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Review

Pharmacology, benefits, unaddressed questions, and pragmatic issues of the newer oral anticoagulants for stroke prophylaxis in non-valvular atrial fibrillation and proposal of a management algorithm

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ABSTRACT

This systematic review aims to provide an update on pharmacology, efficacy and safety of the newer oral direct thrombin and factor Xa inhibitors, which have emerged for the first time in ~60 years as cogent alternatives to warfarin for stroke prophylaxis in non-valvular atrial fibrillation. We also discuss on four of the most common clinical scenarios with several unsolved questions and areas of uncertainty that may play a role in physicians' reluctance to prescribe the newer oral anticoagulants such as 1) patients with renal failure; 2) the elderly; 3) patients presenting with atrial fibrillation and acute coronary syndromes and/or undergoing coronary stenting; and 4) patients planning to receive AF ablation with the use of pulmonary vein isolation. New aspects presented in current guidelines are covered and we also propose an evidence-based anticoagulation management algorithm.

1. Introduction

Non-valvular atrial fibrillation (AF) in the absence of rheumatic mitral stenosis or a prosthetic heart valve is the most common sustained cardiac rhythm disorder worldwide, occurring in 1 to 2% of the general population [1,2]. AF affects over 2 million people in the US and over 6 million across the European Union and occurs more frequently in the elderly [1,2]. As such, the prevalence of AF is projected to double in the next 50 years as much of the population ages [3].

Approximately one in three patients with AF will develop an ischemic stroke in their lifetime, with almost two-thirds being cardioembolic and one-third being atherothrombotic [4].

Atrial fibrillation-related strokes are more likely to be massive, are often fatal or associated with long-term disability and exhibit high recurrence rates compared to strokes of other etiologies [5]. Due to the nature of these events, strokes represent a major public health problem with a huge economic burden. In the US, the estimated direct and indirect costs of stroke were $34.3 billion in 2008 [6].

The long-term risk of stroke in AF depends on the clinical predictors collectively assessed in the $CHADS_2$ scoring scheme in which *C*ongestive heart failure, *H*ypertension, *A*ge ≥ 75 years and *D*iabetes mellitus are each assigned one point or two points for a history of *S*troke/transient ischemic attack [TIA] or CHA_2DS_2-VASc, which considers additional risk factors, such as *v*ascular disease (myocardial infarction [MI], complex aortic plaque, peripheral artery disease) and *s*ex *c*ategory (female sex), each of which is awarded one point, including age of 65 to 74 years, and 2 points if age ≥ 75 years [7–9].

The American College of Chest Physicians and European Society of Cardiology guidelines recommend that all patients with AF and a $CHADS_2$ or CHA_2DS_2-VASc score ≥ 1 should be on long-term oral anticoagulation [1,10].

Warfarin, the most prescribed oral anticoagulant acts by lowering the serum levels of vitamin K-dependent pro-coagulant proteins and is highly effective for the prevention of AF-related stroke, resulting in a 64% risk reduction compared to placebo and a 37% risk reduction compared with antiplatelet therapy [11]. However, warfarin has several drawbacks (slow onset and offset of action; narrow therapeutic range [international normalized ratio, INR of 2.0–3.0] that requires regular monitoring; several interactions with food, alcohol, and drugs; potential ethnic, genetic, and age-related variations in dose response; and high bleeding risk [0.3–0.5%/yr]), which have resulted in its suboptimal use in clinical practice and promoted the search for more convenient and safer oral anticoagulants [12–18].

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The recent introduction of newer oral anticoagulants (NOACs) into the clinical arena, including the direct factor IIa (thrombin) inhibitor, dabigatran etexilate (hereafter dabigatran) and the factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, has resulted in a paradigm shift that, for the first time in ~60 years, has challenged the supremacy of warfarin for stroke prophylaxis in AF.

We aim to review the pharmacology, efficacy and safety of these NOACs systematically and to address several unanswered clinical questions and pragmatic issues regarding their use in four of the most common clinical scenarios of everyday medical practice: 1) patients with renal failure; 2) the elderly; 3) patients presenting with both AF and acute coronary syndromes (ACS) and/or undergoing percutaneous coronary intervention (PCI)/stenting; and 4) patients planning to receive catheter ablation for AF with the use of pulmonary vein isolation. New aspects available in current guidelines are covered, and we propose an evidence-based anticoagulation management algorithm.

2. Pharmacology

The NOACs are synthetic low-weight molecules that exert their specific anticoagulant effect by reversibly blocking thrombin or factor Xa (Table 1). Their pharmacodynamic and pharmacokinetic properties differ slightly, but all four come much closer to fitting the profile of a more favorable oral anticoagulant compared with warfarin. They possess the following traits: 1) quick onset of action; 2) shorter half-lives and time to therapeutic anticoagulation; 3) more stable dose-related anticoagulant effects; and 4) fewer drug–drug interactions than warfarin, with no known dietary restrictions [19–23].

These properties allow for fixed dosing without the need for laboratory monitoring. Dabigatran and apixaban are given twice daily (BID), and rivaroxaban and edoxaban, once a day (QD). Dabigatran, rivaroxaban and apixaban have been approved in the US, European Union, Canada and many other countries, and it is likely that edoxaban will soon be licensed.

These agents are metabolized primarily by the cytochrome P4503A enzyme (rivaroxaban and apixaban) and/or efflux transporter P-glycoprotein (P-gp; [dabigatran and edoxaban]), which contributes to their predictable pharmacokinetic responses [19–23]. As a result, practitioners should be aware of potential interactions between NOACs and strong CYP3A or P-gp inhibitors or inducers.

For dabigatran, the co-administration of P-gp inducers, such as rifampin and St John's wort, should be avoided. Close clinical surveillance for bleeding is required if dabigatran is co-administered with strong P-gp inhibitors, such as amiodarone, verapamil, quinidine, ketoconazole and clarithromycin, due to an increase in its plasma concentration [19].

For rivaroxaban, apixaban and edoxaban, concomitant use of combined strong P-gp and CYP3A inhibitors, such as azole antimycotics or human immunodeficiency virus protease inhibitors, may increase their plasma concentrations and should be avoided. The concomitant use of a strong P-gp, strong CYP3A4 inducer, or both, including rifampin, St. John's wort, carbamazepine and phenytoin with factor Xa inhibitors, should be avoided or requires vigilance [20–23].

Clearly, concomitant medications that inhibit platelet function, such as aspirin, P2Y12 inhibitors (e.g., clopidogrel, prasugrel or ticagrelor) and nonsteroidal anti-inflammatory drugs, may increase the risk of bleeding during treatment with NOACs. The concomitant use of proton-pump inhibitors and H_2-blockers does not constitute a contraindication for any NOAC.

The foremost shortcomings of these agents are the following: 1) there is no readily-available, reliable measure of their anticoagulant effect, and 2) no specific antidotes are available to date.

The activated partial thromboplastin time (aPTT) and prothrombin time (PT) may only provide a qualitative assessment of the presence of dabigatran and factor Xa inhibitors, respectively, and are not sufficiently sensitive for the quantitative measurement of their anticoagulation effects. If the aPTT and PT levels 12–24 h after ingestion of the NOACs still exceed two times the upper limit of normal, this condition may be hypothetically associated with a higher risk of bleeding and may warrant caution, mostly in patients with bleeding risk factors. Although quantitative tests for direct thrombin and factor Xa inhibitors are available (diluted thrombin-time and chromogenic assays, respectively), they may not yet be routinely available in most hospitals. Moreover, there are no data on a cut-off of these tests, below which elective or urgent surgery is safe; consequently their use cannot be recommended at this time [24].

At present, there is no specific reversal or antidote agent clinically available for NOACs. However, new "proof of concept" data from Phase I and II studies in human volunteers on a recombinant Xa-analog without biological properties that can reverse the anticoagulant action of factor Xa inhibitors and on a fragment of an antibody (Fab) that acts as a specific antidote to dabigatran have been recently presented [25,26]. These two antidotes for NOACs have shown exciting results, with both bringing about the immediate reversal of the anticoagulant effects with no indication of prothrombotic complications [25,26]. Phase III studies are expected to start in the second half of 2014.

Table 1
Clinical pharmacology and dosing of the newer oral anticoagulants as tested in phase III randomized trials.

	Dabigatran[20]	Rivaroxaban[21]	Apixaban[22]	Edoxaban[23,24]
Pro-drug	Dabigatran etexilate	No	No	No
Mechanism	F-IIa direct inhibitor	F-Xa direct inhibitor	F-Xa direct inhibitor	F-Xa direct inhibitor
Bioavailability	6–7%	> 80%	> 50%	62%
Protein binding	35%	> 90%	87%	40–59%
Half-life	12–17 h	5–13 h	12–13 h	6–11 h
Time to C_{max}	1–2 h	2–4 h	3–4 h	1–2 h
Offset of effect	Parallels half-life	24–48 h	Parallels half-life	Parallels half-life
Substrate of P-gp drug transporter	Yes	Yes	Yes	Yes
CYP metabolism	0%	32%	~25%	Insignificant
Renal clearance	80%	36%	27%	49%
Dosing*	150 mg BID 110 mg BID	20 → 15 mg QD •CrCl 30–49 mL/min	5 → 2.5 mg BID •Age ≥ 80 years •Weight ≤ 60 kg •Creatininemia ≥ 1.5 mg/dL	60 → 30; 30 → 15 mg QD •CrCL 30–50 mL/min •Weight ≤ 60 kg •Strong P-gp inhibitors
Drug interactions	Strong P-gp inducers (i.e., rifampin) and inhibitors (i.e., dronedarone)	Combined P-gp and strong CYP3A4 inducers (i.e., carbamazepine) and combined P-gp and strong CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir)	Strong inducers of both P-gp and CYP3A4 (i.e., rifampin) and strong inhibitors of both P-gp and CYP3A4 (i.e., ketoconazole)	Strong P-gp inhibitors (i.e., verapamil, quinidine, dronedarone)

C_{max}, maximum concentration of drug; CYP, cytochrome P450; P-gp, P-glycoprotein; BID, twice daily; QD, once daily; CrCL, creatinine clearance. *Doses of rivaroxaban, apixaban and endoxaban are adjusted based on the patients' characteristics as listed.