Article

Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation

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Abstract

Background and objectives The relative efficacy and safety of apixaban compared with no anticoagulation have not been studied in patients on maintenance dialysis with atrial fibrillation. We aimed to determine whether apixaban is associated with better clinical outcomes compared with no anticoagulation in this population.

Design, setting, participants, & measurements This retrospective cohort study used 2012–2015 US Renal Data System data. Patients on maintenance dialysis with incident, nonvalvular atrial fibrillation treated with apixaban (521 patients) were matched for relevant baseline characteristics with patients not treated with any anticoagulant agent (1561 patients) using a propensity score. The primary outcome was hospital admission for a new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism. The secondary outcome was fatal or intracranial bleeding. Competing risk survival models were used.

Results Compared with no anticoagulation, apixaban was not associated with lower incidence of the primary outcome: hazard ratio, 1.24; 95% confidence interval, 0.69 to 2.23; $P=0.47$. A significantly higher incidence of fatal or intracranial bleeding was observed with apixaban compared with no treatment: hazard ratio, 2.74; 95% confidence interval, 1.37 to 5.47; $P=0.004$. A trend toward fewer ischemic but more hemorrhagic strokes was seen with apixaban compared with no treatment. No significant difference in the composite outcome of myocardial infarction or ischemic stroke was seen with apixaban compared with no treatment. Compared with no anticoagulation, a significantly higher rate of the primary outcome and a significantly higher incidence of fatal or intracranial bleeding and of hemorrhagic stroke were seen in the subgroup of patients treated with the standard apixaban dose (5 mg twice daily) but not in patients who received the reduced apixaban dose (2.5 mg twice daily).

Conclusions In patients with kidney failure and nonvalvular atrial fibrillation, treatment with apixaban was not associated with a lower incidence of new stroke, transient ischemic attack, or systemic thromboembolism but was associated with a higher incidence of fatal or intracranial bleeding.

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Introduction

Patients with kidney failure on hemodialysis have a very high prevalence of atrial fibrillation (up to 40%) (1). However, despite the high prevalence of atrial fibrillation, it is unclear whether these patients should be anticoagulated. Currently, no randomized data exist regarding use of either vitamin K antagonists or direct oral anticoagulants (DOACs) in this population. Conversely, several well conducted cohort studies have analyzed the safety and efficacy of warfarin. These studies had conflicting results, but most failed to show a benefit from warfarin administration compared with no treatment with respect to stroke prevention, whereas warfarin use was associated with significantly higher risk of bleeding (2).

Off-label use of dabigatran or rivaroxaban in patients on hemodialysis with atrial fibrillation was associated with even more major bleeding events and higher risk of death from bleeding when compared with warfarin in one study (3). In addition, it was unclear whether use of either agent reduced the risk of stroke.

Apixaban has lower elimination by the kidneys compared with other DOACs (25%–29%). It is the most commonly used drug among DOAC-treated patients with kidney failure in the United States (4). However, appropriate dose adjustment may be an issue because the drug accumulates with prolonged use, with the standard dose leading to supratherapeutic drug levels in some patients on hemodialysis and the reduced dose leading to drug levels at the lower range of the therapeutic interval (5). A recently published retrospective cohort study, using the US Renal Data System, showed that apixaban-treated patients had similar event rates for ischemic stroke or systemic thromboembolism compared with warfarin-treated patients but benefited from significantly lower major bleeding event rates (6). Furthermore, apixaban

at the standard dose of 5 mg twice daily was associated with significantly lower risk for ischemic stroke or systemic thromboembolism compared with warfarin, in contrast to what was observed with the reduced dose of 2.5 mg twice daily.

These data are reassuring regarding the potential benefits of apixaban compared with warfarin. However, given the relative inefficacy of warfarin in preventing stroke or systemic thromboembolism in patients with kidney failure and the high bleeding event rates associated with anticoagulation in this patient group, it is critical to assess the relative efficacy and safety of apixaban compared with no anticoagulation before advocating for its use in patients receiving maintenance dialysis. To address this question, we aimed to determine whether apixaban is associated with better clinical outcomes compared with no anticoagulation in patients on maintenance dialysis with atrial fibrillation.

Materials and Methods

Study Population

This retrospective cohort study used US Renal Data System data from 2012 to 2015 (7). We identified all patients on hemodialysis or peritoneal dialysis on January 1, 2012 (prevalent population) or who were started on hemodialysis or peritoneal dialysis between January 1, 2012 and December 31, 2015 (incident population).

We next identified all individuals with a primary or secondary diagnosis of atrial fibrillation or flutter on the basis of at least one inpatient or two outpatient claims using condition-specific diagnostic codes (International Classification of Diseases, ninth and tenth revisions). To verify whether this was a new diagnosis or a preexisting comorbidity, the claims dataset (ESKD and pre-ESKD) was reviewed for the year preceding the date of entry in the cohort. We restricted our analysis to patients who (1) had a new diagnosis of atrial fibrillation after January 1, 2012; (2) were alive on day 30 postdiagnosis, in order to exclude patients who developed atrial fibrillation in the setting of a serious intercurrent illness; (3) had continuous Medicare Part A and B coverage for the year prior to diagnosis; (4) had part D enrollment for ≥6 months prior to diagnosis; (5) did not have valvular atrial fibrillation; and (6) did not have a prescription of any anticoagulant agent in the 6 months prior to diagnosis (8). Atrial fibrillation was considered to be valvular if the patient had a prosthetic valve or mitral stenosis.

Relevant baseline characteristics and medication prescription (new and prevalent) were retrieved for each patient from institutional and physician claims (the 2728 form was not used). The congestive heart failure, hypertension, age, diabetes, stroke, vascular history (CHA_2DS_2-Vasc) score and a modified hypertension, kidney disease, liver disease, stroke, prior bleeding or predisposition to bleeding, labile international normalized ratios, age, medication, alcohol use (HAS-BLED) score were calculated. The modified HAS-BLED score used all variables of the original score except labile international normalized ratios (9,10).

We compared patients treated with apixaban with patients who did not receive any anticoagulation.

Restrictions apply to the availability of these data, which were used under license for this study and, therefore, are not publicly available. The Partners Healthcare institutional review board approved the study (2016P001613/BWH) and ruled that informed consent was not necessary. This work was carried out in accordance with the Declaration of Helsinki.

Outcomes

The primary outcome was hospital admission for a new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism. The secondary outcomes were any stroke (ischemic or hemorrhagic), fatal or intracranial bleeding, clinically important bleeding, ischemic stroke, hemorrhagic stroke, a composite outcome of myocardial infarction or ischemic stroke, a composite outcome of all-cause mortality and the primary outcome, and all-cause mortality. We additionally examined two outcomes not expected to be related to use of apixaban to assess the specificity of our findings: pneumonia and hip fracture. The institutional inpatient claims dataset was used, and one condition-specific diagnostic code was requested for each outcome (Supplemental Table 1).

Clinically important bleeding was defined as any bleeding resulting in death; any bleeding occurring at a critical site (intracranial, intraocular, retroperitoneal, intra-articular, pericardial, airway); or any gastrointestinal, urinary tract, or gynecologic bleeding requiring hospitalization.

The follow-up period (time 0) started 30 days after atrial fibrillation diagnosis to allow enough time for patients to fill a prescription and to exclude patients who developed atrial fibrillation in the setting of a serious intercurrent illness. Patients were followed up to the date of death, kidney transplantation, or December 31, 2015. For the outcome of all-cause mortality, patients were followed up to the date of death, kidney transplantation, or August 1, 2017 because data for mortality were available until this date. Time to event data for each outcome in the apixaban and the control group are shown in Supplemental Table 2.

Statistical Analyses

Multivariable logistic regression was used to calculate a propensity score for apixaban prescription versus no anticoagulation including 23 parameters at baseline selected for their potential association with cardiovascular or bleeding outcomes (shown in Table 1). Apixaban users were matched 1:3 without replacement according to the propensity score (caliper width of 0.5%) to patients not treated with any anticoagulant agent. Standardized differences were calculated to assess balance of the matched cohorts, with a cutoff of ≤0.1 considered to indicate a negligible difference (11).

Cox proportional hazard models were used to examine the association between apixaban prescription and the clinical outcomes, considering death from any cause as a competing risk, as described by Fine and Gray (12). For the main "as-treated" analysis, we censored patients when Medicare Part A, B, or D coverage was lost. We also censored apixaban users at the date of the last available prescription plus drug supply days. To account for

Table 1. Baseline characteristics of the unmatched and matched cohort

Characteristics	Unmatched Cohort			Matched Cohort		
	No Treatment	Apixaban	Standardized Difference	No Treatment	Apixaban	Standardized Difference
No. of patients	10,976	521		1561	521	
Demographics						
Age	67±13	68±11	−0.03	68±13	68±11	0.04
Men	5920 (54%)	281 (54%)	0.00	824 (53%)	281 (54%)	0.02
Black race	3378 (31%)	116 (22%)	−0.19	333 (21%)	116 (22%)	0.02
Hemodialysis	9831 (90%)	453 (87%)	−0.08	1374 (88%)	453 (87%)	−0.03
Dialysis vintage, mo	26 (10–57)	19 (6–33)	0.33	19 (6–38)	19 (6–33)	0.01
Comorbidities						
Hypertension	10,916 (100%)	520 (100%)	0.05	1557 (100%)	520 (100%)	0.02
Diabetes	8778 (80%)	419 (80%)	0.01	1251 (80%)	419 (80%)	0.01
Coronary disease	8302 (76%)	387 (74%)	−0.03	1150 (74%)	387 (74%)	0.01
Heart failure	8243 (75%)	397 (76%)	0.03	1187 (76%)	397 (76%)	0.00
Myocardial infarction	2953 (27%)	110 (21%)	−0.14	349 (22%)	110 (21%)	−0.03
Stroke history	4375 (40%)	178 (34%)	−0.12	564 (36%)	178 (34%)	−0.04
PVD	6571 (60%)	285 (55%)	−0.11	854 (55%)	285 (55%)	0.00
Dyslipidemia	9333 (85%)	472 (91%)	0.17	1420 (91%)	472 (91%)	−0.01
Malignancy	3163 (29%)	149 (29%)	0.00	457 (29%)	149 (29%)	−0.02
Alcohol-related disease	1603 (15%)	59 (11%)	−0.10	175 (11%)	59 (11%)	0.00
Liver disease	3550 (32%)	134 (26%)	−0.15	371 (24%)	134 (26%)	0.04
COPD	4755 (43%)	207 (40%)	−0.07	606 (39%)	207 (40%)	0.02
Bleeding history	6346 (58%)	254 (49%)	−0.18	752 (48%)	254 (49%)	0.01
Medication						
ACEI	3301 (30%)	134 (26%)	−0.10	384 (25%)	134 (26%)	0.03
ARB	2030 (19%)	97 (19%)	0.00	293 (19%)	97 (19%)	−0.01
Antiplatelet agent	2688 (25%)	117 (23%)	−0.05	356 (23%)	117 (23%)	−0.01
β-Blocker	7564 (69%)	379 (73%)	0.08	1126 (72%)	379 (73%)	0.01
Statin	5806 (53%)	313 (60%)	0.15	942 (60%)	313 (60%)	0.00

Results are presented as mean ± SD, median (interquartile range), or number (percentage). PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

immortal time bias for patients prescribed apixaban at >30 days from atrial fibrillation diagnosis, we examined apixaban prescription as a time-varying covariate (13). For the primary analysis, hazard ratios (HRs) were not adjusted. For the secondary analysis, HRs were adjusted for (1) CHA$_2$DS$_2$-Vasc score for the primary outcome, ischemic stroke, any stroke, and all-cause mortality; (2) modified HAS-BLED score for fatal or intracranial bleeding, hemorrhagic stroke, and clinically important bleeding; and (3) history of hypertension, diabetes mellitus, dyslipidemia, and myocardial infarction for the composite outcome of myocardial infarction or ischemic stroke.

We performed a subgroup analysis including only patients with apixaban either 5 mg twice daily or 2.5 mg twice daily to study the effect of the standard dose and the reduced dose on relevant clinical outcomes. We also separately present outcomes for the subgroup of patients on maintenance hemodialysis.

We performed three sensitivity analyses: (1) an "intention-to-treat" analysis, where we assumed that each patient remained on apixaban throughout the whole follow-up period (14); (2) a prescription time-distribution matching to account for immortal time bias: the time to apixaban prescription was assessed for users (for each nonuser, an assigned "time to apixaban" was randomly

selected from this distribution of observed times to apixaban start; the two groups were followed from the date of apixaban prescription [real or assigned] until the occurrence of an event or the end of follow-up, and nonusers with an event prior to assigned time 0 were excluded from this analysis [13]); and (3) a marginal structural model where stabilized inverse probability weights were estimated and then used in Cox proportional hazards regression. The primary analysis was also performed in a larger dataset to further include patients with prevalent atrial fibrillation at the time of dialysis initiation.

Statistical analyses were performed in SPSS Statistics (version 24.0, Released 2016; IBM Corp., Armonk, NY) or in Stata (version 14 IC; College Station, TX). P values =0.05 were considered statistically significant.

Results
Cohort and Patient Characteristics
Population selection is detailed in Figure 1. The final cohort included 10,976 patients who did not receive any anticoagulant agent and 521 patients on apixaban. After propensity-score matching, the cohort included 2082 patients (521 on apixaban and 1561 without any anticoagulant prescription). Baseline characteristics of the final and
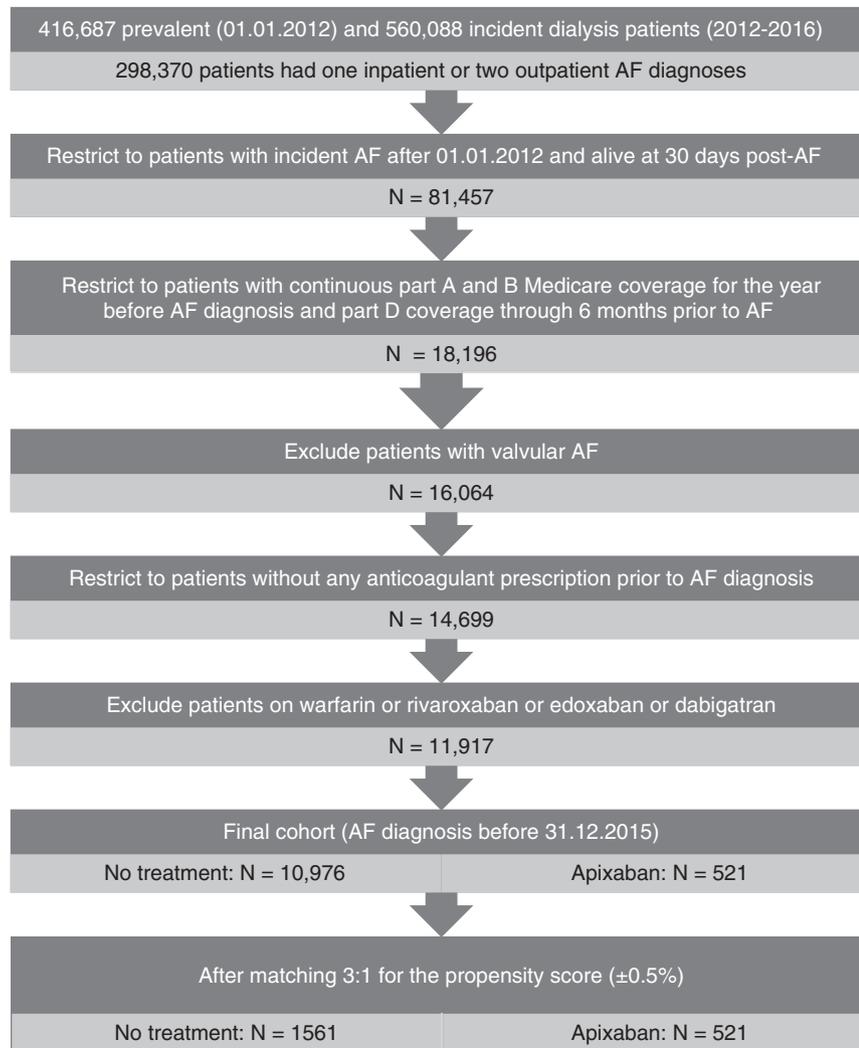
Figure 1. | Study flowchart: population selection from the US Renal Data System. AF, atrial fibrillation.

matched cohorts that could be considered as potential confounders are shown in Supplemental Table 3 and Table 1 for the subgroup of patients on maintenance hemodialysis and the whole cohort, respectively. The matched cohort was well matched for all baseline characteristics.

The median time between atrial fibrillation diagnosis and apixaban initiation was 24 days (interquartile range, 0–200 days). The mean duration of apixaban use was 155±150 days (median, 96 days; interquartile range, 30–225 days). A total of 207 patients received the standard dose (5 mg twice daily), and 257 patients received the reduced dose (2.5 mg twice daily), whereas 57 patients switched doses.

Primary Outcome

Compared with no anticoagulant therapy, apixaban use was not associated with lower risk of a new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism: 7.5 events per 100 patient-years in apixaban-treated patients versus 7.0 events in

patients who did not receive any anticoagulant (HR, 1.24; 95% confidence interval [95% CI], 0.69 to 2.23; P=0.47) (Table 2).

Although a tendency that did not reach statistical significance toward fewer ischemic strokes was identified with apixaban compared with no treatment, it was offset by a tendency toward more hemorrhagic strokes in apixaban-treated patients (Table 2).

Secondary Outcomes

Apixaban use was associated with a significantly higher incidence of fatal or intracranial bleeding events compared with no treatment: 4.9 versus 1.6 events per 100 patient-years (HR, 2.74; 95% CI, 1.37 to 5.47; P=0.004) (Table 2). This finding translates into one fatal or intracranial bleeding event per 30 patients treated with apixaban per year.

A similar incidence of clinically important bleeding events was observed with apixaban compared with no treatment (Table 2). No significant difference in the composite outcome of myocardial infarction or ischemic stroke and the composite outcome of any stroke was seen with apixaban compared with no treatment (Table 2).

Table 2.   Clinical outcomes in the "as-treated" population (main analysis)

Outcome	Incidence in Apixaban Users	Incidence in Nonusers	Crude Hazard Ratio (95% Confidence Interval)	P Value	Adjusted[a] Hazard Ratio (95% Confidence Interval)	P Value
Any stroke, TIA, or embolism	7.5 (13)	7.0 (114)	1.24 (0.69 to 2.23)	0.47	1.29 (0.72 to 2.33)	0.39
Any stroke	5.8 (<11)	5.8 (96)	1.13 (0.58 to 2.19)	0.72	1.17 (0.60 to 2.28)	0.64
Major bleeding	4.9 (<11)	1.6 (45)	**2.74 (1.37 to 5.47)**	**0.004**	**2.76 (1.38 to 5.52)**	**0.004**
Clinically important bleeding	59.2 (77)	56.9 (695)	1.15 (0.90 to 1.47)	0.26	1.15 (0.90 to 1.46)	0.26
Ischemic stroke or MI	27.6 (43)	25.1 (373)	1.24 (0.90 to 1.71)	0.18	1.25 (0.91 to 1.72)	0.17
Ischemic stroke	3.5 (<11)	5.0 (81)	0.81 (0.35 to 1.89)	0.63	0.85 (0.36 to 1.98)	0.71
Hemorrhagic stroke	2.3 (<11)	1.3 (22)	1.89 (0.65 to 5.47)	0.24	1.89 (0.65 to 5.49)	0.24

Incidence rates are presented as number of events per 100 patient-years, with the number of events per group shown in parentheses. Patients were followed up to the date of death; kidney transplantation; December 31, 2015; loss of Medicare A–B or D coverage; or the date of the last available apixaban prescription (plus drug supply days). Death was considered as a competing risk. TIA, transient ischemic attack; MI, myocardial infarction.
[a]Hazard ratios were adjusted for the CHA_2DS_2-Vasc (congestive heart failure, hypertension, age, diabetes, stroke, vascular history) score for the outcomes of any stroke; any stroke, TIA, or systemic thromboembolism; and ischemic stroke; for a modified HAS-BLED (hypertension, kidney disease, liver disease, stroke, prior bleeding or predisposition to bleeding, labile international normalized ratio, age, medication, alcohol use) score for major bleeding, hemorrhagic stroke, and clinically important bleeding; and for history of hypertension, diabetes mellitus, dyslipidemia, and MI for the outcome of ischemic stroke or MI. Statistically significant differences appear in bold.

Mortality and Composite Outcome

Apixaban use was associated with lower all-cause mortality rates compared with no anticoagulation (HR, 0.58; 95% CI, 0.43 to 0.78). Similarly, apixaban use was associated with lower incidence of the composite outcome of all-cause mortality or stroke or systemic thromboembolism compared with no treatment (HR, 0.56; 95% CI, 0.41 to 0.76).

To evaluate the hypothesis of healthy user bias, we evaluated two more outcomes that should not be influenced by apixaban use: hospital admission for pneumonia or hip fracture. For both outcomes, a lower incidence was seen in apixaban users: HR, 0.77 for pneumonia (95% CI, 0.55 to 1.07) and HR, 0.19 for hip fracture (95% CI, 0.03 to 1.36).

Standard-Dose and Reduced-Dose Apixaban Compared with No Treatment

Compared with no anticoagulation, a significantly higher rate of the primary outcome and significantly higher incidence of fatal or intracranial bleeding and of

Any stroke or TIA or systemic embolism
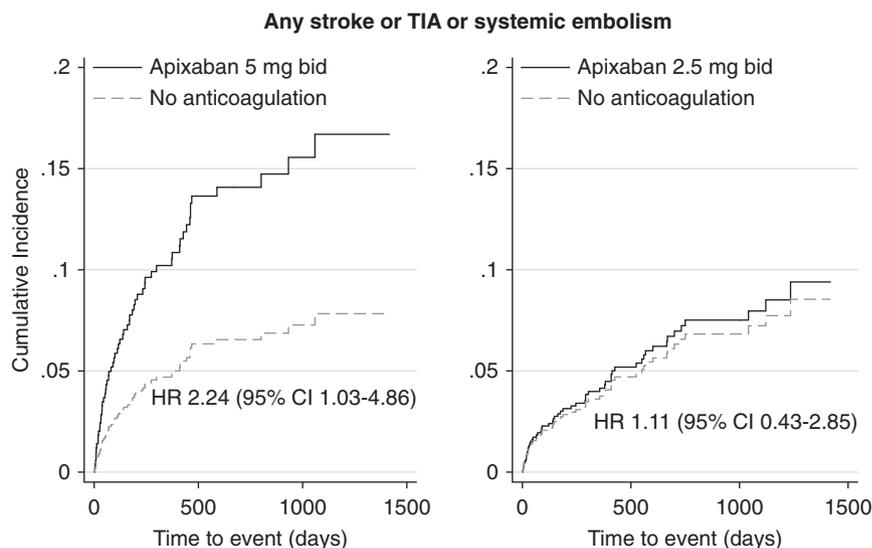
Figure 2. | A significantly higher incidence of any stroke, transient ischemic attack (TIA), or systemic thromboembolism was seen in the subgroup of patients treated with the standard apixaban dose but not in patients who received the reduced apixaban dose, compared with patients who did not receive any anticoagulants. Adjusted hazard ratios (HRs) are depicted. Death was considered as competing risk. Apixaban prescription was examined as a time-varying covariate. bid, twice daily; 95% CI, 95% confidence interval.

hemorrhagic stroke were seen in the subgroup of patients treated with the standard apixaban dose (*n*=207 patients) but not in patients who received the reduced apixaban dose (*n*=257 patients) (Figures 2 and 3, Table 3). On the contrary, a higher rate of the composite outcome of myocardial infarction or ischemic stroke was observed in the subgroup of patients who received the reduced apixaban dose compared with no treatment (Figure 4, Table 3).

Subgroup and Sensitivity Analyses

Results for patients on maintenance hemodialysis are shown in Supplemental Table 4 and were qualitatively consistent with the main analysis. The number of patients on peritoneal dialysis who received apixaban was very small, and no strokes were observed in this subgroup. Therefore, no meaningful conclusions can be drawn for patients on peritoneal dialysis. The "intention-to-treat" analysis, the time-distribution matched analysis, and the marginal structural model analysis yielded qualitatively similar results compared with the main analysis with respect to the primary and secondary outcomes (Supplemental Table 5).

When patients with prevalent atrial fibrillation were included in the dataset (1266 patients on apixaban matched with 3797 patients without anticoagulation), results were qualitatively similar to those observed in the incident population (Supplemental Table 6). In this larger dataset, no significant difference was observed between the two apixaban dose regimens with respect to the primary or secondary outcomes. The incidence of the primary outcome was similar among patients treated with either apixaban dose or patients who did not receive any anticoagulation. A higher rate of fatal or intracranial bleeding was observed with both apixaban doses compared with no treatment (HR, 5.14; 95% CI, 2.72 to 9.72; *P*<0.001 with the standard dose and HR, 2.63; 95% CI, 1.25 to 5.55; *P*=0.01 with the reduced dose). We also studied the effect of apixaban in

different strata. These hypothesis-generating analyses are shown in Supplemental Table 7.

Discussion

To the best of our knowledge, this is the first study to examine the effect of apixaban compared with no treatment in patients on maintenance dialysis with atrial fibrillation. The incidence of the primary outcome was similar in patients treated with apixaban compared with no treatment. Although a trend toward fewer ischemic strokes was seen with apixaban, it was offset by a trend toward more hemorrhagic strokes in these patients. In addition, we found that apixaban was associated with higher incidence of fatal or intracranial bleeding events and a similar incidence of clinically important bleeding, compared with no treatment. Furthermore, significantly higher rates of the primary outcome, of fatal or intracranial bleeding, and of hemorrhagic stroke were seen in the subgroup of patients treated with the standard apixaban dose but not in patients who received the reduced apixaban dose, compared with no treatment.

Comparison of apixaban with warfarin in the dataset by Siontis *et al.* (6) did not demonstrate any difference in the incidence of stroke, and several cohort studies of similar design failed to show any benefit from warfarin in ESKD (8,14–17). The lower mortality among apixaban users suggests that our results are unlikely to be confounded by selection of sicker patients at higher risk of stroke to receive apixaban while lower-risk patients are selected for no treatment. Stroke mechanisms seem to be different in patients with kidney failure, with higher relative incidence of hemorrhagic stroke potentially accounting for the similar incidence of any stroke observed with anticoagulant agents or no treatment.

Furthermore, the standard apixaban dose was associated with a higher incidence of the primary outcome compared

Fatal or intracranial bleeding
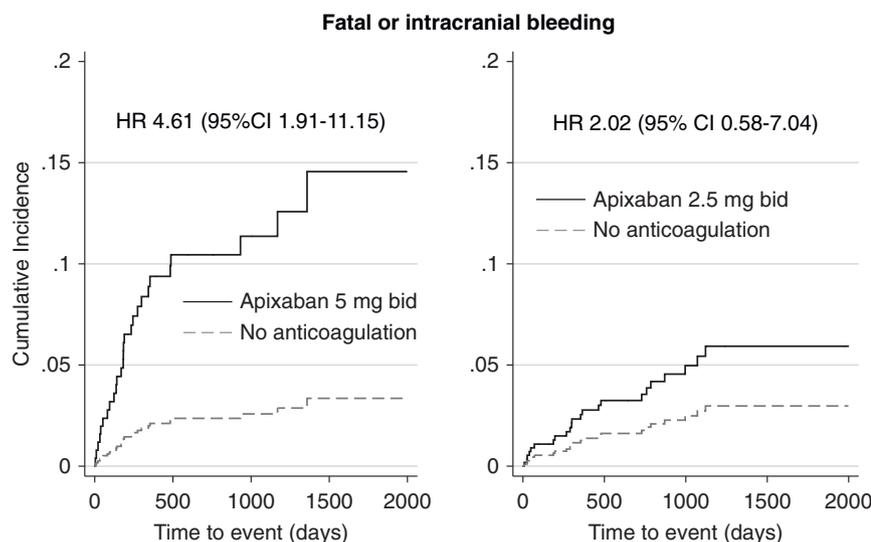
Figure 3. | **A significantly higher incidence of fatal or intracranial (major) bleeding was seen in the subgroup of patients treated with the standard apixaban dose but not in patients who received the reduced apixaban dose, compared with patients who did not receive any anticoagulants.** Adjusted HRs are depicted. Death was considered as competing risk. Apixaban prescription was examined as a time-varying covariate.

Table 3. Clinical outcomes in patients treated with apixaban at the standard or reduced dose compared with patients who received no treatment

Outcome	Incidence in Apixaban Users	Incidence in Nonusers	Crude Hazard Ratio (95% Confidence Interval)	P Value	Adjusted[a] Hazard Ratio (95% Confidence Interval)	P Value
Standard-dose apixaban (5 mg twice daily) versus no treatment						
Any stroke, TIA, or embolism	13.6 (<11)	7.6 (51)	1.80 (0.84 to 3.86)	0.13	**2.24 (1.03 to 4.86)**	**0.04**
Any stroke	10.3 (<11)	6.4 (43)	1.61 (0.66 to 3.90)	0.29	1.94 (0.79 to 4.75)	0.15
Major bleeding	9.8 (<11)	1.7 (20)	**4.33 (1.81 to 10.35)**	**0.001**	**4.61 (1.91 to 11.15)**	**0.001**
Clinically important bleeding	77.2 (34)	57.2 (291)	1.31 (0.91 to 1.89)	0.15	1.36 (0.94 to 1.96)	0.10
Ischemic stroke or MI	22.0 (12)	24.2 (151)	0.91 (0.50 to 1.66)	0.76	0.89 (0.49 to 1.62)	0.70
Ischemic stroke	3.4 (<11)	4.8 (32)	0.72 (0.16 to 3.17)	0.66	0.90 (0.20 to 4.01)	0.89
Hemorrhagic stroke	6.8 (<11)	2.1 (14)	**3.31 (1.07 to 10.22)**	**0.04**	**3.43 (1.10 to 10.77)**	**0.03**
Reduced-dose apixaban (2.5 mg twice daily) versus no treatment						
Any stroke, TIA, or embolism	5.7 (<11)	6.1 (50)	1.15 (0.45 to 2.93)	0.77	1.11 (0.43 to 2.85)	0.84
Any stroke	4.5 (<11)	5.2 (43)	1.04 (0.37 to 2.93)	0.94	0.99 (0.35 to 2.81)	0.99
Major bleeding	2.9 (<11)	1.4 (20)	2.03 (0.59 to 7.04)	0.26	2.02 (0.58 to 7.04)	0.27
Clinically important bleeding	51.4 (33)	54.7 (338)	1.06 (0.74 to 1.52)	0.75	1.03 (0.71 to 1.47)	0.89
Ischemic stroke or MI	31.8 (25)	24.2 (180)	**1.53 (1.00 to 2.34)**	**0.05**	**1.56 (1.02 to 2.39)**	**0.04**
Ischemic stroke	4.5 (<11)	4.7 (39)	1.17 (0.41 to 3.29)	0.77	1.11 (0.39 to 3.17)	0.84
Hemorrhagic stroke	No events	0.5 (<11)	—		—	

Incidence rates are presented as number of events per 100 patient-years, with the number of events per group shown in parentheses. Patients were followed up to the date of death; kidney transplantation; December 31, 2015; loss of Medicare A–B or D coverage; or the date of the last available apixaban prescription (plus drug supply days). Death was considered as a competing risk. TIA, transient ischemic attack; MI, myocardial infarction.
[a]Hazard ratios were adjusted for the CHA_2DS_2-Vasc (congestive heart failure, hypertension, age, diabetes, stroke, vascular history) score for the outcomes of any stroke; any stroke, TIA, or systemic thromboembolism; and ischemic stroke; for a modified HAS-BLED (hypertension, kidney disease, liver disease, stroke, prior bleeding or predisposition to bleeding, labile international normalized ratios, age, medication, alcohol use) score for major bleeding, hemorrhagic stroke, and clinically important bleeding; and for history of hypertension, diabetes mellitus, dyslipidemia, and MI for the outcome of ischemic stroke or MI. Statistically significant differences appear in bold.

with no treatment. This result is in contrast with recently reported superiority of the standard-dose regimen compared with warfarin for stroke prevention and is due to the higher incidence of hemorrhagic stroke among patients on apixaban at the standard dose compared with no

anticoagulation (6). Methodological differences between the two studies may explain this discrepancy: incident versus prevalent population, warfarin versus no anticoagulation for control group, and only ischemic stroke versus any stroke for the outcome of interest.
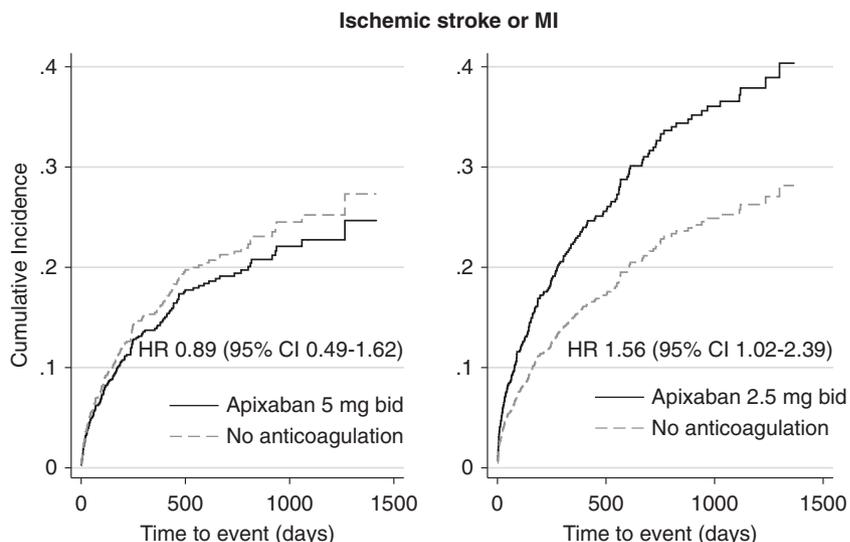
Figure 4. | **A significantly higher incidence of ischemic stroke or MI was seen in the subgroup of patients treated with the reduced apixaban dose but not in patients who received the standard apixaban dose, compared with patients who did not receive any anticoagulants.** Adjusted HRs are depicted. Death was considered as competing risk. Apixaban prescription was examined as a time-varying covariate.

DOACs have been used in patients with recent acute coronary syndromes or stable coronary artery disease on the top of antiplatelet therapy in an attempt to improve cardiac mortality or adverse cardiovascular events. Low-dose apixaban and rivaroxaban have been associated with numerically lower or significantly lower cardio-vascular event rates, respectively, at the expense of more fatal or intracranial bleeding events (18,19). In our analysis, no significant difference was observed between the standard apixaban dose and no anticoagulation with respect to a composite outcome of myocardial infarction or ischemic stroke. On the contrary, a higher rate of myocardial infarction or ischemic stroke was seen with reduced-dose apixaban compared with no treatment. A pharmacologic study in hemodialysis showed that pa-tients on reduced-dose apixaban were close to the tenth percentile of the predicted therapeutic level for the area under the curve, trough, and peak levels seen with the standard dose in patients with preserved kidney func-tion, possibly accounting for more ischemic events with reduced-dose apixaban in this setting (5). Nevertheless, there is no established indication for DOACs use for cardiovascular event prevention in kidney failure, at least at this time.

Our observation of lower all-cause mortality among apixaban users compared with no treatment is probably due to selection bias, with "healthier" patients being prescribed apixaban and between-group differences not fully accounted for despite propensity-score matching and adjustment for stroke or bleeding risk scores. The lower incidence of pneumonia or hip fracture among apixaban users supports this hypothesis. It will be important to assess these alternative possibilities, preferably in random-ized trials, before any recommendations on use of apixaban for the reduction of mortality can be considered. Moreover, if "healthier" patients were prescribed apixaban in this cohort, stroke and fatal or intracranial bleeding outcomes could be even worse with apixaban compared with no treatment in a randomized setting.

Apixaban has been shown to be safer than warfarin in patients on maintenance hemodialysis with respect to major bleeding events, both at the standard dose and the reduced dose (6). In our analysis, despite being associated with a nonsignificant reduction in ischemic stroke, apixaban was associated with a significantly higher risk of fatal or in-tracranial bleeding and of hemorrhagic stroke compared with no treatment. This finding was observed in the subgroup of patients who received the standard but not the reduced apixaban dose. Fewer clinically significant bleeding events were observed with the reduced dose compared with the standard dose, as expected from pharmacokinetic data (5). However, bleeding events were observed at very high rates even without anticoagulation, suggesting prudence with anticoagulant agents in this population.

Our study had important limitations. It is an observa-tional retrospective cohort study using diagnostic codes (20). The number and proportion of patients treated with apixaban were small, suggesting that these were "un-usual" patients. The last year of data is 2015 and probably reflects an earlier era with possibly greater challenges of treatment selection. Although patients in both groups were propensity-score matched without important differences in baseline characteristics, between-group dif-ferences may not be fully accounted for with this ap-proach. Residual confounding and selection bias may explain part of the results. Aspirin use may differ between apixaban users and nonusers and could not be captured in this cohort. We did not have any information on important confounders, such as BP control, body mass index, residual kidney function, dialysis prescription, or anticoagulation prescription during dialysis. Nevertheless, inclusion of patients with new-onset atrial fibrillation, similar results in the intention-to-treat and as-treated analyses, and exclu-sion of patients who died within a short interval post-diagnosis, suggesting atrial fibrillation in the setting of a serious intercurrent illness, are important strengths of our analysis. In addition, use of competing risk models has been recently shown to be critically important in the analysis of atrial fibrillation data and is another strength of this study (21).

A randomized trial with apixaban at the standard dose versus warfarin had to terminate enrollment due to slower than anticipated recruitment (NCT02942407). A second trial is currently ongoing with apixaban at the reduced dose versus warfarin in patients on maintenance hemodialysis with atrial fibrillation (NCT02933697) and will provide important information. Another randomized study will compare apixaban at the standard dose, warfarin, and no anticoagulation in this population (NCT03987711). However, our results suggest that a randomized trial comparing both apixaban doses with no anticoagulation is of utmost impor-tance in this population. Awaiting randomized data, prudence in prescribing apixaban to patients on maintenance dialysis, especially at the standard dose, is warranted.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN. 11650919/-/DCSupplemental.

Supplemental Table 1. Condition-specific International Classification of Diseases, ninth and tenth revisions diagnostic codes used in this study.

Supplemental Table 2. Time to event data for each outcome in the apixaban and no anticoagulation groups.

Supplemental Table 3. Baseline characteristics of the unmatched and matched cohorts for patients on hemodialysis.

Supplemental Table 4. Clinical outcomes for patients on hemodialysis.

Supplemental Table 5. Sensitivity analyses.

Supplemental Table 6. Clinical outcomes in the prevalent atrial fibrillation dataset.

Supplemental Table 7. Effect of apixaban on any stroke, transient ischemic attack, or systemic thromboembolism and on major bleeding in selected strata (prevalent atrial fibrillation dataset).

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Supplemental Material Table of Contents

Supplemental Table 1. Condition-specific ICD-9 and ICD-10 diagnostic codes used in this study

Cardiovascular Mortality	**DEATHFM:** 23, 25, 26, 27, 28, 29, 30, 31, 32
Ischemic stroke or transient ischemic attack	**ICD-9-CM:** 362.3x, 433.x1, 434.x1, 436 **ICD-10 CM**: H34.1, I63
Systemic embolism	**ICD-9-CM:** 434.1, 444.xx, 445.xx **ICD-10 CM**: I74, I75
Myocardial infarction	**ICD-9-CM**: 410.xx **ICD-10 CM**: I21.x(x), I22.x(x)
Hemorrhagic stroke	**ICD-9-CM**: 430, 431, 432 **ICD-10 CM**: I60, I61, I62
Major bleeding	
1. Resulting in death	**DEATHFM**: 38, 39, 40, 41, 42, 43, 72
2. Intracranial	**ICD-9-CM**: 430, 431, 432.x **ICD-10 CM**: I60, I61, I62
Clinically significant bleeding	
1. Resulting in death	**DEATHFM**: 38, 39, 40, 41, 42, 43, 72
2. In a critical site:	
- Intracranial	**ICD-9-CM**: 430, 431, 432.x **ICD-10 CM**: I60, I61, I62
- Intraocular	**ICD-9-CM**: 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 376.32, 377.42, 379.23 **ICD-10 CM**: H44.81, H35.73x, H35.6x, H31.30x, H31.31x, H31.41x, H05.23x, H43.1x, H47.02x
- Pericardial	**ICD-9-CM**: 423.0 // **ICD-10 CM**: I31.2
- Airway	**ICD-9-CM**: 784.8, 786.30, 786.39 // **ICD-10 CM**: R04.x(x)
- Intra-articular	**ICD-9-CM**: 719.1x // **ICD-10 CM**: M25.0x(x)
- Retroperitoneal	**ICD-9-CM**: 568.81// **ICD-10 CM**: K66.1
3. Resulting in hospitalization: - GI	One of the following codes in the institutional inpatient files: **ICD-9-CM**: 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.5x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1, 537.83, 537.84, 578.x, 562.x2, 562.x3, 569.3, 569.85 **ICD-10 CM**: I85.x1, K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.x1, K31.811, K31.82, K92.0, K92.1, K92.2, K57.x1, K57.x3, K62.5, K55.21
- Urinary	**ICD-9-CM**: 596.7, 602.1, 599.7x **ICD-10 CM**: N42.1, R31.0, R31.9
- Gynecological	**ICD-9-CM**: 620.7, 621.4, 623.6, 624.5, 626.6, 626.8, 626.9, 627.0, 627.1 **ICD-10 CM**: N83.6, N83.7, N85.7, N92.0, N92.1, N92.4, N92.5, N93.8, N93.9, N95.0
- Other	**ICD-9-CM**: 459.0, 958.2, 729.92, 285.1
Pneumonia (viral or bacterial)	**ICD-9-CM**: 480.x, 481, 482.x(x), 483.x, 484.x, 485, 486, 487.0, 488.x1

ICD-10-CM: J09.X1, J10.0_, J11.0_, J12, J13, J14, J15, J16, J18

Hip fracture **ICD-9-CM**: 820.x(x), 821.xx
ICD-10-CM: S72.x

Supplemental Table 2. Time to event data for each outcome in the apixaban and the no anticoagulation group.

Time to outcome (days)	No anticoagulation	Apixaban
Time to stroke, TIA, or embolism	212 (65-523)	173 (49-379)
Time to stroke	214 (65-532)	173 (48-384)
Time to ischemic stroke	216 (67-532)	174 (49-384)
Time to hemorrhagic stroke	218 (68-538)	180 (52-386)
Time to clinically significant bleeding	140 (42-357)	124 (32-272)
Time to ischemic stroke-MI	184 (55-462)	163 (43-348)
Time to death	293 (87-636)	184 (52-387)

Results are shown as median (interquartile range). TIA, transient ischemic attack; MI, myocardial infarction

Supplemental Table 3. Baseline characteristics of the unmatched and matched cohort for patients on hemodialysis

Characteristics	Unmatched cohort			Matched cohort		
	No anticoagulation	Apixaban	St. dif.	No anticoagulation	Apixaban	St. dif.
Number of patients	9831	453		1374	453	
Demographics						
Age	68 ± 13	67 ± 11	-0.01	68 ± 13	67 ± 11	-0.08
Male sex	5283 (54%)	241 (53%)	-0.01	722 (53%)	241 (53%)	0.01
Black race	3151 (32%)	108 (24%)	-0.19	310 (23%)	108 (24%)	0.03
Dialysis vintage (months)	26 (10-59)	19 (6-33)	-0.32	19 (5-39)	19 (6-33)	0.00
Comorbidities						
Hypertension	9781 (100%)	452 (100%)	0.05	1370 (100%)	452 (100%)	0.02
Diabetes	7934 (81%)	375 (83%)	0.05	1111 (81%)	375 (83%)	0.05
Coronary disease	7514 (76%)	342 (76%)	-0.02	1036 (75%)	342 (76%)	0.00
Heart failure	7559 (77%)	351 (78%)	0.01	1076 (78%)	351 (78%)	-0.02
Myocardial infarction	2684 (27%)	102 (23%)	-0.11	315 (23%)	102 (23%)	-0.01
Stroke history	4010 (41%)	161 (36%)	-0.11	511 (37%)	161 (36%)	-0.04
PVD	5973 (61%)	257 (57%)	-0.08	771 (56%)	257 (57%)	0.01
Dyslipidemia	8365 (85%)	414 (91%)	0.20	1249 (91%)	414 (91%)	0.02
Malignancy	2793 (28%)	123 (27%)	-0.03	391 (29%)	123 (27%)	-0.03

Alcohol-related disease	1481 (15%)	51 (11%)	-0.11	161 (12%)	51 (11%)	-0.01
Liver disease	3240 (33%)	118 (26%)	-0.15	335 (24%)	118 (26%)	0.04
COPD	4375 (45%)	187 (41%)	-0.06	570 (42%)	187 (41%)	0.00
Bleeding history	5716 (58%)	224 (49%)	-0.18	675 (49%)	224 (49%)	0.01
Medication						
ACEI	2975 (30%)	120 (27%)	-0.08	335 (24%)	120 (27%)	0.05
ARB	1819 (19%)	87 (19%)	0.02	252 (18%)	87 (19%)	0.02
Antiplatelet agent	2450 (25%)	106 (23%)	-0.04	324 (24%)	106 (23%)	0.00
Beta-blocker	6777 (69%)	330 (73%)	0.09	997 (73%)	330 (73%)	0.00
Statin	5183 (53%)	274 (61%)	0.16	830 (60%)	274 (61%)	0.00

Results are presented as mean ± standard deviation, median (interquartile range) or number (percentage). Standardized differences <0.10 are considered to be negligible.

St. dif., standardized difference; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Supplemental Table 4. Clinical outcomes for patients on hemodialysis (453 patients on apixaban matched with 1374 patients without any anticoagulation)

Outcome	Incidence in apixaban users	Incidence in non-users	Crude HR (95% CI)	p value	Adjusted* HR (95% CI)	p value
Any stroke or TIA or embolism	8.5 (13)	7.3 (105)	1.36 (0.75-2.46)	0.31	1.41 (0.78-2.55)	0.26
Any stroke	6.5 (<11)	6.1 (88)	1.24 (0.64-2.42)	0.53	1.27 (0.65-2.49)	0.48
Major bleeding	4.4 (<11)	1.6 (41)	**2.42 (1.12-5.23)**	**0.03**	**2.44 (1.13-5.28)**	**0.02**
Clinically important bleeding	58.9 (69)	57.5 (621)	1.15 (0.89-1.48)	0.30	1.15 (0.89-1.49)	0.28
Ischemic stroke- MI	27.3 (38)	25.9 (341)	1.20 (0.85-1.69)	0.30	1.19 (0.85-1.67)	0.31
Ischemic stroke	3.9 (<11)	5.2 (75)	0.88 (0.38-2.07)	0.78	0.91 (0.39-2.15)	0.84
Hemorrhagic stroke	2.6 (<11)	1.3 (19)	2.19 (0.75-6.46)	0.15	2.21 (0.75-6.51)	0.15

Incidence rates are presented as number of events per 100 patient-years (total number of events). The number of outcomes per group is shown in parentheses. For the outcomes of any stroke, any stroke or TIA or thromboembolism, major bleeding, clinically important bleeding, ischemic stroke or myocardial infarction, ischemic stroke, and hemorrhagic stroke, patients were followed up to the date of death, kidney transplantation, on December 31st, 2015, loss of Medicare A-B or D coverage, or at the date of the last available apixaban prescription (plus drug supply days). Death was considered as a competing risk.

*, Hazard ratios were adjusted for: CHA_2DS_2-Vasc score for the composite outcome of any stroke, any stroke or TIA or systemic thromboembolism and for the outcome of ischemic stroke; modified HAS-BLED score for major bleeding, hemorrhagic stroke, and clinically-important bleeding;

history of hypertension, diabetes mellitus, dyslipidemia, and myocardial infarction for the composite outcome of ischemic stroke or myocardial infarction.

HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; MI, myocardial infarction

Supplemental Table 5. Sensitivity analyses

Outcome	Crude HR (95% CI)	p value	Adjusted* HR (95% CI)	p value
Intention to treat analysis				
Stroke or embolism	1.09 (0.68-1.72)	0.73	1.07 (0.67-1.70)	0.78
Major bleeding	1.16 (0.58-2.31)	0.68	1.13 (0.57-2.27)	0.73
Clinically important bleeding	1.02 (0.83-1.25)	0.86	1.00 (0.81-1.22)	0.94
Ischemic stroke or MI	0.94 (0.71-1.24)	0.66	0.93 (0.70-1.23)	0.59
Time-distribution matching analysis				
Stroke or embolism	0.88 (0.48-1.61)	0.68	0.93 (0.51-1.71)	0.83
Major bleeding	1.92 (0.88-4.18)	0.10	1.94 (0.89-4.23)	0.10
Clinically important bleeding	0.95 (0.74-1.21)	0.66	0.95 (0.74-1.21)	0.66
Ischemic stroke or MI	0.99 (0.71-1.38)	0.93	1.00 (0.72-1.40)	0.99
Marginal structural model				
Stroke or embolism	1.21 (0.67-2.20)	0.53	1.08 (0.60-1.92)	0.81
Major bleeding	3.29 (0.46-23.62)	0.24	3.16 (0.44-22.70)	0.25
Clinically important bleeding	0.88 (0.65-1.17)	0.37	0.83 (0.63-1.10)	0.20
Ischemic stroke or MI	1.12 (0.74-1.70)	0.58	1.03 (0.70-1.53)	0.87

For the intention to treat analysis, patients were followed up to the date of death, kidney transplantation, or on December 31st, 2015. Death was considered as a competing risk.

For the time-distribution matching analysis, patients were censored at the date of the last available apixaban prescription (plus drug supply days) for all outcomes.

For the marginal structural models, the following parameters were used to calculate the inverse probability weights: age, sex, race dialysis modality, dialysis vintage, stroke history, MI history, bleeding history, hypertension, diabetes, heart failure, coronary disease, dyslipidemia, peripheral vascular disease, liver disease, alcohol-related disease, cancer, chronic obstructive lung disease, and use of medication (renin-angiotensin-aldosterone inhibitors, beta-blockers, statins, or antiplatelet agents).

* Hazard ratios were adjusted for: CHA$_2$DS$_2$-Vasc score for the outcomes of stroke (ischemic or hemorrhagic, transient ischemic) or systemic thromboembolism; modified HAS-BLED score for major bleeding and clinically important bleeding; history of hypertension, diabetes mellitus, dyslipidemia, and myocardial infarction for the outcome of ischemic stroke or myocardial infarction.

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction

Supplemental Table 6. Clinical outcomes in the prevalent atrial fibrillation dataset: 1266 patients on apixaban and 3797 patients without any anticoagulation.

Outcome	Crude HR (95% CI)	p value	Adjusted* HR (95% CI)	p value
Any stroke or TIA or embolism	0.98 (0.65-1.48)	0.91	0.96 (0.64-1.46)	0.87
Any stroke	0.82 (0.52-1.30)	0.40	0.80 (0.51-1.27)	0.35
Major bleeding	**3.19 (2.00-5.09)**	**<0.001**	**3.18 (2.00-5.08)**	**<0.001**
Clinically important bleeding	**1.36 (1.15-1.59)**	**<0.001**	**1.34 (1.14-1.58)**	**<0.001**
Ischemic stroke or MI	**1.26 (1.01-1.57)**	**0.04**	1.21 (0.97-1.50)	0.09
Ischemic stroke	1.01 (0.65-1.56)	0.98	0.99 (0.63-1.53)	0.95
Hemorrhagic stroke	**3.11 (1.89-5.13)**	**<0.001**	**3.09 (1.88-5.10)**	**<0.001**

For the outcomes of any stroke, any stroke or transient ischemic attack or thromboembolism, major bleeding, clinically important bleeding, ischemic stroke or myocardial infarction, ischemic stroke, and hemorrhagic stroke, patients were followed up to the date of death, kidney transplantation, on December 31st, 2015, loss of Medicare A-B or D coverage, or at the date of the last available apixaban prescription (plus drug supply days). Death was considered as a competing risk.

*, Hazard ratios were adjusted for: CHA_2DS_2-Vasc score for the outcome of any stroke, the composite outcome of any stroke or transient ischemic attack or systemic thromboembolism, and the outcome of ischemic stroke; modified HAS-BLED score for major bleeding, hemorrhagic stroke, and clinically important bleeding; history of hypertension, diabetes mellitus, dyslipidemia, and myocardial infarction for the composite outcome of ischemic stroke or myocardial infarction.

HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; MI, myocardial infarction

Supplemental Table 7. Effect of apixaban compared with no anticoagulation on any stroke and major bleeding in selected strata (prevalent atrial fibrillation dataset: 1266 patients on apixaban and 3797 patients without any anticoagulation).

Outcome	Stratum	HR (95% CI)	p value	p for interaction
Any stroke or transient ischemic attack or systemic embolism	Age≥ 75	0.54 (0.22-1.33)	0.18	0.11
	Age < 75	1.23 (0.77-1.97)	0.39	
	Males	1.19 (0.69-2.04)	0.53	0.30
	Females	0.80 (0.42-1.54)	0.50	
	Black race	1.82 (0.85-3.89)	0.12	0.11
	Other races	0.79 (0.48-1.30)	0.35	
	Prior stroke	0.99 (0.55-1.78)	0.97	0.80
	No prior stroke	0.94 (0.52-1.71)	0.84	
	High risk for stroke[*]	1.09 (0.71-1.67)	0.70	0.14
	Low risk for stroke[*]	0.24 (0.03-1.70)	0.15	
Fatal or intracranial bleeding	Age>= 75	1.15 (0.36-3.70)	0.81	0.04
	Age < 75	4.47 (2.66-7.52)	<0.001	
	Males	3.27 (1.85-5.79)	<0.001	0.85
	Females	2.88 (1.29-6.45)	0.01	
	Black race	3.44 (1.78-10.03)	0.02	0.80
	Other races	3.06 (1.82-5.14)	<0.001	
	Prior stroke	3.59 (1.68-7-70)	0.001	0.60
	No prior stroke	2.90 (1.60-5.28)	<0.001	
	High risk for bleeding[#]	2.64 (1.38-5.05)	0.003	0.36
	Low risk for bleeding[#]	3.89 (1.99-7.62)	<0.001	

* High risk for stroke was defined as a CHA_2DS_2-Vasc score >=5 and low risk for stroke as a CHA_2DS_2-Vasc score <5.

High risk for bleeding was defined as a HAS-BLED score >3 and low risk for stroke as a HAS-BLED score <=3.

Crude hazard ratios are reported. Death was considered as a competing risk. Patients were followed up to the date of death, kidney transplantation, on December 31st, 2015, loss of Medicare A-B or D coverage, or

at the date of the last available apixaban prescription (plus drug supply days). HR, hazard ratio; CI, confidence interval