JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 3, 2020

PUBLISHED BY ELSEVIER

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)

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, New York; [b]Department of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan; [c]Department of Cardiology, Detroit Medical Center, Detroit, Michigan; [d]Diabetes and Metabolism Information Center, Research Institute, Center for Global Health and Medicine, Tokyo, Japan; [e]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; [f]Department of Public Health/Health Policy, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan; [g]Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, New York; [h]Department of Cardiology, Japanese Red Cross Ashikaga Hospital, Ashikaga, Japan; [i]Division of Cardiovascular Medicine, Section of Heart Failure and Transplantation, University of Iowa, Iowa City, Iowa; and the [j]Division of Cardiovascular Medicine, New York University School of Medicine, New York, New York. Dr. Shimada is supported in part by unrestricted grants from the American Heart Association National Clinical and Population Research Award and Career Development Award, Honjo International Scholarship Foundation, and Korea Institute of Oriental Medicine. Dr. Bangalore is supported by grants from Abbott Vascular and the National Heart, Lung, and Blood Institute; and is a member of the Advisory Board of Abbott Vascular, Biotronik, Amgen, Pfizer, and Reata. Dr. Burger holds stock in Potola Pharmaceutical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Louise Pilote, MD, MPH, PhD, served as Guest Associate Editor for this paper.

Manuscript received July 30, 2019; revised manuscript received October 28, 2019, accepted October 29, 2019.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.10.059

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

DOAC = direct oral anticoagulant

ESKD = end-stage kidney disease

HR = hazard ratio

OAC = oral anticoagulant

Atrial fibrillation (AF) is common and increasing among patients with end-stage kidney disease (ESKD) on long-term dialysis, with a prevalence of approximately 10% (1). Oral anticoagulants (OACs) are recommended in patients with AF to reduce the risk of stroke and thromboembolic events. In addition, data from randomized controlled trials showed that direct oral anticoagulants (DOACs) were noninferior to warfarin (and superior with certain agents) with respect to the risk of thromboembolic events in patients without severe kidney disease (2,3). Because patients on long-term dialysis are not only at high bleeding risk due to uremic platelet dysfunction but also at high risk for ischemic stroke, it is not clear if the net clinical benefit of OACs extends to the ESKD and long-term dialysis population (4–6). National and international clinical practice guidelines therefore state "it might be reasonable to prescribe warfarin or apixaban for patients with dialysis, CHA_2DS_2-VASc score >2 in men, 3 in women," with a Class IIb recommendation, because of the limited evidence in this cohort (6).

SEE PAGE 286

The pharmacokinetics of rivaroxaban might allow use in this population; however, previous studies showed high bleeding risk with rivaroxaban and dabigatran in the ESKD cohort (7,8). Recently, a retrospective cohort study of Medicare beneficiaries with AF on long-term dialysis suggested lower major bleeding risk and similar thromboembolic risk with apixaban 5 mg twice daily dosing compared with warfarin (8–10). However, apixaban should be compared with no anticoagulant because whether to use anticoagulation therapy for patients with AF on long-term dialysis is still questionable.

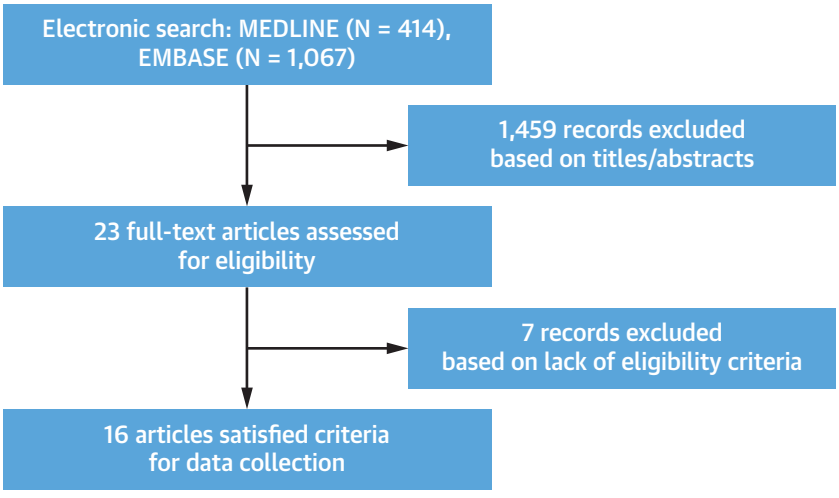
We therefore sought to investigate the safety and efficacy of OACs (DOACs and warfarin) compared with no anticoagulation for patients with AF on long-term dialysis.

METHODS

SEARCH STRATEGY. All studies that investigated the impact of OAC strategy for AF on stroke and/or systemic thromboembolism, survival, and major bleeding events in patients on long-term dialysis were identified using a 2-level search strategy. First, MEDLINE and EMBASE were searched through June 10, 2019 using web-based search engines. Second, relevant studies were identified through a manual search of secondary sources, including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses (**Figure 1**).

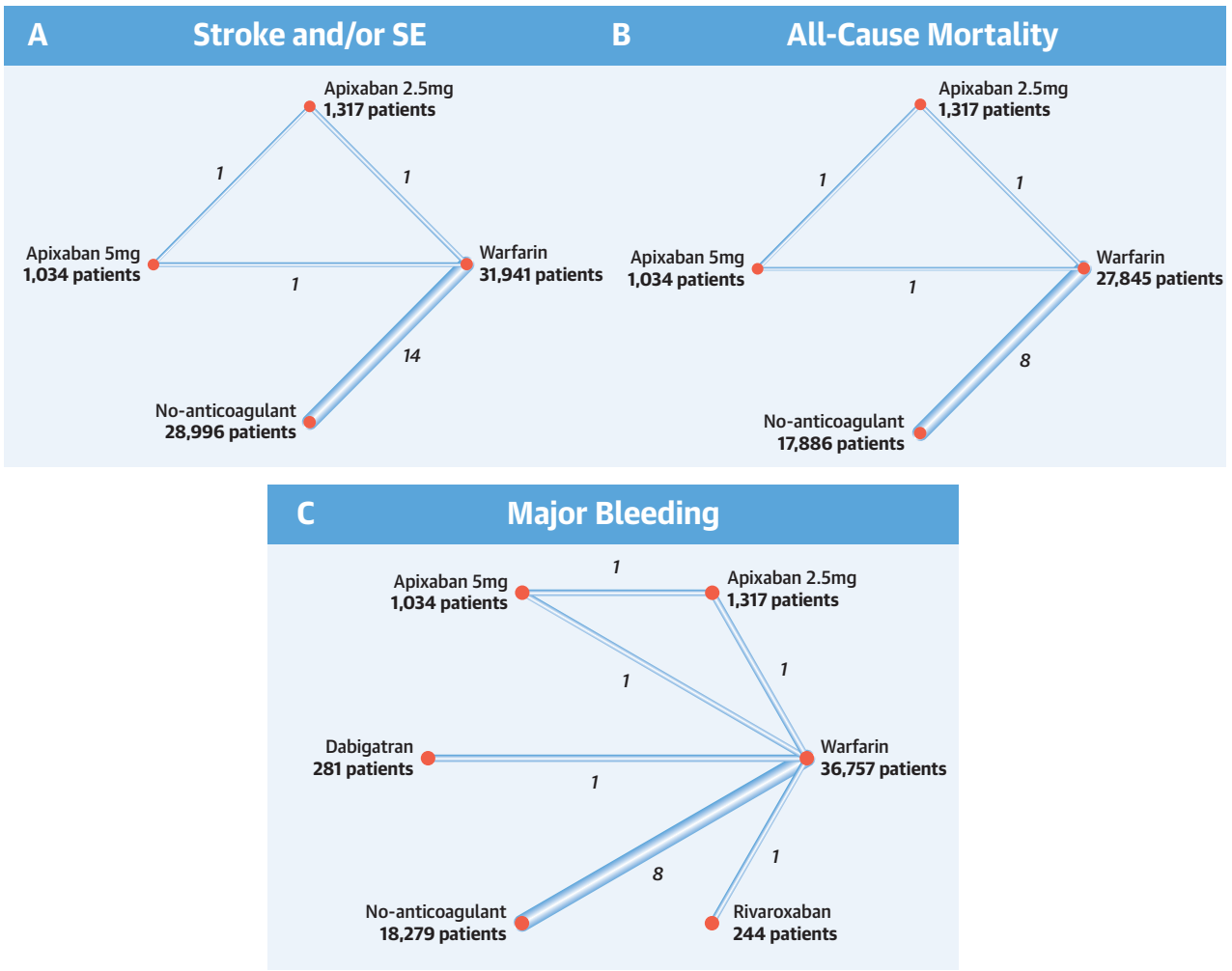
Search terms included atrial fibrillation, dialysis OR hemodialysis OR end-stage kidney disease OR end-stage kidney disease OR end-stage renal disease OR advanced renal disease, warfarin OR coumadin OR vitamin K antagonist OR novel oral anticoagulant OR NOAC OR direct oral anticoagulant OR DOAC OR apixaban OR dabigatran OR rivaroxaban OR edoxaban OR anticoagulation OR anticoagulant. Two independent and blinded authors (T.K. and H.T.) reviewed

FIGURE 1 Selection of Studies



Flow diagram of the literature search.

FIGURE 2 **Network of Anticoagulant Comparisons**



The width of connecting lines between anticoagulant strategies reflects the number of studies available for each comparison. **Italic number** means the number of study arms between 2 strategies. **(A)** Stroke and/or systemic embolism (SE). **(B)** All-cause mortality. **(C)** Major bleeding.

the search results separately to select the studies based on inclusion and exclusion criteria. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (11).

INCLUSION AND/OR EXCLUSION CRITERIA. Studies that met the following criteria were included: 1) the study was published in peer-reviewed journals; 2) the design was a comparative study of patients on long-term dialysis with AF who received different OACs or no anticoagulant; and 3) the study reported at least 1 of all-cause mortality, stroke, and/or systemic thromboembolism as efficacy outcomes and major bleeding as a safety outcome. For each study, the adjusted hazard ratio (HR) was abstracted if available. No data were available regarding the safety and efficacy of edoxaban for patients with AF on long-term dialysis. Thus, we investigated dabigatran versus rivaroxaban versus apixaban versus warfarin versus no anticoagulant.

OUTCOMES. The primary efficacy endpoint was stroke and/or systemic thromboembolism; the secondary efficacy endpoint was all-cause mortality. The primary safety endpoint was major bleeding. Major bleeding was defined variously in the studies as bleeding that required hospitalization, that required transfusion, and bleeding that led to death, as well as gastrointestinal bleeding or intracranial hemorrhage.

QUALITY ASSESSMENT. To assess the quality assessment, we used the Newscastle-Ottawa Assessment Scale (12). Two investigators (T.K. and H.T.)

TABLE 1 Baseline Characteristics

First Author (Ref. #)	Follow-Up (Months)	No. of Patients			Age (yrs)			Male (%)			Hypertension (%)		
		DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC
Chan et al. (17)	19.2		508	480		72.6	71.3		57.8	54.4		79.7	79.8
Chan et al. (18)	24.0	Dabi: 281 Riva: 244	8,064		Dabi: 68.4 ± 12 Riva: 66.9 ± 12	70.6 ± 11.0		Dabi: 59.2 Riva: 60.5	61.2		Dabi: 86.9 Riva: 84.9	88.5	
Chan et al. (19)	18.0		67	118		69.5 ± 9.5	69.4 ± 12.7		58.2	61.9		62.7	63.6
Chen et al. (20)	50.1		294	2,983		NA	NA		41.5	46.6		81.0	83.1
Garg et al. (21)	25.2		119	183		75.0 ± 7.0	78.0 ± 7.0		55.4	51.3		84.8	88.0
Genovesi et al. (22)	48.0		134	156		76.0	76.0		64.2	54.6		76.1	85.3
Phan et al. (23)	24.0		115	361		67.3 ± 10.8	62.9 ± 13.3		58.3	57.6		100	100
Shah et al. (24)	NA		756	870		75.3 ± 8.1	75.1 ± 8.1		61.0	61.0		77.0	75.0
Shen et al. (25)	NA		1,838	10,446		61.2 ± 12.4	62.1 ± 13.6		49.7	48.7		97.2	98.6
Siontis et al. (10)	NA	Api: 2,351	23,172		Api: 68.9 ± 11.5	68.2 ± 11.9		Api: 54.4	54.3		Api: 99.6	99.6	
Tan et al. (26)	NA		1,651	4,114		73.9	75.1		43.6	43.0		98.1	98.8
Wakasugi et al. (27)	NA		28	32		67.8 ± 9.4	68.4 ± 8.5		57.0	72.0		NA	NA
Wang et al. (28)	52.8		59	82		59.8 ± 10.5	62.1 ± 11.8		77.0	69.0		98.3	89
Winkelmayer et al. (29)	18.0–24.0		249	2,064		68.6 ± 12.1	70.1 ± 11.9		42.6	42.5		82.7	80.7
Yodogawa et al. (30)	47.0		30	54		69.5 ± 10.7	70.4 ± 10.2		80.0	65.0		57.0	48.0
Yoon et al. (31)	15.9		2,921	7,053		67.8 ± 11.0	66.1 ± 12.6		59.9	57.5		89.4	79.2

Values are n, mean ± SD, mean, or %, unless otherwise indicated.
AC = anticoagulant; Api = apixaban; Dabi = dabigatran; DOAC = direct oral anticoagulant; NA = not available; Riva = rivaroxaban.

reviewed the studies and judged selection, comparability, and outcomes.

STATISTICAL ANALYSIS. For each study, hazard ratio (HR) was abstracted. If propensity score–matched analysis was performed, we used data from the propensity score–matched cohort. We performed network meta-analysis using the "netmeta" 3.3.2 package (R Foundation for Statistical Computing, Vienna, Austria) (13). Within the framework, I^2 and Q statistics, which represent the proportion of total variation in study estimates that is due to heterogeneity, were used to quantify heterogeneity (14,15). The I^2 statistic represents the proportion of variability that is not attributable to chance. I^2 values >50% indicate substantial heterogeneity. The Q statistics are the sum of a statistic for heterogeneity, as well as a statistic for inconsistency, that represents the variability of treatment effect between direct and indirect comparisons at the meta-analytical level (16). We used the random-effect model because of the high heterogeneity. As a sensitivity analysis, we performed an analysis that excluded studies that focused on only patients on peritoneal dialysis.

RESULTS

Our search identified 16 eligible studies that enrolled a total of 71,877 patients with AF on long-term dialysis. Mean follow-up periods were 18.0 to 52.8 months (10,17–31). All studies were nonrandomized observational studies. One study compared apixaban 5 mg twice daily versus apixaban 2.5 mg twice daily versus warfarin (10). Another study investigated the bleeding outcomes for dabigatran versus rivaroxaban versus warfarin for patients on long-term dialysis who had AF (18). The characteristics of the network are shown in Figure 2. Patients' baseline characteristics are summarized in Tables 1 and 2. There was only 1 study that reported data based on time-varying exposure to OACs; as such, a sensitivity analysis using this methodology could not be performed (26).

STROKE AND/OR SYSTEMIC THROMBOEMBOLISM. OACs were not associated with a statistically significant lower risk of stroke and/or systemic thromboembolism compared with no anticoagulant (Table 3, Figure 3). However, there was significant heterogeneity in this analysis (I^2: 70.7%; $p < 0.0001$) but no significant inconsistency ($p = 0.90$).

ALL-CAUSE MORTALITY. Apixaban 5 mg twice daily was associated with significantly lower risk of mortality than other treatments (Table 3, Figure 4). However, there were significant heterogeneity in this analysis (I^2: 80.2%; $p < 0.0001$) but no significant inconsistency ($p = 0.70$).

MAJOR BLEEDING. Warfarin was associated with significantly higher risk of major bleeding than apixaban and no anticoagulant (Table 3, Figure 5). Dabigatran and rivaroxaban were also associated with significantly higher risk of major bleeding than

TABLE 2 Baseline Characteristics

First Author (Ref. #)	Diabetes Mellitus			Coronary Artery Disease			Congestive Heart Failure			Cerebrovascular Disease			Peritoneal Dialysis			Aspirin or Antiplatelet Therapy		
	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC	DOAC	Warfarin	No AC
Chan et al. (17)					41.7	32.3		58.3	52.9		NA	NA		0.0	0.0		0.0	0.0
Chan et al. (18)	Dabi: 70.4 Riva: 67.8	67.9		NA	NA		Dabi: 14.6 Riva: 14.1	20.8		Dabi: 11.2 Riva: 14.6	12.0		Dabi: 0.0 Riva: 0.0	0.0		Dabi: 5.6 Riva: 3.4	3.1	
Chan et al. (19)		38.8	39.0		35.8	20.3		29.9	20.3		17.9	10.2		100	100		0.0	0.0
Chen et al. (20)		45.9	47.6		61.9	54.9		57.8	52.1		5.1	6.6		1.7	14.0		0.0	0.0
Garg et al. (21)		58.8	55.1		77.3	80.9		89.9	91.2		20.1	23.0		0.0	0.0		ASA: 75.6 CLP: 18.4	ASA 68.3 CLP: 23.5
Genovesi et al. (22)		29.1	33.3		45.5	50.6		43.3	36.5		15.7	14.1		NA	NA		23.9	68.6
Phan et al. (23)		72.2	75.1		46.1	44.3		54.8	46.0		20.0	21.1		100	100		ASA: 13.9, $P2Y_{12}$ inhibitor: 26.1	ASA: 17.2, $P2Y_{12}$ inhibitor: 33.5
Shah et al. (24)		44.0	39.0		62.0	59.0		41.0	34.0		6.0	5.0		NA	NA		ASA: 22, CLP: 4.0	ASA: 28.0, CLP: 7.0
Shen et al. (25)		69.1	70.8		37.0	42.6		67.3	68.3		22.0	26.8		0	0		21.5	23.0
Siontis et al. (10)	75.4	74.9		Api: 26.9 (MI)	26.8 (MI)		Api: 79.5	77.5		Api: 33.1	33.2		Api: 5.7	5.4		Api: 6.6	7.4	
Tan et al. (26)		68.2	73.0		63.5	67.5		64.9	70.6		18.9	22.6		4.0	3.1		25.9	25.0
Wakasugi et al. (27)		21.0	28.0		NA	NA		NA	NA		14.0	26.0		0.0	0.0		61.0	47.0
Wang et al. (28)		39.0	45.0		42.0	59.0		16.0	27.0		16.0	13.0		21.0	23.0		NA	NA
Winkelmayer et al. (29)		60.2	59.1		46.2	53.0		77.5	74.9		22.9	23.6		4.8	4.4		NA	NA
Yodogawa et al. (30)		37.0	43.0		NA	NA		20.0	13.0		10.0	2.0		0.0	0.0		40.0	54.0
Yoon et al. (31)		43.1	35.9		NA	NA		NA	NA		NA	NA		0.0	0.0		ASA: 44.6, other: 25.6	ASA: 56.0, other: 30.6

Values are %.

ASA = acetylsalicylic acid; CLP = clopidogrel; MI = myocardial infarction; other abbreviations as in Table 1.

TABLE 3 Outcomes of All Studies

	Ischemic Stroke and/or SE				Major Bleeding						All-Cause Mortality			
First Author (Ref. #)	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC (Definition)	Dabigatran	Rivaroxaban	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC (Definition)	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC
Chan et al. (17)			n = NA, IR = 7.1 1.93 (1.29 −2.90)	n = NA, IR=2.9 1 (no definite definition)									n = NA, IR = 27.4 1.10 (0.94−1.30) (as warfarin users)	n = NA, IR = 25.7 1 (as non-warfarin users)
Chan et al. (18)					n = NA, IR = 83.1 1.48 (1.21−1.81)	n = NA, IR = 68.4 1.38 (1.03−1.83)			n = NA, IR = 35.9 1(bleeding which caused death/ hospitalization)					
Chan et al. (19)			n = NA, IR = NA 0.19 (0.06 −0.65)	n = NA, IR = NA 1 (ischemic stroke)										
Chen et al. (20)			n = NA, IR = NA 1.02 (0.67 −1.54)	n = NA, IR = NA 1 (ischemic stroke)										
Garg et al. (21)			n = 13, IR = NA 0.93 (0.49 −1.82)	n = 21, IR = NA 1 (ischemic stroke)					n = 26, IR = NA 1.53 (0.94−2.51)	n = 26, IR = NA 1 (transfusion and hospitalization)			n = 97, IR = NA 1.03 (0.91−1.15)	n = 145, IR = NA 1
Genovesi et al. (22)			n = 11, IR = 3.2 0.44 (0.16 −1.20)	n = 17, IR = 4.5 1 (no definite definition)					n = 59, IR = 17 1.16 (0.48−2.82)	n = 36, IR = 9.5 1 (hospitalization and transfusion, causing hemoglobin reduction > 2 g/dl)			n = 75, IR = 22.0 0.91 (0.56−1.48)	n = 95, IR = 25.0 1
Phan et al. (23)			n = 10, IR = .2 2.30 (0.94 −5.4)	n = 11, IR = 2.4 1 (ischemic stroke)					n = 13, IR = 9.1 1.20 (0.60−2.3)	n = 30, IR = 6.4 1 (hospitalization/ ED visit for GI/ICH/ other bleeding)			n = 32, IR 19.9 0.80 (0.53−1.2)	n = 98, IR 21.0 1
Shah et al. (24)			n = NA, IR = NA 1.14 (0.78 −1.67)	n = NA, IR = NA 1 (ischemic stroke)					n = NA, IR = NA 1.44 (1.13−1.85)	N−NA, IR = NA 1 (GI/ICH)				
Shen et al. (25)			n = 63, IR = 2.3 0.68 (0.47 −0.99)	n = 503, IR = 3.4 1 (ischemic stroke)					n = 153, IR = 5.9 1.00 (0.69−1.44)	n = 833, IR = 5.9 1 (GI)			n = 832, IR = 33.0 1.01 (0.92−1.11)	n = 4,595, IR = 32.5 1
Siontis et al. (10)	n = 81, IR = 12.4 0.64 (0.42 −0.97)	1.11 (0.82−1.50)	n = 373, IR = 11.8 1 (ischemic stroke and/or SE)				n = 129, IR = 19.7 0.71 (0.53−0.95)	0.71 (0.56−0.91)	n = 715, IR = 22.9 1 (GI/ICH/ transfusion)		n = 159, IR = 23.7 0.63 (0.46−0.85)	1.07 (0.87−1.33)	n = 753, IR = 24.9 1	

Continued on the next page

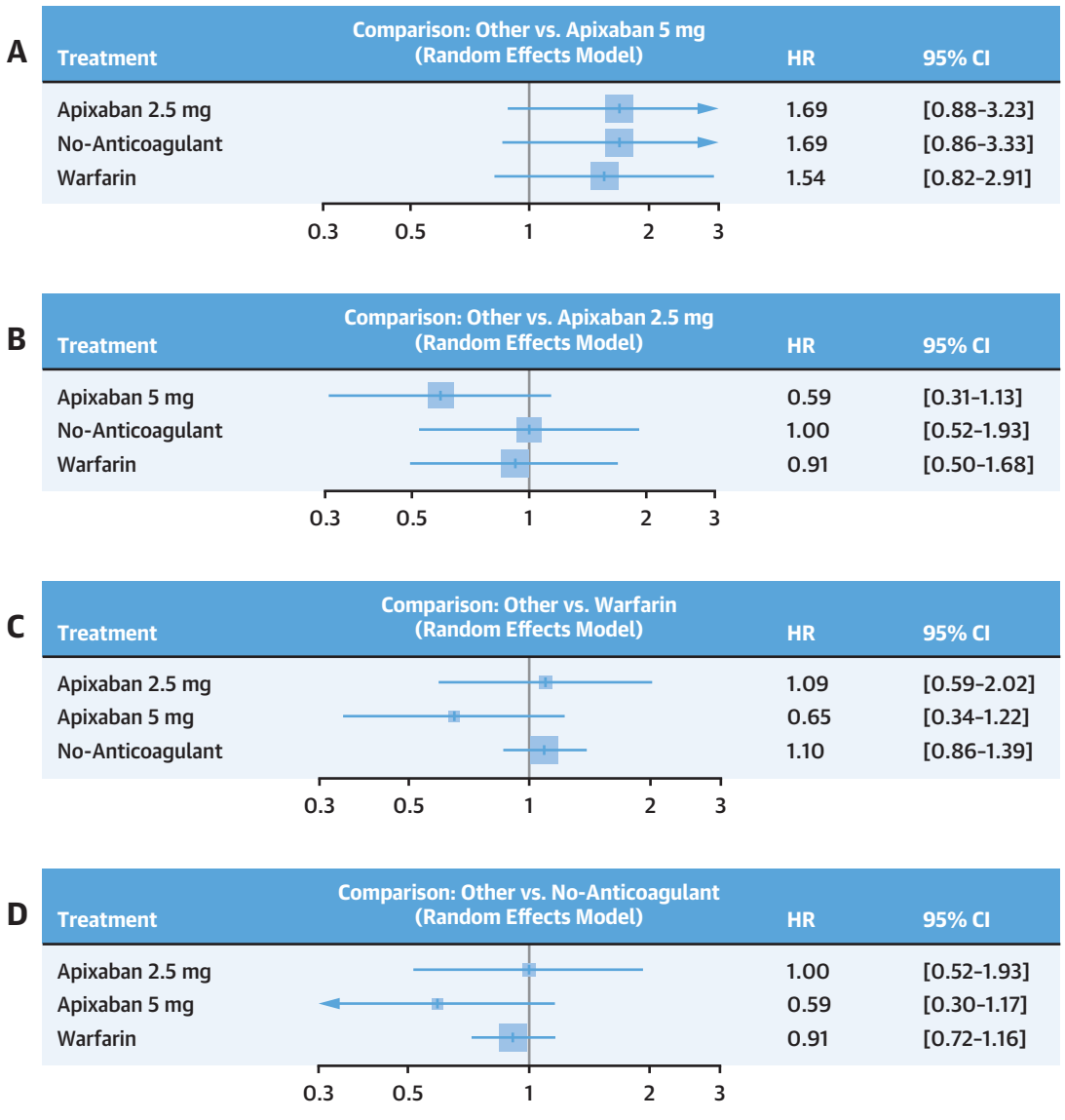
TABLE 3 Continued

	Ischemic Stroke and/or SE				Major Bleeding						All-Cause Mortality			
First Author (Ref. #)	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC (Definition)	Dabigatran	Rivaroxaban	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC (Definition)	Apixaban 5 mg	Apixaban 2.5 mg	Warfarin	No AC
Tan et al. (26)			n = 93, IR = 8.2 0.87 (0.70–1.09)	n = 644, IR = 10.8 1 (ischemic stroke)					n = 407, IR = 41.7 1.48 (1.32–1.66)	n = 1,559, IR = 32.3 1 (GI/ICH/ hospitalization)			n = 476, IR = 37.0 0.72 (0.65–0.79)	n = 3,349, IR = 52.0 1
Wakasugi et al. (27)			n = 8 IR = 14.8 3.36 (0.67–16.7)	n = 5, IR = 8.9 1 (ischemic stroke)										
Wang et al. (28)			n = 8, IR = NA 1.01 (0.50–2.04)	n = 11, IR = NA 1 (ischemic stroke and/or SE)					n = 22, IR = NA 1.44 (0.71–2.92)	n = 24, IR = NA 1 (GI/ICH/ transfusion)			n = 44, IR = NA 0.83 (0.40–1.72)	n = 64, IR = NA 1
Winkelmayer et al. (29)			n = 29, IR = 7.4 0.92 (0.61–1.37)	n = 135, IR = 7.8 1 (ischemic stroke)					n = 48, IR = 13.4 0.96 (0.70–1.31)	n = 216, IR = 13.6 1 (GI)			n = 181, IR = 42.9 1.06 (0.90–1.24)	n = 750, IR = 40.2 1
Yodogawa et al. (30)			n = 2, IR = NA 1.07 (0.20–5.74)	n = 5, IR = NA 1 (no definite definition)										
Yoon et al. (31)			n = 221 0.95 (0.78–1.15)	n = 457 1 (ischemic stroke)										

Values are n of events, incident rates (IR), or hazard ratios (95% confidence intervals).

ED = emergency department; GI = gastrointestinal; ICH = intracranial hemorrhage; SE = systemic embolism; other abbreviations as in Table 1.

FIGURE 3 Effect of Anticoagulant on the Primary Efficacy Outcome (Stroke/SE)



Forest plots for the comparisons among anticoagulants (random effects model): **(A)** versus apixaban 5 mg; **(B)** versus apixaban 2.5 mg; **(C)** versus warfarin; and **(D)** versus no-anticoagulant. CI = confidence interval; HR = hazard ratio; SE = systemic embolism.

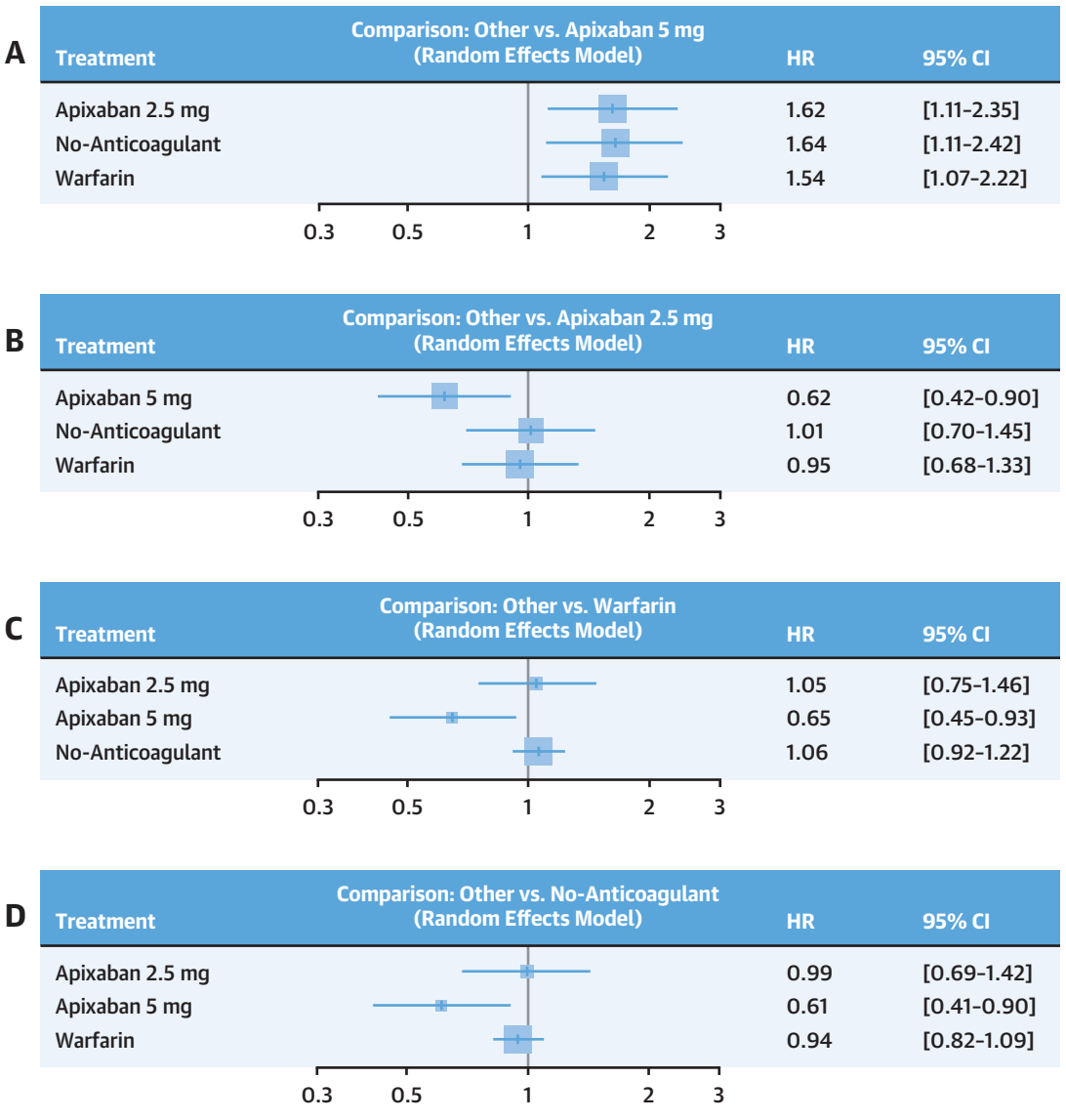
apixaban and no anticoagulant, and dabigatran was associated with a significantly higher risk of major bleeding than warfarin (Table 3, Figure 5). There was no significant heterogeneity (I^2: 23.6%; p = 0.16), and no significant inconsistency (p = 0.97).

SENSITIVITY ANALYSIS. Outcomes of sensitivity analyses that excluded studies that focused on only patients on long-term peritoneal dialysis were largely similar (Online Figures 1 to 3).

DISCUSSION

The salient findings of our network meta-analysis on the safety and efficacy of OACs in patients with AF and long-term dialysis can be summarized as follows (Central Illustration): 1) OACs were not associated with a reduced risk of stroke and/or systemic thromboembolism compared with no anticoagulant; 2) apixaban 5 mg twice daily had significantly lower risk of mortality than apixaban 2.5 mg twice daily,

FIGURE 4 Effect of Anticoagulant on the Secondary Efficacy Outcome (Death)

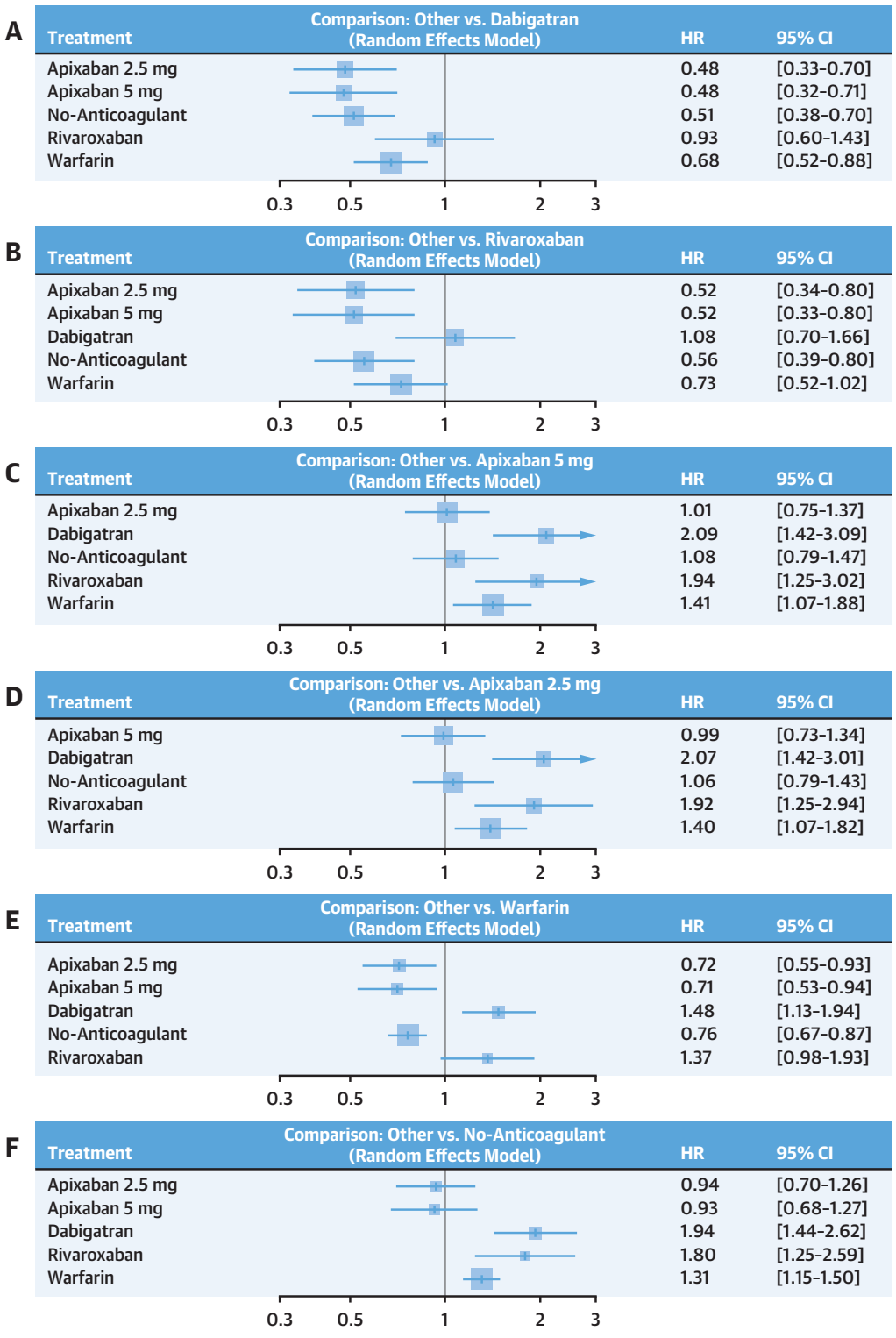


Forest plots for the comparisons among anticoagulants (random effects model): **(A)** versus apixaban 5 mg; **(B)** versus apixaban 2.5 mg; **(C)** versus warfarin; and **(D)** versus no-anticoagulant. Abbreviations as in Figure 3.

warfarin, and no anticoagulant; and 3) warfarin, dabigatran, and rivaroxaban had significantly higher risk of major bleeding than apixaban 5 mg twice daily, 2.5 mg twice daily, and no anticoagulant. Although these results should be interpreted cautiously because of high heterogeneity, warfarin, dabigatran, and rivaroxaban might not be preferred options because of their increased risk of bleeding in patients with AF on long-term dialysis. Further study is warranted to establish the benefit-to-risk ratio of OACs in patients with AF on long-term dialysis.

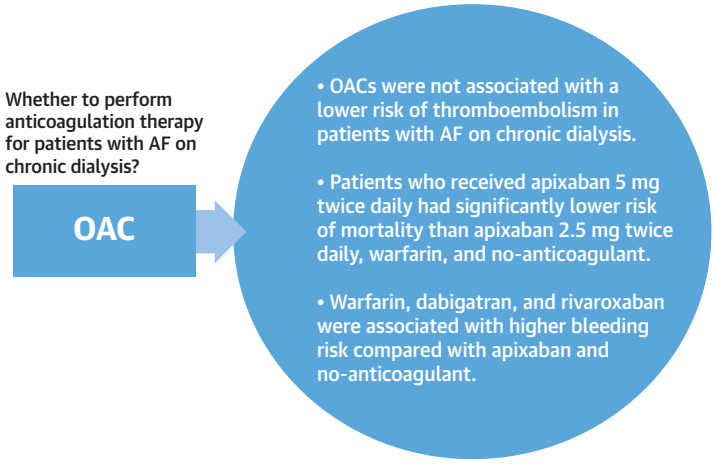
Patients on long-term dialysis were reported to have 5 times higher risk for a new stroke (32,33); however, these patients were also at high bleeding risk due to uremic platelet dysfunction and ischemic stroke (4,5). Thus, the bleeding risk of OACs with warfarin for these patients might outweigh its

FIGURE 5 Effect of Anticoagulant on the Primary Safety Outcome (Major Bleeding)



Forest plots for the comparisons among anticoagulants (random effects model): **(A)** versus dabigatran; **(B)** versus rivaroxaban; **(C)** versus apixaban 5 mg; **(D)** versus apixaban 2.5 mg; **(E)** versus warfarin; and **(F)** versus no-anticoagulant. Abbreviations as in Figure 3.

CENTRAL ILLUSTRATION **Patients With Oral Anticoagulation Management**



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

AF = atrial fibrillation; OAC = oral anticoagulant.

potential benefits. Previous meta-analyses reported that warfarin use did not show a reduction in stroke and mortality but did show an increased bleeding risk (34). There were several potential explanations of these findings. First, patients on hemodialysis routinely received heparin during dialysis, which also increased the risk of bleeding and posed a questionable effect of warfarin against stroke prevention (17,35). Second, warfarin might accelerate vascular calcification by inhibiting matrix G1a protein and Gas-6, which lead to higher risk of calcific arteriolopathy (calciphylaxis), which might increase the risk of ischemic stroke (24,36). Third, uremia was shown to interfere with warfarin metabolism through hepatic P450, which made it difficult to control the international normalized ratio within the therapeutic range (37,38). For all of the preceding reasons, we speculated that the previous studies did not show the benefit of warfarin among patients with AF on long-term dialysis; however, frequent international normalized ratio monitoring could lead to a better time to the therapeutic international normalized ratio range and could potentially lead to better outcomes in this cohort (24,38–40).

A previous study demonstrated higher bleeding risk of dabigatran and rivaroxaban compared with warfarin in patients on long-term dialysis (18). Moreover, our network meta-analysis showed dabigatran and rivaroxaban had higher bleeding risks than apixaban, which suggested dabigatran and rivaroxaban were not reasonable choices for patients with AF on long-term dialysis. Although rivaroxaban 10 mg can be used for patients with AF on long-term dialysis based on previous pharmacokinetic data (7), further studies are needed to compare the efficacy and safety of rivaroxaban 10 mg versus apixaban in this cohort.

Apixaban is mainly excreted by cytochrome P450, the intestines, and biliary excretion, with only 20% to 25% renal excretion (9). Although the ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation) trial excluded patients on dialysis, the Food and Drug Administration approved using apixaban 5 mg twice daily cautiously in patients on long-term dialysis based on limited data of pharmacokinetics in only 8 patients (2,9). A recent meta-analysis showed apixaban had lower risk of bleeding and relative effectiveness with thromboembolic events than warfarin for patients with ESKD, but this study mixed patients with and without dialysis, and those with venous thromboembolism (41). Our study did not reveal the efficacy to prevent stroke and/or systemic thromboembolism of apixaban 5 mg/2.5 mg against no anticoagulant, whereas it revealed less bleeding than warfarin. Moreover, apixaban 5 mg twice daily was associated with a reduction in mortality compared with no anticoagulant. Because warfarin was not

associated with lower stroke and showed higher risk of bleeding (34,39), further randomized controlled trials are needed to assess the feasibility of apixaban 5 mg twice daily compared with no anticoagulant to use in patients with AF on long-term dialysis.

STUDY LIMITATIONS. First, there were limited data from observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban for patients with AF on long-term dialysis. Thus, we could not assess the reason why apixaban 5 mg had lower mortality, due to lack of data regarding cardiovascular events other than stroke. In contrast, low bleeding rates were known to be associated with lower mortality (42). Moreover, outcomes of dabigatran and rivaroxaban were limited to major bleeding. Because only 2 studies were available regarding DOACs, most of the studies investigated warfarin versus no anticoagulant, which was the subject of previous meta-analyses (34). However, the fact that there was only 2 studies that directly compared the outcomes of DOACs and others underlines the importance of our network meta-analysis by adding more data to this important clinical question. Second, because we did not have access to individual patients' data, our data should be interpreted carefully. Third, there was only 1 study available that reported outcomes using time-varying exposure to OACs; there were no studies available that reported crossover information. Incorporation of time-varying OAC use and crossover information would prevent misclassification of exposure, which would result in estimates that more closely model the true effect. Fourth, differences in the characteristics of patients who were prescribed OACs versus not prescribed OACs might have contributed to the results, despite using adjusted effect size. Finally, there were some proportions of aspirin and/or antiplatelet prescriptions, which might have affected our results.

CONCLUSIONS

OACs were not associated with a reduced risk of thromboembolism in patients with AF who were on long-term dialysis. Patients who received apixaban 5 mg twice daily had a significantly lower risk of mortality than apixaban 2.5 mg twice daily, warfarin, and no anticoagulant. 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.

ADDRESS FOR CORRESPONDENCE: Dr. Toshiki Kuno, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, First Avenue, 16th Street, New York, New York 10003. E-mail: Toshiki.Kuno@mountsinai.org. Twitter: @ToshikiKuno.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with atrial fibrillation on long-term dialysis, apixaban 5 mg twice daily was associated with a lower risk of mortality than either warfarin or no anticoagulant.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to assess the efficacy and safety of target-specific OACs in patients with AF on long-term dialysis.

REFERENCES

1. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. J Am Soc Nephrol 2011;22:349–57.

2. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

4. Seliger SL, Gillen DL, Longstreth WT Jr., Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int 2003;64:603–9.

5. Suzuki S, Yamashita T, Kato T, et al. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. Circ J 2007;71:761–5.

6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104–32.

7. De Vriese AS, Caluwe R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis 2015;66:91–8.

8. Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, Battistella M. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrol Dial Transplant 2019;34:265–77.

9. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol 2017;28:2241–8.

10. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation 2018;138:1519–29.

11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.

12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of

nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.

13. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. PLoS One 2014;9:e115065.

14. Rucker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods 2012;3:312–24.

15. You R, Cao YS, Huang PY, et al. The changing therapeutic role of chemo-radiotherapy for locoregionally advanced nasopharyngeal carcinoma from two/three-dimensional radiotherapy to intensity-modulated radiotherapy: a network meta-analysis. Theranostics 2017;7:4825–35.

16. Ribassin-Majed L, Marguet S, Lee AWM, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma? An individual patient data network meta-analysis. J Clin Oncol 2017;35:498–505.

17. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009;20:2223–33.

18. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015;131:972–9.

19. Chan PH, Huang D, Yip PS, et al. Ischaemic stroke in patients with atrial fibrillation with chronic kidney disease undergoing peritoneal dialysis. Europace 2016;18:665–71.

20. Chen JJ, Lin LY, Yang YH, Hwang JJ, Chen PC, Lin JL. Anti-platelet or anti-coagulant agent for the prevention of ischemic stroke in patients with end-stage renal disease and atrial fibrillation–a nation-wide database analyses. Int J Cardiol 2014;177:1008–11.

21. Garg L, Chen C, Haines DE. Atrial fibrillation and chronic kidney disease requiring hemodialysis - does warfarin therapy improve the risks of this lethal combination? Int J Cardiol 2016;222:47–50.

22. Genovesi S, Rebora P, Gallieni M, et al. Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study. J Nephrol 2017;30:573–81.

23. Phan D, Yang SJ, Shen AY, Lee MS. Effect of warfarin on ischemic stroke, bleeding, and mortality in patients with atrial fibrillation receiving peritoneal dialysis. Am J Cardiovasc Drugs 2019;19:509–15.

24. Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129:1196–203.

25. Shen JI, Montez-Rath ME, Lenihan CR, et al. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. Am J Kidney Dis 2015;66:677–88.

26. Tan J, Bae S, Segal JB, Zhu J, Alexander GC, Segev DL, McAdams-DeMarco M. Warfarin use and the risk of stroke, bleeding, and mortality in older adults on dialysis with incident atrial fibrillation. Nephrology 2019;24:234–44.

27. Wakasugi M, Kazama JJ, Tokumoto A, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. Clin Ex Nephrol 2014;18:662–9.

28. Wang TK, Sathananthan J, Marshall M, Kerr A, Hood C. Relationships between anticoagulation, risk scores and adverse outcomes in dialysis patients with atrial fibrillation. Heart Lung Circ 2016;25:243–9.

29. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol 2011;6:2662–8.

30. Yodogawa K, Mii A, Fukui M, Iwasaki YK, et al. Warfarin use and incidence of stroke in Japanese hemodialysis patients with atrial fibrillation. Heart Vessels 2016;31:1676–80.

31. Yoon CY, Noh J, Jhee JH, et al. Warfarin use in patients with atrial fibrillation undergoing hemodialysis: a nationwide population-based study. Stroke 2017;48:2472–9.

32. Seliger SL, Gillen DL, Tirschwell D, Wasse H, Kestenbaum BR, Stehman-Breen CO. Risk factors for incident stroke among patients with end-stage renal disease. J Am Soc Nephrol 2003;14:2623–31.

33. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.

34. Harel Z, Chertow GM, Shah PS, et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis. A systematic review and meta-analysis. Can J Cardiol 2017;33:737–46.

35. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. J Am Coll Cardiol 2011;57:1339–48.

36. Al-ani M, Parperis K. Warfarin-induced calciphylaxis. BMJ Case Rep 2016;2016.

37. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. J Am Soc Nephrol 2001;12:326–32.

38. Yang F, Hellyer JA, Than C, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. Heart 2017;103:818–26.

39. Tan J, Liu S, Segal JB, Alexander GC, McAdams-DeMarco M. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. BMC Nephrol 2016;17:157.

40. Wong CX, Odutayo A, Emdin CA, Kinnear NJ, Sun MT. Meta-analysis of anticoagulation use, stroke, thromboembolism, bleeding, and mortality in patients with atrial fibrillation on dialysis. Am J Cardiol 2016;117:1934–41.

41. Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, Kaewput W, Pachariyanon P, Cheungpasitporn W. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: meta-analysis. Pacing Clin Electrophysiol 2018;41:627–34.

42. Connolly SJ. Anticoagulant-related bleeding and mortality. J Am Coll Cardiol 2016;68:2522–4.

KEY WORDS anticoagulant, atrial fibrillation, dialysis, network meta-analysis

APPENDIX For supplemental figures, please see the online version of this paper.