

Direct Oral Anticoagulants after Ischemic Stroke: Which Patient? Which Drug? And How Early?

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Abstract

Keywords

- ▶ stroke
- ▶ atrial fibrillation
- ▶ anticoagulation
- ▶ timing

Direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF) and ischemic stroke. The main advantage of DOAC over VKA is the lower rate of bleeding and mortality. This review covers challenges clinicians can encounter when treating patients with AF and ischemic stroke, including timing of DOAC start and ongoing randomized clinical trials, appropriate dosing, and available comparative evidence across DOACs. For patients without AF but with an ischemic stroke, the review outlines the role of DOACs. Finally, the risk of thrombotic events associated with specific DOAC reversal agents and DOAC pausing is reviewed.

Introduction

Atrial fibrillation (AF) increases the risk of ischemic stroke up to five times, and is associated with more severe and twice as fatal strokes as compared with other etiologies.^{1,2} For patients with an ischemic stroke linked to AF, current guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs), except for AF in the presence of a mechanical heart valve and moderate-to-severe mitral stenosis.^{3,4} The recommendation is based on four pivotal, phase-3 randomized clinical trials (RCTs) comparing DOACs to VKAs in patients with AF: ARISTOTLE (apixaban), RE-LY (dabigatran), ENGAGE AF-TIMI 48 (edoxaban), and ROCKET AF (rivaroxaban).^{5–8} The main advantage of DOACs over VKAs was the halved rate of intracranial hemorrhage (ICH)—resulting in a lower mortality—with a similar rate of stroke and systemic embolism (SE). In this brief review, we discuss the role of DOACs among patients with ischemic stroke.

Appropriate Direct Oral Anticoagulant Dosing

RE-LY and ENGAGE AF were the only RCTs that randomized AF patients to two different DOAC doses—in RE-LY: dabigatran 150 mg, 110 mg twice daily; in ENGAGE AF: edoxaban

60 mg, 30 mg daily.^{6,7} The allocation to the low-dose trial arm was randomized and independent of renal function. In a prespecified meta-analysis, the low dabigatran and edoxaban doses were associated with an increased risk of ischemic stroke compared with VKAs (relative risk: 1.28, 95% confidence interval [CI]: 1.02–1.60; $p = 0.045$), and—like the full doses—with less bleedings (0.65, 0.43–1.00; $p = 0.05$).⁹ A retrospective study confirmed that reduced DOAC doses are associated with an increased risk of ischemic stroke.¹⁰ Since all DOACs are eliminated mainly through the kidney, renal impairment mandates a reduction of the DOAC dose. In the pivotal RCTs—with the exception of RE-LY⁶—patients with renal impairment received a reduced DOAC dose in ARISTOTLE (apixaban 2.5 mg [instead of 5 mg] twice daily in 4.7% of the overall cohort),⁵ ROCKET-AF (rivaroxaban 15 mg [instead of 20 mg] daily in 21%),⁸ and ENGAGE-AF (edoxaban 30 mg [instead of 60 mg] or 15 mg [instead of 30 mg] daily in 25%).⁷ In the ORBIT-AF registry with 5,738 patients, 1 in 8 patients received DOAC doses inconsistent with labeling: 9.4% were underdosed and 3.4% overdosed. Underdosing was associated with a 26% higher risk of cardiovascular hospitalization and overdosing with an almost twofold risk of all-

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cause mortality.¹¹ This underscores not to reduce the DOAC dose, unless mandated by the label. Fear of bleeding alone is not an indication to reduce the DOAC dose.

DOAC versus VKA after an Ischemic Stroke

Can we generalize one-to-one the findings of the RCT to patients with AF and ischemic stroke? No. In the four pivotal RCTs, the majority of patients with AF did not have a history of ischemic stroke, transient ischemic attack (TIA), or SE (19% in ARISTOTLE, 20% in RE-LY, 28% in ENGAGE-AF, and 55% in ROCKET-AF). In a meta-analysis on 20,500 patients with AF and previous stroke or TIA, DOACs were associated with a significant reduction of recurrent stroke/SE (relative risk reduction: 13.7%, absolute risk reduction: 0.78%, number needed to treat to prevent one event: 127) and ICH (relative risk reduction: 46.1%, absolute risk reduction: 0.88%, number needed to treat: 113) over 1.8 to 2.8 years.¹² Recently, two multicenter observational studies compared DOACs to VKAs among patients with AF and ischemic stroke or TIA. The first study was an individual-patient data meta-analysis with 4,912 patients from Europe and Japan, with a median follow-up of 1.2 years. In the DOAC group, less ICH occurred (hazard ratio [HR]: 0.42; 95% CI: 0.24–0.71) with no significant differences in the rate of recurrent ischemic stroke (HR: 0.91; 95% CI: 0.70–1.19) and all-cause mortality (HR: 0.83; 95% CI: 0.68–1.03). The second study included 1,251 patients with AF and stroke from the United States.¹³ Follow-up was shorter (90 days), and the median time between strokes to therapeutic international normalized ratio was 8 days (interquartile range: 4–13). In contrast with the prior study, there were fewer recurrent ischemic strokes in the DOAC group (HR: 0.51; 95% CI: 0.29–0.87), whereas the risk of ICH did not differ compared with the VKA group (HR: 0.57; 95% CI: 0.22–1.48). The different conclusions suggest that the benefit of DOAC over VKA evolves over time. In the first few weeks after stroke, immediate anticoagulation with DOAC translates into fewer ischemic strokes, compared with the delayed treatment effect with VKA. On the longer run, the more selective the anticoagulation achieved with DOACs, the lower the ICH rate. If an ICH occurs, its 30-day fatality is lower among patients treated with DOACs than those treated with VKAs, as seen in a recent meta-analysis of 11 observational studies (relative risk: 0.70, 95% CI: 0.51–0.95).¹⁴

How Early?

A further reason why RCTs cannot be generalized to patients with ischemic stroke is the timing of DOAC start after an ischemic stroke. In all four RCTs, a key exclusion criterion was ischemic stroke within 1 week and 6 months prior to randomization, with a median time between ischemic stroke and randomization over 1 year.^{15,16} The reason for such long waiting times was the fear of hemorrhagic transformation. The “1-3-6-12” rule of thumb stems from the pre-DOAC era and is not backed by evidence. The rule advocates to start oral anticoagulation (OAC) after 1 day in TIA, 3 days in minor strokes, 6 days in moderate strokes, and 12 days in large infarcts.¹⁷ However, in clinical practice, DOACs tend to be

started much earlier compared to RCTs: median timing of DOAC initiation was between 5 and 11 days in the four observational studies with clinical follow-up of at least 3 months.^{18–21} Despite such early starts, the fear of hemorrhagic transformation of the infarcted brain did not materialize. Rather, the risk of recurrent ischemic stroke was three times higher than the risk of ICH (annualized average rate of 6.6 vs. 2.2% for recurrent stroke and ICH, respectively).²² This evidence is observational and randomized trials comparing early versus late starts are currently ongoing—their results are eagerly awaited (ELAN [Switzerland/International], NCT03148457; TIMING [Sweden], NCT02961348; OPTIMAS [United Kingdom], EduraCT 2018–003859–38; START [United States], NCT03021928). The best current practice is to enroll patients in these trials, rather than start DOAC early based on the available nonrandomized evidence.

Comparative DOAC Efficacy and Safety in Atrial Fibrillation

We cannot state that one DOAC is better than the other, since there are no randomized controlled trials comparing DOACs head to head. Moreover, the baseline risk of stroke—measured with the CHADS₂ score—varied considerably across the four RCTs (mean of 3.5 in ROCKET-AF, 2.8 in ENGAGE-AF, and 2.1 in RE-LY and ARISTOTLE), making it difficult to compare DOACs across trials.^{5–8} There are, however, observational studies that compared DOACs to each other. One of the latest studies included 52,476 patients with AF from nationwide registries in Norway and compared dabigatran, rivaroxaban, and apixaban over a median follow-up of 18 months.²³ Overall, the risk of stroke or SE was similar across the DOACs in the propensity score analysis, while the risk of major bleeding was significantly lower for dabigatran and apixaban compared with rivaroxaban. Of interest, in the subgroup with a history of stroke (13% of the overall cohort), rivaroxaban was superior to both apixaban and dabigatran in preventing recurrent strokes, with a similar bleeding rate.

The largest comparative study was a retrospective analysis on 434,046 patients from the Medicare and Medicaid in the United States (the ARISTOPHANES study).²⁴ Apixaban was associated with a lower rate of stroke and major bleeds compared with dabigatran and rivaroxaban (stroke –28 and –20%, respectively; bleedings: –22 and –45%, respectively). Dabigatran, compared with rivaroxaban, had a similar rate of stroke with a lower bleeding rate (–29%). In the subgroup with a history of stroke (12% of the overall cohort), the advantage of apixaban over rivaroxaban and dabigatran in protecting against stroke/SE dissipated, with rivaroxaban still being associated with a higher bleeding rate compared with apixaban and dabigatran. The median follow-up of 4 months in ARISTOPHANES is a major limitation, given that DOACs for AF are prescribed long term. The conflicting results in secondary prevention—with rivaroxaban favored in one study, disfavored in the other—highlight the limitations of nonrandomized studies. Such studies should be rather seen as hypothesis-generating, rather than change practice.

DOACs in Absence of AF in Patients with Ischemic Stroke

Among patients without AF—but with coronary heart disease, peripheral artery disease, or carotid stenosis >50%—rivaroxaban 2.5 mg twice daily combined with aspirin 100 mg daily was compared with aspirin 100 mg alone in the COMPASS trial among 27,395 patients.²⁵ Patients with a stroke ≥ 1 month earlier were allowed in the trial, where they represented 3.8% of patients. The primary outcome—a composite of cardiovascular death, stroke, or myocardial infarction—occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (HR: 0.76, 95% CI: 0.66–0.86, $p < 0.001$).²⁵ The benefit in the combination group was driven by the reduction in ischemic stroke events over aspirin alone (0.9 vs. 1.6%/year).²⁶ The types of ischemic stroke that were reduced most were cardioembolic and embolic strokes of unknown origin, suggesting a modest but relevant anticoagulatory effect of rivaroxaban 2.5 mg twice daily.²⁷ Major bleedings occurred more often in the rivaroxaban-plus-aspirin group (HR: 1.70, 95% CI: 1.40–2.05, $p > 0.001$), with no significant difference in intracranial or fatal bleeding.²⁵ Among patients with a history of stroke, the risk of major hemorrhage was higher (HR: 3.79, 95% CI: 1.07–13.4, $p = 0.04$), calling for caution when prescribing the combination therapy after a stroke.²⁶ Following an ischemic stroke, the waiting time should be at least 1 month prior to start of the dual antithrombotic therapy.

There is no indication for DOACs among patients with an ischemic stroke with an embolic pattern on brain magnetic resonance imaging but without any identified cause (embolic stroke of unknown source): compared with aspirin, rivaroxaban and dabigatran brought no benefit in the NAVIGATE and RESPECT-ESUS trials, respectively.^{28,29}

Specific Reversal Agents and Thrombotic Risk

Idarucizumab is a monoclonal antibody fragment that binds dabigatran. In RE-VERSE AD, idarucizumab reversed the anticoagulant effect of dabigatran within 4 hours among 503 patients with uncontrolled bleeding or about to undergo an urgent procedure.³⁰ Andexanet alfa is a modified recombinant form of human factor Xa. In ANNEXA-4, andexanet alfa reduced antifactor Xa activity due to factor Xa inhibitors among 352 patients with acute major bleeding (ICH in two-thirds of patients).³¹ Neither study had a control arm. In patients requiring idarucizumab or andexanet alfa, the incidence of thrombotic events was 5.5% (95% CI: 2.0–10.1%) within 30 to 90 days, and all-cause mortality was 13.3% (95% CI: 9.6–17.5%), according to a recent meta-analysis of 13 studies on idarucizumab and three studies on andexanet alfa.³² Most thrombotic events were stroke and venous thromboembolism. Compared with idarucizumab, more thrombotic events were seen with andexanet alfa (3.3 vs. 10.6%). Firm comparative conclusions are not possible, given the low number of studies with andexanet alfa.

Thrombotic events do not seem to be directly related to the antidotes, since most thrombotic events occurred when resumption of DOAC was delayed or never occurred.

In ANNEXA-4, no thrombotic event occurred after restart of oral anticoagulation.³¹ Therefore, and despite the absence of solid efficacy, reversal of DOACs with specific agents should be considered in patients with moderate to severe bleeding that cannot be stopped by other means (such as in intracranial bleeding), and where the bleeding does not already seem to be fatal. After a major bleeding, it appears prudent to resume OAC as soon as the clinician judges it to be safely possible.

Conflict of Interest

Dr. De Marchis reports personal fees and other from Bayer, personal fees from BMS/Pfizer, outside the submitted work.

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