Renal Function in Atrial Fibrillation

A Multifaceted Dilemma

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Cardiac function and renal function gradually decrease with aging. Therefore, atrial fibrillation, as an expression of myocardial dysfunction, and conditions with reduced renal filtration of endogenous and exogenous substances often coexist. Both cardiac dysfunction and renal dysfunction are associated with increased risk of thromboembolism, which is further amplified by concurrent atrial fibrillation. Oral anticoagulation for stroke prevention is therefore commonly used in patients with atrial fibrillation and poor or worsening renal function. The clinical dilemma of balancing the risk of ischemic stroke and the risk of major bleeding when deciding on treatment with a non–vitamin K antagonist oral anticoagulant (NOAC) or vitamin K antagonist is thus frequently being encountered in elderly patients with atrial fibrillation. These issues are highlighted by 2 articles in this issue of *Circulation*[1,2] and several other recent articles.[3–7] Nearly 1 of 5 of the patients enrolled in the atrial fibrillation trials comparing different NOACs with warfarin had a creatinine clearance <50 mL/min.[4,6,7] In these trials, the risk of stroke, death, and bleeding was higher among patients with lower renal function at baseline in both the warfarin and NOAC arms. Substudies on outcomes in relation to renal function for the factor Xa inhibitors apixaban and rivaroxaban and the factor IIA inhibitor dabigatran have demonstrated that the superior efficacy and safety of these NOACs seen in the overall trial population extend to patients with renal dysfunction.[4,6,7] Apixaban was even associated with a larger benefit in major bleeding compared with warfarin in patients with atrial fibrillation and renal dysfunction.[7] The consistent effects of factor Xa inhibitors in patients with renal dysfunction are further supported by the current findings from the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48).[1] In the main trial, the factor Xa inhibitor edoxaban at a dose of 60 mg once daily was noninferior to warfarin for the prevention of stroke or systemic embolism and lowered the risk of major bleeding by 20%. The current data demonstrated that these results were sustained in patients with renal dysfunction at entry into the trial (creatinine clearance of 30–50 mL/min).[8]

The NOACs have different pharmacokinetic profiles with variable proportions of renal elimination for each compound.[8–11] Thus, for all NOACs, there are recommendations to use a lower dose in patients with poor renal function according to the individual summary of product characteristics. So far, the focus has been on the consequences of renal impairment in relation to cardiovascular risk and the selection of the most suitable antithrombotic treatment. However, little is known about the optimal dose in patients with good renal function, for example, in those with high creatinine clearance (>95 mL/min). This issue was initially highlighted during the US Food and Drug Administration Advisory Committee review on edoxaban with the unexpected finding of higher rates of stroke with edoxaban compared with warfarin in

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patients with atrial fibrillation and a creatinine clearance >95 mL/min. In the article by Bohula et al,[1] additional investigations into the efficacy and safety of edoxaban 60 mg once daily in patients with creatinine clearance >95 mL/min verified a signal of higher thromboembolic rates with edoxaban compared with warfarin in this setting, although this finding was based on small numbers of patients and events. This issue seems to be less a problem with apixaban[5] and dabigatran,[12] for which the efficacy and safety effects were also consistent at good renal function.

In this issue of *Circulation*, Fordyce and colleagues[2] highlight the question of the potential impact of gradual deterioration of renal function on the efficacy and safety of oral anticoagulation. So far, the information on renal function changes over time in patients with atrial fibrillation is scarce. In the ROCKET-AF trial (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation), the factor Xa inhibitor rivaroxaban, with ≈35% renal elimination, at 20 mg once daily was noninferior to warfarin in the prevention of stroke or systemic embolism and major bleeding both in the total cohort and in patients with poor renal function at baseline.[4,11] In this ROCKET AF substudy focusing on serial assessments of renal function, ≈25% of participants had worsening renal function during follow-up defined as a decrease in creatinine clearance of ≥20% from baseline. Patients with worsening renal function during the study had a higher mortality and composites of thromboembolic and cardiovascular events compared with those with stable renal function throughout the trial. Overall, it can be concluded that rivaroxaban compared with warfarin demonstrated at least preserved efficacy and safety in patients with worsening in renal function. Recently, an ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) substudy evaluating renal function changes over time demonstrated that apixaban remained superior to warfarin, regardless of normal, poor, or worsening renal function during the trial.[5] Similarly, preliminary data show that the advantages of dabigatran over warfarin also were sustained over time regardless of normal or poor renal function.[12] These accumulated results emphasize that the advantages of NOACs are maintained and that these treatments may be continued in patients with deteriorating kidney function, although the dose might need to be adjusted at lower levels of renal function.

CURRENT STATUS AND DILEMMAS AHEAD

The body of evidence for the superior efficacy and safety of NOACs compared with warfarin in atrial fibrillation is steadily increasing. The accumulated results on the performance of the different NOACs compared with warfarin at poor renal function are presented in the Figure. Overall, the advantages and safety/efficacy profiles of the different NOACs compared with warfarin are maintained at poor and deteriorating renal function. However, we still lack head-to-head comparisons of the different NOACs in different patient groups and different settings, which would allow us to further personalize treatment. There is also a need for more information on the best choice of compound and dose in patients with good renal function (>95 mL/min). An additional area that remains poorly understood is the potential long-term benefit of NOACs compared with warfarin, considering an eventual more rapid deterioration of renal function resulting from warfarin-induced vascular calcification.[3] Furthermore, antithrombotic strategies in patients with atrial fibrillation and end-stage renal disease remain a rather uncharted field. The evidence so far is based mainly on retrospective registry studies with conflicting results, with an obvious need

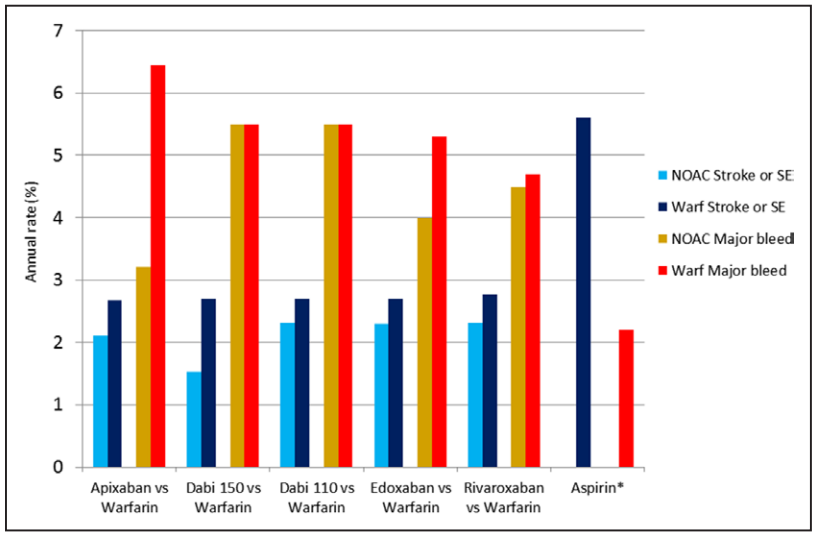

Figure. Rates of stroke and major bleeding.
Rates of stroke and major bleeding for the different non–vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin within each respective trial in the subset of patients with a creatinine clearance ≤50 mL/min. The inclusion criteria varied between trials.[8–11] *Event rates from 857 patients with atrial fibrillation and a creatinine clearance of 30 to 60 mL/min randomized to aspirin in AVERROES trial (A Phase III Study of Apixaban in Patients With Atrial Fibrillation).[13] Dabi indicates dabigatran; SE, systemic embolism; and Warf, warfarin.

for future prospective studies.[14,15] Finally, considering that the majority of patients with atrial fibrillation and renal dysfunction are elderly with a higher risk of stroke and bleeding, there is an even greater need for dynamic decision support tools to help physicians continuously balance the risk of stroke and the risk of bleeding during ongoing anticoagulant treatment. The recent development of new biomarker-based risk scores for stroke and bleeding seems to be one road worth testing further to improve outcomes in patients with renal dysfunction.[16–18]

DISCLOSURES

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FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

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