

Potential new uses of non-vitamin K antagonist oral anticoagulants to treat and prevent stroke

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ABSTRACT

Background: Non-vitamin K antagonist oral anticoagulant (NOAC) drugs are at least equivalent to warfarin for ischemic stroke prevention in patients with atrial fibrillation and have a lower risk of intracranial hemorrhage. The role of these agents in the prevention and treatment of other types of cerebrovascular disease remains unclear.

Methods: We reviewed the literature (randomized trials, exploratory comparative studies, and case series) on the use of NOACs in patients with atrial fibrillation, venous thromboembolism, and cerebrovascular disease independent of atrial fibrillation.

Results: The literature on the use of NOACs for treatment and prevention of cerebrovascular disease in patients without atrial fibrillation is sparse. The potential benefit of vitamin K antagonists over antiplatelet agents for primary and secondary prevention in certain subsets of patients with cerebrovascular disease is offset by the increased risk of major and intracranial hemorrhage. Given that NOACs are equivalent to vitamin K antagonists in preventing ischemic stroke and systemic embolism in patients with atrial fibrillation with less bleeding risk, clinical trials are needed to investigate the short- and long-term use of NOACs in populations of patients with other forms of cerebrovascular disease, including those with cryptogenic stroke with or without evidence of patent foramen ovale and low ejection fraction, cervical artery dissection, large artery atherosclerosis, venous thrombosis, and stuttering lacunar stroke.

Conclusion: There may be a role for NOACs in stroke prevention and treatment beyond atrial fibrillation. Randomized controlled trials are needed to compare NOACs to current stroke prevention and treatment strategies in certain subgroups of patients with cerebrovascular disease.

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GLOSSARY

APAS = antiphospholipid antibody syndrome; **CI** = confidence interval; **CVT** = cerebral venous thrombosis; **ESUS** = embolic stroke of undetermined source; **HR** = hazard ratio; **INR** = international normalized ratio; **NAVIGATE ESUS** = Rivaroxaban vs Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source; **NOAC** = non-vitamin K antagonist oral anticoagulant; **NT-proBNP** = N-terminal fragment of the prohormone brain natriuretic peptide; **PFO** = patent foramen ovale; **PTAS** = percutaneous angioplasty and stenting; **RE-SPECT ESUS** = Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source; **VKA** = vitamin K antagonist; **WARCEF** = Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction; **WARSS** = Warfarin vs Aspirin Recurrent Stroke Study; **WASID** = Warfarin-Aspirin Symptomatic Intracranial Disease.

Atrial fibrillation remains the only condition for which oral anticoagulation has been demonstrated in large-scale clinical trials to be effective for stroke prevention. However, anticoagulants are used in several other situations by practicing neurologists, including cervical artery dissection, cryptogenic stroke with or without patent foramen ovale (PFO), cerebral venous thrombosis (CVT), and fluctuating stroke. Anticoagulation is occasionally used in all of these cerebrovascular conditions with varying degrees of supportive evidence.¹ Non-vitamin K antagonist oral anticoagulant (NOAC) drugs have been shown to be at least noninferior to vitamin K antagonists (VKAs) in preventing ischemic stroke and systemic embolism with lower bleeding risk.²⁻⁵ Furthermore, one trial showed that among patients with atrial fibrillation deemed to be ineligible to receive VKA for various reasons, including inability to comply with monitoring

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regimens and high risk of hemorrhage, apixaban reduced the risk of stroke with similar major bleeding risk compared with aspirin.⁶ Thus, one may logically consider the use of these agents in these other situations in which anticoagulation is often used or recommended. In this review, we discuss the potential for future use of NOACs in cerebrovascular disease.

METHODS We performed a nonsystematic review of the literature on the use of NOACs in patients with atrial fibrillation, venous thromboembolism, and, where available, cerebrovascular disease independent of atrial fibrillation. This literature included the major randomized trials demonstrating the efficacy and risks of dabigatran, rivaroxaban, apixaban, and edoxaban compared with VKAs, and of apixaban compared with aspirin. We also searched the literature for exploratory comparative studies regarding the use of VKAs, antiplatelet agents, and NOACs in the setting of cerebrovascular disease among patients without atrial fibrillation, including patients with cryptogenic stroke, atherosclerosis, arterial dissection, CVT, and others. This literature was interpreted in light of prior comparative studies of antiplatelet agents and VKAs for the treatment and prevention of various forms of cerebrovascular disease.

RESULTS NOACs in atrial fibrillation and risk of bleeding. Anticoagulation is superior to antiplatelet therapy in primary and secondary stroke prevention in patients with atrial fibrillation.¹ Recent evidence suggests that NOACs are as effective as VKAs in the prevention of recurrent ischemic stroke and systemic embolism, with a lower risk of intracranial hemorrhage. Moreover, in a meta-analysis among 54,875 patients, the NOACs considered as a group significantly reduced total and cardiovascular mortality, with an approximately 50% decrease in the risk of intracranial hemorrhage and approximately 0.5% per year decrease in the risk of major hemorrhage compared with warfarin.⁷ Dabigatran 150 mg twice per day compared with warfarin was associated with reduced risk of ischemic stroke, systemic embolism, and intracranial hemorrhage; dabigatran 110 mg twice per day was associated with reduced risk of intracranial bleeding and major bleeding but with similar risk of ischemic stroke and systemic embolism compared with warfarin.³ Apixaban was superior to warfarin in prevention of stroke and systemic embolism with a lower risk of intracranial hemorrhage.⁴ Rivaroxaban and edoxaban had a similar efficacy in the prevention of stroke and systemic embolism but lower risk of intracranial hemorrhage compared with warfarin.^{2,5} Dabigatran is the only NOAC thus far that has been associated with reduced risk of ischemic stroke as compared with warfarin,³ whereas only apixaban and edoxaban were superior to warfarin in reduced risk of major bleeding.^{4,5} In addition, rivaroxaban and

dabigatran are associated with a higher rate of major gastrointestinal bleeding when compared with warfarin.³

NOACs in cryptogenic stroke. Cryptogenic stroke generally refers to a nonlacunar infarction occurring in the absence of a specific identifiable high-risk stroke mechanism, such as atrial fibrillation, valvular heart disease, or large artery stenosis. Cryptogenic stroke accounts for 30% to 40% of ischemic strokes.⁸ The term *embolic stroke of undetermined source* (ESUS) has also been used recently in reference to patients with nonlacunar stroke in whom there is no evidence of ipsilateral intracranial or extracranial stenosis of $\geq 50\%$, major risk source of cardiac embolism (such as atrial fibrillation), or other identified stroke mechanism.⁹ Use of the term ESUS implies that a thorough evaluation to exclude other causes of stroke has been performed. With the advent of mobile continuous outpatient telemetry and implantable loop recorders, paroxysmal atrial fibrillation may be detected in up to one-third of patients with cryptogenic stroke, depending on the pretest diagnostic evaluation, i.e., with a higher risk among patients with embolic-appearing infarcts or frequent atrial ectopy.^{10–12} In up to 65% of patients from the Stroke Databank who had infarcts of undetermined cause, the infarcts were considered to be due to less well-documented sources of embolism on further evaluation.¹³

In population-based studies, the risk of stroke recurrence in patients with cryptogenic stroke is about 6% at 30 days and 10% at 90 days.¹⁴ Since up to 20% of patients with cryptogenic stroke are found to have paroxysmal atrial fibrillation on mobile continuous outpatient telemetry,⁸ it is reasonable to consider anticoagulation therapy in patients with ESUS pending the results of further monitoring. The short-term use of NOACs may be considered in this patient population given the higher efficacy and lower risk of bleeding as compared with warfarin in patients with paroxysmal atrial fibrillation.

The long-term use of warfarin at an international normalized ratio (INR) of 1.4 to 2.8 was not superior to aspirin for the prevention of recurrent stroke among patients with noncardioembolic stroke in the Warfarin vs Aspirin Recurrent Stroke Study (WARSS).¹⁵ Among the prespecified subgroup of patients with cryptogenic stroke in WARSS, however, there was some evidence of benefit, with a reduction of 2-year stroke recurrence or death risk in patients on warfarin (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.61–1.39).¹⁵ In a further subgroup analysis of the WARSS data, there was a reduction in the risk of recurrent ischemic stroke or death in patients with cryptogenic stroke and no history of hypertension (HR 0.45, 95% CI 0.22–0.96) and in

those with posterior circulation strokes and no brainstem involvement (HR 0.14, 95% CI 0.04–0.47).¹⁶ The risk of major bleeding on warfarin compared with aspirin was only marginally increased as well (2.2% on warfarin vs 1.5% on aspirin, $p = 0.1$). These data provide a rationale for considering oral anticoagulation for cryptogenic stroke patients and further suggest consideration of the use of anticoagulants with lower risks of bleeding than warfarin (NOACs generally) or with a risk of bleeding shown to be comparable with aspirin for atrial fibrillation (apixaban) in cryptogenic stroke patients. Randomized trials comparing dabigatran (NCT02239120) and rivaroxaban (NCT02313909) with aspirin in patients with ESUS are under way. The Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source (RESPECT ESUS) investigators plan to randomize 6,000 patients with ESUS to dabigatran vs aspirin for a period of 3 years. The primary outcome is time to first recurrent stroke (ischemic or hemorrhagic). The Rivaroxaban vs Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial is randomizing patients to rivaroxaban 15 mg daily vs aspirin 100 mg daily for 3 years, and the primary outcomes are time to recurrent stroke (ischemic or hemorrhagic) or systemic embolism and time to first occurrence of major bleeding.

NOACs in patients with left atrial dysfunction. Atrial fibrillation, with its implied intracavitary stasis in the setting of irregular atrial wall contractile function, has been long considered to provide a direct mechanistic explanation for embolism. Recent evidence, however, challenges this concept of atrial fibrillation itself as the primary mechanism of stroke in patients with atrial dysfunction.¹⁷ Other biomarkers, including serum, ECG, and echocardiographic markers of left atrial dysfunction, have also been associated with increased risk of stroke, even in the absence of documented atrial fibrillation. The N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP), for example, is a serum biomarker of cardiac contractile dysfunction¹⁸ and atrial fibrillation¹⁹ and is associated with cardioembolism.²⁰ Results from the left atrial appendage closure trials demonstrate that occlusion of the left atrial appendage reduces the risk of ischemic stroke to 1.7% per year, which is lower than the predicted rates based on CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/TIA) scores,²¹ suggesting that left atrial structural and functional abnormalities, and not just atrial fibrillation, are the major determinants of stroke risk in this class of patients.

Atrial arrhythmias and ECG findings have also been associated with stroke risk in the absence of atrial fibrillation. In a statewide administrative database study, paroxysmal supraventricular tachycardia was associated with a 2-fold increase in risk of ischemic stroke even in the absence of atrial fibrillation.²² Furthermore, P wave terminal force in lead V1 on ECG has been associated with increased risk of ischemic stroke,²³ and particularly those related to embolism (cardioembolic and cryptogenic stroke subtypes).

Left atrial enlargement is also associated with the risk of first ischemic stroke in the absence of atrial fibrillation,²⁴ subclinical cerebrovascular disease,²⁵ and detection of atrial fibrillation in patients with cryptogenic stroke.²⁶ In population-based studies, recent evidence suggests that left atrial size is associated with increased risk of recurrent stroke related to embolism (cryptogenic or cardioembolic), an association independent of atrial fibrillation.²⁷ Other left atrial findings on echocardiogram suggestive of embolism are left atrial spontaneous echocardiographic contrast, or “smoke.”^{21,28}

At present, there is no definitive evidence that anticoagulation is superior to antiplatelet therapy for patients with cryptogenic stroke and evidence of left “atrial cardiopathy” suggested by the presence of these atrial biomarkers. A post hoc analysis of the WARSS trial, however, which enrolled patients without known atrial fibrillation, showed that warfarin was superior to aspirin in reducing the 2-year risk of stroke or death among the 5% of patients with the most highly elevated NT-proBNP. In patients with NT-proBNP >750 pg/mL, the 2-year event rate per 100 person-years in the warfarin group was 16.6% vs 45.9% in the aspirin group (HR 0.30, 95% CI 0.12–0.84; $p = 0.021$).²⁹

These data suggest that a biomarker of left atrial dysfunction might select a group of patients most likely to benefit from anticoagulation, even in the absence of evidence of atrial fibrillation. Given the increased efficacy and safety of NOACs as compared with warfarin, stroke prevention trials comparing NOACs with antiplatelet therapy among patients with atrial cardiopathies may be considered.

NOACs in patients with low ejection fraction. In patients with congestive heart failure and low ejection fraction, there is evidence from the Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study to suggest that warfarin is superior to aspirin in reducing the risk of ischemic stroke over a median of 5 years (HR 0.52, 95% CI 0.33–0.88).³⁰ This benefit was offset, however, by an increased risk of major hemorrhage (HR 2.05, 95% CI 1.36–3.12).³⁰ A subgroup analysis of the WARCEF study showed that the stroke risk is higher in patients with an

ejection fraction $\leq 15\%$ (HR 2.33, 95% CI 1.30–4.18) or a history of stroke (HR 2.66, 95% CI 1.59–4.55),³¹ subgroups that may thus particularly benefit from anticoagulation therapy. Given the approximately 0.5% per year decreased risk of major hemorrhage as compared with warfarin,³² NOACs could potentially maintain the efficacy of anticoagulation in patients with stroke and low ejection fraction and attain a safety profile comparable to aspirin. This hypothesis could also be tested in randomized controlled trials; however, the relatively high mortality rate of patients with congestive heart failure poses difficulties in performing such a trial.

NOACs in patients with cryptogenic stroke and PFO. A PFO is present in approximately 25% to 30% of stroke patients,³³ with a higher prevalence in patients with cryptogenic stroke as compared with other stroke subtypes.³⁴ The mechanism of stroke in patients with PFO is unclear. In patients with cryptogenic stroke whose stroke is thought to be related to the PFO, one of the major mechanisms is paradoxical embolism. This mechanism is also supported by a higher prevalence of chronic deep vein thrombosis³⁵ and venous anomalies such as iliac vein compression³⁶ in patients with PFO and cryptogenic stroke as compared with other stroke subtypes. In addition, other venous anomalies have been associated with increased stroke risk, an association possibly mediated by paradoxical embolism.³⁷ To date, there is no evidence to support the superiority of PFO closure over medical therapy in patients with cryptogenic stroke, but there was a trend toward benefit in the “as treated” post hoc analysis of the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial.³⁸ Furthermore, an ancillary study of the WARSS trial failed to provide evidence that warfarin was superior to aspirin for the prevention of recurrent stroke among patients with cryptogenic stroke and PFO.³³ Given the efficacy of NOACs in the prevention of recurrent venous thromboembolic events,^{39,40} and since paradoxical embolism is the most likely mechanism of PFO-related stroke, NOACs may be considered in secondary prevention of PFO-related stroke, although randomized trials are needed. In addition, secondary analyses of the RE-SPECT ESUS and NAVIGATE ESUS trials may provide data on the efficacy of NOACs in patients with PFO.

NOACs in patients with intracranial atherosclerosis. Patients with symptomatic intracranial atherosclerosis have high early and long-term stroke recurrence rates despite aggressive medical management, with rates of about 5% at 30 days⁴¹ and 20% at 2 years.⁴² The stenting and aggressive medical management for the prevention of stroke in intracranial stenosis

(SAMMPRIS) study investigated the use of percutaneous angioplasty and stenting (PTAS) vs aggressive medical management and showed that aggressive medical management was superior to PTAS because of the relatively high stroke rate in the PTAS arm and the lower-than-expected stroke rate in the medical arm.⁴¹ Furthermore, the data from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study comparing warfarin with aspirin in patients with symptomatic intracranial atherosclerosis showed that warfarin provided no benefit in reducing the risk of stroke as compared with aspirin but was associated with higher risk of major bleeding.⁴³ However, a post hoc analysis from the WASID study showed that in patients on warfarin whose INR was maintained in the ideal therapeutic window, i.e., between 2.0 and 3.0, the risk of stroke was reduced to 5.1% per year (95% CI 2.7%–8.7%) from 24.9% per year (95% CI 15.8%–37.3%) among those whose INR was < 2.0 . Moreover, the risk of major hemorrhage for those whose INR was between 2.0 and 3.0 was 3.5% per year (95% CI 1.6%–6.6%) compared with 15.2% (95% CI 6.6%–30.0%) for those whose INR was 3.1 to 4.4 and even higher for those whose INR was ≥ 4.5 .⁴³ It is possible, however, that if the ideal therapeutic window had been maintained in all patients, then a benefit with warfarin would have been seen. NOACs could provide an opportunity to maintain a beneficial treatment effect in the narrow therapeutic window required to prevent ischemia without increasing risk of hemorrhage among patients with intracranial atherosclerosis. The apparent efficacy of warfarin in patients whose INR was maintained in the 2 to 3 range might also be attributable to the fact that easy-to-control patients are inherently at lower risk of stroke. Since anticoagulant use is theoretically geared toward preventing thrombus formation, the use of NOACs to prevent the progression of atherosclerosis in patients with intracranial atherosclerosis is unclear and therefore clinical trials are needed to compare NOACs with antiplatelet agents to potentially improve stroke prevention strategies in such patients.

NOACs in patients with lacunar stroke. Lipohyalinosis is thought to be the main pathomechanism in patients with lacunar stroke, but up 25% of patients with apparent lacunar stroke have a mechanism other than microvascular disease, including large artery atherosclerosis or embolism.⁴⁴ A significant proportion of patients with lacunar strokes, moreover, have stuttering or progressive symptoms that may respond to more aggressive antithrombotic approaches.⁴⁵ The combination of aspirin and clopidogrel in patients with mild deficits was associated with a lower risk of neurologic deterioration compared with matched

controls (OR 17.2, $p = 0.002$).⁴⁶ In those patients, mechanisms such as a substenotic ulcerated plaque in the main vessel may be the cause. Indirect evidence for a more aggressive antithrombotic approach among patients with small vessel disease also comes from the original National Institute of Neurological Disorders and Stroke trial of IV tissue plasminogen activator in acute ischemic stroke, which demonstrated an even greater benefit for tissue plasminogen activator treatment among patients with small vessel stroke (25% absolute risk reduction of a poor outcome on the Barthel Index) than among patients with other stroke subtypes.⁴⁷ A clinical trial comparing the efficacy of apixaban vs aspirin plus clopidogrel in patients with nondisabling strokes is under way (NCT00379899), but it is being performed in China and may not be applicable elsewhere given potential race-ethnic disparities in stroke and bleeding risk.

NOACs in patients with cervical artery dissection. The treatment of patients with cervical artery dissection is controversial. A large meta-analysis showed no difference in stroke recurrence and hemorrhage rates between patients treated with anticoagulation vs antiplatelet therapy.⁴⁸ However, short-term anticoagulation with VKA is widely used.⁴⁹ A recent single-center retrospective study provides evidence that vascular neurologists at a major academic center continue to use anticoagulants and have also begun to use NOACs in this setting despite the absence of randomized clinical trial data to support this approach.⁵⁰ These investigators reported that in patients with cervical artery dissection, the rate of stroke was similar in patients treated with NOACs (comprising 26.2% of patients), warfarin (comprising 47%), and antiplatelet agents (comprising 26.8%). More major hemorrhagic events occurred in the warfarin group (11.4%) compared with the NOAC (0.0%) and antiplatelet (2.5%) groups ($p = 0.034$). These data must be interpreted with caution because there was nonrandom allocation of treatment and the numbers are small. Nonetheless, patients with cervical artery dissection may constitute a group of patients in which NOACs may prove useful. Moreover, recent evidence from the Cervical Artery Dissection in Stroke Study suggests that a randomized clinical trial of antithrombotic vs antiplatelet therapy would need to be prohibitively large and expensive, and is unlikely to be completed.⁵¹ Assuming an annual stroke risk of 2%, one would need 600 dissection patients in each group (1,200 total) with average follow-up of 4 years to demonstrate a 50% relative reduction in stroke risk with NOACs vs aspirin.

NOACs in venous sinus thrombosis. CVT is an uncommon but serious condition associated with about 15%

overall rate of death or functional dependence on follow-up.⁵² Despite an absence of randomized controlled trial evidence to support anticoagulation therapy in CVT, recent American Heart Association/American Stroke Association guidelines on the diagnosis and management of CVT state that it is reasonable to start low-molecular-weight heparin or unfractionated heparin followed by oral VKAs even in the presence of hemorrhage.⁵³ These recommendations are based on the results of small trials that in meta-analysis suggested a benefit of anticoagulation with a low rate of hemorrhage. None of the recent trials of NOACs in venous thromboembolism, however, included patients with CVT.^{39,40} Therefore, extrapolating from the available evidence and current practice guidelines, one may reasonably consider NOACs as alternatives to VKAs in patients with CVT.^{54,55} Performing a randomized trial comparing NOACs with VKAs may be difficult. Assuming an annual recurrence rate of 3%, one would need 1,800 patients in each group (3,600 total) with average follow-up of 4 years to demonstrate a 25% relative reduction with NOACs vs warfarin for recurrent CVT, which is very difficult to perform given the low overall prevalence of CVT.

Antiphospholipid antibody syndrome. In patients with antiphospholipid antibody syndrome (APAS), anticoagulation is the mainstay of treatment to prevent recurrent thrombotic events.¹ In this patient population, the main advantage for using NOACs is the difficulty monitoring INR levels in a group of patients with APAS because of the presence of antiphospholipid antibodies.⁵⁶ A trial investigating the use of rivaroxaban in patients with APAS is under way (NCT02116036).

Other situations. Other situations in which NOACs could be investigated include hereditary and cancer-associated hypercoagulability, in which anticoagulation therapy is typically used. However, one study investigated the use of dabigatran in patients with mechanical valves and showed that VKAs were superior in reducing the risk of major cardiovascular events (8% vs 2%, $p = 0.11$) and were associated with a lower risk of major hemorrhage (27% vs 12%, $p = 0.01$).⁵⁷ Therefore, caution may be needed in extrapolating results from one patient population to another.

CONCLUSION The use of NOACs in stroke prevention can potentially be expanded to encompass a wide variety of patients to improve current stroke prevention strategies. The limited data available at present on the safety and efficacy of the NOACs suggest that there are several situations in which NOACs could be used in the treatment and secondary prevention of

stroke in patients without diagnosed atrial fibrillation. Randomized controlled trials are needed to compare NOACs with the current stroke prevention strategies in certain subgroups of patients with ischemic stroke.

AUTHOR CONTRIBUTIONS

Shadi Yaghi: literature review, drafting of manuscript. Hooman Kamel: critical review of manuscript, statistical analysis, literature review. Mitchell Elkind: literature review, critical review of manuscript, supervision, and funding.

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