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Review article

Intracranial bleedings in patients on long-term anticoagulant treatment: Benefits from oral thrombin and factor Xa inhibitors in clinical practice

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ABSTRACT

Dabigatran, a direct thrombin inhibitor and activated factor X inhibitors, rivaroxaban and apixaban, used in the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF), have several advantages over vitamin K antagonists (VKAs). The non-vitamin K oral anticoagulants (NOACs) have been shown to reduce the risk of intracranial bleedings by 50%. The current review summarizes the available data on the epidemiology, mechanisms and treatment of intracranial bleedings observed on oral anticoagulation with the focus on the specificity of NOACs in this context.

1. Introduction

Atrial fibrillation (AF) is the most common preventable cause of ischaemic stroke in the general population, with an increasing prevalence with age from 1% to above 20% at the age of 80–89 [1]. Strokes associated with AF, which represent 15–20% of all strokes, have a high mortality up to 20–25% within the first 30 days, since the ischaemic event commonly causes severe neurological deficits [1]. The incidence of AF-associated stroke decreases by 65% with oral vitamin K antagonist (VKA) therapy. However, almost 50% of AF patients do not receive anticoagulation [2,3]. Although effective, the major obstacle to the use of VKAs is bleeding complications. Intracranial bleeding is the most devastating complication of VKA use, comprising about 8.7% of all major bleeding episodes and resulting in a 46–55% mortality rate [4].

The anticoagulants, previously termed new oral anticoagulants, comprise a thrombin inhibitor, dabigatran, and two activated factor X (FXa) inhibitors, rivaroxaban and apixaban, which are approved worldwide for the prevention of stroke and peripheral embolism in patients with nonvalvular AF [5].

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Table 1 – Characteristics of target-specific oral anticoagulants (reprinted from Undas A et al. [6] with permission of the publisher Medycyna Praktyczna).

Variable	Warfarin	Dabigatran etexilate[a]	Rivaroxaban	Apixaban
Mode of action	↓ Synthesis vitamin K-dependent coagulation factors	Direct selective and reversible thrombin inhibitor	Direct selective and reversible activated factor X inhibitor	Direct selective and reversible activated factor X inhibitor
Time to peak plasma concentration	90 min (peak action after 4–5 d)	0.5–2 h	2–4 h	1–4 h
Half-life	36–42 h	12–14 h	5–9 h (young) 11–13 h (age >65 y)	8–13 h
Substrate of P-glycoprotein transporter	No	Yes	Yes	Yes
Substrate of CYP enzymes	Yes (CYP3A4, CYP2C9)	No	Yes (CYP3A4/5, CYP2J2)	Yes (CYP3A4, CYP2C9)
Route of elimination	Various[c]	80% renal	66% renal (33% unchanged)	25% renal
Protein binding	99%	35%	90%	90%
Basic daily dose in AF	~5 mg (1–18 mg) Target INR, 2–3	2 × 150 mg	1 × 20 mg	2 × 5 mg
Reduced daily dose	Not applicable	2 × 110 mg[b]	1 × 15 mg	2 × 2.5 mg
Indications for reduced dosage	Not applicable	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points – Age ≥80 y – Coadministration of verapamil	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points	– Creatinine ≥133 μM – Age ≥80 y – Body weight ≤60 kg (2 or 3 criteria met)

[a] A prodrug that undergoes biotransformation to the active molecule, dabigatran, by esterases.
[b] In the United States: 2 × 75 mg daily (2 × 110 mg not approved).
[c] The anticoagulant effect of warfarin is eliminated through synthesis of functionally active coagulation factors rather than through elimination of warfarin; coagulation factor synthesis is hastened by exogenous vitamin K.
Abbreviations: INR, international normalized ratio.

Compared with VKAs, the non-vitamin K oral anticoagulants (NOACs) are characterized by rapid onset of action, shorter half-life, few drug–drug interactions, a predictable anticoagulant response, and no need for routine coagulation monitoring (Table 1) [6].

The benefits of NOACs in nonvalvular AF have been documented in large clinical trials (Randomized Evaluation of Long-Term Anticoagulation Therapy [RELY], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]) [7,8]. The use of all the three NOACs was non-inferior to therapy with VKAs in reducing stroke or systemic embolism in patients with nonvalvular AF. The current European Society of Cardiology (ESC) Guidelines on the Management of AF recommend long-term anticoagulation in all patients with nonvalvular AF with at least moderate (1 point in the CHA_2DS_2-VASc score) thromboembolic risk [9]. Of note, NOACs are a preferred prophylactic option over VKAs in nonvalvular AF patients [10]. Indirect analysis including 14,527 patients treated with NOACs showed that these anticoagulants were associated with reduced risk of stroke or systemic embolism (odds ratio [OR], 0.85; 95% CI, 0.74–0.99) compared with warfarin [11].

2. Characteristics of intracranial bleeding in patients anticoagulated with NOACs

Large randomized controlled trials [7–9], nationwide cohort studies in real-world general practice settings in American [12], Asian [13] and European [14] populations have compellingly shown that the use of NOACs in patients with AF results in markedly fewer intracranial haemorrhagic adverse events (0.3–0.6 per 100 patient-years) as compared to warfarin. The reduced risk of intracranial bleeding is one of the major advantages of these agents over VKAs. There are no direct head-to-head comparisons of NOACs in this regard. Effectiveness and safety of all the NOACs approved to clinical use are supported by several meta-analyses [15–19]. Trials on NOACs in AF patients have demonstrated that the lowest rate of intracranial haemorrhage (ICH) as compared to warfarin was observed for dabigatran at a dose of 110 mg BID, while the highest rate of ICH and the highest hazard ratio (HR) were observed for rivaroxaban (Table 2) [7–9]. During dabigatran treatment with a dose of 150 mg BID intracerebral and subdural haemorrhages were the most common types of ICH (46% each), but the rate of subdural haematoma did not differ from that observed in patients treated with warfarin [the rate per 100 patient-years was 0.20 vs. 0.31, respectively; HR (95% CI): 0.65 (0.39–1.1), $P < 0.01$]. Dabigatran at a dose of 110 mg BID significantly reduced the risk of all types of ICH including traumatic ICH as compared to warfarin [20]. Moreover, the incidence of ICH in subjects treated with apixaban at a daily dose of 5 mg (2.5 mg BID) is comparable with that observed in patients treated with aspirin 81–324 mg daily, so in terms of ICH apixaban seems to be the safest of all NOACs [21,22]. The absolute rates of fatal intracranial haemorrhages were lower with dabigatran than with warfarin [20]. However, there were no differences in fatal ICH between the treatment with rivaroxaban and warfarin [23]. Such detailed subanalysis was not performed in trials with apixaban where the rate of fatal ICH was calculated together with other