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Warfarin Use and Increased Mortality in End Stage Renal Disease

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Abstract

Background—Controversy exists regarding the benefits and risks of warfarin therapy in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. In this study, we assessed mortality and cardiovascular outcomes associated with warfarin treatment in patients with stage 3–5 CKD and ESRD at the University of California-Irvine Medical Center.

Methods—In a retrospective matched cohort study, we identified 59 adult patients with stage 3–6 CKD initiated on warfarin during the period 2011–2013, and 144 patients with stage 3–6 CKD who had indications for anticoagulation therapy but were not initiated on warfarin. All-cause mortality risk associated with warfarin treatment was estimated using Cox proportional hazard regression analysis, and risk of significant bleeding and major adverse cardiovascular events were analyzed with Poisson regression analysis. Adjustment models were used to account for age, gender, diabetes mellitus, use of antiplatelet agents and pre-existing cardiovascular disease, and stratified by pre-dialysis CKD stage 3–5 versus ESRD.

Findings—During 5.8 years of follow-up, unadjusted mortality risk was higher in CKD patients on warfarin therapy (HR 2.34 with 95% CI 1.25–4.39, $p < 0.01$). After multivariate adjustment and stratification by CKD stage, the mortality risk remained significant in ESRD patients receiving warfarin (hazard ratio HR 6.62 with 95% CI 2.56–17.16, $p < 0.001$). Furthermore, adjusted rates of significant bleeding (incident rate ratio IRR 3.57 with 95% CI 1.51–8.45, $p < 0.01$) and

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myocardial infarction (IRR 4.20 with 95% CI 1.78–9.91, $p < 0.01$) were higher among warfarin users. No differences in rates of ischemic or hemorrhagic strokes were found between the two groups.

Conclusions—Warfarin use was associated with several-fold higher risk of death, bleeding and myocardial infarction in dialysis patients. If additional studies suggest similar associations, use of warfarin in dialysis patients warrants immediate reconsideration.

Keywords

Chronic kidney disease; warfarin; mortality; bleeding; stroke

Introduction

Chronic kidney disease (CKD) is an independent contributor to the development of cardiovascular diseases and all-cause mortality.[1,2] These risks are increased at higher degree of proteinuria and with progression of glomerular filtration rate (GFR) loss.[3–6] As such, patients with end-stage renal disease (ESRD) are at especially high risk of thromboembolic events, such as myocardial infarction and stroke, and death.[7]

The role of oral anticoagulation in the treatment and prophylaxis of thromboembolism in the CKD population is complex.[8] While the prevalence of atrial fibrillation, deep-vein thrombosis, and pulmonary embolism is high in CKD/ESRD patients,[9–12] the risk of bleeding and vascular calcification is simultaneously increased in this cohort.[7,13–16] To our knowledge, no randomized, prospective trials have been done to evaluate the net clinical benefit and safety of warfarin treatment in advanced CKD and ESRD, and only a small number of observational studies have compared the survival and bleeding outcomes associated with warfarin use among ESRD patients.[17–20] Retrospective studies that analyzed warfarin use and outcomes in CKD/ESRD patients have largely focused on atrial fibrillation, with conflicting findings[16,21–25] as compared to the general population where warfarin anticoagulation reduces stroke risk by 64% in the setting of atrial fibrillation.[26] Three large meta-analyses in CKD patients with atrial fibrillation were published in the past year which included data on >30,000 hemodialysis patients. Tan and colleagues reported an association between warfarin therapy with increased stroke and bleeding events,[27] while the studies by Dahal's group and van der Meersch et al. reported increased bleeding but no effect on stroke or mortality outcomes in hemodialysis patients.[24,28] In recent years, warfarin use has also been associated with increased prevalence and progression of vascular calcification in hemodialysis patients.[20,29] Despite the limited and conflicting evidence for optimal management of long-term anticoagulation in the setting of reduced renal function, data from single-center studies indicates that warfarin is prescribed in 8.3–25% of ESRD patients.[18,26]

Given the current paucity of data on the subject, there is a need to better determine the effects of warfarin use on cardiovascular events and all-cause mortality in this challenging population. The objective of this study was to investigate the survival and cardiovascular outcomes associated with incident warfarin use in a population of stage 3–5 CKD and ESRD patients with various indications for anticoagulation (including vascular thrombosis, atrial

fibrillation, pulmonary embolism, hypercoagulable states) at the University of California, Irvine Medical Center.

Methods

Patient Population

In this observational retrospective study, we identified patients≥18 years of age with Stage 3–5 CKD and ESRD who were initiated on warfarin between January 1, 2011 to December 31, 2012 at the University of California-Irvine Medical Center (Orange, CA, USA) using the University of California Research eXchange (UC Rex) Data Explorer. Stage 3–5 CKD and ERSD patients were identified in UC Rex using their respective international classification of disease (ICD-9) codes.[31,32] Exclusion criteria included: patients with less than one month follow-up, lack of documentation on warfarin treatment start date, any documented warfarin use prior to CKD or ESRD diagnosis, or any documentation of warfarin use prior to start of follow-up for at least one year. The indications for anticoagulation included atrial fibrillation, pulmonary embolism and infarction, other venous embolism and thrombosis, hypercoagulable states, transient cerebral ischemia, heart valve replacement, old myocardial infarction or chronic ischemic heart disease, and other indications (arterial embolism/stenosis, arterial pseudoaneurysm, peripheral vascular disease, ventricular thrombosis).

A matched cohort of CKD/ESRD patients who were not warfarin-treated, as defined by absence of warfarin use for at least one year prior to follow-up until end of follow-up, but had indications for anticoagulation, was used as a comparison group. Matching criteria included: (1) gender, (2) age difference <5 years, and (3) indication for anticoagulation (identified by their respective ICD-9 codes).

Data Collection and Clinical Characteristics

All data were recorded and exported using an Electronic Data Capture (EDC) instrument designed with the Research Electronic Data Capture (REDCap Version 6.14.2) online software. The study protocol was approved by the University of California, Irvine Institutional Review Board.

Information on patient demographics, CKD stage, warfarin indications and contraindications, medication use, and comorbidities were obtained from chart review of the first admission or clinic visit from January 1, 2011 to December 31, 2012. Chart review was done of all available clinic notes and hospital notes up to study end-date of October 10, 2016 to collect data on hospitalizations and mortality.

Outcome Definitions

The primary end-point of the study was all-cause death. Secondary end-points include: significant bleeding, myocardial infarction, heart failure, ischemic stroke, hemorrhagic stroke, and a composite outcome of cardiovascular events (combined myocardial infarction, heart failure, and ischemic stroke).

Myocardial infarction was defined as a documented diagnosis consistent with symptoms of coronary ischemia with sudden changes on electrocardiogram and/or rise in cardiac

biomarker enzymes. Heart failure was defined as a documented diagnosis consistent with pulmonary congestion on radiographic imaging and clinical hypoxemia requiring admission. Ischemic and hemorrhagic stroke were defined as documented diagnoses consistent with sudden neurologic change with positive findings on neuroimaging suggestive of infarction and intraparenchymal/subarachnoid hemorrhage, respectively. Significant bleeding was defined as bleeding that required transfusion, hospital admission, in-hospital workup, or bleeding causing anemia.

Statistical Analysis

All data analyses were performed using the STATA software (StataCorp LLC., TX, USA) and Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp, Chicago, IL). Categorical variables were expressed in frequencies with percentages, while continuous variables were expressed in mean ± standard deviation (SD) or median with interquartile range (IQR) according to parametric distribution. Differences between the group's baseline and outcome variables were tested with Pearson's $\chi 2$ test for categorical variables, and Student's t test for continuous variables (age). For group size of less than 5, Fisher's exact test was used for categorical variables. Statistical significance was defined as a *p*-value of less than 0.05 with two-sided testing. Survival and time-to-event curves were plotted using the Kaplan-Meier method. All analyses were conducted using unadjusted data and 3 adjustment models: 1- age and gender; 2- diabetes; 3- age, gender, use of antiplatelet agents (aspirin, clopidogrel) and pre-existing diabetes, hypertension, myocardial infarction/ congestive heart failure and stroke. The association between exposure and outcome was analyzed using Cox proportional hazard regression for time-to-event data, and Poisson regression for event rates. Log-rank test was performed for equality of survivor functions. Within the multivariate adjusted Model 3, analyses were tested by strata of CKD 3–5 versus ESRD and tested for interaction using the Wald test. Hazard ratios (HR) or incident rate ratios (IRR) are reported along with 95% Confidence Intervals (CI).

Results

We identified 59 patients who were initiated on warfarin therapy between January 1, 2011 to December 31, 2012, and 144 matched patients with CKD and ESRD who had indications for anticoagulation therapy but did not receive warfarin treatment. Baseline characteristics of the no-warfarin and warfarin-treated groups are shown in Table 1. There was no statistically significant difference between the two groups in terms of mean age (60 ± 15 vs 60 ± 17; p = 0.947), proportion of females (45% vs 49%; p = 0.63), and presence of diabetes, hypertension, myocardial infarction/heart failure, or stroke at the start of follow-up. Patients in both groups had similar baseline pharmacologic profiles, however patients in the no-warfarin group were more likely to receive antiplatelet agents compared to the warfarin-treated group (66.7% vs 50.8%; p = 0.035). There was a higher proportion of ESRD patients in the no-warfarin group (65.3% vs 45.8%) with a corresponding lower proportion of stage 3–5 CKD patients in the no-warfarin group (34.7% vs 54.2% in the warfarin-treated group). Mean follow-up period in the warfarin treated-group from start of treatment was 2.8 ± 1.6 years versus 4.0 ± 1.5 years in the no-warfarin group from date of anticoagulation indication

diagnosis ($p < 0.001$). Median duration of warfarin treatment was 12 months (IQR 3.7–23.9 months).

Among warfarin users, 45.8% had an indication for anticoagulation due to venous embolism/thrombosis, 30.5% had atrial fibrillation, and 10.2% had pulmonary embolism compared to 56.9%, 33.3%, and 13.9% in the no-warfarin group, respectively ($p = 0.147$, 0.696, 0.472). Three patients had two indications for anticoagulation. For the no-warfarin controls, the most common reasons for avoidance of warfarin therapy included recent surgery (36.8%), gastrointestinal ulcer or bleeding (21.5%) and increased hemorrhagic risk (16%); reason for warfarin non-initiation could not be determined from chart review in 34% of cases (Table 1). Of note, in the non-warfarin group, six patients were on apixaban and one patient was on dabigatran during the study follow-up duration.

Supplemental Table 1 shows the cumulative incidence of primary and secondary outcomes from the start of follow-up until the study end-date of October 10, 2016. The differences in cumulative incidence of adverse outcomes were not statistically significant between the two groups. However, time-to-event and rate-based analyses showed significant differences in outcomes between the groups. Kaplan-Meier survival analysis demonstrated significantly lower survival in the warfarin-treated group, shown in Figure 1 (Log rank test = 0.0064). Results from Cox and Poisson regression analyses with univariate and multivariate adjustments are shown in Table 2. With multivariate adjustment in Model 3 stratified by CKD stage 3–5 vs ESRD, there was a strong association between all-cause mortality and warfarin therapy in the ESRD strata (HR 6.62, 95% CI 2.56–17.16, $p < 0.001$). This mortality association was non-significant in the CKD stage 3–5 strata (HR 1.26, 95% CI 0.45–3.52, $p = 0.661$), p-value for interaction = 0.035. We further analyzed rate of adverse events that occurred within 90 days of death in both study groups. In the warfarin-treated group, 5 of the 16 deaths (31.3%) were preceded by a major adverse event within 90 days (4 myocardial infarction, 1 heart failure), vs 3 of the 26 deaths (11.5%) in the no-warfarin cohort (1 myocardial infarction, 1 heart failure, 1 significant bleeding event).

In terms of secondary outcome measures, warfarin treatment was strongly associated with higher rates of myocardial infarction (IRR 3.28, 95% CI 1.45–7.43, $p = 0.004$) and significant bleeding (requiring transfusion or hospitalization, IRR 3.57, 95% CI 1.55–8.24, $p = 0.003$) in univariate analyses. No statistically significant association was found between warfarin use and rate of heart failure, ischemic stroke, or the composite outcome of cardiovascular events. Multivariate adjustment and stratification by CKD strata did not change the statistical relationships.

Discussion

In this retrospective matched cohort study, incident warfarin therapy was associated with higher risk of all-cause mortality in ESRD patients ($p < 0.001$). Secondary analysis showed a higher rate of bleeding and myocardial infarction with warfarin therapy in both stage 3–5 CKD and ESRD patients, while rates of stroke and heart failure were not significantly different.

Few studies have examined the impact of warfarin on all-cause mortality in the advanced CKD and ESRD population. In a observational study, Chan et al[19] showed an increased morality in the hemodialysis population (n = 2,369) associated with warfarin, aspirin, and clopidogrel use compared to nonusers (n = 24,740) over 5 years of follow-up. In the same study, warfarin and clopidogrel users also had significantly higher risk for death or hospitalization from bleeding. In a systematic review, Elliott et al[18] concluded that warfarin use, when compared to subcutaneous heparin or no warfarin use, is associated with a higher bleeding risk in hemodialysis patients. The present study is consistent with these findings, as warfarin was associated with higher risk of all-cause mortality in the ESRD group and trended towards a higher rate of bleeding in both the stage 3–5 CKD and ESRD strata. The higher rate of preceding adverse cardiovascular or bleeding events within 90 days of death (31.3% in the warfarin group vs 11.5% in the non-warfarin controls) suggests that warfarin-related morbidity may impact mortality risk, however this needs to be validated in larger cohorts.

Vitamin K is an essential factor for the carboxylation and activation of matrix G1a protein (MGP), a potent endogenous inhibitor of arterial calcification that is produced by vascular smooth muscle cells.[33,34] Warfarin, a vitamin K antagonist, blocks the carboxylation of MGP and thereby increases risk of vascular calcification. In a study utilizing serial, annual mammogram data from 451 women on warfarin therapy, warfarin was associated with a 50% increase in breast arterial calcification compared to untreated women matched for age and diabetes mellitus; severity of calcification increased with duration of therapy.[35] Warfarin therapy has been associated with increased calcification of the coronary arteries, peripheral arteries, mitral valves, and aortic valves in cross-sectional, image-based studies primarily in patients with atrial fibrillation or valvular disease.[33] Notably, vascular calcification and arterial stiffness are more prevalent in CKD than in the general population, and have been shown to be independent prognostic markers of all-cause mortality and cardiovascular events in patients with stage 4–5 CKD and ESRD.[36–38]

To our knowledge, although numerous studies have examined outcomes in patients with atrial fibrillation, very few have evaluated the potential relationship between warfarin use and cardiovascular events in the CKD and ESRD population. Mac-Way et al[29] reported vitamin K deficiency and accelerated aortic stiffness with warfarin use in 19 hemodialysis patients after a mean exposure of 29 months. Furthermore, the degree of vitamin K deficiency was found to be associated with a higher risk of mortality. In a multi-center cross sectional study, Fusaro et al[20] similarly concluded that hemodialysis patients (n = 387) on warfarin had higher odds of aortic and iliac calcifications and risk of all-cause mortality after 3 years of follow up. Our present study found that warfarin-treated ESRD patients had higher risk of all-cause death, while warfarin therapy in both strata of stage 3–5 CKD and ESRD patients was associated with higher risk of myocardial infarction and no protective effects on ischemic stroke. The increased myocardial infarction risk may be explained (at least in part) by warfarin driving vascular calcification, with subsequent increased arterial stiffness and increased systolic blood pressure and reduced diastolic blood pressure. These changes compromise perfusion of the coronary arteries during diastole and promote left ventricular remodeling.[39] Calcific uremic arteriolopathy (formerly called calciphylaxis) is a rare but often fatal syndrome of calcification in cutaneous blood vessels leading to skin

necrosis, that occurs in 5% of ESRD patients. Approximately 50% of such patients with calciphylaxis are on warfarin.[33] In the present study we observed one case of calciphylaxis in the warfarin-treatment group, and none in the no-warfarin group. Taken together, the evidence suggests that warfarin-induced vitamin K dysfunction leads to arterial stiffness and explains, at least in part, the associations observed in the CKD/ESRD warfarin-treated cohort.

This study possesses several limitations. First, the study is vulnerable to underreporting and/or misclassification of diagnoses and medication use due to its retrospective, observational nature. Information that is inconsistently available such as smoking history, ethnicity, socioeconomic status, and baseline laboratory findings cannot be captured reliability from this database. Specific cause of death was not reported. Second, we do not have information regarding INR levels and warfarin dosage among patients in the warfarin-treated group. While we included only patients with incident, as opposed to prevalent, warfarin use to control for exposure duration, it is possible that some patients in this group had suboptimal or supratherapeutic levels during follow-up, which could be a potential confounding factor. Third, selection bias regarding treatment decisions may be present for patients who have a higher risk of thromboembolism at baseline, thereby exaggerating the risks of adverse outcomes in the treatment group. Some of these biases may not have been fully accounted for in our multivariate adjustment models, although we adjusted for all major comorbidities associated with CKD/ESRD as well as all components of the CHADS2 score.[40] In the no-warfarin group, the most common identified reasons for warfarin avoidance were related to bleeding tendency (recent surgery, gastrointestinal bleeding, pre-existing hemorrhagic risk; Table 1), however we did not note an omission bias (i.e., greater stroke or mortality rates in the no-treatment cohort due to physicians placing a higher value on avoiding a bleed than on avoiding a stroke). Finally, generalizability of our results is limited since our study was conducted in a single academic center. With a limited sample size, stratification of patients based on predictors of mortality such as the Charlson comorbidity index would not yield sufficient power for meaningful conclusions.

In the past decade, new oral anticoagulants (NOACs) have been released on the market that include the direct thrombin inhibitor dabigatran and factor Xa inhibitors such as apixaban and rivaroxaban. In the current non-warfarin cohort, 7/144 patients were exposed to a NOAC during the follow up period. The factor Xa inhibitors in particular are promising alternatives to warfarin for use in CKD patients since these agents are predominantly metabolized by the hepatic (not renal) route and may have less off-target effects. Apixaban was recently approved by the Food and Drug Administration for use in ESRD patients.[41] However, randomized controlled clinical trials are needed to confirm the safety profile of oral factor Xa inhibitors in advanced CKD. There have been four large Phase III trials since 2009 comparing NOACs against warfarin in patients with atrial fibrillation but all the studies excluded CKD stage 4/5 and ESRD patients.[42–45]

In summary, we observed a higher risk of all-cause death and higher rate of bleeding in CKD/ESRD patients who were initiated in warfarin therapy. Of note, there was a higher baseline prevalence of cardiovascular risk factors including diabetes, hypertension, and history of myocardial infarction/heart failure in our study compared to rates reported in

large-scale clinical and epidemiologic literature.[7,9–12] Hence, warfarin's effects on vascular calcification and potential survival reduction in advanced CKD may be somewhat accelerated in our patient population. We conclude that additional studies need to be done in CKD/ESRD patients who are at high risk for cardiovascular events to determine the risks vs benefits of warfarin as compared to other oral anticoagulants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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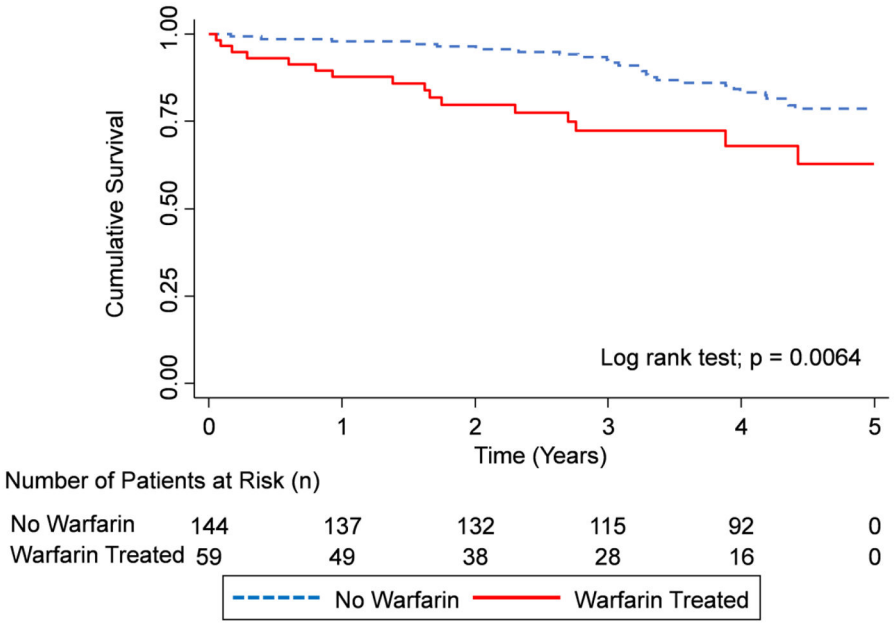

Figure 1.
Kaplan-Meier Survival Analysis for CKD Patients with or without Warfarin Therapy.

Table 1

Baseline Demographics and Clinical Characteristics of CKD Patients with or without Warfarin Therapy.

	No Warfarin	Warfarin Treated	p-value*
Total number of patients	144	59	
Mean Age (years ± SD)	60 ± 15	60 ± 17	0.947
% Female	45	49	0.603
CKD stage % (n)			0.006
3	21.5 (31)	42.4 (25)	
4	12.5 (18)	8.5 (5)	
5	0.7 (1)	3.4 (2)	
ERSD/hemodialysis	65.3 (94)	45.8 (27)	
Comorbidity % (n)			
Diabetes	64.6 (93)	71.2 (42)	0.365
Hypertension	87.5 (126)	93.2 (55)	0.234
Myocardial Infarction/Heart Failure	37.5 (54)	37.3 (22)	0.977
Stroke	17.4 (25)	6.8 (4)	0.075
Medications % (n)			
ACEi/ARB	56.9 (82)	47.5 (28)	0.218
Beta blocker	70.8 (102)	78.0 (46)	0.299
Calcium Channel Blocker	52.1 (75)	50.8 (30)	0.873
Statin	60.4 (87)	66.1 (39)	0.448
Antiplatelets (aspirin, clopidogrel)	66.7 (96)	50.8 (30)	0.035
Indication for Anticoagulation† % (n)			
Atrial Fibrillation	33.3 (48)	30.5 (18)	0.696
Pulmonary embolism/infarction	13.9 (20)	10.2 (6)	0.472
Other venous embolism/thrombosis	56.9 (82)	45.8 (27)	0.147
Hypercoagulable states	0 (0)	6.8 (4)	0.007
Transient cerebral ischemia	2.1 (3)	1.7 (1)	1.000
Heart valve replacement	2.8 (4)	1.7 (1)	1.000
Peripheral vascular disease	4.2 (6)	5.1 (3)	0.721
Other	-	3.4 (2)	
Two Indications for Anticoagulation % (n)	-	5.1 (3)	
Warfarin Contraindications† % (n)			
Hemorrhagic tendencies	16.0 (23)	-	
Gastrointestinal ulceration or overt bleeding	21.5 (31)	-	
Unsupervised/Senility	1.4 (2)	-	
Recent procedure	36.8 (53)	-	
Hypersensitivity	0.7 (1)	-	
Malignant hypertension	7.6 (11)	-	

	No Warfarin	Warfarin Treated	p-value*
Patient refusal	1.4 (2)	-	
Other/Unknown	34.0 (49)	-	

*Student's t test used for age. For all other variables, Pearson's $\chi 2$ test used for n≥5; Fisher's exact test used for n<5.

†Patient may have more than one indication or contraindication for anticoagulation

ACEi = Angiotensin-converting-enzyme inhibitor; ARB = Angiotensin II receptor blocker; CKD = Chronic Kidney Disease; ESRD = End-stage Renal Disease

Table 2

Hazard and Incident Rate Ratios for Various Adverse Outcomes CKD Patients with or without Wfarfarin Use. TABLE 1

	HR	95% CI	p-value
all-cause mortality *			
unadjusted	2.34	1.25–4.39	0.008
Model 1	2.28	1.21–4.31	0.011
Model 2	2.24	1.19–4.21	0.012
Model 3	2.43	1.28–4.61	0.007
Model 3 by CKD stage			
stage 3–5 CKD	1.26	0.45–3.52	0.661
ERSD/hemodialysis	6.62	2.56–17.16	< 0.001
test for interaction			0.035
	IRR	95% CI	p-value
myocardial infarction **			
unadjusted	3.28	1.45–7.43	0.004
Model 1	3.21	1.41–7.31	0.005
Model 2	3.24	1.43–7.36	0.005
Model 3	4.20	1.78–9.91	0.001
Model 3 by CKD stage			
stage 3–5 CKD	5.30	1.36–20.63	0.016
ERSD/hemodialysis	9.47	1.90–47.29	0.006
test for interaction			0.678
bleeding **			
unadjusted	3.57	1.55–8.24	0.003
Model 1	3.34	1.45–7.73	0.005
Model 2	3.44	1.49–7.95	0.004
Model 3	3.57	1.51–8.45	0.004
Model 3 by CKD stage			
stage 3–5 CKD	4.61	0.92–21.13	0.064
ERSD/hemodialysis	3.69	0.93–14.67	0.063
test for interaction			0.901
heart failure **			
unadjusted	0.71	0.36–1.41	0.333
Model 1	0.69	0.35–1.37	0.290
Model 2	0.68	0.34–1.34	0.267
Model 3	0.73	0.37–1.45	0.366
Model 3 by CKD stage			
stage 3–5 CKD	0.87	0.35–2.18	0.772

	HR	95% CI	p-value
ERSD/hemodialysis	0.35	0.05–2.62	0.306
test for interaction			0.308
ischemic stroke [**, †]			
unadjusted	0.45	0.06–2.57	0.448
Model 1	0.44	0.05–3.52	0.437
Model 2	0.41	0.05–3.28	0.401
Model 3	1.76	0.17–18.23	0.636
cardiovascular events [**]			
unadjusted	1.33	0.85–2.17	0.250
Model 1	1.30	0.80–2.13	0.289
Model 2	1.28	0.79–2.10	0.317
Model 3	1.50	0.91–2.48	0.110
Model 3 by CKD stage			
stage 3–5 CKD	1.64	0.82–3.29	0.159
ERSD/hemodialysis	1.36	0.47–3.99	0.572
test for interaction			0.487

[*] Step-wise Cox regression for time-to-event analysis

[**] Poisson regression for event rate analysis

Model 1: age and gender

Model 2: diabetes

Model 3: age, gender, use of anti-platelets, and existing diabetes, hypertension, myocardial infarction/congestive heart failure, and stroke

[†] inadequate number of event for stratification

Cardiovascular events defined as a composite outcome of myocardial infarction, heart failure and ischemic stroke. HR = Hazard Ratio; CI = Confidence Interval; CKD = Chronic Kidney Disease; ESRD = End-stage Renal Disease; IRR= Incident Rate Ratio