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Review Article

Direct acting oral anticoagulant: Bench to bedside

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ABSTRACT

Vitamin K antagonists are an effective group of oral anticoagulants. However because of genetic variability in their metabolism and multiple food and drug interactions, these drugs have narrow therapeutic window with unpredictable anticoagulant effects requiring constant monitoring. Several newer direct acting oral anticoagulants have been approved for prevention of stroke in patients with nonvalvular atrial fibrillation and treatment or prevention of venous thromboembolism. The direct acting oral anticoagulants include the direct thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). These have a better safety and efficacy profile compared to Vitamin K antagonists. Some of the limitations of these drugs include increased risk of gastrointestinal bleeding (except apixaban), increased risk for thrombotic complication upon sudden cessation of therapy and inability to monitor the anticoagulation efficacy. Recent availability of the antidote to these drugs has further strengthened their safety profile. In the current review we will discuss these agents with focus on their potential clinical uses and limitations.

Introduction

Vitamin K antagonists (VKA) have till recently been the only oral anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation (AF) and treatment or prevention of venous thromboembolism (VTE). They have reduced the incidence of stroke by two-thirds in patients with nonvalvular AF.[1] Anticoagulation potential of VKA is often suboptimal due to genetic variability in its metabolism and drug or dietary interactions.[2,3] VKA have a narrow therapeutic window leading to inconvenient frequent monitoring.[2,3] In addition, they also carry a significant risk for hemorrhagic complications.[4]

Since 2010, several direct acting oral anticoagulants (DOAC) have been approved for use in patients with VTE and nonvalvular AF. These agents have overcome several of the limitations associated with VKA; in that, they have faster onset of action (0.5–4 h), shorter half lives (12–17 h), fewer food and drug interactions, and no need for coagulation monitoring.[3] These differences may translate into similar efficacy with greater ease of administration and lower bleeding risk. This

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review focuses on the current indication of DOACs along with process of choosing the appropriate drug for patients with nonvalvular AF and VTE.

Classification of DOAC

There are a lot of acronyms in use for this new class of anticoagulants. These acronyms include direct oral anticoagulants (DOACs), target-specific oral anticoagulants (TSOACs), oral direct inhibitors (ODIs), and novel oral anticoagulants (NOACs). The International Society on Thrombosis and Haemostasis (ISTH) in their 2015 recommendation statement has suggested the usage of DOAC as acronym for these agents. The earlier most widely used acronym for these agents, NOAC, has some safety limitations; in that, in some instances, it has been interpreted as ''No oral anticoagulantion''. The use of acronym DOAC for this class of anticoagulants should be encouraged. Two classes of DOACs are currently available, the oral direct thrombin inhibitors (dabigatran) and actor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Unlike VKAs, these drugs block the activity of one single step in coagulation cascade. The pharmacokinetic and pharmacodynamic properties of the DOAC are as given in Table 1.

Dabigatran etexilate a direct thrombin inhibitor was the first DOAC studied and approved by FDA based on the results of the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) trial.[5] Dabigatran capsules should be kept away from moisture as this can lead to product breakdown and loss of potency. The capsules should not be crushed or opened before administration as this can result in dramatic increases in oral bioavailability.[6] **Rivaroxaban** is a competitive and dose-dependent direct inhibitor of factor Xa. It was approved by the FDA based on the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF).[7,8] **Apixaban** is a direct, reversible, competitive, and selective inhibitor of factor Xa.[9,10] It is predominantly metabolized by the liver. Rivaroxaban and apixaban are contraindicated for use along with drugs capable of inducing or inhibiting CYP3A4.[10] **Edoxaban** is another reversible factor Xa inhibitor.[11] The drug is a substrate for P-glycoprotein; hence concomitant use of potent glycoprotein inhibitors (verapamil or quinidine) will require dose modification as these drugs will raise the drug levels of Edoxaban.[12] The indications, dosage, and contraindications for DOACs are as given in Table 2. The choice of DOAC in a given clinical situation is as given in Table 3.

Summary of DOAC trials

Summary of the major clinical trials of DOACs is as given in Table 4.[5,7,10,12] Clinical trial data with DOAC showed a similar or lower incidence of major bleeding compared with Warfarin. The risk of intracranial hemorrhage (ICH) was 33–70% lower in patients treated with a DOAC. The rate of fatal bleeding was lower in patients treated with apixaban, rivaroxaban, edoxaban, and low-dose (110 mg bid) dabigatran compared with patients treated with Warfarin. However, a similar rate of fatal bleeding was seen in patients treated with high-dose (150 mg bid) dabigatran.[5] The incidence of major gastrointestinal (GI) bleeding was lower with low-dose (30 mg od) edoxaban group[12]; apixaban and low-dose dabigatran (110 mg bid) groups; while it was higher in patients treated with high-dose (150 mg bid) dabigatran, rivaroxaban, or high-dose edoxaban (60 mg od). Dabigatran-treated patients had a significantly greater incidence of dyspepsia compared with Warfarin-treated patients.[5]

Meta-analysis of these trials (RE-LY,[5] ROCKET AF,[7] ARISTOTLE,[10] ENGAGE AF-TIMI[12]) as a group compared to dose adjusted Warfarin was associated with a reduction in all-cause mortality (RR 0.90, 95% CI 0.85–0.95, $P = 0.0003$).[13] DOACs

Table 1 – Comparison of Warfarin with direct oral anticoagulants.

Characteristics	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Bioavailability	95%	<50% for 10 mg dose	6%	66% without food up to 100% with food	<60% for 60 mg dose
Time to peak activity	48–96 h	3–4 h	0.5–2 h	2.0–4 h	1–2 h
Half life	20–60 h	<12 h	11–14 h	6–12 h, slightly prolonged in elderly	6–11 h
Dosing frequency	Once daily	Twice daily	Twice daily	Once daily	Once daily
Drug interactions	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong inducers and inhibitors of P-gp	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong P-gp inhibitor
Renal elimination	<5%	<25%	85%	35%	<50%
Hepatic elimination	Yes	Yes	No	Yes	No
Laboratory measurement of anticoagulant effect	PT (INR)	Anti–factor Xa assay,	aPTT or TT,	Anti–factor Xa assay	Anti–factor Xa assay,
Reversal agent	Available (Vit K)	Under trial	Idarucizumab	Under trial	Under trial
Procoagulant used	FFP	PCC	aPCC	PCC	PCC

CYP, cytochrome P450; P-gp, P-glycoprotein; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate.