Korean Circ J. 2018 Oct;48(10):873-889
https://doi.org/10.4070/kcj.2018.0261
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Review Article

Check for updates

Anticoagulation for Stroke Prevention in Older Adults with Atrial Fibrillation and Comorbidity: Current Evidence and Treatment Challenges

Avi Sabbag, MD[1], Xiaoxi Yao, PhD[2], Konstantinos C. Siontis, MD[1], and Peter A. Noseworthy, MD[1,2]

[1]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
[2]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA

OPEN ACCESS

Received: Aug 9, 2018
Revised: Aug 14, 2018
Accepted: Aug 30, 2018

Correspondence to
Peter A. Noseworthy, MD
Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: noseworthy.peter@mayo.edu

ORCID iDs
Avi Sabbag
https://orcid.org/0000-0003-4295-6679
Peter A. Noseworthy
https://orcid.org/0000-0002-4308-0456

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Noseworthy P; Supervision: Noseworthy P; Writing - original draft: Sabbag A, Noseworthy P; Writing - review & editing: Yao X, Siontis KC.

ABSTRACT

The burden of atrial fibrillation (AF) is projected to increase substantially over the next decade in parallel with the aging of the population. The increasing age, level of comorbidity, and polypharmacy will complicate the treatment of older adults with AF. For instance, advanced age and chronic kidney disease have been shown to increase the risk of both thromboembolism and bleeding in patients with AF. Frailty, recurrent falls and polypharmacy, while very common among elderly patients with AF, are often overlooked in the clinical decision making despite their significant interaction with oral anticoagulant (OAC) and profound impact on the patient's clinical outcomes. Such factors should be recognized, evaluated and considered in a comprehensive decision-making process. The introduction of non-vitamin K oral anticoagulants has radically changed the management of AF allowing for a more individualized selection of OAC. An understanding of the available data regarding the performance of each of the available OAC in a variety of at risk patient populations is paramount for the safe and effective management of this patient population. The aim of this review is to appraise the current evidence, point out the gaps in knowledge, and provide recommendations regarding stroke prevention in older adults with AF and comorbid conditions.

Keywords: Frailty; Warfarin; NOAC; Stroke; Bleeding

INTRODUCTION

The overall prevalence of atrial fibrillation (AF) is increasing due to population aging and an increase in prevalence of other conditions that predispose to AF. It is projected that by 2030 there will be 12.1 million AF cases in the US alone.[1)2)] Advanced age is a critical determinant of the AF-related stroke and systemic embolic risks mandating oral anticoagulant (OAC) therapy.[3)] However, advanced age is associated with an increase in bleeding risk, which compounds the risk associated with anticoagulation.[4)]

This risk is further exacerbated by the fact that advanced age is often accompanied a higher comorbidity burden, polypharmacy, and frailty that further increase the risk of bleeding

kcj
Korean Circulation Journal

creating a therapeutic challenge for clinicians. Chronic kidney disease (CKD) is of particular interest since up to one-third of outpatients with AF have CKD,[5] and 15–20% of CKD patients have AF.[6][7] As the incidence of CKD is increasing,[8] an ever-growing patient population with both AF and CKD will require our attention. Also, current approaches of estimating the thromboembolic or bleeding risks with scores such as Congestive Heart Failure, Hypertension, Age ≥75 (Doubled), Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack (Doubled), Vascular Disease, Age 65–74, Female (CHA_2DS_2-VASc) and Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) may be insufficient in fully appreciating the net clinical benefit of OAC use in elderly patients in whom frailty and multi-comorbidity may play more important roles than traditional clinical risk factors.

A patient's risk of adverse outcomes, particularly major bleeding and more importantly the net clinical benefit of OAC may not be fully approached by simply calculating the CHA_2DS_2-VASc and HAS-BLAD scores. A comprehensive analysis of patient's correct clinical status and treatment regimen is needed. The aim of this review is to appraise the current evidence, review the challenges, and provide recommendations on the decision-making for stroke prevention in older adults with AF and comorbid conditions including kidney disease, frailty, recurrent falls, and polypharmacy (**Table 1**).

Table 1. Factors to consider in the management of elderly patients with AF

Factors	Details
Age	Net clinical benefit of warfarin over placebo was shown in all age groups[14][15] Dabigatran – equally effective as warfarin but associated with more extracranial major bleeding at age ≥80.[16] Apixaban – superior to warfarin in both safety and efficacy.[21] Edoxaban – equivalent to warfarin in efficacy, less bleeding in all age groups.[12] Rivaroxaban – equivalent to warfarin in both safety and efficacy.[19]
CKD (CrCl ≥30 mL/min)	Warfarin – clear net clinical benefit of warfarin over no treatment.[57-59] Apixaban – equal to warfarin in prevention of SEE regardless of CKD level. Safety advanced over warfarin increases in parallel to a decrease in CrCl.[64] Rivaroxaban – equal to warfarin in both safety and efficacy regardless of CKD level.[62] Edoxaban – equal to warfarin in both safety and efficacy regardless of CKD level. Dabigatran 150 mg – superior to warfarin in SSE prevention, equal risk of major bleeding. Not recommended in CrCl <50 mL/min.[63][82] Dabigatran 110 mg – equal efficacy to warfarin. lower bleeding in CrCl ≥50 mL/min.[63]
ESRD	No data showing clear benefit of OAC over no treatment. Rivaroxaban – evidence of more bleeding compared to warfarin.[73] Dabigatran – evidence of higher risk of major bleeding and death.[73] Apixaban 5 mg b.i.d. – reduced bleeding risk and similar stroke risk compared to warfarin.[78]
Frailty	No data showing clear benefit of OAC over no treatment. This is particularly concerning in severe frailty. Rivaroxaban – reduced SSE with similar bleeding risk compared to warfarin.[37] Apixaban and dabigatran – equivalent to warfarin in safety and efficacy.[37]
Recurrent falls	With few exceptions (uncontrolled epilepsy advanced multisystem atrophy) recurrent fall should not be a reason to withhold OAC. Edoxaban – reduction in all-cause mortality and major bleeding compared to warfarin in patients with high risk of falling.[97] Apixaban – superior safety and efficacy compared to warfarin.[98]
Polypharmacy	Risk of adverse effects increase including bleeding with number concomitant drug. Apixaban – consistent reduction in SSE regardless of the number concomitant drug. Apixaban also has a superior safety profile but the advantage is lost when ≥9 are used.[105] Rivaroxaban – safety and efficacy unaffected by number concomitant drug.[109]

AF = atrial fibrillation; b.i.d. = twice a day; CKD = chronic kidney disease; ESRD = end-stage renal disease; OAE = oral anticoagulant; SSE = stroke or systemic embolism.

https://doi.org/10.4070/kcj.2018.0261

kcj Korean Circulation Journal

ADVANCED AGE

Advanced age is one of the most important patient-related factors one needs to consider in the management of AF particularly when aiming to prevent thromboembolic events. The elderly generally have a higher burden of comorbidities, polypharmacy[9] and are more often frail. This combination complicates the decision-making of anticoagulation use due to the more significant competing risks as compared to younger populations. Increased age is one of the strongest independent predictors of thromboembolic events in patients with AF, accounting for a 1.5-fold increase in the relative risk of stroke for every additional decade.[3] However, the risk of stroke is paralleled by an increase in treatment-related bleeding, and particularly intracranial bleeding,[4] giving clinicians pause before initiating OAC therapy. This duality is well represented by the inclusion of age as a risk variable in both CHA_2DS_2-VASc and HAS-BLED scores.[10][11] Some evidence suggests that advanced age has a greater impact on the risk of bleeding than the risk of stroke, particularly above the age of 75 years.[12][13]

Warfarin

The landmark randomized controlled trials that compared warfarin to placebo and established its role in stroke prevention among patients with AF included only a modest (up to 20%) representation of individuals aged 75 years or above.[14] This population was directly addressed by the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial that randomized 973 patients aged ≥75 years to international normalized ratio (INR)-guided warfarin or aspirin 75 mg daily.[13] The study demonstrated that warfarin was superior to aspirin, with a 2% absolute annual reduction in stroke and arterial embolism. The annual risk of major bleeding with warfarin was 1.8% and it was comparable to treatment with aspirin. These findings may be cautiously further extended to nonagenarians based on a large observational study comprising 15,756 patients with AF and 14,658 without AF, all 90 years or older.[15] The study confirmed the higher risk of ischemic stroke among patients with AF, but found no increase in the risk of intracranial hemorrhage. Among patients with AF in this cohort, warfarin was associated with a 31% reduction in stroke risk (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.49–0.96) with no significant increase in the risk of intracranial hemorrhage. Therefore, when compared to no antithrombotic therapy or antiplatelet drugs, warfarin was associated with a positive net clinical benefit. However, theses result may be significantly affected by selection bias as only 3.9% of the AF population was treated with warfarin. Nevertheless, a subgroup analysis of the BAFTA trial showed consistent results and found no interaction with advanced age (grouped in to 75–79, 80–84, ≥85 years) and the efficacy of warfarin.[13]

Dabigatran

A total of 7,258 (40%) of the participants of the Long-Term Anticoagulation Therapy (RE-LY) trial were ≥75 years of age and the representation of this age group was well balanced in the 3 treatment arms of dose-adjusted warfarin, dabigatran 110 mg twice a day (b.i.d.) and dabigatran 150 mg b.i.d. A subgroup analysis compared the safety and efficacy of dabigatran to warfarin across 4 age groups (<75, 75 to <80, 80 to <85 and ≥85 years).[16] Both doses of dabigatran were as effective as warfarin in preventing thromboembolism with no significant interaction with age. However, that study showed a clear interaction between age and the risk of major bleeding in the different treatment arms. While both dabigatran doses were associated with lower major bleeding rates than warfarin among patients <75 years of age, the advantage of dabigatran was lost in older patients and the risk was higher compared to warfarin among those aged ≥80 years who were treated with dabigatran 150 mg b.i.d. This

https://doi.org/10.4070/kcj.2018.0261

kcj Korean Circulation Journal

was driven mainly by extracranial bleeding and there was no interaction between age group and treatment arm with respect to intracranial bleeding. Importantly, both dabigatran doses were found to have an interaction with age for the effect on all-cause mortality. Both dabigatran doses reduced mortality at lower ages (<75 years), but were similar to warfarin in patients 85 years or older. Furthermore, a meta-analysis of real world observational studies showed higher rates of gastrointestinal bleeding among patients aged ≥75 years compared to warfarin.[17]

Rivaroxaban

The Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial included 6229 patients (44%) aged ≥75 years.[18] Rivaroxaban was found to non-inferior to warfarin for the prevention of thromboembolism, resulted in a similar rate of bleeding events (both major an non major) but was associated with less intracranial bleeding. A subgroup analysis compared the safety and efficacy of rivaroxaban 20 mg once daily (o.d.) (or 15 mg o.d. if CrCl was <50 mL/min) to dose adjusted warfarin among patients aged ≥75 versus <75 years at recruitment.[19] There was no interaction between age and treatment for the effect on the composite endpoint of stroke/systemic embolism, major bleeding or mortality.

Apixaban

Of the total 18,201 patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[20] 30% (n=5,471) were <65 years old, 39% (n=7,052) were 65–75 years old, and 31% (n=5,672) were ≥75 years old. The safety and efficacy of apixaban 5 mg b.i.d. (or 2.5 mg b.i.d. in patients with 2 or more of the following factors: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL) was compared to warfarin across these 3 age groups.[21] There was no interaction between age and treatment with regards to stroke or systemic embolism, major bleeding, intracranial hemorrhage or mortality and apixaban resulted in lower rates of stroke or systemic embolism and major bleeding among patients aged ≥65. Furthermore, an additional analysis of patients aged ≥80 yielded consistent results with comparable rates of stroke or systemic embolism, and lower risk of major bleeding and intracranial hemorrhage as in the main analysis.

Edoxaban

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial randomized 21,105 patients to warfarin or edoxaban (60 or 30 mg o.d.).[22] Both doses of edoxaban were non-inferior to warfarin in the prevention of stroke or ischemic embolism, but were associated with less major bleeding or cardiovascular death. A subgroup analysis addressed the effect of age on the various treatment regimens by stratifying the cohort into 3 age groups: <65 (n=5,497, 26%), 65 to 74 (n=7,134, 34%), and ≥75 (n=8,474, 40%) years. There was no significant interaction between age and edoxaban with regards to stroke or systemic embolism, major bleeding or intracranial bleeding.[12] Post-hoc analyses of patients aged ≥80 years (n=3,591, 17% of the cohort) and patients aged ≥85 (n=899, 4.3% of the cohort) yielded consistent results.

https://doi.org/10.4070/kcj.2018.0261

kcj Korean Circulation Journal

FRAILTY

While aging is inevitably associated with some physiological decline, the extent this decline varies widely between individuals. Frailty may be viewed as an exaggeration of the aging process[23] resulting in loss of reserve and a diminished ability to withstand stress.[24] Frailty is very common with an estimated prevalence of 9.9% among individuals aged over 60 according to a large British study.[25] The prevalence is higher among women, the elderly and among racial and ethnic minorities.[25-27] It is associated with increased risk of adverse outcomes including falls, delirium, disability and mortality.[27-30] Identifying and quantifying frailty is not straightforward. Therefore, the use of well validated scales is important. The most widely used and validated models[31] are the phenotype model[28] and the Canadian Study of Health and Aging (CSHA) frailty index.[24]

AF is common among frail patients; moreover, AF has been shown to be associated with frailty independently of age, sex and other common comorbidities.[32] While frailty correlates with higher CHA_2DS_2-VASc and HAS-BLED scores in AF patients, it may be independently predictive of both cardiovascular and all-cause mortality.[33] It is, therefore, unsurprising that frailty is a common reason for discontinuing or not starting OAC.[34][35] There is very little information about the risk and benefits of long-term OAC treatment in this population. There are no randomized control trials (RCTs) comparing OAC to placebo and observational studies have the potential to be influenced by selection bias.

A large observational study based on US claims data compared propensity matched frail patients with AF treated with novel oral anticoagulants (NOACs) to patients treated with warfarin.[36] Frailty was defined by the Johns Hopkins Claims-based Frailty Indicator,[37] an algorithm design to identify patients meeting the Fried's Frailty Phenotype.[28] A total of 2,700, 2,784, and 5,270 patients on apixaban, dabigatran, and rivaroxaban respectively, were compared separately to an equal number of patients treated with warfarin. Apixaban and dabigatran resulted in similar rates of thromboembolism as warfarin. However, rivaroxaban was associated with reduced thromboembolic risk at 2 years without a significant difference in bleeding. However, these findings should be interpreted cautiously due to potential limitations of low statistical power and residual confounding.[37]

CHRONIC KIDNEY DISEASE

CKD is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or longer or with the presence of albuminuria.[38] It is independently associated with a 3.7-fold increase in the risk of stroke. CKD has a profound impact on platelet function, coagulation factors and the endothelium resulting in a pro-thrombotic state. This leads to increased activity of the coagulation system and platelet aggregation[39] which have additive effects in addition to AF-related thrombogenesis. In patients with both AF and CKD there is a 35% increase in relative risk of death[40] and more than a 2-fold increase in major cardiovascular adverse effects.[41]

The combination of AF and CKD is increasingly common, partly due to population aging and the increase in the prevalence of shared risk factors such as hypertension, diabetes and advanced age but also due to sheared pathophysiological processes that create a bidirectional relationship.[42] Thus, subjects with CKD are at a higher risk of developing AF

https://doi.org/10.4070/kcj.2018.0261

and the presence of AF increases the risk of developing renal dysfunction.[42] Moreover, AF is associated with more rapid progression of CKD and a 67% higher risk of developing end-stage renal disease (ESRD),[43] contributing to adverse outcomes and mandating close follow up with dose adjustments or even discontinuation of antiarrhythmic drugs, anticoagulants and other medications over time.

Patients with AF and CKD present a particular therapeutic challenge due to the higher bleeding risk.[44] Several large registries have demonstrated an increased risk of both intracranial and gastrointestinal bleeding that parallels the degree of renal dysfunction. Furthermore, renal dysfunction is associated with larger intracranial hematoma volumes, worst outcome after intracerebral hemorrhage[45] and an increased risk of hemorrhagic transformation after ischemic stroke.[46] This is the result of a multifactorial paradoxical decrease in platelet adhesion and aggregation. Possible pathophysiological mechanisms include decreased storage and secretion of platelet-activating mediators, altered intra-platelet calcium mobilization, disturbances in platelet aggregation, increased formation of vascular prostaglandin I2, impaired platelet glycoprotein IIb-IIIa receptor activation and its binding to fibrinogen and von Willebrand factor, anemia, and the presence of uremic toxins.[47-49]

Current guidelines[50][51] recommend using the CHA_2DS_2-VASc score as the default risk assessment tool for thromboembolic events, which, however, does not incorporate CKD as one of its component risk variables. Despite evidence of higher thromboembolic risk, CKD is not routinely considered as part of the thromboembolic risk stratification process. Attempts to incorporate CKD into the CHA_2DS_2-VASc score failed to show consistent improvement in its predictive value.[52][53] This is likely the result of strong associations with the other co-variants that comprise the score.[54] In light of these results, it is unclear if there is a subpopulation of AF patients in whom a certain degree of CKD may justify OAC despite an otherwise low or borderline CHA_2DS_2-VASc score.

Nevertheless, CKD is a component of all major bleeding risk scores, namely, the HAS-BLED, Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA), and Outcomes Registry for Better Informed Treatment (ORBIT) scores, with varying definitions of CKD between scores. All 3 scores have been validated for both warfarin[10][55] and the non-vitamin K antagonists (VKA) in current use and have been found to have a modest predictive value for bleeding. According the European Society of Cardiology (ESC) guidelines, a high score in one of those scales should not be considered a reason to withhold anticoagulation but rather a reminder to better control all the reversible factors such as labile international normalized ratios, excess alcohol, or concomitant use of nonsteroidal anti-inflammatory drugs and aspirin. Furthermore, in general the net clinical benefit of ischemic stroke prevention versus serious bleeding may even be greater in patients with a high HAS-BLED score.[56]

Vitamin K antagonists

The evidence of net clinical benefit of VKA use in patients with non-end-stage CKD is robust and is derived from several large retrospective observational cohort studies. These individual studies as well as a meta-analysis incorporating 19 of them,[57] suggested a significant decrease in incidence of thromboembolic events and the combined endpoint of bleeding and thromboembolic events.[58] A large prospective observational study from the SWEDEHEART registry[59] showed that warfarin treatment versus no treatment was associated with significant decrease in the composite outcome of death, myocardial infarction, and ischemic stroke without an increase in the risk of bleeding. The benefit was consistent irrespective of the

https://doi.org/10.4070/kcj.2018.0261

degree of CKD, even with epidermal GFR as low as 15 mL/min/1.73 m^2. Importantly, a large cohort study found that patients with moderate-to-severe CKD had a reduced time in therapeutic range during warfarin treatment despite similar monitoring intensity compared to patients with milder CKD. This indicates the importance of closer monitoring in such patients or consideration of alternative therapies.[60]

Non-vitamin K antagonists

All currently available non-VKAs are at least partly eliminated by the kidneys. The proportion of renal elimination is highest for dabigatran (up to 80%), lowest for apixaban (up to 27%), and intermediate for rivaroxaban and edoxaban (up to 36% and 50% respectively). Therefore, renal function should play a major role in the choice of specific agent and its dose. The safety and efficacy of all NOACs compared to warfarin in patients with mild to moderate CKD (CrCl ≥30 mL/min) was evaluated by subgroup analyses of pivotal NOAC studies.[61-64] Rivaroxaban was found to be equivalent to warfarin for both the risk of stroke and bleeding regardless of renal dysfunction level. The relative safety advantage of edoxaban was preserved throughout the spectrum of mild to moderate CKD.[61] For dabigatran, the rates of stroke or systemic embolism were lower for the 150 mg dose and similar to warfarin for the 110mg dose irrespective of renal function. However, the benefit of reduced bleeding with the dabigatran 110 mg dose over warfarin was absent in patients with CrCl <50 mL/min.[63] Lastly, an analysis of the ARISTOTLE trial data demonstrated that apixaban was associated with lower major bleeding risk compared to warfarin across the spectrum of renal function categories. In particular, the comparative safety of apixaban over warfarin became more apparent with advancing CKD severity, while maintaining the same comparative effects on stroke prevention.[64]

The cumulative data would suggest that NOACs as a group should be preferred over warfarin in this population, as is also supported by a recent Cochran review.[65] An important caveat is the lack of any randomized controlled data on the use of NOACs in patients with stage 4 CKD as those patients were excluded from the NOAC trials. Despite that, reduced dose regimens of apixaban, edoxaban and rivaroxaban are approved in Europe for use in patients with severe CKD (stage 4, i.e. a CrCl of 15–29 mL/min). Similarly, in the United States the Food and Drug Administration (FDA) has approved dabigatran, 75 mg b.i.d.; rivaroxaban, 15 mg o.d.; and apixaban, 2.5 mg b.i.d., for patients with stage 4 CKD.

END-STAGE RENAL DISEASE

The net benefit of OAC treatment in patients with ESRD undergoing dialysis remains a matter of debate since it has never been addressed in a placebo controlled randomized controlled trial. The risk of thromboembolism is particularly high in this population,[44][66][67] but it is accompanied by a significant increase in bleeding risk.[68] Furthermore, AF is associated with a significant increase in mortality risk in ESRD patients.[67] There is abundant evidence that warfarin lowers the risk of stroke in patients with severe CKD including those treated with dialysis, but it is equally well established that it also results in a significant increase in bleeding risk.[44][69] The question of net clinical benefit among dialysis patients was directly addressed in an analysis of a large national Danish registry.[58] The authors found no decrease in the combined endpoint of stroke of bleeding, nor a decrease in all-cause mortality or cardiovascular death. Furthermore, use of warfarin in ESRD is associated with a higher risk of calciphylaxis[70] possibly due to the inhibition of Matrix Gla protein, which is a vitamin

https://doi.org/10.4070/kcj.2018.0261

K-dependent inhibitor of vascular calcification.[71] The prevalence of calciphylaxis in chronic dialysis patients is estimated at 4% and warfarin may increase this risk more than 3-fold.[72]

Patients with ESRD were excluded from all NOAC RCTs and therefore all the available data regarding their use stems from observational studies. The largest cohort to date included 281 and 244 patients treated with dabigatran and rivaroxaban, respectively, and showed that both were associated with an increase in major bleeding compared to warfarin.[73] Dabigatran was even associated with a higher risk of hemorrhagic death. Importantly, the bleeding risk was significantly lower when rivaroxaban 15 mg o.d. or dabigatran 75 mg b.i.d. were used. The rates of stroke were too low to allow for any comparison. These results are unsurprising considering the pharmacokinetic studies that demonstrated significant exposure to the drugs in ERSD.[74][75]

Similar to dabigatran and rivaroxaban, ESRD patients were not included in the pivotal trial that led to the FDA approval of apixaban. However, the FDA approved an updated labeling for use of apixaban in ESRD based on a pharmacokinetic study.[76] The FDA-approved dose is 5 mg b.i.d. (unless the usual criteria for dose reduction are met) although other studies suggest that this may result in supra-therapeutic levels.[77] Data on clinical outcomes with use of apixaban in dialysis-dependent ESRD patients is very limited. A meta-analysis of 5 small observational studies concluded that apixaban was associated with a reduced bleeding risk and a similar stroke rate compared to warfarin.[78] Similar conclusions were reached by a larger administrative claims-based analysis of Medicare beneficiaries in the United States that included 2,351 patients on apixaban and 23,172 patients on warfarin.[79] In prognostic score-matched cohorts, there was no difference in the rates of thromboembolism between the apixaban and warfarin groups, but apixaban was associated with significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.87; p<0.001).These data support the use of apixaban over warfarin for stroke prevention in ESRD patients on dialysis who do not have a prohibitive bleeding risk and in whom anticoagulation is to be used. The larger question of which patients on dialysis would benefit anticoagulation and which would do better without this therapy remains largely unanswered.

The efficacy and long-term safety of edoxaban in ESRD patients was never tested in a clinical study. The drug levels, short-term safety and biomarkers of blood coagulation and fibrinolysis of a reduced dose (15 mg once a day [q.d.]) were tested in a small group of patients severe CKD (30≥ CrCl ≥15 mL/min). Plasma drug levels were comparable patients with normal real function receiving 60mg qD as was the bleeding rate.[80] Similar results have been reported regarding reduced dose of apixban (2.5 mg b.i.d.) in dialysis[77] patients and rivaroxaban (10 mg q.d.) in ESRD.[81] However these are not enough to insure long term safety and provide no information about efficacy. Therefore, the European Heart Rhythm Association issued no recommendation for routine use of any anticoagulation for ESRD patients with AF[50][82] and the American Heart Association and American College of Cardiology referend from recommending any of the NOACs in this setting.[83]

ANTICOAGULATION-RELATED NEPHROPATHY

Renal function is affected by multiple factors, including medications and comorbidities. As described previously, AF is associated with a higher risk of new CKD and more rapid progression of existing CKD.[42][43] An important consideration in this regard is

anticoagulation-related nephropathy (ARN), a common but often underdiagnosed syndrome that is estimated to affect 20% of patients treated with warfarin.[84] It is defined as acute kidney injury (AKI) without obvious etiology in the setting of an INR >3.0. ARN can lead to new-onset or progression of CKD, and is associated with significant increases in short-term and long-term mortality.[84-86] Renal biopsies of these patients reveal dysmorphic red blood cells in the glomerulus under electron microscopy, a uniform presence of hemorrhage and the absence of active glomerulonephritis or other inflammatory process.[86] A high index of suspicion is warranted in high-risk populations that include patients with CKD, diabetes mellitus, hypertension and the elderly.[84] The diagnosis should be suspected in warfarin-treated patients with unexplained hematuria in whom other causes of AKI have been ruled out. Treatment is supportive and is focused on controlling the INR, preventing hypertension and discontinuing concomitant treatment with anti-aggregants.[87]

There is evidence that NOACs may be more nephron-protective. A post hoc analysis of the RE-LY cohort showed a more accelerated decline in renal function in patients treated with warfarin compared to both dosages of dabigatran.[88] Importantly, poor control of INR (time in therapeutic range <65%) and diabetes were both associated with faster decline in renal function. A post hoc analysis of the ARISTOTLE trial found a similar proportion of decline in renal function in patients on warfarin and apixaban.[89] However, apixaban was superior to warfarin in both safety and efficacy regardless of the changes in renal function over time. A nationwide observational study form Taiwan found that all NOACs were associated with a lower risk of acute kidney injury compared to warfarin.[90] An analysis of a large U.S. administrative database suggested that NOACs, particularly dabigatran and rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin.[91]

RECURRENT FALLS

Like other markers of deconditioning and frailty, history of falls has been shown to independently predict a higher risk for all-cause mortality and thromboembolism.[92] Robust data regarding the management of patients at high risk of falls that require OAC have demonstrated that the benefit of stroke prevention generally outweighs the possible increased risk of intracranial bleeding.[93-96] Therefore, current ESC guidelines recommend OAC for this patient population with a few exceptions (e.g. epilepsy or advanced multisystem atrophy with backwards falls).[50] These recommendations are based mainly on experiences with warfarin use. A recent subgroup analysis of the ENGAGE AF-TIMI 48 trial showed consistent reductions in all-cause mortality and severe bleeding with edoxaban among patients at risk of falling.[97] Another analysis of the ARISTOTLE population showed that the superiority of apixaban with respect to safety and efficacy was consistent with or without a history of falls.[98] There are no similar data describing the net benefit of dabigatran or rivaroxaban in patients at high risk of falls.

POLYPHARMACY

Polypharmacy, the concomitant use of multiple different drugs, is common in AF patients, and particularly in the elderly.[9] Estimations vary widely depending on the population studied and the definition used. A large systematic review comprising of 10,455 individuals aged ≥65 years found that about 1 in 3 patients were prescribed ≥6 drugs.[99] Rates of

https://doi.org/10.4070/kcj.2018.0261

polypharmacy among AF patients may be even higher, ranging from 40% to 95%.[100][101] Polypharmacy is associated with an increased risk of mortality, adverse drug reactions, longer hospitalizations, higher re-hospitalization rates and higher risk for both thromboembolism and major bleeding.[102-105]

The extent of possible drug interactions with warfarin is well-established, as is the mechanism of those interactions. Warfarin is metabolized by the cytochrome P450 system with Cytochrome P450 2C9 isozyme (CYP2C9) as the most dominant component. Potent inhibitors of this system like amiodarone, gemfibrozil and antifungal agents thereby increase the bioavailability of warfarin and the risk of bleeding.[106] Antibiotics that reduce vitamin K production like quinolones and macrolides can also increase the risk of bleeding. Nonselective nonsteroidal anti-inflammatory drugs also potentiate the bleeding effects of OAC via the indirect inhibition of platelet activation.[107]

All 4 NOACs are excreted by the P-glycoprotein (P-gp) transporter. Several common cardiac drugs such as verapamil, dronedarone, amiodarone, and quinidine inhibit P-gp activity resulting in a significant increase in the plasma levels of all NOACs.[82] Cytochrome P450 3A4 has a more minor role in the elimination of apixaban and rivaroxaban, therefore, drugs that inhibit its function will increase drugs levels to a smaller degree. A recent analysis of 91,330 NOAC users from Taiwan, showed a significant increase in major bleeding when amiodarone, fluconazole, rifampin or phenytoin were concomitantly used with a NOAC.[108] The net benefit of apixaban and rivaroxaban over warfarin in patients treated with ≥5 drugs was specifically tested in post hoc analyses of the ARISTOTLE and ROCKET AF trials, respectively.[105][109] Apixaban showed a consistent reduction in the risk stroke or systemic embolism (SSE) regardless of number of concomitant drugs used, but the reduction in bleeding risk diminished with the increase in the number of concomitant drugs.[105] The extent of polypharmacy or use of ≥1 combined cytochrome P450 3A4 and P-gp inhibitors (like verapamil, diltiazem or amiodarone) did not affect the primary efficacy or safety outcomes of rivaroxaban in comparison to warfarin.[109]

CONCLUSION

The optimal use of OAC for stroke prevention in older patients with AF and comorbidities including kidney disease, frailty, recurrent falls, and polypharmacy remains a challenge for clinicians. Consistent with the RCT evidence in the general AF population, the NOACs appear to preserve their overall superior safety profile over warfarin in this population. However, currently available risk scores may be insufficient to characterize the attendant stroke and bleeding risks in this patient population. Therefore, individualized and thoughtful shared decision making that acknowledges current knowledge gaps is crucial.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. *Circulation* 2014;129:837-47.
PUBMED | CROSSREF
2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119-25.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2018.0261

3. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;69:546-54.
PUBMED | CROSSREF
4. Lopes RD, Guimarães PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood* 2017;129:2980-7.
PUBMED | CROSSREF
5. Kooiman J, van de Peppel WR, van der Meer FJ, Huisman MV. Incidence of chronic kidney disease in patients with atrial fibrillation and its relevance for prescribing new oral antithrombotic drugs. *J Thromb Haemost* 2011;9:1652-3.
PUBMED | CROSSREF
6. Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. *Can J Cardiol* 2013;29:S71-8.
PUBMED | CROSSREF
7. Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J* 2010;159:1102-7.
PUBMED | CROSSREF
8. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;382:260-72.
PUBMED | CROSSREF
9. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002;287:337-44.
PUBMED | CROSSREF
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100.
PUBMED | CROSSREF
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.
PUBMED | CROSSREF
12. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc* 2016;5:e003432.
PUBMED | CROSSREF
13. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503.
PUBMED | CROSSREF
14. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492-501.
PUBMED | CROSSREF
15. Chao TF, Liu CJ, Lin YJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 2018;138:37-47.
PUBMED | CROSSREF
16. Lauw MN, Eikelboom JW, Coppens M, et al. Effects of dabigatran according to age in atrial fibrillation. *Heart* 2017;103:1015-23.
PUBMED | CROSSREF
17. Romanelli RJ, Nolting L, Dolginsky M, Kym E, Orrico KB. Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2016;9:126-34.
PUBMED | CROSSREF
18. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
PUBMED | CROSSREF
19. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation* 2014;130:138-46.
PUBMED | CROSSREF
20. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
PUBMED | CROSSREF

21. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J* 2014;35:1864-72.
PUBMED | CROSSREF

22. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.
PUBMED | CROSSREF

23. Kanapuru B, Ershler WB. Inflammation, coagulation, and the pathway to frailty. *Am J Med* 2009;122:605-13.
PUBMED | CROSSREF

24. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489-95.
PUBMED | CROSSREF

25. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing* 2015;44:162-5.
PUBMED | CROSSREF

26. Harttgen K, Kowal P, Strulik H, Chatterji S, Vollmer S. Patterns of frailty in older adults: comparing results from higher and lower income countries using the Survey of Health, Ageing and Retirement in Europe (SHARE) and the Study on Global AGEing and Adult Health (SAGE). *PLoS One* 2013;8:e75847.
PUBMED | CROSSREF

27. Bandeen-Roche K, Seplaki CL, Huang J, et al. Frailty in older adults: a nationally representative profile in the United States. *J Gerontol A Biol Sci Med Sci* 2015;70:1427-34.
PUBMED | CROSSREF

28. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-57.
PUBMED | CROSSREF

29. Rockwood K, Howlett SE, MacKnight C, et al. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. *J Gerontol A Biol Sci Med Sci* 2004;59:1310-7.
PUBMED | CROSSREF

30. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. *Ageing Res Rev* 2013;12:719-36.
PUBMED | CROSSREF

31. Sourial N, Wolfson C, Bergman H, et al. A correspondence analysis revealed frailty deficits aggregate and are multidimensional. *J Clin Epidemiol* 2010;63:647-54.
PUBMED | CROSSREF

32. Polidoro A, Stefanelli F, Ciacciarelli M, Pacelli A, Di Sanzo D, Alessandri C. Frailty in patients affected by atrial fibrillation. *Arch Gerontol Geriatr* 2013;57:325-7.
PUBMED | CROSSREF

33. Kim SW, Yoon SJ, Choi JY, et al. Clinical implication of frailty assessment in older patients with atrial fibrillation. *Arch Gerontol Geriatr* 2017;70:1-7.
PUBMED | CROSSREF

34. Lefebvre MC, St-Onge M, Glazer-Cavanagh M, et al. The effect of bleeding risk and frailty status on anticoagulation patterns in octogenarians with atrial fibrillation: the FRAIL-AF study. *Can J Cardiol* 2016;32:169-76.
PUBMED | CROSSREF

35. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age Ageing* 2009;38:156-62.
PUBMED | CROSSREF

36. Martinez BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation. *J Am Heart Assoc* 2018;7:e008643.
PUBMED | CROSSREF

37. Segal JB, Chang HY, Du Y, Walston JD, Carlson MC, Varadhan R. Development of a claims-based frailty indicator anchored to a well-established frailty phenotype. *Med Care* 2017;55:716-22.
PUBMED | CROSSREF

38. Andrassy KM. Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. *Kidney Int* 2013;84:622-3.
PUBMED | CROSSREF

39. Yagmur E, Frank RD, Neulen J, Floege J, Mühlfeld AS. Platelet Hyperaggregability is highly prevalent in patients with chronic kidney disease: an underestimated risk indicator of thromboembolic events. *Clin Appl Thromb Hemost* 2015;21:132-8.
PUBMED | CROSSREF

40. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of incident atrial fibrillation and subsequent survival in Medicare patients. *J Am Heart Assoc* 2012;1:e002097.
PUBMED | CROSSREF

41. Hwang HS, Park MW, Yoon HE, et al. Clinical significance of chronic kidney disease and atrial fibrillation on morbidity and mortality in patients with acute myocardial infarction. *Am J Nephrol* 2014;40:345-52.
PUBMED | CROSSREF

42. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J* 2009;158:629-36.
PUBMED | CROSSREF

43. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation* 2013;127:569-74.
PUBMED | CROSSREF

44. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;367:625-35.
PUBMED | CROSSREF

45. Molshatzki N, Orion D, Tsabari R, et al. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. *Cerebrovasc Dis* 2011;31:271-7.
PUBMED | CROSSREF

46. Lee JG, Lee KB, Jang IM, et al. Low glomerular filtration rate increases hemorrhagic transformation in acute ischemic stroke. *Cerebrovasc Dis* 2013;35:53-9.
PUBMED | CROSSREF

47. Sohal AS, Gangji AS, Crowther MA, Treleaven D. Uremic bleeding: pathophysiology and clinical risk factors. *Thromb Res* 2006;118:417-22.
PUBMED | CROSSREF

48. Benigni A, Boccardo P, Galbusera M, et al. Reversible activation defect of the platelet glycoprotein IIb–IIIa complex in patients with uremia. *Am J Kidney Dis* 1993;22:668-76.
PUBMED | CROSSREF

49. Ng KP, Edwards NC, Lip GY, Townend JN, Ferro CJ. Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation. *Am J Kidney Dis* 2013;62:615-32.
PUBMED | CROSSREF

50. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962.
PUBMED | CROSSREF

51. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1-76.
PUBMED | CROSSREF

52. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R_2CHADS_2 index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013;127:224-32.
PUBMED | CROSSREF

53. Roldán V, Marín F, Manzano-Fernandez S, et al. Does chronic kidney disease improve the predictive value of the $CHADS_2$ and CHA_2DS_2-VASc stroke stratification risk scores for atrial fibrillation? *Thromb Haemost* 2013;109:956-60.
PUBMED | CROSSREF

54. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GY. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. *J Am Coll Cardiol* 2016;68:1452-64.
PUBMED | CROSSREF

55. Lip GY, Skjoth F, Nielsen PB, Kjaeldgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *Am J Med* 2018;131:574.e13-27.
PUBMED | CROSSREF

56. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;106:739-49.
PUBMED | CROSSREF

57. Providência R, Marijon E, Boveda S, et al. Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol* 2014;114:646-53.
PUBMED | CROSSREF

58. Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol* 2014;64:2471-82.
PUBMED | CROSSREF

59. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500-10.
PUBMED | CROSSREF

60. Yang F, Hellyer JA, Than C, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. *Heart* 2017;103:818-26.
PUBMED | CROSSREF

61. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 2016;134:24-36.
PUBMED | CROSSREF

62. Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;32:2387-94.
PUBMED | CROSSREF

63. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014;129:961-70.
PUBMED | CROSSREF

64. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012;33:2821-30.
PUBMED | CROSSREF

65. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev* 2017:CD011373.
PUBMED | CROSSREF

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

67. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant* 2012;27:3816-22.
PUBMED | CROSSREF

68. Poli D, Antonucci E, Zanazzi M, et al. Impact of glomerular filtration estimate on bleeding risk in very old patients treated with vitamin K antagonists. Results of EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics). *Thromb Haemost* 2012;107:1100-6.
PUBMED | CROSSREF

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

70. Galloway PA, El-Damanawi R, Bardsley V, et al. Vitamin K antagonists predispose to calciphylaxis in patients with end-stage renal disease. *Nephron* 2015;129:197-201.
PUBMED | CROSSREF

71. Lomashvili KA, Wang X, Wallin R, O'Neill WC. Matrix Gla protein metabolism in vascular smooth muscle and role in uremic vascular calcification. *J Biol Chem* 2011;286:28715-22.
PUBMED | CROSSREF

72. Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol* 2016;27:3421-9.
PUBMED | CROSSREF

73. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation* 2015;131:972-9.
PUBMED | CROSSREF

74. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010;49:259-68.
PUBMED | CROSSREF

75. Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol* 2010;70:703-12.
PUBMED | CROSSREF

76. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol* 2016;56:628-36.
PUBMED | CROSSREF

77. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol* 2017;28:2241-8.
PUBMED | CROSSREF

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

79. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in end-stage kidney disease patients with atrial fibrillation in the United States. *Circulation*. 2018 [Epub ahead of print].
PUBMED | CROSSREF

80. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. *Circ J* 2015;79:1486-95.
PUBMED | CROSSREF

81. De Vriese AS, Caluwé R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis* 2015;66:91-8.
PUBMED | CROSSREF

82. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330-93.
PUBMED | CROSSREF

83. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199-267.
PUBMED | CROSSREF

84. Brodsky SV, Collins M, Park E, et al. Warfarin therapy that results in an international normalization ratio above the therapeutic range is associated with accelerated progression of chronic kidney disease. *Nephron Clin Pract* 2010;115:c142-6.
PUBMED | CROSSREF

85. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011;80:181-9.
PUBMED | CROSSREF

86. Brodsky SV, Satoskar A, Chen J, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis* 2009;54:1121-6.
PUBMED | CROSSREF

87. Ware K, Brodsky P, Satoskar AA, et al. Warfarin-related nephropathy modeled by nephron reduction and excessive anticoagulation. *J Am Soc Nephrol* 2011;22:1856-62.
PUBMED | CROSSREF

88. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. *J Am Coll Cardiol* 2015;65:2481-93.
PUBMED | CROSSREF

89. Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: Insights from the aristotle randomized clinical trial. *JAMA Cardiol* 2016;1:451-60.
PUBMED | CROSSREF

90. Chan YH, Yeh YH, Hsieh MY, et al. The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: a nationwide cohort study in Taiwan. *Int J Cardiol* 2018;265:83-9.
PUBMED | CROSSREF

91. Yao X, Tangri N, Gersh BJ, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2017;70:2621-32.
PUBMED | CROSSREF

92. Banerjee A, Clementy N, Haguenoer K, Fauchier L, Lip GY. Prior history of falls and risk of outcomes in atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Am J Med* 2014;127:972-8.
PUBMED | CROSSREF

93. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677-85.
PUBMED | CROSSREF

94. Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med* 2005;118:612-7.
PUBMED | CROSSREF

95. Garwood CL, Corbett TL. Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Ann Pharmacother* 2008;42:523-32.
PUBMED | CROSSREF

96. Donzé J, Clair C, Hug B, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;125:773-8.
PUBMED | CROSSREF

97. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 analysis. *J Am Coll Cardiol* 2016;68:1169-78.
PUBMED | CROSSREF

98. Rao MP, Vinereanu D, Wojdyla DM, et al. Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE trial. *Am J Med* 2018;131:269-275.e2.
PUBMED | CROSSREF

99. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging* 2008;3:383-9.
PUBMED | CROSSREF

100. Proietti M, Raparelli V, Olshansky B, Lip GY. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. *Clin Res Cardiol* 2016;105:412-20.
PUBMED | CROSSREF

101. Wang Y, Singh S, Bajorek B. Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation. *Pharm Pract (Granada)* 2016;14:706.
PUBMED | CROSSREF

102. Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the elderly: a marker of increased risk of mortality in a population-based prospective study (NEDICES). *Gerontology* 2015;61:301-9.
PUBMED | CROSSREF

103. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13:57-65.
PUBMED | CROSSREF

104. Lim LM, McStea M, Chung WW, et al. Prevalence, risk factors and health outcomes associated with polypharmacy among urban community-dwelling older adults in multi-ethnic Malaysia. *PLoS One* 2017;12:e0173466.
PUBMED | CROSSREF

105. Jaspers Focks J, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ* 2016;353:i2868.
PUBMED | CROSSREF

106. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e152S-184S.
PUBMED | CROSSREF

107. Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med* 2005;165:189-92.
PUBMED | CROSSREF

108. Chang SH, Chou IJ, Yeh YH, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA* 2017;318:1250-9.
PUBMED | CROSSREF

109. Piccini JP, Hellkamp AS, Washam JB, et al. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. *Circulation* 2016;133:352-60.
PUBMED | CROSSREF