, Utah, Colorado, Arizona, New Mexico, Alaska, and Hawaii (United States Census Bureau, 2013).
Coverage by Medicare plans Part A and Part B	For each month, the variable (mon1-mon264) is coded as 0 = Not entitled, 1= Part A only, 2 = Part B only, or 3 = Part A and B. The number of months of coverage was the total number of consecutive months with Part A and B coverage (where the indicator variable has a value of 3).
Participation in Medicare managed care plans	For each month, the variable (gho1-gho264) is coded as 0 = Not a member of HMO, 1 = Non-Lock-in, CMS to process provider claims , 2 = Non-Lock-in, GHO to process in-plan Part A & in-area Part B claims, 4 = Chronic care disease management organizations-FFS plan , A = Lock-in, CMS to process provider claims, B = Lock-in, GHO to process in-plan Part A & in-area Part B claims, C = Lock-in, GHO to process all Part A and Part B claims. Participation in a managed care plan was identified by a month where the GHO variable has a value which is not 0.
DVT	ICD-9-CM diagnosis codes 451.11, 451.19, 451.2, 451.81, 451.83, 451.84, 453.1, 453.2, 453.40, 453.41, 453.42, 453.8, 453.9
PE	ICD-9-CM diagnosis codes 415.1 and 415.19
OTE	ICD-9-CM diagnosis codes 362.35, 362.36, 437.6, 451.0, 451.82, 451.89
MI	ICD-9-CM diagnosis codes 410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61,

	Coding Definitions
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IS	ICD-9-CM diagnosis codes 433.0, 433.00, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 433.90, 433.91, 434.0, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 437.1 Restrict to diagnoses captured on hospitalizations only.
Any chemotherapy	Use of any chemotherapy was defined by ICD-9-CM diagnosis codes V58.1, V58.11, V66.2, and V67.2; ICD-9-CM procedure codes 00.10, 99.25; a HCPCS code indicating chemotherapy or chemotherapy administration (96400-96549, C8953, C8954, C8955, C9214, C9239, C9257, J8999-J9999, Q2024, S0088, S0116, and for 2005 only, G0355-G0362 and Q0083-Q0085, excluding J9015, J9214); NDC codes in the Durable Medical Equipment or prescription drug event files indicating chemotherapy drugs (listed below); and revenue codes 0331, 0332, and 0335 (Applied Research Program, 2013; Lund et al., 2013). **NDC Code, Generic Name, Brand Name** 00008117901, TEMSIROLIMUS, TORISEL 00008117905, TEMSIROLIMUS, TORISEL 00026848858, SORAFENIB, NEXAVAR 00069014501, AXITINIB, INLYTA 00069015111, AXITINIB, INLYTA 00069055030, SUNITINIB, SUTENT 00069055038, SUNITINIB, SUTENT 00069077030, SUNITINIB, SUTENT 00069077038, SUNITINIB, SUTENT 00069098030, SUNITINIB, SUTENT 00069098038, SUNITINIB, SUTENT 00078056651, EVEROLIMUS, AFINITOR 00078056661, EVEROLIMUS, AFINITOR 00078056751, EVEROLIMUS, AFINITOR 00078056761, EVEROLIMUS, AFINITOR 00078059451, EVEROLIMUS, AFINITOR 00078059461, EVEROLIMUS, AFINITOR 00078062051, EVEROLIMUS, AFINITOR 00078062651, EVEROLIMUS, AFINITOR DISPERZ 00078062851, EVEROLIMUS, AFINITOR DISPERZ 00173080409, PAZOPANIB, VOTRIENT 50242006001, BEVACIZUMAB, AVASTIN 50242006002, BEVACIZUMAB, AVASTIN 50242006101, BEVACIZUMAB, AVASTIN 50242006201, ERLOTINIB, TARCEVA 50242006301, ERLOTINIB, TARCEVA 50242006401, ERLOTINIB, TARCEVA 50419048858, SORAFENIB, NEXAVAR 54569598300, SUNITINIB, SUTENT 54868544700, ERLOTINIB, TARCEVA 54868547400, ERLOTINIB, TARCEVA 68817013450, PACLITAXEL, ABRAXANE 00013128683, DOXORUBICIN, ADRIAMYCIN PFS 00013126683, DOXORUBICIN, ADRIAMYCIN PFS 00013123691, DOXORUBICIN, ADRIAMYCIN PFS

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	10139006311, FLUOROURACIL, FLUOROURACIL
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	62991148601, Fluorouracil, FLUOROURACIL
	68152010100, LEVOLEUCOVORIN, FUSILEV
	63323012550, GEMCITABINE, GEMCITABINE HCL
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	00781328275, GEMCITABINE, GEMCITABINE HCL
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	00002750201, GEMCITABINE, GEMZAR
	00002750101, GEMCITABINE, GEMZAR
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	00078043815, IMATINIB, GLEEVEC
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	50242013468, TRASTUZUMAB, HERCEPTIN
	50242013460, TRASTUZUMAB, HERCEPTIN
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	10518010311, IRINOTECAN, IRINOTECAN HCL

Coding Definitions
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Coding Definitions
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63323071100, LEUCOVORIN, LEUCOVORIN CA
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38779017806, Leucovorin Calcium, LEUCOVORIN CALCIUM
49452403604, Leucovorin Calcium, LEUCOVORIN CALCIUM
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63370015415, METHOTREXATE, METHOTREXATE
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38779003515, Methotrexate Sodium, METHOTREXATE
38779003525, Methotrexate Sodium, METHOTREXATE
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61703040807, METHOTREXATE, METHOTREXATE LPF
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00555057249, METHOTREXATE, METHOTREXATE SOD
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00054855010, METHOTREXATE, METHOTREXATE SOD

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63323012108, METHOTREXATE, METHOTREXATE SOD
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10019094001, METHOTREXATE, METHOTREXATE SOD
53905003110, METHOTREXATE, METHOTREXATE SOD

	Coding Definitions
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	66758004101, METHOTREXATE, METHOTREXATE SOD
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	61703040841, METHOTREXATE, METHOTREXATE SOD
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	63323012302, METHOTREXATE, METHOTREXATE SOD
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	00186142013, METHOTREXATE, METHOTREXATE SOD
	00186142113, METHOTREXATE, METHOTREXATE SOD
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	51927364200, MITOMYCIN, MITOMYCIN
	38779055307, MITOMYCIN, MITOMYCIN
	16729010811, MITOMYCIN, MITOMYCIN
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	55390025301, MITOMYCIN, MITOMYCIN
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	63323019120, MITOMYCIN, MITOMYCIN
	63323019020, MITOMYCIN, MITOMYCIN
	49452478502, Mitomycin, MITOMYCIN
	00015300222, MITOMYCIN, MUTAMYCIN
	00015300220, MITOMYCIN, MUTAMYCIN
	00015305920, MITOMYCIN, MUTAMYCIN
	00015300120, MITOMYCIN, MUTAMYCIN
	50419048858, SORAFENIB, NEXAVAR
	00026848858, SORAFENIB, NEXAVAR
	00172375675, PACLITAXEL, ONXOL
	00172375377, PACLITAXEL, ONXOL
	00172375473, PACLITAXEL, ONXOL
	63323017650, OXALIPLATIN, OXALIPLATIN
	41616017840, OXALIPLATIN, OXALIPLATIN
	41616017640, OXALIPLATIN, OXALIPLATIN
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	61703036322, OXALIPLATIN, OXALIPLATIN
	63323065020, OXALIPLATIN, OXALIPLATIN
	00703398601, OXALIPLATIN, OXALIPLATIN

	Coding Definitions
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	61703036318, OXALIPLATIN, OXALIPLATIN
	00703398501, OXALIPLATIN, OXALIPLATIN
	55390011420, PACLITAXEL, PACLITAXEL
	61703034222, PACLITAXEL, PACLITAXEL
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	00703476701, PACLITAXEL, PACLITAXEL
	66758004303, PACLITAXEL, PACLITAXEL
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	55390031450, PACLITAXEL, PACLITAXEL
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	00172375494, PACLITAXEL, PACLITAXEL
	00015321430, CARBOPLATIN, PARAPLATIN
	00015321530, CARBOPLATIN, PARAPLATIN
	00015321330, CARBOPLATIN, PARAPLATIN
	00015321630, CARBOPLATIN, PARAPLATIN
	00015321130, CARBOPLATIN, PARAPLATIN
	00015321230, CARBOPLATIN, PARAPLATIN
	00015321030, CARBOPLATIN, PARAPLATIN
	00015321076, CARBOPLATIN, PARAPLATIN
	00015322122, CISPLATIN, PLATINOL AQ
	00015322097, CISPLATIN, PLATINOL AQ

Coding Definitions
00015322022, CISPLATIN, PLATINOL AQ
67253058042, METHOTREXATE, RHEUMATREX
00005450704, METHOTREXATE, RHEUMATREX
67253058043, METHOTREXATE, RHEUMATREX
00005450705, METHOTREXATE, RHEUMATREX
67253058044, METHOTREXATE, RHEUMATREX
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67253058045, METHOTREXATE, RHEUMATREX
00005450709, METHOTREXATE, RHEUMATREX
00005450791, METHOTREXATE, RHEUMATREX
67253058046, METHOTREXATE, RHEUMATREX
00015335222, DOXORUBICIN, RUBEX
00069055038, SUNITINIB, SUTENT
00069055030, SUNITINIB, SUTENT
00069077038, SUNITINIB, SUTENT
00069077030, SUNITINIB, SUTENT
00069098038, SUNITINIB, SUTENT
00069098030, SUNITINIB, SUTENT
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54868544700, ERLOTINIB, TARCEVA
50242006201, ERLOTINIB, TARCEVA
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00015347620, PACLITAXEL, TAXOL SEMI-SYN
00015347911, PACLITAXEL, TAXOL SEMI-SYN
00015347530, PACLITAXEL, TAXOL SEMI-SYN
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00075800301, DOCETAXEL, TAXOTERE
00075800180, DOCETAXEL, TAXOTERE
00075800404, DOCETAXEL, TAXOTERE
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00015309520, ETOPOSIDE, VEPESID
00015309595, ETOPOSIDE, VEPESID
00015308420, ETOPOSIDE, VEPESID
00015306220, ETOPOSIDE, VEPESID
00015306120, ETOPOSIDE, VEPESID
00173080409, PAZOPANIB, VOTRIENT
00173063225, LEUCOVORIN, WELLCOVORIN

	Coding Definitions
	00173063155, LEUCOVORIN, WELLCOVORIN 00081063120, LEUCOVORIN, WELLCOVORIN 00173063120, LEUCOVORIN, WELLCOVORIN 54868414301, CAPECITABINE, XELODA 00004110051, CAPECITABINE, XELODA 00004110020, CAPECITABINE, XELODA 54868414300, CAPECITABINE, XELODA 68258903601, CAPECITABINE, XELODA 00004110175, CAPECITABINE, XELODA 00004110150, CAPECITABINE, XELODA 54868526002, CAPECITABINE, XELODA 54569571700, CAPECITABINE, XELODA 54868526004, CAPECITABINE, XELODA 54868526009, CAPECITABINE, XELODA 00004110116, CAPECITABINE, XELODA 54868526005, CAPECITABINE, XELODA 54868526000, CAPECITABINE, XELODA 54868526006, CAPECITABINE, XELODA 54868526001, CAPECITABINE, XELODA 54868526007, CAPECITABINE, XELODA 54868526008, CAPECITABINE, XELODA 54868526003, CAPECITABINE, XELODA
Any immunotherapy	ICD-9-CM diagnosis code V58.12; ICD-9-CM procedure codes 00.15, 99.28; HCPCS codes indicating immunotherapy J9015, J9214; NDC codes in the Durable Medical Equipment or prescription drug event data files indicating immunotherapy drugs : **NDC Code, Generic Name, Brand Name** 00078049561, ALDESLEUKIN, PROLEUKIN 00085012002, INTERFERON ALFA 2B, INTRON-A 00085012003, INTERFERON ALFA 2B, INTRON-A 00085012004, INTERFERON ALFA 2B, INTRON-A 00085012005, INTERFERON ALFA 2B, INTRON-A 00085028502, INTERFERON ALFA 2B, INTRON-A 00085053901, INTERFERON ALFA 2B, INTRON-A 00085057102, INTERFERON ALFA 2B, INTRON-A 00085057106, INTERFERON ALFA 2B, INTRON-A 00085064703, INTERFERON ALFA 2B, INTRON-A 00085064704, INTERFERON ALFA 2B, INTRON-A 00085064705, INTERFERON ALFA 2B, INTRON-A 00085068901, INTERFERON ALFA 2B, INTRON-A 00085076901, INTERFERON ALFA 2B, INTRON-A 00085095301, INTERFERON ALFA 2B, INTRON-A 00085111001, INTERFERON ALFA 2B, INTRON-A 00085113301, INTERFERON ALFA 2B, INTRON-A 00085116801, INTERFERON ALFA 2B, INTRON-A 00085117901, INTERFERON ALFA 2B, INTRON-A 00085117902, INTERFERON ALFA 2B, INTRON-A 00085118401, INTERFERON ALFA 2B, INTRON-A

	Coding Definitions
	00085118402, INTERFERON ALFA 2B, INTRON-A 00085119101, INTERFERON ALFA 2B, INTRON-A 00085119102, INTERFERON ALFA 2B, INTRON-A 00085123501, INTERFERON ALFA 2B, INTRON-A 00085124201, INTERFERON ALFA 2B, INTRON-A 00085125401, INTERFERON ALFA 2B, INTRON-A 00339650099, INTERFERON ALFA 2B, INTRON-A 00339650199, INTERFERON ALFA 2B, INTRON-A 00339650299, INTERFERON ALFA 2B, INTRON-A 00339650399, INTERFERON ALFA 2B, INTRON-A 00339651199, INTERFERON ALFA 2B, INTRON-A 00339651299, INTERFERON ALFA 2B, INTRON-A 53905099101, ALDESLEUKIN, PROLEUKIN 54868334100, INTERFERON ALFA 2B, INTRON-A 65483011607, ALDESLEUKIN, PROLEUKIN
Nephrectomy	ICD-9-CM procedure codes (55.4, 55.5, 55.51, 55.52, 55.53, 55.54) and Current Procedural Terminology (CPT) procedure codes (50220, 50225, 50230, 50234, 50236, 50240, 50320, 50545, 50543, 50546).
Diabetes	ICD-9-CM diagnosis codes 250.xx
Atherosclerosis	ICD-9-CM diagnosis codes 440.xx, 441.xx, 442.xx, 443.89, 444.xx, and 445.xx.
Varicose veins	ICD-9-CM diagnosis codes 454, 454.0, 454.1, 454.2, 454.8, 454.9.
High risk cardiovascular surgeries	ICD-9-CM procedure codes (35.x, 36.x, 37.1x, 37.24, 37.25, 37.3x, 37.4x, 37.6x, 37.9x, 38.0x, 38.1x, 38.3x, 38.4x, 38.6x, 38.7x, 39.0x, 39.2x, 39.4x, 39.5x, 39.7x); CPT codes 32160, 32658 – 3266, 33015, 33020, 33025, 33030, 33031, 33050, 33120, 33130, 33140, 33141, 33200 – 33203, 33206 – 33208, 33210 – 33218, 33220, 33222 – 33226, 33233 – 33238, 33240 – 33247, 33249 – 33251, 33253 – 33256, 33261, 33300, 33305, 33310, 33315, 33320 – 33322, 33330, 33332, 33335, 33400, 33401, 33403- 33406, 33410 – 33417, 33420, 33422, 33425 – 33427, 33430, 33460, 33463 – 33465, 33468, 33470 – 33472, 33474 – 33476, 33478, 33496, 33500 – 33508, 33510 – 33514, 33516 – 33519, 33521 – 33523, 33530, 33533 – 33536, 33542, 33545, 33548, 33572, 33600, 33602, 33606, 33608, 33610 - 33612, 33615, 33617, 33619, 33641, 33645, 33647, 33660, 33665, 33670, 33675 - 33677, 33681, 33684, 33688, 33690, 33692, 33694, 33697, 33702, 33710, 33720, 33722, 33724, 33726, 33730, 33732, 33735 - 33737, 33750, 33755, 33762, 33764, 33766 - 33768, 33770, 33771, 33774 - 33781, 33786, 33788, 33800, 33802, 33803, 33813, 33814, 33820, 33822, 33824, 33840, 33845, 33851 - 33853, 33860, 33861, 33863, 33870, 33875, 33877, 33880, 33881, 33883, 33884, 33886, 33889, 33891, 33910, 33915 - 33920, 33922, 33924 - 33926, 33940, 33960, 33961, 33967, 33968, 33970, 33971, 33973 - 33980, 33999, 34001, 34051, 34101, 34111, 34151, 34201, 34203, 34401, 34421, 34451, 34471, 34490, 34501, 34502, 34510, 34520, 34530, 34800, 34802 - 34805, 34808, 34812, 34813, 34820, 34825, 34826, 34830 - 34834, 34900, 35001, 35002, 35005, 35011, 35013, 35021, 35022, 35045, 35081, 35082, 35091, 35092, 35102, 35103, 35111, 35112, 35121, 35122, 35131, 35132, 35141, 35142, 35151, 35152, 35161, 35162, 35180, 35182, 35184, 35188, 35189, 35190, 35201, 35206, 35207, 35211, 35216, 35221, 35226, 35231, 35236, 35241, 35246, 35251, 35256, 35261, 35266, 35271, 35276, 35281, 35286, 35301, 35311, 35321, 35331, 35341, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35390, 35450, 35452, 35454, 35456, 35458, 35459, 35460, 35470 - 35476, 35480 - 35485, 35490 - 35495, 35500, 35501, 35506 - 35512, 35515, 35516, 35518, 35521, 35526, 35531, 35533, 35536, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35560, 35563, 35565, 35566, 35571, 35572, 35582, 35583, 35585, 35587, 35600, 35601, 35606,

	Coding Definitions
	35612, 35616, 35621, 35623, 35626, 35631, 35636, 35637, 35638, 35641, 35642, 35645, 35646, 35647, 35650, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681 - 35683, 35685, 35686, 35691, 35693, 35694, 35695, 35700, 35701, 35721, 35741, 35761, 35800, 35820, 35840, 35860, 35870, 35875, 35876, 35879, 35881, 35883, 35884, 35900, 35901, 35903, 35905, 35907, 35910, 36260, 36261, 36262, 36470, 36471, 36800, 36810, 36815, 36818 - 36822, 36825, 36830 - 36835, 36860, 36861, 36870, 37140, 37145, 37160, 37180 - 37188, 37190, 37204 - 37208, 37500, 37565, 37600, 37605 - 37607, 37609, 37615 - 37618, 37620, 37650, 37660, 37788, 37790, 37799, 50100, 60600, 60605, 61609 - 61613, 61623, 61624, 61626, 61630, 61635, 61640 - 61642, 61680, 61682, 61684, 61686, 61690, 61692, 61697, 61698, 61700, 61702, 61703, 61705, 61708, 61710, 61711, 92961, 92970, 92971, 92975, 92977, 92986, 92987, 92990, 92992, 92993, 93536, 93580, 93581; and HCPCS codes 0001T, 0002T, 0005T, 0033T, 0034T, 0035T, 0036T, 0037T, G0269, G0297, G0298, G0299, G0300, G0365, M0301, S2130, S2131, S2204, S2205, S2206, S2207, S2208, S2209.
Placement of a CVC	HCPCS or CPT codes C1751, S5520, S5522, 36488, 36489, 36490, 36491, 36493, 36530, 36531, 36532, 36536, 36537, 36555, 36556, 36557, 36558, 36560, 36561, 36563, 36565, 36566, 36568, 36569, 36570, 36571, 36575, 36576, 36578, 36580, 36581, 36582, 36583, 36584, 36585, 36589, 36590, 36595, 36596, 36597, 75998
Kidney disease	ICD-9-CM diagnosis codes 403, 403.0, 403.00, 403.01, 403.1, 403.10, 403.11, 403.9, 403.90, 403.91, 404, 404.0, 404.00, 404.01, 404.02, 404.03, 404.1, 404.10, 404.11, 404.12, 404.13, 404.9, 404.90 , 404.91 , 404.92, 404.93, 582 , 582.0, 582.1, 582.2, 582.4, 582.8, 582.81, 582.89, 582.9, 584, 584.5, 584.6, 584.7, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4 , 585.5, 585.6, 585.9, 586.

Appendix C. Adapted Charlson Comorbidity Index

Note. Based on publically-available code retrieved from http://www.appliedresearch.cancer.gov/seermedicare/program/charlson.comorbidity.macro.txt

	Condition	Weight	Codes
Diagnoses			ICD-9-CM Diagnosis Codes
	Myocardial Infarction	1	410 – 410.9
	Old Myocardial Infarction	1	412
	Congestive Heart Failure	1	428 – 428.9
	Peripheral Vascular Disease	1	441-441.9, 443.9, 785.4, V43.4
	Cerebrovascular Disease	1	430 – 437.9, 438
	Chronic Obstructive Pulmonary Disease	1	490 – 496.9, 500 – 505.9, 506.4
	Dementia	1	290-290.9
	Paralysis	2	342-342.9, 344.1
	Diabetes	1	250, 250.0-250.3, 250.7
	Diabetes with Sequelae	2	250.4-250.6, 250.8-250.9
	Chronic Renal Failure	2	582-582.9, 583-583.9, 585, 586, 588-588.9
	Various Cirrhodites	1	571.2, 571.4, 571.5, 571.6
	Moderate to Severe Liver Disease	3	572.2-572.8, 456.0-456.1, 456.2, 456.20, 456.21
	Ulcers	1	531-531.9, 532-532.9, 533-533.9, 534-534.9
	Rheumatoid Arthritis	1	710.0, 710.1, 710.4 , 714.0-714.2, 714.81, 725
	AIDS	6	042.0 – 044.9
Procedures			
	Peripheral Vascular Disease	1	ICD-9-CM Procedure codes: 381.3 , 381.4, 381.6, 381.8, 383.3, 383.4, 383.6, 383.8, 384.3, 384.4, 384.6, 384.8, 392.2-392.6, 392.8, 392.9 HCPCS: '35011', '35013', '35045', '35081', '35082', '35091', '35092', '35102', '35103', '35111', '35112', '35121', '35122', '35131', '35132', '35141', '35142', '35151', '35152', '35153', '35311', '35321', '35331', '35341', '35351', '35506', '35507', '35511', '35516', '35518', '35521', '35526', '35531', '35533', '35536', '35541', '35546', '35548', '35549', '35551','35556', '35558', '35560', '35563', '35565', '35566', '35571','35582', '35583', '35585', '35587', '35601', '35606', '35612','35616', '35621', '35623', '35626', '35631', '35636', '35641','35646', '35650', '35651', '35654', '35656', '35661', '35663','35665', '35666', '35671', '35694',

		'35695', and '35355' to '35381'
Cerebrovascular Disease	1	ICD-9-CM Procedure codes: 381.2, 384.2 HCPCS: '35301', '35001', '35002', '35005', '35501', '35508', '35509', '35515', '35642', '35645', '35691', '35693'
Moderate to Severe Liver Disease	3	ICD-9-CM Procedure codes: 391, 429.1 HCPCS: '37140', '37145', '37160', '37180', '37181', '75885', '75887', '43204', '43205'

Appendix D. Code to Calculate the Charlson Comorbidity Score Weights

Note. Publically available code retrieved from http://healthcaredelivery.cancer.gov/seermedicare/program/comorbidity.html

```
/*********************************************************************
Changes have been made to the remove.ruleout.dxcodes.macro.txt on
July 22, 2010 to remove code (below) that made a selection
on HCPCS. Now all the claims are looked at for conditions.

if (&FILETYPE='M') or
  ('00100' <= &HCPCS <= '01999' or '10021' <= &HCPCS <= '69979' or
   '77261' <= &HCPCS <= '79999' or
   '90918' <= &HCPCS <= '91299' or '92950' <= &HCPCS <= '99199');

Please make sure you use the current remove.ruleout.dxcodes.macro.txt
before running this macro.

*********************************************************************
This SAS macro uses a dataset of claim records to calculate a
comorbidity index for a patient with respect to cancer. This code
reflects the Deyo adaptation of the Charlson comorbidity index, with
several procedure codes that reflect the Romano adaptation.
(NOTE: since cancer is the disease of interest, it is not included
in the comorbidity index given below.)  The dataset must contain
lists of diagnosis and surgery codes. There are other specific
variables needed to complete this task.

In order to use this program:
  1. Include this file in your SAS program
        %include '/directory path/charlson.comorbidity.macro.sas';
  2. Create a clean file of claim records to send to the macro.
        If you wish to remove diagnoses for procedures done for
        'rule out' purposes, you must do so externally to this macro.
        (SEE remove.ruleout.dxcodes.macro.sas from SEER-Medicare web site)
        You may include claim information from any file, including
        MEDPAR, Outpatient SAF and Physicial/Supplier (NCH). All claim
        records of interest should be included into the same file.
        You must sort the claim records by your person identifier.
  3. After setting up your data file, call the macro COMORB:
     COMORB(ClmData, RegCase, Ind_Pri, LOS, dx01-dx10, 10, surg01-surg10, 10, HCPCS, Source)
        would send the data set 'ClmData', sorted by the person
        identifier 'RegCase' to the macro. The variable 'Ind_Pri'
        must be set on each record as either index (I) or Prior event (P)
        with respect to the cancer of interest. The number of
        days for a hospital stay is found in the variable 'LOS'.
        There are 10 diagnosis codes in the array variables 'dx01-dx10'.
        Similarly, there are 10 surgery codes in the array variables
        'surg01-surg10'. Diagnosis and surgery codes are in ICD-9 format.
     HCPCS are the procedure codes from the SAF and NCH files. Only CPT-4
        codes are used in this program. The file source of each claim
```

```
            record is found in the variable 'Source' (M=Medpar, O=Outpatient,
            N=NCH).

   This returns the data set COMORB which contains 1 record for each person
   that had at least one claim record. The variables included in this data set are
   the person identifier (in the example, RegCase), Charlson scores for
   prior conditions, index conditions and prior+index conditions, and the
   condition indicator flags for prior and for index time frames.

   NCI usually uses PCHRLSON calculated using claims from
           (Date of Diagnosis - 12 months) through (Date of DX - 1 month)
  ********************************************************************/

  /* internal macro to set indicators */
%MACRO FLAGSET(VAR,FLAG,NFLAGS,POSISHN);
  &FLAG = &POSISHN;
  &NFLAGS = &NFLAGS + 1;
  &VAR = 1;
%MEND;

  /* Main macro COMORB */
%MACRO
COMORB(SETIN,PATID,IDXPRI,DAYS,DXVARSTR,NDXVAR,SXVARSTR,NSXVAR,HCPCS,FILE
TYPE);
  /*******************************************************************
   SETIN:    Dataset name: a dataset that contains the following:
   PATID:    Variable name: Unique ID for each patient. &SETIN must be
           sorted by &PATID. There may be more than 1 record per patient.
   IDXPRI:   Variable name: indicates for each record if the Dx and Surg
             codes are Index 'I' or Prior 'P' to the event of interest.
             If the variable does not equal I or P, the record will not be
             used. This variable should be set by the calling program.
   DAYS:     Variable name: contains the length of stay for hospital visits.
   DXVARSTR: Variable names: the diagnosis codes in ICD-9, ie 'DX01-DX10'
   NDXVAR:   Number: the actual number of diagnosis codes in DXVARSTR
   SXVARSTR: Variable names: the surgery codes in ICD-9, ie 'SURG01-SURG10'
   NSXVAR:   Number: the actual number of surgery codes in SXVARSTR
   HCPCS:    Variable name: the SAF and NCH file procedure codes in CPT-4.
   FILETYPE: Variable name: the source of the claim record. Only important
             value is 'M' for MEDPAR (inpatient hospital records). If this
             is 'M', the check for Acute MI will include &DAYS > 2.
  ********************************************************************/

 DATA COMORB;
  RETAIN CVPRIO01-CVPRIO18
       CVINDX01-CVINDX18;
  LENGTH DEFAULT=3;
  SET &SETIN;
  BY &PATID;

  /* Flag arrays, diagnosis and surgery code arrays */
  ARRAY CLPRIO (18) CVPRIO01-CVPRIO18;
```

```
ARRAY CLINDX (18) CVINDX01-CVINDX18;
ARRAY COVAR  (18) ACUTEMI OLDMI CHF VASCUL1 VASCUL2 CVD
             PULMON1 DEMENTIA PARALYS DIABET1 DIABET3 RENAL1
             LIVER1 LIVER2 ULCER1 ULCER2 RHEUM AIDS;
ARRAY FLAGS (*) FLAG01-FLAG18;
ARRAY DX (&NDXVAR) $ &DXVARSTR;
ARRAY SX (&NSXVAR) $ &SXVARSTR;

/* Initialization */
IF FIRST.&PATID THEN DO;
  DO M=1 TO 18;
    CLPRIO(M)=0;
    CLINDX(M)=0;
    END;
  END;

DO M=1 TO 18;
  COVAR(M)=0;
  FLAGS(M)=0;
  END;

NFLAGS=0;

/* Diagnosis code loop */
DO K=1 TO &NDXVAR;
  dx_4 = substr(dx(k),1,4);
  dx_3 = substr(dx(k),1,3);

  /********** MYOCARDIAL INFARCTION WEIGHT = 1 ***************/
  IF ACUTEMI=0 THEN DO;
    IF dx_3 = '410' then do;                    /* 410 thru 4109 */
      IF ((&FILETYPE='M') & (&DAYS > 2)) | NOT (&FILETYPE='M') THEN DO;
        %FLAGSET(ACUTEMI,FLAGS(NFLAGS+1),NFLAGS,1);
        END;
      END;
    END;

  IF OLDMI=0 THEN DO;
    IF DX(K) = '412  ' then do;
      %FLAGSET(OLDMI,FLAGS(NFLAGS+1),NFLAGS,2);
      END;
    END;

  /********** CHF ***** WEIGHT = 1 ****************************/
  IF CHF=0 THEN DO;
    IF dx_3 = '428' then do;                    /* 428 thru 4289 */
      %FLAGSET(CHF,FLAGS(NFLAGS+1),NFLAGS,3);
      END;
    END;

  /*********** PERIPHERAL VASCULAR DISEASE ******* WEIGHT = 1**/
  IF VASCUL1=0 THEN DO;                         /* 441 thru 4419 */
```

```
  IF dx_3 = '441' | dx_4 in ('4439', '7854', 'V434', 'v434') then do;
    %FLAGSET(VASCUL1,FLAGS(NFLAGS+1),NFLAGS,4);
    END;
  END;

/********* CEREBROVASCULAR DISEASE ******* WEIGHT = 1 *******/
IF CVD=0 THEN DO;                                          /* 430 thru 4379 */
  IF '430' <= dx_3 <= '437' | DX(K)= '438  ' then do;
    %FLAGSET(CVD,FLAGS(NFLAGS+1),NFLAGS,6);
    END;
  END;

/********** COPD ********************** WEIGHT = 1 ********/
IF PULMON1=0 THEN DO;
  IF '490' <= dx_3 <= '496' | '500' <= dx_3 <= '505' |
    dx_4 = '5064' THEN DO;
    %FLAGSET(PULMON1,FLAGS(NFLAGS+1),NFLAGS,7);
    END;
  END;

/********  DEMENTIA ****** WEIGHT = 1 **********************/
IF DEMENTIA=0 THEN DO;
  IF dx_3 = '290' then do;                                 /* 290 thru 2909 */
    %FLAGSET(DEMENTIA,FLAGS(NFLAGS+1),NFLAGS,8);
    END;
  END;

/********* PARALYSIS ***************** WEIGHT = 2 ************/
IF PARALYS=0 THEN DO;
  IF dx_3 = '342' | dx_4 = '3441' then do;           /* 342 thru 3429 */
    %FLAGSET(PARALYS,FLAGS(NFLAGS+1),NFLAGS,9);
    END;
  END;

/******** DIABETES ************* WEIGHT = 1 *****************/
IF DIABET1=0 THEN DO;
  IF DX(K)= '250  ' | dx_4 = '2507' | '2500' <= dx_4 <= '2503' then do;
    %FLAGSET(DIABET1,FLAGS(NFLAGS+1),NFLAGS,10);
    END;
  END;

/********* DIABETES WITH SEQUELAE ****** WEIGHT = 2 *********/
IF DIABET3=0 THEN DO;
  IF ('2504' <= dx_4 <= '2506') | ('2508' <= dx_4 <= '2509') THEN DO;
    %FLAGSET(DIABET3,FLAGS(NFLAGS+1),NFLAGS,11);
    END;
  END;

/********* CHRONIC RENAL FAILURE ******* WEIGHT = 2 *********/
IF RENAL1=0 THEN DO;             /* 582 - 5829; 583 - 5839, 588 - 5889 */
  IF dx_3 in ('582', '583', '585', '586', '588') then do;
    %FLAGSET(RENAL1,FLAGS(NFLAGS+1),NFLAGS,12);
```

```
    END;
  END;

 /************** VARIOUS CIRRHODITES ******** WEIGHT = 1 *****/
 IF LIVER1=0 THEN DO;                /* includes 5714x ICD-9-CM codes */
  IF dx_4 in ('5712', '5714', '5715', '5716') then do;
    %FLAGSET(LIVER1,FLAGS(NFLAGS+1),NFLAGS,13);
    END;
  END;

 /************** MODERATE-SEVERE LIVER DISEASE *** WEIGHT = 3*/
 IF LIVER2=0 THEN DO;
  IF ('5722' <= dx_4 <= '5728') | ('4560' <= dx_4 <= '4561') |
    DX(K) in ('4562 ', '45620',  '45621') THEN DO;
    %FLAGSET(LIVER2,FLAGS(NFLAGS+1),NFLAGS,14);
    END;
  END;

 /*************** ULCERS ********** WEIGHT = 1 ***************/
 IF ULCER1=0 THEN DO;
  IF '5310' <= dx_4 <= '5313' | '5320' <= dx_4 <= '5323' |
    '5330' <= dx_4 <= '5333' | '5340' <= dx_4 <= '5343' |
    dx_4 in ('531 ', '5319', '532 ', '5329', '533 ', '5339',
              '534 ', '5349') THEN DO;
    %FLAGSET(ULCER1,FLAGS(NFLAGS+1),NFLAGS,15);
    END;
  END;
 IF ULCER2=0 THEN DO;
  IF '5314' <= dx_4 <= '5317' | '5324' <= dx_4 <= '5327' |
    '5334' <= dx_4 <= '5337' | '5344' <= dx_4 <= '5347' THEN DO;
    %FLAGSET(ULCER2,FLAGS(NFLAGS+1),NFLAGS,16);
    END;
  END;

 /*************** RHEUM  ********** WEIGHT = 1 ***************/
 IF RHEUM=0  THEN DO;
  IF DX(K) in ('71481', '725  ', '7100 ', '7101 ', '7104 ') |
    '7140' <= dx_4 <= '7142' THEN DO;
    %FLAGSET(RHEUM,FLAGS(NFLAGS+1),NFLAGS,17);
    END;
  END;

 /*************** AIDS   ********** WEIGHT = 6 ***************/
 IF AIDS=0   THEN DO;
  IF '042' <= dx_3 <= '044' then do;          /* 042 thru 0449 */
    %FLAGSET(AIDS,FLAGS(NFLAGS+1),NFLAGS,18);
    END;
  END;

END; /* end of Diagnosis code loop */

/* Surgery code loop */
```

```
DO J=1 TO &NSXVAR;
 /********** PERIPHERAL VASCULAR DISEASE ******* WEIGHT = 1**/
 IF VASCUL2=0 THEN DO;
  IF SX(J) = '3813' | SX(J) = '3814' | SX(J) = '3816' |
    SX(J) = '3818' | SX(J) = '3843' | SX(J) = '3844' |
    SX(J) = '3846' | SX(J) = '3848' | SX(J) = '3833' |
    SX(J) = '3834' | SX(J) = '3836' | SX(J) = '3838' |
    '3922' <=SX(J)<= '3929' & SX(J) ^= '3927' THEN DO;
    %FLAGSET(VASCUL2,FLAGS(NFLAGS+1),NFLAGS,5);
    END;
  END;

 /********* CEREBROVASCULAR DISEASE ******* WEIGHT = 1 *******/
 IF CVD=0 THEN DO;
  IF SX(J) = '3812' | SX(J) = '3842' THEN DO;
    %FLAGSET(CVD,FLAGS(NFLAGS+1),NFLAGS,6);
        END;
  END;

 /************** MODERATE-SEVERE LIVER DISEASE *** WEIGHT = 3*/
 IF LIVER2=0 THEN DO;
  IF SX(J) = '391 ' | SX(J) = '4291' THEN DO;
    %FLAGSET(LIVER2,FLAGS(NFLAGS+1),NFLAGS,14);
        END;
  END;

END; /* end of Surgery code loop */

/* HCPCS procedure code */
/********** PERIPHERAL VASCULAR DISEASE ******* WEIGHT = 1**/
IF VASCUL2=0 THEN DO;
 IF &HCPCS IN ('35011', '35013',  '35045', '35081', '35082',
        '35091', '35092', '35102', '35103', '35111', '35112', '35121',
        '35122', '35131', '35132', '35141', '35142', '35151', '35152',
        '35153', '35311', '35321', '35331', '35341', '35351', '35506',
        '35507', '35511', '35516', '35518', '35521', '35526', '35531',
        '35533', '35536', '35541', '35546', '35548', '35549', '35551',
        '35556', '35558', '35560', '35563', '35565', '35566', '35571',
        '35582', '35583', '35585', '35587', '35601', '35606', '35612',
        '35616', '35621', '35623', '35626', '35631', '35636', '35641',
        '35646', '35650', '35651', '35654', '35656', '35661', '35663',
        '35665', '35666', '35671', '35694', '35695') OR
   '35355' <= &HCPCS <= '35381'
        THEN DO;
   %FLAGSET(VASCUL2,FLAGS(NFLAGS+1),NFLAGS,5);
   END;
 END;

/********* CEREBROVASCULAR DISEASE ******* WEIGHT = 1 *******/
IF CVD=0 THEN DO;
 IF &HCPCS IN ('35301', '35001', '35002', '35005', '35501', '35508',
        '35509', '35515', '35642', '35645', '35691', '35693') THEN DO;
```

```
    %FLAGSET(CVD,FLAGS(NFLAGS+1),NFLAGS,6);
    END;
  END;

/************** MODERATE-SEVERE LIVER DISEASE *** WEIGHT = 3*/
IF LIVER2=0 THEN DO;
  IF &HCPCS IN ('37140', '37145', '37160', '37180', '37181', '75885',
    '75887', '43204', '43205') THEN DO;
    %FLAGSET(LIVER2,FLAGS(NFLAGS+1),NFLAGS,14);
    END;
  END;

/* end HCPCS procedure code */


/* Use general indicators to turn on Prior and Index indicators */
IF NFLAGS > 0 THEN DO;
  DO M=1 TO NFLAGS;
    I=FLAGS(M);
    IF COVAR(I) THEN DO;
      IF &IDXPRI = 'P'   THEN  CLPRIO(I)=1;
      ELSE IF &IDXPRI = 'I'   THEN  CLINDX(I)=1;
      END;
    END;
  END;

IF LAST.&PATID THEN DO;
  /* CALCULATE THE COEFFICIENT FOR PRIOR CONDITIONS ONLY */
  PCHRLSON = (CVPRIO01 | CVPRIO02) +
          (CVPRIO03) +
          (CVPRIO04 | CVPRIO05) +
          (CVPRIO06) +
          (CVPRIO07) +
          (CVPRIO08) +
          ((CVPRIO10) & ^(CVPRIO11)) +
          ((CVPRIO13) & ^(CVPRIO14)) +
          (CVPRIO15 | CVPRIO16) +
          (CVPRIO17) +
          ((CVPRIO09) * 2) +
          ((CVPRIO12) * 2) +
          ((CVPRIO11) * 2) +
          ((CVPRIO14) * 3) +
          ((CVPRIO18) * 6);

  /* CALCULATE THE COEFFICIENT FOR PRIOR AND INDEX COND */
  CHRLSON = (CVPRIO01 | CVPRIO02 | CVINDX02) +
         (CVPRIO03) +
         (CVPRIO04 | CVINDX04 | CVPRIO05 | CVINDX05) +
         (CVPRIO06) +
         (CVPRIO07 | CVINDX07) +
         (CVPRIO08 | CVINDX08) +
         ((CVPRIO10 | CVINDX10) & ^(CVPRIO11 | CVINDX11)) +
```

```
        ((CVPRIO13 | CVINDX13) & ^(CVPRIO14 | CVINDX14)) +
        (CVPRIO15) +
        ((CVPRIO09) * 2) +
        ((CVPRIO12 | CVINDX12) * 2) +
        ((CVPRIO11 | CVINDX11) * 2) +
        ((CVPRIO14 | CVINDX14) * 3);

  /* CALCULATE THE COEFFICIENT FOR INDEX CONDITIONS ONLY */
  XCHRLSON = (CVINDX02) +
         (CVINDX04 | CVINDX05) +
         (CVINDX07) +
         (CVINDX08) +
         ((CVINDX10) &^ (CVINDX11)) +
         ((CVINDX13) &^ (CVINDX14)) +
         ((CVINDX12) * 2) +
         ((CVINDX11) * 2) +
         ((CVINDX14) * 3);

  OUTPUT;
  END;

 KEEP &PATID PCHRLSON CHRLSON XCHRLSON CVPRIO01-CVPRIO18 CVINDX01-
CVINDX18;
 Label PCHRLSON = 'Prior Charlson comorbidity score'
     CHRLSON  = 'Prior+Index Charlson comorbidity score'
     XCHRLSON = 'Index Charlson comorbidity score'

     CVPRIO01 = 'Prior: MYOCARDIAL INFARCTION (1)'
     CVPRIO02 = 'Prior: OLD MYOCARDIAL INFARCTION (1)'
     CVPRIO03 = 'Prior: CHF (1)'
     CVPRIO04 = 'Prior: PERIPHERAL VASCULAR DISEASE (DX, 1)'
     CVPRIO05 = 'Prior: PERIPHERAL VASCULAR DISEASE (SURG, 1)'
     CVPRIO06 = 'Prior: CEREBROVASCULAR DISEASE (1)'
     CVPRIO07 = 'Prior: COPD (1)'
     CVPRIO08 = 'Prior: DEMENTIA (1)'
     CVPRIO09 = 'Prior: PARALYSIS (2)'
     CVPRIO10 = 'Prior: DIABETES (1)'
     CVPRIO11 = 'Prior: DIABETES WITH SEQUELAE (2)'
     CVPRIO12 = 'Prior: CHRONIC RENAL FAILURE (2)'
     CVPRIO13 = 'Prior: VARIOUS CIRRHODITES (1)'
     CVPRIO14 = 'Prior: MODERATE-SEVERE LIVER DISEASE (3)'
     CVPRIO15 = 'Prior: ULCERS1 (1)'
     CVPRIO16 = 'Prior: ULCERS2 (1)'
     CVPRIO17 = 'Prior: RHEUM (1)'
     CVPRIO18 = 'Prior: AIDS (6)'

     CVINDX01 = 'Index: MYOCARDIAL INFARCTION (1)'
     CVINDX02 = 'Index: OLD MYOCARDIAL INFARCTION (1)'
     CVINDX03 = 'Index: CHF (1)'
     CVINDX04 = 'Index: PERIPHERAL VASCULAR DISEASE (DX, 1)'
     CVINDX05 = 'Index: PERIPHERAL VASCULAR DISEASE (SURG, 1)'
     CVINDX06 = 'Index: CEREBROVASCULAR DISEASE (1)'
```

```
     CVINDX07 = 'Index: COPD (1)'
     CVINDX08 = 'Index: DEMENTIA (1)'
     CVINDX09 = 'Index: PARALYSIS (2)'
     CVINDX10 = 'Index: DIABETES (1)'
     CVINDX11 = 'Index: DIABETES WITH SEQUELAE (2)'
     CVINDX12 = 'Index: CHRONIC RENAL FAILURE (2)'
     CVINDX13 = 'Index: VARIOUS CIRRHODITES (1)'
     CVINDX14 = 'Index: MODERATE-SEVERE LIVER DISEASE (3)'
     CVINDX15 = 'Index: ULCERS1 (1)'
     CVINDX16 = 'Index: ULCERS2 (1)'
          CVINDX17 = 'Index: RHEUM (1)'
          CVINDX18 = 'Index: AIDS (6)'
          ;

run;
%MEND;
```

Appendix E: Unadjusted Kaplan-Meier Survival Curves

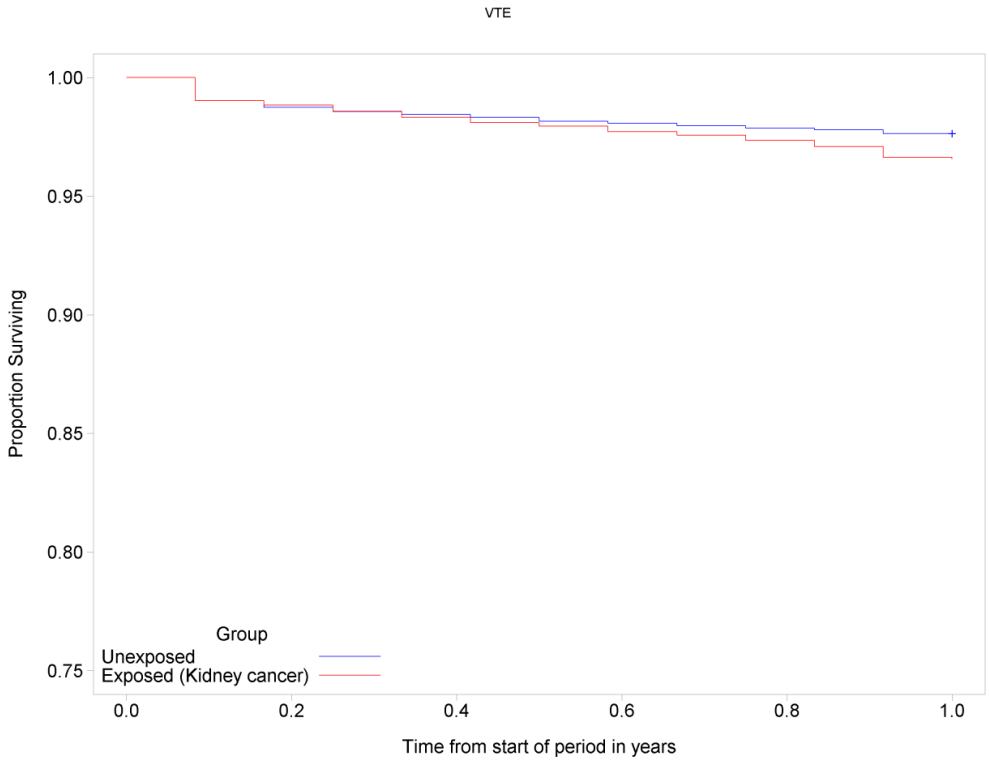

Figure E1. Time to Any VTE in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

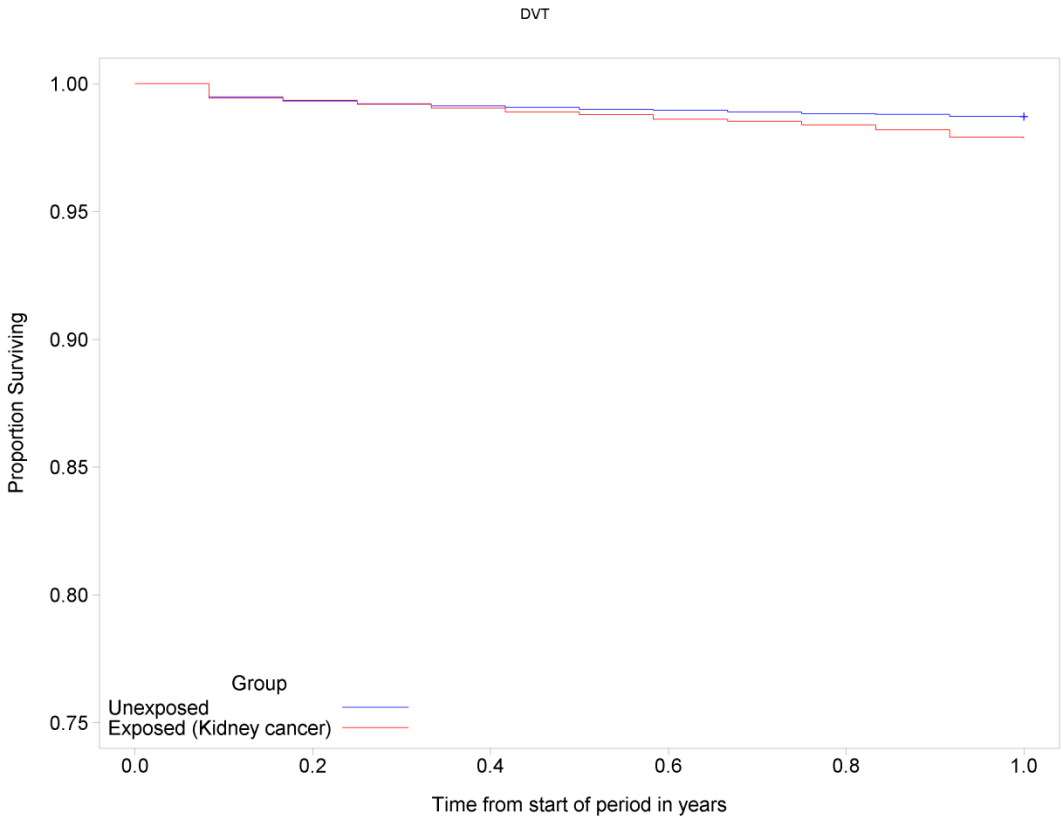

Figure E2. Time to DVT in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

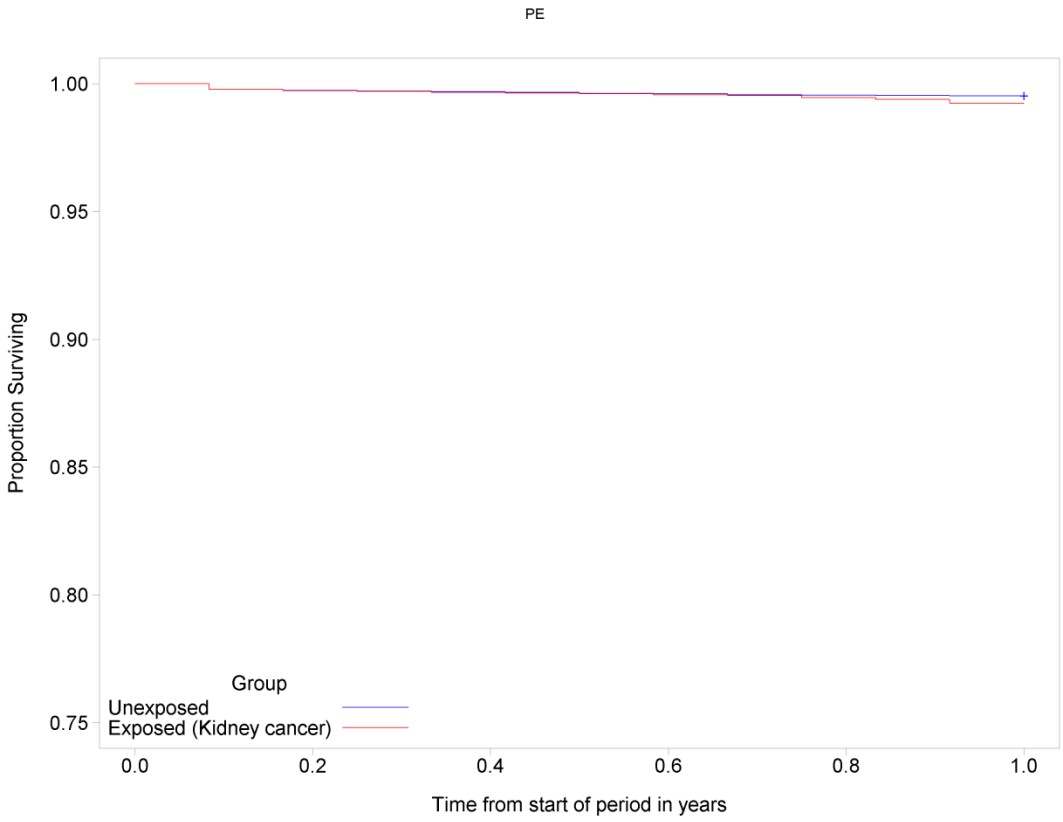

Figure E3. Time to PE in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

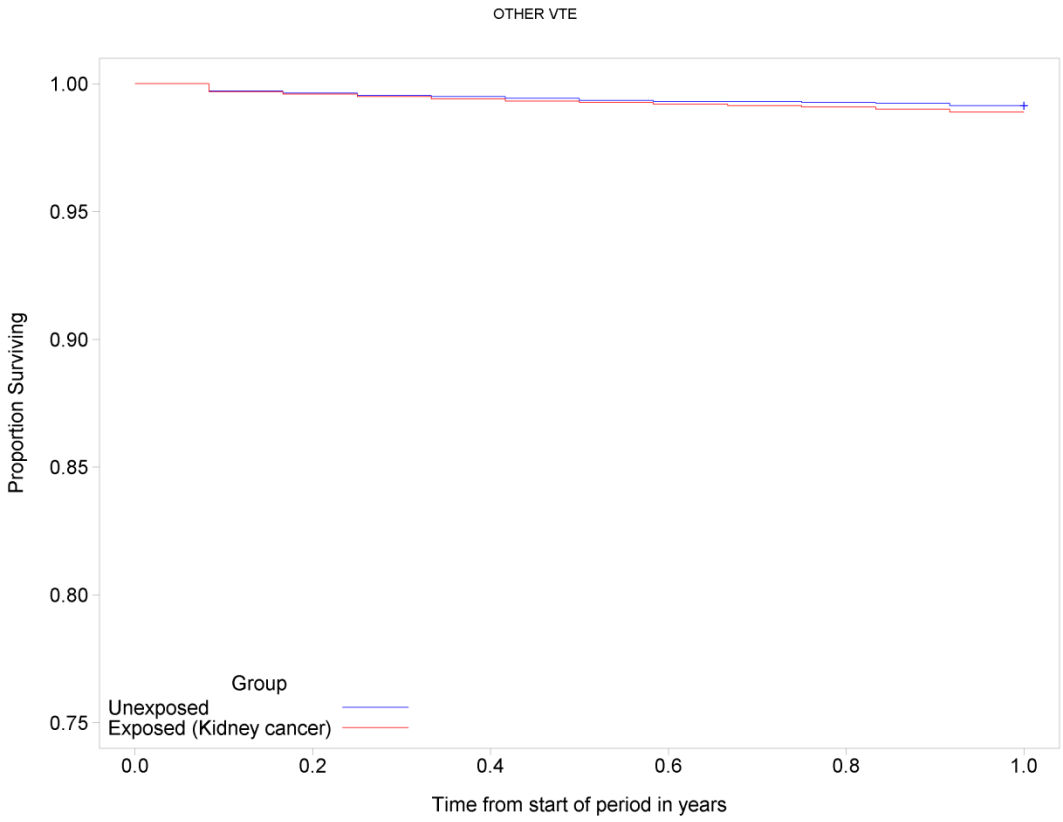

Figure E4. Time to Other VTE in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

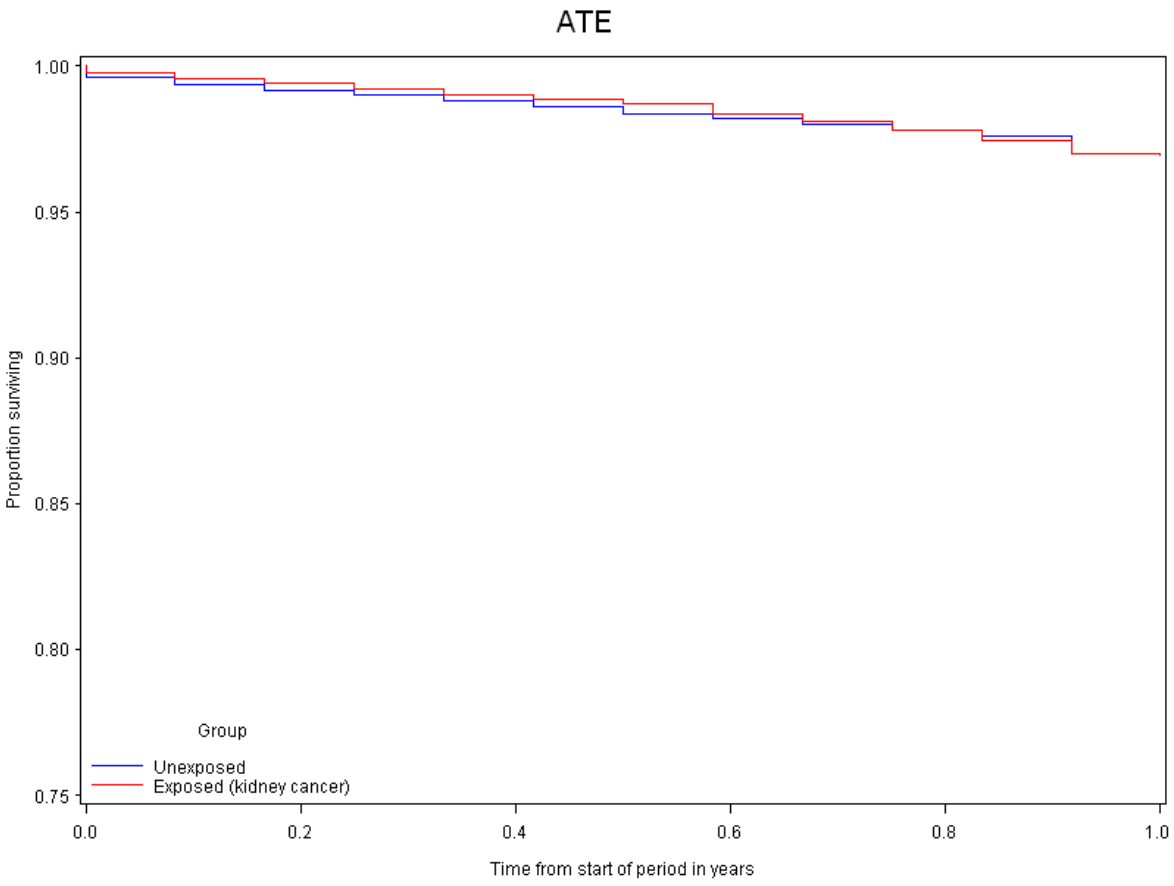

Figure E5. Time to Any ATE in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

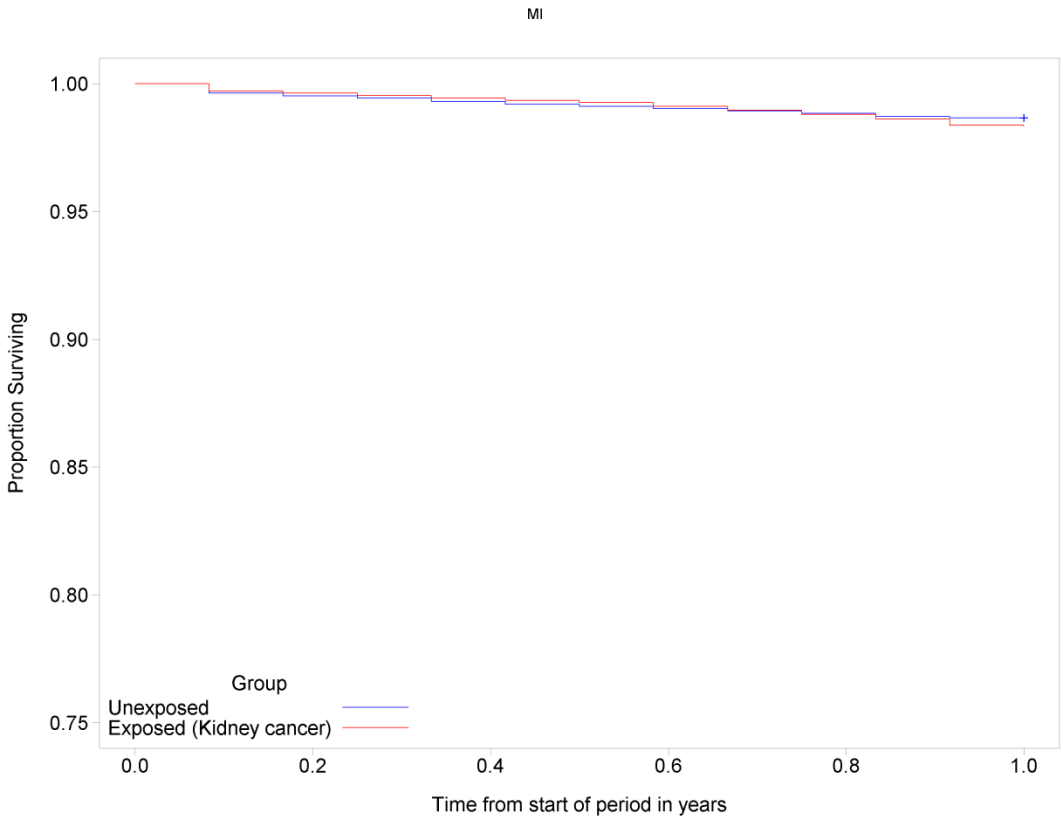

Figure E6. Time to MI in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

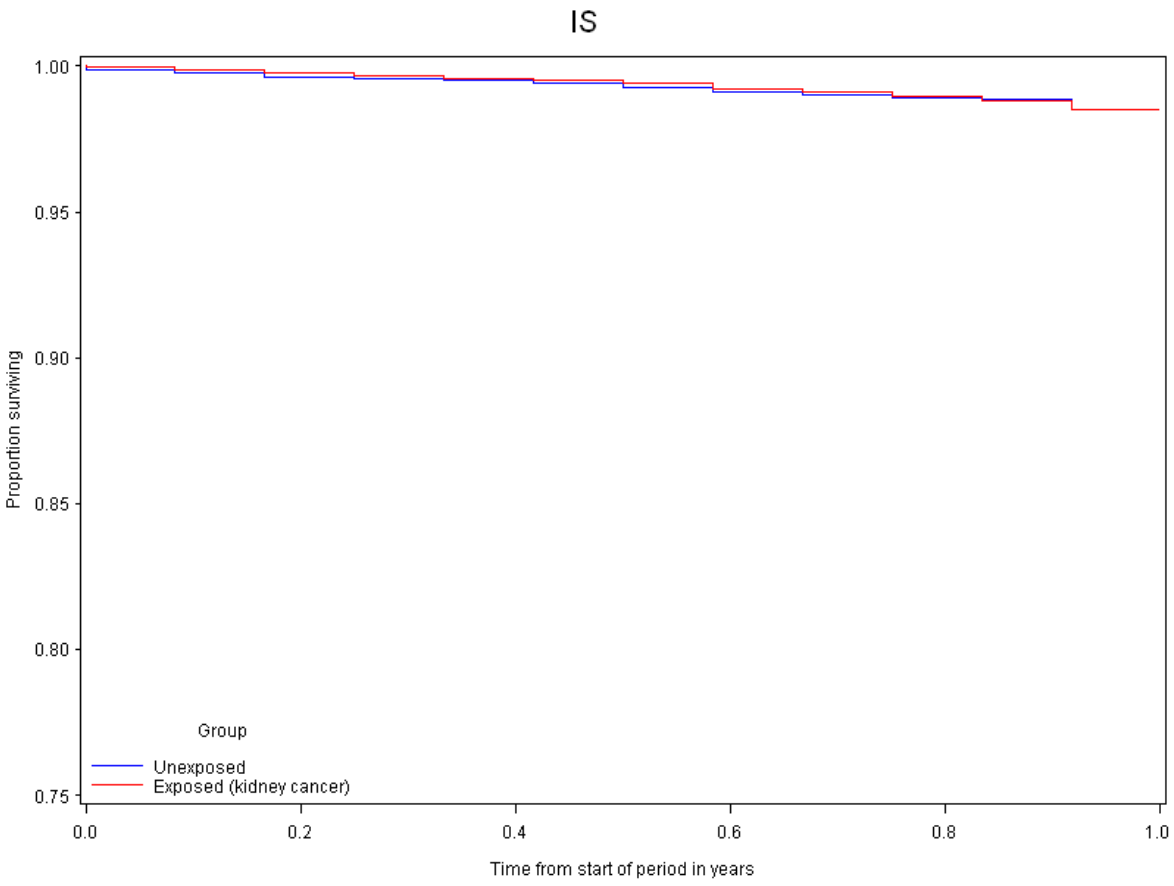

Figure E7. Time to IS in the year prior to index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

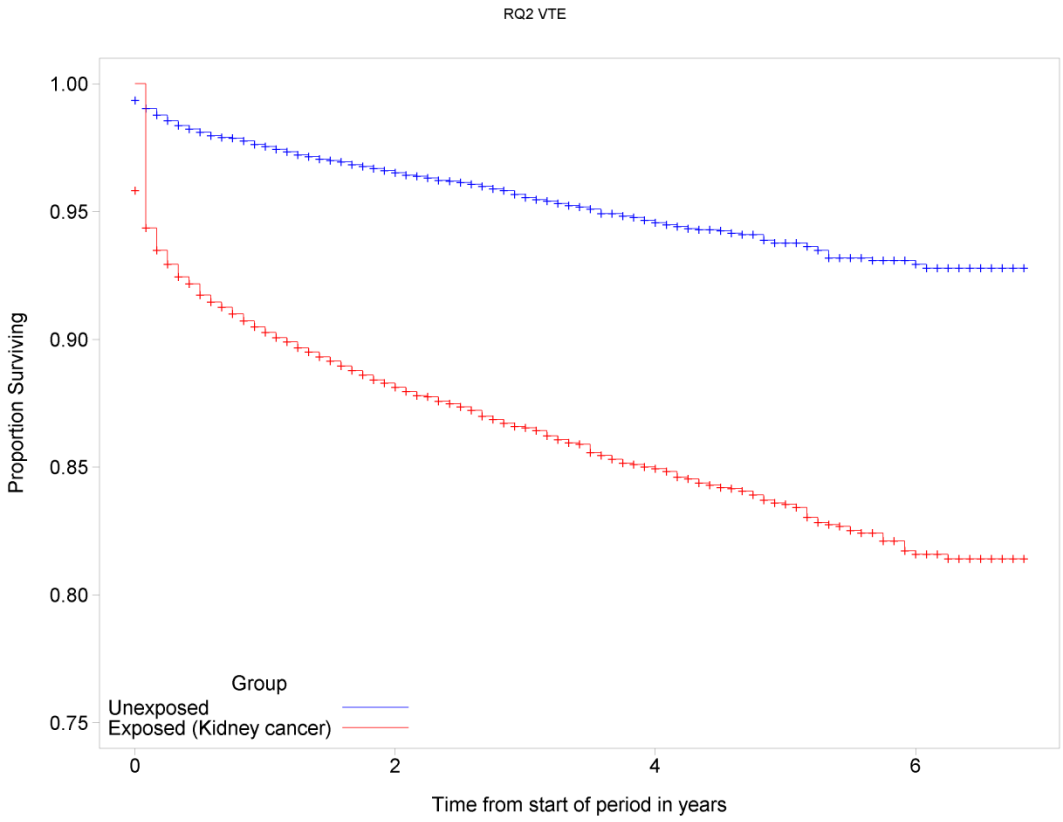

Figure E8. Time to Any VTE in the follow-up period after index date by exposure status.
Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

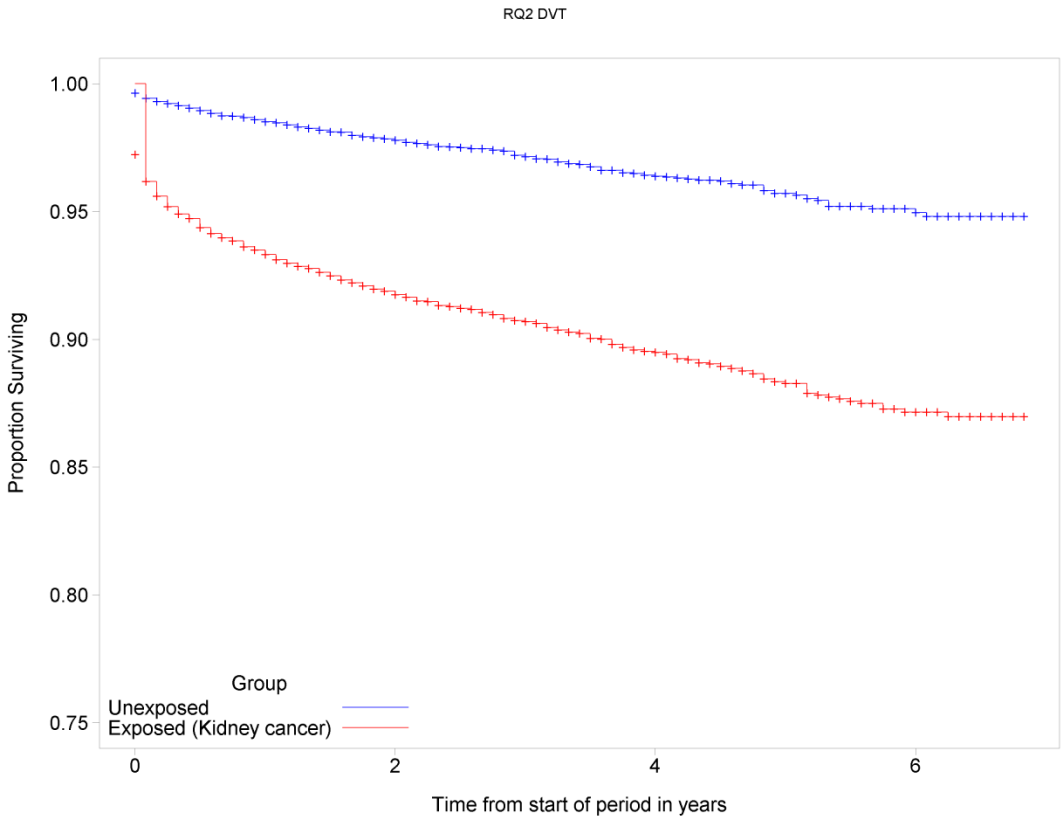

Figure E9. Time to DVT in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

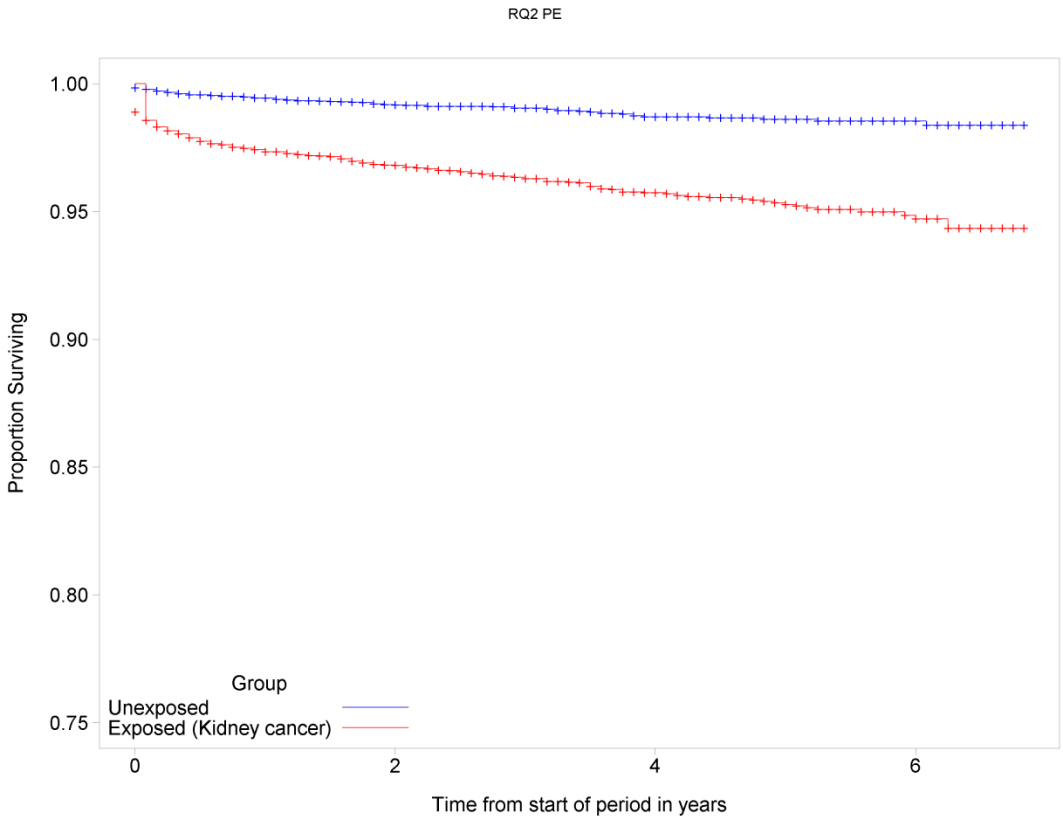

Figure E10. Time to PE in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

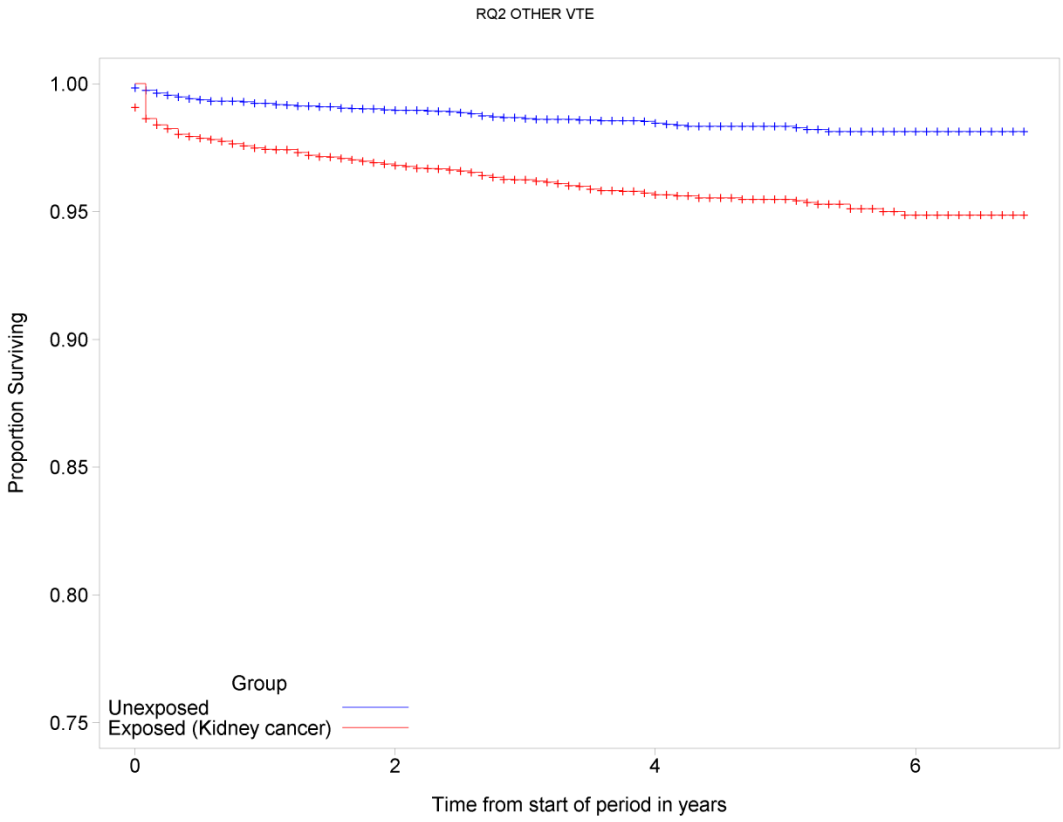

Figure E11. Time to Other VTE in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

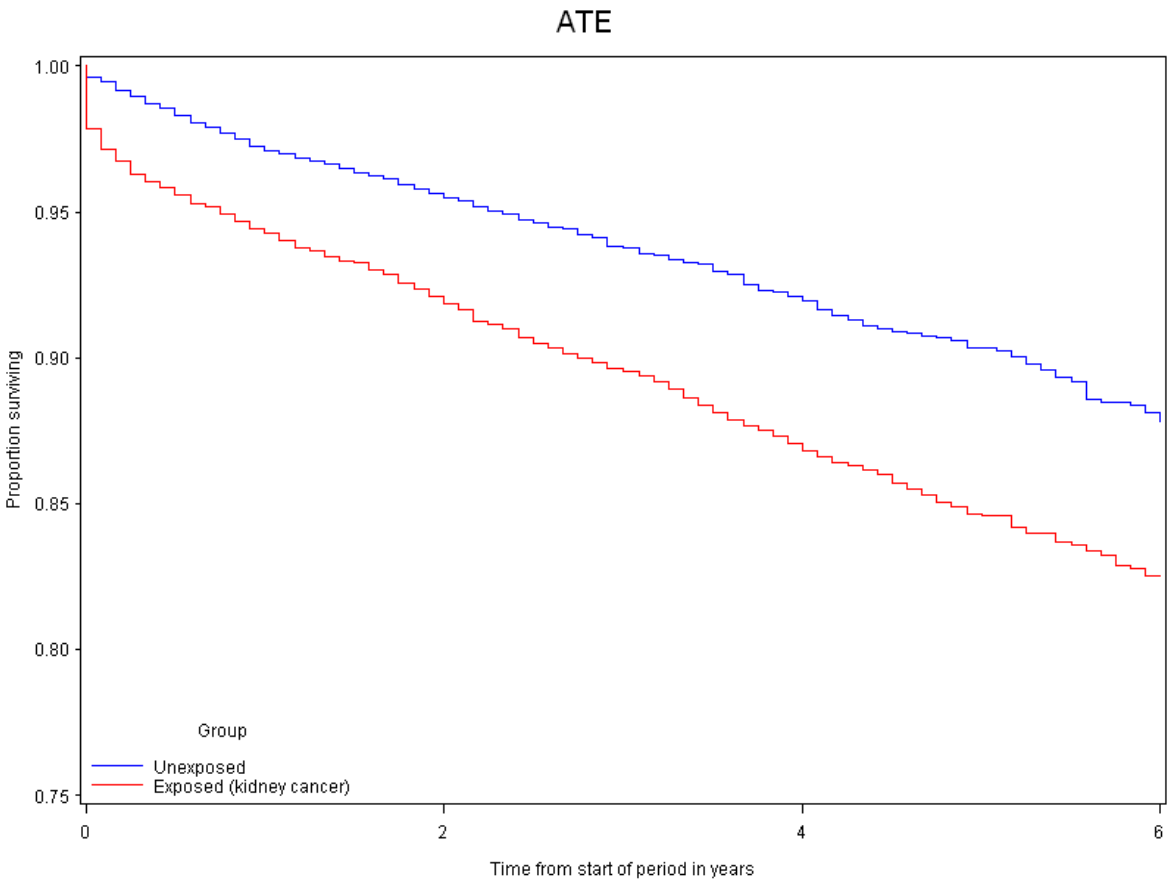

Figure E12. Time to Any ATE in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

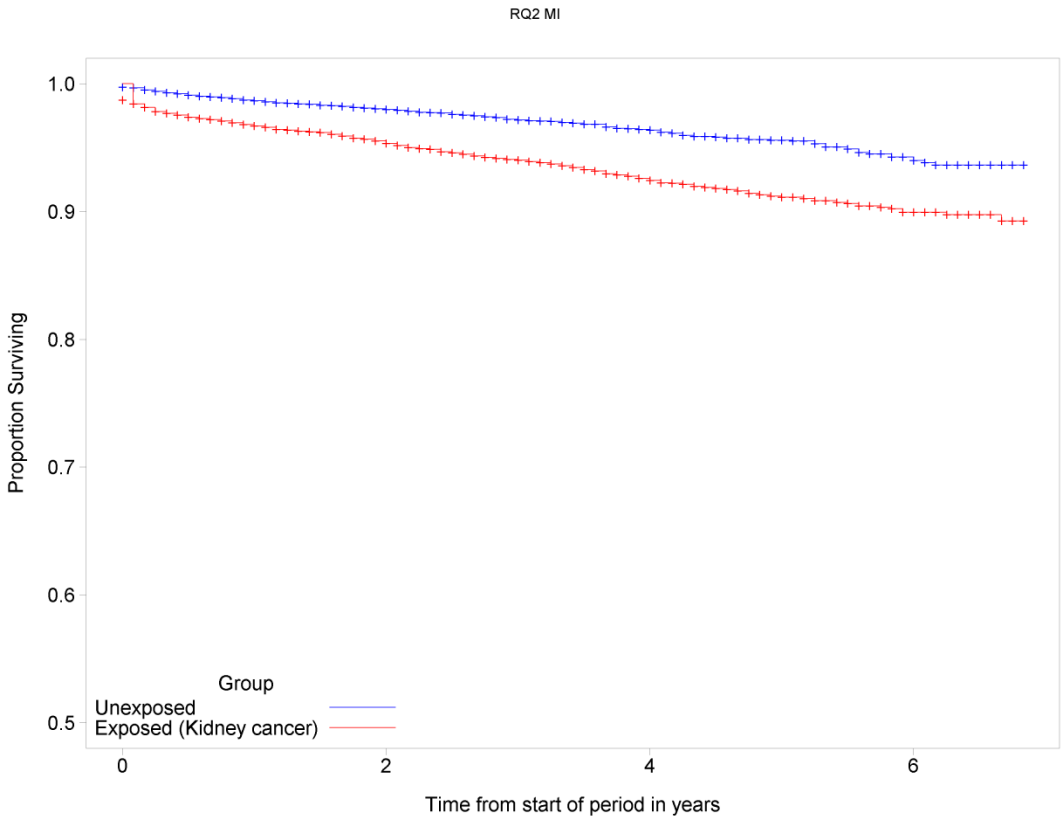

Figure E13. Time to MI in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

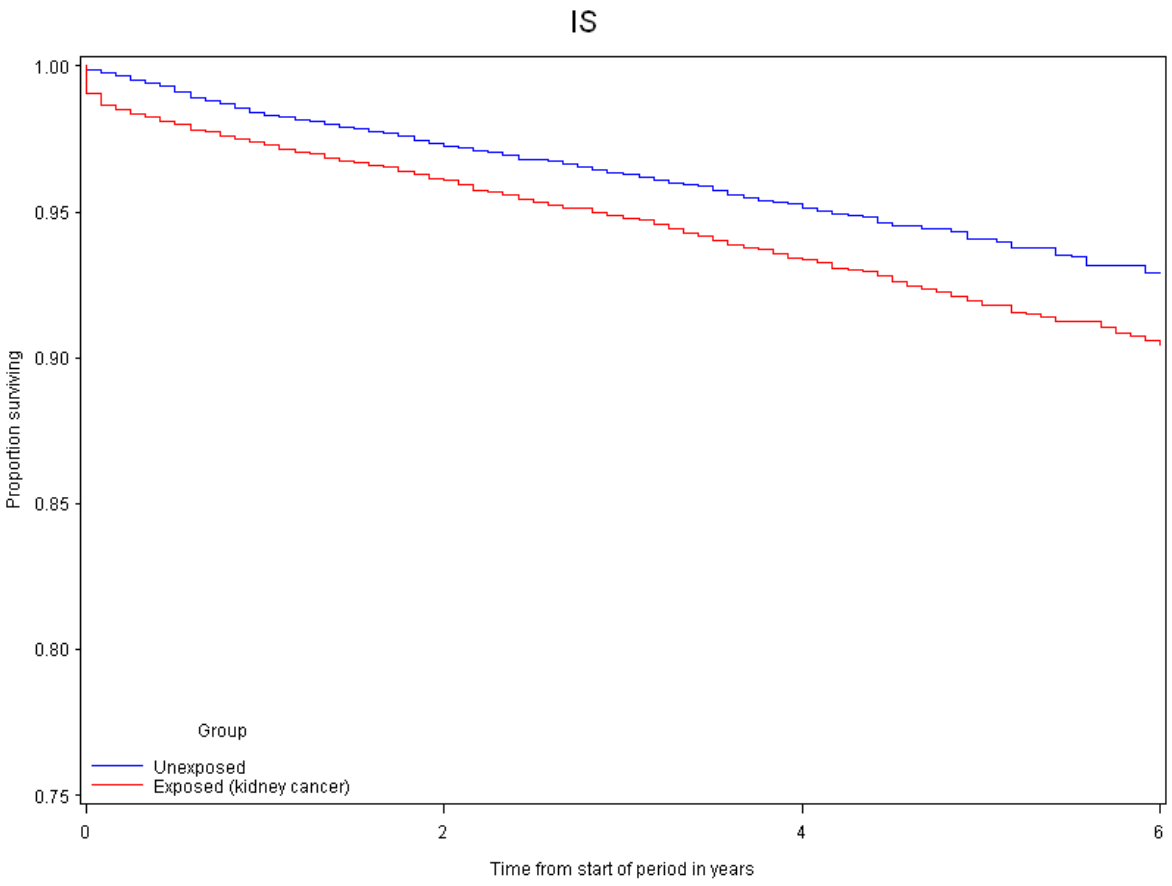

Figure E14. Time to IS in the follow-up period after index date by exposure status. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

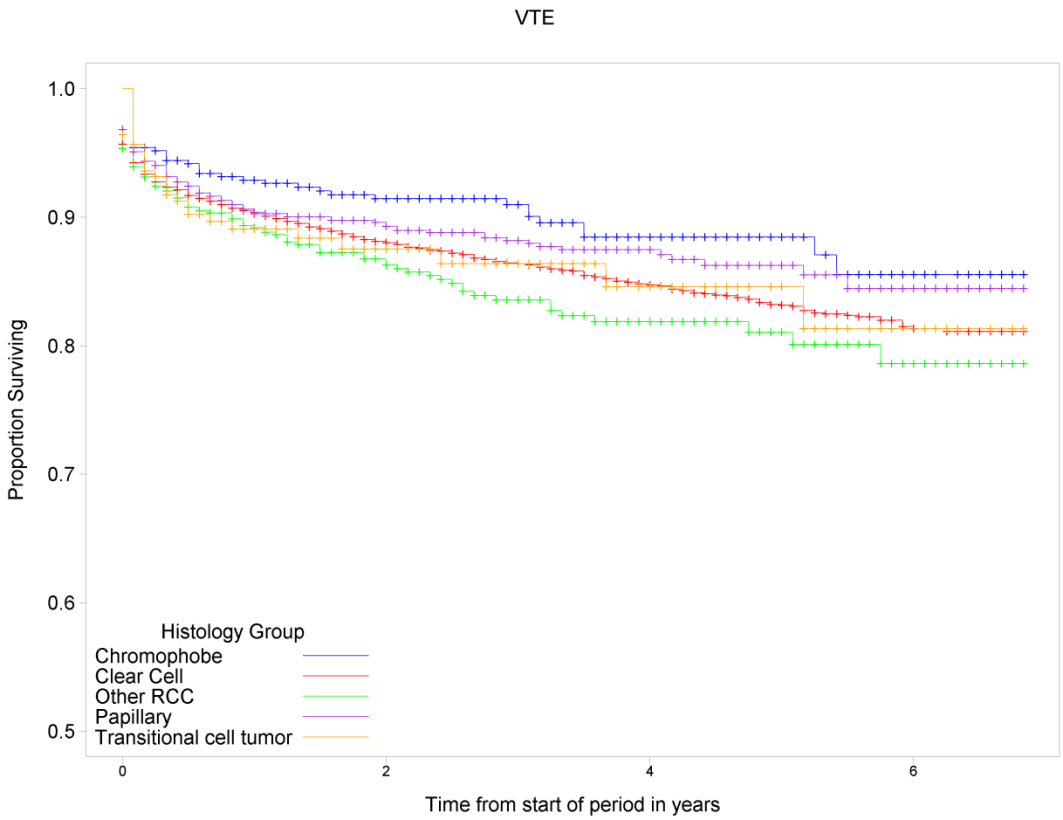

Figure E15. Time to Any VTE in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

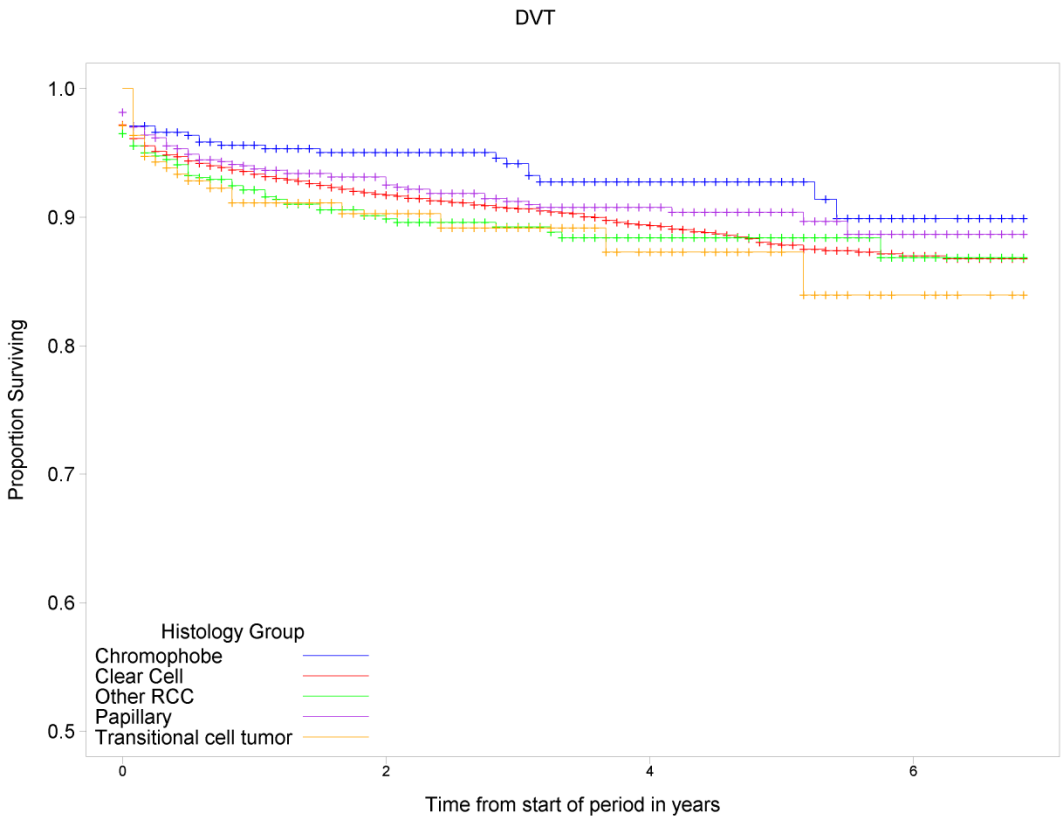

Figure E16. Time to DVT in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

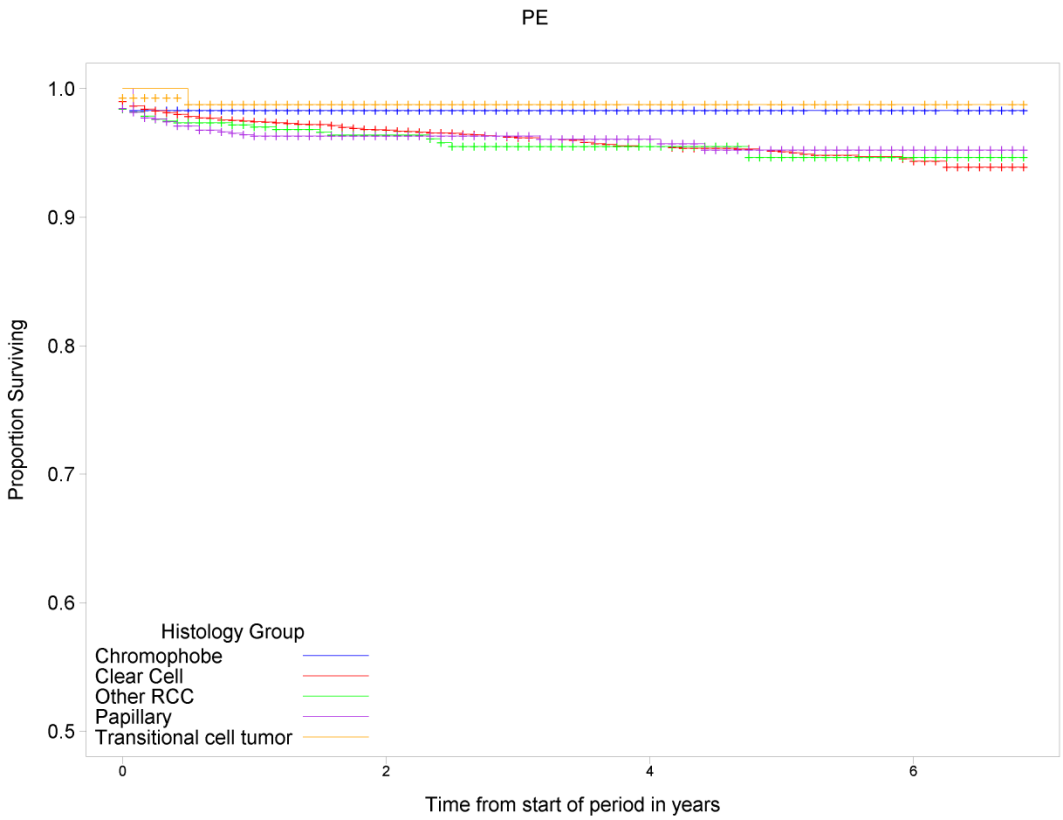

Figure E17. Time to PE in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

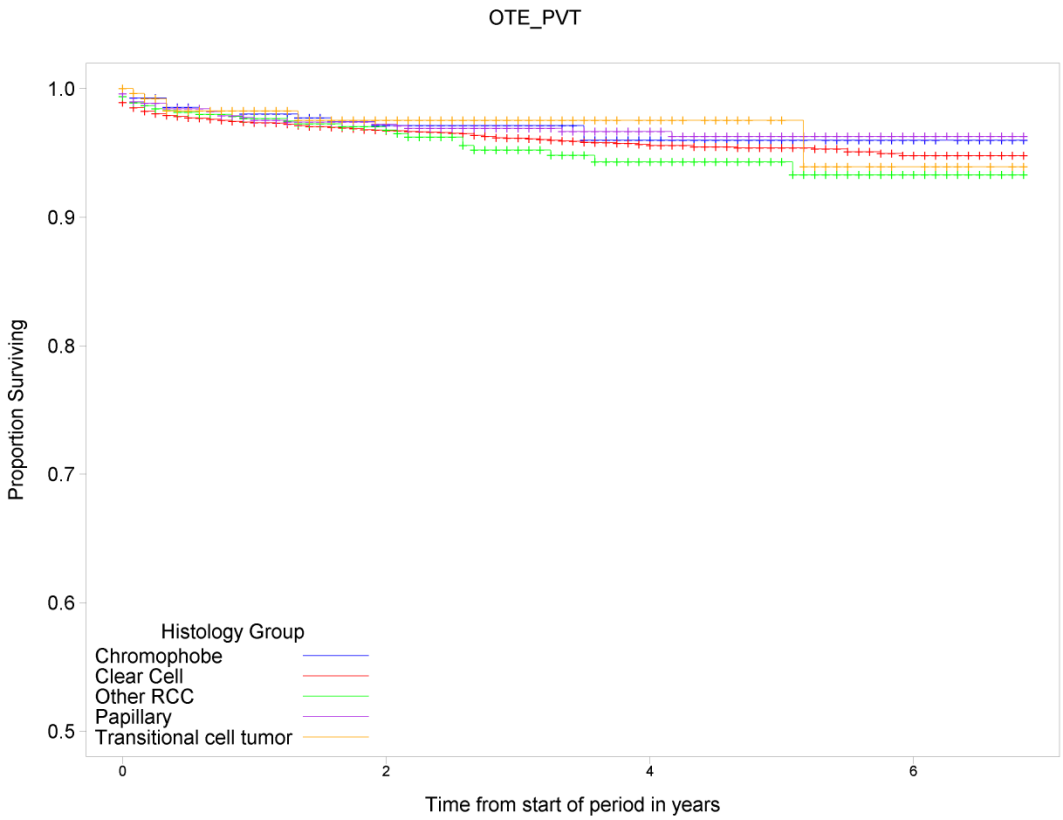

Figure E18. Time to Other VTE in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

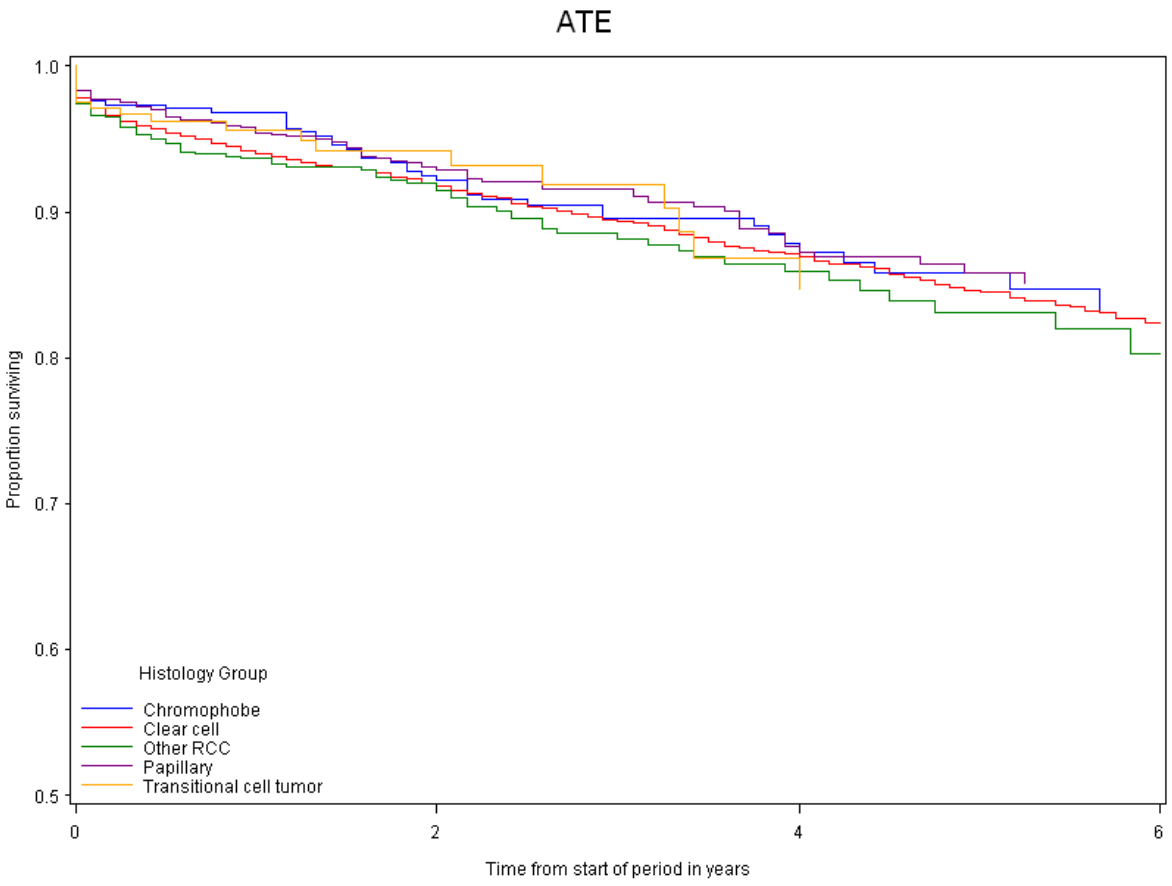

Figure E19. Time to Any ATE in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

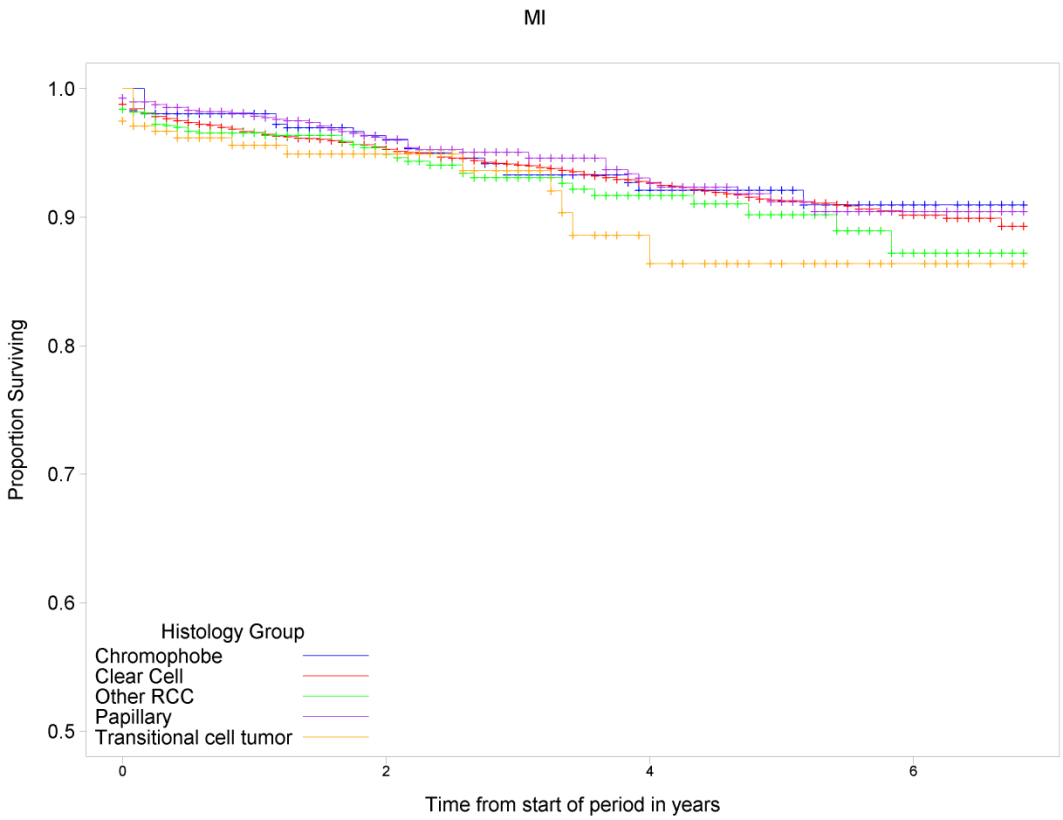

Figure E20. Time to MI in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.

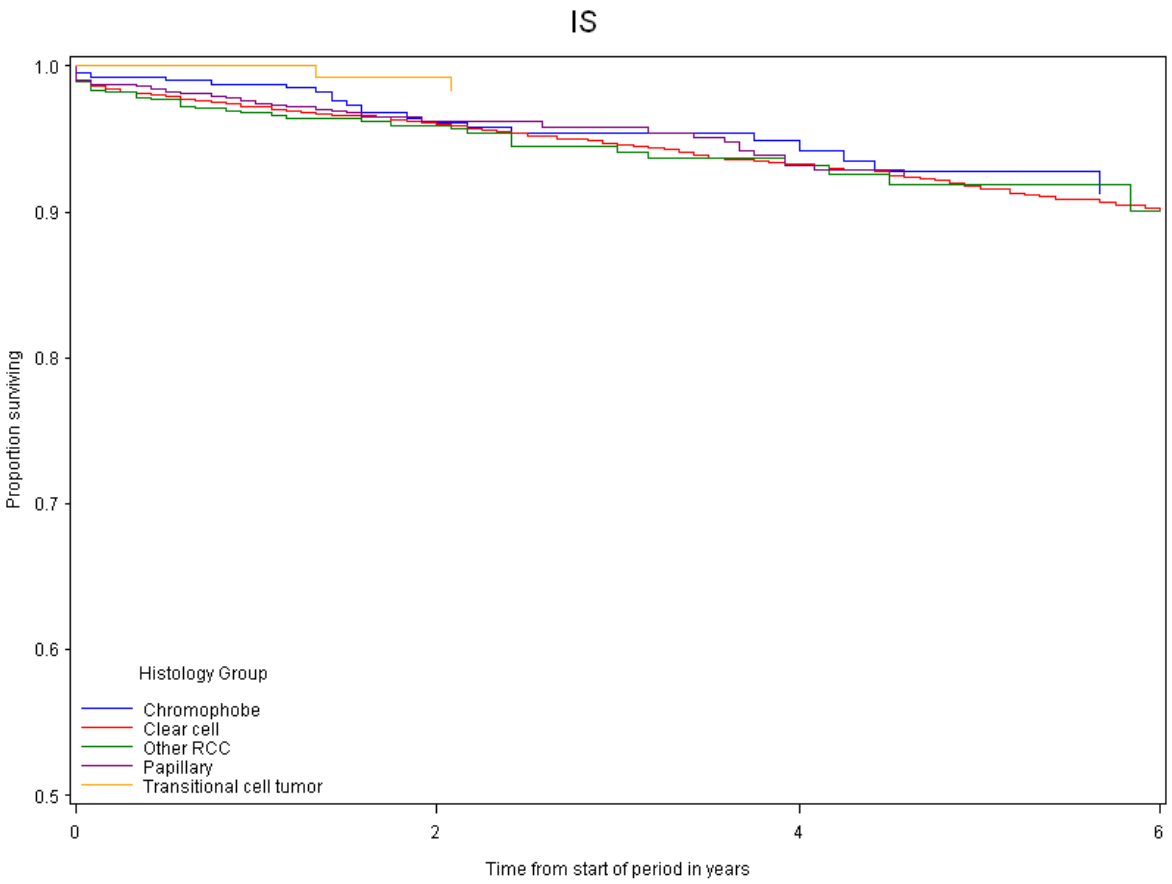

Figure E21. Time to IS in kidney cancer patients in the follow-up period after index date by histology group. Any ATE = any arterial thromboembolic event (MI or IS); DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; Other VTE = other venous thromboembolic event; PE = pulmonary embolism; VTE = venous thromboembolic event.