Demystifying the Benefits and Harms of Anticoagulation for Atrial Fibrillation in Chronic Kidney Disease

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Abstract

Patients with CKD represent a vulnerable population where the risks of atrial fibrillation, ischemic stroke, and bleeding are all heightened. Although large randomized, controlled trials in the general population clearly demonstrate that the benefits of warfarin and direct-acting oral anticoagulants outweigh the risks of bleeding, no such studies have been conducted in patients when their creatinine clearance falls below 25–30 ml/min. Without randomized, controlled trial data, the role of anticoagulation in patients with CKD with atrial fibrillation remains unclear and our practice is informed by a growing body of imperfect literature such as observational and pharmacokinetic studies. This article aims to present a contemporary literature review of the benefits versus harms of anticoagulation in atrial fibrillation for patients with CKD stages 3, 4, 5, and 5 on dialysis. Although unanswered questions and areas of clinical equipoise remain, this piece serves to assist physicians in interpreting the complex body of literature and applying it to their clinical care.

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Introduction

Stroke is a disabling and sometimes fatal complication of atrial fibrillation (1,2). Anticoagulation is recommended to reduce the risk of stroke but also increases the risk of intracranial hemorrhage and other potentially life-threatening bleeding complications. Multiple large randomized, controlled trials (RCTs) in the general population clearly demonstrate that the benefits of warfarin outweigh its risks of severe bleeding (3,4). However, this risk/benefit ratio remains less clear for certain subgroups, such as those with CKD states 4, 5, and 5 on dialysis (5[D]) (5–8).

Patients with advanced CKD or dialysis and atrial fibrillation represent a vulnerable population where the risks of atrial fibrillation, stroke, and bleeding are all heightened such that evidence-based guidance on anticoagulation is needed (9,10). However, patients with a creatinine clearance <25–30 ml/min were excluded from almost all pivotal phase 3 trials on anticoagulation such that it remains unclear whether these drugs confer more benefit than harm in advanced CKD (11–14). A recent Kidney Disease Quality Outcome Initiative survey confirms this state of equipoise: among 5063 physicians 55% were in favor of anticoagulation in atrial fibrillation for patients with ESKD, whereas the remaining were not (15). The introduction of direct-acting oral anticoagulants (DOACs) further complicates anticoagulation practices by offering new options in the setting of limited efficacy and safety data in patients with advanced CKD and dialysis.

In this article, we provide a focused review of the clinical literature on oral anticoagulation from the perspective of risk versus benefit in patients with atrial fibrillation with CKD 3, 4, 5, and 5(D) (Table 1). Given that anticoagulation in advanced CKD is controversial, we strive to demystify the complex body of literature to provide more clarity on the latest evidence for and against anticoagulation in this population.

Benefits versus Risks of Warfarin in CKD 3, 4, and 5

Warfarin came into medical use in 1954 in an era that preceded Food and Drug Administration (FDA) regulation of rigorous clinical trials in subpopulations such as CKD. Meta-analysis of six RCTs in the general population reported a 62% reduction in all-cause stroke with dose-adjusted warfarin to an achieved international normalized ratio (INR) 2.0–2.6 compared with placebo (number needed to treat=32), with a small but significant increased risk for extracranial hemorrhage (number needed to harm=333) (3); however, most of these trials did not enroll patients with CKD. Only Stroke Prevention in Atrial Fibrillation III enrolled 516 patients with stage 3 CKD (eGFR 30–59 ml/min per 1.73 m^2) and a *post hoc* analysis of the RCT reported reduced risk in ischemic stroke and systemic thromboembolism with dose-adjusted warfarin (mean INR=2.4) compared with fixed dose warfarin (mean INR=1.3) plus aspirin, with no difference in major hemorrhage. These results suggest that warfarin is both effective and safe in CKD 3 (Table 2) (16).

In patients with an eGFR<30 ml/min warfarin's effectiveness and safety can only be inferred from observational studies. The results from these observational studies are mixed, which convolutes our understanding of warfarin's risks versus benefits. For instance, an observational Danish national registry cohort of 3587 individuals with atrial fibrillation and CKD 3, 4, and 5 reported a nonsignificant decrease in risk of hospitalization or death from all-cause stroke or systemic thromboembolism with warfarin compared

Table 1. Pharmacologic properties of oral anticoagulants relevant to CKD

Anticoagulant	Mechanism of Action	$T_{1/2}$ (h)	Metabolism	Kidney Clearance (%)	Dose eCrCl≥51 ml/min	Dose eCrCl<51–31 ml/min	Dose eCrCl<31 ml/min and Dialysis	Approved Reversal Agent
Warfarin (Coumadin)	Vitamin K antagonist (factors II, VII, IX, and X)[a]	25–60 (mean 40)[b]	CYP450 2C9[c]	0	INR 2–3	INR 2–3	INR 2–3	Yes: Vitamin K (oral or intravenous)
Dabigatran (Pradaxa)	Factor II (thrombin) inhibitor	12–14	P-gp	80	150 mg twice daily	150 mg twice daily[d]	75 mg twice daily (eCrCl 30–15 ml/min)	Yes: Idarucizumab (intravenous)[e]
Apixaban (Eliquis)	Factor Xa inhibitor	12	CYP450 3A4 P-gp	25	5 mg twice daily	2.5 mg twice daily if 2 of 3 criteria[f]	2.5 mg twice daily if 2 of 3 criteria[f]	Yes: Andexanet alfa (intravenous)
Rivaroxaban (Xarelto)	Factor Xa inhibitor	7–11	CYP450 3A4 -gp	35	20 mg once daily	15 mg once daily	15 mg once daily (eCrCl30–15ml/min)	Yes: Andexanet alfa (intravenous)
Edoxaban (Savaysa)	Factor Xa inhibitor	8–10	CYP450 3A4 P-gp	40	60 mg once daily[g]	30 mg once daily	No	Yes: Andexanet alfa[h] (intravenous)

eCrCl, estimated creatinine clearance as measured by Cockcroft–Gault equation; CYP450 3A4, cytochrome P 450; INR, international normalized ratio; P-gp, glycoprotein.
[a]Warfarin diminishes the total quantity of clotting factors II, VII, IX, and X by 30%–50%.
[b]Warfarin $t_{1/2}$ depends on the clearance time for each clotting factor (*e.g.*, $T_{1/2}$ of factor II=59 h and factor VII=6 h).
[c]Genetic variations in CYP450 influence the metabolism of warfarin (*i.e.*, factor IX mutation in hereditary resistance to warfarin). Notable drug-drug interactions include selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, verapamil, diltiazem, and digoxin. There are additional food interactions with green leafy vegetables containing vitamin K.
[d]Some experts recommend 110 mg twice daily for patients with creatinine clearance (CrCl) <51 ml/min; however, this dose is not approved in the United States.
[e]Idarucizumab is an mAb approved as a 5 mg iv infusion without dose adjustment for kidney impairment for reversal of dabigatran in 2015.
[f]Dose determined according to ≥2 of the criteria: (*1*) age≥80 yr, (2) body wt ≤60 kg, or (*3*) serum creatinine (SCr)≥1.5 mg/dl.
[g]Not Food and Drug Administration approved with CrCl≥95 ml/min due to decreased efficacy to prevent arterial thromboembolism. However, *post hoc* analyses found that the net clinical benefit of edoxaban versus warfarin was consistent across kidney function.
[h]Andexanet is a factor Xa decoy protein designated as Breakthrough Therapy for reversal of apixaban, rivaroxaban, and edoxaban.

Table 2. Subgroup analysis of a single randomized clinical trial of warfarin for stroke prevention in CKD not on dialysis with atrial fibrillation

Study Characteristics[a]	Publication and Sponsor	Intervention and Control	CKD Stage (*n*/*N*, %)[b]	Outcomes	Results[a]	Conclusion
Post hoc CKD subgroup analysis unblinded RCT of Stroke Prevention in Atrial Fibrillation trials 1993–1997 United States and Canada, 1.3 mean yr follow-up[4]	Robert G. Hart, *CJASN* 2011 National Institute of Neurologic Disorders and Stroke	Dose-adjusted warfarin, INR 2–3 (mean achieved 2.4). Fixed, low-dose warfarin (1–3 mg/d, mean INR achieved 1.3) plus 325 mg aspirin/d.	Stage 3 CrCl<60 ml/min 516 of 1044 (49%) (267 dose-adjusted warfarin and 249 fixed low-dose warfarin). Baseline creatinine >3 mg/dl excluded.	Primary: Ischemic stroke and or systemic thromboembolism. Secondary: Relevant bleeding[c]	The 2-yr event rate with dose-adjusted warfarin was 6 of 267 and low-dose warfarin and ASA was 23 of 249. The 2-yr event rate for dose-adjusted warfarin was 5 of 267 and low-dose warfarin and ASA was 6 of 249.	76% RR (95% CI, 42 to 90) of ischemic stroke and systemic thrombo-embolism with dose-adjusted warfarin over fixed low-dose warfarin and ASA. Too few events to compare relevant bleeding. Dose-adjusted warfarin offers benefit over fixed low-dose warfarin and ASA 325 mg/din reduction of ischemic stroke and systemic embolism in individuals with CKD stage 3.

RCT, randomized controlled trial; *CJASN*, *Clinical Journal of the American Society of Nephrology*; INR, international normalized ratio; CrCl, creatinine clearance; ASA, aspirin; RR, risk reduction; 95% CI, 95% confidence interval.
[a]Intention-to-treat analyses.
[b]Stage 4/5 (CrCl<30 ml/min), 27 of 1044 (3%) were removed from analyses. There are no randomized, controlled trials or subgroup analyses in stage 4/5 CKD.
[c]Relevant bleeding defined as occurring 14 d of receiving warfarin without a predictable precipitating cause (*e.g.*, major trauma, cardiac surgery).

with no anticoagulation (hazard ratio [HR], 0.84; 95% confidence interval [95% CI], 0.69 to 1.01) and an increased risk of bleeding (HR, 1.36; 95% CI, 1.17 to 1.59) (17) (Table 3). A subsequent study in the same registry of nondialysis patients with atrial fibrillation and CKD (61% CKD 4, 5) attempted to quantify total benefit/harm of warfarin using a "net clinical benefit" outcome. Net clinical benefit was defined as a composite of fatal all-cause stroke and fatal bleeding such that there was more "net benefit" in warfarin users than no treatment in atrial fibrillation (HR, 0.71; 95% CI, 0.57 to 0.88) (18). Although helpful, the net outcome did not account for morbidity from nonfatal bleeding. Utilization of methods to calculate net benefit of unequally weighted outcomes would yield more relevant outcomes (19). Another study of 6292 individuals with CKD not on dialysis is notable for distinguishing benefits versus harms by CKD stage. The risk of ischemic stroke and transient ischemic attack while on warfarin compared with no anticoagulation was significantly reduced in CKD 3 but not statistically significant in CKD 4 and 5 (HR, 0.54; 95% CI, 0.26 to 1.13); however, there was no difference in bleeding risk across stages of CKD (20) (Table 3). In total, there have been at least six well conducted observational studies comparing stroke benefit versus bleeding harm for atrial fibrillation in nondialysis patients with CKD on warfarin in comparison to no anticoagulation. Even among these select studies there is large heterogeneity in results; 67% of these studies reported that warfarin reduced stroke risk and 33% reported no change. Similarly, for bleeding, 67% reported that warfarin increased risk and 33% reported no change (Table 3). As such, the association between warfarin with stroke and bleeding is not reproducible between these studies and the heterogeneity in results may be attributed to bias from observational analyses and variations in study design, which include:

1. Confounding by indication which occurs when patients prescribed warfarin are sicker than patients not prescribed warfarin and sicker patients are at higher risk for stroke and bleeding.
2. Unmeasured confounding which occurs when INR levels are not measured. This makes it impossible to adjust for the degree of anticoagulation if patients are not given therapeutic doses of warfarin.
3. Early drug discontinuation occurring in an intention-to-treat analysis will bias results toward the null.
4. Misclassification bias given that stroke and bleeding outcomes were typically ascertained from claims data and not validated against imaging results.

Benefits versus Risks of DOACs in CKD 3, 4, and 5

The introduction of DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) presents physicians with new options which are equivalent if not superior to warfarin at preventing stroke and major bleeding among patients with atrial fibrillation without kidney impairment (Table 4) (11–14). When compared with warfarin, DOACs do not require INR monitoring or heparin bridging and are minimally affected by foods containing vitamin K. They may also have fewer drug-drug interactions; however, a recent study highlighted the risk of concurrent use of CYP3A4 and P-glycoprotein modulators which may affect DOAC-related bleeding outcomes (21). Although not

Table 3. Observational studies on anticoagulants for stroke prevention in CKD stages 3–5 not on dialysis with atrial fibrillation

Study Characteristics and Publication	Intervention, Control, and Analysis Type	Effectiveness and Harm Outcomes[a]	Conclusion
Retrospective population analysis Denmark, 1997–2008. Follow-up not given, *n*=3587, CKD stages 3–5, not on dialysis, Olesen, *NEJM* 2012	Warfarin±aspirin (*n*=609) versus nonwarfarin± aspirin (*n*=2978). As treated.	Incidence rate of all-cause stroke or systemic embolism in 100 person yr 6.4. Risk with warfarin compared with no warfarin, HR, 0.84 (95% CI, 0.69 to 1.01). Incidence rate of major bleeding in 100 person yr 8.8[b]. Increased risk with warfarin compared with no warfarin, HR, 1.36 (95% CI, 1.17 to 1.59).	Warfarin approaches statistical significance to reduce all-cause stroke or thromboembolism but also does associate with higher bleeding risk compared with nonwarfarin.
Retrospective population analysis Denmark, 1997–2011. Follow-up 0.85 yr, *n*=4519, CKD stages 3–5, not on dialysis, Bonde, *JACC* 2014	Warfarin±aspirin (*n*=1130) versus no warfarin±aspirin (*n*=3389). As treated.	"Net clinical benefit" defined as composite of fatal all-cause stroke/ fatal bleeding. 753 fatal all-cause stroke/fatal bleed events. Warfarin associates with a lower risk of fatal stroke/fatal bleeding, HR, 0.71 (95% CI, 0.57 to 0.88)[c].	There is a net clinical benefit to warfarin over nonwarfarin in preventing deaths from stroke and bleeding.
Retrospective population analysis Alberta, Canada, 2003–2012. Follow-up 1 yr, *n*=2272, CKD stages 3–5, not on dialysis, age≥66 yr, Jun, *AJKD* 2017	Warfarin±aspirin (*n*=1136) matched to no anti-coagulation± aspirin (*n*=1136). Intention to treat.	Ischemic stroke/TIA: HR (95% CI) warfarin versus nonwarfarin eGFR 45–59: 0.60 (0.44 to 0.84); eGFR 30–44: 0.59 (0.38 to 0.94); eGFR<30: 0.54 (0.26 to 1.13). Major bleeding[d]: HR (95% CI) warfarin versus nonwarfarin eGFR 45–59: 1.00 (0.79 to 1.27); eGFR 30–44: 0.82 (0.62 to 1.09); eGFR<30: 0.95 (0.60 to 1.50).	In older patients, warfarin associates with reduced risk of ischemic stroke/TIA compared with nonwarfarin with no significant difference in major bleeding.
Retrospective population analysis Ontario, Canada. Follow-up 0.73 yr, *n*=1417, CKD stages 3–5, not on dialysis on anti-coagulation, age≥66 yr, Keskar, *KI* 2017	Anti-coagulation±aspirin (*n*=1417) matched to no anti-coagulation± aspirin (*n*=1417). Anti-coagulation group includes: warfarin 91%, heparin 3%, DOACs 6%. As treated.	Incidence rate per 1000 person yr of ischemic stroke 41.3 on anti-coagulation and 34.4 not on anti-coagulation. Risk on anti-coagulation compared with no anti-coagulation, HR, 1.12 (95% CI, 0.90 to 1.39). Incidence rate per 1000 person yr of major bleeding[e] 61.3 on and 34.3 not on anti-coagulation. Risk on anti-coagulation compared with no anti-coagulation, HR, 1.60 (95% CI, 1.31 to 1.97).	Anti-coagulation associates with increased risk of bleeding and no reduction in stroke compared with no anti-coagulation in older adults.
Retrospective population analysis England and Wales, 2006–2016. Follow-up 1.39 yr, *n*=6977, CKD stages 3–5, not on dialysis, age>65 yr, Kumar, *BJM* 2018	Anti-coagulation±anti-PLTs (*n*=2424) versus no anti-coagulation± aspirin (*n*=2424). Anti-coagulation group includes: warfarin 72%, rivaroxaban 13%, apixaban 11%, dabigatran 3%, edoxaban 0.2%, heparin 2%. As treated.	Incidence rates per 100 person yr for ischemic stroke were 4.6 on anti-coagulation and 1.5 not on anti-coagulation. Risk in anti-coagulation versus no anti-coagulation, HR, 2.6 (95% CI, 2.0 to 3.4). Incidence rates per 100 person yr for hemorrhagic stroke and GIB were 1.2 on anti-coagultion and 0.4 not on anti-coagulation. Risk on anti-coagulation versus not on anti-coagulation, HR, 2.4 (95% CI, 1.4 to 4.1)	Anti-coagulation associates with increased risk of ischemic strokes and bleeding compared with no anti-coagulation in older adults.

Table 3. (Continued)

Study Characteristics and Publication	Intervention, Control, and Analysis Type	Effectiveness and Harm Outcomes[a]	Conclusion
Retrospective analysis in United States, 2010–2017. Follow-up not given[f], *n*=1990, with CKD stages 3–5, Jung-Im Shin, *CJASN* 2018	DOACs (*n*=1990) apixaban 32%, rivaroxaban 41%, dabigatran 27%, matched to warfarin (*n*=1990). As treated.	Ischemic stroke event rates per 100 person yr 8.8 in DOACs versus 7.8 in warfarin users, HR, 1.02 (0.76 to 1.37). Major bleeding[e] event rates per 100 person yr 26.3 bleeding DOACs versus 20.1 in warfarin users, HR, 1.23 (95% CI, 1.02 to 1.48)	DOACs associated with similar benefits from prevention of ischemic stroke but slightly higher risk of bleeding versus warfarin.

As-treated analysis refers to time on drug as often done with statistical techniques using time-varying exposures (*e.g.*, time-dependent Cox proportional hazards models) or censoring if there is no anticoagulant prescription refill within a defined period of time. Only the primary analysis is reported. Intention-to-treat analyses use exposure (*e.g.*, warfarin versus no anticoagulation) as a time-fixed binary variable. *NEJM*, *New England Journal of Medicine*; HR, hazard ratio; 95% CI, 95% confidence interval; *JACC*, *Journal of the American College of Cardiology*; *AJKD*, *American Journal of Kidney Disease*; TIA, transient ischemic attack; *KI*, *Kidney International*; DOACs, direct-acting oral anticoagulants; *BJM*, *British Journal of Medicine*; anti-PLTs, antiplatelets (includes aspirin and clopidogrel); GIB, gastrointestinal bleed; *CJASN*, *Clinical Journal of the American Society of Nephrology*.

[a]Adjusted analyses are reported.

[b]Hospitalization or death from all-cause stroke (ischemic and or hemorrhagic) or systemic thromboembolism (peripheral-artery embolism, ischemic stroke, and TIA). Hospitalization or death from major bleeding (gastrointestinal, intracranial, urinary tract, or airway). Outcome events were not separated by treatment group.

[c]This study was designed to evaluate net clinical benefit; outcomes of stroke/systemic thromboembolism/all bleeding and fatal stroke/fatal bleeding were not reported separately. The numbers of outcome events were not separated by treatment group.

[d]Major bleeding defined by first hospitalization or emergency department visit for intracranial, upper or lower gastrointestinal, or other bleeding.

[e]Bleeding defined as a code for major (*i.e.*, bleeding at critical site [intracranial, retroperitoneal, intraspinal, intraocular, pericardial, or intraarticular] or bleeding requiring transfusion) and minor. Bleeding with a corresponding trauma code was excluded.

[f]Major bleeding defined as fatal, intracranial, ocular causing blindness, articular, or retroperitoneal requiring intervention or transfusion ≥2 U of packed red cells, or hemoglobin drop ≥2 g/dl. Results from intention-to-treat and time-varying analyses were similar. Four percent (*n*=253) had eGFR<30 ml/min and dialysis patients were included. A composite of all minor and major bleeding was used.

proven, DOACs theoretically pose less risk of arterial calcification compared with warfarin because they do not inhibit the vitamin K–dependent γ-carboxylase enzyme (22,23). These factors are relevant in CKD where polypharmacy, malnutrition, and coronary artery calcification are highly prevalent.

All DOACs are cleared by the kidney which can lead to drug bioaccumulation, supra-therapeutic dosing, and unintended bleeding in patients with kidney impairment (24–26). Reversal agents such as idarucizumab and andexanet alfa are approved and are given as intravenous infusions and require less volume than fresh frozen plasma (Table 1). However, these medications remain costly, prohibiting their penetration onto hospital formularies. They also carry a risk of thrombotic complications. In the idarucizumab trial, thrombotic events occurred in 5.6% of patients after receiving therapy and included deep-vein thrombosis, pulmonary embolism, left atrial thrombus, myocardial infarction, and ischemic stroke (27). In the phase 2 trials of andexanet alfa in healthy volunteers, no thromboembolic events were reported (28). However, an interim analysis of the ongoing phase 3 trial in patients with acute major bleeding reported thrombotic events in 11% and death in 12% of patients within 30 days after administration (29). The use of these agents requires caution, especially while they are still being tested and their safety is not completely understood.

Unlike warfarin, all phase 3 DOAC trials enrolled CKD 3 subjects (dabigatran 3554 of 17,951 [20%], apixaban 4714 of 23,721 [20%], rivaroxaban 3234 of 16,142 [20%], and edoxaban 2860 of 14,071 [24%]) but patients with creatinine clearance ≤30–25 ml/min were excluded. Similar to the trial results reported in the general population, subgroup analyses of CKD 3 showed equivalent or superior efficacy and safety of DOACs compared with warfarin (13,30–32) (Table 4). A recent Cochrane review of 12,545 patients with CKD (97% with CKD 3) enrolled in five RCTs reported reduced risk of all-cause stroke and systemic thromboembolism (HR, 0.81; 95% CI, 0.65 to 1.00) and major bleeding (HR, 0.79; 95% CI, 0.59 to 1.04) in comparison with warfarin (33). Similar findings were also reported in a meta-analysis of DOACs in moderate CKD (34).

A United States observational study published this July compared outcomes in 3206 DOAC users (dabiatran, rivaroxaban, and apixaban) matched to warfarin users stratified by eGFR (35). In this study, eGFR did not statistically modify (*P*-interaction=0.70) the risk of ischemic stroke in DOACs when compared with warfarin in participants with eGFR>60 ml/min (HR, 0.94; 95% CI, 0.74 to 1.180) or in participants with eGFR<60 ml/min (HR, 1.02; 95% CI, 0.76 to 1.37). Risk for major and minor bleeding in DOACs was slightly higher when compared with warfarin for eGFR<60 ml/min (HR, 1.23; 95% CI, 1.02 to 1.48) versus eGFR>60 ml/min (HR, 1.01; 95% CI, 0.88 to 1.17) but effect modification was also NS (*P*-interaction=0.10). Subgroup analyses for users with an eGFR<30 ml/min (*n*=253) showed lower ischemic stroke rates (9.2 versus

Table 4. Subgroup analyses of randomized, controlled trials of direct-acting oral anticoagulants for stroke prevention in CKD stages 3–5 nondialysis with atrial fibrillation

Study	Sponsor, Publication	Year	Intervention	Control[a]	CKD Stage 3 eGFR≤60 ml/m (*n* of *N*, %)	CKD Stage 4/5 eGFR<30–25 ml/m (*n*/*N*, %)	Follow-Up (yr)	Primary Efficacy[b] in CKD, HR (95% CI)	Primary Safety[c] in CKD, HR (95% CI)
RE-LY	Boehringer Ingelheim Pharmaceutical	2009	Dabigatran 110 or 150 mg twice a day	Warfarin	3554 of 17,951 (19.8)	None, eGFR<30 excluded	2.0	0.73 (0.46 to 1.14)	0.99 (0.74 to 1.33)
ARISTOTLE	Bristol-Myers Squibb, Pfizer	2010	Apixaban 5 or 2.5 mg twice a day[d]	Warfarin	3017 of 18,122 (17.0)	270 of 3017 (8.9%) eGFR 30–25, eGFR<25 or Cr>2.5 mg/dl excluded	1.8	0.81 (0.51 to 1.28)[a]	0.50 (0.36 to 0.70)
AVERROES	Bristol-Myers Squibb and Pfizer	2011	Apixaban 5 or 2.5 mg twice a day[d]	Aspirin 81–325 mg	1697 of 5599 (30.3)	None, eGFR<25 or Cr>2.5 mg/dl excluded	1.1	0.45 (0.32 to 0.62)	1.13 (0.74 to 1.75)
ROCKET AF	Johnson & Johnson, Bayer Pharmaceutical	2011	Rivaroxaban 15 mg every day	Warfarin	2950 of 14,264 (20.7)	None, eGFR<30 excluded	1.9	0.84 (0.57 to 1.26)	0.96 (0.69 to 1.33)
J-ROCKET AF	Yakuhin Bayer Pharmaceutical	2012	Rivaroxaban 10 mg every day	Warfarin	284 of 1278 (22.2)	None, eGFR<30 excluded	2.5	0.81 (0.22 to 2.96)	0.89 (0.33 to 2.38)
ENGAGE AF-TIMI 48	Daiichi Sankyo Pharma	2013	Edoxaban 30 mg every day	Warfarin	2860 of 14,071 (23.9)	None, eGFR<30 excluded	2.8	0.85 (0.53 to 1.36)	0.75 (0.54 to 1.06)
Overall[e]								0.81 (0.65 to 1.00)	0.79 (0.59 to 1.04)

HR, hazard ratio; 95% CI, 95% confidence interval; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; Cr, serum creatinine; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; J-ROCKET AF, Japan Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48.

[a]Warfarin dose adjusted to INR range of 2.0–3.0. All studies allowed ≤100 or ≤165 mg/d of aspirin. All were sponsor open and double blinded, except RE-LY 2009 in which warfarin was unblinded.

[b]Primary efficacy outcome was all-cause stroke (ischemic or hemorrhagic) and/or systemic thromboembolism.

[c]The primary safety outcome was major bleeding, defined as clinically overt bleeding accompanied by ≥1 of the following: hemoglobin drop ≥2 g/dl over 24 h, transfusion ≥2 U of packed red cells, critical location (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatality.

[d]Dose determined according to ≥2 of the criteria: (*1*) age≥80 yr, (*2*) body wt ≤60 kg, or (*3*) serum creatinine≥1.5 mg/dl.

[e]Cochrane review all of the above studies excluding AVERROES (46).

10.6 per 100 patient years) and more bleeding (38.1 versus 30.4 per 100 patient years) with DOAC compared with warfarin (35). Although the sample size was underpowered to detect statistical differences, these findings suggest that systemic DOAC levels increase when kidney disease becomes advanced thereby reducing the risk stroke and increasing the risk of bleeding.

Benefits versus Risks of Warfarin: CKD 5(D)

There are no RCTs of warfarin in patients on dialysis and observational, often retrospective, studies are used to guide practice (Table 5). The results of these observational studies are conflicting. A population-based analysis from Denmark of 901 individuals on dialysis found that warfarin reduced risk of all-cause stroke and systemic thromboembolism by 44% ($P=0.002$) but did not significantly increase the risk of bleeding (HR, 1.27; 95% CI, 0.91 to 1.77) when compared with no therapy (17). Whereas the risk in bleeding with warfarin is replicated across many studies, the benefit in stroke reduction is less consistent. For example, a United States study of 1671 individuals on dialysis reported a 74% increased risk for all-cause stroke (HR, 1.74; 95% CI, 1.11 to 2.72) among warfarin versus nonwarfarin users (36). However, other studies report more modest findings, such as a Canadian retrospective population analysis from 1998 to 2007 which reported a nonsignificant increased risk for ischemic stroke (HR, 1.14; 95% CI, 0.78 to 1.67) with warfarin in comparison with no anticoagulation (37) (Table 5). In a meta-analysis of 14 observational studies with 20,398 patients on dialysis, warfarin did not associate with reduced risk of ischemic stroke (HR, 0.77; 95% CI, 0.55 to 1.07) when compared with no warfarin (34). Within this meta-analysis, a large but nonsignificant increased risk of hemorrhagic stroke (HR, 1.93; 95% CI, 0.93 to 4.00) and a modest but also nonsignificant increased risk of gastrointestinal bleeding (HR, 1.19; 95% CI, 0.8 to 1.76) were reported in warfarin users compared with nonwarfarin users (34). These observational studies should be interpreted with caution because they are subject to bias from patient selection, intention-to-treat analyses that do not account for early drug discontinuation, time in therapeutic range, and misclassification through nonadjudicated claims for outcomes.

Benefits versus Risks of DOACs: CKD 5(D)

Even though the pivotal RCTs excluded patients with eGFR<25–30 ml/min, DOACs are FDA approved for use down to an eGFR of 15 ml/min on the basis of limited dose pharmacokinetic modeling without clinical safety data (38–41). The US FDA label also makes pharmacokinetically based dose recommendations for the use of rivaroxaban (15 mg daily) and apixaban (5 mg twice daily reduced to 2.5 mg twice daily when age>80 years or weight<60 kg) for patients on dialysis; however, the label cautions that these recommendations lack clinical efficacy and safety data validation (39,40). As such, we are once again left to rely on observational data to derive effectiveness and safety profiles for DOACs in ESKD.

In late June of this year an observational study of maintenance dialysis Part D Medicare beneficiaries compared 2351 apixaban users to 7053 prognostic score–matched warfarin users (3:1 match) (Table 5). There was no difference in risk of ischemic stroke or systemic embolism (HR, 0.88; 95% CI, 0.69 to 1.12) and a 28% reduced risk of major bleeding (HR, 0.72; 95% CI, 0.59 to 0.87) in the apixiban group compared with warfarin. Ischemic stroke/systemic embolism reduction was greater in the 5 mg twice daily group (HR, 0.61; 95% CI, 0.37 to 0.98) and bleeding risk was not higher (HR, 0.98; 95% CI, 0.68 to 1.42) compared with the 2.5 mg twice daily group (42).

An earlier study reported significant off-label use of dabigatran and rivaroxaban among 8589 patients on maintenance hemodialysis (43). Dose reduction for kidney impairment was not seen among 15% of dabigatran users and 32% of rivaroxaban users. In a time-on-treatment analysis, increased risks of hospitalization for bleeding were reported in dabigatran (HR, 2.59; 95% CI, 1.89 to 3.54) and rivaroxaban (HR, 1.90; 95% CI, 1.19 to 3.04) users when compared with warfarin. Fatal bleeding rate ratios were even higher, likely because reversible agents were not available at the time of the study: dabigatran rate ratio, 1.78 (95% CI, 1.18 to 2.68), and rivaroxaban rate ratio, 1.71 (95% CI, 0.94 to 3.12), when compared with warfarin (43). The risk was attenuated in subgroup analyses of individuals prescribed a reduced dose. The study was underpowered to compare stroke or systemic embolism outcomes due to the infrequency of these events.

Quantification of Stroke and Bleeding Risk in CKD 4, 5, and 5(D)

A key aspect of patient care is quantifying individual risk. In general, stroke risk stratification scores ($CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, ATRIA) and bleeding risk scores (HAS-BLED, $HEMORR_2HAGES$, ATRIA, and ORBIT) provide minimal-to-moderate predictive value in the CKD population. In fact, one study found that these scores were no better than physician subjective assessments (44). CHA_2DS_2-VASc, the most widely used stroke risk stratification tool, has been validated in CKD and dialysis; however, it has poor accuracy in discriminating patients who will have a stroke versus those who will not (concordance statistic <0.6 in CKD stage 3 and <0.7 in CKD stages 4, 5, and dialysis) (45). Bleeding risk scores have poor discrimination in the general population (*e.g.*, $HEMORR_2HAGES$ concordance statistic of 0.66–0.72) and have not been validated in the advanced CKD population.

Recommendations: Benefits versus Risks of Oral Anticoagulation in CKD with Atrial Fibrillation

In patients with CKD 3, our recommendations are consistent with cardiology and nephrology guidelines which advise oral anticoagulation for patients with nonvalvular atrial fibrillation with a CHA_2DS_2-VASc score ≥2 on the basis of extrapolation from general practice (46,47). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines conclude noninferior efficacy in prevention of stroke and systemic thromboembolism and likely superior safety of DOACs compared with warfarin in patients with CKD 3 (47). Similarly, we recommend the use of a DOAC over warfarin because there are rigorous RCT data suggesting that DOACs are equivalent or superior to warfarin in safety and efficacy when the eGFR is >30 ml/min in concurrence with recent KDIGO statements (47). We also recommend following kidney function at least twice yearly

Table 5. Observational studies on anticoagulants for stroke prevention in CKD stage 5 on dialysis with atrial fibrillation

Study Characteristics and Publication	Intervention, Control, and Type of Analysis	Effectiveness and Harm Outcomes[a]	Conclusion
Retrospective population analysis Denmark, 1997–2008. Follow-up yr not given, *n*=901, CKD stage 5 on dialysis, Olesen, *NEJM* 2012	Warfarin±aspirin (*n*=178) versus no nonwarfarin± aspirin (*n*=723). As treated.	Rates of all-cause stroke or thromboembolism per 100 person yr 5.6. Reduced risk in warfarin compared with no warfarin, HR, 0.44 (95% CI, 0.26 to 0.74). Rates of major bleeding per 100 person yr 8.9[b]. Increased risk with warfarin compared with no warfarin, HR, 1.27 (95% CI, 0.91 to 1.77).	Warfarin associates with reduced risk of stroke or systemic thromboembolism and increased risk of bleeding compared with no anti-coagulation in patients on dialysis.
Retrospective population analysis Denmark, 1997–2011. Median follow-up 1.65 yr, *n*=1728, CKD stage 5 on dialysis, Bonde, *JACC* 2014	Warfarin±aspirin (*n*=186) versus no warfarin± aspirin (*n*=1129). As treated.	"Net clinical benefit" defined as composite of fatal all-cause stroke/fatal bleeding[c]. 130 fatal all-cause stroke/fatal bleeding events. Risk was nonsignificantly higher with warfarin compared with no warfarin, HR, 1.30 (95% CI, 0.77 to 2.20).	No conclusions can be made on the net clinical benefit of warfarin in regard to risk of fatal all-cause stroke/fatal bleeding in patients on dialysis.
Retrospective population analysis Quebec, Canada, 1998–2007. Follow-up yr not given, *n*=1626, CKD stage 5 on HD, age>65 yr, Shah, *Circulation* 2014	Warfarin±aspirin (*n*=756) versus nonwarfarin± aspirin (*n*=870). Intention to treat.	Incidence rates per 100 person yr of ischemic stroke were 3.37 on warfarin and 2.91 not on warfarin. Nonsignificant increased risk with warfarin in comparison with no-warfarin use, HR, 1.14 (95% CI, 0.78 to 1.67). Incidence rates per 100 person yr of major bleeding[d] were 10.88 on warfarin and 7.31 not on warfarin. Increased risk of major bleeding, HR, 1.44 (95% CI, 1.13 to 1.85) with warfarin in comparison with no warfarin use.	Warfarin does not associate with reduced risk of ischemic stroke but associates with increased risk of bleeding in older adult patients on dialysis.
Prospective cohort study ≥1500 dialysis clinics in North America, 2010–2014. Follow-up 3839 patient yr[e], *n*=8589, CKD stage 5 on HD, Chan, *Circulation* 2015	Warfarin (*n*=8064), dabigatran (*n*=281), rivaroxaban (*n*=244)± aspirin. As treated.	Dabigatran rate ratio 1.78 (95% CI, 1.18 to 2.68) and rivaroxaban rate ratio 1.71 (95% CI 0.94, 3.12) were associated with a higher risk of hemorrhagic death relative to warfarin and higher risk of hospitalization or death from bleeding compared with warfarin (dabigatran rate ratio, 1.48; 95% CI, 1.21 to 1.81; rivaroxaban rate ratio, 1.38; 95% CI, 1.03 to 1.83).	The risk of mortality from bleeding and hospital-related bleeding is higher with dabigatran and rivaroxaban compared with warfarin in patients on dialysis. There were too few events of stroke and TE to detect meaningful differences.
Retrospective observational cohort United States Renal Data System, 2007–2011. Mean follow-up 1.41 yr, *n*=12,284, Shen, *AJKD* 2015	Warfarin±aspirin (*n*=1838) versus no anti-coagulation±aspirin (*n*=10,466). Intention to treat[f].	Rate of ischemic stroke per 100 person yr 2.3 on warfarin and 3.4 not on warfarin. Reduced risk of ischemic stroke on warfarin compared with no warfarin, HR, 0.68 (95% CI, 0.47 to 0.99). Rate of hemorrhagic stroke per 100 person yr 1.09 warfarin and 1.05 not on warfarin. Rates of GIB per 100 person yr 0.97 on warfarin and 0.98 not on warfarin. No difference in risk of hemorrhagic stroke, HR, 0.82 (95% CI, 0.37 to 1.81) or GIB, HR, 1.00 (95% CI, 0.69 to 1.44) with warfarin compared with no anti-coagulation.	In patients on maintenance HD, warfarin modestly reduced the risk of ischemic stroke.

Table 5. (Continued)

Study Characteristics and Publication	Intervention, Control, and Type of Analysis	Effectiveness and Harm Outcomes[a]	Conclusion
Retrospective observational cohort in the United States Renal Data System, 2010–2015. Follow-up time not given[f], n=9404, Siontis, *Circulation* 2018	Apixaban (n=2351) standard dose 5 mg twice daily (n=1034) and (n=1317) reduced dose 2.5 mg twice daily, matched 3:1 with warfarin (n=7053). As treated.	Ischemic stroke event rates per 100 person yr 8.8 in apixiban versus 11.8 in warfarin users, HR, 0.88 (95% CI, 0.69 to 1.12). Ischemic stroke event rates per 100 person yr 8.8 in apixiban standard dose versus 15.3 in reduced dose, HR, 0.61 (95% CI, 0.37 to 0.98). Bleeding event[g] rates per 100 person yr 18.3 bleeding apixiban versus 21.9 in warfarin users, HR, 0.72 (95% CI, 0.59 to 0.87). Major bleeding event rate per 100 person yr 18.3 in apixiban standard dose versus 20.3 in reduced dose, HR, 0.98 (95% CI, 0.68 to 1.42).	Apixaban at the standard 5 mg twice a day dose associated with lower risk of major bleeding compared with warfarin and no difference in ischemic stroke/systemic embolism.

As-treated analysis refers to time on drug as often done with statistical techniques using time-varying exposures (*e.g.*, time-dependent Cox proportional hazards models) or censoring if there is no anticoagulant prescription refill within a defined period of time. Intention-to-treat analyses use exposure (*e.g.*, warfarin versus no anticoagulation) as a time-fixed binary variable. Only the primary analysis is reported. *NEJM*, *New England Journal of Medicine*; HR, hazard ratio; 95% CI, 95% confidence interval; *JACC*, *Journal of the American College of Cardiology*; HD, hemodialysis; TE, thromboembolic; GIB, gastrointestinal bleed; TIA, transient ischemic attack; *AJKD*, *American Journal of Kidney Disease*.

[a]Adjusted analyses are reported.

[b]Hospitalization or death from all-cause stroke (ischemic and or hemorrhagic) or systemic thromboembolism (peripheral-artery embolism, ischemic stroke, and TIA). Hospitalization or death from major bleeding (gastrointestinal, intracranial, urinary tract, or airway). Outcome events were not separated by treatment group.

[c]This study was designed to evaluate net clinical benefit; outcomes of stroke/systemic thromboembolism/all bleeding, and fatal stroke/fatal bleeding were not reported separately. The numbers of outcome events were not separated by treatment group.

[d]Stroke defined as hospitalization or emergency department visit for ischemic cerebrovascular disease, TIA, or retinal infarct. Bleeding defined as hospitalization or emergency department visit for intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding.

[e]Follow up in patient years; 3226 for no anticoagulation, 123 for dabigatran, and 72 for rivaroxaban.

[f]As-treated analyses were also done for each outcome.

[g]Bleeding events included GIB, intracranial bleeding or major bleeding was defined by a critical site (such as intracranial), need for blood transfusion, or death.

so that dose adjustments can be made if GFR changes substantially.

In patients with CKD 4, 5, and 5(D), American Heart Association/American College of Cardiology/Heart Rhythm Society (ACC/AHA/HRS) guidelines recommend anticoagulation in patients with a CHA_2DS_2-VASc score >2 on the basis of extrapolation from general practice. They support the use of warfarin or reduced doses of DOACs in CKD 4 and 5 even though the safety and efficacy of DOACs have not been established in this group; moreover, ACC/AHA/HRS do not support dabigatran and rivaroxaban use once patients start dialysis (46). In contrast, KDIGO statements do not support any routine anticoagulation for stroke prevention in in CKD 4, 5, and 5(D) because there are no RCTs to support use of anticoagulation, in addition to the heighted risk of bleeding in this population, warfarin's association with accelerated vascular calcifications, and likely reduced effectiveness of anticoagulation from competing high mortality rates in CKD 4, 5, and 5(D) (5). As such, we believe that this represents clinical equipoise: we do not know whether the benefits outweigh the risks of anticoagulation in patients with atrial fibrillation with CKD 4, 5, and 5(D). For DOACs, accumulating evidence suggests a favorable benefit/risk ratio in advanced CKD through pharmacokinetically guided dosing (48) in addition to replicable stroke and bleeding outcomes in moderate CKD subgroup analyses from the original RCT (11–14), with similar results in an observational dialysis study (42); however, we believe that the totality of evidence is still inadequate to support the safe prescribing of DOACs in CKD 4, 5, and 5(D). If anticoagulation is desired in patients with GFR<30 ml/min, we recommend warfarin and await further evidence from ongoing safety RCTs being conducted in the dialysis population.

Our recommendations differ in the setting of calciphylaxis where prolonged warfarin is associated with developing the disease (49–51). Although rare (3.5 new cases per 1000 patient years), calciphylaxis carries a poor prognosis, with 45%–80% 1-year mortality rate (49). We encourage discontinuing warfarin in patients with calciphylaxis given that the competing risk of mortality is so high, which severely diminishes the stroke prevention benefits of anticoagulation. If anticoagulation is to be used, reduced dose apixaban (2.5 mg twice daily) is appropriate given that pharmacokinetic studies indicated drug bioaccumulation at 5 mg, twice daily dose in ESKD (24–26). Rivaroxaban 15 mg daily may also be reasonable (49).

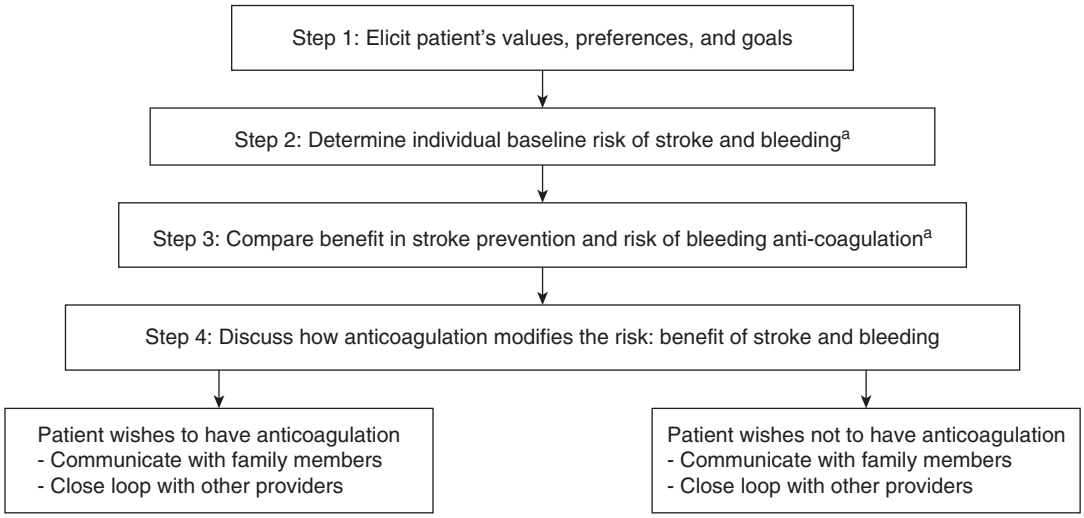

Figure 1. | **Anticoagulation is a shared decision between patients and physicians.** [a]Offer to refer the patient to the American College of Cardiology online decision-making tools on stroke and bleeding risks and treatment options for anticoagulation (Blood Thinners for Atrial Fibrillation: A Smart Decision Guide, https://www.cardiosmart.org/SDMAFib).

Shared Decision Making

Without robust evidence on anticoagulation in CKD stages 4, 5, and 5(D), we advise a shared decision-making process between the physician and patient on the basis of (*1*) the patient's values, preferences, and goals; (*2*) subjective assessment of the individual's baseline risk of stroke and bleeding; (*3*) guidance on the benefit in stroke prevention and risk of bleeding with anticoagulation; and (*4*) understanding of the available options for anticoagulation (Figure 1). Patients benefit from communication with their physicians through health awareness and empowerment (52). As emphasized in the KDIGO clinical controversies summary, a collaborative team-based approach through communication between primary care, cardiology, and nephrology is important to this complex decision. The American College of Cardiology has created online decision-making tools for clinicians to engage effective conversations with patients about treatment options for anticoagulation (Blood Thinners for AF: A Smart Decision Guide, https://www.cardiosmart.org/SDMAFib).

Future Direction

Two phase 3 RCTs of patients on maintenance dialysis are underway: RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) (ClinicalTrials Identifier: NCT02942407, $n=762$) and AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation [AF] and End-Stage Kidney Disease [ESKD]) (ClinicalTrials Identifier: NCT02933697, $n=222$). These are noninferiority trials with patients randomized to apixaban versus warfarin dose adjusted for INR 2–3. RENAL-AF uses 5 mg twice daily and 2.5 mg twice daily in patients who meet criteria for reduced dose for 15 months. AXADIA uses 2.5 mg twice daily for all patients for 6–24 months. The primary outcome is clinically relevant, nonmajor bleeding. Unfortunately, both of these trials lack a placebo arm and are unlikely to have adequate power to report stroke differences. A third RCT in the dialysis population, Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) (ClinicalTrials Identifier: NCT02886962, $n=855$), aims to compare the hemorrhagic and thrombotic risks of oral anticoagulation with vitamin K antagonists in comparison with no anticoagulation over 2 years.

Patients with advanced CKD and dialysis represent a vulnerable population at high risk for atrial fibrillation, stroke, and bleeding. Currently, we lack RCTs to answer the fundamental question of whether anticoagulation versus placebo confers more stroke prevention benefit than bleeding risk. Until such rigorous and adequately powered trials are executed, the role of anticoagulation in advanced CKD and dialysis will remain a mystery.

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