Warfarin Use and the Risk for Stroke and Bleeding in Patients With Atrial Fibrillation Undergoing Dialysis

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Background—Current observational studies on warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation (AF) undergoing dialysis found conflicting results.

Methods and Results—We conducted a population-based retrospective cohort study of patients aged ≥65 years admitted to a hospital with a primary or secondary diagnosis of AF, in Quebec and Ontario, Canada from 1998 to 2007. The AF cohort was grouped into dialysis (hemodialysis and peritoneal dialysis) and nondialysis patients and into warfarin and no-warfarin users according to the first prescription filled for warfarin within 30 days after AF hospital discharge. We determined the association between warfarin use and the risk for stroke and bleeding in dialysis and nondialysis patients. The cohort comprised 1626 dialysis patients and 204 210 nondialysis patients. Among dialysis patients, 46% (756/1626) patients were prescribed warfarin. Among dialysis patients, warfarin users had more congestive heart failure and diabetes mellitus, but fewer prior bleeding events in comparison with the no-warfarin users. Among dialysis patients, warfarin use, in comparison with no-warfarin use, was not associated with a lower risk for stroke (adjusted hazard ratio, 1.14; 95% confidence interval, 0.78–1.67) but was associated with a 44% higher risk for bleeding (adjusted hazard ratio, 1.44; 95% confidence interval, 1.13–1.85) after adjusting for potential confounders. Propensity score–adjusted analyses yielded similar results.

Conclusions—Our results suggest that warfarin use is not beneficial in reducing stroke risk, but it is associated with a higher bleeding risk in patients with AF undergoing dialysis. **(*Circulation*. 2014;129:1196-1203.)**

Key Words: atrial fibrillation ■ dialysis ■ hemorrhage ■ stroke ■ warfarin

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Patients with atrial fibrillation (AF) who have severe chronic kidney disease (CKD) have a higher risk for stroke and bleeding.[1,2] AF is the most common cardiac arrhythmia and is an independent risk factor for a new stroke.[3,4] Patients with AF who have severe CKD, which requires treatment with dialysis, have a 5-fold higher risk for a new stroke.[3,4] AF is becoming increasingly prevalent among patients with severe CKD, predisposing a patient to a much higher risk for a new stroke.[1,5,6] Historically, warfarin, a vitamin K antagonist, has been considered the preferred anticoagulant for reducing the risk of stroke in most patients with AF.[7] However, warfarin use has been shown to accelerate vascular calcification in CKD patients, which eventually may further increase the risk for ischemic stroke.[5,8–10] Therefore, uncertainty still exists regarding whether warfarin confers similar protection to reduce the risk for stroke in patients with AF who have severe CKD.[11–14]

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CKD is also considered as an independent risk factor for bleeding, and, therefore, warfarin use in patients who have severe CKD could increase the risk for bleeding.[2] Moreover, in patients with AF undergoing hemodialysis, it is routine practice to administer heparin, which could also increase the risk for bleeding.[15]

Current observational studies on warfarin use and the risk for stroke and bleeding in patients with AF undergoing dialysis present conflicting results.[1,8,16,17] Globally, because of a lack of evidence from randomized, controlled trials, AF

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management guidelines have yet to make strong recommendations regarding anticoagulation management for patients with AF undergoing dialysis.[18–23] Owing to the recognized limitations of warfarin use, such as frequent blood monitoring for a therapeutic international normalized ratio, numerous food and drug interactions, uncertainty regarding benefit for reducing stroke risk, and possible augmentation of bleeding risk, clinicians often raise concern about warfarin's safety and effectiveness in patients with AF undergoing dialysis.[7,11–15]

To enhance the knowledge on this issue, we determined the association between warfarin use and the risk for stroke and bleeding in patients with AF undergoing dialysis in Quebec and Ontario, Canada.

Methods

Study Design

We conducted a population-based retrospective cohort study of patients aged ≥65 years admitted to a hospital with a primary or secondary diagnosis of AF from 1998 to 2007, in Quebec and Ontario, Canada. Residents in Quebec and Ontario have universal access to hospital care and physician services, and those ≥65 years of age have universal prescription drug coverage. For this study, we obtained institutional review board approval from McGill University Faculty of Medicine, Montreal (Quebec) and from Sunnybrook Health Sciences Center, Toronto (Ontario).

Study Population and Data Sources

Cohort formation has been described in detail elsewhere.[24,25] In brief, we identified patients with a primary or secondary diagnosis of AF according to the *International Classification of Diseases*, 9th/10th revision codes (427.3, 427.31, or 427.32 / I48) with the use of the following hospital discharge abstract databases in Quebec and Ontario: Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière and the Canadian Institute for Health Information Discharge Abstract Database, respectively. The primary (principal) diagnosis code is the main condition treated or investigated during the admission. However, up to 7 diagnosis codes may be recorded by the hospital. The remaining diagnoses (secondary) are considered to be the subsidiary diagnoses. For patients with >1 eligible admission with an AF diagnosis, the date of the first admission with an AF diagnosis was considered the index date of entry into the study cohort. We determined patients' baseline characteristics, outcome data, and drug prescriptions from linkage between hospital discharge, physician claims, prescription drug claims, and vital status databases in Quebec and Ontario (Table I in the online-only Data Supplement). For the stroke and bleeding outcomes, we used data from emergency department visits in addition to the information from the hospital discharge databases. We used validated database codes (whenever possible) to determine stroke and bleeding outcomes.[26–30]

We used the physician claims databases maintained by la Régie de l'assurance maladie du Québec and the Ontario Health Insurance Plan, which contain information on in- and outpatient diagnostic and therapeutic procedures. We also used the la Régie de l'assurance maladie du Québec and the Ontario Drug Benefit Plan drug claims databases, which contain information on dispensed outpatient medications for patients aged ≥65 years. Drug prescriptions were identified from these databases by using drug identification numbers. These prescription claims databases provide highly accurate information on dispensed outpatient medications.[31–33]

We grouped the selected AF cohort into dialysis and nondialysis patients according to the presence of ≥3 dialysis procedural codes (same or different codes for hemodialysis and peritoneal dialysis) within the 12 months preceding AF hospitalization (database codes in Table II in the online-only Data Supplement). Our 3-code rule attempted to select patients undergoing maintenance dialysis. For all patients, we assessed demographic characteristics and comorbidities at and within 1 year preceding AF hospitalization by using validated codes, whenever possible. We obtained information on the first prescription filled for warfarin, rate control drugs (β-blockers, calcium channel blockers, and digoxin), rhythm control drugs (class Ia, Ic, and III antiarrhythmics), aspirin, clopidogrel, and nonsteroidal anti-inflammatory drugs within 30 days after AF hospital discharge.

We grouped dialysis and nondialysis patients into warfarin and no-warfarin users. We selected a 30-day period to capture the majority of patients with the first prescription for warfarin after AF hospital discharge, while minimizing the potential for survival bias.[34] Our follow-up period was started 30 days after AF hospital discharge (from the first day after the 30-day period). The outcomes of interest were the first hospital admission or emergency department visit for (1) stroke or (2) bleeding at any point during follow-up period. We defined stroke as ischemic cerebrovascular disease including transient ischemic attack (TIA) and retinal infarct. We did not include intracerebral hemorrhages in the stroke outcome because intracerebral hemorrhages could be a complication of warfarin use. We defined bleeding as intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding.

We calculated $CHADS_2$ score by assigning 1 point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus, and 2 points for history of stroke/TIA; the $CHADS_2$ scores ranged between 0 and 6.[35] The $CHADS_2$ score is a widely used clinical prediction score for estimating the risk for stroke and serves to guide clinicians in determining suitable usage of warfarin in AF.[35] We also calculated the HAS-BLED risk stratification score, the clinical prediction score for estimating the risk for bleeding.[36,37] The HAS-BLED score is calculated by assigning 1 point each for hypertension, abnormal renal function, abnormal liver function, history of stroke/TIA, history of bleeding, labile international normalized ratio, age ≥ 65 years, drug therapy (antiplatelet agents, nonsteroidal anti-inflammatory drugs), and alcohol intake.[36,37] Because our databases do not provide information on labile international normalized ratio and alcohol intake, we calculated a modified HAS-BLED score, with a maximum score of 7 rather than 9.[36,37]

Statistical Analyses

Descriptive analyses were used to compare demographic characteristics, comorbidities, and prescription for medications between warfarin and no-warfarin users in the group of dialysis and nondialysis patients. We presented continuous variables as mean±standard deviation and dichotomous variables as number (%). We calculated crude stroke and bleeding incidence rate (per 100 person-years) for the group of dialysis and nondialysis patients. We also stratified crude stroke and bleeding incidence according to warfarin use, $CHADS_2$ score (for stroke incidence rate), and HAS-BLED score (for bleeding incidence rate). Owing to restrictions to access and merge databases, we did separate analyses in Quebec and Ontario, and then combined study results from both the provinces. Results for descriptive analyses and incidence rate are weighted averages for the results from Quebec and Ontario.

To determine the association between dialysis status and warfarin filled prescription, we conducted a multivariable logistic regression analysis. To determine the association between warfarin use and the risk for stroke and bleeding in the group of dialysis and nondialysis patients, we conducted multivariable Cox proportional regression analyses. In multivariable Cox proportional hazards models, we considered warfarin use versus no-warfarin use as a time-fixed binary variable, where we assumed that patients who were prescribed warfarin within 30 days after AF hospital discharge remained on the same prescription throughout the follow-up period. This approach is akin to an intention-to-treat analysis in randomized, controlled trials.[38]

To account for the effect of potential confounders in the warfarin and stroke risk analyses, we adjusted for age (years), sex, and specific components of $CHADS_2$ score (congestive heart failure, hypertension, diabetes mellitus, and history of stroke/TIA). In the warfarin and bleeding risk analyses, we adjusted for age (years), sex, and specific components of HAS-BLED score (liver disease, hypertension, history of stroke/TIA, history of bleeding, and use of aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs). For each patient in the warfarin or no-warfarin users, we derived a propensity score for

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receiving warfarin treatment from the following variables: age ≥ 75 (years), sex, type of AF admission (primary diagnosis versus secondary diagnosis), $CHADS_2$ scores (1 and ≥2), liver disease, congestive heart failure, hypertension, diabetes mellitus, history of stroke/TIA, history of bleeding, use of rate control drug, rhythm control drug, aspirin, clopidogrel, and nonsteroidal anti-inflammatory drugs. To verify the results of stroke and bleeding risk analyses, we performed Cox proportional regression analyses adjusted for a propensity score covariate.[39] The propensity score is a good alternative to reduce bias when there is a risk of statistical overfitting as a result of a low number of events per potential confounder (ie, a low number of stroke and bleeding events in the dialysis group).[40] The propensity score indicated the likelihood of receiving warfarin given that a particular patient-related characteristic is present.[39] We used multivariable logistic regression models to derive individual propensity scores for the group of dialysis and nondialysis patients, respectively.

Results are expressed as an odds ratio for logistic regression analysis or hazard ratios (HRs) for Cox regression analyses with 95% confidence intervals (CIs). To combine results from Quebec and Ontario, we pooled the odds ratio (or HR) for each predictor by using a fixed-effects model, weighted for the inverse of the variance of the province-specific parameter estimate, *ln* (odds ratio) [or *ln* (HR)].[41] We performed all statistical analyses using SAS 9.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

The AF cohort includes 1626 dialysis patients and 204 210 nondialysis patients. Dialysis patients were younger, more likely to be men, and had more congestive heart failure, hypertension, diabetes mellitus, coronary artery disease, and past history of bleeding event, in comparison with nondialysis patients (Table 1). A larger proportion of dialysis patients, in comparison with nondialysis patients, had a high risk score for stroke ($CHADS_2$ score ≥ 2: 72% [1176/1626] versus 55% [112 049/204 210]) and bleeding (HAS-BLED score ≥ 3: 85% [1381/1626] versus 25% [50 203/204 210]).

Prescription Pattern of Warfarin

Comparable proportions of the dialysis patients and the nondialysis patients filled a prescription for warfarin within 30 days after AF hospital discharge (46% [756/1626] versus 51% [103 473/204 210]). In the multivariable logistic regression model, dialysis status was associated with a lower proportion of filled prescriptions for warfarin (adjusted odds ratio, 0.83; 95% CI, 0.74–0.92).

Among dialysis patients, those who filled a prescription for warfarin had more congestive heart failure and diabetes mellitus, but fewer previous bleeding events in comparison with the no-warfarin users. Patients who filled a prescription for warfarin had a higher proportion of patients with the high risk score for stroke ($CHADS_2$ ≥ 2: 77% [580/756] versus 69% [596/870]) in comparison with the no-warfarin users, but the proportion of high risk score for bleeding (HAS-BLED ≥ 3: 84% [637/756] versus 86% [744/870]) was similar between both the groups.

Stroke Outcome

Among dialysis patients, warfarin users did not have a lower crude incidence rate for stroke in comparison with the no-warfarin users (unadjusted incidence rate, 3.37 versus 2.91/100 person-years; P=0.44; Table 2). On the contrary, among the nondialysis patients, warfarin users did exhibit a lower crude incidence rate for stroke in comparison with the no-warfarin users (unadjusted incidence rate, 2.19 versus 2.51/100 person-years; P<0.001).

After adjusting for potential confounders, warfarin use, in comparison with no-warfarin use, was not associated with a lower risk for stroke in dialysis patients (adjusted HR, 1.14; 95% CI, 0.78–1.67); however, it was associated with a 13% lower risk for stroke in nondialysis patients (adjusted HR, 0.87; 95% CI, 0.85–0.90; Table 3). We observed similar results when we performed propensity score–adjusted Cox proportional regression analyses (dialysis patients: adjusted HR, 1.17; 95% CI, 0.79–1.75; nondialysis patients: adjusted HR, 0.89; 95% CI, 0.87–0.92).

Bleeding Outcome

Among dialysis patients, warfarin users had a higher crude incidence rate for bleeding events in comparison with the no-warfarin users (unadjusted incidence rate, 10.88 versus 7.31/100 person-years; P<0.001; Table 2). Similarly, among nondialysis patients, warfarin users had a higher crude incidence rate for bleeding events in comparison with the no-warfarin users (unadjusted incidence rate, 4.64 versus 4.00/100 person-years; P<0.001).

After adjusting for potential confounders, warfarin use, in comparison with no-warfarin use, was associated with a 44% and a 19% higher risk for bleeding event in dialysis patients (adjusted HR, 1.44; 95% CI, 1.13–1.85) and nondialysis patients (adjusted HR, 1.19; 95% CI, 1.16–1.22), respectively (Table 3). We observed similar results when we performed propensity score–adjusted Cox proportional regression analyses (dialysis patients: adjusted HR, 1.41; 95% CI, 1.09–1.81; nondialysis patients: adjusted HR, 1.20; 95% CI, 1.17–1.23).

Discussion

Our study indicates that, in dialysis patients with AF, warfarin use, in comparison with no-warfarin use, did not reduce the risk for stroke but was associated with a 44% higher risk for bleeding event, whereas warfarin use in nondialysis patients with AF was associated with a 13% lower risk for stroke and only a 19% higher risk for bleeding event. Thus, the risk-benefit profile does not appear to be favorable to support a recommendation of routine warfarin use for stroke reduction in dialysis patients with AF.

Dialysis patients have several platelet and coagulation abnormalities and also have associated comorbidities such as uncontrolled hypertension and diabetes mellitus, which all contribute to an increase in the risk for stroke and bleeding.[8,42] Further, dialysis patients routinely receive heparin during dialysis procedures, which also increases the risk for bleeding.[8,42] Moreover, warfarin use in dialysis patients, through the inhibition of Matrix Gla protein and Gas-6, can accelerate vascular calcification, which eventually might increase the risk for ischemic stroke.[5,8–10] These factors could explain why, in our study, warfarin was not associated with a lower risk for ischemic stroke in dialysis patients, but rather was associated with an increased risk for bleeding.

We summarize the results of our current study and evidence from previous published studies of warfarin use and

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Table 1. Baseline Characteristics of Patients with Atrial Fibrillation

	Dialysis Patients N=1626		Nondialysis Patients N=204 210	
	Warfarin Users n=756	No-Warfarin Users, n=870	Warfarin Users, n=103 473	No-Warfarin Users, n=100 737
Patients diagnosed with AF				
AF as a main diagnosis, n (%)	150 (20)	125 (14)	34 710 (34)	19 802 (20)
Age at the index AF admission in years, mean±SD*	75.3±8.1	75.1±8.5	77.9±9.5	78.8±10.6
Male sex, n (%)	459 (61)	533 (61)	49 133 (48)	50 425 (50)
Length of hospitalization in days, mean±SD*	19.4±37.2	21.1±44.5	10.4±20.9	10.5±24.0
Comorbidities, n (%)				
Coronary artery disease	470 (62)	517 (59)	40 163 (39)	40 199 (40)
Acute myocardial infarction	201 (27)	249 (29)	15 489 (15)	16 413 (16)
Valvular heart disease	131 (17)	115 (13)	15 633 (15)	10 140 (10)
Liver disease	28 (4)	33 (4)	1792 (2)	2413 (2)
History of bleeding event	65 (9)	139 (16)	4680 (5)	9042 (9)
Specific components of $CHADS_2$ score†, n (%)				
Congestive heart failure	312 (41)	299 (34)	33 659 (33)	27 494 (27)
Hypertension	582 (77)	655 (75)	47 972 (46)	41 738 (41)
Age ≥ 75 y	386 (51)	415 (48)	65 333 (63)	65 814 (65)
Diabetes mellitus	330 (44)	340 (39)	21 574 (21)	19 756 (20)
History of stroke/TIA	42 (6)	44 (5)	9464 (9)	5283 (5)
$CHADS_2$ score†, n (%)				
Low risk (0)	23 (3)	59 (7)	11 870 (11)	14 308 (14)
Moderate risk (1)	153 (20)	215 (25)	31 533 (30)	34 450 (34)
High risk (≥ 2)	580 (77)	596 (69)	60 070 (58)	51 979 (52)
HAS-BLED score‡, n (%)				
Low and moderate risk§ (1–2)	119 (16)	126 (14)	80 747 (78)	73 260 (73)
High risk (≥ 3)	637 (84)	744 (86)	22 726 (22)	27 477 (27)
First filled prescription within 30 days after AF discharge, n (%)				
Rate control drugs	519 (69)	462 (53)	75 656 (73)	55 167 (55)
Rhythm control drugs	203 (27)	172 (20)	23 512 (23)	16 508 (16)
Aspirin	166 (22)	241 (28)	11 814 (11)	24 544 (24)
Clopidogrel	30 (4)	58 (7)	1843 (2)	4158 (4)
NSAIDs	8 (1)	20 (2)	2109 (2)	3336 (3)

Results are weighted average for results from Quebec and Ontario. We presented continuous variables as mean±SD and dichotomous variables as number (%). AF indicates atrial fibrillation; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; and TIA, transient ischemic attack.

*We used the following formula to combine SD: $SD_{combined}=\sqrt{(SD_1)^2+(SD_2)^2}$.

†$CHADS_2$ score is a clinical prediction score for estimating the risk for stroke.

‡HAS-BLED score is a clinical prediction score for estimating the risk for bleeding.

§HAS-BLED score has minimum score of 1 and 2 for nondialysis patients and dialysis patients, respectively. In this study, all AF patients are aged ≥ 65 y, which accounts for 1 point. In the dialysis group, all patients have abnormal renal function, which also accounts for 1 point.

the risk for stroke and bleeding in patients with AF undergoing dialysis in Figure 1 and Figure 2, respectively. In a retrospective cohort study of 1671 AF patients undergoing hemodialysis, Chan et al[8] observed a 1.9-fold higher risk for the composite stroke/death outcome with warfarin use. In another observational study analyzing data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS), Wizemann et al[17] stratified patients with AF undergoing hemodialysis according to age categories, ≤65, 65 to 75, and >75 years. The authors reported that warfarin use in patients >75 years of age (n=1107) was associated with a 2.2-fold higher risk for the composite stroke/death outcome.[17] In the younger age groups, the authors noticed that warfarin use did not reduce the risk for the composite stroke/death outcome.[17] Winkelmayer et al[16] conducted a retrospective cohort study in hemodialysis patients with incidental AF and performed propensity score matched analyses (warfarin users, 237; matched nonusers, 948). The authors found that warfarin use did not reduce the risk for ischemic stroke but was associated with a 2.4-fold higher risk for hemorrhagic stroke.[16] Olesen et al,[1] in 901 dialysis patients, were the only researchers to observe that warfarin use was associated

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Table 2. Crude Incidence Rate for Stroke and Bleeding Events

	Dialysis Patients N=1626		Nondialysis Patients N=204 210	
	No. of Events	Incidence* Rate per 100 Person-Years	No. of Events	Incidence* Rate per 100 Person-Years
Stroke†	107	3.12	19 489	2.35
According to warfarin prescription (within 30 days postdischarge)				
Yes	52	3.37	9241	2.19
No	55	2.91	10 248	2.51
According to $CHADS_2$ score‡				
Low risk (0)	4	1.99	2270	1.49
Moderate risk (1)	23	2.35	6078	2.06
High risk (≥ 2)	80	3.55	11 141	2.91
Bleeding§	275	8.89	34 035	4.32
According to warfarin prescription (within 30 days postdischarge)				
Yes	149	10.88	18 340	4.64
No	126	7.31	15 695	4.00
According to HAS-BLED‖ score				
Low and moderate risk# (1–2)	43	8.00	26 129	4.07
High risk (≥ 3)	232	9.08	7906	5.45

AF indicates atrial fibrillation; and TIA, transient ischemic attack.

*Incidence rates were calculated with the following formula: No. of events/total follow-up time (100 person-years). Incidence rates are weighted average for results from Quebec and Ontario.

†Stroke was defined as the first hospital admission or emergency department visit for ischemic cerebrovascular disease, TIA, or retinal infarct at any point during the follow-up period.

‡$CHADS_2$ score is a clinical prediction score for estimating the risk for stroke.

§Bleeding was defined as the first hospital admission or emergency department visit for intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding at any point during the follow-up period.

‖HAS-BLED score is a clinical prediction score for estimating the risk for bleeding.

#HAS-BLED score has minimum score of 1 and 2 for nondialysis patients and dialysis patients, respectively. In this study, all AF patients are aged ≥ 65 yr, which accounts for 1 point. In the dialysis group, all patients have abnormal renal function, which also accounts for 1 point.

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with a 56% decrease in the risk for the composite stroke/death outcome. However, there were several limitations to this study.[1,43–45] A larger proportion of dialysis patients had unusually low HAS-BLED scores (HAS-BLED score: 2–35% [312/901]; 0 or 1–43% [390/901]).[1,44] Contrary to our study and DOPPS, dialysis patients had a low prevalence of

Table 3. Association between Warfarin Use and the Risk for Stroke and Bleeding in Patients with Atrial Fibrillation

Patients With AF	Outcomes	Adjusted* HR (95% CI)	Propensity Score† Adjusted HR (95% CI)
Dialysis (n=1626)	Stroke‡	1.14 (0.78–1.67)	1.17 (0.79–1.75)
	Bleeding§	1.44 (1.13–1.85)	1.41 (1.09–1.81)
Nondialysis (n=204 210)	Stroke‡	0.87 (0.85–0.90)	0.89 (0.87–0.92)
	Bleeding§	1.19 (1.16–1.22)	1.20 (1.17–1.23)

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; and TIA, transient ischemic attack.

*Stroke outcome was adjusted for age (years), sex, specific components of $CHADS_2$ stroke prediction score (congestive heart failure, hypertension, diabetes mellitus, and history of stroke/TIA).

*Bleeding outcome was adjusted for: age (years), sex, specific components of HAS-BLED bleeding prediction score (liver disease, hypertension, history of stroke/TIA, history of bleeding, and use of aspirin, clopidogrel, or NSAIDs).

†Propensity score was derived from the following variables: age ≥75 y, sex, type of AF (primary vs secondary), $CHADS_2$ scores (1 and ≥2), liver disease, congestive heart failure, hypertension, diabetes mellitus, history of stroke/TIA, history of bleeding, use of rate control drug, rhythm control drug, aspirin, clopidogrel, and NSAIDs.

‡Stroke was defined as the first hospital admission or emergency department visit for ischemic cerebrovascular disease, TIA, or retinal infarct at any point during the follow-up period.

§Bleeding was defined as the first hospital admission or emergency department visit for intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding at any point during the follow-up period.

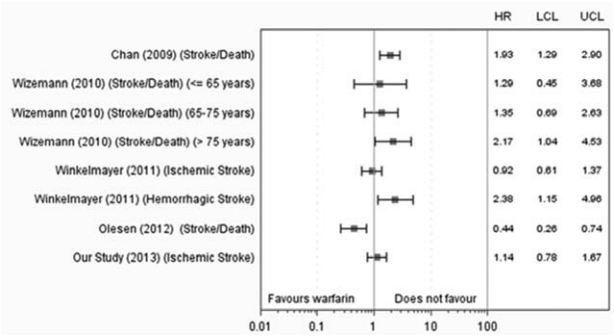

Figure 1. Warfarin use and the risk for stroke in patients with atrial fibrillation undergoing dialysis. Chan et al[8] defined stroke outcome as hospitalization or death from ischemic stroke, hemorrhagic stroke, or TIA. Forty-five percent (747/1671) of patients were receiving warfarin.[8] Wizemann et al[17] defined stroke outcome as hospitalization or death from stroke or cerebrovascular event. Fifteen percent (146/1001) patients, 17% (192/1137) patients, and 15% (171/1107) patients in age groups ≤65 years, 66 to 75 years, and >75 years were receiving warfarin, respectively.[17] Winkelmayer et al[16] defined stroke outcome as ischemic or hemorrhagic stroke. Eleven percent (249/2313) of patients were receiving warfarin.[16] Two hundred thirty-seven warfarin users were matched to 948 nonusers.[16] Olesen et al[1] defined stroke outcome as hospitalization or death from stroke or systemic thromboembolism (ischemic stroke, peripheral artery embolism, and TIA). Twenty percent (178/901) of patients were receiving warfarin only.[1] Our study defined stroke as the first hospital admission or emergency department visit for ischemic cerebrovascular disease, TIA, or retinal infarct at any point during the follow-up period. Forty-six percent (756/1626) of patients were receiving warfarin. HR indicates hazard ratio; LCL, lower confidence limit; TIA, transient ischemic attack; and UCL, upper confidence limit.

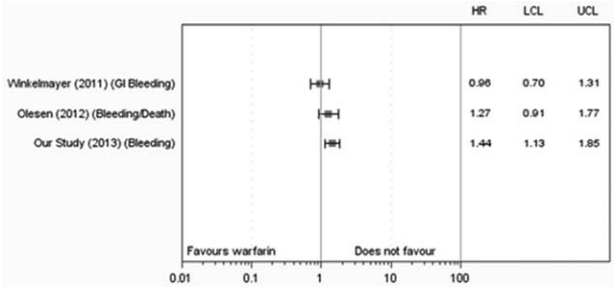

Figure 2. Warfarin use and the risk for bleeding in patients with atrial fibrillation undergoing dialysis. Winkelmayer et al[16] defined bleeding outcome as GI bleeding. Eleven percent (249/2313) of patients were receiving warfarin.[16] Two hundred thirty-seven warfarin users were matched to 948 nonusers.[16] Olesen et al[1] defined bleeding outcome as hospitalization or death from GI, intracranial, urinary tract, and air-way bleeding. Twenty percent (178/901) of patients were receiving warfarin only.[1] Our study defined bleeding outcome as the first hospital admission or emergency department visit for intracerebral bleeding, GI bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding at any point during the follow-up period. Forty-six percent (756/1626) of patients were receiving warfarin. GI indicates gastrointestinal; HR, hazard ratio; LCL, lower confidence limit; and UCL, upper confidence limit.

diabetes mellitus (14% [129/901]) and hypertension (54% [486/901]).[1,43] It is possible that a selection bias of healthier patients undergoing dialysis could explain the reason for the decreased risk of stroke with warfarin use in the study by Olesen et al.[1,43]

Contrary to our results of increased bleeding risk in dialysis patients, Winkelmayer et al[16] and Olesen et al[1] observed no association between warfarin use and the risk for gastrointestinal bleeding and the composite bleeding/death outcome, respectively.

A major consideration in the comparison of our study results for stroke and bleeding risk with previous studies is the heterogeneity in stroke and bleeding definitions across the different studies.[1,8,16,17] In our study, we included ischemic stroke, TIA, and retinal infarct in the stroke definition and excluded intracerebral hemorrhages. Contrary to the composite stroke/death and bleeding/death outcomes in previous studies,[1,8,17] we did not include death in our stroke and bleeding definitions.

Our study has a number of strengths. Our large sample size allowed us to study the association between warfarin use and the risk for stroke and bleeding in the AF cohort. Unlike other studies, we attempted to reduce concerns about statistical overfitting[46] and included only the most relevant covariates in the adjusted analyses. Finally, the information available within the large Quebec and Ontario healthcare databases reflects routine clinical practice in Canada and may be less prone to participation biases that can arise in other types of studies.[47]

There are some limitations to our study. First, biases attributable to residual confounding from unknown or unmeasured confounders and also confounding by indication are well described in observational studies on drug effects.[48,49] To overcome confounding bias, we adjusted for most appropriate covariates that may confound the association between warfarin use and the study outcomes, and we also performed sensitivity analyses by using the propensity score approach.[39,50] However, we still cannot rule out residual confounding.[48] Second, our health administrative databases do not contain information on international normalized ratio levels or heparin use during dialysis procedures, and, therefore, we could not account for these variables in the adjusted analyses. Third, the accuracy of database codes for patients' related health information is a known concern in observational studies based on health administrative databases. In an attempt to limit this concern, we used database codes with the best validation whenever possible.

In summary, current and previous observational studies on warfarin use and the risk for stroke and bleeding in patients with AF undergoing dialysis failed to provide much evidence in favor of warfarin use, yet there was a signal for an increased bleeding risk.[1,8,16,17] Recently, the Canadian Cardiovascular Society AF guidelines (2012) made a conditional recommendation (on a low quality of evidence) that patients with AF undergoing dialysis should not routinely receive anticoagulation treatment for the primary prevention of stroke.[23] This is consistent with the recommendation from the Kidney Disease: Improving Global Outcomes.[22] Nevertheless, with no evidence from randomized, controlled trials, there is a lack of strong recommendations for anticoagulation management guidelines for this patient population.[18–23] Because of the observational nature of our and previous studies, the study results may not be conclusive. We propose that a large multicenter randomized, controlled trial should be undertaken to clarify this issue and to guide AF management guideline bodies around the world.

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Dr Pilote had full access to all of the data in Quebec and Dr Jackevicius had full access to all of the data in Ontario, and they take responsibility for the integrity of the data and the accuracy of the data analysis. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by Canadian Institutes of Health Research (CIHR), Institute for Clinical Evaluative Sciences (ICES), or the Ontario Ministry of Health and Long-term Care (MOHLTC) is intended or should be inferred. We thank la Régie de l'assurance maladie du Québec (RAMQ) and Brogan Inc, Ottawa for use of its Drug Product and Therapeutic Class Database.

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CLINICAL PERSPECTIVE

Patients with atrial fibrillation (AF) undergoing dialysis have a higher risk for stroke and bleeding attributable to platelet and coagulation abnormalities, associated comorbidities, routine heparinization during dialysis, and warfarin-associated vascular calcification. Interestingly, current observational studies on warfarin use and the risk for stroke and bleeding in patients with AF undergoing dialysis found conflicting results and there is a lack of randomized, controlled trials on this issue. To enhance the knowledge on this issue, we conducted a population-based retrospective cohort study of patients aged ≥ 65 years admitted to a hospital with a diagnosis of AF from 1998 to 2007, in Quebec and Ontario, Canada. We observed that dialysis patients (n=1626), in comparison with nondialysis patients (n=204 210), had high risk score for stroke ($CHADS_2$ score ≥ 2: 72.3% versus 54.9%) and bleeding (HAS-BLED score ≥ 3: 84.9% versus 24.6%). We found that in patients with AF undergoing dialysis, warfarin use, in comparison with no-use, was not associated with a lower risk for stroke, but was associated with a 44% higher risk for bleeding event. Thus, the risk-benefit profile does not appear to be favorable for routine warfarin use for the reduction of stroke in patients with AF undergoing dialysis. Because of the observational nature of our study, we propose to conduct a large multicenter randomized, controlled trial to clarify this issue and also to guide AF management guideline bodies around the world.

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