Review Article

A Narrative Review of Nonvitamin K Antagonist Oral Anticoagulant Use in Secondary Stroke Prevention

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The prevalence of atrial fibrillation (AF), the most common cardiac arrhythmia, increases with age, predisposing elderly patients to an increased risk of embolic stroke. With an increasingly aged population the number of people who experience a stroke every year, overall global burden of stroke, and numbers of stroke survivors and related deaths continue to increase. Anticoagulation with vitamin K antagonists (VKAs) reduces the risk of ischemic stroke in patients with AF; however, increased bleeding risk is well documented, particularly in the elderly. Consequently, VKAs have been underused in the elderly. Alternative anticoagulants may offer a safer choice, particularly in patients who have experienced previous stroke. The aim of this narrative review is to examine available evidence for the effective treatment of patients with AF and previous cerebral vascular events with non-VKA oral anticoagulants, including the most appropriate time to start or reinitiate treatment after a stroke, systemic embolism, or clinically relevant bleed. For patients with AF treated with oral anticoagulants it is important to balance increased protection against future stroke/systemic embolism and reduced risk of major bleeding events. For patients with AF who have previously experienced a cerebrovascular event, the use of oral anticoagulants alone also appears more effective than low-molecular weight heparin (LMWH) alone or LMWH followed by oral anticoagulants. Available data suggest that significant reduction in stroke, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days from acute stroke can be achieved if oral anticoagulation is initiated at 4-14 days from stroke onset.

Key Words: Cerebrovascular events—nonvitamin K antagonist oral anticoagulant—treatment reinitiation—intracranial hemorrhage—prior stroke—NOAC timing

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and its prevalence increases with age, predisposing elderly patients to an increased risk of embolic stroke.[1-3] Thus, with an ever increasing aged population, the absolute numbers of people who experience a stroke every year, overall global burden of stroke, and numbers of stroke survivors and related deaths continue to increase.[1] Although it is well established that oral anticoagulant therapy with vitamin K antagonists (VKAs) effectively reduces the risk of ischemic stroke in patients with AF,[4] increased bleeding risk with this treatment, particularly in the elderly, is well documented.[3] As a result of this, historically, VKAs have been underused in the elderly, despite their increased risk of stroke.[5,6] Intracranial hemorrhage (ICH), one of the most feared complications of oral anticoagulation therapy, has a poor prognosis which has not significantly improved with modern management.[7] ICH particularly

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afflicts patients with previous stroke who are also at high risk for thromboembolism.[8,9]

The size and location of an ischemic lesion affects both the presentation of acute stroke and outcome. Particularly, involvement of cortical tissue is related to worse outcomes compared with subcortical infarctions.

As prevention of stroke in patients with AF remains a high clinical priority, the use of alternative anticoagulants may offer physicians a safer choice to VKAs, particularly in patients who have experienced previous stroke. The aim of this narrative review is to examine available evidence for the effective treatment of patients with AF and previous cerebrovascular events with non-VKA oral anticoagulants (NOACs), including the most appropriate time to start or reinitiate treatment after a stroke, systemic embolism, or clinically relevant bleed.

Risk of Stroke With AF

Patients with AF have a 4- to 5-fold increased risk of developing a stroke.[10] While the attributable risk for stroke associated with AF is 1.5% at age 50-59 years, this steeply increases to 23.5% by the age of 80-89 years.[10,11] However, the specific per patient stroke risk can be challenging to establish given that the absolute risk of stroke can vary up to 20-fold among patients with AF according to age and associated vascular comorbidities.[12] In addition, while several stroke risk stratification schemes have been developed and validated, they can yield varying results and underestimate the true risk of stroke in patients with previous ischemic stroke or transient ischemic attack (TIA).[12,13] When applied to secondary stroke prevention, the $CHADS_2$ stroke-risk index has a limitation in patients with previous stroke/TIA and no other risk factors. While stroke risk assessment may indicate a score 2 on the $CHADS_2$ scale (point estimate of thromboembolic risk 2.50 per 100 patient-years) in such patients, validation studies of this scale have demonstrated that patients with prior stroke or TIA can suffer from an average 7.40-10.8 strokes per 100 patient-years.[12] The CHA_2DS_2-VASc index has since been developed to refine the risk calculation of $CHADS_2$ by including additional variables.[12]

Prevention of Stroke in Patients With AF: Current Treatment Options and Clinical Data

Physicians attempt to minimize the risks of anticoagulants in patients with AF by striking a balance between the risk of having a stroke while using less effective anticoagulation versus that of having a major bleeding event while on more effective anticoagulation.[14] When selecting an anticoagulant regimen for a patient with AF, physicians tend to favor suboptimal anticoagulant regimens, which typically will not offer optimal protection against future stroke or systemic embolism, but should reduce the risk of major bleeds. Thus, many studies have identified underuse of anticoagulation, particularly VKAs, in populations who are at high risk of stroke, including patients with AF.[15] The observational Global Anticoagulant Registry in the FIELD study demonstrated that 38.0% of patients with AF and a $CHADS_2$ score greater than or equal to 2 did not receive anticoagulant therapy, in contrast with 42.5% of patients at low risk ($CHADS_2$ score 0) who did. On the other hand, the PREvention oF thromboembolic events—European Registry in AF (PREFER in AF) demonstrated that the majority of patients with a CHA_2DS_2-VASc score greater than or equal to 2 received oral anticoagulants (85.6%). Similar to the Global Anticoagulant Registry in the FIELD registry, PREFER in AF demonstrated that a large proportion of patients at low risk of stroke (CHA_2DS_2-VASc score 0) also received oral anticoagulation.[16] In PREFER in AF, ~16% of patients had experienced a previous stroke or TIA.

VKAs and Antiplatelet Agents

A meta-analysis of 6 placebo-controlled studies (N = 2900) has shown that adjusted-dose warfarin significantly reduced the risk of stroke by 64% (95% CI: 49%, 74%) versus placebo in patients with AF.[17] In contrast, data from 8 studies which used antiplatelet agents (N = 4876) demonstrated a relatively lower reduction in stroke risk (22%; [95% confidence interval {CI}: 6%, 35%]) versus placebo.[17] Of note, a study (European Atrial Fibrillation Trial) in AF patients with a previous TIA or stroke failed to show any significant risk reduction with aspirin compared with placebo.[17]

However, while adjusted-dose warfarin was substantially more effective than antiplatelet therapy (relative risk [RR] reduction: 39%; [95% CI: 22%, 52%]; N = 12,963) for the reduction in stroke risk, it doubled the risk of major extracranial bleeding and ICH.[17]

The annual incidence of anticoagulant-associated ICH increased 5-fold in the US population between 1988 and 1999;[18] for patients receiving warfarin or heparin, anticoagulant-associated ICH cases comprised 5% of reported ICH in 1988, increasing to 17% in 1999 ($P < .001$). Most of this change appears to be explained by an increased use of warfarin. A recent study of patients with ICH in the US reported 10.6% were taking warfarin and 3.5% taking NOACs preceding ICH.[19]

Good control of warfarin is important to reduce the associated risk of ICH.[8] This observational study reported that intracranial bleeding did not appear to increase with warfarin anticoagulation until the international normalized ratio (INR) exceeded 3.5-4.0, and no increase in ICH was associated with INRs of 2.0-3.0 compared with lower INRs. Similarly, in a cohort of patients with AF from the General Practice Research Database, those who spent at least 70% of their time in therapeutic range (TTR) had a 79% reduced risk of stroke compared with patients who had a TTR less than or equal to 30% (adjusted relative

rate: .21 [95% CI: .18, .25]), demonstrating the importance of effective INR control.[20] Mortality rates were also significantly lower with a TTR greater than or equal to 70%. A retrospective study from the United States also reported an association between warfarin-related ICH, INR values, and mortality. The in-hospital mortality rate in patients with prior use of NOACs (26.5%) was significantly lower than among patients with prior use of warfarin with therapeutic INR (33.4%; INR 2-3). Subtherapeutic INR (<2) was 25.7% for warfarin and supratherapeutic was 39.2% for warfarin.[19]

Other factors that appear to reduce the risk of intracranial bleeding with warfarin include the avoidance of combining this treatment with aspirin and the improved control of existing hypertension.[8]

NOACs for the Prevention of Stroke in Patients With AF

Efficacy

The NOACs including dabigatran, apixaban, rivaroxaban, and edoxaban have all demonstrated at least noninferior efficacy compared with warfarin for the prevention of stroke/systemic embolism.[21-24]

In the RE-LY study involving patients with AF (N = 18,113), the use of dabigatran (110 mg twice daily [BID] dose) achieved reduced rates of stroke or systemic embolism (1.53% per year) that were similar to those associated with warfarin (1.69% per year; RR with dabigatran: .91; [95% CI: .74, 1.11]; $P < .001$ for noninferiority), along with lower rates of major hemorrhage with dabigatran versus warfarin.[21] A higher dose of dabigatran (150 mg BID) provided even lower rates of stroke and systemic embolism (1.11% per year; RR: .66; [95% CI: .53, .82]; $P < .001$ for superiority), but had similar rates of major hemorrhage.

Apixaban demonstrated superiority to warfarin in preventing stroke or systemic embolism, causing less bleeding, and resulting in lower mortality in patients with AF in the ARISTOTLE study.[23] This randomized, double-blind study compared apixaban (5 mg BID) with warfarin (target INR: 2.0-3.0) in patients with AF and at least one additional risk factor for stroke (N = 18,201). The rates of the primary outcome (ischemic or hemorrhagic stroke or systemic embolism) were 1.27% per year and 1.60% per year in the apixaban and warfarin groups, respectively (hazard ratio [HR] with apixaban: .79; [95% CI: .66, .95]; $P < .001$ for noninferiority; $P = .01$ for superiority).

Rivaroxaban demonstrated noninferiority to warfarin for the prevention of stroke or systemic embolism in patients with AF in the ROCKET AF study.[24] In this double-blind, randomized study, patients with nonvalvular AF at an increased risk of stroke received either rivaroxaban (20 mg once daily [QD]) or adjusted-dose warfarin (N = 14,264). The rates of the primary outcome were 1.7% per year and 2.2% per year in the rivaroxaban and warfarin groups, respectively (HR in the rivaroxaban group: .79; [95% CI: .66-.96]; $P < .001$ for noninferiority).

Both regimens of edoxaban (60/30 mg QD and 30/15 mg QD) have demonstrated noninferiority to warfarin with respect to the prevention of stroke or systemic embolism in the ENGAGE AF-TIMI 48 trial,[22] a randomized, double-blind, double-dummy study in 21,105 patients with AF. The rate of the primary outcome (stroke or systemic embolism) during treatment was 1.50% per year with warfarin (median TTR: 68.4%), compared with 1.18% per year with edoxaban 60/30 mg (HR: .79; [97.5% CI: .63, .99]; $P < .001$ for noninferiority) and 1.61% per year with edoxaban 30/15 mg (HR: 1.07; [97.5% CI: .87, 1.31]; $P = .005$ for noninferiority). It must be noted that edoxaban 30/15 mg dose is not approved for use by regulatory authorities.

Safety

Rates of both ICH and hemorrhagic stroke have been shown to be lower with dabigatran, apixaban, rivaroxaban, and edoxaban compared with warfarin.[21-23,25-27] In the RE-LY study, the rates of major bleeding were 3.36%, 2.71% ($P = .003$) and 3.11% ($P = .31$) per year, and that of hemorrhagic stroke were .38%, .12% ($P < .001$), and .10% ($P < .001$), in the warfarin, dabigatran 110 and 150 mg groups, respectively.[21] In addition, the rates of ICH with warfarin, dabigatran 110 mg and 150 mg, were .76%, .23%, and .31% per year, respectively ($P < .001$ for either dabigatran dose versus warfarin).[27] Fewer fatal ICHs were reported among patients who received dabigatran 110 mg or 150 mg (n = 11 and n = 13, respectively) versus warfarin (n = 32; $P < .01$ for both), and fewer traumatic ICHs occurred with dabigatran (11 patients with each dose) compared with warfarin (24 patients; $P < .05$ for both dabigatran doses versus warfarin).

In the ARISTOTLE study, the rate of major bleeding with apixaban was 2.13% per year versus 3.09% per year with warfarin (HR: .69; [95% CI: .60, .80]; $P < .001$). In addition, the rate of hemorrhagic stroke was .24% per year with apixaban versus .47% per year with warfarin (HR: .51; [95% CI: .35, .75]; $P < .001$), and the rate of ischemic or uncertain type of stroke was .97% per year and 1.05% per year in the apixaban and warfarin groups, respectively (HR: .92; [95% CI: .74, 1.13]; $P = .42$).[23]

In the ROCKET AF study, significant, independent predictors of ICH were identified as race, age, reduced serum albumin, reduced platelet count below 210×10^9/L, previous stroke or TIA, and increased diastolic blood pressure.[26] The risk of ICH was significantly lower in patients with AF and heart failure who were randomized to receive rivaroxaban instead of warfarin (HR: .60; [95% CI: .44, .82]).

The ENGAGE AF-TIMI 48 study demonstrated that edoxaban reduces cardiovascular mortality, along with the incidence of major bleeding and ICH compared with warfarin.[22] The rate of major bleeding was 3.43% per year with warfarin compared with 2.75% per year with

edoxaban 60/30 mg (HR: .80; [95% CI: .71, .91]; $P < .001$) and 1.61% per year with edoxaban 30/15 mg (HR: .47; [95% CI: .41, .55]; $P < .001$). The corresponding rates of death from cardiovascular causes were 3.17% per year (60/30 mg dose; HR: .86; [95% CI: .77, .97]; $P = .01$) and 2.71% (30/15 mg dose; HR: .85; [95% CI: .76, .96]; $P = .008$). Further analysis of this data set demonstrated that edoxaban reduced mortality primarily by reducing fatal ICH in patients with AF.[25] Fewer ICHs were reported with edoxaban 60/30 mg (n = 79; .50% per year; $P < .001$ versus warfarin) and 30/15 mg (n = 60; .37% per year; $p < .001$ versus edoxaban 60/30 mg and warfarin). Given that age has a greater influence on major bleeding than thromboembolic risk in patients with AF, Kato et al assessed data from the ENGAGE AF-TIMI 48 study and found that treatment of elderly patients (≥75 years) with edoxaban provided an even greater absolute reduction in safety events over warfarin, compared to treatment of younger patients with edoxaban versus warfarin.[28] The rates of stroke and systemic embolism remained similar between edoxaban and warfarin in elderly patients (≥75 years), while major bleeding was significantly reduced with edoxaban (HR: .83; [95% CI: .70, .99]). The absolute risk differences in both major bleeding (−82 events/10,000 patient years) and ICH (−73 events/10,000 patient years) favored edoxaban over warfarin in older patients.

A meta-analysis of patients from RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 studies confirmed reductions in ICH with NOACs overall compared with warfarin.[29] NOACs were found to significantly reduce all-cause mortality (HR: .90; [95% CI: .85, .95]; $P = .0003$) and ICH (.48, [95% CI: .39, .59]; $P < .0001$), compared with warfarin. This reduction of mortality is due to the better safety profile and is mainly driven by the reduction of ICH. These data, along with those from the pivotal Phase III studies, provide a strong rationale for selecting a NOAC rather than warfarin for the prevention of stroke in patients with AF.

Efficacy and Safety of NOACs in Patients With AF and Previous Ischemic Event

Patient demographics data from the ENGAGE AF-TIMI 48 study suggest that patients with AF and previous ischemic stroke or TIA are at high risk of recurrent thromboembolism and bleeding.[9] The rate of stroke or systemic embolism in patients with or without prior ischemic stroke or TIA was 2.83% versus 1.42% per year (adjusted HR 1.97; [95% CI: 1.73, 2.24; $P < .001$]). Rost et al deemed this difference to be mainly driven by a higher annual rate of primary ischemic stroke (2.35% versus 1.07%; adjusted HR 2.19; [95% CI: 1.89, 2.53]) among patients who had experienced previous ischemic stroke or TIA; in contrast, annual rates of primary hemorrhagic stroke were numerically, but not significantly higher (.37% versus .27%; $P = .12$). These findings suggest that patients with history of prior ischemic stroke or TIA represent a vulnerable population of patients with AF, who appear to be at high risk of recurrent cerebrovascular events despite anticoagulation.[9]

All 4 NOACs have demonstrated similar efficacy and improved safety compared with warfarin in patients with AF and previous stroke or TIA (Table 1).[9,30-33]

A subgroup analysis of the RE-LY trial demonstrated that dabigatran 110 mg or 150 mg BID reduced the risk of stroke or systemic embolism in patients with AF with previous stroke or TIA (N = 3623), with findings consistent with those for the overall patient population (Table 1).[30] Dabigatran was also associated with significantly less major bleeding compared with warfarin (Table 1).

Similarly, data from the ROCKET AF trial suggested no differences in relative efficacy and safety with rivaroxaban use (versus warfarin) in patients who had or had not experienced a prior stroke or TIA (Table 1).[32] Likewise, reported major and nonmajor clinically relevant bleeding events per 100 patient-years in patients treated with rivaroxaban versus warfarin was consistent among patients with previous stroke or TIA and those without.

In the ARISTOTLE study, the efficacy and safety of apixaban compared with warfarin were also consistent in patients with AF who had or had not previously experienced stroke or TIA.[31] Compared with warfarin, apixaban was associated with greater absolute reductions in major bleeding in patients with previous stroke or TIA (Table 1).

A prespecified analysis of data from the ENGAGE AF-TIMI 48 trial has demonstrated that edoxaban was at least as effective as warfarin in the prevention of stroke or systemic embolism regardless of the presence or absence of prior ischemic stroke or TIA, while also providing a lower rate of ICH in patients with previous ischemic stroke or TIA (Table 1).[9] Thus, the use of edoxaban appears to offer generally greater absolute benefits versus well-managed warfarin in patients with AF and a history of previous ischemic stroke or TIA compared with AF alone.

A meta-analysis of 20,500 patients with AF and previous stroke or TIA from ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET-AF trials demonstrated the benefits of NOACs compared with warfarin in reducing stroke, systemic embolic events and major bleeding.[33] NOACs reduced the RR for recurrent stroke and systemic embolic events by 14% (odds ratio [OR]: .86; [95% CI: .75, .98]). Moreover, the RR of hemorrhagic stroke was reduced by 49% (OR: .51; [95% CI: .38, .69]) and mortality by 10% (OR: .90; [95% CI: .82, 1.00]) with NOACs compared with warfarin.[33]

The European Society of Cardiology (ESC) guidelines for the management of patients with AF recommended the use of NOACs in preference to VKAs or aspirin in patients with AF and a previous stroke (Class I Level B recommendation).[34] Additionally, the American Heart Association, American College of Cardiology, and Heart Rhythm Society Guidelines for the Management of Patients with AF recommend NOACs over warfarin for the prevention of stroke in patients with AF (Class I Level

Table 1. *Outcomes from the Phase III NOAC trials in patients with atrial fibrillation with and without a previous stroke or TIA*

No. of events (%/year)	RE-LY[30]					ARISTOTLE[31]		
	Warfarin	Dabigatran 110 mg BID	HR (95% CI) vs warfarin	Dabigatran 150 mg BID	HR (95% CI) vs warfarin	Warfarin	Apixaban 5 mg BID	HR (95% CI) vs warfarin
Stroke/SEE								
Previous stroke or TIA	65 (2.78)	55 (2.32)	.84 (.58-1.20)	51 (2.07)	.75 (.52-1.08)	98 (3.24)	73 (2.46)	.76 (.56-1.03)
No previous stroke or TIA	137 (1.45)	128 (1.34)	.93 (.73-1.18)	83 (.87)	.60 (.48-.78)	167 (1.23)	139 (1.01)	.82 (.65-1.03)
Major bleeding								
Previous stroke or TIA	97 (4.15)	65 (2.74)	.66 (.48-.90)	102 (4.15)	1.01 (.77-1.34)	106 (3.91)	77 (2.84)	.73 (.55-.98)
No previous stroke or TIA	324 (3.43)	277 (2.91)	.85 (.72-.99)	297 (3.10)	.91 (.77-1.06)	356 (2.91)	250 (1.98)	.68 (.58-.80)
Hemorrhagic stroke								
Previous stroke or TIA	18 (.77)	2 (.08)	.11 (.03-.47)	5 (.20)	.27 (.10-.72)	31 (1.00)	12 (.40)	.40 (.21-.78)
No previous stroke or TIA	27 (.29)	12 (.13)	.44 (.22-.86)	7 (.07)	.25 (.11-.59)	47 (.34)	28 (.20)	.59 (.37-.94)
ICH								
Previous stroke or TIA	30 (1.28)	6 (.25)	.20 (.08-.47)	13 (.53)	.41 (.21-.79)	41 (1.49)	15 (.55)	.37 (.21-.67)
No previous stroke or TIA	60 (.63)	21 (.22)	.35 (.21-.57)	26 (.27)	.43 (.27-.68)	81 (.65)	37 (.29)	.44 (.30-.66)
	ENGAGE-AF TIMI 48[9]					ROCKET-AF[32]		
	Warfarin	Edoxaban 60/30 mg QD	HR (95% CI) vs warfarin	Edoxaban 30/15 mg QD	HR (95% CI) vs warfarin	Warfarin	Rivaroxaban 20 mg QD	HR (95% CI) vs warfarin
Primary efficacy outcome								
Previous stroke or TIA	145 (2.85)	125 (2.44)	.86 (.67-1.09)	165 (3.19)	1.10 (.88-1.38)	187 (2.96)	179 (2.79)	.94 (.77-1.16)
No previous stroke or TIA	192 (1.41)	171 (1.24)	.88 (.72-1.08)	218 (1.60)	1.14 (.94-1.38)	119 (1.88)	90 (1.44)	.77 (.58-1.01)
Major bleeding								
Previous stroke or TIA	167 (3.86)	138 (3.25)	.84 (.67-1.06)	89 (2.01)	.52 (.40-.67)	183 (3.22)	178 (3.13)	.97 (.79-1.19)
No previous stroke or TIA	390 (3.47)	306 (2.72)	.79 (.68-.91)	203 (1.75)	.51 (.43-.60)	203 (3.69)	217 (4.10)	1.11 (.92-1.34)
Hemorrhagic stroke								
Previous stroke or TIA	31 (.59)	16 (.31)	.52 (.28-.94)	12 (.22)	.37 (.19-.73)	30 (.46)	22 (.34)	.73 (.42-2.16)
No previous stroke or TIA	59 (.43)	33 (.24)	.55 (.36-.85)	18 (.13)	.30 (.18-.52)	27 (.42)	11 (.17)	.41 (.20-.83)
ICH								
Previous stroke or TIA	48 (1.09)	27 (.62)	.57 (.36-.92)	18 (.40)	.37 (.21-.63)	46 (.80)	34 (.59)	.74 (.47-1.15)
No previous stroke or TIA	84 (.73)	34 (.30)	.41 (.27-.61)	23 (.20)	.27 (.17-.43)	38 (.68)	21 (.39)	.57 (.34-.97)

BID, twice daily; CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; QD, once daily; SEE, systemic embolic event; TIA, transient ischemic attack.

A recommendation).[35,36] The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic stroke or TIA which are at the same time important risk factors for warfarin-related ICH,[8,27] emphasising the need for OAC in these patients. Elderly patients were well represented in the Phase III NOAC trials; the mean age of patients with a previous cerebrovascular event treated with a NOAC ranged between 70.1 and 71.0 years across the trials.[9,30-32] Therefore, these results support the use of NOACs in elderly patients with a previous cerebrovascular event.

In addition, given that the highest risk of recurrent stroke is in the early phase following a first stroke or TIA, it remains important to perform a timely clinical assessment at patient level to ascertain the risk-benefit ratio of any OAC treatment in order to reduce the incidence of further ischemic events.[37]

Timing of Administration, Discontinuation, and Reinitiation: Considerations for Anticoagulation Treatment Following a Cerebrovascular Event

Despite available guideline recommendations, the optimal time for administering anticoagulation therapy in acute cardioembolic stroke remains unclear. Guidelines from the ESC for the management of AF recommend that in patients who suffer a moderate-to-severe ischemic stroke while on anticoagulation, this treatment should be interrupted for a period of 3-12 days to allow a multidisciplinary assessment of acute stroke and bleeding risk.[34] For acute ischemic stroke in patients presenting within 4.5 hours of symptom onset, systemic thrombolysis with recombinant tissue plasminogen activator is recommended, although this approach is contraindicated in patients on an established regimen of therapeutic oral anticoagulation. ESC guidelines suggest recombinant tissue plasminogen activator can be administered to patients treated with a VKA provided that they have an INR less than 1.7, while patients using therapeutic dabigatran require a normal activated partial thromboplastin time and last intake of drug to be greater than 48 hours prior to thrombolysis. Of note, the ESC guidelines acknowledge that the use of specific NOAC antidotes prior to thrombolysis requires further investigation (Fig 1).[34]

A prospective cohort study of patients with acute stroke and AF, evaluated the risks of recurrence and bleeding associated with anticoagulant therapy and its starting time after the acute stroke.[38] Of the patients enrolled (N = 1029), 77 (7.6%) had ischemic stroke or TIA or systemic embolism, 37 (3.6%) symptomatic cerebral bleeding, and 14 (1.4%) major extracranial bleeding. When assessing timeframes for initiating anticoagulation, a significant reduction in primary study outcome (composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days from acute stroke) was achieved when initiating anticoagulation at 4-14 days from stroke onset compared with initiating treatment before 4 or after 14 days (HR: .53; [95% CI: .30, .93]). The use of OAC alone achieved better outcomes compared with either low weight molecular heparin (LMWH) alone or LMWH followed by OAC; approximately 7% of the patients treated with OAC alone had an outcome event versus 16.8% and 12.3% of the patients treated with LMWHs alone or LMWH followed by OAC, respectively (P= .003). Thus, this study confirmed that the type of anticoagulant and regimen used independently led to increased risk of recurrence and bleedings. The exclusion of hemorrhagic transformation with computerized tomography or magnetic resonance imaging performed at 48-72 hours from stroke onset also supports the "4-14 days from stroke onset" timeframe for initiating anticoagulation treatment for secondary stroke prevention.[39]

The use of NOACs following a cardioembolic stroke has been assessed in a number of observational studies. The SAMURAI-NVAF study demonstrated that following NOAC initiation, within a median of 4 days poststroke, no ICH was observed.[40] Furthermore, in another observational study no significant difference in recurrent ischemic events was observed with poststroke NOAC initiation either less than or equal to 7 days or greater than 7 days following the initial event (P= .53).[41]

Early recurrences and major bleeding events (within 90 days) and the timing of these events in patients with an acute ischemic stroke and AF who received a NOAC following the initial event were assessed in the prospective observational multicenter RAF-DOAC study. An early recurrent event occurred in 32 patients (2.8%) and major bleeding in 27 patients (2.4%). Rates of early recurrence varied between the NOACs, ranging from 1.6% in patients receiving rivaroxaban to 4.0% in those receiving apixaban. Major bleeding occurred less frequently in those receiving dabigatran (.5%) with higher rates of bleeding in the rivaroxaban (2.5%) and apixaban (2.9%) groups.

The composite rate of recurrence and major bleeding was 12.4% for patients initiating NOACs less than or equal to 2 days after the acute stroke, 2.1% for those initiating between days 3 and 14, and 9.1% for those initiating NOACs greater than 14 days after the initial stroke. The combined rate of recurrent and major bleeding within 90 days was 5% in patients treated with NOACs following an acute stroke.[42] Currently, there are 4 trials underway assessing the use of early or delayed anticoagulation with NOACs in patients with previous ischemic stroke and AF, results from these trials will help to further establish the optimal timing of anticoagulation postischemic event.[43]

Randomized clinical studies have been unable to provide any evidence to support the administration of anticoagulants or heparin in patients with acute ischemic stroke within 48 hours from stroke onset.[39] This suggests that aspirin should be administered in this time frame to all patients.

Figure 1. *Initiation of anticoagulation following an acute ischemic event.*[50] *CT, computed tomography; INR, international normalized ratio; MRI, magnetic resonance imaging; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack.*

Treatment Options for ICH and Reinitiation of Oral Anticoagulation

NOAC Reversal Agents

With the rising incidence and prevalence of AF, the use of NOACs for thromboembolic stroke prevention is likely to increase. The initial lack of reversal agents has been a hindrance in facilitating the use of NOACs in AF. However, despite the lack of reversal strategies in Phase III NOAC trials, these studies have consistently shown that NOACs cause less intracranial and less life-threatening bleedings than warfarin. In addition, mortality of NOAC-related hemorrhage is lower compared with warfarin.[19]

Reversal of the anticoagulant effects of NOACs is needed in the event of clinically relevant bleeding, NOAC overdose or delayed clearance, emergency surgery, or when emergency intervention is required in patients receiving a NOAC.[44-46] NOACs have shorter half-lives versus warfarin (10-14 hours versus 36-42 hours, respectively) and hence, without reversal, the period of supportive therapy for bleeding is shorter with NOACs compared with warfarin, and a delay of 8-12 hours is likely to be sufficient to allow a major surgery in most cases.[47]

While NOACs are associated with less serious bleeding than warfarin, life-threatening bleeding can still occur which requires immediate intervention.[48,49] In addition, the risk of perioperative bleeding is typically increased in patients treated with NOACs, which can create an obstacle to urgent surgery or other interventions. So, can we reverse the pharmacological effects of NOACs? The availability of an effective reversal drug that has a rapid onset and completely reverses the anticoagulant action would limit the time a patient is off anticoagulation therapy for an invasive procedure, but importantly allow anticoagulation to be re-established.[48] Such reversal agents could also be used to treat ICH in the respect that they would reduce the activity of the NOAC potentially responsible either wholly or in part for the cerebrovascular event.

Several agents have been evaluated for the reversal of NOAC activity, and are also detailed in the European Heart Rhythm Association 2018 practical guide.[50] Idarucizumab is a humanized monoclonal antibody fragment (Fab) which is a highly specific antagonist of dabigatran activity.[51] Animal studies have demonstrated that idarucizumab is able to neutralize dabigatran activity rapidly and completely without binding known thrombin substrates. In addition, this Fab fragment has no activity in coagulation tests or platelet aggregation. Na et al showed that excess intracerebral hematoma formation could be prevented upon administration of idarucizumab to dabigatran-treated mice.[52] Studies have also confirmed that idarucizumab can completely reverse the anticoagulant effect of dabigatran "within minutes" when administered to patients with an uncontrolled bleed or requiring emergency surgery[49]; the anticoagulant effect of dabigatran was rapidly and completely reversed in 88-98% of patients with elevated clotting times at baseline.[49]

Andexanet alpha is a recombinant modified human Factor Xa decoy protein designed to reverse anticoagulation effects of Factor Xa inhibitors by acting as a decoy to bind molecules that inhibit Factor Xa.[53] An initial bolus and subsequent 2-hour infusion of andexanet alpha substantially reduced anti-Factor Xa activity in patients with acute major bleeding associated with Factor Xa inhibitors, including apixaban, rivaroxaban and edoxaban; effective hemostasis was achieved in 79% of patients by 12 hours postandexanet infusion.[53]

Ciraparantag, a new synthetic water-soluble molecular entity, binds to heparin and the oral direct Factor Xa and Factor IIa inhibitors by charge interaction; this removes these drugs from their intended target and enables rapid re-establishment of normal hemostasis.[48] A single intravenous dose of ciraparantag (100-300 mg) administered to healthy subjects after they had received a single therapeutic dose of edoxaban (60 mg) restored baseline hemostasis within 10-30 minutes of administration; this normal level of hemostasis was sustained for greater than or equal to 12 hours. Prothrombin complex concentrates (PCC) also appear to be suitable for reversal of the effects of a therapeutic dose of edoxaban.[44] PCCs contain substantial concentrations of 3 (II, IX, and X) or 4 factors (II, VII, IX, and X) and vitamin K-dependent proteins. Administration of a 4-factor PCC (50 IU/kg) to healthy subjects demonstrated a dose-dependent reversal of the anticoagulation effects of edoxaban 60 mg, with complete reversal of bleeding duration and endogenous thrombin potential, along with partial reversal of prothrombin time.[44] As 4F-PCC is readily available and widely marketed, it represents an important option for rapid treatment in the unlikely event of an ICH or other clinically relevant bleeds following NOAC treatment.

Reinitiating OAC After ICH

Patients with AF who survive an ICH are at increased risk of subsequent ischemic stroke.[54] However, the best approach to reducing further risk of stroke in a patient with AF who has previously experienced an ICH or other clinically relevant bleed can be confusing. Clearly, any treatment approach in a patient with AF needs to balance the competing risks of ischemic stroke and recurrent ICH.[54] So, should OAC treatment be used again in a patient with AF following recovery from ICH (or other clinically relevant bleed), and if so, when is the best time to restart?

A Danish Cohort study using national registry data demonstrated that oral anticoagulation was associated with a significant reduction in ischemic stroke/all-cause mortality, supporting the reintroduction of OACs after the resolution of ICH.[54] Patients with AF and incident ICH were stratified by treatment regimens (no treatment, oral anticoagulant treatment, or antiplatelet therapy) after ICH, with event rates assessed 6 weeks after hospital

discharge. One-year follow-up data (N = 1752) showed that the rate of ischemic stroke/systemic embolism and all-cause mortality (per 100 person-years) was 13.6 with oral anticoagulants, 27.3 with no treatment, and 25.7 with antiplatelet therapy. The adjusted HR of ischemic stroke/systemic embolism and all-cause mortality was .55 (95% CI: .39, .78) in patients on oral anticoagulant treatment compared with no treatment. Moreover, rates of recurrent ICH after 1 year were 8.0 patients treated with oral anticoagulants compared with 8.6 for no antithrombotic treatment (HR: .91 [95% CI: .56, 1.49]) and 5.3 for antiplatelet therapy (HR: .60 [95% CI: .37, 1.03]).[54] While this observational study was not designed to define the optimal time frame for reintroduction of oral anticoagulation following ICH, it did support the feasibility and clinical importance of reintroducing OACs as soon as clinically possible following ICH. Of note, Nielsen et al highlighted the need to address potentially correctable risk factors for ICH such as uncontrolled hypertension and the concomitant use of aspirin or nonsteroidal anti-inflammatory drugs.[54] Liaising with a neurosurgical service is also suggested given that previous ICH may be related to prior trauma or a vascular anomaly.

More recently, an observational study suggested that anticoagulant treatment can be initiated 7-8 weeks after ICH in patients with AF to optimize the benefit from treatment and minimize stroke risk.[55] Of 2619 ICH survivors with AF, anticoagulant treatment was associated with a reduced risk of vascular death and nonfatal stroke in patients deemed to be high risk yet without any significant increased risk of severe hemorrhage. This therapeutic benefit appeared to be greatest when treatment was started 7-8 weeks after ICH. Notably, the ESC guidelines recommend that after ICH, oral anticoagulation in AF patients may be reinitiated after 4-8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.

Left atrial appendage occlusion (LAAO) is an alternative option for patients in whom long-term anticoagulation is unsuitable (Fig 2).[34,50] LAAO has been shown to be

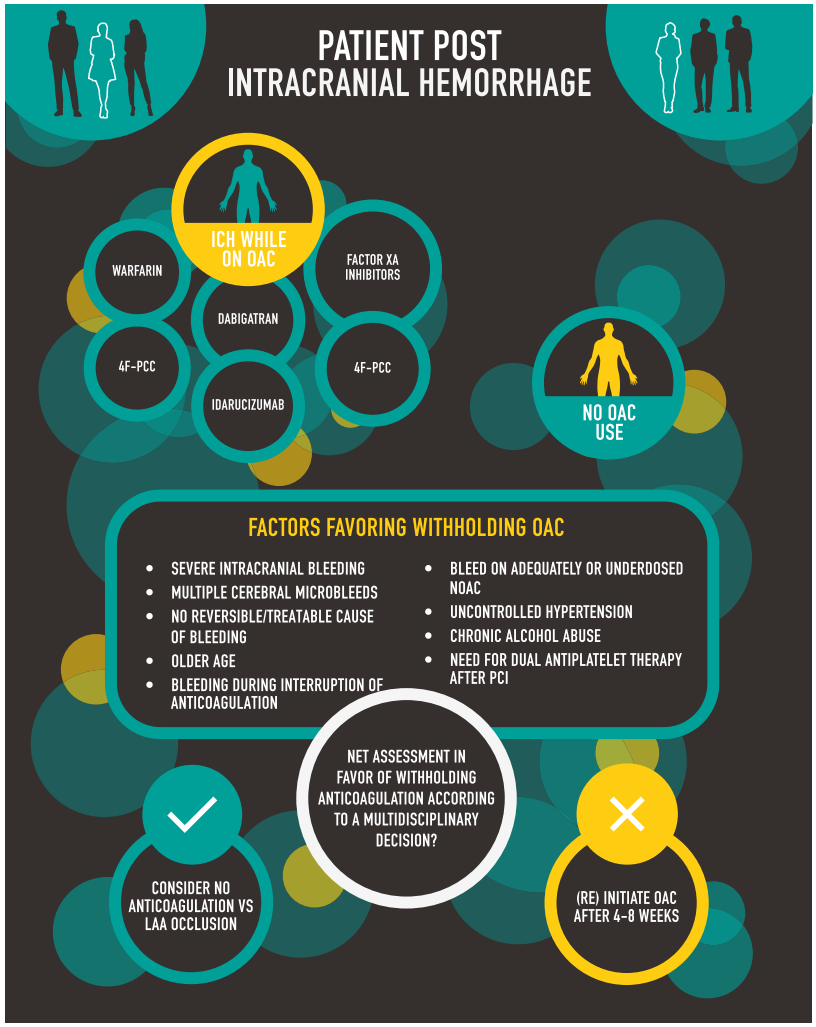

Figure 2. *Initiation of oral anticoagulation following an intracerebral hemorrhage.*[50] *4F-PCC, 4 factor prothrombin complex concentrate; ICH, intracranial hemorrhage; LAA, left atrial appendage; OAC, oral anticoagulation; PCI, percutaneous coronary intervention.*

effective in reducing hemorrhagic and ischemic events in patients with AF and a previous ICH[56,57]; however, it is important to note that these studies only included small numbers of patients. There is a lack of evidence-based data comparing the use of LAAO with NOACs in patients with a previous ICH; however, the ongoing Occlusion-AF trial (NCT03642509) will compare the efficacy and safety of LAAO versus NOACs in patients with AF and prior ischemic stroke or TIA.

The question of starting or reinitiating OAC treatment in patients with AF and spontaneous ICH also depends on the underlying etiology. The most frequent cause is arterial hypertension (Fig 3A) and if adequate blood pressure control is achieved, the benefit of OAC treatment in high-risk patients will surpass the risk of further ICH which is estimated at about 2% per year.[58] In contrast, in patients with lobar ICH due to suspected cerebral amyloid angiopathy (Fig 3B), the estimated risk of ICH recurrence is about 5-15% per year, making these patients ineligible for OAC treatment.

The use of antiplatelets in patients surviving an antithrombotic-associated ICH is currently being investigated in the ongoing REstart or Stop Antithrombotics Randomized Trial (RESTART).[59] The primary end point for this study will be the recurrence of ICH in adult patients initiated with antiplatelet drugs versus those not initiated with antiplatelet

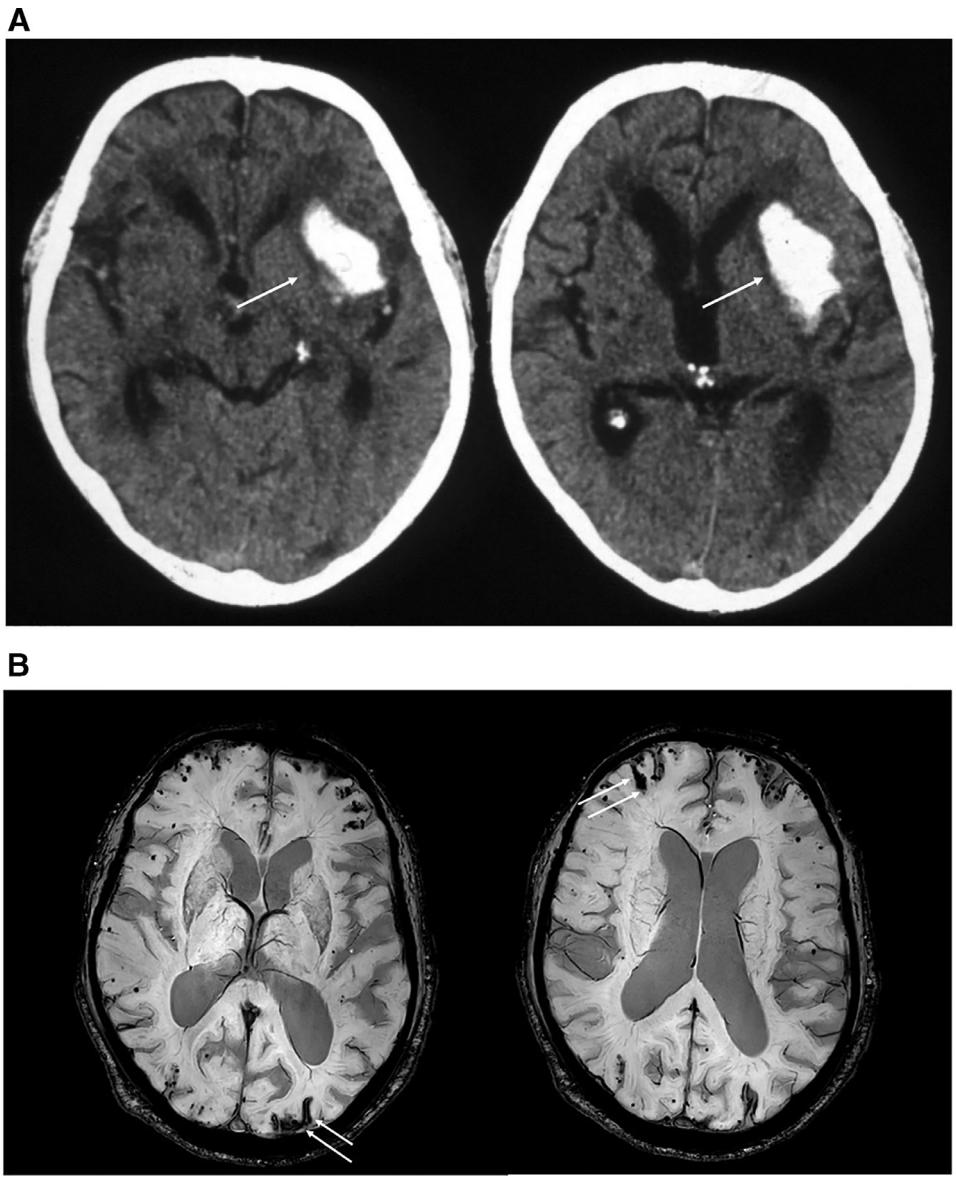

Figure 3. *(A). CT scan of spontaneous intracerebral hemorrhage in loco typico (hypertensive "deep" ICH) due to arterial hypertension. Initiation for OAC after blood pressure control is recommended if stroke risk due to AF is high. (B). MRI scan of multiple cortical and subcortical bleeds, frontal and posterior hemorrhage localized to the cortical sulci at the convexity of the brain (convexity subarachnoid hemorrhage). Imaging is highly suggestive of ICH due to cerebral amyloid angiopathy and oral anticoagulation is not recommended.*

drugs. Moreover, an MRI substudy of RESTART aims to investigate the heterogeneity of the presences of cerebral microbleeds, which are thought to be predictors of ICH, increased future stroke risk and worsening outcomes.[60-62] RESTART will provide data on approximately 720 patients with an antithrombotic-associated ICH from 122 hospitals in the United Kingdom.[59]

Moreover, the PREvention of STroke in Intracerebral hemorrhaGE survivors with AF initiative aims to further address the unmet need of the ideal antithrombotic strategy for stroke prevention in patients with a prior ICH.[63]

Summary

For patients with AF, physicians need to minimize the associated risks of anticoagulation by striking a balance between increased protection against future stroke/systemic embolism and reduced risk of a major bleeding event. Patients treated with NOACs alone seem to have a better outcome compared with warfarin mainly driven by the reduction of OAC-related ICH. For patients with AF who have previously experienced a cerebrovascular event, the use of oral anticoagulants alone also appears more effective than those treated with LMWH alone or LMWH followed by oral anticoagulants. Guidelines from the ESC recommend the use of NOACs in preference to VKAs or aspirin in patients with AF and a previous stroke. However, the timing of treatment initiation or restart in patients with previous cerebrovascular events remains a crucial factor that influences both efficacy and safety findings. Available data suggest that significant reduction in stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days from acute stroke can be achieved if oral anticoagulation is initiated at 4-14 days from stroke onset.

Conflicts of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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