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Venous Thromboembolism in Patients With Reduced Estimated GFR: A Population-Based Perspective

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Abstract

Background—An increased frequency of venous thromboembolism (VTE) has been shown among patients with reduced kidney function as measured by a decreased estimated glomerular filtration rate (eGFR). However, current practices with respect to VTE prevention and management in patients with a reduced eGFR in general population settings remain uncertain.

Study Design—Observational study.

Setting & Participants—Community investigation of 1,509 metropolitan Worcester (Massachusetts) residents with validated VTE during 1999, 2001, and 2003 with further follow-up for up to 3 years.

Predictor—VTE patients further classified according to their eGFR on presentation: < 30, 30-59, 60-89, or ≥ 90 ml/min/1.73m^2 (reference group).

Outcomes—Recurrent VTE, major bleeding episodes, and all-cause mortality.

Measurements—Demographic and clinical characteristics, treatment practices, and study outcomes were extracted from patients' hospital and outpatient medical records; eGFR was estimated using the Chronic Kidney Disease Epidemiology equation.

Results—VTE patients with eGFR < 30 ml/min/1.73m^2 were at an increased risk for recurrent VTE (HR, 1.83; 95% CI, 1.03-3.25), major bleeding episodes (HR, 2.30; 95% CI, 1.28-4.16) and

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all-cause mortality (HR, 1.70; 95% CI, 1.12-2.57) over 3-year follow-up. Patients with reduced eGFR also presented with more co-morbidities and were less likely to be discharged on any form of anticoagulant therapy (72.6%, 81.0%, 82.1%, and 87.3% for eGFR < 30, 30-59, 60-89, and ≥ 90 mL/min/1.73m^2, respectively; p<0.001).

Limitations—Reduced eGFR status is presumed based on creatinine values on clinical presentation. The impact of drug dosage, timing, type of anticoagulant therapy, and medication adherence on study outcomes could not be evaluated.

Conclusions—Severe reductions in eGFR are associated with an increased risk of long-term recurrent VTE, bleeding, and total mortality in patients with VTE. A greater frequency of serious co-morbidities, difficulties implementing available management strategies, and suboptimal VTE prophylaxis during hospital admissions likely contributed to our findings.

Index words

reduced kidney function; venous thromboembolism; recurrences; major bleeds; mortality

Venous thromboembolism (VTE), consisting of deep vein thrombosis and pulmonary embolism, is the third most common cardiovascular disorder in the United States with approximately 300,000 new cases diagnosed annually[1-4]. Patients with kidney disease have been shown to have a higher prevalence of VTE and other cardiovascular conditions in comparison to patients with normal kidney function[5-9].

Despite recent advances in our understanding of the natural history of VTE[1-3, 10-12], considerable uncertainty remains regarding the optimal prevention and therapeutic management of patients with decreased kidney function. Unfortunately, patients with reduced kidney function, as measured by a decreased estimated glomerular filtration rate (eGFR), are often excluded in contemporary treatment studies of VTE since they are at increased risk for bleeding[5, 9, 13]. As a result, guidelines on anticoagulant selection and dosing in patients with decreased estimated GFR for the prevention and treatment of VTE are not clearly established, likely leading to variation in the management of these patients in the broader community setting with an unclear impact on patient outcomes.

The objectives of this observational study carried out in residents of a large central New England metropolitan area were to describe differences in the clinical and demographic characteristics, management practices, and occurrence of all-cause mortality, VTE recurrences, and major bleeding episodes in patients with independently validated VTE further classified according to their levels of estimated GFR. Data from the population-based Worcester Venous Thromboembolism Study were used for purposes of this investigation[1, 2, 14].

METHODS

Study Design, Sampling, and Data Abstraction

The Worcester Venous Thromboembolism Study is an ongoing, population-based surveillance study examining the descriptive epidemiology of VTE, including its magnitude, prophylaxis and management strategies, in-hospital and post-discharge outcomes, and long-term recurrence, bleeding, and all-cause mortality rates, among residents from a large central New England metropolitan area[1, 2, 14]. The catchment area for this study included all twelve hospitals serving residents of the Worcester, MA, Standard Metropolitan Statistical Area (2000 census = 478,000). Details of this study have been previously reported[1, 2, 14].

A total of 7,222 medical records were obtained of greater Worcester residents diagnosed with ICD-9 codes consistent with potential VTE during the 3 study years of 1999, 2001, and 2003[1] (The ICD-9 codes for VTE classification provided in Item S1, available as online supplementary material). Trained physician and nurse abstractors independently validated each potential case of new onset VTE based on a modified classification schema[15]; each VTE event was independently adjudicated by the lead investigator (F.A.S.). Sociodemographic, clinical, and treatment variables were abstracted from hospital and outpatient medical records. Heart rate, blood pressure, and laboratory levels were obtained at the time closest to the diagnosis of VTE. Medical history variables defined as "recent" included conditions reported by a physician that were occurring or active in the 3 months prior to the diagnosis of VTE. Patients with cancer were considered to have had a malignancy that was currently being treated or palliated (except for basal cell skin cancer). The "surgery" variable included patients who had major operations where general or epidural anesthesia lasted 30 minutes or longer. The aggregated "vascular disease" variable included patients with prior coronary heart disease, those who had previously undergone a percutaneous coronary intervention or coronary artery bypass surgery, or who had been previously diagnosed with peripheral vascular or cerebrovascular disease. Similarly, cardiac procedures were defined to include electrophysiology studies, percutaneous coronary interventions, pacemaker implantations, and implantable cardiac defibrillator placements. Serious infections were limited to those involving the blood, bone and joint, central nervous, cardiovascular, gastrointestinal, and respiratory systems (pneumonia only), surgical sites, or the skin and requiring hospitalization and/or intravenous antibiotics.

Major bleeding was defined as any episode of bleeding requiring transfusion or hospitalization, or that was life threatening (e.g., resulted in myocardial infarction, stroke, or death). Potential recurrent events of VTE were classified using criteria identical to that employed for incident cases, with the exception being that a definite or probable recurrence of deep vein thrombosis or pulmonary embolism required the documentation of thrombosis in a previously uninvolved venous or pulmonary arterial segment by diagnostic imaging (compression ultrasound, ventilation perfusion imaging, or CT scan). The study's principal investigator reviewed the medical records and diagnostic imaging reports of each case of potential VTE recurrence, and only definite or probable events were included[1]. Patients' long-term vital status was determined through the review of their medical records and death certificates[1].

Serum creatinine levels were obtained from each hospital's laboratory at the time of diagnosis of VTE. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation[16, 17]. Patients with VTE were stratified into 4 comparison groups according to baseline levels of eGFR: eGFR < 30 ml/min/1.73m^2, eGFR = 30-59 ml/min/1.73m^2, eGFR = 60-89 ml/min/1.73m^2 and eGFR ≥ 90 ml/min/1.73m^2. Patients on dialysis (n=43) were excluded from the present analysis since the natural history of VTE and its associated complications, diagnosis, and management may be significantly different from those not undergoing dialysis. In addition, patients with missing eGFR data (n=350) were excluded. The final study sample consisted of 1,509 greater Worcester residents with an independently validated episode of VTE during the study years of 1999 (n=470), 2001 (n=532), and 2003 (n=507)[1].

Statistical Analysis

Differences in demographic and clinical characteristics as well as use of therapeutic modalities were compared for patients who presented with VTE across categories of eGFR using Mantel-Haenszel chi-square tests for discrete variables and ANOVA tests for continuous variables. Short-term (30-day) and long-term (3-year) rates of VTE recurrence, major bleeding (censoring subjects at the time of death), and all-cause mortality were

calculated using Kaplan-Meier estimates. Short-term and long-term event rates per 100 person-years were also estimated for study outcomes.

Cox proportional hazards models were constructed to evaluate whether decreased eGFR was associated with outcomes of all-cause mortality, VTE recurrences, and major bleeding episodes while simultaneously adjusting for several demographic and clinical factors as well as duration of study follow-up; proportional hazards assumptions were satisfied for all models. Potential confounders included in our regression models were determined *a priori*, based on clinical relevance and findings from the published literature, for each of the individual exposure-outcome relationships. Further refinement of potential confounding factors was performed using univariate analyses identifying possible risk factors with a significance level of $p < 0.25$. All models were adjusted for study year and setting of VTE (hospital vs. outpatient) occurrence to account for residual confounding that may have occurred due to unmeasured covariates within each of the study cohorts and within hospital or outpatient settings. Multivariable adjusted hazards ratios (HR) and accompanying 95% CIs were computed in a standard fashion using VTE patients with eGFR ≥ 90 ml/min/1.73m^2 as the reference category.

RESULTS

Demographic and Clinical Characteristics

Of the 1,509 patients with confirmed VTE, 122 patients had eGFR < 30 ml/min/1.73m^2, 432 had eGFR of 30-59 ml/min/1.73m^2, 575 had eGFR of 60-89 ml/min/1.73m^2, while the remainder (n=380) had eGFR ≥ 90 ml/min/1.73m^2. The prevalence of reduced eGFR (< 60 ml/min/1.73m^2) in our total study sample was essentially similar across the 3 study years; 37.7% of patients had reduced eGFR in 1999, 36.8% in 2001, and 35.7% in 2003 (p=0.8). At initial VTE presentation, deep vein thrombosis was most common among patients with eGFR ≥ 90 ml/min/1.73m^2 (72.4%) while pulmonary embolism was most frequent among patients with eGFR of 30-59 ml/min/1.73m^2 (19.7%) or eGFR of 60-89 ml/min/1.73m^2 (19.3%); both DVT and pulmonary embolism were observed more often in patients with eGFR of 30-59 ml/min/1.73m^2 (19.2%) or eGFR < 30 ml/min/1.73m^2 (18.2%). Unprovoked VTE was least common among patients with eGFR < 30 ml/min/1.73m^2 (Table 1).

In comparison to patients with eGFR ≥ 90 ml/min/1.73m^2, VTE patients with reduced eGFR were more likely to be older, female, of Caucasian descent, and have several co-morbidities present including cancer, chronic lung disease, heart failure, hypertension, diabetes, and vascular disease; they were also more likely to have undergone a cardiac procedure (Table 1). In addition, VTE patients with reduced eGFR were more likely to have lower hematocrit levels and lower average heart rates at the time of clinical presentation. On the other hand, VTE patients with reduced kidney function were less likely to be smokers or to have undergone recent surgery compared to VTE patients with eGFR ≥ 90 ml/min/1.73m^2 (Table 1). Lastly, VTE patients with either eGFR < 30 ml/min/1.73m^2 (23.0%) or eGFR ≥ 90 ml/min/1.73m^2 (28.4%) were more likely to have had a recent placement of a central venous catheter compared to those with eGFR = 30-59 ml/min/1.73m^2 (13.9%) or eGFR of 60-89 ml/min/1.73m^2 (16.0%) (Table 1).

Prior Prophylaxis of At Risk Patients

Utilization of anticoagulant VTE prophylaxis prior to a VTE event occurring during a hospitalization for another diagnosis (including heparin, low molecular weight heparin, hirudin, and warfarin) did not differ across eGFR categories (49.4%, 51.7%, 50.3%, and 51.4%, respectively, for eGFR values of < 30, 30-59, 60-89, and ≥ 90 ml/min/1.73m^2; p=0.9). On average, about 43% (range, 39%-49%) of patients in each of our eGFR strata had

been hospitalized in the 3 months prior to their VTE event. Use of anticoagulant prophylaxis during patient's prior hospitalizations also did not differ by eGFR status (41.4%, 44.7%, 37.6%, and 47.2%, respectively; p=0.7).

Treatment and Management Practices

Patients with reduced eGFR and VTE were less likely to be treated with low molecular weight heparin (32.8%, 38.7%, 44.5%, and 53.2%, respectively, for eGFR <30, 30-59, 60-89, and ≥ 90 ml/min/1.73m^2; p<0.001) or warfarin (60.7%, 74.5%, 75.5%, and 79.0%, respectively; p <0.001). However, patients with reduced eGFR were more likely to have an inferior vena cava filter implanted as part of their management (17.7%, 15.6%, 13.1%, and 9.1%, respectively; p = 0.003). Interestingly, almost 15% of VTE patients with eGFR < 30 ml/min/1.73m^2 had received no initial anticoagulant therapy compared to only 5-6% of VTE patients in each of the remaining eGFR groups (p = 0.01). Among those who survived to hospital discharge (n=1,418), patients with reduced eGFR were significantly less likely to have been discharged on any form of anticoagulant therapy (72.6%, 81.0%, 82.1%, and 87.3%, respectively; p<0.001).

Recurrent Episodes of VTE and Decreased eGFR

Compared with that of the higher eGFR groups, the incidence of VTE recurrences was highest among patients with eGFR < 30 ml/min/1.73m^2 for both short-term and long-term follow-up (Table 2; Figure 1). After Cox regression analysis, patients with eGFR < 30 ml/min/1.73m^2 were significantly more likely to have experienced a recurrent episode of VTE during long-term follow-up (HR, 1.83; 95% CI, 1.03-3.25) in comparison to those with eGFR ≥ 90 ml/min/1.73m^2 (Table 3); no significant differences in the short or long-term risk of recurrent episodes of VTE were observed for patients with eGFR of 30-59 ml/min/1.73m^2 or 60-89 ml/min/1.73m^2 as compared to patients with eGFR ≥ 90 ml/min/1.73m^2 after covariate adjustment.

Major Bleeding Episodes and Decreased eGFR

Compared with the higher eGFR groups, patients with eGFR < 30 ml/min/1.73m^2 were significantly more likely to have developed an episode of major bleeding (Table 2; Figure 2) (p <0.001). In examining bleeding risks after controlling for several potentially confounding factors, patients with eGFR < 30 ml/min/1.73m^2 were significantly more likely to have experienced a major bleeding episode as compared to patients with eGFR ≥ 90 ml/min/1.73m^2 at the time of both short-term (HR, 2.48; 95% CI, 1.16-5.27) and long-term follow-up (HR, 2.30; 95% CI, 1.28-4.16) (Table 3). No difference in bleeding risk was found among VTE patients with eGFR of 30-59 or 60-89 ml/min/1.73m^2 as compared to patients with eGFR ≥ 90 ml/min/1.73m^2 at either 30-days or 3-years after their index VTE event following covariate adjustment.

All-Cause Mortality and Decreased eGFR

Compared with the higher eGFR groups, patients with eGFR < 30 ml/min/1.73m^2 were significantly more likely to have died over the course of our follow-up (Table 2; Figure 3) (p <0.001). After adjusting for differences in duration of follow-up and holding potential covariates constant, there was a significantly higher risk of dying for patients with eGFR < 30 ml/min/1.73m^2 as compared to those with eGFR ≥ 90 ml/min/1.73m^2 at the time of both short-term (HR, 2.39; 95% CI, 1.01-5.64) and long-term follow-up (HR, 1.70; 95% CI, 1.12-2.57) (Table 3).

DISCUSSION

The incidence and prevalence of kidney disease have nearly doubled over the past decade, presently affecting more than 20 million Americans[18-20]. Given the increasing magnitude of this disease, the frequency with which these patients are hospitalized, and increased bleeding risk associated with most anticoagulants, a better understanding of the clinical profile, current management, and outcomes of patients with reduced kidney function who are at risk for, and/or develop VTE, is needed.

In our population-based study, patients with decreased eGFR on clinical presentation comprised more than one-third of patients experiencing VTE in this large, central New England community. Approximately 8% of patients with VTE during our study years had severe reductions in eGFR (eGFR < 30 ml/min/1.73m^2) at the time of clinical presentation. The prevalence of reduced kidney function in our study population was approximately two times greater than national estimates of kidney disease prevalence in the United States population[18]. Not surprisingly, patients with decreased eGFR were older and more likely to have important underlying co-morbidities present as compared to patients with eGFR ≥ 90 ml/min/1.73m^2 at the time of initial VTE presentation.

Approximately 35-45% of patients with reduced eGFR experienced their VTE event during a hospitalization for another condition or had a recent (< 3 month), non-VTE related hospitalization. Accordingly, adequate prophylaxis during hospital encounters may be the most effective way to decrease the risk of VTE in these high-risk patients. Although it was encouraging that prior anticoagulant prophylaxis in these patients did not differ according to the extent of kidney function as measured by eGFR, the overall use of these anticoagulants during these at-risk periods remained woefully suboptimal (40-50%). Even though appropriate dosing of low-molecular weight heparin in patients with kidney disease for VTE prophylaxis remains somewhat controversial, there are data to suggest limited bioaccumulation of low molecular weight heparin in this population at standard doses for finite periods[21, 22]. Furthermore, low-dose unfractionated heparin remains an option in patients with severe kidney disease[23].

Patients with reduced eGFR were significantly less likely to have been started on anticoagulant therapy for acute VTE. Approximately 1 in 6 patients with decreased eGFR had an inferior vena cava filter placed as part of their acute management. More than 20% of subjects with reduced eGFR were discharged without anticoagulation. Among patients with severe declines in kidney function not discharged on anticoagulant therapy, 32% had suffered in-hospital major bleeding episodes compared to 23% of those with eGFR ≥ 90 ml/min/1.73m^2. While we cannot adequately explore the rationale for treatment decisions using these retrospective observational data, they most likely reflect a combination of perceived increased bleeding risk and early post-treatment bleeding events in patients with kidney disease.

Prior studies have demonstrated a heightened risk of developing subsequent VTE events in patients who have already experienced a first VTE episode, with the greatest risk of recurrence occurring during the first 6 to 12 months after the index event[24-27]. Cumulative incidence rates of recurrent events have ranged from approximately 1-5% within the first month to 15-20% within 3 years following the incident VTE episode[25, 27-31]. Our data fall within the range of these previously reported results; between 4-7% of our patients experienced a recurrent episode of VTE during the first 30-days of the index VTE episode and between 13-19% developed a recurrence within 3-years of the initial event. Patients with eGFR > 30 ml/min/1.73m^2 were at increased risk for experiencing a recurrent episode of VTE compared to patients with eGFR ≥ 90 ml/min/1.73m^2 over our extended follow-up.

Although we cannot satisfactorily explore the reasons for this increased risk, which is most likely multi-factorial, an increase in thrombotic risk in patients with kidney disease can be postulated. However, it is also likely that additional co-morbidities resulting in frequent hospitalizations and interruptions of initial VTE therapy due to bleeding related issues (as well as concomitant increased use of inferior vena cava filters) contributed to these findings.

With respect to major bleeding episodes, patients with reduced kidney function often suffer from platelet dysfunction and impaired platelet-vessel wall interaction leading to an increased tendency for bleeding[32-34]. However, bleeding is also a common complication of VTE, primarily resulting from anticoagulant use for therapeutic management[35-37]. Our results show that the risk of major bleeding events is substantially increased in VTE patients with eGFR < 30 ml/min/1.73m^2 as compared to patients with eGFR ≥ 90 ml/min/1.73m^2. During the first 30-days after the initial VTE event, almost 15% of patients with severe reductions in eGFR experienced a major bleeding episode as compared to only 6% of patients with eGFR ≥ 90 ml/min/1.73m^2. Within 3-years of the initial VTE episode, bleeding risk more than doubled for patients with severe reductions in eGFR as compared to patients with normal eGFR ranges. These findings are consistent with several studies that have evaluated the risk of bleeding in patients with chronic kidney disease (CKD), and other disease states requiring anticoagulation[38-40]. For example, in a nationally representative sample of patients hospitalized with myocardial infarction, higher rates of bleeding were observed in patients with severe CKD as compared to patients with mild/moderate or no CKD[38]. Similarly, data from the Global Registry of Acute Coronary Events (GRACE)[40] as well as from the OASIS 5 trials[39] found that, among patients with acute coronary syndromes, bleeding rates increased with greater severity of CKD in comparison to acute coronary syndrome patients without evidence of CKD.

Long-term mortality was very high in patients with reduced eGFR and VTE in our study, mirroring rates generally seen in patients with heart failure in the community[41, 42]. Between 40-50% of patients with eGFR of 30-59 or 60-89 ml/min/1.73m^2, and 70% of patients with eGFR < 30 ml/min/1.73m^2, died over our 3-year follow-up. In agreement with previously published results, significant differences in mortality were observed in VTE patients with decreased eGFR in comparison to patients with normal kidney function[9, 13]. Accelerated rates of cardiovascular disease in patients with kidney disease have been shown to increase their risk of dying as compared to patients without kidney disease[42]. However, whether or not complications of VTE, such as recurrent pulmonary embolism, contribute to the observed mortality rates in this high-risk population warrants further study beyond the scope of this present investigation.

The strengths of the present study include the generalizability of our population-based design that represents all patients with independently validated VTE from a well-defined, large central New England metropolitan area and our independent review and validation of patients' medical records.

Similar to the design and conduct of any observational study, the present study has several limitations that must be kept in mind when interpreting the study results. Although a broad screening was conducted for identifying all possible VTE cases that occurred in the greater Worcester population, complete ascertainment of index VTE events, VTE recurrences, or major bleeding episodes may not have been obtained, especially for residents who sought care outside of our catchment area following initial presentation for VTE. Failure to capture these patients likely underestimated the magnitude of these endpoints in our study sample, potentially diluting our study results. Deaths due to VTE recurrences or bleeding episodes were unable to be estimated in this study because of the low autopsy rates. Because patients with moderate/severe kidney disease are more likely to receive transfusions because of their

lower baseline hemoglobins, the occurrence of major bleeding episodes in these patients may be overestimated. We cannot comment on the use of non-pharmacological approaches to prophylaxis, including the use of sequential compression devices, or the influence of patients with nephrotic syndrome, proteinuria, or an elevated serum urea nitrogen on study outcomes since these data were not collected; hence, the utilization of prophylactic procedures in our population may not be generalizable to additional patient populations. In addition, we cannot differentiate between patients with acute or CKD since our methods of stratification were based on initial creatinine values. Finally, we cannot comment on the impact of drug dosage, timing, type of anticoagulant therapy during VTE-related adverse events, and issues related to medication adherence on the subsequent risks of death, VTE recurrence, or bleeding. Further study of the influence of long-term treatment strategies on selected patient outcomes remains of crucial importance in decreasing the overall risks of adverse complications associated with VTE.

The results of our population-based study demonstrate significant differences in the clinical characteristics, management approaches, and occurrence of short and long-term outcomes in VTE patients with reduced eGFR on presentation as compared to patients with normal eGFR ranges. Given the increased prevalence, clinical impact, and economic burden of kidney disease, our results may be used to inform efforts designed to improve the monitoring and treatment of VTE complications by health practitioners in these high risk patients. Future studies evaluating novel anticoagulants for the prophylaxis and treatment of deep vein thrombosis should include these high-risk patients given current limitations in available treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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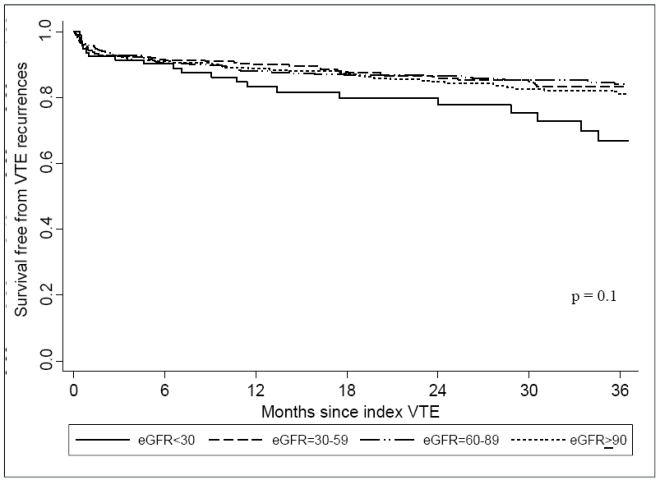

Figure 1.
Survival free from VTE recurrence for up to 3 years following index VTE according to eGFR

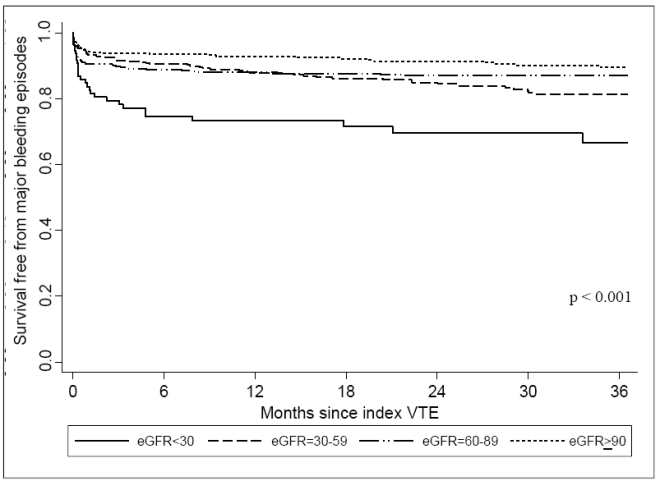

Figure 2.
Survival free from major bleeding episodes for up to 3 years following index VTE according to eGFR

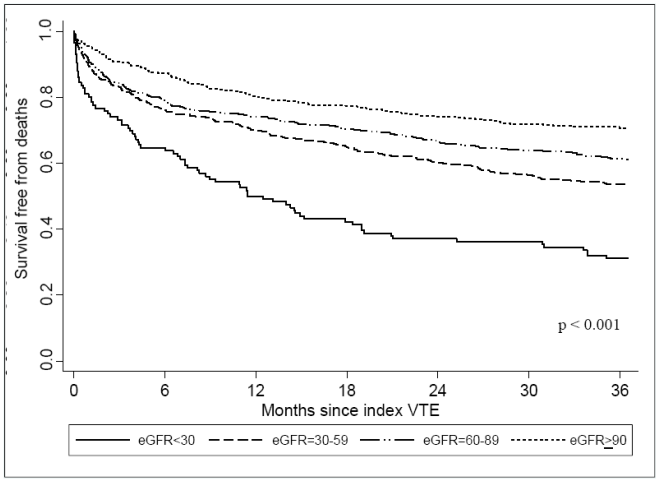

Figure 3.
Survival free from mortality for up to 3 years following index VTE according to eGFR

Table 1

Demographic and Clinical Characteristics of VTE Patients According to eGFR

Characteristic	eGFR (mL/min/1.73 m2)				P for Trend
	<30 [n = 122]	30-59 [n = 432]	60-89 [n = 575]	≥90 [n = 380]	
Demographic					
Age (y)	76.5 +/- 11.6	75.9 +/- 11.7	66.4 +/- 14.7	49.2 +/- 15.1	<0.001
Male	26.2	37.3	47.5	56.6	<0.001
BMI (kg/m^2)	27.7 +/- 7.2	28.4 +/- 7.2	29.1 +/- 8.0	29.3 +/- 7.8	0.2
Caucasian	93.2	96.0	95.6	87.9	<0.001
Physiologic					
Heart rate (bpm)	85.8 +/- 18.8	88.8 +/- 21.7	87.8 +/- 19.4	91.6 +/- 18.0	0.01
Systolic BP (mmHg)	129.2 +- 29.4	133.2 +/- 24.8	131.6 +/- 22.0	128.9 +/- 21.1	0.05
Hematocrit (%)	33.9 +/- 5.1	36.0 +/- 5.7	36.2 +/- 5.6	36.1 +/- 6.0	<0.001
SCr (mg/dL)	2.6 +/- 1.1	1.3 +/- 0.3	0.9 +/- 0.2	0.7 +/- 0.2	<0.001
Hospitalization History					
Admission with non-VTE related Dx	37.7	31.3	29.4	32.9	0.6
Other hospitalization in prior 3 mo*	48.7	42.6	41.0	38.6	0.06
Length of hospitalization (d)	7.0 [6]	5.0 [6]	6.0 [6]	6.0 [8]	0.2
Recent (<3 mo) Medical Conditions					
Chemotherapy	4.1	8.1	9.4	10.0	0.06
Hormone Therapy	5.7	7.4	8.2	6.3	1.0
Surgery†	21.0	23.6	31.0	33.7	<0.001
ICU Discharge	22.1	17.4	15.5	22.1	0.5
Intubation	18.9	14.8	16.2	21.8	0.07
Central Venous Catheter	23.0	13.9	16.0	28.4	<0.001
Cardiac Procedures	9.8	4.9	5.0	2.1	0.002
Trauma	17.2	13.0	14.1	15.5	0.8
Cancer	31.2	35.4	34.1	25.5	0.02
Serious Infection	34.4	29.9	24.7	30.0	0.3
Other Medical History					
Current smoker	9.0	11.1	18.6	32.4	<0.001
Chronic Lung Disease	25.4	21.1	19.7	15.8	0.01
Congestive Heart Failure	19.7	11.1	8.2	5.3	<0.001
>48 h Limited Mobility in last month‡	72.2	65.1	58.1	63.3	0.1
Previously Implanted IVC filter§	3.0	7.3	6.8	5.2	0.9
Prior VTE	11.5	18.8	17.7	16.1	0.8
Hypertension	79.5	70.6	51.8	30.8	<0.001
Diabetes	31.2	23.2	17.7	14.2	<0.001
Vascular Disease¶	48.4	44.2	32.2	18.2	<0.001
Type of VTE Event||					
DVT	66.9	61.1	65.9	72.4	} 0.002
PE	14.9	19.7	19.3	16.3	
Both DVT and PE	18.2	19.2	14.8	11.3	
Provoked VTE	53.3	44.0	44.5	52.6	} 0.03
Malignancy-associated VTE	31.2	35.4	34.1	25.5	
Unprovoked VTE	15.6	20.6	21.4	21.8	

Continuous variables are shown as mean +/- SD or median [interquartile range]; categorical variables are shown as percentage.

Abbreviations: BMI, body mass index; BP, blood pressure, Dx, diagnosis; ICU, Intensive Care Unit; IVC, inferior vena cava; VTE, venous thromboembolism; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; DVT, deep vein thrombosis

*Excludes 39 unknown values (n=1470)

†Excludes 14 missing and 26 unknown values (n=1469)

‡Excludes 14 missing and 238 unknown values (n=1257)

§Excludes 188 individuals with non-previously implanted IVC filters (n=1321)

¶Includes prior myocardial infarction, percutaneous coronary interventions/stents, coronary artery bypass surgery, peripheral vascular disease, ischemic heart disease, and cerebrovascular disease

||Excludes 2 missing (n=1507)

Table 2

Frequencies and Event Rates for Outcomes, by eGFR category

	Short-Term (30 d)		Long-Term (3 y)	
	Frequency (%)	Event Rate	Frequency (%)	Event Rate
Recurrent VTE				
eGFR< 30	8 (6.6)	101.9	23 (18.9)	15.9
eGFR=30-59	26 (6.0)	84.9	57 (13.2)	8.2
eGFR=60-89	24 (4.2)	56.9	74 (12.9)	7.5
eGFR ≥ 90	23 (6.1)	81.0	60 (15.8)	8.4
Major Bleeding Episodes				
eGFR< 30	18 (14.8)	246.3	30 (24.6)	23.2
eGFR=30-59	29 (6.7)	95.9	64 (14.8)	9.1
eGFR=60-89	55 (9.6)	136.9	71 (12.4)	7.1
eGFR ≥ 90	21 (5.5)	74.2	34 (9.0)	4.6
All-Cause Mortality				
eGFR< 30	28 (23.0)	340.6	86 (70.5)	52.5
eGFR=30-59	55 (12.7)	170.4	206 (47.7)	24.7
eGFR=60-89	59 (10.3)	134.9	228 (39.7)	19.0
eGFR ≥ 90	18 (4.7)	60.1	111 (29.2)	12.5

Note: event rates are shown per 100 person-years. eGFR given in mL/min/1.73 m2 (factor for conversion factor to ml/s/1.73 m2, ×0.01667).

Abbreviations: eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism.

Table 3

Short- and Long-Term Risk of Outcomes, by eGFR category

	Short-Term (30 d)			Long-Term (3 y)		
	Crude	Adjusted	P for Trend	Crude	Adjusted	P for Trend
Recurrent VTE						
eGFR< 30	1.08 (0.44-2.70)	1.64 (0.59-4.54)	0.3	1.57 (0.95-2.59)	1.83[‡] (1.03-3.25)	0.05
eGFR=30-59	0.97 (0.53-1.80)	1.63 (0.76-3.50)		0.90 (0.62-1.31)	1.01[‡] (0.63-1.62)	
eGFR=60-89	0.67 (0.36-1.25)	0.93 (0.47-1.84)		0.86 (0.61-1.22)	0.91[‡] (0.61-1.35)	
eGFR ≥ 90	1.00 (reference)[§]	1.00 (reference)[§]		1.00 (reference)[§]	1.00 (reference)[§]	
Major Bleeding Episodes[¶]						
eGFR< 30	3.03 (1.62-5.69)	2.48 (1.16-5.27)	0.01	3.64 (2.23-5.95)	2.30 (1.28-4.16)	0.006
eGFR=30-59	1.14 (0.64-2.02)	0.93 (0.47-1.85)		1.73 (1.14-2.63)	1.15 (0.68-1.92)	
eGFR=60-89	1.67 (1.00-2.78)	1.40 (0.79-2.48)		1.40 (0.93-2.12)	1.07 (0.67-1.70)	
eGFR ≥ 90	1.00 (reference)[§]	1.00 (reference)[§]		1.00 (reference)[§]	1.00 (reference)[§]	
All-Cause Mortality						
eGFR< 30	5.08 (2.78-9.26)	2.39[†] (1.01-5.64)	0.09	3.46 (2.60-4.59)	1.70[*] (1.12-2.57)	<0.001
eGFR=30-59	2.50 (1.46-4.29)	1.29[†] (0.59-2.81)		1.83 (1.45-2.30)	0.90[*] (0.63-1.28)	
eGFR=60-89	1.89 (1.10-3.24)	1.11[†] (0.54-2.29)		1.43 (1.14-1.79)	0.90[*] (0.66-1.22)	
eGFR ≥ 90	1.00 (reference)[§]	1.00 (reference)[§]		1.00 (reference)[§]	1.00 (reference)[§]	

Values shown are Hazard Ratios (95% CI); P values are for adjusted risks. eGFR given in mL/min/1.73 m2 (factor for conversion factor to ml/s/1.73 m2, x0.01667).

Abbreviations: eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism

*Adjusted for sex, age, study year, congestive heart failure, prior VTE, "provoked" VTE (VTE occurring within 3 months of a hospitalization, surgical procedure, pregnancy, trauma, or fracture), and VTE location and setting of occurrence

†Adjusted for sex, age, study year, congestive heart failure, prior VTE, cancer, "provoked" VTE (VTE occurring within 3 months of a hospitalization, surgical procedure, pregnancy, trauma, or fracture), and VTE location and setting of occurrence

‡Adjusted for sex, age, study year, smoking status, congestive heart failure, hypertension, diabetes, cancer, recent hospitalizations (includes admission with non-VTE related diagnosis and recent prior hospitalization), recent surgery/trauma, hematocrit levels, and VTE location and setting of occurrence

§Adjusted for sex, age, study year, BMI, history of vascular disease, smoking status, chronic lung disease, recent hospitalizations (includes admission with non-VTE related diagnosis and recent prior hospitalization), cancer, and setting of VTE occurrence

¶Adjusted for sex, age, study year, BMI, history of vascular disease, congestive heart failure, smoking status, chronic lung disease, recent hospitalizations (includes admission with non-VTE related diagnosis and recent prior hospitalization), cancer, and setting of VTE occurrence

‖Referent Category