Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Research Article

Canadian Journal of Kidney Health and Disease
Volume 4: 1–13

DOI: 10.1177/2054358117735532
journals.sagepub.com/home/cjk
SAGE

Warfarin Use in Hemodialysis Patients With Atrial Fibrillation: A Systematic Review of Stroke and Bleeding Outcomes

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Abstract

Background: Given the lack of clear indications for the use of warfarin in the treatment of atrial fibrillation (AF) in patients on hemodialysis and the potential risks that accompany warfarin use in these patients, we systematically reviewed stroke and bleeding outcomes in hemodialysis patients treated with warfarin for AF.
Objective: To systematically review the stroke and bleeding outcomes associated with warfarin use in the hemodialysis population to treat AF.
Design: Systematic review.
Setting: All adult hemodialysis patients.
Patients: Patients on hemodialysis receiving warfarin for the management of AF.
Measurements: Any type of stroke and/or bleeding outcomes.
Methods: MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) via OVID (1946 to January 11, 2017), and EMBASE via OVID (1974 to January 11, 2017) were searched for relevant literature. Inclusion criteria were randomized controlled trials, observational studies, and case series in English that examined stroke and bleeding outcomes in adult population of patients (over 18 years old) who are on hemodialysis and taking warfarin for AF. Studies with less than 10 subjects, case reports, review articles, and editorials were excluded. Quality of selected articles was assessed using Newcastle-Ottawa Scale (NOS).
Results: Of the 2340 titles and abstracts screened, 7 met the inclusion criteria. Two studies showed an association between warfarin use and an increased risk of stroke (Hazard Ratio: 1.93-3.36) but no association with an increased risk of bleed (HR: 0.85-1.04), while 4 studies showed no association between warfarin and stroke outcomes (HR: 0.12-1.17) but identified an association between warfarin and increased bleeding outcome (HR: 1.41-3.96). And 1 study reported neither beneficial nor harmful effects associated with warfarin use.
Limitations: The major limitation to this review is that the 7 included studies were observational cohort studies, and thus the outcome measures were not specified and predetermined in a research protocol.
Conclusion: Our systematic review demonstrated that for patients with AF who are on hemodialysis, warfarin was not associated with reduced outcomes of stroke but was rather associated with increased bleeding events.

Abrégé

Contexte: En l'absence d'un protocole clair quant à l'utilisation de la warfarine pour le traitement de la fibrillation auriculaire chez les patients hémodialysés, et étant donné les risques potentiels inhérents à son utilisation chez cette population, nous avons procédé à un examen systématique des cas d'hémorragies et d'accidents vasculaires cérébraux (AVC) chez ces patients.
Objectif de l'étude: Notre objectif était de procéder à un examen systématique des cas d'hémorragie ou d'AVC associés à la prise de warfarine pour le traitement de la fibrillation auriculaire chez les patients hémodialysés.
Type d'étude: Il s'agit d'une revue systématique.
Cadre de l'étude: Tous les patients adultes traités par hémodialyse
Patients: Des patients adultes hémodialysés et prenant de la warfarine pour traiter la fibrillation auriculaire.
Mesures: On a répertorié tout type d'hémorragies ou d'AVC.
Méthodologie: Les bases de données MEDLINE[MD] par OVID (de 1946 au 11 janvier 2017) et EMBASE par OVID (de 1974 au 11 janvier 2017), de même que les autres citations et éditoriaux en cours ou non indexés sur MEDLINE[MD] ont été passés en revue afin d'en tirer les documents pertinents. Ont été inclus tous les essais contrôlés à répartition aléatoire, les études observationnelles et les séries de cas rédigés en anglais et examinant une forme ou une autre d'hémorragie ou d'AVC, chez

une population de patients adultes hémodialysés et traités par warfarine pour une fibrillation auriculaire. Les études menées sur moins de 10 sujets, les rapports de cas de même que les articles et éditoriaux de synthèse étaient exclus de l'étude. On a évalué la qualité des articles sélectionnés avec l'échelle de Newcastle-Ottawa.

Limites: La principale limite de notre étude est le fait que sept des études retenues étaient des études de cohorte observationnelles, et que, par conséquent, les résultats cliniques n'étaient ni précisés ni prédéterminés par un protocole de recherche.

Conclusion: Notre revue systématique a démontré que chez les patients hémodialysés et atteints de fibrillation auriculaire, la warfarine n'était pas associée à une réduction des AVC, mais qu'en contrepartie, elle était liée à une augmentation des événements hémorragiques.

Keywords
warfarin, atrial fibrillation, hemodialysis, bleeding, stroke

Received March 30, 2017. Accepted for publication August 18, 2017.

What was known before

There are currently several meta-analyses closely related to our topic of review, investigating the risk of stroke and bleeding in hemodialysis patients taking warfarin for atrial fibrillation, which concluded a lack of association between warfarin use and stroke reduction but rather an association with increased risk of bleeding. These meta-analyses synthesized study outcomes of widely varied definitions, studies with different adjustments for differed covariates, and studies that encompass various renal replacement therapies, and therefore these meta-analyses resulted in a high heterogeneity.

What this adds

We conducted a thorough systematic review that focuses solely on warfarin use in hemodialysis patients with atrial fibrillation. We determined warfarin was not beneficial in reducing stroke risks but was rather associated with a higher bleeding risk. This systematic review provides insights to difficulties, limitations, and biases in the synthesis of studies assessing the stroke and bleeding risks associated with warfarin use in hemodialysis patients with atrial fibrillation.

Introduction

The prevalence of atrial fibrillation (AF) is 14% to 27% in patients on long-term hemodialysis (HD) compared with a prevalence of 2% to 3% in the general population.[1] Stroke is a common and frequent complication of AF, and HD patients with AF are twice as likely to develop strokes than the general AF population. Chronic kidney disease (CKD) complicates AF-related prothrombotic and hypercoagulable states in the AF population by the change in left atrial blood flow, endothelial dysfunction, and platelet hyperaggregability; this increases the risk of thromboembolism-related adverse events together with the traditional AF risk factors such as hypertension and diabetes.[2-4] Furthermore, there is an elevated risk of bleeding in patients on HD due to several factors, including heparin use during dialysis and impaired platelet function secondary to uremia. Thus, patients on HD have a 3 to 10 times higher risk of bleeding compared with the general population.[5]

Oral anticoagulants, specifically warfarin, are frequently used to treat AF in both the general and HD population. In the general population, patients with AF who are treated with warfarin have a 64% risk reduction of stroke with a small increase of bleeding of 1% to 1.4% per year.[6] However, in HD patients the risk-to-benefit trade-off between stroke prevention and bleeding risk is conflicting, and clinical guidelines vary in their recommendations for the use of warfarin. The 2016 Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation suggested HD patients should not routinely receive warfarin for AF while the American College of Cardiology and American Heart Association in 2016 continued to recommend warfarin use with acceptable risks of hemorrhage. The European Society of Cardiology did not make a direct recommendation in their

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newest 2016 Guidelines but rather suggested further controlled studies on warfarin and direct oral anticoagulants (DOACs) are required.[7-9] Although DOACs including dabigatran, rivaroxiban, and apixaban have been shown to have equivalent efficacy and safety profile compared with warfarin for stroke prevention and rates of major bleeding in the general AF population, there are limited studies looking at the pharmacokinetics, pharmacodynamics, and the use of these newer oral anticoagulants in the HD population. Although apixaban is currently the only DOAC approved for use in HD patients in the United States, this approval was based on a single dose trial in 8 patients.[10] Therefore, HD patients with AF are left with warfarin as their primary antithrombotic therapy. Unfortunately, the rate of major bleeding in HD patients increases 10-fold when treated with warfarin.[11] Furthermore, warfarin use may be associated with an increased risk of calciphylaxis and accelerated vascular calcification in dialysis patients.[12,13]

Although several observational studies have described the role of warfarin in dialysis patients with AF, the clinical risk-benefit for stroke prevention has not been fully clarified in these studies.[14-16] Therefore, given the lack of clear benefits for warfarin treatment and the potential risks of bleeding in HD patients, we conducted a systematic review to better understand the stroke and bleeding outcomes associated with warfarin use in the HD population to treat AF.

Methods

Information Sources and Search Strategy

We searched the following databases without any limitations under the guidance of a research librarian from University Health Network: MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) via OVID (1946 to January 11, 2017), and EMBASE via OVID (1974 to January 11, 2017). Literature search strategies were developed using MeSH and text words related to HD and warfarin and their respective combinations (Appendix A). The electronic database search was supplemented by manual search through Google scholar, reference lists of identified seminal studies and gray literature sources from World Health Organization (WHO) website, dissertation websites, World Wide Science.org, and US Federal Science (science.gov) to identify relevant studies. Two study personnel (S.T. and L.Q.M.) independently reviewed titles and abstracts and those that met the eligibility criteria were included for full text review. Another member of the research team (M.B.) resolved disputes.

Study Selection

We included randomized controlled trials (RCTs) and observational studies, including prospective and retrospective cohort studies and case series in our search. We excluded studies with less than 10 subjects, case reports, review articles, and editorials. Studies in English that examined adult population of patients (over 18 years old) who were on HD were included. We included studies if they reported and compared any types of stroke and bleed outcomes in warfarin users against warfarin nonusers.

Data Extraction and Synthesis

Search results were exported as RIS file into Covidence, an Internet-based systematic review software that facilitates collaboration between reviewers during literature screening process (2015, Melbourne). Two reviewers, L.Q.M. and S.T., screened the uploaded articles on Covidence according to the eligibility criteria. Following the selection of relevant studies, 2 reviewers, S.T. and P.P., independently extracted data from included studies directly into a pilot Excel data extraction form developed by the reviewers. Any disagreements were resolved by discussion and consensus.

Extracted data included population characteristics: average age, sex, antithrombotic medications, warfarin target or intensity, adherence to warfarin, comorbidities, CHA_2DS_2-VASc score, and HAS-BLED score. For the outcomes of our study, we extracted the definitions, types and severity of stroke and bleed, and the number/rate/risk of stroke and bleed. We also extracted the study characteristics: study methodology and design, total number of patients, follow-up, type and source of financial support, and publication status of the included studies. Meta-analysis was not conducted due to the heterogeneity of the studies.

Risk of Bias in Individual Studies

Due to the nonrandomized nature of the included studies, the quality of selected articles from full text review was assessed using the Newcastle-Ottawa Scale (NOS) based on 3 broad categories: the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest.[17] The NOS assessed the quality of nonrandomized studies with a star system in which a study was awarded a range of 0 to 9 stars based on these 3 broad categories, the more stars awarded the higher the quality of the study.[17] S.T. and P.P. independently assessed the quality of eligible studies using NOS, and any disagreements were resolved by discussion.

Results

Study Yield

The initial search yielded 2781 articles (Figure 1). After removing duplicates, 2340 titles and abstracts were initially screened; 2305 articles were excluded for being irrelevant to warfarin use in HD or because they were reviews, editorials, or case reports. Thirty-five articles were relevant to warfarin use in dialysis patients with AF. Of these,

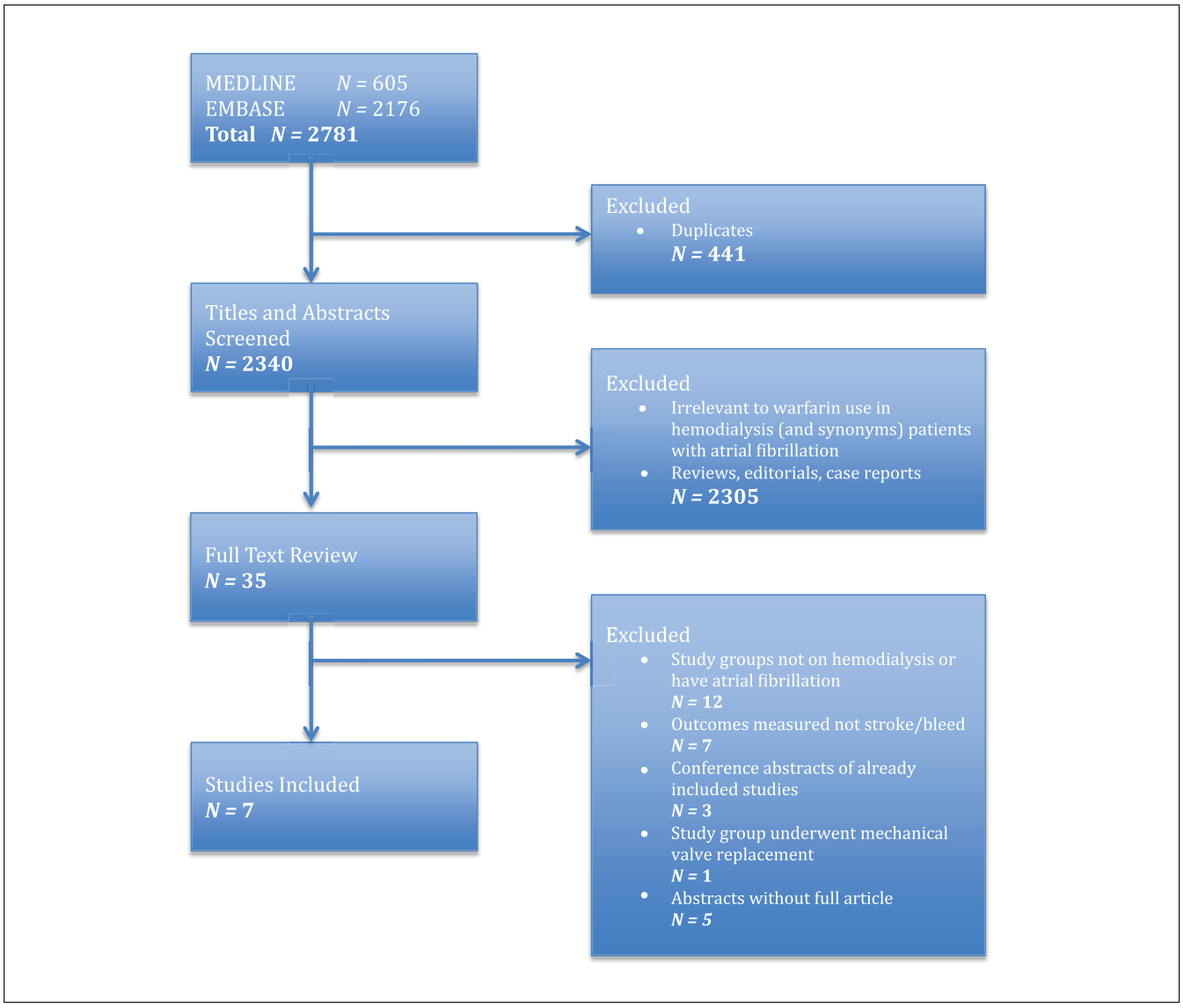

Figure 1. Flow diagram of study selection.

12 studies did not identify subjects who are on HD or have AF as an indication for warfarin, 7 studies did not report stroke and bleeding as outcomes, 3 studies were conference abstracts of already included studies, 1 study reported warfarin use for patients that underwent mechanical heart valve replacement, and 5 abstracts did not have sufficient data for inclusion. The remaining 7 articles met the inclusion criteria.

Systematic Reviews

We identified 7 meta-analyses closely related to the topic of our review, evaluating the risk of stroke and bleeding associated with warfarin use in end-stage renal disease patients with AF.[18-24] These 7 meta-analyses described outcomes differently and therefore produced results with high heterogeneity. Five studies described high heterogeneity on the risk of ischemic stroke and thromboembolism ranging from I^2 = 55.6%-90%, while 2 meta-analyses reported all-cause stroke encompassing hemorrhagic strokes with moderately high study heterogeneity ranging from I^2 = 53.5%-68.1%.[18-24] On the contrary, study heterogeneity on risk of bleeding in these 7 meta-analyses ranged from I^2 = 20.4%-69%.[18-24] This study heterogeneity may be attributed to differences in study design, study population, definition of outcomes, and adjustment for different covariates. Finally, all meta-analyses pooled patients undergoing peritoneal dialysis and kidney transplants together with HD patients. Patients with CKD present widely variable kidney functions which influences warfarin responsiveness and hemorrhagic complications.[25] Therefore, we did not include these patients in our review as it could contribute to heterogeneity of study outcomes measured.

Table 1. Study Characteristics.

Reference	Study design	Mean follow-up (years)	Warfarin treatment group (number of patients)	Comparison group (number of patients)	Age, year (SD)	Male, n (%)	Ascertainment of exposure
Chan et al[14]	Retrospective cohort study	2	508	480	72.6 (1.01)	922 (55.2)	Electronic medical record from Fresenius Medical Care North America dialysis clinics
Garg et al[29]	Retrospective cohort study	2	119	183	77 (7)	160 (53)	No description
Genovesi et al[26]	Prospective cohort study	2	134	156	<65 (20.5%), 65 (26.2%), >75 (53.3%)	174 (60.3)	Clinical charts, no further description
Wakasugi et al[28]	Prospective cohort study	3	28	32	68.1 (8.95)	39 (64.5)	No description
Winkelmayer et al[27]	Retrospective cohort study	12	237	948	68.9 (12.1)	508 (42.2)	US renal data system and health claims from Medicare
Shen et al[16]	Retrospective cohort study	5	1838	10 446	62 (6.3)	6000 (48.8)	US renal data system, medical evidence report, and Medicare claims data
Yodogawa et al[30]	Retrospective cohort study	4	30	54	70.1 (10.4)	59 (70.2)	No description

Study Characteristics

We outlined the references, study design, mean follow-up time, treatment and control groups, and the ascertainment of exposure from the 7 included studies in Table 1. There were 5 retrospective cohort studies and 2 prospective cohort studies.[14,16,26-30] A total number of 15 193 patients with AF undergoing HD were included in this systematic review, with 2894 warfarin users. Study sample sizes ranged from 28 to 1838 patients exposed to warfarin. Four studies were conducted in the United States, 1 in Italy, and 2 in Japan. The mean follow-up duration ranged from 2 to 12 years. With the exception of Winkelmayer et al and Shen et al, studies reported a history of strokes (definitions not specified) of 6% to 20.1% before study entry, and with the exception of Chan et al, Garg et al, and Shen et al, studies reported a history of bleeding (definitions not specified) of 3% to 11.9% before study entry in HD patients with AF being treated with warfarin. Included studies were heterogeneous with respect to the definitions of the bleeding and stroke outcomes.

Quality Assessment

Assessment of quality of included studies using the NOS resulted in high-quality studies with one 8-star study, four 7-star studies, and two 5-star studies (Appendix B).

Stroke Outcomes

Studies included in our systematic review varied with regard to the stroke outcome end points (Table 2). Five studies reported ischemic stroke end point,[14,16,27-29] 1 reported ischemic stroke or thromboembolic pulmonary disease,[26] while 1 reported the first hospital admission of stroke without elaboration.[29] Of the 5 studies that reported ischemic stroke end points,[14,16,27-29] 1 specified the primary outcome as death or hospitalization from new (ischemic) stroke but also considered transient ischemic attacks as part of this primary outcome due to similar management of stroke prevention regardless of diagnosis.[14] Another study defined ischemic strokes as occlusion and stenosis of carotid artery, cerebral embolism, and acute but ill-defined cerebrovascular disease,[27] while the 2 other studies that reported ischemic stroke end points were the only ones to report confirmation of stroke end points by imaging.[28,29] Shen et al also reported any stroke or stroke death.[16] In 2 of the 5 studies that reported ischemic stroke end points, warfarin was shown to be associated with higher stroke incidence rate compared with no warfarin use. One study showed the stroke incidence rate for warfarin of 14.8 compared with the control arm of 8.9 total events per 100 person-years, albeit with a large confidence interval of 0.67 to 16.66,[28] while the other study demonstrated an increase in incidence of stroke with warfarin of 7.1 vs the control arm of 2.9 total events per 100 person-years (confidence interval [CI] of 1.11-2.72).[14]

Table 2. Included Studies of Warfarin Anticoagulation in Hemodialysis Patients With AF: Stroke Outcomes.

Reference	Definition of strokes	Analysis	Total events per 100 person-years: Treatment group	Total events per 100 person-years: Comparison group	Hazard ratio of stroke risk: Warfarin use vs nonuse (95% CI)
Chan et al[14]	New strokes (ischemic)	ITT	7.1	2.9	1.74 (1.11-2.72)[a]
Garg et al[29]	Ischemic stroke requiring hospitalization for focal neurologic deficit and have evidence of acute ischemia on brain imaging	N/A	5.2	5.5	0.93 (0.49-1.82)[b]
Genovesi et al[26]	Ischemic strokes or thromboembolic pulmonary disease	N/A	4.6	7.3	0.12 (0.00-3.59)
Wakasugi et al[28]	Ischemic stroke: rapid onset focal neurologic deficit persisting for >24 hours confirmed by imaging techniques	ITT	14.8	8.9	3.36 (0.67-16.66)[a]
Winkelmayer et al[27]	Ischemic stroke (ICD-9: 433x1, 434x1, 436)	ITT	7.4	7.8	0.92 (0.61-1.37)[a]
Shen et al[16]	Ischemic stroke	AT60	2.7	3.7	0.73 (0.44-1.20)[c]
	Any stroke or stroke death		5.0	5.2	0.87 (0.57-1.32)[c]
Yodogawa et al[30]	First hospital admission of stroke	N/A	1.7	2.4	1.07 (0.2-5.74)[b]

Note. AF = atrial fibrillation; CI = confidence interval; ITT = intention to treat; ICD-9 = *International Classification of Diseases, Ninth Revision*; AT60 = as-treated analysis (patients censored 60 days after drug supply ran out); N/A = not available.
[a]Propensity score-adjusted HR.
[b]Adjusted for CHA_2DS_2-VASc score.
[c]Stratified Cox by year of atrial fibrillation diagnosis.

The 5 other studies illustrated no association between warfarin use and increased risk of reported types of strokes, with incidence rate ranging from 1.7 to 7.4 total events per 100 person-years in warfarin users and 2.4 to 7.8 total events per 100 person-years in warfarin nonusers.[16,26,27] Besides Shen et al, who concluded a marginal association between warfarin use and decrease risk of ischemic strokes, all authors concluded that warfarin is not beneficial in reducing stroke outcomes.

Bleeding Outcomes

Definitions of bleeding end points also varied significantly between studies (Table 3). In terms of bleeding end points, 1 study reported both hemorrhagic stroke and gastrointestinal bleeding end points[27] and 1 reported confounder adjusted hemorrhagic events end point without further specification on the confounders or hemorrhagic events.[26] Five studies reported hospitalizations due to bleeding[14,16,28-30]; however, 1 study reported unadjusted incidence rate and hazard ratios of major bleeding events without further specification.[28] Of the other 4 studies that reported hospitalizations due to bleeding, Shen et al reported bleeding outcome as severe gastrointestinal bleeding reported as cause of death or requiring hospitalization.[16] On the contrary, Chan et al reported incidence of hospitalization from bleeding as a survival and hospitalization analysis associated with stroke instead of a primary outcome where intensity or types of bleed was not specified.[14] Study by Garg et al reported bleeding outcomes as major bleeding from any sites that required hospitalization or blood transfusion and intracranial bleeding detected from brain imaging.[29] Last, study by Yodogawa et al reported bleeding end points as first hospital admission for bleeding without further elaboration.[30]

Three of the studies did not draw conclusions on the bleeding outcomes associated with warfarin usage.[14,28,30] Results from these 3 studies suggested no association between warfarin use and bleeding events. The incidence rates of bleeding events that required hospitalizations were reported, respectively, as follow: 0.09 per 100 person-years in warfarin users vs 0.07 per 100 person-years in warfarin nonusers in Chan et al (HR: 1.04; 95% CI, 0.73-1.46), 5.3 per 100 person-years in warfarin users vs 6.6 per 100 person-years in warfarin nonusers in Wakasugi et al (HR: 0.85; 95% CI, 0.19-3.64), and 2.6 per 100 person-years in warfarin users vs 0.5 per 100 person-years in warfarin nonusers in Yodogawa et al.[14,30] Yodogawa et al reported a lack of association between warfarin use and a statistically significant increase in bleeding risk despite observing a higher bleeding incident rate in the warfarin treatment group. This is likely due to an overall low rate of bleeding in the study population.[30] The other 3 studies confirmed an association between warfarin use and increased bleeding outcomes in HD patients with AF with hazard ratios of hemorrhagic risk ranging from 1.53 to 3.96.[26,27,29] Shen et al (HR: 1.36; 95% CI, 0.89-2.07) identified a marginal association between warfarin use and increased gastrointestinal bleeding.[16]

Table 3. Included Studies of Warfarin Anticoagulation in Hemodialysis Patients With AF: Bleeding Outcomes.

Reference	Definition of bleeding	Analysis	Total events per 100 person-years: Treatment group	Total events per 100 person-years: Comparison group	Hazard ratio of hemorrhagic risk: Warfarin use vs nonuse (95% CI)
Chan et al[14]	Hospitalizations and Mortalities as a result of bleeds	ITT	0.09, hospitalizations 0.41, mortalities	0.07, hospitalizations of warfarin nonusers 0.37, mortalities of warfarin nonusers	1.04 (0.73-1.46),[a] hospitalizations 1.24 (0.26-5.87),[a] mortalities
Garg et al[29]	Major hemorrhage/bleeding from any site requiring hospitalization or blood transfusion; evidence of intracranial bleeding on brain imaging	N/A	10.4, major bleeding 4.4, intracranial bleeding	6.8, major bleeding 2.1, intracranial bleeding	1.53 (0.94-2.51),[b] major bleeding
Genovesi et al[26]	Hemorrhagic events	N/A	Not specified	Not specified	3.96 (1.15-13.68)
Wakasugi et al[28]	Major bleeding defined as fatal bleeding or bleeding that required hospitalization	ITT	5.3	6.6	0.85 (0.19-3.64)
Winkelmayer et al[27]	Hemorrhagic stroke (ICD-9: 430 to 432); GI hemorrhage	ITT	2.6, hemorrhagic stroke 13.4, GI hemorrhage	1.1, hemorrhagic stroke 13.6, GI hemorrhage	2.38 (1.15-4.96), hemorrhagic stroke 0.96 (0.70-1.31), GI hemorrhage
Shen et al[16]	GI bleeding as reported cause of death or required hospitalization	AT60	9.0	6.0	1.36 (0.89-2.07)[c]
Yodogawa et al[30]	First hospital admission of bleed	N/A	2.6	0.5	Not specified

Note. AF = atrial fibrillation; CI = confidence interval; ITT = intention to treat; ICD-9 = *International Classification of Diseases, Ninth Revision*; GI = gastrointestinal; AT60 = as-treated analysis (patients censored 60 days after drug supply ran out).
[a]Propensity score-adjusted HR.
[b]Adjusted to HAS-BLED score.
[c]Stratified Cox by year of AF diagnosis.

Discussion

This systematic review synthesized the evidence of stroke and bleeding outcomes associated with warfarin anticoagulation in HD patients with AF. Of the 7 included studies, 2 were prospective and 5 were retrospective cohort studies. The results from these 7 studies suggested no association between warfarin use and reduction of ischemic stroke; however, the studies suggested a possible association with an increased risk of hemorrhagic events with the use of warfarin. In this systematic review of 7 studies, bleeding risk was increased in 4 and unchanged in 3 studies, while stroke risk was increased in 2 studies, decreased in 2, and unchanged in 3 studies.

A possible explanation for the lack of benefit of warfarin on reduction of ischemic strokes may be secondary to confounding factors in these studies. Although most studies included in this systematic review conducted propensity score matching analysis, they were matched based on different confounding factors, and thus the propensity score matching may have not accounted for all the biases. For example, Wakasugi et al performed Cox regression analyses using propensity score which considered patients' probability of exposure to confounding variables, such as age, gender, dialysis vintage, height, etiology of end-stage renal disease, dialysis facilities, and type of vascular access, while Genovesi et al used propensity score analysis which considered confounding variables such as antiplatelet therapy, age, permanent AF, hypertension, and heart failure (Table S1).[26,28] The residual confounding also explains the heterogeneity between studies and may result in an over or under estimation of the observed increased bleeding risk and lack of stroke reduction associated with warfarin use. Furthermore, because studies differed in the covariates used for propensity score adjustment, the differences in the baseline comorbidities and history of strokes and bleeding in the different studies may have affected direct comparison of stroke and bleeding outcomes. Last, the studies did not address risks of stroke during warfarin initiation (first 30 days) when patients were at the highest risk of stroke due to a transient hypercoagulable state.[28] Another reason for increased risk of strokes associated with warfarin use in the 2 studies may be attributed to inadequate dosage of warfarin or noncompliance. Patients from the Wakasugi et al study had a mean baseline INR (International Normalized Ratio) of 1.5 ± 0.4 as opposed to the recommended target range of INR, between 2.0 and 3.0.[14,28] Furthermore, most of the studies either did not report the INR or was not properly reported. For example, 1 study reported a mean INR of 1.62 ± 0.45, which was only measured once in patients.[30] Therefore, the potential subtherapeutic INRs may be one of the reasons that warfarin was not successful in decreasing stroke outcomes.

Four of the 7 studies observed an association between warfarin use and increased risk of bleeding.[16,26,27,29] Of the 4 studies, 3 reported concurrent use of antiplatelet agents.[16,26,29] However, concurrent use of antiplatelet agents does not appear to be correlated with the increased risk of bleeding in warfarin users as a higher percentage of warfarin nonusers than warfarin users were using antiplatelet agents concurrently.[16,26] Although patients taking anticoagulants are at an increased risk of bleeding, there are potentially other reasons for increased bleeding in dialysis patients. In addition to the anticoagulation effect, the reported higher bleeding outcome may be partially secondary to multifactorial alterations in the coagulation system, as well as defects in platelet secretion, aggregation, and altered interactions between the platelet and the endothelial cells, which are thought to be due to uremia.[31,32,33] Heparin used during dialysis may also contribute to the increased risk of bleeding and hemorrhagic stroke in patients who are also taking warfarin because of an additive anticoagulant response that increases INR.[33,34]

A large retrospective study of 41 425 patients with incident HD but not necessarily AF, which was not included in this systematic review, found that several therapies were associated with increased mortality.[35] Exposure to warfarin and clopidogrel was associated with a significant increase in crude mortality and hospitalization rates from bleeding, and these results remained significant following covariate and propensity score-adjusted analysis.[35] There was a significant association between warfarin use and increased mortality due to bleeding. However, in terms of all-cause mortality, all studies included in this systematic review besides one (HR: 0.84, CI, 0.73-0.97)[16] suggested no significant association between warfarin use and a difference in mortality (Table S2).

Current Canadian Cardiovascular Society Guidelines for management of AF strongly recommend the use of dabigatran, rivaroxaban, apixaban, or edoxaban (when approved) in preference to warfarin for patients with nonvalvular AF, without CKD.[36] The DOACs, dabigatran, apixaban, and rivaroxaban, have been demonstrated in large, blinded, RCTs involving more than 70 000 patients to be noninferior or superior to warfarin for the outcome of all stroke or systemic embolism in the general population with AF.[37-41] None of them caused more major bleeding than warfarin and all were superior for the outcome of intracranial hemorrhage.[36] Therefore, with the numerous RCTs and meta-analysis performed to date, clinicians and patients are able to make informed decisions about the management of AF-related stroke risk in the general population. However, the HD population is left with warfarin as their best AF treatment option as there are limited studies evaluating the safety profile, pharmacokinetics, and pharmacodynamics of the DOACs in HD patients with AF. Patients on HD were largely excluded from clinical trials evaluating stroke preventions by DOACs because they are contraindicated for patients with stage 5 CKD or for patients on HD in Canada. Despite contraindications and the lack of evidence of the DOACs in HD patients, recently, more HD patients are being started on rivaroxaban and dabigatran even when suggested otherwise.[42] Chan et al evaluated the use of dabigatran and rivaroxaban in HD patients and showed an association between dabigatran (rate

ratio, 1.78; 95% CI, 1.18-2.68; $P = .006$) and rivaroxaban (rate ratio, 1.71; 95% CI, 0.94-3.12; $P = .07$) use and an increased risk of hemorrhagic deaths compared with warfarin.[42] Apixaban use in HD patients was recently approved in the United States based on limiting data from a single dose trial at 5 mg twice a day in 8 patients.[10] This study observed a 36% increase in apixaban area under the plasma concentration-versus-time curve AUC (Area Under the Curve) no increase in maximum observed plasma concentration, and limited effects on apixaban clearance due to HD.[10] However, even more recently Mavrakana et al observed in 5 patients that 2.5 mg of apixaban twice daily in HD patients may potentially replace warfarin for stroke prevention as it resulted in comparable drug exposure with that of standard dose (5 mg twice daily) in the general population.[43] Perhaps with further investigation in a larger cohort of patients on HD and assessing clinical outcomes, apixaban use will be approved in Canada in the near future. Until further studies, ideally RCTs, on the management of AF in HD patients are conducted, clinicians must balance the risks of stroke against the risks of bleeding prior to warfarin prescription.

Limitations

The major limitation to this review is that the 7 included studies were observational cohort studies, and thus the outcome measures of stroke and bleed were not specified and predetermined in a research protocol but were rather abstracted from clinical charts and electronic databases. These type of studies result in possible indication bias during charting as caregivers may preferentially record strokes and bleeding events of patients who are known to be anti-coagulated with warfarin or high-risk patients who are more likely to be on warfarin; judgment on severity of bleed may also be affected by predisposed knowledge of patients' anti-coagulating status. Moreover, because only 1 study classified ischemic strokes based on a neuroimaging confirmatory test, diagnosis of stroke may not be accurate. Last, in addition to the wide confidence interval of reported HR of strokes and bleeding risks, the differences in definitions and reporting of outcomes make direct comparison difficult.

Conclusion

Our systematic review of 7 observational studies suggested a lack of association between warfarin use and reduced stroke outcome but an increased bleeding outcome in patients with AF who are on HD. Clinical decision to prescribe warfarin for patients undergoing HD should be considered carefully and tailored to individuals based on their history of strokes and bleed, CHA_2DS_2-VASc and HAS-BLED scores, as well as other comorbidities.

Appendix A

List of Keywords Entered Into the Medline and EMBASE Search Engines via OVID.

No.	Searches	Results
1	exp Warfarin/	15 747
2	warfarin.mp.	23 304
3	"2H-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-".mp.	0
4	"4-hydroxy-3-(3-oxo-1- phenylbutyl)-2h-1-benzopyran-2-one".mp.	3
5	warfant.mp.	0
6	apo-warfarin.mp.	1
7	gen-warfarin.mp.	0
8	tedicumar.mp.	0
9	"1 (4' hydroxy 3' coumarinyl) 1 phenyl 3 butanone".mp.	1
10	"3 (alpha acetonylbenzyl) 4 hydroxycoumarin".mp.	8
11	"3 acetonylbenzonyl 4 hydroxy coumarinedimethylaminoethanol".mp.	0
12	"3 alpha phenyl beta acetylethyl 4 hydroxycoumarin".mp.	1
13	acetonylbenzylhydroxycoumarin.mp.	0
14	adoisine.mp.	1
15	aldocumar.mp.	2
16	"alpha acetonylbenzyl 4 hydroxycoumarin dimethylaminoethanol".mp.	2
17	"antrombin k".mp.	0
18	athrombin.mp.	0
19	"athrombine k".mp.	0
20	athrombinek.mp.	0
21	befarin.mp.	0
22	carfin.mp.	0
23	circuvit.mp.	0

(continued)

Appendix A. (continued)

No.	Searches	Results
24	"compound 42".mp.	36
25	coumadan.mp.	0
26	coumadin.mp.	939
27	coumadine.mp.	20
28	coumafene.mp.	2
29	coumaphene.mp.	1
30	dagonal.mp.	0
31	farin.mp.	10
32	jantoven.mp.	0
33	kumatox.mp.	0
34	maforan.mp.	0
35	marevan.mp.	16
36	orfarin.mp.	0
37	panwarfarin.mp.	0
38	panwarfin.mp.	11
39	prothromadin.mp.	0
40	"simarc-2 sodium warfarinum".mp.	0
41	sofarin.mp.	8
42	tintorane.mp.	0
43	uniwarfin.mp.	0
44	wafarin.mp.	12
45	waran.mp.	10
46	"warf compound 42".mp.	0
47	warfar.mp.	1
48	"warfarin 2 (dimethylamino)ethanol".mp.	0
49	warfarine.mp.	31
50	warfarinum sodium.mp.	1
51	"warfil 5".mp.	0
52	warfilone.mp.	0
53	warnerin.mp.	5
54	(warfarin adj sodium).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	554
55	(warfarin adj potassium).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	41
56	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	23 780
57	exp Kidney Failure, Chronic/	81 433
58	exp Renal Dialysis/	98 049
59	hemodialy*.mp.	54 093
60	haemodialy*.mp.	13 188
61	ESRD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	11 709
62	(end stage adj2 renal*).mp.	28 808
63	(end-stage adj5 renal*).mp.	29 121
64	(end stage adj2 kidney*).mp.	1969
65	(end-stage adj5 kidney*).mp.	3097
66	renal dialy*.mp.	78 779
67	(kidney failure adj5 chronic).mp.	81 736
68	(renal failure adj5 chronic).mp.	22 702
69	kidney dialy*.mp.	193
70	ckd.tw.	15 208
71	chronic kidney disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	25 383
72	or/57-71	1 85 436
73	56 and 72	507
74	remove duplicates from 73	503

Appendix B

Risk of Bias Assessment Using Newcastle-Ottawa Scale for Observational Study.

	Selection				Comparability		Outcomes		
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Reference	Representative or somewhat representative of average dialysis patients in community (age/sex/being at risk of disease)	Drawn from same community as exposed cohort	Secured records, Structured interview	Stroke or bleeding due to warfarin use in atrial fibrillation patients on hemodialysis	Study controls for age	Study controls for any additional factors (history and risk factors of stroke and bleeding)	Independent blind assessment or record linkage	Follow-up >1 year	Complete follow-up (all subjects accounted for) or subjects lost to follow-up unlikely to introduce bias
Chan et al, 2009	[a]	[a]	[a]	—	[a]	[a]	—	[a]	[a]
Winkelmayer et al, 2011	[a]	[a]	[a]	—	[a]	[a]	—	[a]	[a]
Shah et al, 2014	[a]	[a]	[a]	—	[a]	[a]	—	[a]	[a]
Wakasugi et al, 2014	[a]	[a]	[b]	—	[a]	[a]	—	[a]	[a]
Genovesi et al, 2015	[a]	[a]	[a]	—	[a]	[a]	—	[a]	[a]
Garg et al, 2016	[a]	[a]	[b]	—	—	[a]	—	[a]	[a]
Yodogawa et al, 2016	[a]	[a]	[b]	—	—	[a]	—	[a]	[a]

[a]A study can be awarded a maximum of 1 star for each category.
[b]Uncertain.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Supplementary Material Table S1: Statistical model Types Used and Covariates Adjusted for in Models in Included Studies of Warfarin Anticoagulation in HD Patients with AF.
Supplementary Material Table S2: Included Studies of Warfarin Anticoagulation in HD Patients with AF: All Cause Mortality Outcomes.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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