International Journal of Cardiology 202 (2016) 578–585

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Periprocedural management of anticoagulation in patients taking novel oral anticoagulants: Review of the literature and recommendations for specific populations and procedures

Philip L. Mar [a], Dmitry Familtsev [a], Michael D. Ezekowitz [b], Dhanunjaya Lakkireddy [c], Rakesh Gopinathannair [a,*]

[a] Department of Internal Medicine, University of Louisville, Louisville, KY, USA
[b] Division of Cardiovascular Medicine, Lankenau Medical Center, Philadelphia, PA, USA
[c] Division of Cardiovascular Medicine, University of Kansas Hospital, Kansas City, KS, USA

ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form 30 August 2015
Accepted 19 September 2015
Available online 25 September 2015

Keywords:
NOAC
Bridging
Periprocedural anticoagulation
Renal impairment
Ablation

ABSTRACT

An increasing number of individuals are on novel oral anticoagulants (NOAC) for anticoagulation instead of vitamin K antagonists (VKA) and roughly 10% of these individuals will require interruption of these agents for procedures annually. Recent evidence surrounding bridging as well as the FDA approval of a new NOAC call for a comprehensive review and update regarding periprocedural NOAC management.

The periprocedural management of NOACs involves striking a balance between the risks of bleeding and thromboembolism associated with interruption, bridging, and reinitiation of anticoagulation. NOACs have a distinct pharmacokinetic advantage in this setting with their quick onset and elimination from the body. Procedures at low risk for bleeding do not require interruption and can be scheduled at the start of the next dosing interval. Procedures at moderate-high risk of bleeding require interruption of NOAC for 5 half lives prior to the procedure to allow for adequate elimination of the drug. In light of new evidence highlighting the risks of bleeding, and given shorter "unprotected" times with NOAC interruption versus VKA, patients at low-moderate risk for thromboembolism should not be bridged when "unprotected" time is less than 96 h. For patients at high risk for thromboembolism, individual patient and surgical factors need to be considered before the decision to bridge is made. The benefit of bridging these patients who have a considerable risk of bleeding may not outweigh the benefits. Focused randomized studies on periprocedural management of NOACs are urgently needed.

Published by Elsevier Ireland Ltd.

1. Background

An estimated 2.5 million Americans are on oral anticoagulation therapy and ~10% require cessation of anticoagulation for percutaneous and surgical procedures every year [1]. While there is clear consensus regarding the periprocedural management of Vitamin K antagonists (VKA) [2], the evidence and recommendations surrounding the periprocedural management of novel oral anticoagulants (NOAC) are more complex and ambiguous. This is, in part, due to the number of agents available on the market – dabigatran, rivaroxaban, apixaban, and edoxaban – as well as their individually unique pharmacokinetic profiles [3–6]. NOAC use has also increased dramatically since with ~1/3 of patients with atrial fibrillation (AF) using them for stroke prophylaxis [7]. Cost-effective analyses between NOAC and VKA have shown that NOAC can be a cost-effective alternative to VKA, particularly in those with moderate-high risk of stroke and in areas where warfarin time in therapeutic range is low [8]. In recent years, several review papers have been published regarding this topic [9,10]. However, in light of recent studies pertaining to the topic of periprocedural anticoagulation and the entrance of edoxaban into the United States market, a thorough review of this topic with evidence-based recommendations will make navigating around the pitfalls of NOAC management in the periprocedural setting less formidable [11–13].

1.1. Efficacy of NOACs for stroke prophylaxis in AF

The annual incidence of stroke in patients with AF can vary widely between 1.9% and 18.2% based on the CHADS2 risk score [14]. Maintaining the international normalized ratio (INR) between 2 and 3 with warfarin reduces the risk of stroke, with an annual incidence of 1.6–2.2% per year [3–6]. All NOACs are at least non-inferior to warfarin in terms of efficacy, reducing the annual incidence of stroke to 1.2–1.7% per year [3–6]. In terms of major bleeding, all NOACs are also as least as safe as warfarin [3–6].

Abbreviations: NOAC, novel oral anticoagulant; VKA, vitamin K antagonist; AF, atrial fibrillation; VTE, venous thromboembolism; aPTT, activated partial thromboplastin time; LMWH, low-molecular weight heparin; C_{max}, peak concentration; T_{max}, time of peak concentration; AUC, area under curve; ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator.

* Corresponding author at: University of Louisville School of Medicine, ACB/A3L41, 550 So. Jackson St. Louisville, KY 40202, USA.
E-mail address: rakesh.gopinathannair@louisville.edu (R. Gopinathannair).

http://dx.doi.org/10.1016/j.ijcard.2015.09.035
0167-5273/Published by Elsevier Ireland Ltd.

Table 1
Pertinent pharmacologic characteristics for currently available NOACs compared to warfarin.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Pharmacology	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Vitamin K antagonist
Time to peak concentration	1.5 h [22]	1.9 h [20]	1.0–3.3 h [24,105]	1.3 h [21]	2–6 h, but onset of action is 3 days [106]
Half life	12–14 h [26]	7–8 h [23]	11 h [19]	9 h [21]	35 h [106]
CrCl >80 mL/min					
CrCl 50–80 mL/min	16.6 h [38]	8.7 h [36]	14.2 h [37]	12.9 h [11]	35 h [106]
CrCl 30–50 mL/min	18.7 h [38]	9.0 h [36]	18.2 h [37]	16.5 h [11]	35 h [106]
CrCl 15–30 mL/min	27.5 h [38]	9.5 h [36]	N/A	17.5 [11]	35 h [106]
Dietary Restrictions	None [28]	Take with evening meal [33]	None [32]	None [12]	Avoid inconsistent intake of vitamin K [106]
Nonvalvular AF dose	150 mg PO BID [28]	20 mg PO daily [33]	5 mg PO BID [32]	60 mg PO daily [12]	Requires therapeutic drug monitoring [106]
Normal VTE dose	150 mg PO BID (after 5–10 days of parenteral anticoagulation) [28]	20 mg PO daily (after 15 mg BID × 21 days) [33]	5 mg PO BID (after 10 mg PO BID × 7 days) [32]	60 mg PO daily [12]	Requires therapeutic drug monitoring [106]
Renal dosing	For CrCl between 15 and 30 mL/min, dose for nonvalvular AF is 75 mg PO BID; not recommended when CrCl is <15 mL/min; avoid use in VTE when CrCl <30 mL/min [28]	Avoid use when CrCl <30 mL/min [33]	For non-valvular AF, reduce dose to 2.5 mg PO BID in patients who have 2 of the following 3 criteria: 1) Age >80 years 2) Body weight ≤60 kg 3) Serum creatinine ≥1.5 mg/dL No renal dosing adjustment for VTE treatment [32]	For CrCl between 15 and 50 mL/min, decrease dose to 30 mg PO daily; avoid use when CrCl <15 mL/min or >95 mL/min	Dosing dependent on therapeutic drug monitoring [106]
Drug interactions	P-glycoprotein inhibitors [28]	P-glycoprotein and CYP3A4 inhibitors and inducers [33]	P-glycoprotein and CYP3A4 inhibitors and inducers [32]	P-glycoprotein inhibitors [12]	CYP2C9, CYP1A2, CYP3A4 inhibitors and inducers [107]
Dialysis	62–68% of drug removed [38]	Not effective [41]	Not effective [32]	Not effective [42]	Not effective [106]

CrCl — creatinine clearance, BID — twice daily.

1.2. Efficacy of NOACs for the treatment of venous thromboembolism (VTE)

In the initial treatment of VTE, all NOACs were at least non-inferior to warfarin with an incidence of recurrent VTE events ranging between 2.1% and 3.2% at 6–12 months of treatment [15–18]. Similarly, all NOACs were at least as safe as warfarin in terms of major bleeding [15–18].

1.3. Pharmacology of NOACs

All NOACs are synthetic, reversible inhibitors of key factors involved in the coagulation cascade. Whereas dabigatran targets factor IIa (thrombin), apixaban, rivaroxaban, and edoxaban all target factor Xa. After single-dose oral administration, all NOACs achieve peak serum drug concentration (C_{max}) within 1–3 h (T_{max}) [19–22]. All NOACs are eliminated by first order kinetics and are cleared from the body within 5 half-lives after the last dose, predominantly via renal excretion [19–22]. The half-lives range from 7 to 8 h for rivaroxaban to 12–14 h for dabigatran (Table 1), ensuring all NOACs are cleared within 48–72 h after discontinuation in those with normal renal and hepatic function [19–24]. However, the anticoagulation effect of the NOAC becomes clinically irrelevant much sooner. Even dabigatran, which has the longest half-life among NOACs, loses much of its anticoagulation potency 24 h after the last dose with drug concentration dropping to ~25% of C_{max} [22].

1.4. Laboratory monitoring

All the currently available NOACs have predictable pharmacokinetics and routine laboratory monitoring is neither employed nor recommended to assess efficacy of anticoagulation in day-to-day clinical practice. INR and activated partial thromboplastin time (aPTT) cannot be used in the clinical setting due to low sensitivity and large variability in clotting times between the numerous commercially available reagents [19,25]. Anti-factor Xa assays are more sensitive and less variable, making factor Xa activity the most suitable test to monitor drug concentrations of apixaban [25]. Factor Xa activity also correlated well with plasma concentration of rivaroxaban and edoxaban [20,21]. Dabigatran, however, works downstream of factor Xa in the coagulation cascade and its effect cannot be assessed by factor Xa activity. Ecarin clotting time appears to be the most sensitive and useful measurement of dabigatran's anticoagulation activity [22,26,27]. While the manufacturer does report that aPTT levels can be used to approximate anticoagulant effects, a specific aPTT value appropriate for surgery is not known [28]. An accurate, reliable, and widely available assay is not yet available for this class of medication and would be clinically very useful.

2. General principles guiding periprocedural management of NOACs

The risk-benefit assessment of periprocedural NOAC management is similar to that of VKA. The first step is to determine the bleeding risk of the procedure and compare it to the risk of interrupting or withholding anticoagulation during the time leading up to the procedure. If the risk of interrupting anticoagulation is prohibitively higher than the procedural bleeding risk, anticoagulation should not be interrupted or at least be substituted with a low-molecular weight heparin (LMWH) or unfractionated heparin regimen. For patients on chronic warfarin therapy, the usual practice is to stop warfarin 4–5 days before the anticipated procedure with high risk for bleeding [1]. Bridging is then started in those individuals with moderate-high risk for periprocedural thromboembolism in the form of LMWH or unfractionated heparin [1,2]. Post-procedural warfarin is usually reinitiated on postoperative day 0 as long as hemostasis is achieved [1].

The use of a NOAC offers two distinct pharmacokinetic advantages over a VKA in the periprocedural setting. First and foremost, a NOAC provides concentration-dependent, and therefore, predictable levels of anticoagulation [19–22]. Minor dental, dermatologic, and ophthalmologic