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Canadian Nephrologist Views Regarding Stroke and Systemic Embolism Prevention in Dialysis Patients With Nonvalvular Atrial Fibrillation: A Survey

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Abstract

Background: Nonvalvular atrial fibrillation (NVAF) is an independent risk factor for ischemic stroke and is common in chronic kidney disease (CKD) and dialysis patients. The use of oral anticoagulation to prevent stroke and systemic embolism in the setting of kidney disease is controversial. Novel alternatives to vitamin K antagonists include left atrial appendage occlusion devices (LAAOD) and apixaban.

Objective: We sought to elicit Canadian nephrologist views regarding stroke and systemic embolism prevention therapies in CKD and dialysis patients with NVAF.

Design: Survey.

Setting: Online via https://www.surveymonkey.com.

Participants: Canadian Society of Nephrology members actively treating adult dialysis patients with NVAF.

Measurements: Management questions were asked with response options consisting of a Likert scale ranging from 1 to 8 (with 1 being *definitely would not* and 8 being *definitely would*).

Methods: We randomly allocated each respondent to 2 of 4 cases that varied by stroke and bleeding risks (using varying CHADS2 and HASBLED scores, respectively).

Results: There were 91 responses (36.3% response rate) from mostly university (83.5%) and also community with university affiliation (12.1%) and community (4.4%) nephrologists. Warfarin was more likely to be recommended in individuals at high stroke risk and low bleeding risk (mean = 5.47, 95% confidence interval = 4.87-6.07) and less likely to be recommended in individuals at moderate stroke risk and high bleeding risk (mean = 2.89, 95% confidence interval = 2.37-3.41). The likelihood of recommending LAAOD did not vary by stroke or bleeding risks (means ranging from 3.92-4.90). Apixaban was not likely to be recommended in any case (means ranging from 2.60-3.50). However, nephrologists felt there was equipoise regarding anticoagulation strategies allowing participation in appropriate randomized controlled trials (RCTs).

Limitations: The survey only involved nephrologists and only 4 cases with dichotomized risk categories were presented instead of complete range of stroke and bleeding risk combinations. As with any survey, there was the potential for responder bias and treatment decisions are not anchored directly to patient management.

Conclusions: Nephrologists caring for patients with kidney disease appear willing to include patients in clinical trials examining alternatives to warfarin for stroke and systemic embolism prevention for NVAF in the setting of kidney disease.

Abrégé

Contexte: La fibrillation auriculaire non valvulaire (FANV) est un facteur de risque indépendant de l'accident vasculaire cérébral (AVC) ischémique et est fréquente chez les patients atteints d'insuffisance rénale chronique (IRC) et chez les patients dialysés. L'administration orale d'anticoagulants en prévention des AVC et des embolies systémiques en contexte de néphropathie est controversée. Les nouvelles solutions pour remplacer les antagonistes de la vitamine K incluent des dispositifs d'occlusion de l'appendice auriculaire (LAAOD) et l'apixaban.

Objectif: Nous souhaitions sonder les néphrologues canadiens au sujet des traitements préventifs de l'embolie systémique et de l'AVC chez les patients atteints d'IRC et dialysés présentant une FANV.

Type d'étude: Un sondage.

Cadre: Un sondage en ligne au https://www.surveymonkey.com

Participants: Les membres de la Société canadienne de néphrologie traitant des adultes dialysés présentant de la FANV.
Mesures: Des questions concernant la prise en charge des patients ont été posées avec un choix de réponses sous la forme d'une échelle de Likert allant de 1 à 8, où 1 signifiait « certainement pas » et 8 « très certainement ».
Méthodologie: De façon aléatoire, nous avons assigné à chaque répondant de deux à quatre cas variant en sévérité pour les risques d'AVC et d'hémorragie (en fonction des scores CHADS2 et HASBLED respectivement).
Résultats: Nous avons obtenu 91 réponses (taux de réponse de 36,3 %) provenant principalement de néphrologues pratiquant en milieu universitaire (83,5 %), mais également d'un milieu communautaire (4,4 %) ou d'un milieu communautaire affilié à une université (12,1 %). La warfarine s'est avérée plus susceptible d'être recommandée pour les sujets à haut risque d'AVC et présentant de faibles risques d'hémorragie (moyenne : 5,47; IC 95 % : 4,87-6,07). Elle était moins susceptible d'être recommandée aux patients présentant un risque moyennement élevé d'AVC et un haut risque d'hémorragie (moyenne : 2,89; IC 95 % : 2,37-3,41). La probabilité de recommander les LAAOD n'a pas varié en fonction du risque d'AVC ou d'hémorragie (moyennes variant entre 3,92 et 4,90). Dans tous les cas, l'apixaban n'était pas susceptible d'être recommandé (moyennes variant entre 2,60 et 3,50). De leur côté, les néphrologues ont estimé qu'il existait un équilibre entre les différentes stratégies d'anticoagulation, ce qui permettait la participation aux essais contrôlés à répartition aléatoire appropriés.
Limites: Le sondage ne s'adressait qu'aux néphrologues, et seuls quatre cas avec des catégories de risque dichotomiques ont été présentés plutôt qu'une gamme complète de risques combinés d'AVC et d'hémorragie. En outre, les décisions relatives au traitement n'étaient pas directement liées à la prise en charge de patients. Enfin, comme pour tout sondage, celui-ci comporte un potentiel biais de réponse.
Conclusion: Les néphrologues seraient disposés à inclure leurs patients dans des essais cliniques portant sur les solutions de rechange à la warfarine en contexte de néphropathie pour prévenir les AVC et les embolies systémiques en présence de FANV.

Keywords
atrial fibrillation, dialysis, stroke, prevention

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What was known before

There is uncertainty regarding stroke and systemic embolism preventive therapies in dialysis patients.

What this adds

The decision to pursue oral anticoagulation with warfarin depends on stroke and bleeding risks while the likelihood of recommending left atrial appendage occlusion device (LAAOD) and apixaban for stroke and systemic embolism prevention did not vary by underlying individual risks. There is clinical equipoise regarding anticoagulation strategies allowing participation in appropriate randomized controlled trials (RCTs).

Introduction

Chronic kidney disease (CKD) is an independent risk factor for stroke[1] and affects 8% to 16% of the global population.[2] Stroke is a leading cause of disability and death in CKD and dialysis patients with nonvalvular atrial fibrillation (NVAF). NVAF is associated with kidney disease[3] having an incidence of 2.7 per 100 patient-years and prevalence of 11.6% in dialysis with heterogeneity among studies due to different populations, definitions, and ascertainment of NVAF. NVAF is a key contributing factor[4] to the increased risk of stroke in CKD and dialysis patients with rates of stroke varying according to the degree of kidney dysfunction as well as the definition of stroke (ischemic vs hemorrhagic) and its method of ascertainment.[5-7]

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Table 1. 4 Cases by CHADS2, HASBLED Scores.

	Low HASBLED	High HASBLED
Moderate CHADS2	Case 1 CHADS2 = 1 (moderate) HASBLED = 2 (low)	Case 2 CHADS2 = 1 (moderate) HASBLED = 4 (high)
High CHADS2	Case 3 CHADS2 = 5 (high) HASBLED = 3 (low)	Case 4 CHADS2 = 5 HASBLED = 5 (high)

Note. For CHADS2, C = congestive heart failure, H = hypertension, A = age >65, D = diabetes mellitus, S = stroke; for HASBLED, H = hypertension, A = abnormal renal/liver function, S = stroke, B = bleeding tendency or predisposition, L = labile INR, E = age >65, D = drugs (antiplatelets or NSAID); INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

There is controversy over the management of stroke and systemic embolism risk in CKD and dialysis patients with NVAF due to the uncertain efficacy and safety of oral anticoagulation (OAC)[8,9] due to an altered responsiveness to vitamin K antagonists (VKAs),[10,11] platelet dysfunction, and an increased risk of major bleeding.[12-14] Not surprisingly, kidney dysfunction is an independent predictor of bleeding in NVAF patients treated with OAC.[15-17] Left atrial appendage occlusion devices (LAAODs) are a novel intervention that has been shown to be noninferior to VKAs for stroke and systemic embolism prevention in NVAF in the general population. The WATCHMAN LAAOD is associated with more ischemic strokes but less hemorrhagic strokes compared to warfarin with procedural risks including ischemic stroke.[18,19] Apixaban is a factor Xa inhibitor that has been shown to be superior to warfarin for stroke and systemic embolism prevention in NVAF in the general population[20] but randomized trial evidence does not exist for individuals with a creatinine clearance (CrCl) <25 mL/min, including those receiving dialysis.

We surveyed Canadian nephrologists to elicit their views regarding stroke and systemic embolism prevention therapies in CKD and dialysis patients with NVAF and their willingness to let their patients participate in randomized controlled trials (RCTs) of novel alternative therapies to warfarin including LAAODs and apixaban.

Methods

Survey Design and Target Audience

The survey was designed by 2 of the authors (David Collister, MW) and piloted on 2 nephrologists (KSB, CR) and 2 cardiologists (JH, David Conen) for clinical sensibility and comprehension. Its final version was piloted on 4 nephrologists for functionality on the survey platform surveymonkey.com (see the appendix). The survey was circulated to Canadian Society of Nephrology members on April 12, 2017 (n = 251) with the target demographic including Canadian nephrologists actively treating adult CKD (including kidney transplant recipients with estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) and dialysis patients excluding trainees, allied health members, and researchers. Follow-up reminders were sent 1 and 2 weeks later with subsequent individualized email reminders. Responses were anonymous, and all answers required to all questions. Ethics approval was not obtained given waived consent for surveys at our institution.

Previous Experiences With Novel Therapies

The first section of the survey elicited prior experiences treating CKD or dialysis patients with NVAF with the WATCHMAN LAAOD or apixaban. It provided background information regarding these interventions in the general population including the PROTECT-AF[18] and PREVAIL[19] RCTs, an individual patient-level meta-analysis of these trials and their respective registries[21] in addition to ARISTOTLE[20] and its CKD subgroup analysis[22] and an apixaban hemodialysis pharmacokinetic study.[23] Demographic information including the number of years in independent practice (in 5-year increments) and work environment (university, community with university affiliation, university, other) was collected.

Views Regarding for Stroke and Systemic Embolism Prevention

The second section of the survey consisted of 4 cases, of which 2 were randomly assigned to each respondent. Each case involved a 65-year-old Caucasian man on intermittent hemodialysis with NVAF (representative of a typical Canadian dialysis patient eligible for participation in potential clinical trials) but with varying CHADS2[24] (congestive heart failure, hypertension, age >65, diabetes mellitus, stroke) and HASBLED[15] (hypertension, abnormal renal/liver function, stroke, bleeding tendency or predisposition, labile INR, age >65, drugs [eg, concomitant ASA or NSAIDs] or alcohol) scores (Table 1). Risk prediction tools and absolute risks were not explicitly presented.

Respondents were then asked a series of questions regarding the management of each case with a response option of a Likert scale ranging from 1 to 8 with 1 being *definitely would not* and 8 being *definitely would* for the likelihood of

recommending (1) warfarin, (2) the WATCHMAN LAAOD, (3) apixaban and if they would consider enrolling the patient into a RCT comparing, (4) the WATCHMAN LAAOD with warfarin, or (5) apixaban with warfarin.

Last, respondents were asked whether they utilized risk prediction tools to classify stroke and systemic embolism risks as well as bleeding risks when deciding whether or not to prescribe an OAC in their CKD or dialysis patients with NVAF.

Physician Minimal Clinically Important Difference (MCID)

Physician were asked how many major bleeding episodes requiring hospitalization would they would accept to prevent one ischemic stroke with disability with responses of 1, 2, 3, 4, 5 and greater than 5.

Statistical Analysis

A complete case analysis was performed given that responses were required for all questions to progress through the survey. Descriptive statistics were performed to characterize survey respondents. Multilevel multivariable linear regression (cases clustered in physicians) was performed to determine independent predictors of the likelihood of clinical decisions for warfarin, LAAOD, and apixaban. All statistical tests were performed at a $P < .05$ level of significance. All analyses were performed using STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Respondents

A total of 110 responses were received (43.8% response rate) but only 91 complete surveys (36.3% response rate) were analyzed. The characteristics of survey participants are shown in Table 2. The majority of participants did not have any previous clinical experience with the use of LAAODs (91.2%) or apixaban (86.8%) in their dialysis patients. Most (85.7%) used CHADS2 score or an equivalent tool for stroke/systemic embolism risk prediction and 46.2% used HASBLED score or equivalent tool for bleeding risk prediction.

Table 2. Table Survey Participant Characteristics (N = 91).

Year in practice	
<5	17 (18.7%)
>5-10	19 (20.9%)
>10-15	19 (20.9%)
>15-20	14 (15.4%)
>20	22 (24.2%)
Practice setting	
University	76 (83.5%)
Community with university affiliation	11 (12.1%)
Community	4 (4.4%)
Clinical experience with left atrial occlusion devices in dialysis	
Yes	8 (8.8%)
No	83 (91.2%)
Clinical experience with apixaban in dialysis	
Yes	12 (13.2%)
No	79 (86.8%)
Use of a risk prediction tool for ischemic stroke and systemic embolism (eg, CHADS2)	
Yes	78 (85.7%)
No	13 (14.3%)
Use of a risk prediction tool for bleeding (eg, HASBLED)	
Yes	42 (46.2%)
No	49 (54.8%)

Stroke and Systemic Embolism Prevention Therapies

Physician number of years in practice, physician practice setting, use of CHADS2 or HASBLED as risk prediction tools, and physician MCID were not statistically significant predictors of recommending stroke and systemic embolism preventive therapies (not shown). The interaction between stroke and bleeding risks was the only statistically significant predictor of treatment recommendations and was the only variable included in the final multilevel linear regression model (not shown).

Likelihoods by Treatments

The likelihood of recommending treatment with warfarin, a LAAOD, or apixaban for each case (within-group comparisons with warfarin as the reference) is shown in Figure 1. There was heterogeneity in recommendations for warfarin, LAAOD, and apixaban therapy (see Supplemental Figures 1, 2, 3). In case 1 (CHADS2 = 1, HASBLED = 2), apixaban was less likely to be recommended than warfarin ($P = .033$). In case 2 (CHADS2 = 1, HASBLED = 4), a LAAOD was more likely to be recommended than warfarin ($P = .000$). In case 3 (CHADS2 = 5, HASBLED = 3), both a LAAOD and apixaban were less likely to be recommended than warfarin ($P = .008$, $P = .000$, respectively). In case 4 (CHADS2 = 5, HASBLED = 5), apixaban was less likely to be recommended than warfarin ($P = .001$).

Likelihoods by Stroke/Systemic Embolism and Bleeding Risks

The likelihood of recommending therapy with warfarin, a LAAOD, or apixaban across cases (between-group comparisons with case 1 as the reference) is shown in Figure 2. With regard to warfarin, case 2 (CHADS2 = 1, HASBLED

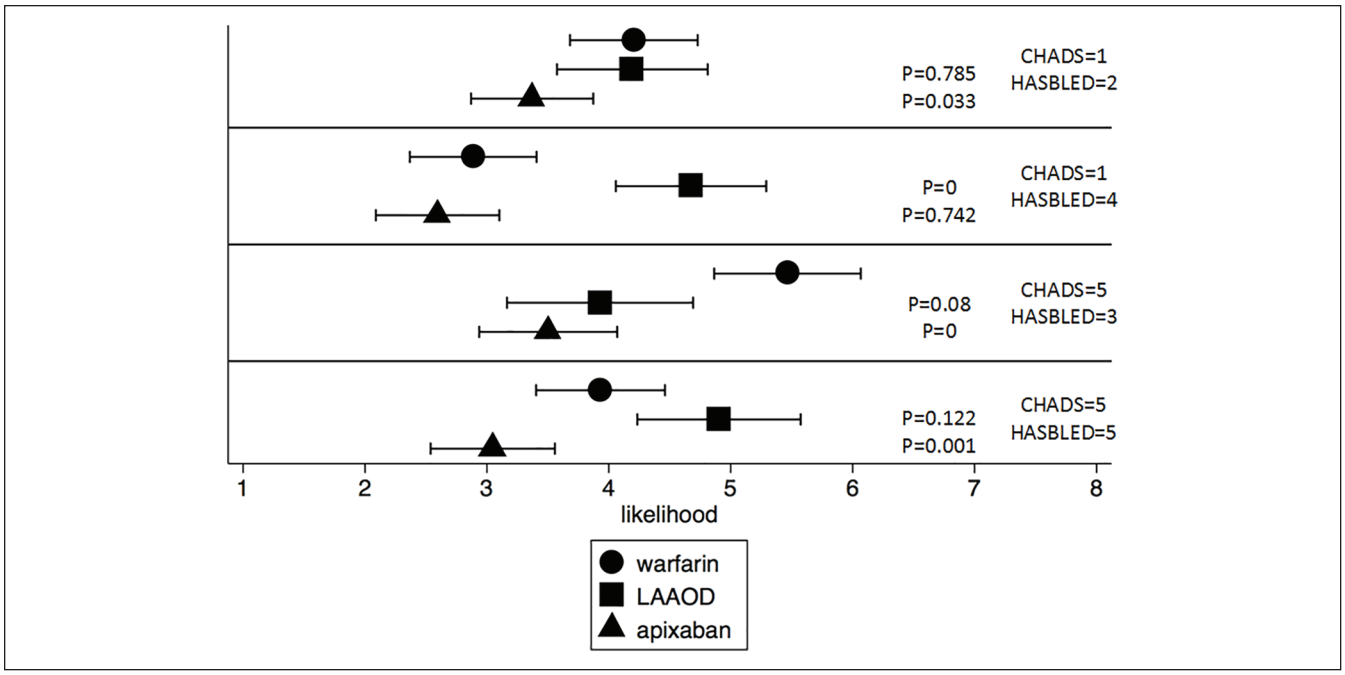

Figure 1. The likelihood of recommending treatment with warfarin, LAAOD, or apixaban for each case (within-group comparison).

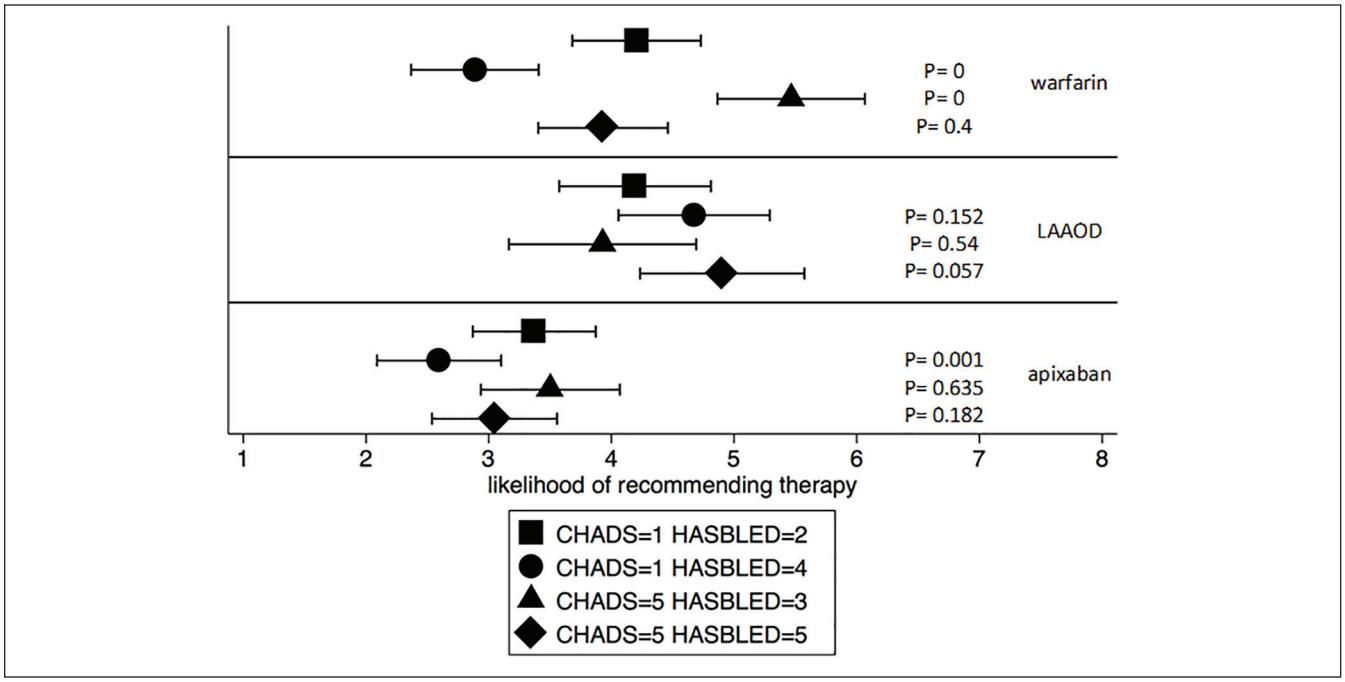

Figure 2. The likelihood of recommending treatment with warfarin, LAAOD, or apixaban for each case (between-group comparison).
Note. LAAOD = left atrial appendage occlusion device.

= 4) was less likely ($P = 0$) and case 3 (CHADS2 = 3, HASBLED = 5) was more likely ($P = 0$) to be recommended warfarin therapy. There was no difference between cases in the likelihood of recommending a LAAOD with overall uncertainty (clustering of responses between 4 and 5 on the Likert scale). With regard to apixaban, it was not likely to be recommended in all 4 cases (all 95% confidence interval [CI] upper limits less than 4.5) but it was the least likely to be recommended in case 2 (CHADS2 = 1, HASBLED = 4, $P = .001$).

MCID

The physician MCID for the number of major bleeds they would accept to prevent one nonfatal disabling ischemic stroke was a mean of 2.33 (SD = 1.21).

Participation in Future RCTs

Clinicians were interested in allowing their patients to participate in RCTs of LAAOD or apixaban (Supplemental Figures 4 and 5).

Discussion

In this survey of Canadian nephrologists to elicit practice patterns for stroke and systemic embolism prevention for NVAF in hemodialysis, we found heterogeneity in the likelihood of recommending warfarin, LAAOD, and apixaban across varying stroke/systemic embolism as well as bleeding risks. Warfarin was more likely to be recommended in individuals at high stroke/systemic embolism risk and low bleeding risk (case 3, CHADS2 = 5, HASBLED = 3) and less likely to be recommended in individuals at moderate stroke/systemic embolism risk and high bleeding risk (case 2, CHADS2 = 1, HASBLED = 4). There was uncertainty regarding recommending LAAOD that did not vary by stroke/systemic embolism or bleeding risks and apixaban was not likely to be recommended in any case. However, nephrologists were willing to enroll their dialysis patients in RCTs comparing both LAAOD and apixaban with warfarin to formally evaluate the safety and efficacy of these novel therapies.

Our finding of heterogeneity of OAC decision making for NVAF for stroke and systemic embolism prevention depending on perceived stroke and bleeding risks in CKD and dialysis is supported by previous studies. A survey of Canadian nephrologists in 2013 consisting of 6 hypothetical scenarios involving CKD and dialysis patients with varying stroke and bleeding risks demonstrated uncertainty regarding the initiation of OAC for NVAF ranging from 16.1% to 48.2% depending on the scenario[25] but did not include novel therapies. A survey of Italian nephrologists in 2010 assessing practice patterns of OAC for NVAF in dialysis patients demonstrated that comorbidities were a driver of nonprescription of OAC (22.4% of cases) and that this factor was more important than both previous major bleeding (8.3%) and falls (1.3%) when recommending warfarin.[26] In the Dialysis Outcomes and Practice Patterns Study, OAC use ranged from 2% in Germany to 26% in the United States to 37% in Canada[27] suggesting regional variation perhaps related to comorbidities or differing values and preferences regarding stroke/systemic embolism prevention and bleeding internationally as well as absence of randomized trials.

Our study demonstrated that stroke risk prediction tools are widely used in CKD and dialysis given their accuracy[28] but bleeding risk prediction tools are employed less often, perhaps due to the belief that all patients with kidney dysfunction are considered at high risk of bleeding regardless of other risk factors. The interaction between stroke and bleeding risks, however, appears to guide physicians when deciding on therapeutic recommendations but how physicians actually incorporate their own as well as their patients' beliefs regarding trade-offs between outcomes remains uncertain. Individualization of therapy is needed that not only acknowledges the uncertainty of the efficacy of OAC in dialysis but also the challenge in determining risks due to their variations across populations[29] and the problematic correlation between stroke and bleeding risks.

This is the first study to report a MCID for bleeding/stroke trade-offs for warfarin in the CKD or dialysis population. Patient and physician MCID for both ASA and warfarin for NVAF stroke prevention have previously been shown to be greater for patients than physicians at 17.4 (SD = 7.1) versus 10.3 (SD = 6.1) (warfarin) and 14.7 (SD = 8.5) versus 6.7 (SD = 6.2) (ASA) episodes of excess bleeding in 100 patients over 2 years.[30] Another study demonstrated variability in physician and patient MCID with clustering of less than 10 bleeds for both groups but also greater than 35 for a group of patients with health utilities (the perceived value of a health state ranging from death [0] to full health [100]) of major stroke and bleeding states being 21.5 (SD = 15.9) and 44.0 (SD = 19.9), respectively.[30] Our physician MCID of 2.33 (SD = 1.21) is different from that reported in general population and is likely due to considerations unique to bleeding in CKD and dialysis patients including the risk of acute kidney injury (AKI)/progression of CKD as well as that of red blood cell transfusions and the development of donor-specific antibodies in addition to other adverse clinical outcomes. However, it should be recognized that our study did not utilize any formal methodologies such as probability trade-offs to determine a physician MCID.

The WATCHMAN LAAOD as an alternative to OAC for stroke and systemic embolism prevention in NVAF is a promising therapy for individuals at significant bleeding risk as it avoids long-term OAC. A systematic review and meta-analysis of 832 RCTs and 1145 registry patients compared with 382 VKA controls showed that the WATCHMAN LAAOD was noninferior to VKA when considering a composite efficacy endpoint but with an overall increase in ischemic strokes but decrease in hemorrhagic strokes.[21] Direct oral anticoagulants (DOACs) have been shown to be safe and are likely effective in less advanced CKD (CrCl = 30-50 mL/min) with a pooled relative risk reduction of 0.64 (95% CI = 0.39-1.04) for stroke and systemic embolism and no statistically significant increase in bleeding in a meta-analysis of 8 RCTs of DOACs (including apixaban, rivaroxaban, dabigatran) versus VKAs.[31] However, limited evidence exists in CKD with a CrCl $<$ 25 mL/min and dialysis with pharmacokinetic data for apixaban in hemodialysis showing negligible dialyzability.[32] Although no RCTs

have evaluated the efficacy of the DOACs in patients with AF receiving dialysis, these agents are being increasingly prescribed in the dialysis population, particularly apixaban, which accounted for almost 11% of prescribed oral anticoagulants in American dialysis recipients.[33] A large observational study of almost 25 000 dialysis recipients in the United States demonstrated that apixaban had a similar risk of stroke/systemic thromboembolism as warfarin.[34] In subgroup analysis, the 5 mg twice a day dose of apixaban was noted to provide a statistically significant decrease in stroke risk versus warfarin (hazard ratio [HR] = 0.64; 95% CI = 0.42-0.97) as compared with the 2.5 mg twice a day dose (HR = 1.11; 95% CI = 0.82-1.50).

Enthusiasm for RCTs in this area has previously been identified in a survey of Canadian nephrologists where 67% of responders reporting they would enroll patients if already on a VKA and 82% if not already VKA into an RCT of VKA versus placebo.[25] AVKDIAL[35] is an unblinded multicenter RCT comparing VKA to no OAC in adult HD patients with AF and a CHADS2VASC score ≥2 at high risk of bleeding that has yet to start enrolling. Other RCTs include RENAL-AF[36] (apixaban vs VKA) and STOP-HARM[37] (LAAOD vs VKA) are ongoing.

The strengths of this study include its size, response rate, and design to limit bias by randomizing participants to cases. However, it does have its limitations. The survey population did not include cardiologists, hematologists, or other health care professionals that might be involved in shared decision making with dialysis patients with NVAF. However, given that nephrologists typically coordinate not only dialysis-specific care but also cardiovascular risk reduction, it is likely that our study sample is representative of current NVAF practice patterns in the Canadian hemodialysis population. We were unable to present all the different combinations of stroke/systemic embolism and bleeding risks but instead focused on 4 cases that dichotomized risk categories to explore treatment decisions where we detected variation without overwhelming respondents. Last, as with any survey, there is the potential for responder bias and likelihood scores for treatment decisions are not anchored to actual patient management so whether or not our results apply to clinical or research settings is unclear.

Conclusions

There is still uncertainty regarding the use of OAC for stroke and systemic embolism prevention in CKD and dialysis patients with NVAF. Alternatives to warfarin are needed given its unclear efficacy and potential for harm, with apixaban and LAAOD currently being evaluated as promising therapies. Nephrologists, their patients, and other subspecialists involved in the care of CKD and dialysis patients with NVAF anxiously await the results of these pivotal trials.

Ethics Approval and Consent to Participate

Ethics approval was not obtained, given waived consent for surveys at our institution.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

Availability of Data and Materials

Data and materials may be made available upon written request to the corresponding author.

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Author Contributions

D Collister and MW contributed to the research idea and study design. D Collister performed data acquisition and statistical analysis. D Collister, JSH, DC, KSB, CR, ZH, MMS, and MW contributed to data analysis/interpretation and article drafting and revision.

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.

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Supplemental Material

Supplemental material for this article is available online.

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