



American Society of Nephrology  
1401 H St NW, Suite 900  
Washington, DC 20005  
Phone: 202-640-4660 | Fax 202-637-9793  
vramsey@kidney360.org

**How to Cite this article:** Thomas Mavrakanas and David Charytan, Apixaban vs no anticoagulation by P2Y12 inhibitor prescription status in dialysis patients with atrial fibrillation, *Kidney360*, Publish Ahead of Print, 2022, 10.34067/KID.0003002022

**Article Type:** Brief Communication

## **Apixaban vs no anticoagulation by P2Y12 inhibitor prescription status in dialysis patients with atrial fibrillation**

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Thomas Mavrakanas and David Charytan

### **Key Points:**

\*In patients with AF on dialysis, the incidence of stroke was similar with apixaban or no anticoagulation, regardless of P2Y12 prescription.

\*In patients with AF on dialysis who were on a P2Y12 inhibitor, apixaban increased the risk of bleeding, compared with no anticoagulation.

\*The incidence of MI or ischemic stroke was similar with apixaban or no anticoagulation, regardless of P2Y12 prescription status.

### **Abstract:**

**Disclosures:** Dr. Mavrakanas received honoraria from Daiichi Sankyo, BMS Canada, Janssen, and Pfizer and has served on advisory boards for Boehringer Ingelheim outside the submitted work. Dr. Charytan reports personal fees and grants from Janssen, personal fees from Boehringer Ingelheim/Eli Lilly, personal fees from Merck, grants and personal fees from NovoNordisk, grants and personal fees from Gilead, personal fees from AstraZeneca, grants and personal fees from Medtronic, grants and personal fees from Amgen, personal fees from GSK, personal fees from Fresenius, and personal fees from Zoll Medical outside the submitted work.

**Funding:** Fonds de Recherche du Québec - Santé (FRQS): Thomas A. Mavrakanas; Québec Society of Nephrology: Thomas A. Mavrakanas

**Author Contributions:** Thomas Mavrakanas: Conceptualization; Data curation; Formal analysis; Writing - original draft David Charytan: Methodology; Project administration; Resources; Supervision; Writing - review and editing

**Data Sharing Statement:** Data cannot be shared: Restrictions apply to the availability of these data, which were used under license for this study, and therefore are not publicly available.

**Clinical Trials Registration:**

**Registration Number:**

**Registration Date:**

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.

**Apixaban vs no anticoagulation by P2Y12 inhibitor prescription status in dialysis patients with atrial fibrillation**

Thomas A. Mavrakanas<sup>1</sup> & David M. Charytan<sup>2</sup>

<sup>1</sup> Division of Nephrology, Department of Medicine, McGill University Health Center, Montreal, QC, Canada

<sup>2</sup> Nephrology Division, Department of Medicine, NYU Langone Medical Center, New York, NY, USA

Corresponding author:

Thomas A. Mavrakanas, MD

McGill University Health Center Research Institute | CORE | Office 2B.44

5252 de Maisonneuve West, Montreal, Quebec, H4A 3S9, Canada

Tel. +1 (514) 934-1934 x 44736; Email: [thomas.mavrakanas@mcgill.ca](mailto:thomas.mavrakanas@mcgill.ca)

**Key points:**

- In patients with AF on dialysis, the incidence of stroke was similar with apixaban or no anticoagulation, regardless of P2Y12 prescription.
- In patients with AF on dialysis who were on a P2Y12 inhibitor, apixaban increased the risk of bleeding, compared with no anticoagulation.
- The incidence of MI or ischemic stroke was similar with apixaban or no anticoagulation, regardless of P2Y12 prescription status.

Atrial fibrillation is common among patients on maintenance dialysis but antithrombotic strategies for stroke prevention are not well established in this population (1). We recently reported that apixaban was not associated with a lower incidence of stroke, transient ischemic attack, or systemic thromboembolism, compared with no anticoagulation in patients with incident atrial fibrillation on maintenance dialysis, but was associated with a higher incidence of fatal or intracranial bleeding (2). In report, we present the incidence of thrombotic and bleeding outcomes by P2Y12 inhibitor prescription status at baseline.

We conducted a retrospective cohort study of patients with incident non-valvular atrial fibrillation who were undergoing long-term dialysis between 2012 and 2015 using United States Renal Data System data (3). Study design and main results have been reported elsewhere (2). In brief, we matched patients who were alive at 30 days post-atrial fibrillation diagnosis and were treated with apixaban with patients without any anticoagulant prescription, using a propensity score. The primary outcome was hospital admission for a new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism. Secondary outcomes included fatal or intracranial bleeding and ischemic stroke or myocardial infarction. Condition-specific diagnostic codes are presented in the **Supplement**. 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. We censored apixaban users at the date of the last available prescription and all patients when Medicare Part A, B, or D coverage was lost. Hazard ratios (HRs) were adjusted for CHA<sub>2</sub>DS<sub>2</sub>-Vasc score for the primary outcome, modified HAS-BLED score for fatal or intracranial bleeding, and hypertension, diabetes, dyslipidemia or myocardial infarction for the outcome of ischemic stroke or myocardial infarction. Statistical analyses were performed in Stata (version 17 SE; College Station, TX). The Partners Healthcare institutional review board approved the study (2016P001613/ BWH) and ruled that informed consent was not needed.

Our propensity score-matched cohort included 2082 patients. Among them, 473 were on a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) at baseline (117 of them also received apixaban whereas 356 did not receive any anticoagulant agents) and 1609 were not on a P2Y12 inhibitor at baseline (404 of them received apixaban whereas 1205 did not receive any anticoagulant agents). Aspirin prescription is not available in this dataset. Baseline characteristics by P2Y12 prescription status are shown in **Figure 1A**.

In the subgroup of patients who were on a P2Y12 inhibitor, apixaban use was not associated with lower risk of stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism: 8.2 versus 9.1 events per 100 patient-years in apixaban-treated patients and in patients who did not receive any anticoagulant, respectively (HR 1.48; 95% confidence interval [95% CI] 0.52 to 4.20; P=0.46). Similarly, in the subgroup of patients who were not on a P2Y12 inhibitor, the incidence of the primary outcome was similar in apixaban-treated patients and in patients who did not receive any anticoagulant (7.3 versus 6.4 events per 100 patient-years): HR 1.22, 95% CI 0.60 to 2.49; P=0.58. There was no interaction between P2Y12 prescription at baseline and the effect of apixaban on stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism (p for interaction 0.66).

The incidence of fatal or intracranial bleeding was higher among apixaban-treated patients compared with patients who did not receive any anticoagulant in the subgroup of patients who were on a P2Y12 inhibitor at baseline (4.9 versus 1.0 events per 100 patient-years): HR 8.82 (95% CI 2.06 to 37.76; p=0.003) (**Figure 1B**). In contrast, the incidence of fatal or intracranial bleeding did not differ between the treatment groups among patients who were not on a P2Y12 inhibitor at baseline (2.3 versus 1.8 events per 100 patient-years): HR 1.85 (95% CI 0.78 to 4.36; p=0.16) (**Figure 1B**). A significant interaction was detected between P2Y12 prescription status at baseline and the effect of apixaban on fatal or intracranial bleeding: bleeding risk with apixaban was more important among patients with a P2Y12 inhibitor at baseline (p for interaction 0.03).

In the subgroup of patients who were on a P2Y12 inhibitor, the incidence of ischemic stroke or myocardial infarction was similar in both the apixaban and the no anticoagulation groups (incidence of 29.0 versus 38.9 events per 100 patient-years; HR 0.91; 95% CI 0.46 to 1.82; P=0.80). Similarly, the incidence of ischemic stroke or myocardial infarction was similar in both treatment groups among patients who were not on a P2Y12 inhibitor at baseline (incident rate of 27.2 versus 21.5 events per 100 patient-years; HR 1.39; 95% CI 0.96 to 2.00; P=0.08). There was no interaction between P2Y12 prescription at baseline and the effect of apixaban on ischemic stroke or myocardial infarction (p for interaction 0.22).

Up to 30% of patients with atrial fibrillation also have coronary disease (4). These patients are frequently treated with a combination of anticoagulant and antiplatelet agents. The AFIRE trial recently assessed antithrombotic strategies in patients with stable coronary disease and atrial fibrillation (5). The study showed that rivaroxaban monotherapy was superior to the combination of rivaroxaban with an antiplatelet agent with respect to major bleeding and non-inferior for the composite efficacy outcome of death from any cause, myocardial infarction, unstable angina requiring revascularization, stroke, or systemic embolism. In this report, we showed that the association of apixaban with a P2Y12 inhibitor significantly increased the risk of fatal or intracranial bleeding, compared with no anticoagulation. In contrast, the incidence of major bleeding was similar in both treatment groups for patients who were not receiving a P2Y12 inhibitor. The incidence of stroke or embolism or the composite outcome of myocardial infarction and ischemic stroke were similar in both treatment groups (apixaban or no anticoagulation), regardless of P2Y12 prescription status at baseline.

Our analysis has important limitations. It is an observational retrospective study using diagnostic codes. Residual confounding may explain part of the results. The crude number of events for each outcome, provided in the **Supplement**, was small for most subgroups. In addition, patients were not matched by P2Y12 prescription status at baseline. Nevertheless, use of competing risk models and similar results in interaction terms and stratified analyses represent important strengths of the study.

In conclusion, the association of apixaban with a P2Y12 inhibitor may be used with caution in patients on maintenance dialysis.

### **Disclosures**

T. Mavrakanas received honoraria from Daiichi Sankyo, BMS Canada, Janssen, and Pfizer and has served on advisory boards for Boehringer Ingelheim outside the submitted work.

D. Charytan reports personal fees and grants from Janssen, personal fees from Boehringer Ingelheim/Eli Lilly, personal fees from Merck, grants and personal fees from NovoNordisk, grants and personal fees from Gilead, personal fees from AstraZeneca, grants and personal fees from Medtronic, grants and personal fees from Amgen, personal fees from GSK, personal fees from Fresenius, and personal fees from Zoll Medical outside the submitted work.

### **Funding**

Dr. Mavrakanas is supported by a Junior 1 Clinician Scholar Award from the Fonds de Recherche du Québec – Santé. He has received operating funds from the Quebec Society of Nephrology.

### **Acknowledgment**

The data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

Restrictions apply to the availability of these data, which were used under license for this study, and therefore are not publicly available.

### **Author Contributions**

Thomas Mavrakanas: Conceptualization; Data curation; Formal analysis; Writing - original draft. David Charytan: Methodology; Project administration; Resources; Supervision; Writing - review and editing.

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## Supplemental Materials

Supplemental Table 1. Crude number of events

Supplemental Table 2. Condition-specific ICD-9 and ICD-10 diagnostic codes used in this study

## References

1. Mavrakanas TA: Should Oral Anticoagulation Be Used in ESKD Patients on Hemodialysis with Atrial Fibrillation? COMMENTARY. *Kidney360* 2: 1412–1414, 2021
2. Mavrakanas TA, Garlo K, Charytan DM: Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. *Clin J Am Soc Nephrol* 15: 1146–1154, 2020
3. United States Renal Data System: 2017USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2017
4. Verheugt FWA, Ten Berg JM, Storey RF, Cuisset T, Granger CB: Antithrombotics: From Aspirin to DOACs in Coronary Artery Disease and Atrial Fibrillation (Part 3/5). *J Am Coll Cardiol* 74: 699–711, 2019
5. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators: Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med* 381: 1103-1113, 2019

## Figure legend

**Figure 1A.** Baseline characteristics by P2Y12 prescription status at baseline (matched cohort).

Results are presented as mean  $\pm$  standard deviation, median (interquartile range) or number (percentage).

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

**Figure 1B.** Clinical outcomes with apixaban by P2Y12 prescription status at baseline

Effect size (ES) is presented as hazard ratio with 95% confidence interval (CI). MI, myocardial infarction

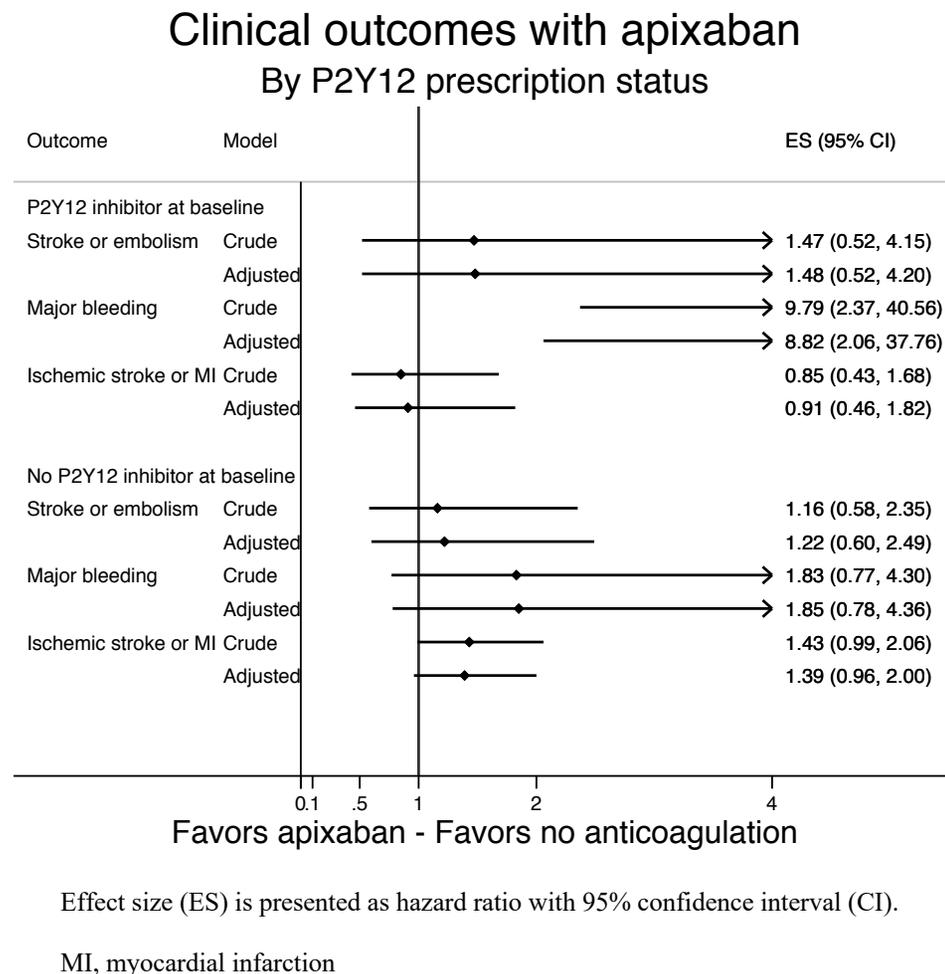
**Figure 1A.** Baseline characteristics by P2Y12 prescription status at baseline (matched cohort)

Characteristics	Patients on a P2Y12 inhibitor			Patients not on a P2Y12 inhibitor		
	No treatment	Apixaban	St. dif.	No treatment	Apixaban	St. dif.
Number of patients	356	117		1,205	404	
<i>Demographics</i>						
Age	69 ± 12	69 ± 10	0.01	68 ± 13	67 ± 12	0.04
Male sex	196 (55%)	65 (56%)	0.01	628 (52%)	216 (54%)	0.03
Black race	70 (20%)	22 (19%)	0.02	263 (22%)	94 (23%)	0.03
Hemodialysis	26 (7%)	<11 (<10%)	0.04	108 (9%)	38 (10%)	0.02
Dialysis vintage (months)	18 (8-40)	18 (5-37)	-0.01	19 (5-37)	19 (7-33)	0.01
<i>Comorbidities</i>						
Hypertension	356 (100%)	117 (100%)	0.00	1201 (99%)	403 (99%)	0.02
Diabetes	309 (87%)	104 (89%)	0.06	942 (78%)	315 (78%)	0.005
Coronary disease	341 (96%)	106 (91%)	0.21	809 (67%)	281 (70%)	0.05
Heart failure	312 (88%)	99 (85%)	0.09	875 (73%)	298 (74%)	0.03
Myocardial infarction	154 (43%)	42 (36%)	0.15	195 (16%)	68 (17%)	0.02
Stroke history	174 (49%)	66 (56%)	0.15	390 (32%)	112 (28%)	0.10
PVD	253 (71%)	83 (71%)	0.003	601 (50%)	202 (50%)	0.002
Dyslipidemia	345 (97%)	112 (96%)	0.06	1075 (89%)	360 (89%)	0.003
Malignancy	103 (29%)	34 (29%)	0.003	354 (29%)	115 (29%)	0.02
Alcohol-related disease	35 (10%)	17 (15%)	0.14	140 (12%)	42 (10%)	0.04
Liver disease	85 (24%)	25 (21%)	0.06	286 (24%)	109 (27%)	0.07
COPD	146 (41%)	56 (48%)	0.14	460 (38%)	151 (37%)	0.02
Bleeding history	184 (52%)	68 (58%)	0.13	568 (47%)	186 (46%)	0.02
<i>Medication</i>						
ACEI	94 (26%)	40 (34%)	0.17	290 (24%)	94 (23%)	0.02
ARB	74 (21%)	27 (23%)	0.05	219 (18%)	70 (17%)	0.02
Beta-blocker	295 (83%)	93 (80%)	0.09	831 (69%)	286 (71%)	0.04
Statin	299 (84%)	93 (80%)	0.12	643 (53%)	220 (55%)	0.02

Results are presented as mean ± standard deviation, median (interquartile range) or number (percentage).

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

**Figure 1B.** Clinical outcomes with apixaban by P2Y12 prescription status at baseline



**Supplemental Table 1.** Crude number of events

Outcome	P2Y12 status at baseline	Events (apixaban arm)	Events (no anticoagulation arm)
Stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism	Yes	<11	29
	No	22	70
Fatal or intracranial bleeding	Yes	<11	<11
	No	<11	37
Ischemic stroke or myocardial infarction	Yes	<11	119
	No	34	254

**Supplemental Table 2.** Condition-specific ICD-9 and ICD-10 diagnostic codes used in this study

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