Use of NOACs for Stroke Prevention Across the Stroke Spectrum: Progress and Prospects

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Abstract

Multiple randomized controlled trials and many real-world evidence studies have consistently shown that non-vitamin K antagonist oral anticoagulants (NOACs) are preferable to vitamin K antagonists for thromboembolic stroke prevention in the majority of patients with atrial fibrillation (AF). However, their role in the management of patients with AF and co-morbidities, as well as in other patient populations with a high risk of stroke, such as patients with prior embolic stroke of undetermined source (ESUS) and those with atherosclerosis, is less clear. There is now increasing evidence suggesting that NOACs have a beneficial effect in the prevention of stroke in patients with AF and co-morbidities, such as renal impairment and diabetes. In addition, while studies investigating the efficacy and safety of NOACs for the prevention of secondary stroke in patients with a history of ESUS demonstrated neutral results, subanalyses suggested potential benefits in certain subgroups of patients with ESUS. One NOAC, rivaroxaban, has also recently been found to be effective in reducing the risk of stroke in patients with chronic cardiovascular disease including coronary artery disease and peripheral artery disease, further broadening the patient groups that may benefit from NOACs. In this article, we will review recent evidence for the use of NOACs across the stroke spectrum in detail, and discuss the progress and future prospects in the different stroke areas.

Introduction

Stroke is one of the leading causes of mortality and disability worldwide.1,2 The majority of strokes are ischaemic strokes, which can be further classified based on their aetiology: approximately 25% are associated with large-artery atherosclerosis, 25% with small artery disease and 20% with cardioembolism.3,4 Approximately 25% of ischemic strokes have no definite etiology and are categorized as cryptogenic.4,5

The term embolic stroke of undetermined source (ESUS) has been used to describe a subset of cryptogenic stroke that accounts for approximately 17% of all ischaemic strokes5,6 and is diagnosed by excluding other aetiologies.4,5 ESUS has been defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources.4 Despite a high risk of stroke recurrence,5 there are no specific guidelines in place for secondary prevention in stroke survivors with ESUS. Antiplatelet therapy has been recommended for patients with cryptogenic or non-cardioembolic stroke.7-9 Recent studies have evaluated the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with ESUS.10,11

The majority of cardioembolic strokes are precipitated by atrial fibrillation (AF),12 which is the most common sustained cardiac arrhythmia.13 AF increases the risk of stroke by approximately fivefold.14 To reduce the risk of stroke in patients with AF, current guidelines recommend the use of NOACs and vitamin K antagonists (VKAs), with a preference for NOACs in most patients.15,16 While the use of NOACs for stroke prevention in patients with AF is well established, their use in the management of patients with AF and co-morbidities is less well studied.

Atherosclerotic vascular disease is a leading cause of ischaemic stroke.4,17 Patients with previous atherothrombotic events and/or chronic cardiovascular (CV) disease have an increased risk of recurrent CV events, which underlines the importance of secondary prevention in these patients.17,18 While antiplatelet therapy is the current standard of care in the prevention of CV events among patients with atherosclerotic disease,18-21 combinations of antiplatelet agents and anticoagulants have also been studied in patients with acute22-26 and chronic CV disease.27

Recent years have seen exciting new data on the use of NOACs for the prevention of cardioembolic stroke in patients with AF, recurrent stroke in patients with ESUS and ischaemic stroke in patients with chronic CV disease. This review aims to summarize these new data, their clinical implications and discuss future prospects in these areas.

What is New in Stroke Prevention in Patients with Atrial Fibrillation?

While reducing the risk of stroke remains the priority in patients with AF, it is important to consider all elements of patient protection, including minimizing the risk of bleeding and preserving renal function, when anticoagulating these patients. The majority of patients with AF have co-morbidities, such as diabetes and renal disease, which have been shown to increase the risk of stroke,13,28 and need to be taken into account when making treatment decisions.

NOACs in Patients with Atrial Fibrillation

The efficacy and safety of NOACs in the prevention of ischaemic stroke in patients with AF have been demonstrated in the four pivotal phase III trials ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY and ROCKET AF, and a large meta-analysis comparing NOACs with warfarin.29-33 NOACs were found to be either equally or more effective than warfarin in reducing the risk of stroke in patients with AF, and were associated with significant reductions in intracranial haemorrhage (ICH) and mortality, with similar rates of major bleeding.29-33 However, except for apixaban, NOACs were shown to increase the rate of gastrointestinal bleeding by approximately 25% compared with warfarin.33 It should be noted that the baseline stroke and bleeding risk of patients in the trials differed substantially, with ROCKET-AF recruiting the highest proportion of patients with a CHADS2 score ≥3. The findings of the four phase III trials are further supported by various real-world studies,34-37 including a recent meta-analysis which also suggested a potential difference in stroke risk reduction between the different NOACs.36 In this meta-analysis, rivaroxaban and dabigatran, but not apixaban, were associated with a significantly lower risk of ischaemic stroke versus VKAs.36 The risk of major bleeding was similar for rivaroxaban and VKAs, and lower for dabigatran or apixaban compared with VKAs.36 However, many studies included in the analysis did not report the dose of NOAC used and, given that the analysis considers real-world data, the inevitable selection biases limit the ability to draw conclusions.36 Inappropriate dosing has been shown to impact the effectiveness of NOACs,38 and will be discussed later in more detail.

Renal Function

Renal function is an important aspect to consider when using anticoagulant therapy in patients with AF (**Fig. 1**).16 Several factors, including AF itself, older age, hypertension and co-morbidities such as diabetes, can increase the risk of renal impairment.39 Impairment of renal function has not only been associated with an increased risk of thromboembolic events but also with an increased rate of bleeding.28,40 In addition, because all four NOACs are partially eliminated via the kidneys, dose reductions are necessary to avoid drug accumulation in patients with renal impairment.16 Therefore, guidelines recommend assessing renal function in patients with AF at treatment initiation and at least yearly thereafter to select the appropriate dose.15,16 If renal function worsens, renal function testing is required more frequently and dosages might need to be adjusted, in line with label recommendations.15,16,41

Prespecified subgroup analyses of the phase III trials of NOACs in AF and a large meta-analysis of these trials demonstrated that the relative efficacy and safety of NOACs versus warfarin was maintained in patients with AF and mild-to-moderately impaired renal function (**Table 1**).33,42-45

In the meta-analysis, NOACs versus warfarin reduced the risk of stroke or systemic embolism (SE) by 21% in patients with creatinine clearance (CrCl) <50 mL/min (hazard ratio [HR] 0.79,95% confidence interval [CI]: 0.65–0.96) and by 25% in patients with CrCl 50–80 mL/min (HR 0.75, 95% CI: 0.66–0.85).33 Major bleeding events were similar for NOACs and warfarin in patients with CrCl <50 mL/min (HR 0.74, 95% CI: 0.52–1.05) and those with CrCl 50–80 mL/min (HR 0.91, 95% CI: 0.76–1.08).33

Real-world evidence (RWE) supports the favourable benefit–risk profile of NOACs versus warfarin46,47 or phenprocoumon48,49 in patients with AF and renal impairment seen in phase III trials. There is only limited evidence for the use of NOACs in patients with AF and advanced chronic kidney disease (CKD) or end-stage renal disease. Patients with an estimated glomerular filtration rate (eGFR) <25–30 mL/min were excluded from all randomized trials comparing NOACs with warfarin29-32 and RWE studies have reported conflicting safety results.50-55 Currently, the Food and Drug Administration provides guidance for the use of apixaban and rivaroxaban, but not dabigatran or edoxaban, in patients with end-stage renal disease on dialysis, which are based on pharmacokinetic studies and limited real-world data.56-59 Results of the randomized trial RENAL-AF, which was stopped early due to loss of funding, were recently presented at the American Heart Association congress 2019.60 After 1-year follow-up, apixaban 5 mg twice daily (bid) was associated with similar rates of bleeding and stroke as warfarin among patients with end-stage renal disease on dialysis.60 The randomized trials AXADIA and SAFE-HD, that are ongoing, will provide more clarity on the treatment effect of NOACs versus VKAs in patients with severe renal disease.61,62

Renal function decline is commonly observed in patients with AF treated with oral anticoagulants41 and has been either linked to vascular calcification or anticoagulant-related nephropathy (ARN).63-65 Anticoagulant-associated worsening of renal function may be caused by renovascular calcification.65 Evidence suggests that vascular calcification is linked to VKAs but not NOACs **(Fig. 2A)**.63,66 ARN is a form of acute kidney injury (AKI) caused by excessive anticoagulation.63,64 Repeated episodes of AKI may accelerate CKD progression.67 ARN has originally been described in patients who received overdoses of warfarin, but it has also been reported occasionally in patients treated with NOACs.63,64,68 Potential underlying molecular mechanisms have been suggested for the roles of warfarin or dabigatran in ARN, including thrombin depletion, reductions in activated protein C and inhibition of factor VII **(Fig. 2B).**63,69,70 Although there is growing evidence that ARN is a potentially serious complication of anticoagulation, the mechanisms are still poorly understood and the true incidence of NOAC-related nephropathy is yet to be determined in clinical studies.63,71,72

Several real-world studies suggest that NOACs may be associated with better preservation of renal function than warfarin in routine clinical practice (**Fig. 3**).41,49,73-80 In a large US administrative database analysis, NOACs, in particular rivaroxaban and dabigatran, were associated with lower risks of renal decline compared with warfarin.41 Cohort studies in Taiwan also suggested a lower risk of AKI for apixaban, dabigatran and rivaroxaban compared with warfarin in patients with and without a history of CKD,74,75 which was also observed in an administrative healthcare database analysis in Quebec, Canada.76 In a large US cohort study that analysed the risk of AKI with NOACs across the spectrum of eGFR, apixaban, dabigatran and rivaroxaban were associated with a 28% risk reduction of AKI versus warfarin in patients with relatively preserved renal function (eGFR ≥ 60 mL/min/1.73 m2).73 In patients with an eGFR of 30–59 mL/min/1.73 m2, only dabigatran reduced the risk of AKI compared with warfarin.73 Evidence for the potential nephroprotective effect of NOACs has been derived from real-world studies with rivaroxaban. The RIVAL study, a retrospective claims analysis using US Truven MarketScan data, suggested that patients receiving rivaroxaban are less likely to develop AKI and progress to stage 5 CKD or need haemodialysis than those receiving warfarin.77 Recent results from the retrospective database analyses RELOADED and CALLIPER further support the nephroprotective effect of rivaroxaban.49,79 The ongoing multicentre registry, XARENO, will provide more information on renal outcomes in patients with AF and renal impairment receiving rivaroxaban for stroke prevention.81 In this study, patients with moderate-to-severe renal impairment (eGFR 15–49 mL/min per 1.73 m2) are allocated to treatment with rivaroxaban, VKA or no treatment, and are prospectively followed for an estimated mean duration of 18 months to assess changes in renal function and clinical outcomes.81

The findings from the clinical trials and RWE studies are also acknowledged in an update to the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines on the management of AF, which state that ‘*Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with a lower risk of adverse renal outcomes than warfarin in patients with AF’.*82 This highlights the need to minimize renal function decline in patients with AF treated with oral anticoagulants.

Diabetes and Atrial Fibrillation

Diabetes, renal function and CV risk are closely interlinked. Diabetes is a common   
co-morbidity in patients with AF, and its presence is associated with an increased risk of developing AF.13,83 Diabetes is also an independent risk factor for CV disease and has been shown to increase the risk of stroke and thromboembolism in patients with AF through several different mechanisms (**Fig. 4**).84-90 In addition, type 2 diabetes is the leading cause of renal failure in the developed world,91 with moderate-to-severe kidney disease estimated to be found in 15–27% of patients with diabetes.92-94 Renal function decline in diabetes may be due to protease-activated receptor-induced inflammatory nephropathy (**Fig. 2C**).95-99

Importantly, the combination of diabetes and renal impairment is associated with a higher risk of CV events and mortality than either co-morbidity alone,92,100 underlining the importance of CV prevention in these particularly vulnerable patients.

Evidence suggests that NOACs are an effective treatment option in stroke prevention in patients with AF and diabetes.33,88,101-104 Subgroup analyses of the phase III trials and meta-analyses of these trials demonstrated that NOACs were at least as effective as warfarin in reducing the risk of stroke and offer a similar safety profile in patients with AF and diabetes **(Table 1)**.33,88,101-104 A subanalysis of patients with diabetes in the ARISTOTLE trial found that apixaban was associated with a 25% risk reduction of stroke/SE (HR 0.75, 95% CI: 0.53–1.05) and an 11% risk reduction of CV death (HR 0.89, 95% CI: 0.66–1.20) compared with warfarin.101 Major bleeding rates were similar for apixaban and warfarin in patients with diabetes.101 In a subanalysis of patients with diabetes in RE-LY, dabigatran 150 mg and dabigatran 110 mg were associated with 39% (HR 0.61, 95% CI: 0.41–0.91) and 26% (HR 0.74, 95% CI: 0.51–1.07) reductions in the risk of stroke/SE and 14% (HR 0.86, 95% CI: 0.65–1.13) and 19% (HR 0.81, 95% CI: 0.62–1.07) reductions in the risk of CV death, respectively.102 The risk of major bleeding was similar for both doses of dabigatran versus warfarin.102 In the prespecified subanalysis of ROCKET AF, rivaroxaban resulted in an 18% risk reduction of stroke/SE (HR 0.82, 95% CI: 0.63–1.08) and a 20% risk reduction (HR 0.80, 95% CI: 0.64–0.99) of CV death compared with warfarin, with no difference in the risk of major bleeding. In the subanalysis of ENGAGE AF-TIMI 48 in patients with diabetes, high-dose edoxaban (60 mg once daily) was similarly effective to warfarin in reducing the risk of stroke/SE (HR 0.93, 95% CI: 0.71–1.23) and reduced the risk of major bleeding (HR 0.79, 95% CI: 0.65–0.96).104

The benefit of NOACs versus VKAs in patients with AF and diabetes seen in phase III trials was further supported by RWE studies (**Fig. 5**).78,105,106 Large retrospective analyses of US claims data showed that rivaroxaban was equally as effective as warfarin in reducing the risk of stroke/SE105 and more effective than warfarin in reducing major adverse CV events (MACE) and major adverse limb events, with no difference in major bleeding.106 In a retrospective analysis using German claims data, rivaroxaban, apixaban and edoxaban were found to have a similar risk of stroke/SE compared with phenprocoumon, and a numerical benefit over phenprocoumon in the risk of ICH.78 Considering the high risk of renal impairment in patients with diabetes, studies also investigated the effect of NOACs on renal function in patients with AF and diabetes. In these retrospective database analyses, NOACs were associated with a lower risk of adverse renal events versus phenprocoumon78 or warfarin,80 supporting the nephroprotective effect of NOACs in patients with AF and diabetes.

Stroke Risk and NOAC Dosing

The four phase III trials, ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY and ROCKET AF, also investigated the efficacy and safety of reduced doses of NOACs in patients meeting specific criteria.29-32 Dose adjustment of NOACs is recommended in the label for patients with moderate renal impairment, according to the dose reduction criteria investigated in these trials.107-110 With regard to apixaban and dabigatran, additional criteria, such as older age and low body weight, need to be met to apply dose reductions.108,109 These dose reduction criteria vary slightly dependent on the regulatory agency. For example, in the EU, reduced doses of dabigatran are recommended for patients with moderate renal impairment who are ≥80 years of age and/or receive concomitant verapamil.109 In patients with moderate renal impairment aged 75–80 years and/or with gastritis, oesophagitis or gastroesophageal reflux, or an increased risk of bleeding, the thromboembolic and bleeding risk will need to be assessed individually to determine the dose.109 Dose reductions for apixaban are indicated for patients with moderate renal impairment aged ≥80 years or body weight ≤60 kg.108 Reduced doses of edoxaban are not only recommended for renal impairment but also for other single criteria, such as concomitant use of P-glycoprotein inhibitors or body weight ≤60 kg.110 Rivaroxaban is the only NOAC for which dose reduction is based solely on renal function.107

Adherence to recommended dosing is important, as inappropriate dosing of NOACs has been shown to impact clinical outcomes.38,111-113 Patients may receive an inappropriate dose because of lack of adjustments for certain clinical features specified by recommended labelling, such as renal function, weight or age. This may be because of physician concerns, such as increased risk of bleeding (particularly when assessing complex patients) or the barriers that multiple parameters may represent in determining the correct dose.38,111,112 Patient-level factors also contribute to poor adherence and persistence to treatment, such as financial barriers or treatment burden.114 Failure to reduce the dose of NOACs in patients with renal disease, in whom it is indicated, may result in an increase in the risk of bleeding; in contrast, inappropriate dose reduction, that is inconsistent with the label, may decrease the effectiveness of stroke prevention.38 Results from a large real-world cohort study demonstrated that lower doses of apixaban in patients with normal or mildly reduced renal function were found to increase the risk of stroke by approximately five times compared with the standard dose.38 While RWE for edoxaban is currently limited, it could be speculated that the same reduction in effectiveness might also be true for inappropriate dose reductions of edoxaban because, like apixaban, the reduced dose is half the full dose. No such reductions have been observed for rivaroxaban or dabigatran where the reduced dose is 75% and 73% respectively of the full dose.

Studies of NOACs in the Secondary Prevention of ESUS

Several clinical trials have been initiated to evaluate the efficacy and safety of NOACs for the secondary prevention of stroke in stroke survivors with ESUS (**Table 2**).10,11,115,116 NAVIGATE ESUS was the first trial that compared a NOAC (rivaroxaban) with aspirin in stroke survivors with a recent history of ESUS.10 The trial was terminated prematurely because use of rivaroxaban resulted in higher rates of major bleeding compared with aspirin (1.8% vs 0.7%; HR 2.72, 95% CI: 1.68–4.39; *p*<0.001), without the benefit of reducing the risk of recurrent stroke/SE (**Fig. 6A**).10 The RE-SPECT ESUS trial that compared dabigatran with aspirin in ESUS has recently been completed.11 Similar to the results of NAVIGATE ESUS, dabigatran did not significantly reduce the risk of recurrent stroke versus aspirin (**Fig. 6A**).11 However, a reduction was reported in the risk of disabling stroke with dabigatran compared with aspirin (0.6% vs 0.9%; HR 0.59, 95% CI: 0.36–0.96). Major bleeding rates with dabigatran were similar to those reported for aspirin (1.7% vs 1.4%; HR 1.19, 95% CI: 0.85–1.66),11 which was much higher than the bleeding rate associated with aspirin in the NAVIGATE ESUS trial. The efficacy and safety of apixaban in secondary stroke prevention in stroke survivors with ESUS are being investigated in the two clinical trials ATTICUS and ARCADIA.115,116 A secondary analysis of NAVIGATE ESUS demonstrated that rivaroxaban versus aspirin was associated with a reduced risk of recurrent ischaemic stroke in stroke survivors with ESUS with moderate or severe left atrial enlargement (1.7% vs 6.5%; HR 0.26, 95% CI: 0.07–0.94; *p*=0.02).117 A subgroup analysis of RE-SPECT ESUS suggested that dabigatran might be effective in reducing the risk of stroke in elderly stroke survivors (≥75 years) compared with aspirin (7.8% vs 12.4%; HR 0.63, 95% CI: 0.43–0.94).11 Therefore, despite the neutral results of NAVIGATE ESUS and RE-SPECT ESUS, there is a possibility that NOACs may provide favourable efficacy and safety profiles in the prevention of recurrent stroke in particular subgroups of stroke survivors enrolled in these trials, although further research is needed.

It is also important to note that several factors, such as dosing or the heterogeneous aetiology of ESUS, could have affected outcomes in these trials. Considering that the standard dose of rivaroxaban for stroke prevention in patients with AF is 20 mg, it is possible that the rivaroxaban dose of 15 mg used in NAVIGATE ESUS was not high enough to achieve the maximum therapeutic effect. In addition, not all potential embolic sources of ESUS, such as covert AF, atrial cardiopathy, left ventricular disease, aortic and non-stenotic carotid atherosclerosis, patent foramen ovale and cancer, respond equally to NOACs.118 A recent analysis demonstrated that there is a major overlap of potential embolic sources in stroke survivors with ESUS, which may explain the neutral results of the NAVIGATE ESUS and RE-SPECT ESUS trials.118 Among all potential embolic sources, patients with AF had the highest risk of stroke recurrence, highlighting the need to identify these patients early.118 In the NAVIGATE ESUS trial, 3% of patients were found to have AF during the course of the study.10 Cardiac rhythm monitoring was performed prior to randomization to exclude patients with AF, but the extent of screening for AF was not specified, other than as a minimal requirement.10 Despite attempts to exclude AF in the NAVIGATE and RE-SPECT ESUS trials, which may be effective in the short term, patients with relatively infrequent AF may suffer AF recurrences in the long term and then derive benefit from NOACs. Ongoing trials are investigating intensified monitoring for AF in patients with ESUS with the aim to identify predictors of covert AF.119,120 However, covert AF now seems to be a less important source of ESUS than originally thought.121

Evidence for NOACs in Atherosclerotic Stroke Prevention

The use of a NOAC combined with an antiplatelet agent has recently been studied in the secondary prevention of CV events, including stroke, in patients with chronic CV disease.27 The COMPASS trial in patients with atherosclerotic vascular disease demonstrated that the combination of rivaroxaban 2.5 mg bid plus aspirin, but not rivaroxaban 5 mg bid alone, was more effective than aspirin alone in reducing the risk of MACE, defined as CV death, stroke or MI.27 Rivaroxaban 2.5 mg bid plus aspirin was associated with a relative risk reduction of MACE of 24% versus aspirin alone (HR 0.76, 95% CI: 0.66–0.86; *p*<0.001) and an absolute risk reduction of 1.3%, corresponding to a number needed to treat of 77. In contrast, monotherapy with rivaroxaban 5 mg bid did not significantly reduce MACE compared with aspirin (HR 0.90, 95% CI: 0.79–1.03; *p*=0.12).27 While the rate of major bleeding was higher with the combination therapy than with aspirin alone, there was no difference in the rates of fatal bleeding or ICH between the two groups.27 Interestingly, the outcome of MACE was driven by a 42% reduction in the risk of stroke and an absolute risk reduction of 0.7%, corresponding to a number needed to treat of 143 (HR 0.58, 95% CI: 0.44–0.76; *p*<0.0001; **Fig. 6B**).27 A recent subanalysis of the COMPASS data showed that this reduction was consistent in patients with coronary artery disease or peripheral artery disease at high risk of stroke, such as those with a previous stroke or those with diabetes.122 This analysis further demonstrated that the beneficial effect of rivaroxaban 2.5 mg bid plus aspirin in stroke prevention was primarily driven by a 49% relative risk reduction in ischaemic stroke (HR 0.51, 95% CI: 0.38–0.69; *p*<0.0001), which was partially offset by a non-significant increase in haemorrhagic stroke.122 A secondary analysis of the COMPASS trial investigating the effect of the combination therapy on different subtypes of ischaemic stroke, showed that rivaroxaban 2.5 mg bid plus aspirin was associated with a significant reduction in cardioembolic stroke (HR 0.40, 95% CI: 0.20–0.78; *p*=0.005) and ESUS (HR 0.30, 95% CI: 0.12–0.74; *p*=0.006) compared with aspirin alone.123 No significant reductions were observed in patients with other subtypes of ischaemic stroke.123 Based on these findings, it is likely that this, and other anticoagulant–antiplatelet combination therapies, will be investigated in randomized controlled trials in patients with ESUS and those with ESUS and atherosclerosis in the near future.

Stroke survivors with heart failure or patients with heart failure and AF with or without sinus rhythm also have an increased risk of stroke compared with the general population.124,125 In COMMANDER HF, rivaroxaban 2.5 mg bid added to antiplatelet therapy and standard heart failure therapy did not reduce the composite of death, stroke or MI compared with placebo in patients with heart failure and reduced ejection fraction, coronary artery disease, and without AF; however, this combination seemed to reduce the risk of stroke alone.126 A post hoc analysis of COMMANDER HF demonstrated that the addition of rivaroxaban 2.5 mg bid to background antiplatelet therapy reduced the risk of all-cause stroke or transient ischaemic attack compared with placebo by 32% (HR 0.68, 95% CI: 0.49–0.94; *p*=0.02).127

The results of the COMPASS trial have led to the approval of rivaroxaban 2.5 mg bid in combination with aspirin for the prevention of atherothrombotic events in patients with atherosclerotic vascular disease.107 Rivaroxaban is so far the only NOAC approved for this indication, and, although it is plausible that combination therapies with aspirin and other NOACs may also be associated with a beneficial effect, current evidence does not support this. Furthermore, other NOAC studies did not evaluate very low doses in combination with an antiplatelet.25,128

Conclusions

In the past few years, new data have been published on the use of NOACs across the stroke spectrum: for the prevention of thromboembolic stroke, ESUS and atherosclerotic stroke. While NOACs are an established treatment option in the prevention of thromboembolic stroke in patients with AF, recent data suggest differential effects of NOACs in patients with co-morbidities such as renal impairment or diabetes. In addition, the efficacy and safety of NOACs have been investigated in the prevention of recurrent stroke in patients with a recent history of ESUS. Even though the trials for rivaroxaban and dabigatran in ESUS were both neutral, subanalyses suggested a potential benefit of these NOACs in certain subgroups of patients with ESUS. Rivaroxaban 2.5 mg bid combined with aspirin was also found to be effective in reducing the risk of stroke and other CV events in patients with chronic CV disease. While these new data contribute to our understanding of NOACs in the prevention of stroke across the stroke spectrum, more data are still needed to fill the remaining gaps in our knowledge.

Conflict of Interest

A.J.C. has received institutional grants and personal fees from Bayer AG, Boehringer Ingelheim, BMS, Daiichi Sankyo and Pfizer, and personal fees from Abbott and Boston Scientific.

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References

1. World Health Organization. The top 10 causes of death. 2018. Available at: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. Accessed 8 September 2020

2. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circ Res 2017;120:439–448

3. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke 2009;40:2068–2072

4. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429–438

5. Tomek A. Embolic stroke of undetermined source (ESUS). CNS 2018;4

6. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke 2017;48:867–872

7. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–2236

8. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008;133:630S–669S

9. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e601S–e636S

10. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191–2201

11. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906–1917

12. Topcuoglu MA, Liu L, Kim DE, Gurol ME. Updates on prevention of cardioembolic strokes. J Stroke 2018;20:180–196

13. LaMori JC, Mody SH, Gross HJ, et al. Burden of comorbidities among patients with atrial fibrillation. Ther Adv Cardiovasc Dis 2013;7:53–62

14. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–988

15. 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;37:2893–2962

16. 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;39:1330–1393

17. Adams HP, Jr. Secondary prevention of atherothrombotic events after ischemic stroke. Mayo Clin Proc 2009;84:43–51

18. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;55:305–368

19. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–477

20. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458–2473

21. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315

22. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969–974

23. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE, Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109–113

24. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699–708

25. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–2789

26. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19

27. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319–1330

28. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009;119:1363–1369

29. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–1151

30. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–891

31. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992

32. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–2104

33. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–962

34. Coleman CI, Peacock WF, Bunz TJ, Alberts MJ. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and previous stroke or transient ischemic attack. Stroke 2017;48:2142–2149

35. Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145–1153

36. Coleman CI, Briere JB, Fauchier L, et al. Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation. J Mark Access Health Policy 2019;7:1574541

37. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2017;48:2494–2503

38. Yao X, Shah N, Sangaralingham LR, Gersh B, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol 2017;69:2779–2790

39. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nat Rev Nephrol 2018;14:337–351

40. Olesen JB, Lip GYH, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367:625–635

41. Yao X, Tangri N, Gersh B, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. Am J Cardiol 2017;70:2621–2632

42. Fox KAA, 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;32:2387–2394

43. 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;129:961–970

44. 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;33:2821–2830

45. 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

46. Weir MR, Berger JS, Ashton V, et al. Impact of renal function on ischemic stroke and major bleeding rates in nonvalvular atrial fibrillation patients treated with warfarin or rivaroxaban: a retrospective cohort study using real-world evidence. Curr Med Res Opin 2017;33:1891–1900

47. Coleman CI, Martinez BK, Turpie AGG, Sood N, Bunz TJ, Kreutz R. Effectiveness and safety of rivaroxaban vs. warfarin in patients with nonvalvular atrial fibrillation and moderate-to-severe chronic kidney disease. Blood 2017;130:2393–2393

48. Bonnemeier H, Huelsebeck M, Kloss S. Comparative effectiveness of rivaroxaban versus a vitamin K antagonist in patients with renal impairment treated for non-valvular atrial fibrillation in Germany - a retrospective cohort study. International journal of cardiology Heart & vasculature 2019;23:100367

49. Bonnemeier H, Kreutz R, Kloss S, Enders D, Häckl D, Schmedt N. Comparative safety and effectiveness of non-vitamin-K oral anticoagulants vs phenprocoumon in patients with non-valvular atrial fibrillation and renal disease - results from the RELOADED study. 5th European Stroke Organisation Conference. Milan, Italy, 22–24 May 2019, Abstract AS25-066. Available at: <https://journals.sagepub.com/toc/esoa/4/1_suppl> Accessed 5 June 2020

50. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015;131:972–979

51. Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. Pharmacotherapy 2017;37:412–419

52. 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;138:1519–1529

53. Coleman CI, Kreutz R, Sood NA, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med 2019;132:1078–1083

54. Chang SH, Wu CV, Yeh YH, et al. Efficacy and safety of oral anticoagulants in patients with atrial fibrillation and stages 4 or 5 chronic kidney disease. Am J Med 2019;132:1335–1343.e1336

55. Marti HP, Serebruany V, Atar D. Challenging anticoagulation in advanced renal failure. Am J Med 2019;132:1258–1259

56. Janssen Pharmaceuticals Inc. Xarelto (rivaroxaban) Prescribing Information. 2020. Available at: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/XARELTO-pi.pdf>. Accessed 8 September 2020

57. Boehringer Ingelheim Pharmaceuticals Inc. Pradaxa® (dabigatran etexilate) Prescribing Information. 2019. Available at: <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>. Accessed 8 September 2020

58. Daiichi Sankyo Inc. Savaysa® (edoxaban) Prescribing information. 2019. Available at: <http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true>. Accessed 08 September 2020

59. Bristol-Myers Squibb Company, Pfizer Inc. Eliquis® (apixaban) Prescribing Information. 2019. Available at: <http://packageinserts.bms.com/pi/pi_eliquis.pdf>. Accessed 8 September 2020

60. Pokorney SD. RENalhemodialysis patients ALlocatedapixaban versus warfarin in Atrial Fibrillation (RENAL-AF). 2019. Available at: <https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=469e5bd88fff4d2bb8ec183e71521637>. Accessed 4 February 2020

61. Atrial Fibrillation Network, Bristol-Myers Squibb, Pfizer. Compare apixaban and vitamin-K antagonists in patients with atrial fibrillation (AF) and end-stage kidney disease (ESKD) (AXADIA). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT02933697>. Accessed 2 September 2019

62. St Michael's Hospital, Canadian Institutes of Health Research. Strategies for the management of atrial fibrillation in patients receiving hemodialysis (SAFE-HD). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT03987711>. Accessed 22 August 2019

63. Wheeler D, Giugliano R, Rangaswami J. Anticoagulation-related nephropathy. J Thromb Haemost 2016;14:461–467

64. Brodsky S, Eikelboom J, Hebert LA. Anticoagulant-related nephropathy. J Am Soc Nephrol 2018;29:2787–2793

65. Posch F, Ay C, Stoger H, Kreutz R, Beyer-Westendorf J. Exposure to vitamin K antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. Res Pract Thromb Haemost 2019;3:207–216

66. Peeters FECM, Dudink EAMP, Kimenai DM, et al. Vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, and vascular calcification in patients with atrial fibrillation. TH Open 2018;2:e391–e398

67. Di Lullo L, Ronco C, Cozzolino M, et al. Nonvitamin K-dependent oral anticoagulants (NOACs) in chronic kidney disease patients with atrial fibrillation. Thromb Res 2017;155:38–47

68. 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;80:181–189

69. Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transplant 2014;29:2228-2234

70. van Gorp RH, Schurgers LJ. New insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs). Nutrients 2015;7:9538–9557

71. de Aquino Moura KB, Behrens PMP, Pirolli R, et al. Anticoagulant-related nephropathy: systematic review and meta-analysis. Clinical kidney journal 2019;12:400–407

72. Brodsky SV, Mhaskar NS, Thiruveedi S, et al. Acute kidney injury aggravated by treatment initiation with apixaban: Another twist of anticoagulant-related nephropathy. Kidney Res Clin Pract 2017;36:387–392

73. Shin JI, Luo S, Alexander GC, et al. Direct oral anticoagulants and risk of acute kidney injury in patients with atrial fibrillation. J Am Coll Cardiol 2018;71:251–252

74. Chan YH, Yeh YH, See LC, et al. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. J Am Coll Cardiol 2016;68:2272–2283

75. 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;265:83–89

76. Klil-Drori AJ, Azoulay L, Nie R, Renoux C, Nessim SJ, Filion KB. Comparative risk of acute kidney injury with oral anticoagulant use among patients with nonvalvular atrial fibrillation. Blood 2017;130:700

77. Coleman CI, Kreutz R, Sood N, et al. Rivaroxaban's impact on renal decline in patients with nonvalvular atrial fibrillation: a US MarketScan claims database analysis. Clin Appl Thromb Hemost 2019;25:1076029619868535

78. Bonnemeier H, Kreutz R, Kloss S, Enders D, Häckl D, Schmedt N. Comparative safety and effectiveness of non-vitamin-K oral anticoagulants vs phenprocoumon in patients with non-valvular atrial fibrillation and diabetes - results from the RELOADED study. 5th European Stroke Organisation Conference. Milan, Italy, 22–24 May 2019, AS25-069. Available at: <https://journals.sagepub.com/toc/esoa/4/1_suppl> Accessed 5 June 2020

79. Vaitsiakhovich T, Coleman CI, Kleinjung F, et al. Worsening of renal function in atrial fibrillation patients with stage 3 or 4 chronic kidney disease treated with warfarin or rivaroxaban - evidence from the real-world CALLIPER study in the US claims. European Society of Cardiology Congress. Paris, France, 31 August–5 September 2019, Poster P4746. Available at: <https://academic.oup.com/eurheartj/article-abstract/40/Supplement_1/ehz745.1122/5596296?redirectedFrom=fulltext>. Accessed 28 February 2020

80. Hernandez AV, Bradley G, Khan M, et al. Rivaroxaban versus warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. Eur Heart J Qual Care Clin Outcomes 2019: doi:10.1093/ehjqcco/qcz047:qcz047

81. GWT-TUD GmbH, ClinStat GmbH. Factor XA - inhibition in renal patients with non-valvular atrial fibrillation - observational registry (XARENO). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT02663076>. Accessed 22 August 2019

82. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140:e125–e151

83. De Sensi F, De Potter T, Cresti A, Severi S, Breithardt G. Atrial fibrillation in patients with diabetes: molecular mechanisms and therapeutic perspectives. Cardiovascular diagnosis and therapy 2015;5:364–373

84. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–189

85. The Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546–554

86. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GYH. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest 2012;141:147–153

87. Fangel MV, Nielsen PB, Larsen TB, et al. Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: a Danish nationwide cohort study. Int J Cardiol 2018;268:137–142

88. Plitt A, McGuire DK, Giugliano RP. Atrial fibrillation, type 2 diabetes, and non-vitamin K antagonist oral anticoagulants: a review. JAMA Cardiol 2017;2:442–448

89. Wang A, Green JB, Halperin JL, Piccini JP, Sr. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. J Am Coll Cardiol 2019;74:1107–1115

90. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2019. Diabetes Care 2019;42:S103–123

91. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis 2018;25:121–132

92. Cavanaugh KL. Diabetes management issues for patients with chronic kidney disease. Clin Diabetes 2007;25:90–97

93. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12

94. Middleton RJ, Foley RN, Hegarty J, et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transpl 2005;21:88–92

95. Hertig A, Rondeau E. Role of the coagulation/fibrinolysis system in fibrin-associated glomerular injury. J Am Soc Nephrol 2004;15:844–853

96. Farquhar A, MacDonald MK, Ireland JT. The role of fibrin deposition in diabetic glomerulosclerosis: a light, electron and immunofluorescence microscopy study. J Clin Pathol 1972;25:657–667

97. Tanaka M, Arai H, Liu N, et al. Role of coagulation factor Xa and protease-activated receptor 2 in human mesangial cell proliferation. Kidney Int 2005;67:2123–2133

98. Sumi A, Yamanaka-Hanada N, Bai F, Makino T, Mizukami H, Ono T. Roles of coagulation pathway and factor Xa in the progression of diabetic nephropathy in db/db mice. Biol Pharm Bull 2011;34:824–830

99. Amdur RL, Feldman HI, Gupta J, et al. Inflammation and progression of CKD: the CRIC study. Clin J Am Soc Nephrol 2016;11:1546–1556

100. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–308

101. Ezekowitz JA, Lewis BS, Lopes RD, et al. Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial. European heart journal Cardiovascular pharmacotherapy 2015;1:86–94

102. Brambatti M, Darius H, Oldgren J, et al. Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: results from the RE-LY trial. Int J Cardiol 2015;196:127–131

103. Bansilal S, Bloomgarden Z, Halperin JL, et al. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: 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). Am Heart J 2015;170:675–682

104. Plitt A, Ruff CT, Goudev A, et al. Efficacy and safety of edoxaban in patients with diabetes mellitus in the ENGAGE AF-TIMI 48 trial. Int J Cardiol 2020;304:185–191

105. Coleman CI, Bunz TJ, Eriksson D, Meinecke AK, Sood NA. Effectiveness and safety of rivaroxaban vs warfarin in people with non-valvular atrial fibrillation and diabetes: an administrative claims database analysis. Diabet Med 2018;35:1105–1110

106. Baker WL, Beyer-Westendorf J, Bunz TJ, et al. Effectiveness and safety of rivaroxaban and warfarin for prevention of major adverse cardiovascular or limb events in patients with non-valvular atrial fibrillation and type 2 diabetes. Diabetes Obes Metab 2019;21:2107–2114

107. Bayer AG. Xarelto® (rivaroxaban) Summary of Product Characteristics. 2020. Available at: <https://www.ema.europa.eu/documents/product-information/xarelto-epar-product-information_en.pdf>. Accessed 30 July 2020

108. Bristol Myers Squibb, Pfizer. Eliquis® (apixaban) Summary of Product Characteristics. 2020. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf>. Accessed 30 July 2020

109. Boehringer Ingelheim International GmbH. Pradaxa® (dabigatran etexilate) Summary of Product Characteristics. 2020. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf>. Accessed 8 September 2020

110. Daiichi Sankyo Europe GmbH. Lixiana® (edoxaban) Summary of Product Characteristics. 2019. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf>. Accessed 9 April 2020

111. Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. J Am Coll Cardiol 2016;68:2597–2604

112. Steinberg BA, Shrader P, Pieper K, et al. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc 2018;7:e007633

113. Atar D, Grundvold I. On-label reduced doses of non-vitamin K anticoagulants prove safe and efficient; yet how to ensure the correct dose for the right patient? Eur Heart J 2019;40:1501–1503

114. Lowres N, Giskes K, Hespe C, Freedman B. Reducing stroke risk in atrial fibrillation: adherence to guidelines has improved, but patient persistence with anticoagulant therapy remains suboptimal. Korean circulation journal 2019;49:883–907

115. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. Int J Stroke 2017;12:985–990

116. Kamel H, Longstreth WT, Jr., Tirschwell DL, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. Int J Stroke 2019;14:207–214

117. Healey JS, Gladstone DJ, Swaminathan B, et al. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. JAMA Neurol 2019;76:764–773

118. Ntaios G, Perlepe K, Lambrou D, et al. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. J Am Heart Assoc 2019;8:e012858

119. University of Thessaly, University of Lausanne, University of Athens. Prediction of AF in ESUS (AF-ESUS). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT02766205>. Accessed 7 October 2019

120. Ingelheim UoBCB. Thirty day heart monitoring for detection of atrial fibrillation among cryptogenic stroke patients (PROPhecy). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT03712865>. Accessed 7 October 2019

121. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. J Am Coll Cardiol 2020;75:333–340

122. Sharma M, Hart RG, Connolly SJ, et al. Stroke outcomes in the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) Trial. Circulation 2019;139:1134–1145

123. Perera KS, Ng KKH, Nayar S, et al. Association between low-dose rivaroxaban with or without aspirin and ischemic stroke subtypes: a secondary analysis of the COMPASS trial. JAMA Neurol 2019: doi:10.1001/jamaneurol.2019.2984

124. Ferreira JP, Girerd N, Gregson J, et al. Stroke risk in patients with reduced ejection fraction after myocardial infarction without atrial fibrillation. J Am Coll Cardiol 2018;71:727–735

125. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA 2015;314:1030–1038

126. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med 2018;379:1332–1342

127. Mehra MR, Vaduganathan M, Fu M, et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. Eur Heart J 2019;40:3593–3602

128. APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective Factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877-2885

Figure Captions

**Fig. 1** Algorithm for the management of patients with non-valvular AF and CKD. CKD stage is defined in terms of ranges of the eGFR. Re-testing of renal function depends on the stage of renal function and the eGFR. RCT evidence for favourable effects of oral anticoagulation (VKAs or NOACs) is much less certain as renal function declines.16

aPatients with CrCl 25–30 mL/min were included in ARISTOTLE. bDabigatran is not approved in Europe for use in patients with severe renal impairment (CrCl <30 mL/min). cLimited data are available from subgroups of registries. AF, atrial fibrillation; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; RCT, randomized control trial; VKA, vitamin K antagonist.

**Fig. 2** Potential mechanisms underlying renovascular calcification63 (**A**), anticoagulation-related nephropathy **(B**),70 and diabetic inflammatory nephropathy **(C)**.95-99

IL-1 β, interleukin 1β; IL-6, interleukin-6; PAR, protease-activated receptor; TNF-α, tumour necrosis factor-α; VKA, vitamin K antagonist.

**Fig. 3** RWE studies on renal outcomes with NOACs versus VKAs in patients with AF.41,49,73-80

AF, atrial fibrillation; AKI, acute kidney injury; CKD, chronic kidney disease; CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; pts, patients; RWE, real-world evidence; VKA, vitamin K antagonist; w, with; w/o, without.

**Fig. 4** Possible mechanisms of stroke in patients with type 2 diabetes.88-90

BMI, body mass index.

**Fig. 5** RWE studies comparing the efficacy and safety of NOACs with VKAs in patients with AF and diabetes.78,105,106

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events; MALE, major adverse limb events; NOAC, non-vitamin K antagonist oral anticoagulant; RWE, real-world evidence; SE, systemic embolism; VKA, vitamin K antagonist.

**Fig. 6** Stroke outcomes in the NAVIGATE ESUS and RE-SPECT ESUS trials10,11 (**A**) and in the COMPASS trial122 (**B**).

bid, twice daily; CI, confidence interval; HR, hazard ratio; SE, systemic embolism.

Tables

**Table 1** Overview of results from prespecified subanalyses of phase III studies of NOACs for stroke prevention

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study (N)** | **Patients (n)** | **Treatment arms** | **Primary outcome Stroke/SE: ARR (%)** | **Primary outcome Stroke/SE: NNTa** |
| **Moderate renal impairment (CrCl ≤50 mL/min)** | | | | |
| ROCKET AF42  (14,264) | 2,950 | Rivaroxaban 15 mg od vs warfarin | 0.45 | 223 |
| RE-LY43  (18,113) | 3,554 | Dabigatran 150 mg bid vs warfarin | 1.17 | 86 |
| ARISTOTLE31,44  (18,201) | 3,017 | Apixaban 5 mg or 2.5 mg bid vs warfarin | 0.56 | 179 |
| ENGAGE AF-TIMI 4845  (21,105) | 2,740 | Edoxaban 30 mg od vs warfarin | 0.40 | 250 |
| **Diabetes** | | | | |
| ROCKET AF103  (14,264) | 5,695 | Rivaroxaban 20 mg or 15 mg od vs warfarin | 0.40 | 250 |
| RE-LY102 (18,133) | 4,221 | Dabigatran 150 mg bid vs warfarin | 0.89 | 113 |
| ARISTOTLE101 (18,201) | 4,547 | Apixaban 5 mg or 2.5 mg bid vs warfarin | 0.47 | 213 |
| ENGAGE AF-TIMI 48104 (21,105) | 7,624 | Edoxaban 60 or 30 mg od vs warfarin | 0.10 | 1,000 |

aThe NNT refers to the number of patients who need to receive treatment with a NOAC to prevent one additional bad outcome.

ARR, absolute risk reduction; bid, twice daily; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; NNT, number needed to treat; NOAC, non-vitamin K antagonist oral anticoagulant; od, once daily; SE, systemic embolism.

**Table 2** Overview of completed and ongoing trials of NOACs in ESUS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Patients (N)** | **Treatment arms** | **Trial status** | **Key efficacy outcomes** | **Key safety outcomes** |
| NAVIGATE ESUS10 | 7,213 | Rivaroxaban 15 mg od vs aspirin 100 mg od | Terminated earlya | * No significant difference in the risk of recurrent stroke/SE  (HR 1.07, 95% CI: 0.87–1.33; *p*=0.52) * ARR: –0.3% * NNT: –334 | * Increased risk of major bleeding with rivaroxaban  (HR 2.72, 95% CI: 1.68–4.39; *p*<0.001) |
| RE-SPECT ESUS11 | 5,390 | Dabigatran 150 mg bid or 110 mg bidb  vs aspirin 100 mg od | Completed | * No significant difference in the risk of recurrent stroke  (HR 0.85, 95% CI: 0.69–1.03; *p*=0.10) * ARR: 0.7% * NNT: 143 | * No significant difference in the risk of major bleeding (HR 1.19, 95% CI: 0.85–1.66) |
| ATTICUS115 | 500 | Apixaban 5 mg bid vs aspirin 100 mg od | Ongoing | Pending | Pending |
| ARCADIA116c | 1,100 | Apixaban 5 mg bid or 2.5 mg bidd vs aspirin 81 mg od | Ongoing | Pending | Pending |

aDue to a lack of benefit in stroke risk reduction and increased bleeding with rivaroxaban. bLower dose of dabigatran for patients aged ≥75 years or with CrCl 30–50 mL/min. cPopulations studied included patients with ESUS and evidence of atrial cardiopathy. dLower dose of apixaban for patients who have at least two of the following criteria: age ≥80 years, body weight ≤60 kg or CrCl ≥1.5 mg/dL. dTheNNT refers the number of patients who need to receive treatment with a NOAC to prevent one additional bad outcome.

ARR, absolute risk reduction; bid, twice daily; CI, confidence interval; CrCl, creatinine clearance; ESUS, embolic stroke of undetermined source; HR, hazard ratio; NNT, number needed to treat; NOAC, non-vitamin K antagonist oral anticoagulant; od, once daily; SE, systemic embolism.