Use of Non-vitamin K Antagonist Oral Anticoagulants 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 comorbidities, 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 comorbidities, 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.

Keywords
- stroke prevention
- non-vitamin K antagonist oral anticoagulants
- atrial fibrillation
- embolic stroke of undetermined source
- atherosclerosis

Introduction

Stroke is one of the leading causes of mortality and disability worldwide.[1,2] The majority of strokes are ischemic strokes, which can be further classified based on their etiology: 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 ischemic strokes[5,6] and is diagnosed by excluding other etiologies.[4,5] ESUS has been defined as a nonlacunar 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]

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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 comorbidities is less well studied.

Atherosclerotic vascular disease is a leading cause of ischemic 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 acute[22–26] 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 ischemic 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 comorbidities, 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 ischemic 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 hemorrhage (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 $CHADS_2$ score $\geq$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 ischemic 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**).[16,39] Several factors, including AF itself, older age, hypertension, and comorbidities such as diabetes, can increase the risk of renal impairment.[40] Impairment of renal function has been associated with not only an increased risk of thromboembolic events but also an increased rate of bleeding.[28,41] 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.[15,16,42]

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**).[33,43–46]

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 of 50 to 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 of 50 to 80 mL/min (HR: 0.91, 95% CI: 0.76–1.08).[33]

Real-world evidence (RWE) supports the favorable benefit–risk profile of NOACs versus warfarin[47,48] or phenprocoumon[49,50] 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 warfarin[29–32] and RWE studies have reported conflicting safety results.[51–56] 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.[57–60] Results of the randomized trial RENAL-AF, which was stopped early due to

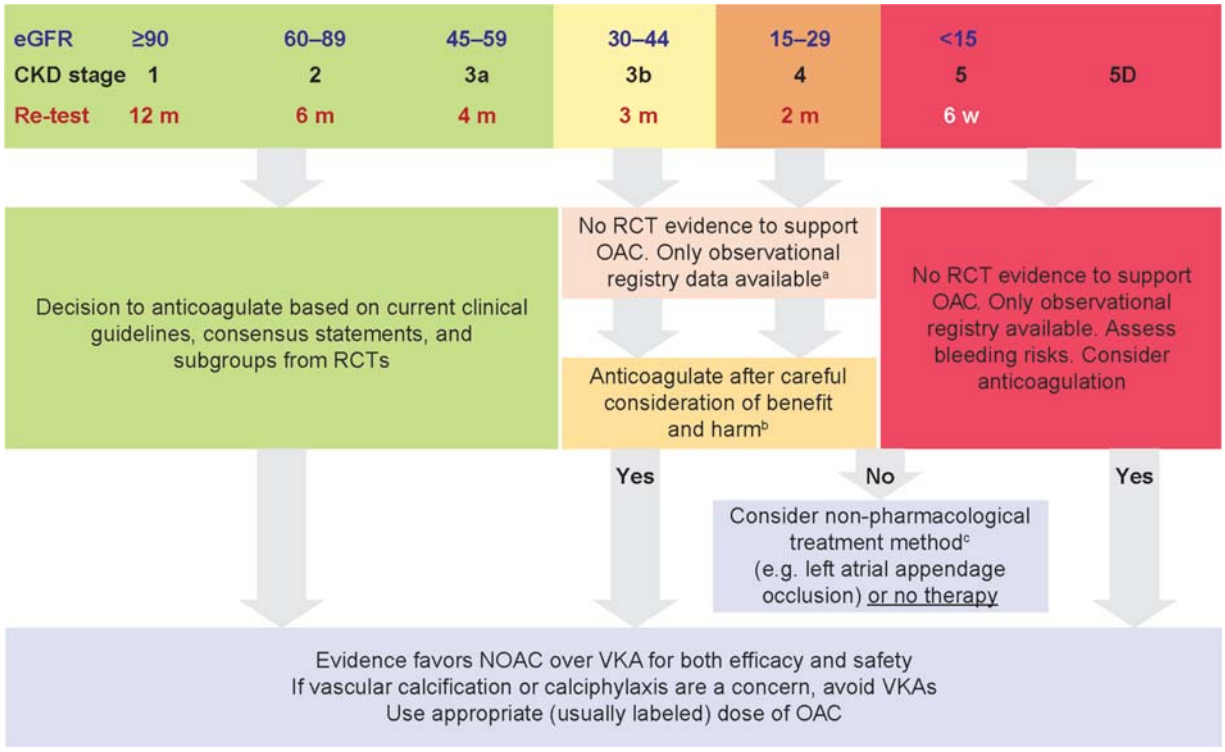


Fig. 1 Algorithm for the management of patients with non-valvular AF and CKD. CKD stage is defined in terms of ranges of the eGFR. Re-testing of renal function depends on the stage of renal function and the eGFR. RCT evidence for favorable effects of oral anticoagulation (VKAs or NOACs) is much less certain as renal function declines.[16] (Figure adapted from Kumar et al[39].) 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. [a]Patients with CrCl 25–30 mL/min were included in ARISTOTLE. [b]Dabigatran is not approved in Europe for use in patients with severe renal impairment (CrCl < 30 mL/min). [c]Limited data are available from subgroups of registries.

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: NNT[a]
Moderate renal impairment (CrCl ≤50 mL/min)				
ROCKET AF[43] (14,264)	2,950	Rivaroxaban 15 mg once daily vs. warfarin	0.45	223
RE-LY[44,b] (18,113)	3,554	Dabigatran 150 mg twice daily vs. warfarin	1.17	86
		Dabigatran 110 mg twice daily vs. warfarin	0.38	264
ARISTOTLE[31,45] (18,201)	3,017	Apixaban 5 mg or 2.5 mg twice daily vs. warfarin	0.56	179
ENGAGE AF-TIMI 48[46] (21,105)	2,740	Edoxaban 30 mg once daily vs. warfarin	0.40	250
Diabetes				
ROCKET AF[104] (14,264)	5,695	Rivaroxaban 20 mg or 15 mg once daily vs. warfarin	0.40	250
RE-LY[103,b] (18,133)	4,221	Dabigatran 150 mg twice daily vs. warfarin	0.89	113
		Dabigatran 110 mg twice daily vs. warfarin	0.59	170
ARISTOTLE[102] (18,201)	4,547	Apixaban 5 mg or 2.5 mg twice daily vs. warfarin	0.47	213
ENGAGE AF-TIMI 48[105] (21,105)	7,624	Edoxaban 60 mg or 30 mg once daily vs. warfarin	0.10	1,000

Abbreviations: ARR, absolute risk reduction; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; NNT, number needed to treat; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism.
[a]The NNT refers to the number of patients who need to receive treatment with a NOAC to prevent one additional bad outcome.
[b]Patients receiving dabigatran in the RE-LY study were randomized to receive dabigatran 150 mg twice daily or dabigatran 110 mg twice daily in a blinded fashion, regardless of baseline renal function.[44]

loss of funding, were recently presented at the American Heart Association congress 2019.[61] After 1-year follow-up, apixaban 5 mg twice daily 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, which are ongoing, will provide more clarity on the treatment effect of NOACs versus VKAs in patients with severe renal disease.[62,63]

Renal function decline is commonly observed in patients with AF treated with oral anticoagulants[42] and has been either linked to vascular calcification or anticoagulant-related nephropathy (ARN).[64–66] Anticoagulant-associated worsening of renal function may be caused by renovascular calcification.[66] Evidence suggests that vascular calcification is linked to VKAs but not NOACs (►**Fig. 2A**).[64,67] ARN is a form of acute kidney injury (AKI) caused by excessive anticoagulation.[64,65] Repeated episodes of AKI may accelerate CKD progression.[68] ARN has originally been described in patients who received overdoses of warfarin, but it has also been reported occasionally in patients treated with NOACs.[64,65,69] 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**).[64,70,71] 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.[64,72,73]

Several real-world studies suggest that NOACs may be associated with better preservation of renal function than warfarin in routine clinical practice (►**Fig. 3**).[42,50,74–81] In a large U.S. 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,[75,76] which was also observed in an administrative health care database analysis in Quebec, Canada.[77] In a large U.S. cohort study that analyzed 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 $\geq$ 60 mL/min/1.73 m^2).[74] In patients with an eGFR of 30 to 59 mL/min/1.73 m^2, only dabigatran reduced the risk of AKI compared with warfarin.[74] 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 U.S. Truven MarketScan data, suggested that patients receiving rivaroxaban are less likely to develop AKI and progress to stage 5 CKD or need hemodialysis than those receiving warfarin.[78] Recent results from the retrospective database analyses RELOADED and CALLIPER further support the nephroprotective effect of rivaroxaban.[50,80] The ongoing multicenter 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/1.73 m^2) 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.[82]

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.*"[83] Taken together, the totality of evidence supports 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 comorbidity in patients with AF, and its presence is associated with an increased risk of developing AF.[13,84] 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**).[85–91] In addition, type 2 diabetes is the leading cause of renal failure in the developed world,[92] with moderate-to-severe kidney disease estimated to be found in 15 to 27% of patients with diabetes.[93–95] Renal function decline in diabetes may be due to protease-activated receptor-induced inflammatory nephropathy (►**Fig. 2C**).[96–100]

Importantly, the combination of diabetes and renal impairment is associated with a higher risk of CV events and mortality than either comorbidity alone,[93,101] 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.[33,89,102–105] 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**).[33,89,102–105] 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.[102] Major bleeding rates were similar for apixaban and warfarin in patients with diabetes.[102] 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.[103] 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 of CV death (HR: 0.80, 95% CI: 0.64–0.99) compared with warfarin, with no difference in the risk of major bleeding. In the subanalysis of ENGAGE AF-TIMI 48

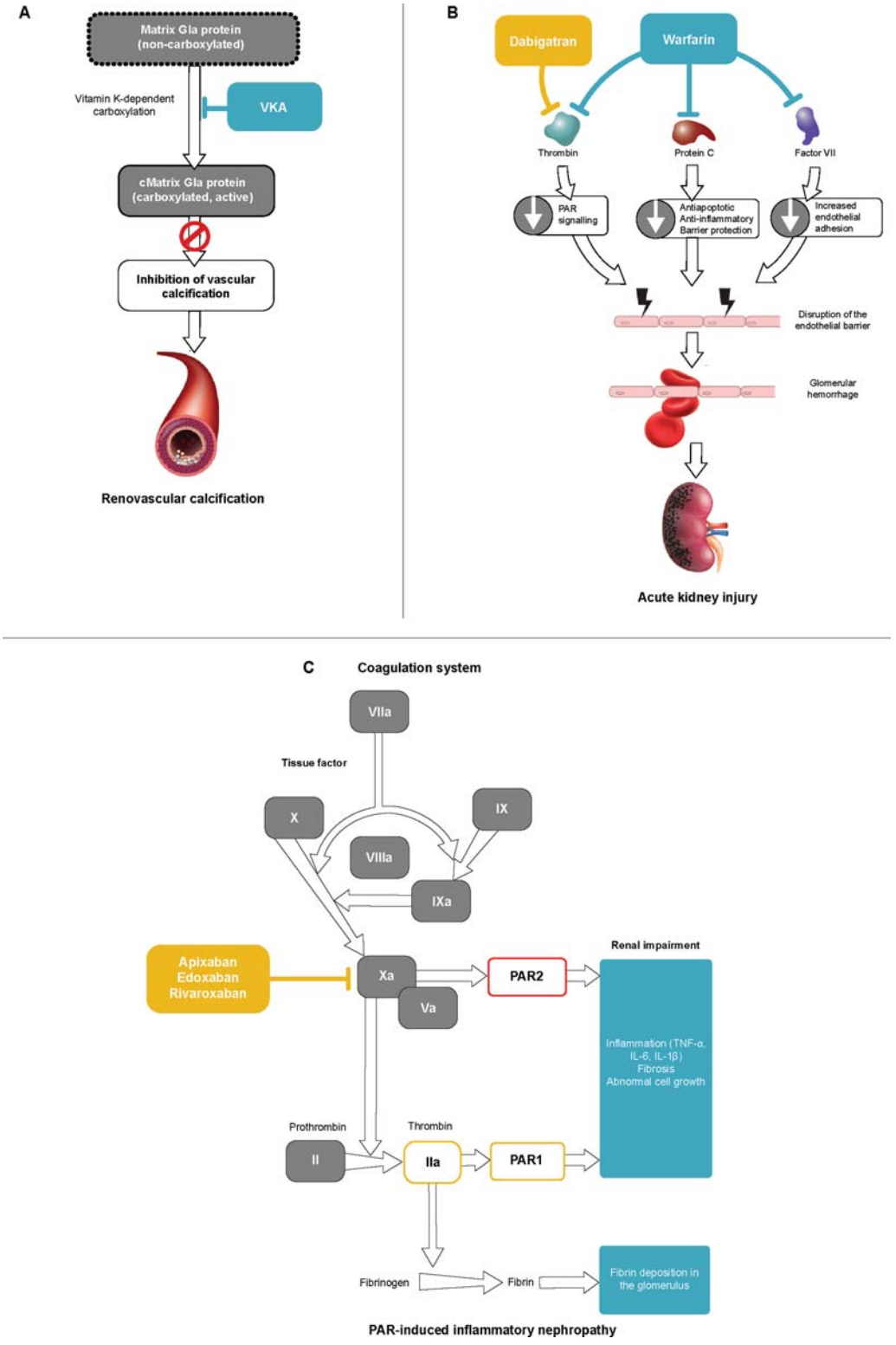
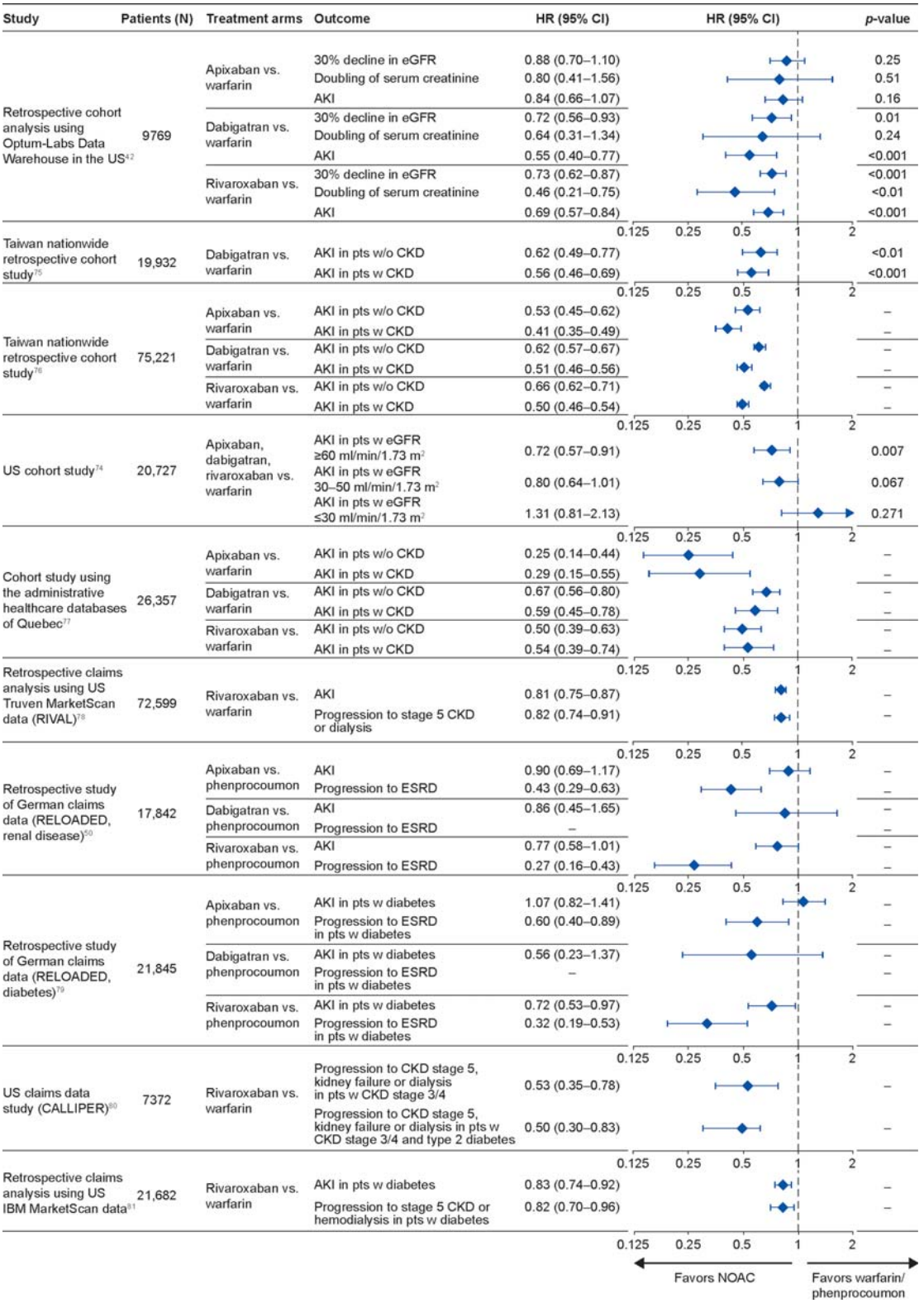


Fig. 2 Potential mechanisms underlying renovascular calcification[64] (**A**), anticoagulation-related nephropathy (**B**)[71] and diabetic inflammatory nephropathy (**C**).[95–99] IL-1 β, interleukin 1β; IL-6, interleukin-6; PAR, protease-activated receptor; TNF-α, tumor necrosis factor-α; VKA, vitamin K antagonist.

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).[105]

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**).[50,106,107] Large retrospective analyses of U.S. claims data showed that rivaroxaban was equally as effective as warfarin in reducing the risk of stroke/SE[106] and more effective than warfarin in reducing major adverse CV events (MACEs) and major adverse limb events, with no difference in major bleeding.[107] In a retrospective analysis using German



Study	Patients (N)	Treatment arms	Outcome	HR (95% CI)	p-value
Retrospective cohort analysis using Optum-Labs Data Warehouse in the US[42]	9769	Apixaban vs. warfarin	30% decline in eGFR	0.88 (0.70–1.10)	0.25
			Doubling of serum creatinine	0.80 (0.41–1.56)	0.51
			AKI	0.84 (0.66–1.07)	0.16
		Dabigatran vs. warfarin	30% decline in eGFR	0.72 (0.56–0.93)	0.01
			Doubling of serum creatinine	0.64 (0.31–1.34)	0.24
			AKI	0.55 (0.40–0.77)	<0.001
		Rivaroxaban vs. warfarin	30% decline in eGFR	0.73 (0.62–0.87)	<0.001
			Doubling of serum creatinine	0.46 (0.21–0.75)	<0.01
			AKI	0.69 (0.57–0.84)	<0.001
Taiwan nationwide retrospective cohort study[75]	19,932	Dabigatran vs. warfarin	AKI in pts w/o CKD	0.62 (0.49–0.77)	<0.01
			AKI in pts w CKD	0.56 (0.46–0.69)	<0.001
Taiwan nationwide retrospective cohort study[76]	75,221	Apixaban vs. warfarin	AKI in pts w/o CKD	0.53 (0.45–0.62)	–
			AKI in pts w CKD	0.41 (0.35–0.49)	–
		Dabigatran vs. warfarin	AKI in pts w/o CKD	0.62 (0.57–0.67)	–
			AKI in pts w CKD	0.51 (0.46–0.56)	–
		Rivaroxaban vs. warfarin	AKI in pts w/o CKD	0.66 (0.62–0.71)	–
			AKI in pts w CKD	0.50 (0.46–0.54)	–
US cohort study[74]	20,727	Apixaban, dabigatran, rivaroxaban vs. warfarin	AKI in pts w eGFR ≥60 ml/min/1.73 m²	0.72 (0.57–0.91)	0.007
			AKI in pts w eGFR 30–50 ml/min/1.73 m²	0.80 (0.64–1.01)	0.067
			AKI in pts w eGFR ≤30 ml/min/1.73 m²	1.31 (0.81–2.13)	0.271
Cohort study using the administrative healthcare databases of Quebec[77]	26,357	Apixaban vs. warfarin	AKI in pts w/o CKD	0.25 (0.14–0.44)	–
			AKI in pts w CKD	0.29 (0.15–0.55)	–
		Dabigatran vs. warfarin	AKI in pts w/o CKD	0.67 (0.56–0.80)	–
			AKI in pts w CKD	0.59 (0.45–0.78)	–
		Rivaroxaban vs. warfarin	AKI in pts w/o CKD	0.50 (0.39–0.63)	–
			AKI in pts w CKD	0.54 (0.39–0.74)	–
Retrospective claims analysis using US Truven MarketScan data (RIVAL)[78]	72,599	Rivaroxaban vs. warfarin	AKI	0.81 (0.75–0.87)	–
			Progression to stage 5 CKD or dialysis	0.82 (0.74–0.91)	–
Retrospective study of German claims data (RELOADED, renal disease)[50]	17,842	Apixaban vs. phenprocoumon	AKI	0.90 (0.69–1.17)	–
			Progression to ESRD	0.43 (0.29–0.63)	–
		Dabigatran vs. phenprocoumon	AKI	0.86 (0.45–1.65)	–
			Progression to ESRD	–	–
		Rivaroxaban vs. phenprocoumon	AKI	0.77 (0.58–1.01)	–
			Progression to ESRD	0.27 (0.16–0.43)	–
Retrospective study of German claims data (RELOADED, diabetes)[79]	21,845	Apixaban vs. phenprocoumon	AKI in pts w diabetes	1.07 (0.82–1.41)	–
			Progression to ESRD in pts w diabetes	0.60 (0.40–0.89)	–
		Dabigatran vs. phenprocoumon	AKI in pts w diabetes	0.56 (0.23–1.37)	–
			Progression to ESRD in pts w diabetes	–	–
		Rivaroxaban vs. phenprocoumon	AKI in pts w diabetes	0.72 (0.53–0.97)	–
			Progression to ESRD in pts w diabetes	0.32 (0.19–0.53)	–
US claims data study (CALLIPER)[80]	7372	Rivaroxaban vs. warfarin	Progression to CKD stage 5, kidney failure or dialysis in pts w CKD stage 3/4	0.53 (0.35–0.78)	–
			Progression to CKD stage 5, kidney failure or dialysis in pts w CKD stage 3/4 and type 2 diabetes	0.50 (0.30–0.83)	–
Retrospective claims analysis using US IBM MarketScan data[81]	21,682	Rivaroxaban vs. warfarin	AKI in pts w diabetes	0.83 (0.74–0.92)	–
			Progression to stage 5 CKD or hemodialysis in pts w diabetes	0.82 (0.70–0.96)	–

Fig. 3 RWE studies on renal outcomes with NOACs versus VKAs in patients with AF.[42,50,74–81] AF, atrial fibrillation; AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; 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.

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.[50] 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

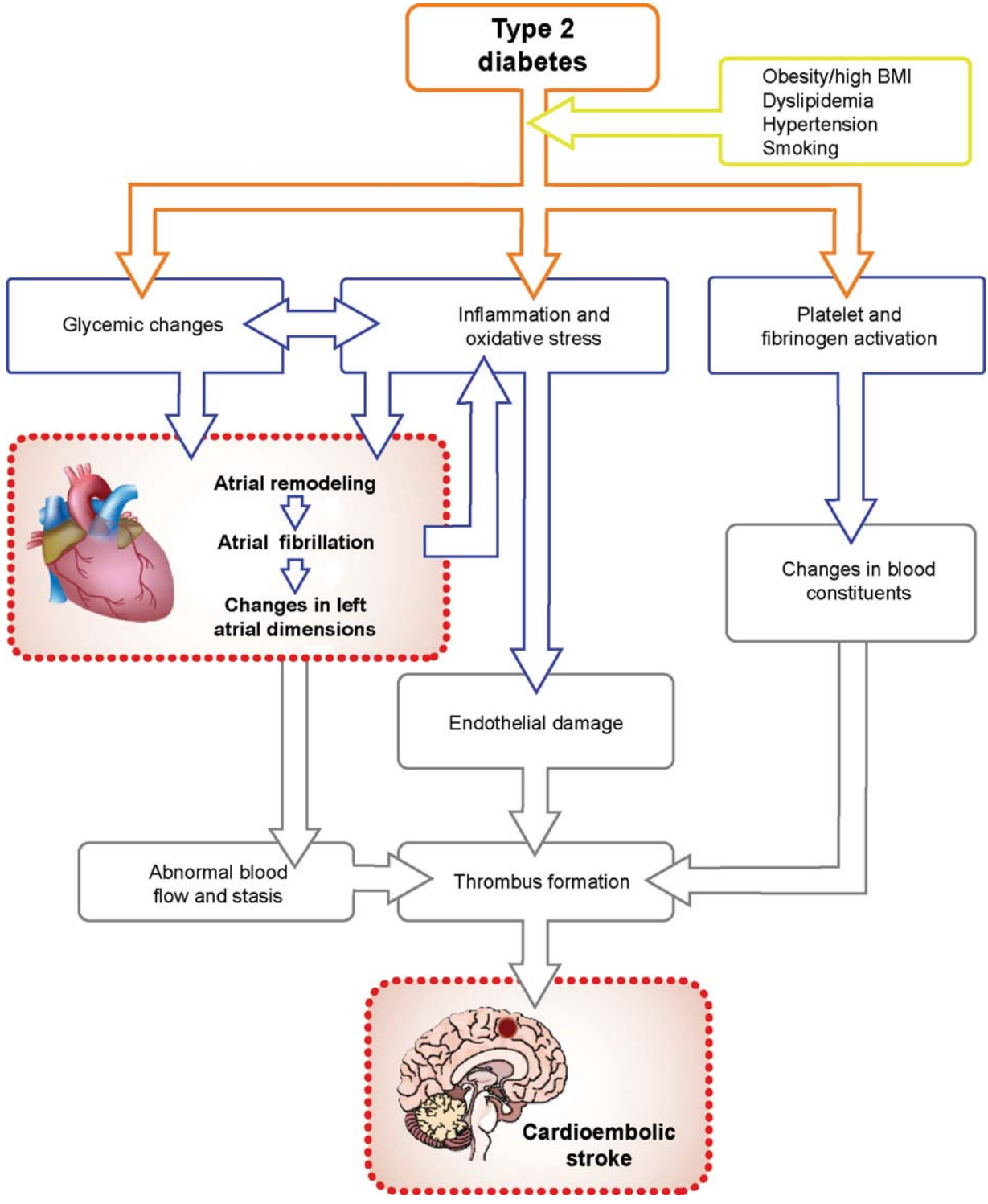


Fig. 4 Possible mechanisms of stroke in patients with type 2 diabetes.[89–91] BMI, body mass index.

phenprocoumon[50] or warfarin,[81] 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, RELY, 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.[108–111] With regard to apixaban and dabigatran, additional criteria, such as older age and low body weight, need to be met to apply dose reductions.[109,110] These dose reduction criteria vary slightly depending on the regulatory agency. For example, in the European Union, reduced doses of dabigatran are recommended for patients with moderate renal impairment who are ≥80 years of age and/or receive concomitant verapamil.[110] In patients with moderate renal

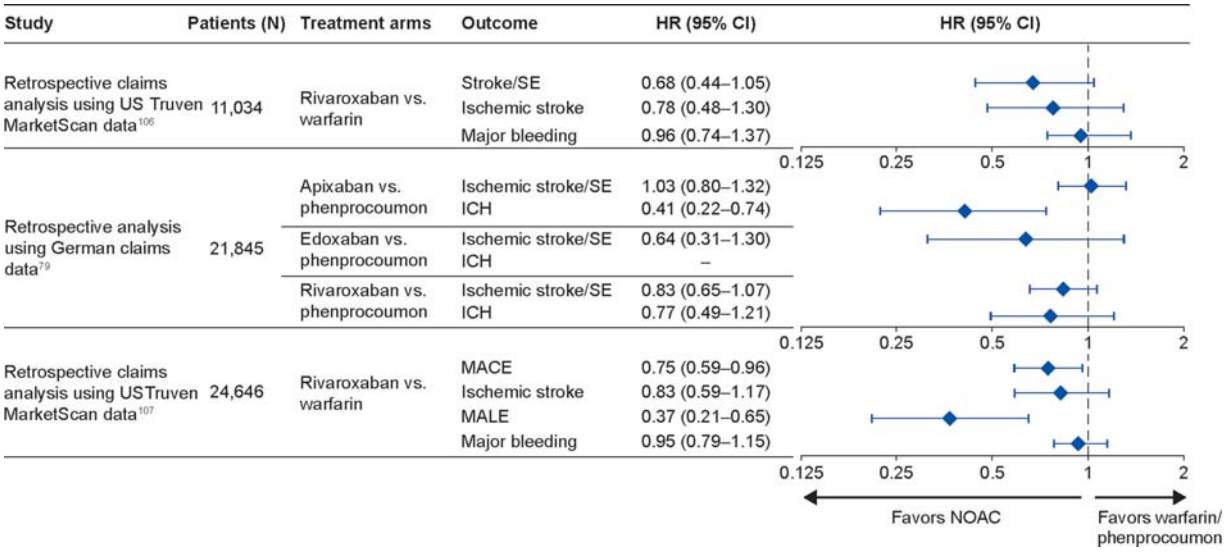


Fig. 5 RWE studies comparing the efficacy and safety of NOACs with VKAs in patients with AF and diabetes.[50,106,107] AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; MACE, major adverse cardiovascular events; MALE, major adverse limb events; NOAC, non-vitamin K antagonist oral anticoagulant; RWE, real-world evidence; SE, systemic embolism; VKA, vitamin K antagonist.

impairment aged 75–80 years and/or with gastritis, esophagitis, or gastroesophageal reflux, or an increased risk of bleeding, the thromboembolic and bleeding risk will need to be assessed individually to determine the dose.[110] Dose reductions for apixaban are indicated for patients with moderate renal impairment aged ≥80 years or body weight ≤60 kg.[109] Reduced doses of edoxaban are not only recommended for renal impairment but also for other single criterion, such as concomitant use of P-glycoprotein inhibitors or body weight ≤60 kg.[111] Rivaroxaban is the only NOAC for which dose reduction is based solely on renal function.[108]

Adherence to recommended dosing is important, as inappropriate dosing of NOACs has been shown to impact clinical outcomes.[38,112–114] Patients may receive an inappropriate dose because of lack of adjustments for certain clinical features specified by recommended labeling, 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.[38,112,113] Patient-level factors also contribute to poor adherence and persistence to treatment, such as financial barriers or treatment burden.[115] 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**).[10,11,116,117] 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.[116,117] A secondary analysis of NAVIGATE ESUS demonstrated that rivaroxaban versus aspirin was associated with a reduced risk of recurrent ischemic 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; $p = 0.02$).[118] 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

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 ESUS[10]	7,213	Rivaroxaban 15 mg once daily vs. aspirin 100 mg once daily	Terminated early[a]	• 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 ESUS[11]	5,390	Dabigatran 150 mg twice daily or 110 mg twice daily[b] vs. aspirin 100 mg once daily	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)
ATTICUS[116]	500	Apixaban 5 mg twice daily vs. aspirin 100 mg once daily	Ongoing	Pending	Pending
ARCADIA[117c]	1,100	Apixaban 5 mg twice daily or 2.5 mg twice daily[d] vs. aspirin 81 mg once daily	Ongoing	Pending	Pending

Abbreviations: ARR, absolute risk reduction; 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; SE, systemic embolism.
[a]Due to a lack of benefit in stroke risk reduction and increased bleeding with rivaroxaban.
[b]Lower dose of dabigatran for patients aged ≥75 years or with CrCl 30–50 mL/min.
[c]Populations studied included patients with ESUS and evidence of atrial cardiopathy.
[d]Lower 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.
[e]The NNT refers the number of patients who need to receive treatment with a NOAC to prevent one additional bad outcome.

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 favorable 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 etiology 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.[119] 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.[119] Among all potential embolic sources, patients with AF had the highest risk of stroke recurrence, highlighting the need to identify these patients early.[119] 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.[119,121] However, covert AF now seems to be a less important source of ESUS than originally thought.[122]

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 twice daily plus aspirin, but not rivaroxaban 5 mg twice daily alone, was more effective than aspirin alone in reducing the risk of MACE, defined as CV death, stroke, or myocardial infarction.[27] Rivaroxaban 2.5 mg twice daily 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 twice daily 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

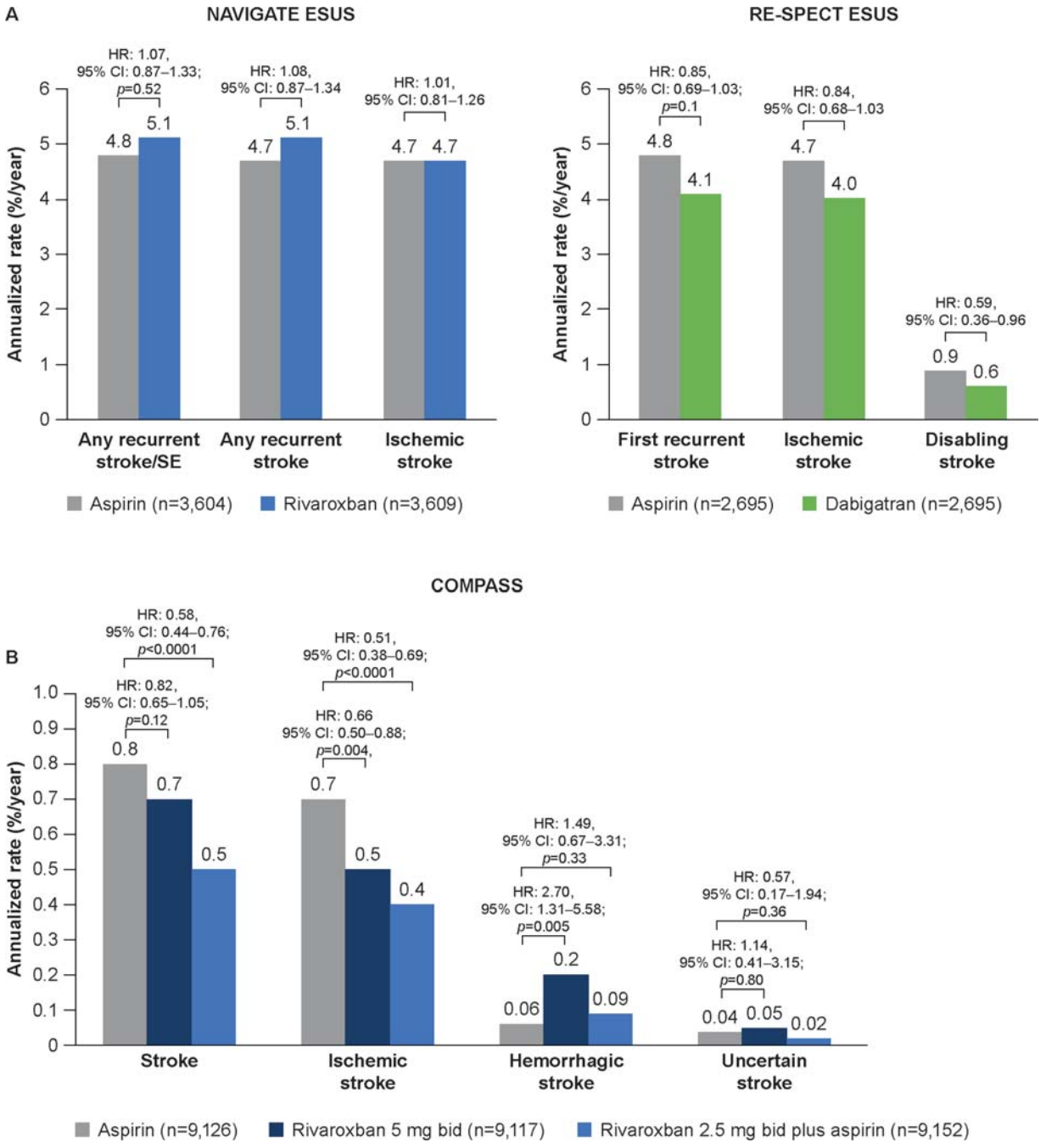


Fig. 6 Stroke outcomes in the NAVIGATE ESUS and RE-SPECT ESUS trials[10,11] (**A**) and in the COMPASS trial[123] (**B**). bid, twice daily; CI, confidence interval; HR, hazard ratio; SE, systemic embolism.

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.[123] This analysis further demonstrated that the beneficial effect of rivaroxaban 2.5 mg twice daily plus aspirin in stroke prevention was primarily driven by a 49% relative risk reduction in ischemic stroke (HR: 0.51, 95% CI: 0.38–0.69; $p < 0.0001$), which was partially offset by a non-significant increase in hemorrhagic stroke.[123] A secondary analysis of the COMPASS trial investigating the effect of the combination therapy on different subtypes of ischemic stroke showed that rivaroxaban 2.5 mg twice daily 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.[124] No significant reductions were observed in patients with other subtypes of ischemic stroke.[124] 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.

The results of the COMPASS trial have led to the approval of rivaroxaban 2.5 mg twice daily in combination with aspirin for the prevention of atherothrombotic events in patients with atherosclerotic vascular disease.[108] 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.[25,129]

Conclusion

Stroke survivors with heart failure and CAD without and AF also have an increased risk of stroke compared with the general population.[125,126] In COMMANDER HF, rivaroxaban 2.5 mg twice daily added to antiplatelet therapy and standard heart failure therapy did not reduce the composite of death, stroke, or myocardial infarction 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.[127] A posthoc analysis of COMMANDER HF demonstrated that the addition of rivaroxaban 2.5 mg twice daily to background antiplatelet therapy reduced the risk of all-cause stroke or transient ischemic attack compared with placebo by 32% (HR: 0.68, 95% CI: 0.49–0.94; $p = 0.02$).[128]

Conclusion

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 comorbidities 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 twice daily 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.

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Conflict of Interest
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