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Updates in SPAF of AF patients with ESRD

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Two questions

- OAC or no OAC
- OAC? Then which OAC? W? DOAC? A particular DOAC? Dose?

OAC or not in AF ESRD patients

- Still controversial
- Numerous observational studies have reported conflicting results for the use of both VKA and NOACs in patients with ESRD regarding effectiveness and bleeding without a clear signal for a benefit of OAC.

Effectiveness and Safety of Warfarin Initiation in Older Hemodialysis Patients with Incident Atrial Fibrillation

Wolfgang C. Winkelmayer,† Jun Liu,* Soko Setoguchi,*† and Niteesh K. Choudhry**

Summary

Background and objectives Although generally recommended in atrial fibrillation (AF) patients, the effectiveness and safety of oral anticoagulation in dialysis patients with AF is unknown.

Design, setting, participants, & measurements We assembled a cohort of older hemodialysis patients who initiated dialysis without prior record of AF and who had prescription drug benefits through three state-administered programs. The index event was a first hospitalization with diagnosed AF; patients with any recorded prior warfarin use were excluded. Eligible patients survived ≥30 days from discharge, and new warfarin use was recorded from prescription records during that 30-day window. Propensity-matched warfarin users and nonusers were compared using Cox regression. Outcomes included ischemic stroke, hemorrhagic stroke, and mortality.

Results Among 2313 patients with new AF who survived 30 days from discharge, 249 (10.8%) filled a prescription for warfarin. Comparing 237 warfarin users and 948 propensity-matched nonusers over 2287 person-years of follow-up, the occurrence of ischemic stroke was similar (HR = 0.92; 95% CI, 0.61 to 1.37), whereas warfarin users experienced twice the risk of hemorrhagic stroke (HR = 2.38; 95% CI, 1.15 to 4.96). The risks of stroke, gastrointestinal hemorrhage, and mortality did not differ between groups. As-treated analyses yielded similar findings, as did analyses restricted to patients with $CHADS_2$ scores ≥2.

Conclusions Although we confirmed association between warfarin use and hemorrhagic stroke in dialysis patients with AF, we found no association between warfarin use and ischemic stroke. Adequately powered randomized trials are required to conclusively determine the risks and benefits of the studied warfarin indication in hemodialysis patients.

Clin J Am Soc Nephrol 6: 2662–2668, 2011. doi: 10.2215/CJN.04550511

Winkelmayer WC, CJASN 2011

Observational data

- OAC (warfarin) vs. no OAC
- DOAC (apixaban) vs. no OAC
- Warfarin vs. Apixaban vs. no OAC – meta-analysis

OAC (warfarin) or not in AF ESRD patients

Oral Anticoagulation and Cardiovascular Outcomes in Patients With Atrial Fibrillation and End-Stage Renal Disease

Sean D. Pokorney, MD, MHS,[a,b] Eric Black-Maier, MD,[a] Anne S. Hellkamp, MS,[b] Daniel J. Friedman, MD,[c] Sreekanth Vemulapalli, MD,[b] Christopher B. Granger, MD,[b] Laine Thomas, PhD,[b] Eric D. Peterson, MD, MPH,[b] Jonathan P. Piccini, Sr, MD, MHS[a,b]

ABSTRACT

BACKGROUND Atrial fibrillation (AF) is common in patients with end-stage renal disease (ESRD). The impact of oral anticoagulation (OAC) in ESRD patients is uncertain.

OBJECTIVES The purpose of this study was to describe patterns of OAC use in ESRD patients with AF and their associations with cardiovascular outcomes.

METHODS Using Medicare fee-for-service 5% claims data from 2007 to 2013, we analyzed treatment and outcomes in a cohort of patients with ESRD and AF. Prescription drug benefit information was used to determine the timing of OAC therapy. Cox proportional hazards modeling was used to compare outcomes including death, all-cause stroke, ischemic stroke, hemorrhagic stroke, and bleeding hospitalizations in ESRD patients treated with or without OAC.

RESULTS The cohort included 8,410 patients with AF and ESRD. A total of 3,043 (36.2%) patients were treated with OAC at some time during the study period. Propensity scores used to match 1,519 patients with AF and ESRD on OAC with 3,018 ESRD patients without OAC. Treatment with OAC was not associated with hospitalization for stroke (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.23 to 1.35; p = 0.97) or death (HR: 1.02; 95% CI: 0.94 to 1.10; p = 0.62). OAC was associated with an increased risk of hospitalization for bleeding (HR: 1.26; 95% CI: 1.09 to 1.46; p = 0.0017) and intracranial hemorrhage (HR: 1.30; 95% CI: 1.07 to 1.59; p = 0.0094).

CONCLUSIONS OAC utilization was low in patients with AF and ESRD. We found no association between OAC use and reduced risk of stroke or death. OAC use was associated with increased risks of hospitalization for bleeding or intracranial hemorrhage. Alternative stroke prevention strategies are needed in patients with ESRD and AF.
(J Am Coll Cardiol 2020;75:1299-308)

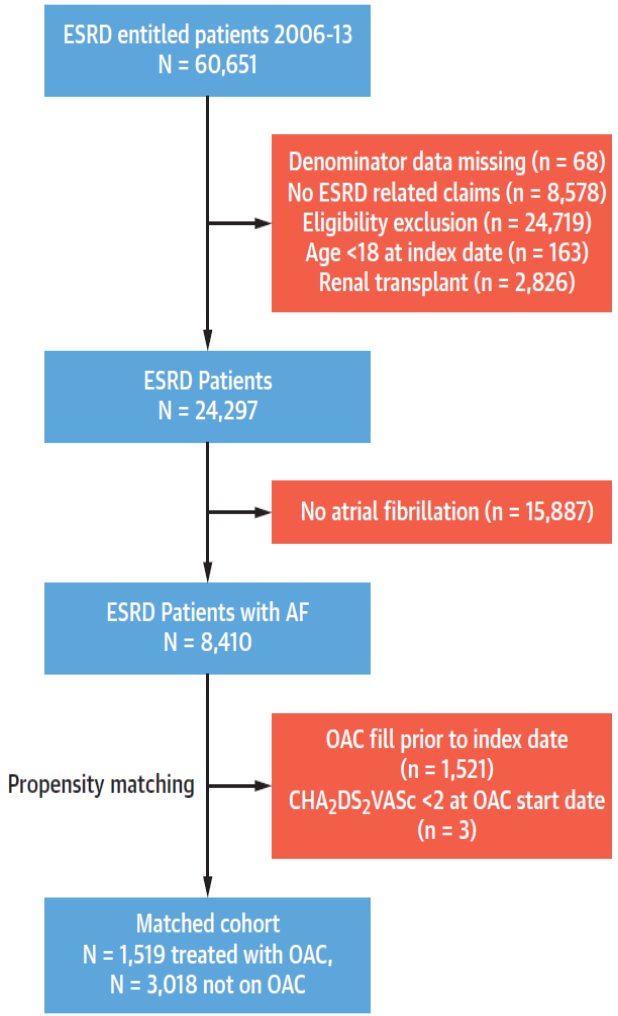
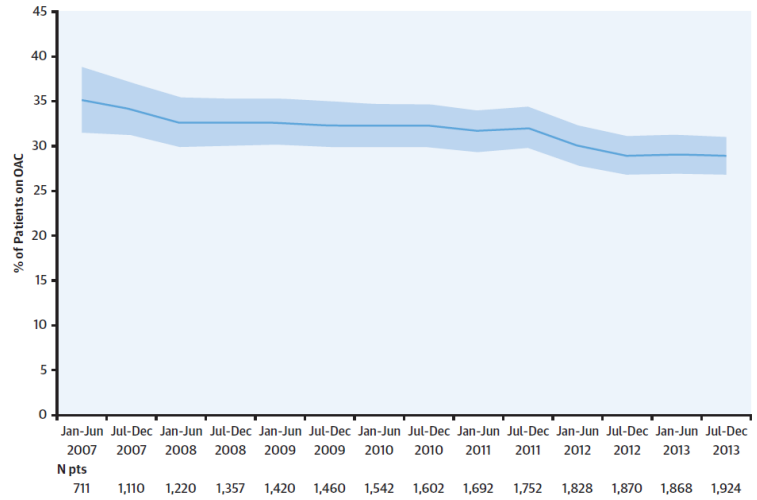


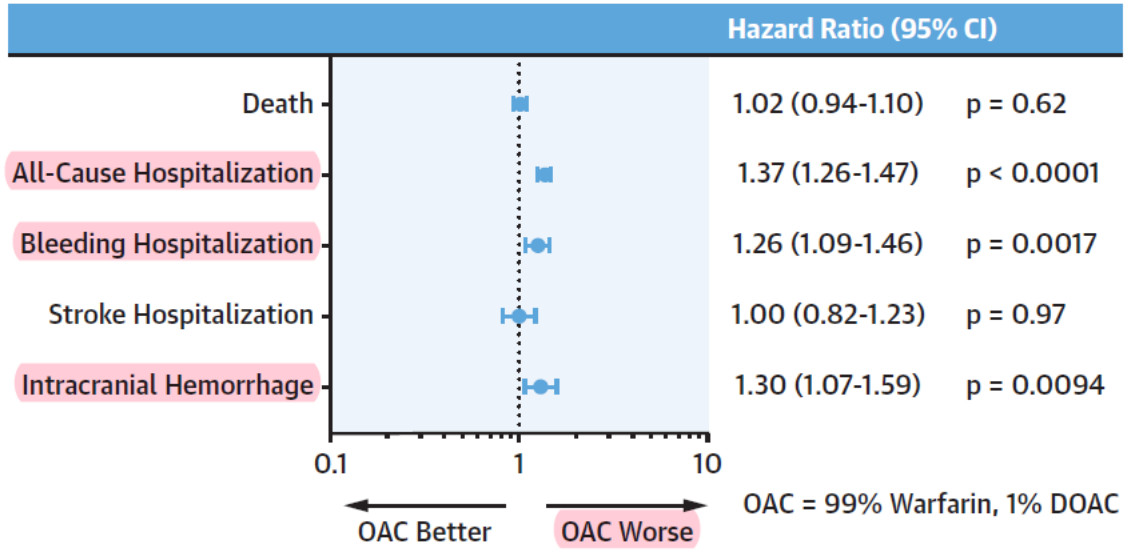
FIGURE 2 Rates of Anticoagulation in Patients With ESRD



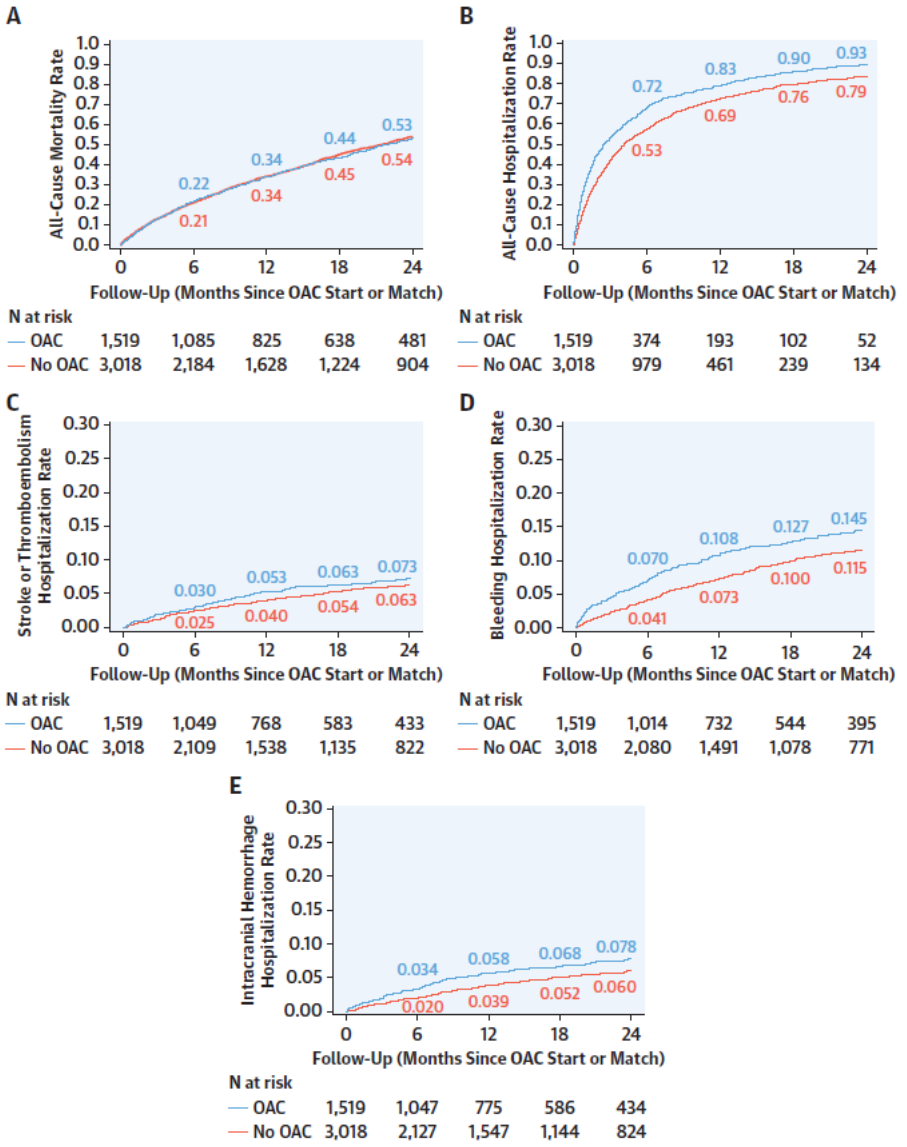
Pokoney SD, JACC 2020

OAC (warfarin) or not in AF ESRD patients

CENTRAL ILLUSTRATION Adjusted Outcomes Among Matched End-Stage Renal Disease-Atrial Fibrillation Patients by Anticoagulant Use at 2 Years



No association bewteen OAC use and reduced risk of stroke or death. OAC use was associated with increased risks of hospitalization for bleeding or intracranial hemorrhage.



Pokoney SD, JACC 2020

OAC (DOAC: apixaban) or not in AF ESRD patients

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

Thomas A. Mavrakanas[1,2] *Katherine Garlo,*[1] *and David M. Charytan*[3]

Abstract

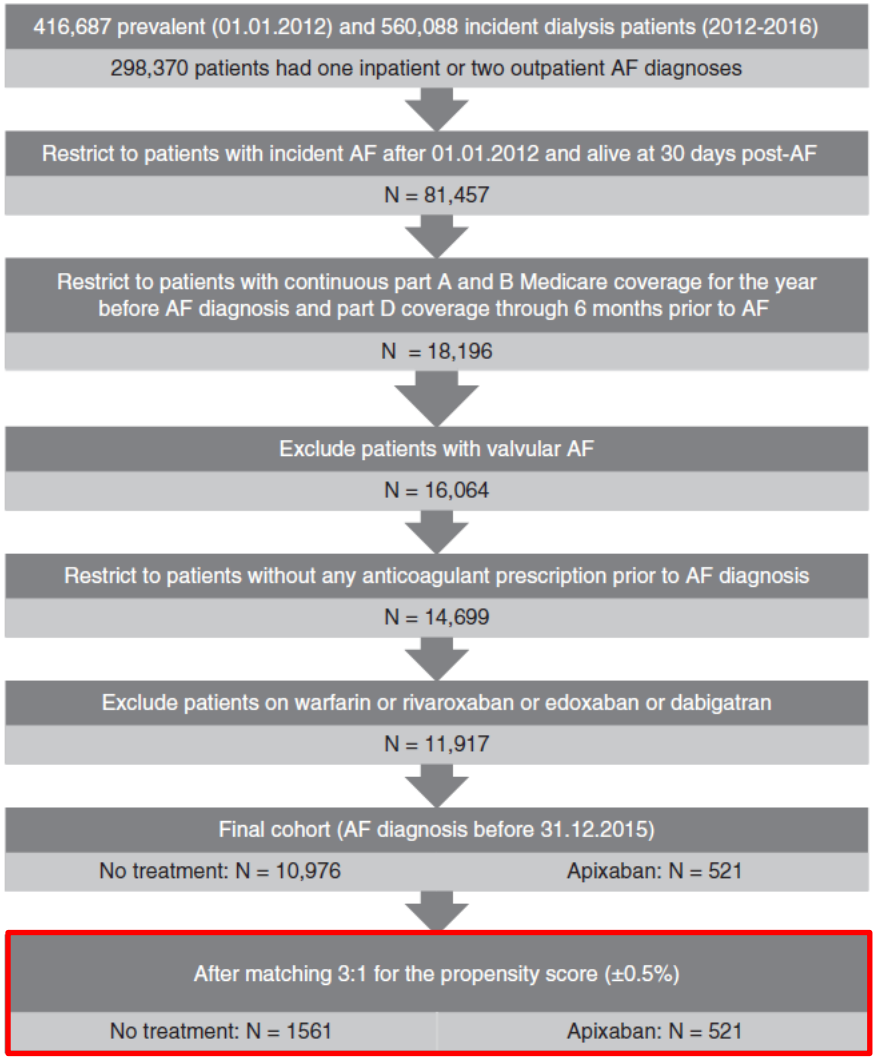
Background and objectives The relative efficacy and safety of apixaban compared with no anticoagulation have not been studied in patients on maintenance dialysis with atrial fibrillation. We aimed to determine whether apixaban is associated with better clinical outcomes compared with no anticoagulation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

CJASN 15: 1146–1154, 2020. doi: https://doi.org/10.2215/CJN.11650919



207 (5mg) ; 257 (2.5mg)

Mavrakanas TA. CJASN 2020

OAC (DOAC: apixaban) or not in AF ESRD patients

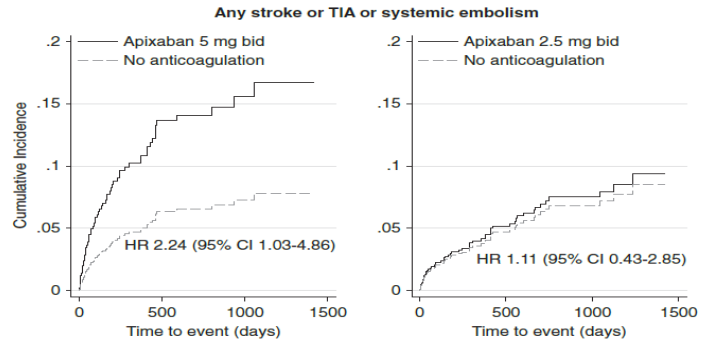
Table 2. Clinical outcomes in the "as-treated" population (main analysis)

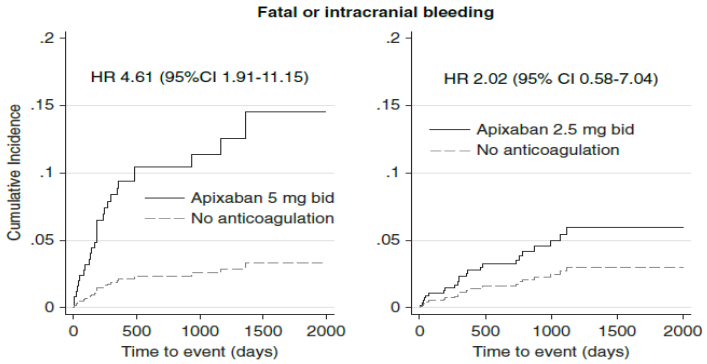
Outcome	Incidence in Apixaban Users	Incidence in Nonusers	Crude Hazard Ratio (95% Confidence Interval)	*P* Value	Adjusted[a] Hazard Ratio (95% Confidence Interval)	*P* Value
Any stroke, TIA, or embolism	7.5 (13)	7.0 (114)	1.24 (0.69 to 2.23)	0.47	1.29 (0.72 to 2.33)	0.39
Any stroke	5.8 (<11)	5.8 (96)	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

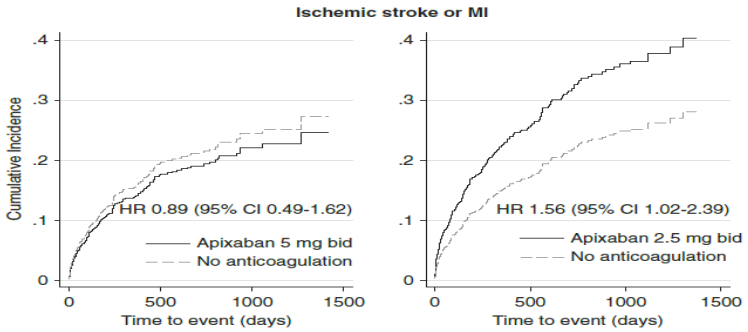
Treatment with apixaban was not associated with a lower incidence of new stroke, TIA, or systemic thromboembolism but was associated with a higher incidence of major bleeding

Mavrakanas TA. CJASN 2020

OAC (DOAC: apixaban) or not in AF ESRD patients







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)	—		—	

Compared with no anticoagulation, a significantly higher rate of the stroke/TIA/systemic embolism 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 twice daily). [Confusing]

Mavrakanas TA. CJASN 2020

Put it all together

Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Dialysis

Toshiki Kuno, MD, PhD,[a] Hisato Takagi, MD, PhD,[b] Tomo Ando, MD,[c] Takehiro Sugiyama, MD, MSHS, PhD,[d,e,f] Satoshi Miyashita, MD,[a] Nelson Valentin, MD, MSc,[a] Yuichi J. Shimada, MD, MPH,[g] Masaki Kodaira, MD, PhD,[h] Yohei Numasawa, MD, PhD,[h] Alexandros Briasoulis, MD, PhD,[i] Alfred Burger, MD,[a] Sripal Bangalore, MD, MHA[j]

ABSTRACT

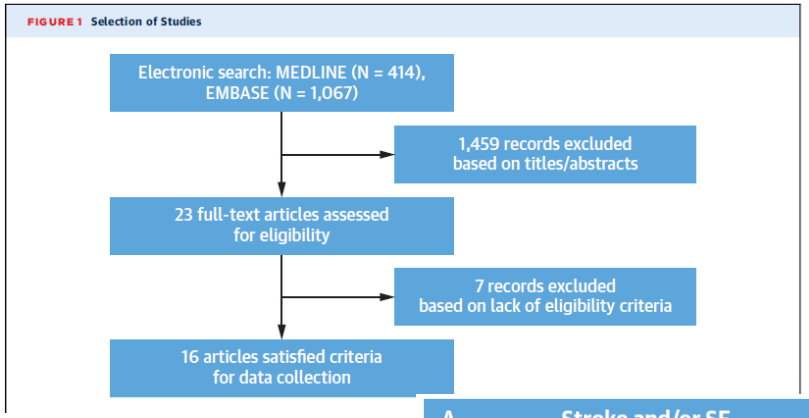
BACKGROUND Patients on long-term dialysis are at increased risk of bleeding. Although oral anticoagulants (OACs) are recommended for atrial fibrillation (AF) to reduce the risk of stroke, randomized trials have excluded these populations. As such, the net clinical benefit of OACs among patients on dialysis is unknown.

OBJECTIVES This study aimed to investigate the efficacy and safety of OACs in patients with AF on long-term dialysis.

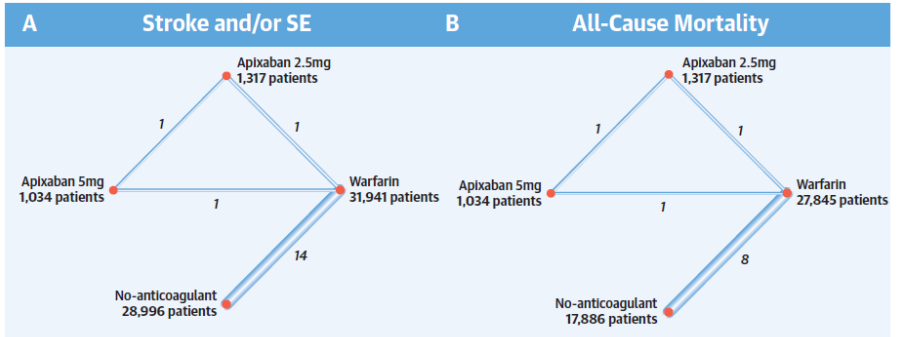
METHODS MEDLINE and EMBASE were searched through June 10, 2019, for studies that investigated the efficacy and safety of different OAC strategies in patients with AF on long-term dialysis. The efficacy outcomes were ischemic stroke and/or systemic thromboembolism, all-cause mortality, and the safety outcome was major bleeding.

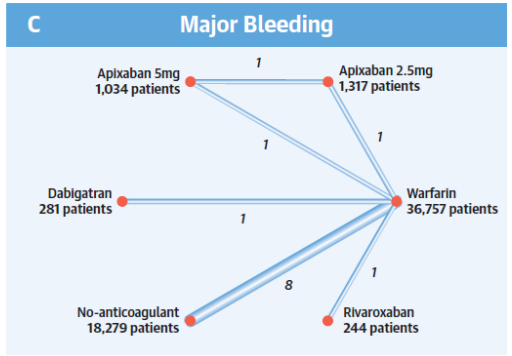
RESULTS This study identified 16 eligible observational studies (N = 71,877) regarding patients on long-term dialysis who had AF. Only 2 of 16 studies investigated direct OACs. Outcomes for dabigatran and rivaroxaban were limited to major bleeding events. Compared with no anticoagulants, apixaban and warfarin were not associated with a significant decrease in stroke and/or systemic thromboembolism (apixaban 5 mg, hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.30 to 1.17; apixaban 2.5 mg, HR: 1.00; 95% CI: 0.52 to 1.93; warfarin, HR: 0.91; 95% CI: 0.72 to 1.16). Apixaban 5 mg was associated with a significantly lower risk of mortality (vs. warfarin, HR: 0.65; 95% CI: 0.45 to 0.93; vs. apixaban 2.5 mg, HR: 0.62; 95% CI: 0.42 to 0.90; vs. no anticoagulant, HR: 0.61; 95% CI: 0.41 to 0.90). Warfarin was associated with a significantly higher risk of major bleeding than apixaban 5 min/2.5 mg and no anticoagulant (vs. apixaban 5 mg, HR: 1.41; 95% CI: 1.07 to 1.88; vs. apixaban 2.5 mg, HR: 1.40; 95% CI: 1.07 to 1.82; vs. no anticoagulant, HR: 1.31; 95% CI: 1.15 to 1.50). Dabigatran and rivaroxaban were also associated with significantly higher risk of major bleeding than apixaban and no anticoagulant.

CONCLUSIONS This meta-analysis showed that OACs were not associated with a reduced risk of thromboembolism in patients with AF on long-term dialysis. Warfarin, dabigatran, and rivaroxaban were associated with significantly higher bleeding risk compared with apixaban and no anticoagulant. The benefit-to-risk ratio of OACs in patients with AF on long-term dialysis warrants validation in randomized clinical trials. (J Am Coll Cardiol 2020;75:273-85)



All observational, No RCT

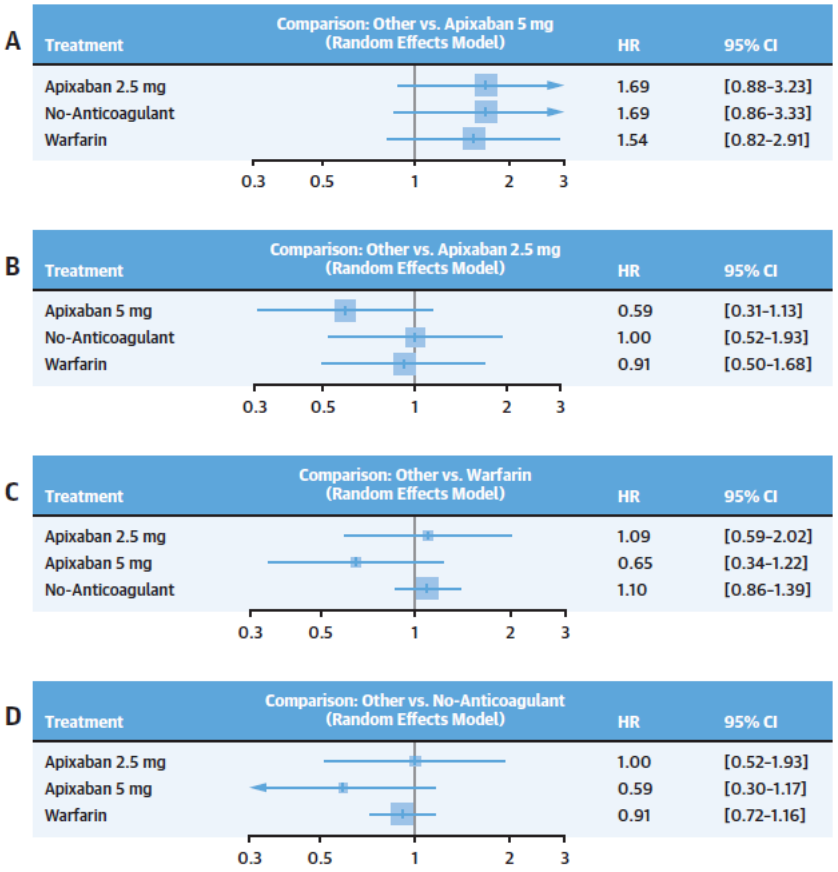




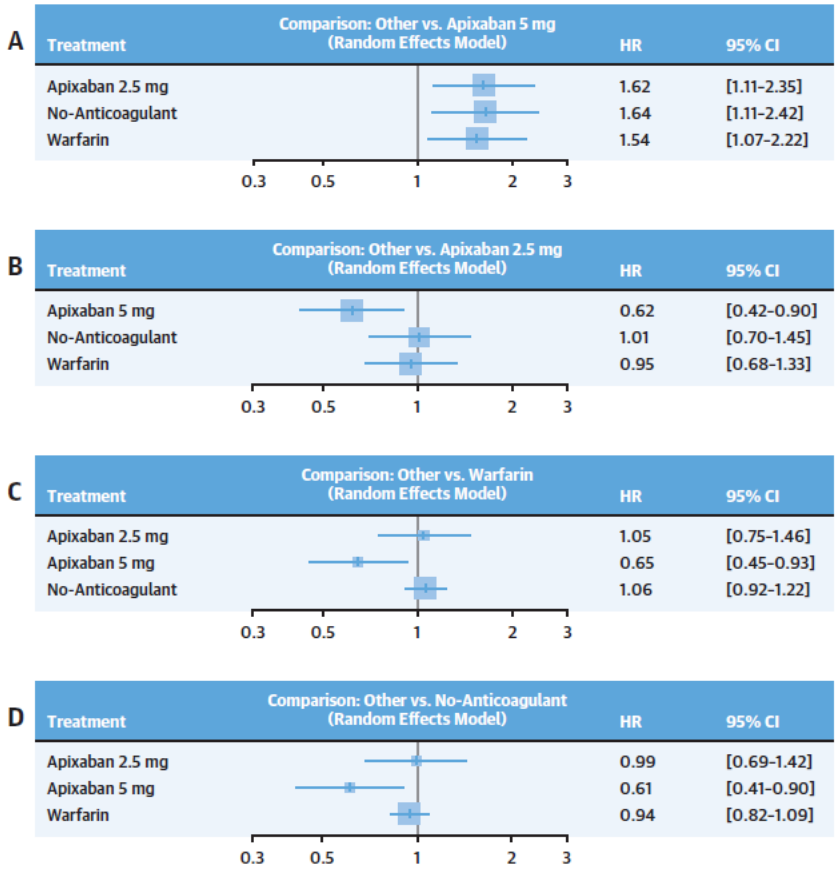
Kuno T, JACC 2020

Stroke, death, and major bleeding

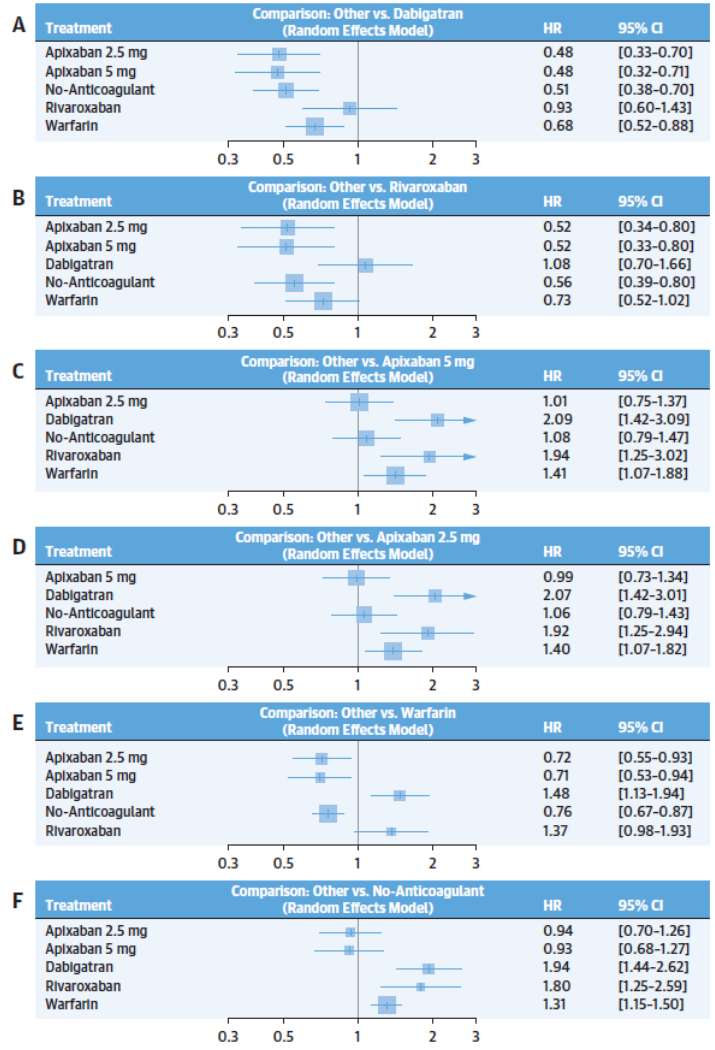
Stroke



Death



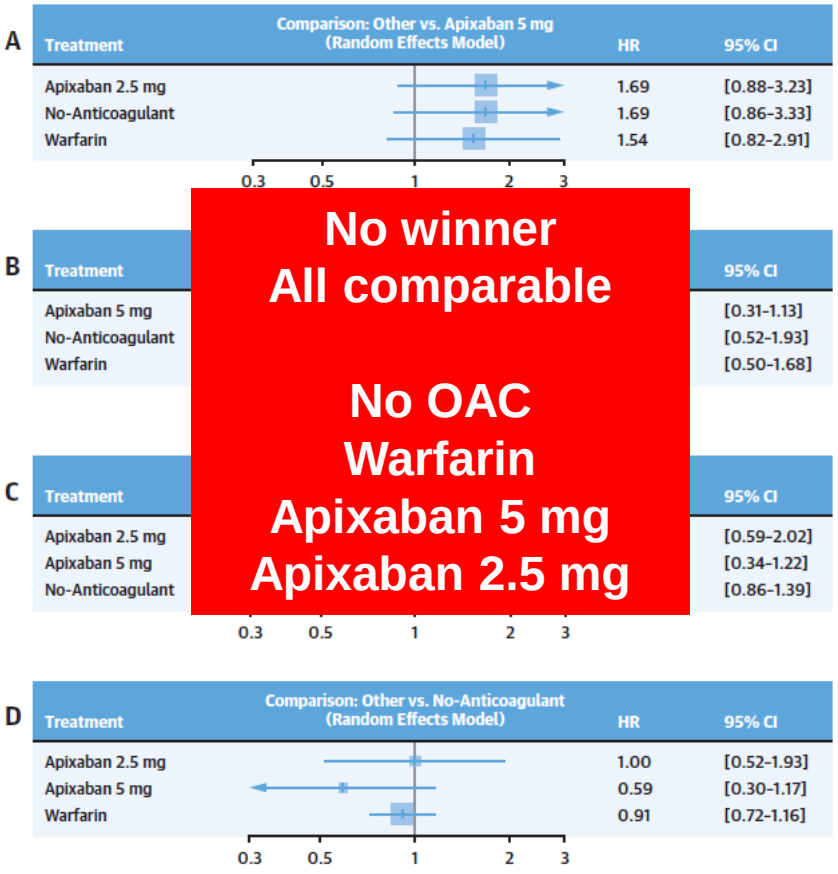
Major bleeding



Kuno T, JACC 2020

Stroke, death, and major bleeding

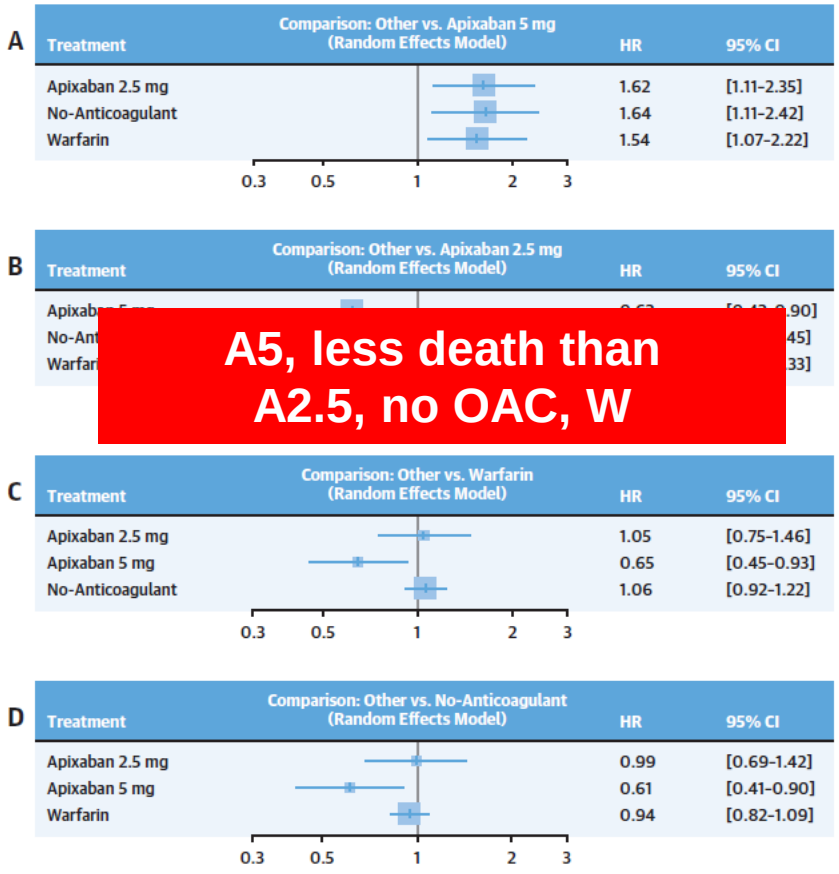
Stroke



No winner
All comparable

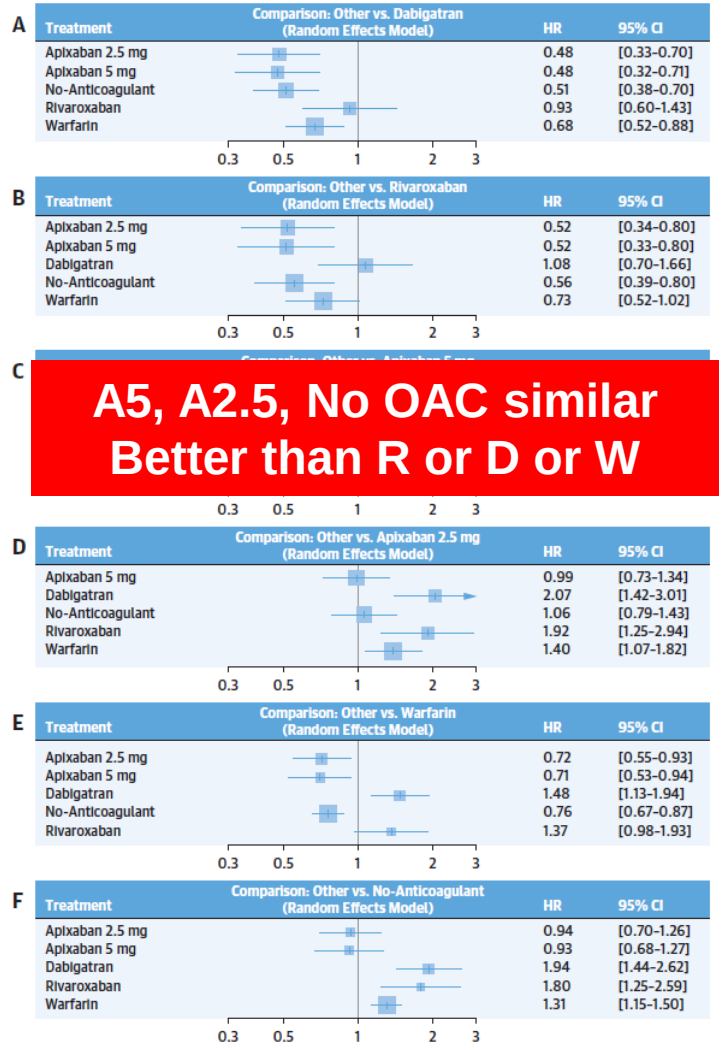
No OAC
Warfarin
Apixaban 5 mg
Apixaban 2.5 mg

Death



A5, less death than
A2.5, no OAC, W

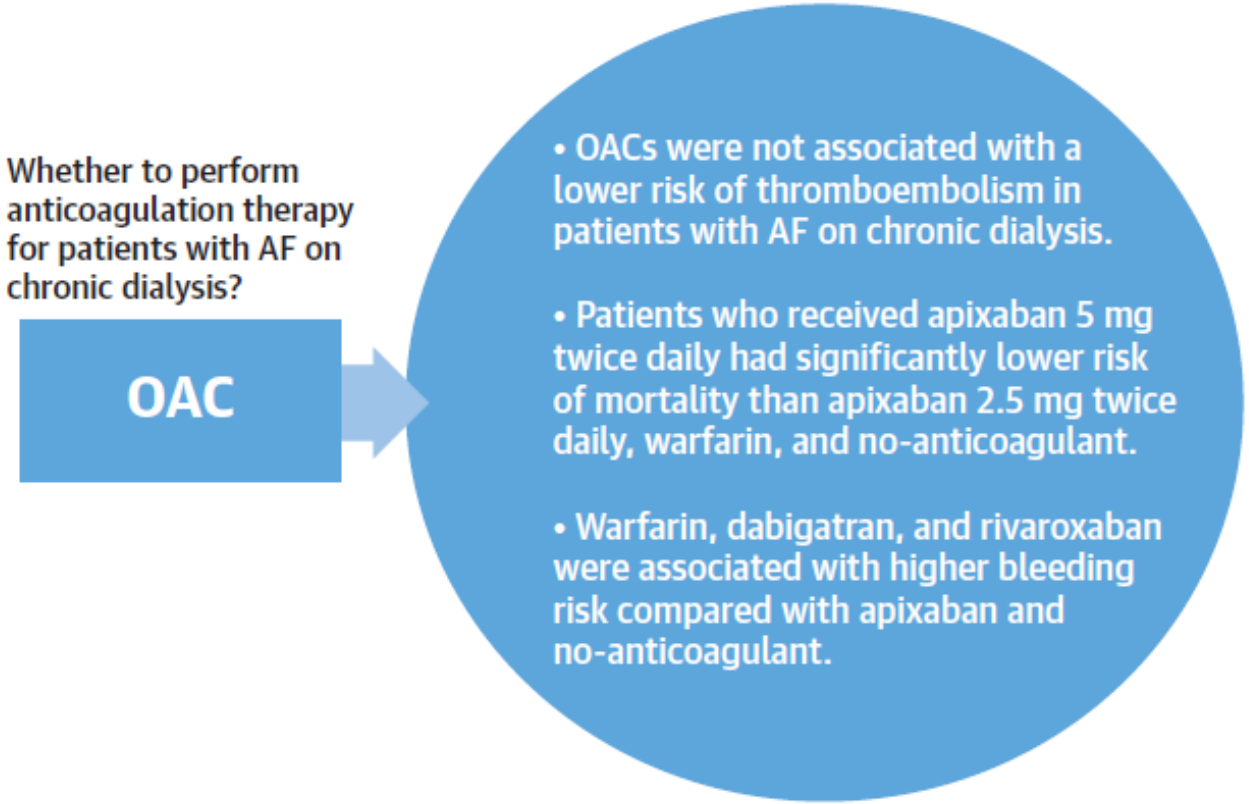
Major bleeding



A5, A2.5, No OAC similar
Better than R or D or W

Kuno T, JACC 2020

Conclusion of comprehensive meta-analysis of current observational studies



Kuno, T. et al. J Am Coll Cardiol. 2020;75(3):273-85.

Kuno T, JACC 2020

OAC was not associated with a lower stroke in AF HD patient, why?

Risks of Death and Stroke in Patients Undergoing Hemodialysis With New-Onset Atrial Fibrillation

A Competing-Risk Analysis of a Nationwide Cohort

Chia-Jen Shih, MD*; Shuo-Ming Ou, MD*; Pei-Wen Chao, MD; Shu-Chen Kuo, MD, PhD; Yi-Jung Lee, MD; Chih-Yu Yang, MD, PhD; Der-Cherng Tarng, MD, PhD; Chih-Ching Lin, MD, PhD; Po-Hsun Huang, MD, PhD; Szu-Yuan Li, MD, PhD; Yung-Tai Chen, MD

Background—Whether oral anticoagulant use should be considered in patients undergoing hemodialysis with atrial fibrillation (AF) remains controversial because of the uncertainty regarding risk-benefit assessments. The purpose of this study was to investigate the risk of ischemic stroke in patients undergoing hemodialysis with new-onset AF, in comparison with those without arrhythmia.

Methods and Results—This nationwide, population-based, propensity score–matched cohort study used data from Taiwan's National Health Insurance Research Database during 1998 to 2011 for patients on hemodialysis with new-onset nonvalvular AF and matched subjects without arrhythmia. The clinical end points were ischemic stroke (fatal or nonfatal), all-cause death, and other serious adverse cardiovascular events. In comparison with the matched cohort, patients with AF (n=6772) had higher risks of ischemic stroke (adjusted hazard ratio [aHR], 1.27; 95% confidence interval [CI], 1.13–1.43), all-cause death (aHR, 1.59; 95% CI, 1.52–1.67), in-hospital cardiovascular death (aHR, 1.83; 95% CI, 1.71–1.94), myocardial infarction (aHR, 1.33; 95% CI, 1.17–1.51), and hospitalization for heart failure (aHR, 1.90; 95% CI, 1.76–2.05). After considering in-hospital death as a competing risk, AF significantly increased the risk of heart failure (HR, 1.56; 95% CI, 1.45–1.68), but not those of ischemic stroke and myocardial infarction. Additionally, the predictive value of the CHA_2DS_2–VASc score for ischemic stroke was diminished in the competing-risk model.

Conclusions—The risk of stroke was only modestly higher in patients undergoing hemodialysis with new-onset AF than in those without AF, and it became insignificant when accounting for the competing risk of in-hospital death.
(*Circulation*. 2016;133:265-272. DOI: 10.1161/CIRCULATIONAHA.115.018294.)

Key Words: atrial fibrillation ■ death ■ dialysis ■ epidemiology ■ risk ■ stroke

Shih CJ, Circulation 2016

OAC was not associated with a lower stroke in AF HD patient, why?

Table 2. Incidence and Risk of Stroke, Myocardial Infarction, and Major Bleeding Among Hemodialysis Patients With and Without AF

	AF		Non-AF		Crude		Adjusted*		Competing Risk†	
	No. of Events	Annual Rate	No. of Events	Annual rate	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Before propensity score matching										
All-cause death	4642	24.72	22 008	9.56	2.57 (2.49–2.66)	<0.001	1.64 (1.59–1.70)	<0.001	–	
In-hospital cardiovascular death	2461	13.11	10 403	4.52	2.88 (2.76–3.01)	<0.001	1.89 (1.80–1.99)	<0.001	1.71 (1.63–1.80)	<0.001
Ischemic stroke	600	3.35	3963	1.77	1.88 (1.73–2.05)	<0.001	1.25 (1.15–1.37)	<0.001	1.03 (0.94–1.12)	0.558
Hemorrhagic stroke	278	1.40	2101	0.92	1.52 (1.34–1.72)	<0.001	1.28 (1.12–1.46)	<0.001	1.03 (0.90–1.18)	0.683
Myocardial infarction	517	2.84	3312	1.46	1.94 (1.76–2.12)	<0.001	1.30 (1.18–1.44)	<0.001	1.14 (1.03–1.27)	0.010
Hospitalization for heart failure	1719	10.88	7822	3.58	2.95 (2.80–3.11)	<0.001	1.95 (1.84–2.06)	<0.001	1.63 (1.54–1.72)	<0.001
After propensity score matching										
All-cause death	4380	24.33	3548	14.84	1.59 (1.52–1.66)	<0.001	1.59 (1.52–1.67)	<0.001	–	
In-hospital cardiovascular death	2,322	12.90	1,629	6.81	1.82 (1.71–1.94)	<0.001	1.83 (1.71–1.94)	<0.001	1.65 (1.55–1.76)	<0.001
Ischemic stroke	563	3.28	573	2.50	1.27 (1.13–1.42)	<0.001	1.27 (1.13–1.43)	<0.001	1.01 (0.90–1.14)	0.832
Hemorrhagic stroke	245	1.38	254	1.07	1.24 (1.04–1.49)	0.015	1.24 (1.04–1.48)	0.015	0.99 (0.83–1.18)	0.882
Myocardial infarction	499	2.86	483	2.07	1.33 (1.18–1.51)	<0.001	1.33 (1.17–1.51)	<0.001	1.06 (0.94–1.21)	0.327
Hospitalization for heart failure	1636	10.77	1153	5.25	1.90 (1.76–2.05)	<0.001	1.90 (1.76–2.05)	<0.001	1.56 (1.45–1.68)	<0.001

Among ESRD patients, AF patients showed numerically higher incidence of all clinical event including ischemic stroke than non AF patients. However, after adjusting for in-hospital death from causes other than outcomes of interest as a competing risk, AF was associated significantly only with in-hospital cardiovascular death and heart failure, but not those of ischemic stroke and myocardial infarction.

Shih CJ, Circulation 2016

OAC was not associated with a lower stroke in AF HD patient, why?

Table 4. Event Rate and Risks of Ischemic Stroke in Hemodialysis Patients With AF

CHA2DS2-VASc Score	No. of Events	Ischemic Stroke Annual rate(%)*	Crude Hazard Ratio (95% CI)	Crude *P* Value	Adjusted† Hazard Ratio (95% CI)	Adjusted† *P* Value	Competing Risk‡ Hazard Ratio (95% CI)	Competing Risk‡ *P* Value
0	11	1.82	Reference		Reference		Reference	
1	17	1.15	0.63 (0.30–1.35)	0.237	0.62 (0.29–1.32)	0.215	0.58 (0.28–1.24)	0.148
2	43	1.97	1.08 (0.56–2.10)	0.821	1.05 (0.54–2.04)	0.889	0.86 (0.45–1.65)	0.645
3	77	2.81	1.52 (0.81–2.86)	0.195	1.46 (0.77–2.75)	0.244	1.07 (0.57–1.99)	0.831
4	77	2.56	1.36 (0.72–2.57)	0.338	1.30 (0.69–2.45)	0.418	0.86 (0.46–1.60)	0.634
5	110	3.84	2.03 (1.09–3.78)	0.026	1.90 (1.02–3.55)	0.044	1.13 (0.61–2.08)	0.706
6	103	4.30	2.24 (1.20–4.18)	0.012	2.11 (1.13–3.95)	0.020	1.14 (0.62–2.11)	0.667
7	74	5.02	2.57 (1.36–4.87)	0.004	2.39 (1.26–4.54)	0.008	1.17 (0.63–2.18)	0.622
8	57	7.25	3.58 (1.87–6.87)	<0.001	3.37 (1.75–6.48)	<0.001	1.43 (0.75–2.72)	0.274
9	31	8.66	4.12 (2.06–8.24)	<0.001	3.87 (1.93–7.78)	<0.001	1.43 (0.72–2.82)	0.306

CHA_2DS_2-VASc scores ≥3 increased the risk of ischemic stroke relative to scores of 0, although the difference was significant only for CHA_2DS_2-VASc scores ≥5.
However, when in-hospital death was treated as a competing risk in the Cox model,
a higher CHA_2DS_2-VASc score was not associated with an increased risk of ischemic stroke.

Shih CJ, Circulation 2016

Which OAC? Warfarin vs. DOAC?

- Observational study
  - Apixaban vs W (Circulation 2018)

- Randomized clinical trials
  - Rivaroxaban vs W (JASN 2021)
  - RENAL-AF (Circulation 2022)
  - AXADIA-AFNET8 (Circulation 2023)

Observational study: Apixaban vs. Warfarin

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

Editorials, see p 1530 and p 1534

BACKGROUND: Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concerns regarding the safety of dabigatran and rivaroxaban, but apixaban has not been evaluated despite current labeling supporting its use in this population. The goal of this study was to determine patterns of apixaban use and its associated outcomes in dialysis-dependent patients with ESKD and AF.

METHODS: We performed a retrospective cohort study of Medicare beneficiaries included in the United States Renal Data System (October 2010 to December 2015). Eligible patients were those with ESKD and AF undergoing dialysis who initiated treatment with an oral anticoagulant. Because of the small number of dabigatran and rivaroxaban users, outcomes were only assessed in patients treated with apixaban or warfarin. Apixaban and warfarin patients were matched (1:3) based on prognostic score. Differences between groups in survival free of stroke or systemic embolism, major bleeding, gastrointestinal bleeding, intracranial bleeding, and death were assessed using Kaplan–Meier analyses. Hazard ratios (HRs) and 95% CIs were derived from Cox regression analyses.

RESULTS: The study population consisted of 25 523 patients (45.7% women; 68.2±11.9 years of age), including 2351 patients on apixaban and 23 172 patients on warfarin. An annual increase in apixaban prescriptions was observed after its marketing approval at the end of 2012, such that 26.6% of new anticoagulant prescriptions in 2015 were for apixaban. In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR, 0.88; 95% CI, 0.69–1.12; *P*=0.29), but apixaban was associated with a significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.87; *P*<0.001). In sensitivity analyses, standard-dose apixaban (5 mg twice a day; n=1034) was associated with significantly lower risks of stroke/systemic embolism and death as compared with either reduced-dose apixaban (2.5 mg twice a day; n=1317; HR, 0.61; 95% CI, 0.37–0.98; *P*=0.04 for stroke/systemic embolism; HR, 0.64; 95% CI, 0.45–0.92; *P*=0.01 for death) or warfarin (HR, 0.64; 95% CI, 0.42–0.97; *P*=0.04 for stroke/systemic embolism; HR, 0.63; 95% CI, 0.46–0.85; *P*=0.003 for death).

CONCLUSIONS: Among patients with ESKD and AF on dialysis, apixaban use may be associated with a lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk.

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Key Words: atrial fibrillation ▪ anticoagulation ▪ bleeding ▪ dialysis ▪ stroke prevention

Sources of Funding, see page 1528

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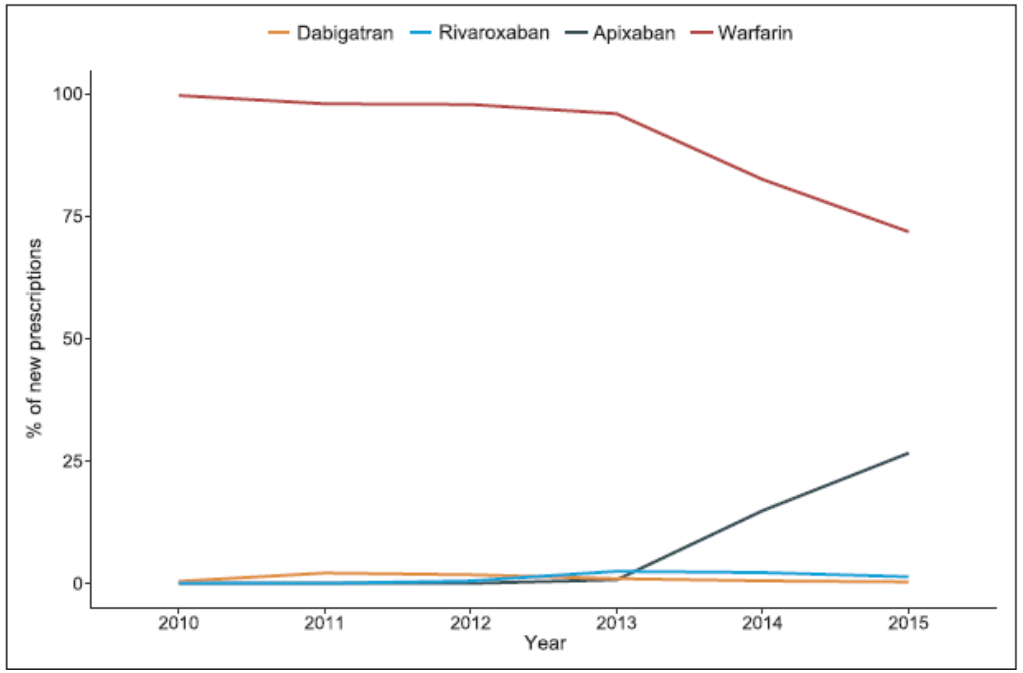


Trend in new OAC prescription in patients with AF and ESRD on dialysis in the US (2010-2015)

An annual increase in apixaban prescriptions was observed after its marketing approval at the end of 2012, such that 26.6% of new anticoagulant prescriptions in 2015 were for apixaban.

Siontis KC, Circulation 2018

Observational study: Apixaban vs. Warfarin

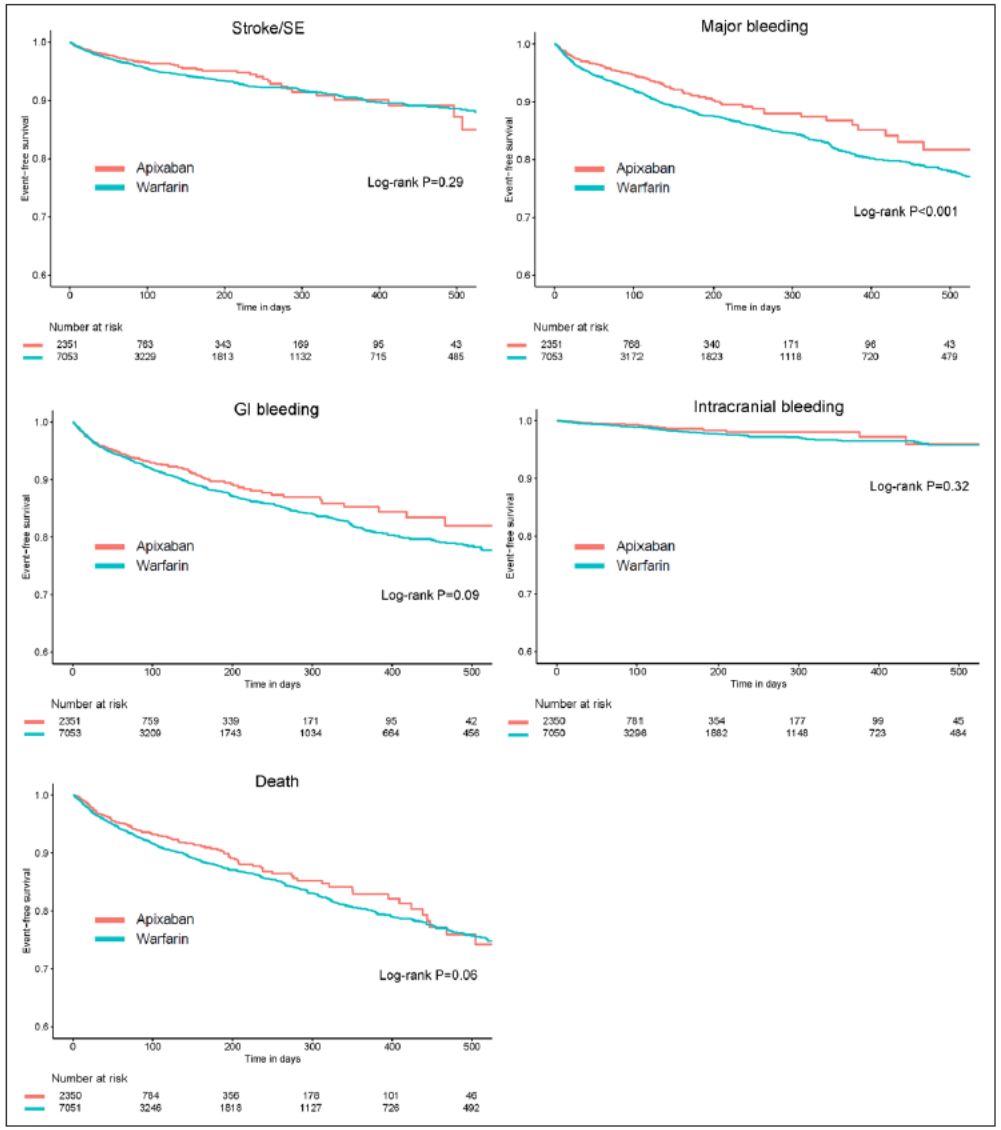


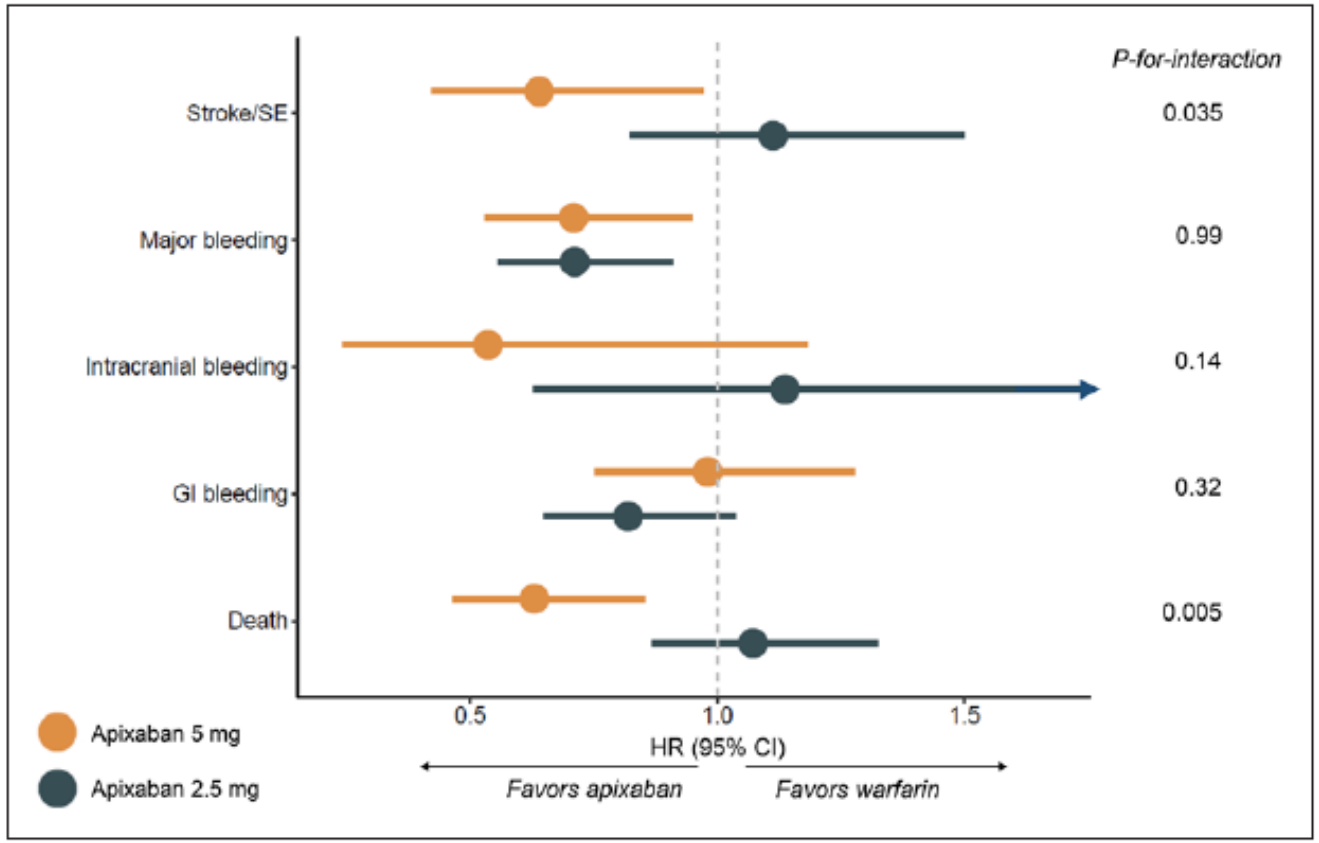
Table 2. Event Rates and Association Estimates From Cox Regression Analyses in Prognostic Score–Matched Cohorts of Apixaban and Warfarin

Outcome	Overall	Apixaban	Warfarin	Hazard Ratio (95% CI)	*P* Value
Stroke/systemic embolism					
No. of patients	9404	2351	7053	0.88 (0.69–1.12)	0.29
No. of events	454	81	373		
Event rate per 100 PY	11.9	12.4	11.8		
Major bleeding					
No. of patients	9404	2351	7053	0.72 (0.59–0.87)	<0.001
No. of events	844	129	715		
Event rate per 100 PY	22.3	19.7	22.9		
Gastrointestinal bleeding					
No. of patients	9404	2351	7053	0.86 (0.72–1.02)	0.09
No. of events	865	155	710		
Event rate per 100 PY	23.4	23.8	23.4		
Intracranial bleeding					
No. of patients	9400	2350	7050	0.79 (0.49–1.26)	0.32
No. of events	132	21	111		
Event rate per 100 PY	3.4	3.1	3.5		
Death					
No. of patients	9404	2351	7053	0.85 (0.71–1.01)	0.06
No. of events	912	159	753		
Event rate per 100 PY	24.7	23.7	24.9		

In matched cohorts, there was no difference in the risks of stroke/systemic embolism bewteen apixaban and warfarin (HR 0.88; 95% CI, 0.69-1.12; p=0.29), but apixaban was associated with a significantly lower risk of major bleeding (HR, 0.72; 95% CI 0.59-0.87; p<0.001)

Siontis KC, Circulation 2018

Sensitivity analysis for dose



Standard dose apixaban (5mg bid, n=1034) was associated with significantly lower risks of stroke/systemic embolism and death as compared with either reduced dose apixaban (2.5mg bid, n=1317) or warfarin

Siontis KC, Circulation 2018

Randomized clinical trials: DOAC vs. W

- Rivaroxaban vs W (JASN 2021)
- RENAL-AF (Circulation 2022)
- AXADIA-AFNET8 (Circulation 2023)

Rivaroxaban vs. Warfarin, Valkyrie study

- 132 patients on HD with AF
- Rivaroxaban 10mg vs. VKA vs. rivaroxaban and vitamin K2
- 18-month follow-up

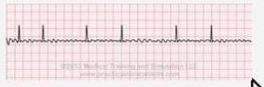
- Primary efficacy: a composite of fatal and nonfatal CV events
- Secondary efficacy: individual component of the composite outcome and all-cause death
- Safety end points: life-threatening, major, and minor bleeding

Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter RCT

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

N=132



VKA INR 2-3

Rivaroxaban 10 mg od

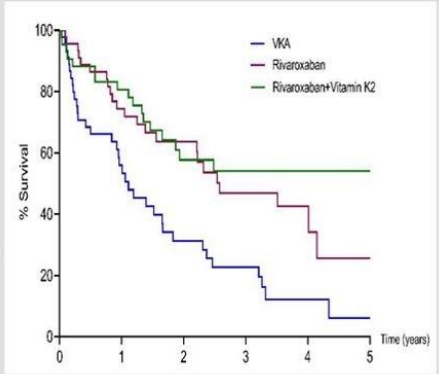
Rivaroxaban+vitamin K2

OUTCOME

Primary efficacy end point:

HR for composite of fatal and non-fatal stroke, cardiac events and other vascular events (95% CI, P-value vs VKA):

- Rivaroxaban: 0.41 (0.25-0.68, P=0.0006)
- Rivaroxaban+vitamin K2: 0.34 (0.19-0.61, P=0.0003)



Safety end point:

Outcome parameter	VKA (n=44)	Rivarox (n=46)	Rivarox + vit K2 (n=42)	$P_{Cox-adj}$
Life-threatening or major bleeding	17 (30)	8 (11)	9 (12)	P=0.048
Minor bleeding	13 (19)	16 (27)	16 (22)	P=0.639
Gastrointestinal bleeding	12 (23)	9 (16)	13 (19)	P=0.478

number of patients with at least one bleeding episode (total number bleeding episodes)

Conclusion
In hemodialysis patients with AF, rivaroxaban reduced the composite of fatal and non-fatal cardiovascular events and major bleeding complications in comparison to VKA.

doi: 10.1681/ASN.2020111566

De Vriese AS, JASN 2021

Valkyrie study: Baseline

Table 1. Baseline patient characteristics

Baseline Characteristics	VKA (*n*=44)	Rivaroxaban (*n*=46)	Rivaroxaban and Vitamin K2 (*n*=42)	*P*[a]
Age (yr), median (IQR)	80.3 (71.5–84.3)	79.9 (74.4–83.9)	79.6 (73.2–83.1)	0.92
Male, *n* (%)	25 (56.8)	35 (76.1)	28 (66.7)	0.16
History of stroke, *n* (%)	16 (36.4)	15 (32.6)	9 (21.4)	0.30
History of gastrointestinal bleeding, *n* (%)	12 (27.3)	9 (19.6)	16 (38.1)	0.16
Diabetes, *n* (%)	20 (45.5)	20 (43.5)	22 (52.4)	0.74
History of AMI, *n* (%)	21 (47.7)	21 (45.7)	19 (45.2)	0.98
Congestive heart failure, *n* (%)	9 (20.5)	17 (37.0)	15 (35.7)	0.18
Preexisting vascular disease, *n* (%)	28 (63.6)	25 (54.3)	17 (40.5)	0.10
Dialysis vintage (yr), median (IQR)	1.8 (0.4–5.5)	2.7 (0.9–5.9)	2.7 (0.6–5.1)	0.64
Incident dialysis (<3 mo), *n* (%)	9 (20.5)	4 (8.7)	9 (21.4)	0.18
$CHAD_2DS_2$-VASc score[b]				
Mean (SD)	4.8 (1.5)	4.7 (1.4)	4.5 (1.4)	
Median (IQR)	5 (4–6)	5 (4–5)	4 (4–5)	0.52
Score of ≥2 (men) or ≥3 (women), *n* (%)	44 (100)	46 (100)	42 (100)	–
HAS-BLED score[c]				0.61 = *P* value for median
Mean (SD)	4.7 (0.9)	4.6 (0.8)	4.7 (0.9)	
Median (IQR)	5 (4–5)	4 (4–5)	5 (4–5)	
VKA vintage (yr), median (IQR)	0.9 (0.1–4.7)	1.1 (0.0–2.8)	1.5 (0.0–6.3)	0.46
VKA naive (<3 mo), *n* (%)	14 (31.8)	18 (39.1)	15 (35.7)	0.87
Aspirin, *n* (%)	14 (31.8)	15 (32.6)	17 (40.5)	0.67
Amiodarone, *n* (%)	9 (20.5)	5 (10.9)	8 (19.0)	0.41

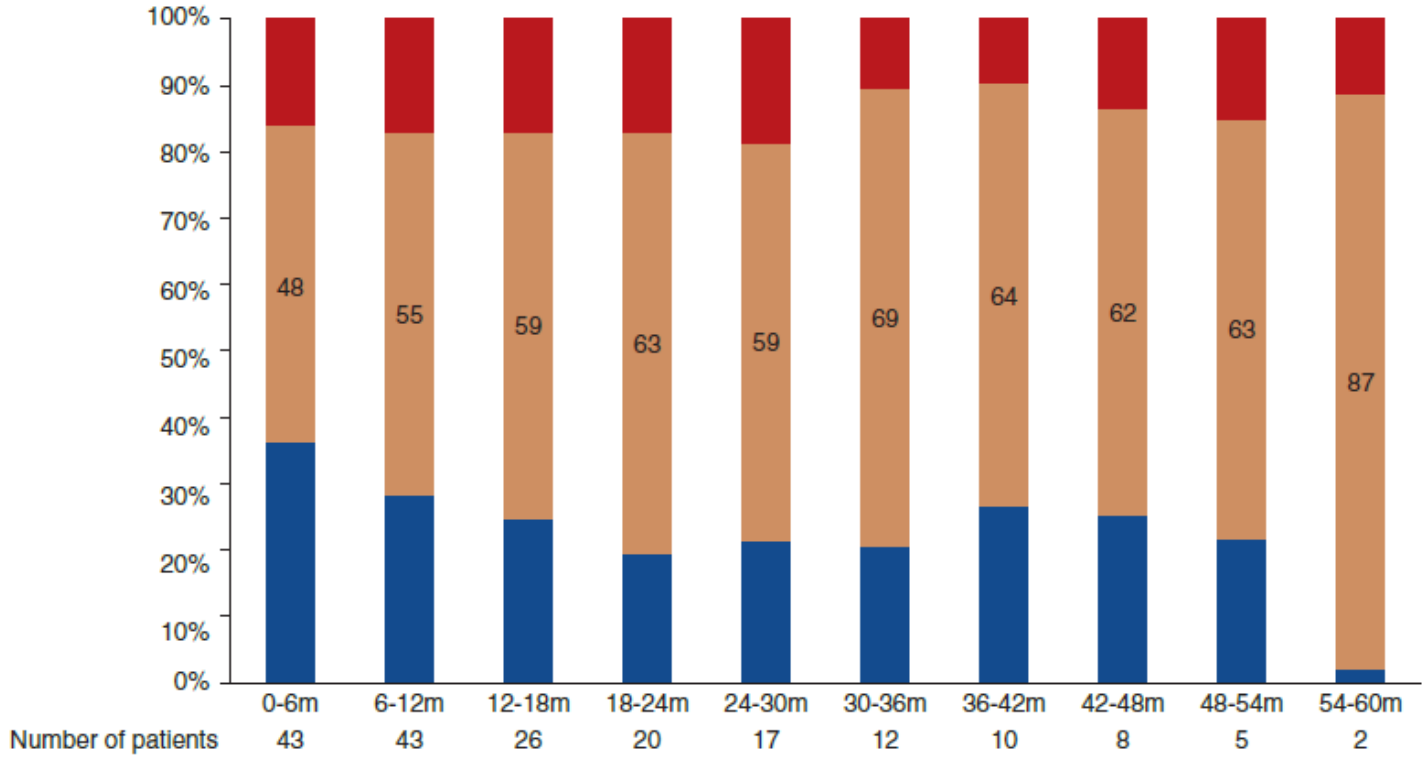
De Vriese AS, JASN 2021

Valkyrie study: Treatment quality of VKA

Table 2. Premature permanent discontinuation of anticoagulation

Parameter	VKA (*n*=44)	Rivaroxaban (*n*=46)	Rivaroxaban and Vitamin K2 (*n*=42)[a]	*P*[b]
Any withdrawal, *n* (%)	14 (31.8)	9 (19.6)	10 (23.8)	0.42
Time on anticoagulation/ total observation time	0.89	0.88	0.87	0.71
Bleeding, *n*	8	8	9	
Calciphylaxis, *n*	2	0	0	
Labile INR, *n*	3	—	—	
Clinical deterioration, *n*	1	0	0	
Registration on transplant list, *n*	0	1	0	
Wish of the patient, *n*	0	0	1	

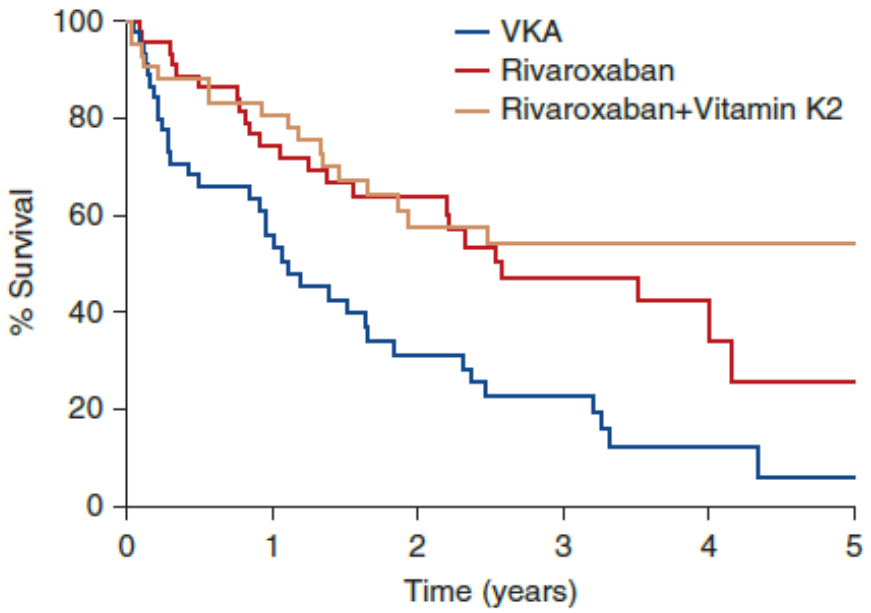
[a]Only rivaroxaban was withdrawn and vitamin K2 supplements were continued.
[b]According to Fisher exact or Kruskal–Wallis test.



VKA group
First 6-month TTR, 48.0%

De Vriese AS, JASN 2021

Valkyrie study: Outcome



Primary efficacy outcome:
63.8 per 100 PY in VKA,
26.2 per 100 PY in R,
21.4 per 100 PY in R+VK2

Competing risk-adjusted HR compared to VKA
R: 0.41 (95% CI 0.25-0.68, p = 0.0006)
R+VK2 : 0.34 (95% CI 0.19-0.61, p = 0.0003)

Table 3. Secondary efficacy outcomes

Outcome Parameter	VKA (*n*=44)	Rivaroxaban (*n*=46)	Rivaroxaban and Vitamin K2 (*n*=42)	*P*[a]
Death from any cause, *n* (%)	32 (72.7)	30 (65.2)	27 (64.3)	0.66
Sudden death, *n*	5	7	4	0.75
Stroke or systemic embolism, *n*				
Ischemic or uncertain type of stroke	7	4	2	0.20
Hemorrhagic stroke	2	0	0	0.21
Systemic embolism	0	0	0	—
Cardiac disease, *n*				
Acute coronary syndrome	6	9	2	0.12
Symptom-driven revascularization[b]	2	6	1	0.15
Hospitalization for heart failure	5	2	2	0.47
Symptomatic aortic-valve stenosis	2	0	0	0.21
Death from cardiac cause	5	4	2	0.58
Other vascular disease, *n*				
Symptomatic lower-limb ischemia	20	10	9	0.02
Calciphylaxis	4	2	0	0.14
Bowel ischemia	1	2	2	0.87

Table 4. Bleeding outcomes in the entire patient population

Outcome Parameter	VKA (*n*=44)	Rivaroxaban (*n*=46)	Rivaroxaban and Vitamin K2 (*n*=42)	P_{Cox}	$P_{Cox\text{-}adj}$
Total bleeding	24 (49)	21 (38)	22 (34)	0.03	0.19
Life-threatening bleeding	11 (12)	3 (3)	6 (8)	0.05	0.08
Major bleeding	10 (18)	6 (8)	4 (4)	0.12	0.19
Life-threatening or major bleeding	17 (30)	8 (11)	9 (12)	0.04	0.05
Minor bleeding	13 (19)	16 (27)	16 (22)	0.85	0.64
Gastrointestinal bleeding	12 (23)	9 (16)	13 (19)	0.35	0.48

Net clinical benefit:
84.2 per 100 PY in VKA vs. 35.2 per 100 PY in Pooled R
HR 0.45 (95% CI 0.29-0.69, p < 0.0001)

De Vriese AS, JASN 2021

Valkyrie study: Conclusion

- In patients on HD with AF, a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events and major bleeding complications compared with VKA.

De Vriese AS, JASN 2021

RENAL-AF

- Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in AF
- Prospective, randomized, open-label, blinded-outcome evaluation

- A vs. W in patients receiving HD with AF and a CHA_2DS_2-VASc score ≥2
- 1:1 random assign, apixaban 5mg twice daily
- Apixaban 2.5mg twice daily: ≥80 years of age, weight ≤60 kg, or both
- 22 (29%) patients prescribed apixaban 2.5mg twice daily; 15 patients (68%) met the dose reduction criteria.

- Primary outcome: Major or clinically relevant nonmajor bleeding
- Secondary outcome: stroke, mortality, and apixaban pharmacokinetics

Pokoney SD, Circulation 2022

RENAL-AF

- 154 patients were randomly assigned: **82** apixaban and **72** warfarin
- The trial stopped prematurely because of enrollment challenges.
- TTR of warfarin group: 44% (target INR 2.0-3.0)

- 32% of apixaban group and 33% of warfarin group prematurely and permanently discontinued the study drug; **death (38%)** was the most common reason for discontinuation.

Pokoney SD, Circulation 2022

RENAL-AF: Baseline characteristics

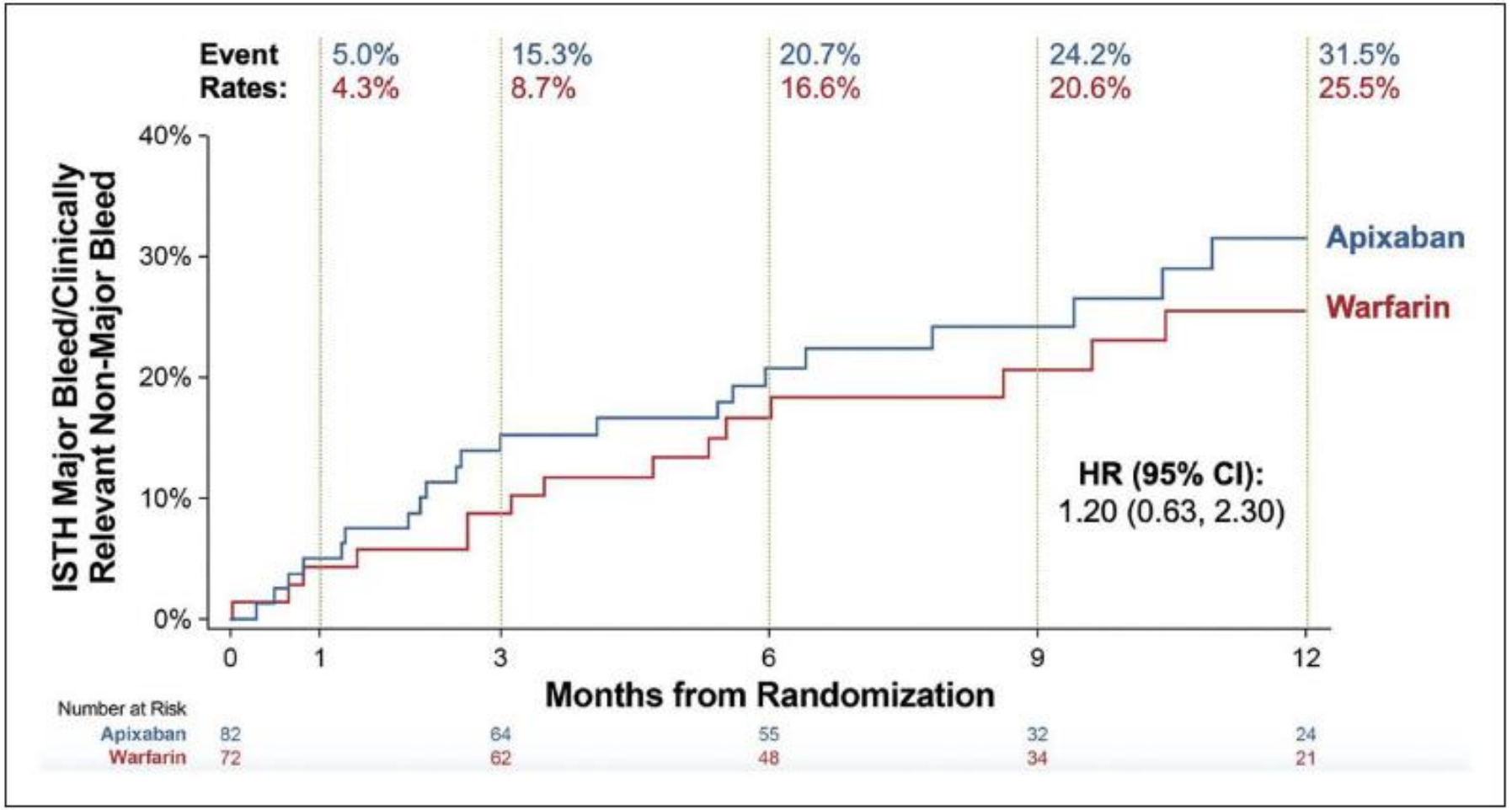
Characteristics	Apixaban (n=82)	Warfarin (n=72)	All patients (N=154)
Age, y	69.0 (61.0, 76.0)	68.0 (60.5, 72.5)	68.0 (61.0, 75.0)
<65	32 (39.0)	25 (34.7)	57 (37.0)
≥65 to <75	26 (31.7)	32 (44.4)	58 (37.7)
≥75	24 (29.3)	15 (20.8)	39 (25.3)
Female	34 (41.5)	22 (30.6)	56 (36.4)
Black	35 (42.7)	34 (47.2)	69 (44.8)
Time since dialysis initiation, y	2.8 (1.6, 5.7)	3.0 (1.2, 6.3)	3.0 (1.5, 5.7)
Weight, kg	86.3 (69.5, 100.5)	90.5 (72.8, 112.2)	88.3 (71.5, 107.4)
Resting systolic blood pressure, mm Hg*	131.0 (115.5, 151.5)	136.0 (120.5, 149.0)	134.5 (118.0, 149.5)
CHA_2DS_2-VASc score	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Warfarin and nonvitamin K antagonist naive	10 (12.2)	4 (5.6)	14 (9.1)
Taking nonvitamin K antagonist at randomization	19 (23.2)	21 (29.2)	40 (26.0)
Type of atrial fibrillation			
Paroxysmal	45 (54.9)	40 (55.6)	85 (55.2)
Persistent	24 (29.3)	20 (27.8)	44 (28.6)
Permanent	13 (15.9)	12 (16.7)	25 (16.2)
Time since atrial fibrillation diagnosis, y*	2.2 (1.1, 4.4)	2.5 (0.8, 4.8)	2.4 (1.0, 4.7)
Myocardial infarction	16 (19.5)	22 (30.6)	38 (24.7)
Fall within the past year	6 (7.3)	7 (9.7)	13 (8.4)
Chronic hypertension	79 (96.3)	67 (93.1)	146 (94.8)
Chronic heart failure	43 (52.4)	41 (56.9)	84 (54.5)
Current New York Heart Association class*			
I	10/42 (23.8)	11/38 (28.9)	21/80 (26.3)
II	23/42 (54.8)	23/38 (60.5)	46/80 (57.5)
III	9/42 (21.4)	3/38 (7.9)	12/80 (15.0)
IV	0/42 (0.0)	1/38 (2.6)	1/80 (1.3)
Diabetes	42 (51.2)	47 (65.3)	89 (57.8)
Stroke	17 (20.7)	12 (16.7)	29 (18.8)
Time since most recent stroke, y*	6.4 (2.4, 10.0)	4.2 (1.6, 7.2)	5.8 (2.0, 9.2)

Age 68-69 yr
CHA_2DS_2-VASc 4
Time since dialysis initiation 3.0 yr
Bwt 86-90 kg
Warfarin and DOAC naïve 5.6-12.2%
Taking DOAC at randomization 23.2-29.2%

Paroxysmal AF 55%
Time since AF diagnosis 2.2-2.5 yr
Prior stroke 16.7-20.7%
Time since most recent stroke 4.2-6.4 yr

Pokoney SD, Circulation 2022

RENAL AF: Primary outcome



The 1-year rates for major or clinically relevant nonmajor bleeding were 32% and 26% in apixaban and warfarin groups, respectively (hazard ratio, 1.20 [95% CI, 0.63–2.30]),

Pokoney SD, Circulation 2022

RENAL-AF: Details of bleeding

Primary safety outcome	Apixaban n=82	Warfarin n=72
International Society for Thrombosis and Haemostasis major bleed/clinically relevant nonmajor bleed	21 (26)	16 (22)
Intracranial	1 (1)	1 (1)
Gastrointestinal	2 (2)	6 (8)
Hemodialysis access site	11 (13)	6 (8)
Other	7 (9)	3 (4)
International Society for Thrombosis and Haemostasis major bleed	9 (11)	7 (10)
Intracranial	1 (1)	1 (1)
Gastrointestinal	4 (5)	5 (7)
Hemodialysis access site	1 (1)	0 (0)
Other	3 (4)	1 (1)
International Society for Thrombosis and Haemostasis clinically relevant nonmajor bleed	14 (17)	10 (14)
Intracranial	0 (0)	0 (0)
Gastrointestinal	0 (0)	2 (3)
Hemodialysis access site	10 (12)	6 (8)
Other	4 (5)	2 (3)

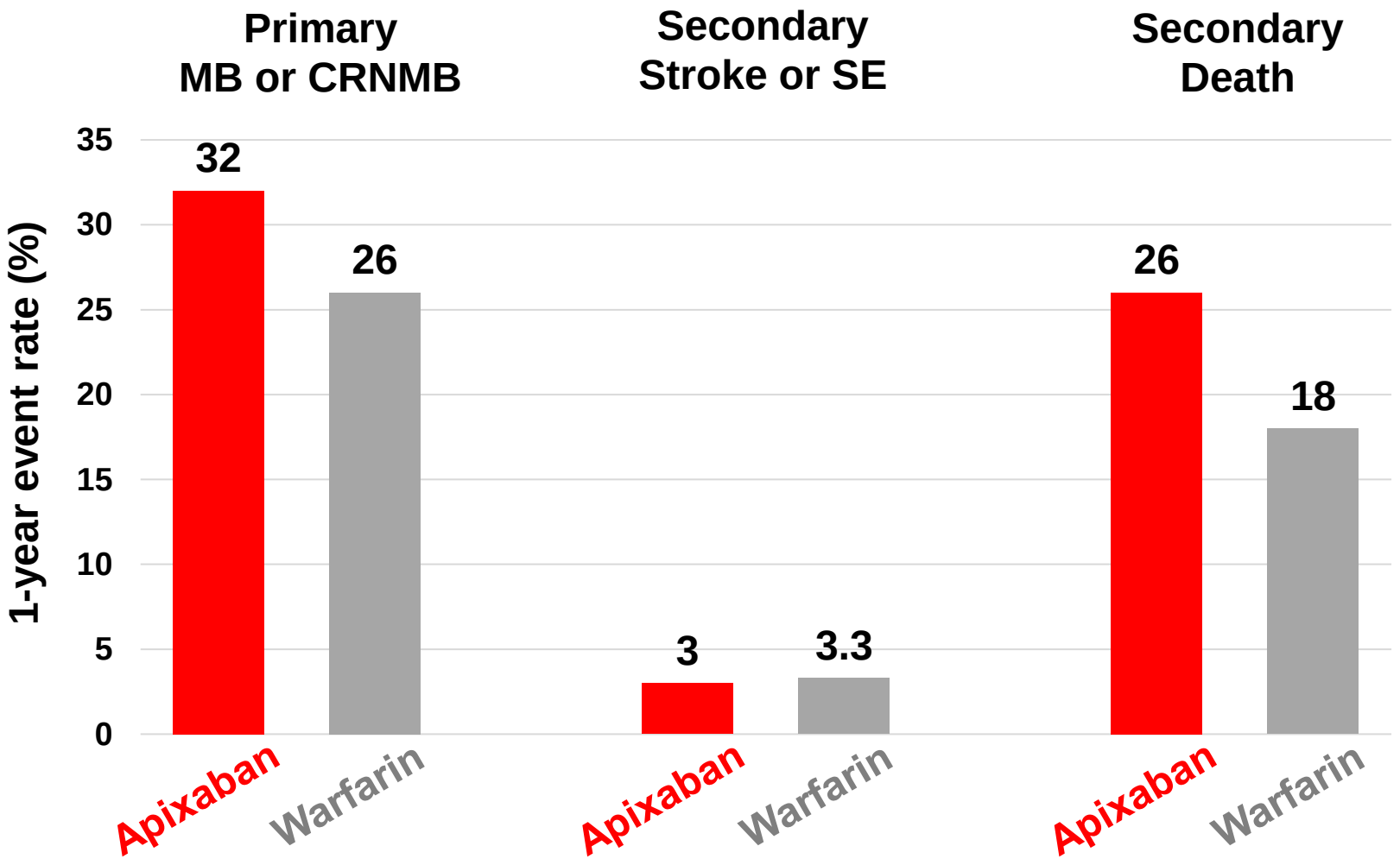
Secondary outcomes	Apixaban n=82	Warfarin n=72
Stroke, n (%)	2 (2)	2 (3)
Ischemic	1 (1)	2 (3)
Hemorrhagic	1 (1)	0 (0)
Systemic embolism, n (%)	0 (0)	0 (0)
Death, n (%)	21 (26)	13 (18)
Cardiovascular	9 (11)	4 (6)
Noncardiovascular	5 (6)	8 (11)
Undetermined	7 (9)	1 (1)
Major bleeding-related death*	1 (1)	2 (3)

*Major bleed occurred within 30 days of death.

Hemodialysis access site bleeding events were responsible for the majority of the clinically relevant nonmajor bleeds in both the apixaban (10/14; 71%) and warfarin (6/10; 60%) groups.

Pokoney SD, Circulation 2022

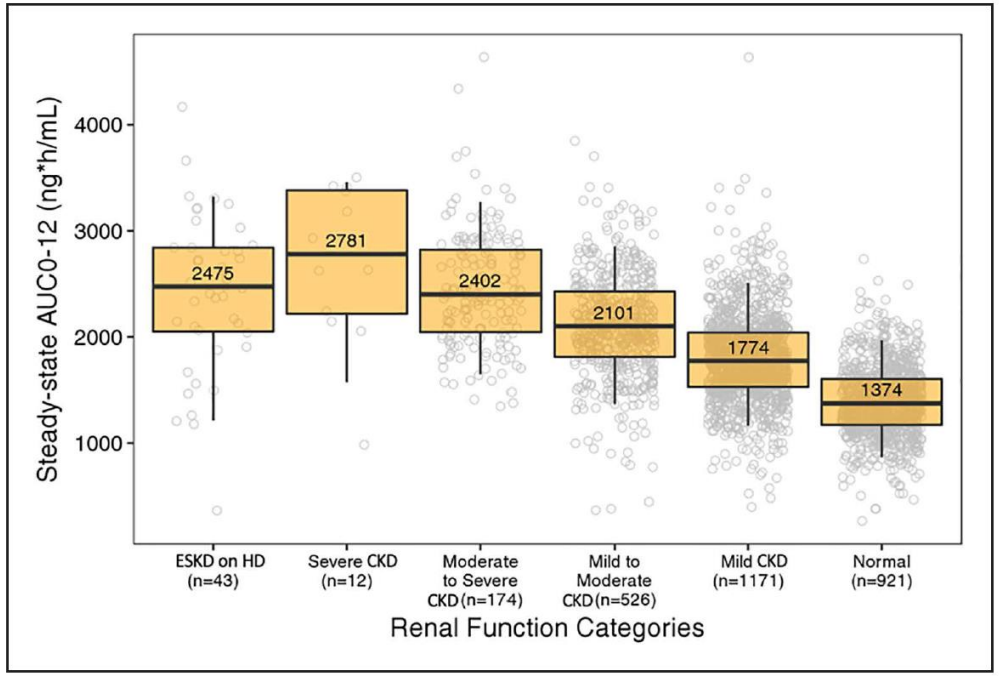
RENAL AF: Secondary outcome



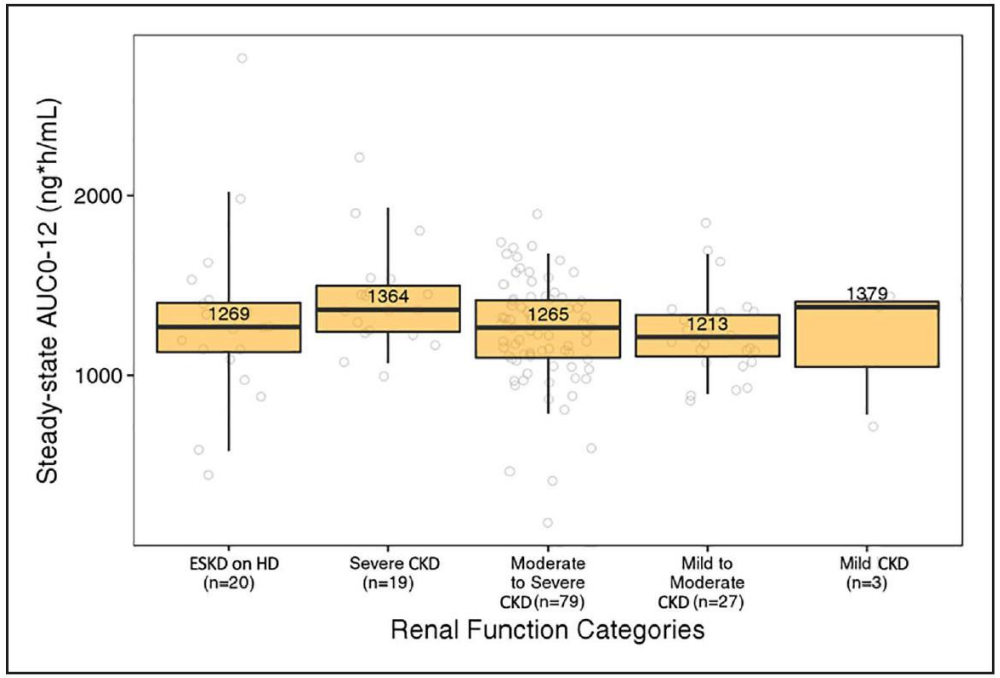
Pokoney SD, Circulation 2022

Pharmacokinetics (ARISTOTLE & RENAL-AF)

Apixaban 5 mg twice daily



Apixaban 2.5 mg twice daily



Median steady-state 12-hour area under the curve was **2475** ng/mL×h (10th to 90th percentiles, 1342–3285) for 5 mg of apixaban twice daily and **1269** ng/mL×h (10th to 90th percentiles, 615–1946) for 2.5 mg of apixaban twice daily.

Pokoney SD, Circulation 2022

Comparison of PK values among patients with and without bleeding

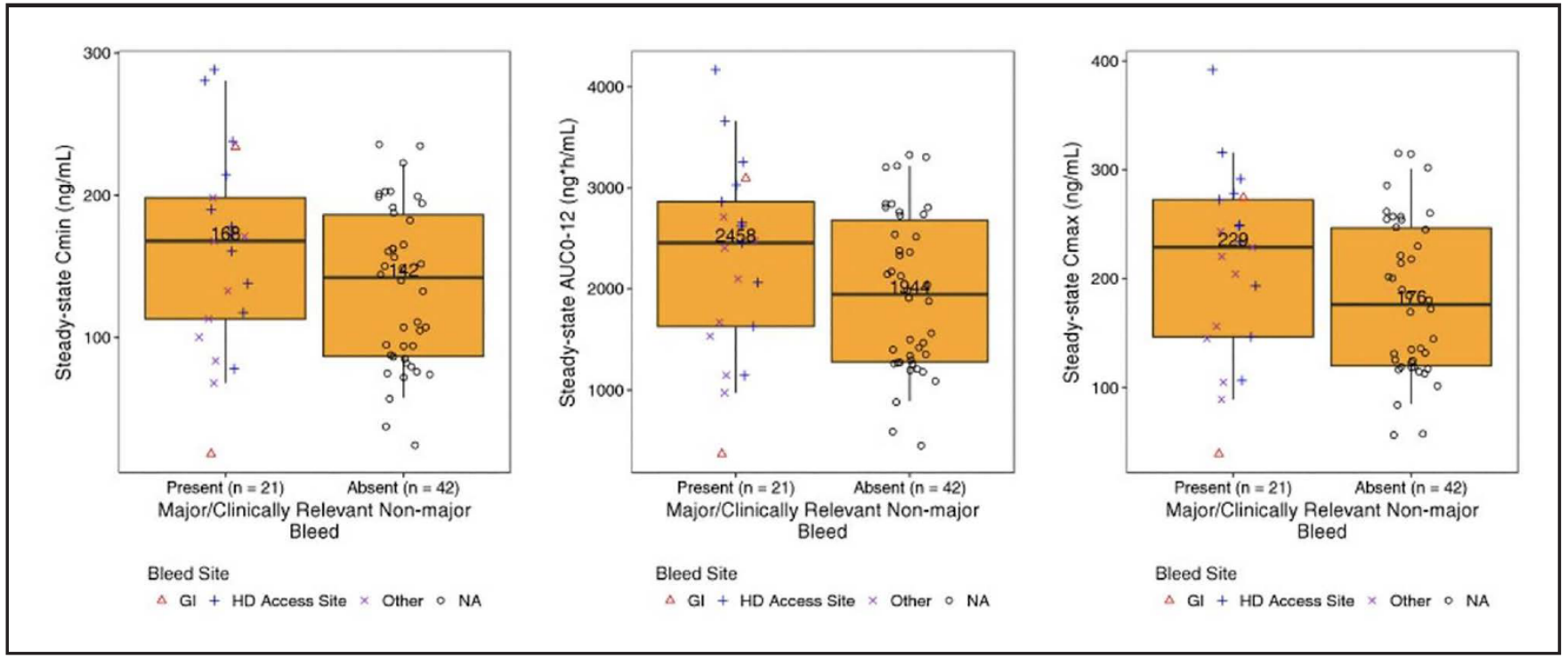


Figure 4. Comparison of pharmacokinetic values among patients with and without a major or clinically relevant nonmajor bleeding event.

There was **substantial overlap** between minimum apixaban blood concentration, 12-hour area under the curve, and maximum apixaban blood concentration for patients with and without a major or clinically relevant nonmajor bleeding event.

Pokoney SD, Circulation 2022

RENAL-AF: Conclusion

- There was inadequate power to draw any conclusion regarding rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and ESRD on HD.

- Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism among this population on anticoagulation, highlighting the need for future randomized studies evaluating the risks versus benefits of anticoagulation among patients with AF and ESRD on HD.

Pokoney SD, Circulation 2022

AXADIA-AFNET8 trial

- From June 2017 through May 2022
- Compare Apixaban and VKA in Patients With AF and ESKD
- Investigator-initiated prospective randomized open blinded end point
- AF on chronic hemodialysis, apixaban 2.5 mg bid vs. VKA phenprocoumon (INR 2.0-3.0_actual TTR 50.7%)

- Primary safety outcome: a composite of a first event of major bleeding, clinically relevant nonmajor bleeding, or all-cause death
- Primary efficacy outcome: a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism

- Hypothesis: Apixaban is noninferior to VKA

Reinecke H, Circulation 2023

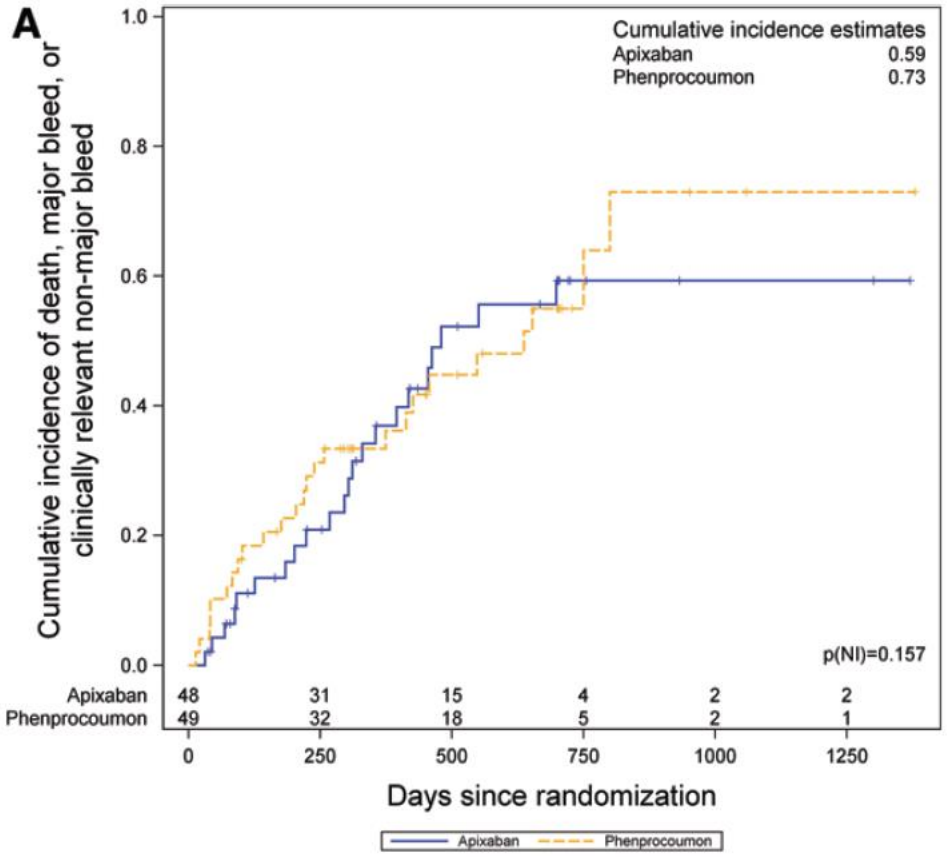
AXADIA-AFNET8 trial: Baseline characteristics

- 97 pateints were enrolled (48 in apixaban, 49 in VKA)
- 75 years old
- BMI 29
- Previous stroke – not mentioned
- AF type – non mentioned
- CHA_2DS_2-VASc median 4.5
- HAS-BLED median 4.2

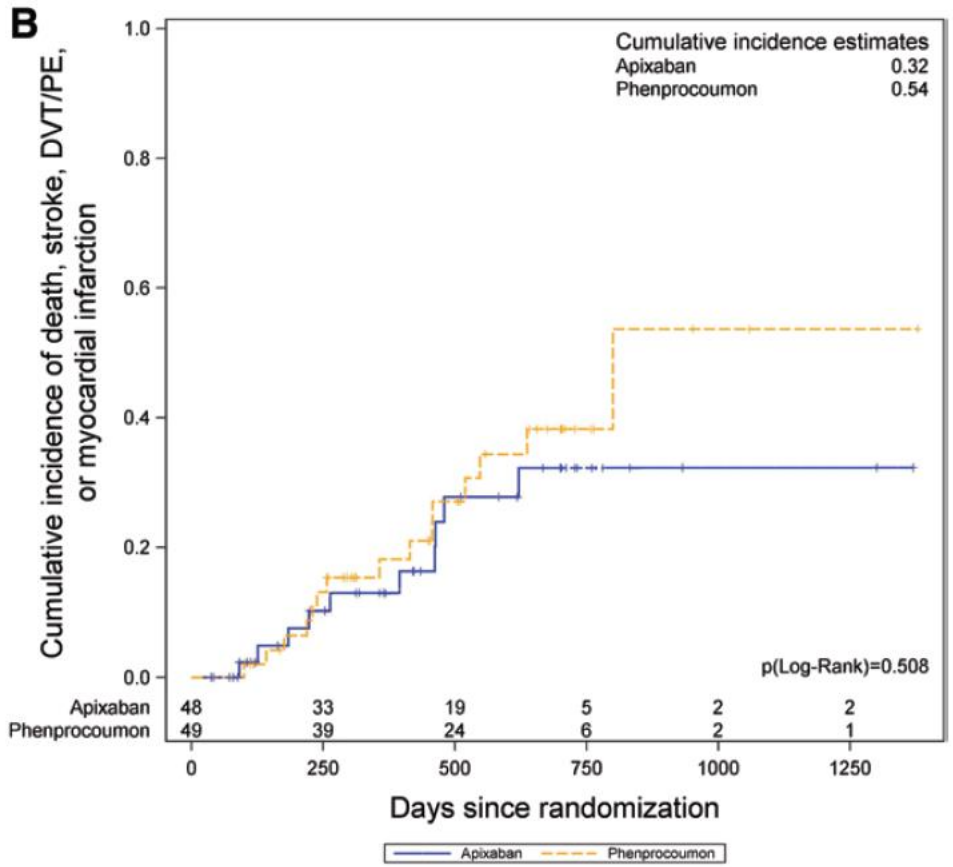
Reinecke H, Circulation 2023

AXADIA-AFNET8 trial: Outcomes

Primary safety



Primary efficacy



Treatment with apixaban (2.5 mg BID) showed **no apparent differences in safety and efficacy** compared with VKA therapy in patients with AF on chronic hemodialysis, although the prespecified noninferiority test requirements were not met because of slow enrollment. .

Reinecke H, Circulation 2023

Current guidelines

- EHRA 2021
- KHRS 2022

EHRA NOAC practical guideline 2021:
OAC in patients with end-stage CKD (CrCl of 15 mL/min and/or dialysis)

Numerous observational studies have reported conflicting results for the use of both VKA and NOACs in patients with end-stage renal disease regarding effectiveness and bleeding without a clear signal for a benefit of OAC.[129–132] A propensity score matched analysis of 4,537 Medicare patients as well as a meta-analysis of 16 studies with 71 877 dialysis-dependent patients with AF (about 3000 with NOACs) did not demonstrate a benefit regarding the risk for stroke and thromboembolism but instead found a markedly increased incidence of bleeding complications in patients with OAC compared to those without.[133,134]

The use of VKA in end-stage CKD may in some cases result in calciphylaxis, a painful and often lethal condition caused by calcification and occlusion of cutaneous arteries and arterioles.[135] Moreover, there is also an ongoing controversy about the clinical relevance of aggravated calcifications of the large vessels as well as those of the kidney itself under VKA.

The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear and subject to ongoing studies. Plasma levels while on treatment with apixaban 2.5 mg BID[136] (as well as with 5 mg, Pokorney *et al.*, presented at ESC 2020), edoxaban 15 mg QD,[137] and rivaroxaban 10 mg QD[138] or 15 mg[139] were found to be similar to patients with the full dose and normal renal function. Initial registry data had indicated a higher incidence of hospitalization or death from bleeding in dialysis-dependent patients with dabigatran or rivaroxaban as compared to VKA.[140] More recent analyses indicated more similar thromboembolic- and bleeding rates with apixaban and rivaroxaban vs. VKA; however, residual confounding is likely to be substantial in these analyses precluding any definitive answer regarding efficacy and safety of NOACs in these patients.[124,141–143]

OAC in AF ESRD on HD, controversial, no clear benefit

Plasma level of apixaban 2.5 (as well as apixaban 5 mg), edoxaban 15mg, rivaroxaban 10 or 15mg were found to be similar to patients with the full dose and normal renal function.

In observational study, R and A is not bad compared to W, but residual confounding is likely to be substantial…

EHRA NOAC practical guideline 2021:
OAC in patients with end-stage CKD (CrCl of 15 mL/min and/or dialysis)

Furthermore, two randomized controlled trials have been initiated comparing apixaban vs. VKA ['RENal Hemodialysis Patients ALlocated Apixaban vs. Warfarin in Atrial Fibrillation' (RENAL-AF) in the US (NCT02942407), and 'A Safety Study Assessing Oral Anticoagulation With Apixaban vs. Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment' (AXADIA) in Germany (NCT02933697)[144]]. Both studies lacked a third treatment arm without any OAC and both suffered from severe recruitment problems. RENAL-AF has been stopped prematurely after including 154 patients and reported similar rates of major and clinically relevant non-major bleeds as well as a (numerical) doubling of cardiovascular deaths with apixaban vs. warfarin (presented at AHA 2019). Of note, a large proportion of warfarin patients were outside the therapeutic range (TTR 44%) and about 50% of apixaban patients received 5 mg BID. A third, smaller trial (NCT03987711) comparing warfarin, apixaban, and no anticoagulation is currently ongoing. Despite the lack of data for NOACs (or OAC in general) in dialysis-dependent patients, their usage seems to be increasing.[145]

In summary, given the lack of strong evidence the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization. Measurements of NOAC plasma levels (see 'NOAC plasma level measurements: technical approach, indications, pitfalls' section), although intuitively appealing for this situation, has equally never been prospectively investigated for hard clinical endpoints, and should hence be reserved to highly specialized centres. Patients need to be informed of the lack of data as well as the 'off label' character of whichever strategy or drug is chosen, including the uncertain benefit and the increased risk of complications. Ideally, such patients

Results of RCTs, inconclusive
RENAL-AF : incomplete study
AXADIA : still waiting

Still, lack of strong evidence the decision to anticoagulated and (if so) whether to use a DOAC or warfarin in AF ESRD HD patients.

Patients should be informed about the uncertain benefit and the increased risk of complications of OAC use.

11.1.3. 말기 신질환 환자 (CrCl < 15 mL/min 또는 투석치료)

말기 신질환이 있는 심방세동 환자에서 와파린과 NOAC 의 효능 및 출혈에 대해서 비교한 관찰 연구들이 있으나, 결과에 다른 부분이 많아서 NOAC의 사용이 이득이라고 말하기는 어려운 상태이다.[224-227] 말기 신질환 환자에서 NOAC 의 사용이 혈전 예방의 이득은 없이 오히려 출혈 위험성을 유의미하게 증가시킨다는 연구 결과도 있다.[228, 229] 와파린의 사용은 가끔 저항성 칼슘 형성을 유발할 수 있고, 논란의 여지는 있지만 혈관의 칼슘 석회화도 촉발시킨다는 위험성이 있을 수 있다.[230]

말기 신질환 환자에게 리바록사반의 경우는 15 mg 또는 10 mg 1일 1회, 아픽사반의 경우 5 mg 또는 2.5 mg 1일 2회, 에독사반의 경우 15 mg 1일 1회 사용 시 정상 신기능 환자에게 정상 용량을 사용했을 때와 유사한 것으로 확인되었다. 최근의 분석에서는 아픽사반 또는 리바록사반이 와파린과 비교했을 때 비슷한 수준의 혈전 및 출혈 효과를 보이는 것으로 나타났지만 해석에는 매우 주의가 필요하다.[222, 233-235] 아픽사반과 와파린을 비교하는 RENAL-AF 연구와 AXADIA 연구가 진행되고 있었으나 RENAL-AF 연구는 조기에 종료되었다. RENAL-AF 연구에서는 두 그룹 모두 출혈에 의한 사망률이 크게 증가하였는데, 와파린 그룹에서는 INR 수치가 잘 조절되지 않았고, 아픽사반 그룹은 5 mg 1일 2회 요법을 사용했었다. 말기 신질환 또는 투석을 하는 환자에서 NOAC 을 사용할 명확한 근거는 충분치 않지만, 상기 분석결과들을 토대로 점점 NOAC 을 처방하는 빈도는 증가하는 것으로 보인다.[236]

미국 식약처에서는 리바록사반 1일 15 mg 용법과 아픽사반 5 mg 1일 2회 용법을 만성 신질환 G5와 G5D 단계의 환자 대상으로 승인했다. 이에 관해 약동학 및 약리학 데이터를 기반으로 리바록사반과 아픽사반의 사용을 승인했으며, 임상적 안전성은 확인되지 않았으나 이를 이용할 수 있을 때까지 "first do no harm"의 원칙을 적용했다고 설명되고 있다.[237]

결론적으로 현재 말기 신질환 또는 투석을 하는 환자에 있어서 NOAC이 좋은지 와파린이 좋은지에 대한 답은 없다. 환자 개개인의 상황, 상태에 맞추어 약을 처방해야 하겠으며 약제의 사용에 따른 부작용 또한 설명하는 것이 필요하겠다. 추가로 신장이식을 받은 심방세동 환자에서도 NOAC 사용의 데이터가 부족하니, 해당 환자에서 NOAC을 사용하고자 한다면 면역억제제를 투여하는 분과와 긴밀한 협의가 필요하겠다.

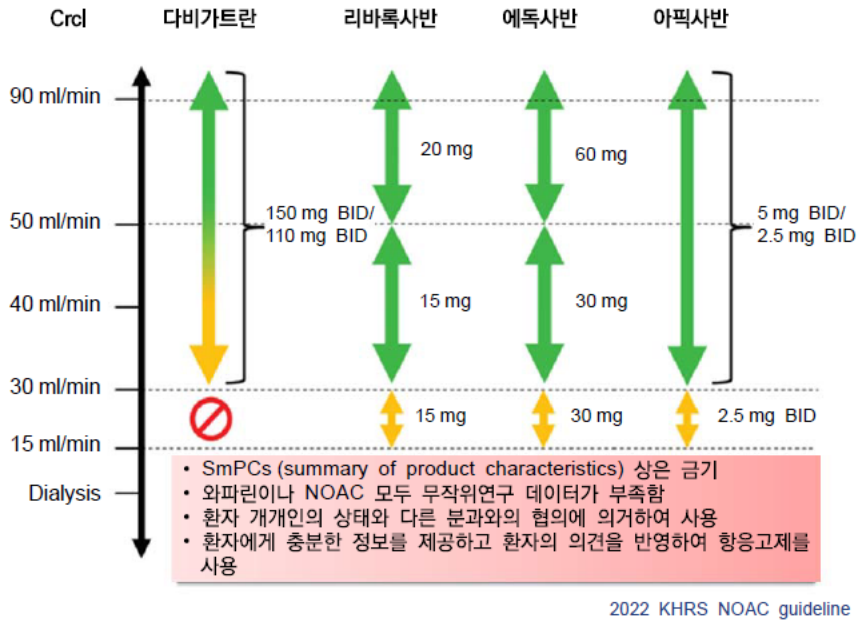


그림 17. 신기능에 따른 NOAC 의 사용

KHRS NOAC practical guideline 2022

11.1.3. 말기 신질환 환자 (CrCl < 15 mL/min 또는 투석치료)

말기 신질환이 있는 심방세동 환자에서 와파린과 NOAC 의 효능 및 출혈에 대해서 비교한 관찰 연구들이 있으나, 결과에 다른 부분이 많아서 NOAC의 사용이 이득이라고 말하기는 어려운 상태이다.[224-227] 말기 신질환 환자에서 NOAC 의 사용이 혈전 예방의 이득은 없이 오히려 출혈 위험성을 유의미하게 증가시킨다는 연구 결과도 있다.[228, 229] 와파린의 사용은 가끔 저항성 칼슘 형성을 유발할 수 있고, 논란의 여지는 있지만 혈관의 칼슘 석회화도 촉발시킨다는 위험성이 있을 수 있다.[230]

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- OAC in AF ESRD, still controversial.
- DOAC vs. warfarin: comparable bleeding and stroke
- US FDA approved R15 mg once daily and A5 mg twice daily

조절되지 않았고, 아픽사반 그룹은 5 mg 1일 2회 요법을 사용했었다. 말기 신질환 또는 투석을 하는 환자에서 NOAC 을 사용할 명확한 근거는 충분치 않지만, 상기 분석결과들을 토대로 점점 NOAC 을 처방하는 빈도는 증가하는 것으로 보인다.[236]

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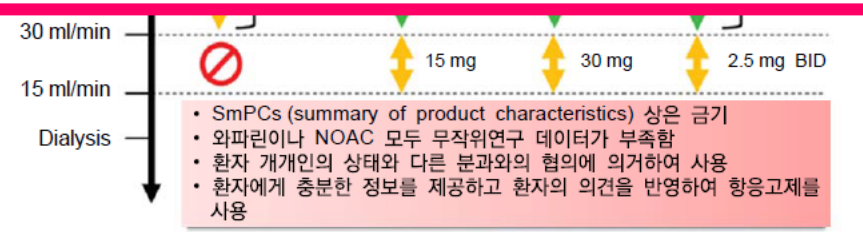


그림 17. 신기능에 따른 NOAC 의 사용

Korean data

Patients with AF between 2014 and 2020 (n=1,061,456)

Patients who had prescription records of OAC after AF diagnosis (n=537,397)

Patients who were naïve to OAC since 2014 (n=384,285)

N=312,167

Patients on HD or PD (ESRD) (n=5609)

Warfarin (n=3483)

DOAC (n=2019)

Apixaban (n=1273)

Edoxaban (n=339)

Rivaroxaban (n=407)

Patients who were not prescribed OAC after AF diagnosis (n=524,059)

Patients who prescribed OAC within a 2-year from the index date (n=153,111)

Patients aged under 20 years (n=4116)
Patients with valvular AF (n=11,599)
Patients with alternative indications of OAC
- Joint replacement surgery (n=24,284)
- Pulmonary embolism (n=20,875)
- Deep vein thrombosis (n=11,244)

Patients without ESRD (n=306,558)

Patients with dabigatran (n=106)

Baseline

HD 97%
Age 67-70 years
Men 61-62%
CHA_2DS_2-VASc 4.8
CCI 8.2-8.4
Prior stroke 26-27%
Prior ICH 2.2-3.0%
Prior GIB 15-17%

DOAC dose

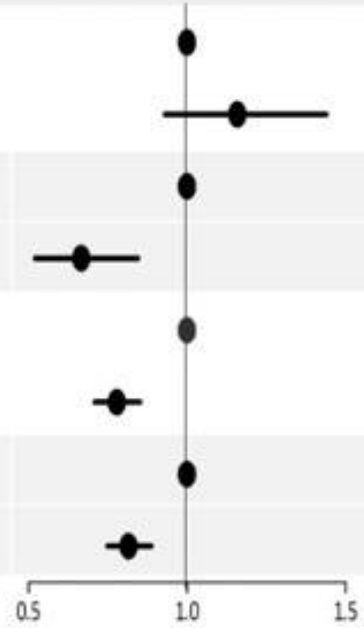
Low 72.5%; Very low 6.4%
R20 24.3%; R15 49.7%; R10 27.0%
A5 20.7%; A2.5 79.3%
E60 18.6%; E30 75.8%; E15 5.6%

Lee SR, Choi EK, Lip GYH [Manuscript preparation]

Korean data: Warfarin versus pooled DOAC

Ischemic stroke: comparable
Major bleeding, All-cause death, NCO: DOAC was associated with lower risks than warfarin

	Group	Weighted IR	Weighted HR (95% CI)	P-value
Ischemic stroke	Warfarin	3.24	1 (reference)	0.187
	Pooled DOAC	4.48	1.159 (0.929-1.440)	
Major bleeding	Warfarin	4.09	1 (reference)	0.001
	Pooled DOAC	2.99	0.667 (0.520-0.847)	
All-cause death	Warfarin	23.45	1 (reference)	<0.001
	Pooled DOAC	20.29	0.779 (0.708-0.854)	
Net clinical outcome	Warfarin	28.61	1 (reference)	<0.001
	Pooled DOAC	26.33	0.816 (0.748-0.889)	

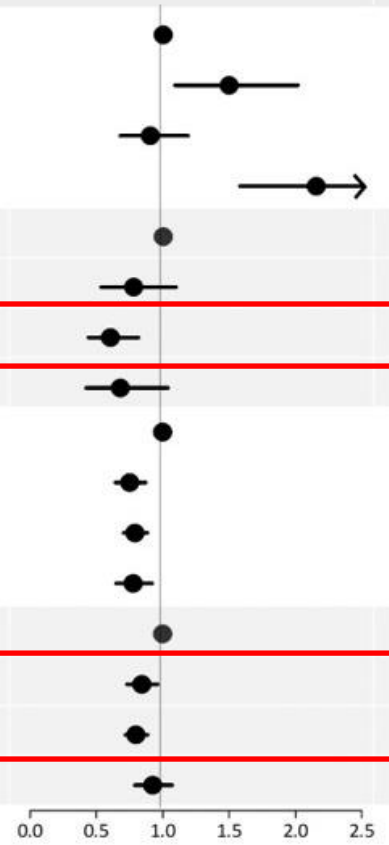


Lee SR, Choi EK, Lip GYH [Manuscript preparation]

Korean data: Warfarin versus each DOAC

Cautious interpretation is need.
Consistent with currently available data, R and A were associated with lower NCO than W.

	Group	Weighted IR	Weighted HR (95% CI)	P-value
Ischemic stroke	Warfarin	3.25	1 (reference)	
	Rivaroxaban	5.08	1.499 (1.089-2.020)	0.010
	Apixaban	3.79	0.903 (0.676-1.188)	0.476
	Edoxaban	8.21	2.157 (1.580-2.890)	<0.001
Major bleeding	Warfarin	4.09	1 (reference)	
	Rivaroxaban	3.26	0.776 (0.530-1.097)	0.170
	Apixaban	2.78	0.600 (0.434-0.812)	0.001
	Edoxaban	2.99	0.676 (0.416-1.036)	0.091
All-cause death	Warfarin	23.45	1 (reference)	
	Rivaroxaban	18.10	0.753 (0.645-0.872)	<0.001
	Apixaban	21.59	0.792 (0.706-0.886)	<0.001
	Edoxaban	19.89	0.777 (0.649-0.921)	0.004
Net clinical outcome	Warfarin	28.62	1 (reference)	
	Rivaroxaban	24.80	0.842 (0.732-0.963)	0.013
	Apixaban	27.15	0.799 (0.719-0.887)	<0.001
	Edoxaban	29.42	0.924 (0.790-1.072)	0.306



Lee SR, Choi EK, Lip GYH [Manuscript preparation]

Summary

- OAC vs. no OAC in patients with AF ESRD : conflicting, no definite benefit
- In patient requiring anticoagulation: R (15, 10) or A (5?, 2.5) should be considered.
- Upcoming RCTs: AVKDIAL trial (OAC vs. no AOC in HD), SAFE-D trial (A5, A2.5, W, no OAC)
- Role of LAAO, Factor XIa inhibitor in the future: more clinical trials are needed.

Thank you for your attention