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REVIEW

Periprocedural Management of Novel Oral Anticoagulants During Atrial Fibrillation Ablation: Controversies and Review of the Current Evidence

Hany S. Abed, B. Pharm., MBBS, FRACP, PhD [a,c,d], Vivien Chen, MBBS, BA, FRACP, PhD, FRCPA [b,d], Michael J. Kilborn, MBBS, FRACP, PhD [a,c,d], Raymond W. Sy, MBBS, FRACP, PhD [a,c,d*]

[a]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[b]Department of Haematology, Concord Repatriation General Hospital, Sydney, NSW, Australia
[c]Department of Cardiology, Concord Repatriation General Hospital, Sydney, NSW, Australia
[d]University of Sydney, NSW, Australia

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Oral anticoagulation (OAC) has been the cornerstone for the prevention of thromboembolic complications in patients with atrial fibrillation (AF) at significant risk of stroke. Catheter ablation is an established efficacious technique for the treatment of AF. Ameliorating the risk of stroke or transient ischaemic attack (TIA) in patients with AF undergoing ablation requires meticulous planning of pharmacotherapy. The advent of non-vitamin K oral anticoagulants (NOACs) has broadened the therapeutic scope, representing a viable alternative to traditional vitamin K antagonists (VKA) in non-valvular AF. Potential advantages of NOACs include greater pharmacokinetic predictability, at least comparable efficacy as compared to VKA and a superior haemorrhagic complication profile. However, robust evidence for the safety and efficacy of periprocedural NOAC use for AF ablation remains uncertain with a non-uniform clinical approach between and within institutions.

The following review will summarise the current and emerging evidence on periprocedural management of NOACs in patients undergoing catheter ablation of AF. An overview of NOAC pharmacology will provide a foundation for the review of reversal agents in the context of catheter ablation of AF. The purpose of the review is to outline key studies and identify key areas for further critical research with the ultimate aim of developing evidence-based guidelines for optimal care.

Keywords Non-vitamin K antagonists • Atrial fibrillation ablation • Peri-procedural

Introduction

Traditional use of VKAs has been fraught with difficulties in compliance with periodic blood sampling and maintenance of a therapeutic international normalised ratio (INR). The emergence of NOACs appears to have simplified anticoagulation therapy for patients and physicians, primarily through more predictable pharmacodynamics. Current NOACs are either direct inhibitors of Factor IIa (FIIa) or Factor Xa (FXa). The pharmacological and pharmacokinetic profiles of the four currently available agents; dabigatran, rivaroxaban, apixaban and most recently edoxaban, are outlined in Table 1.

Atrial fibrillation confers a cerebral thromboembolic risk of 1% to 18% per annum, depending on validated scoring

*Corresponding author at: Department of Cardiology Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050, AUSTRALIA Tel.: +612 9515 8063; fax: +612 9550 6262, Email: raymond.sy01@gmail.com

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Table 1 Pharmacokinetic and pharmacodynamic profiles of currently available NOACs non-valvular AF.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosage (mg) and frequency	150 twice daily *(CrCl≥50mL/min)* **OR** 110 twice daily *(CrCl 30-50mL/min or age ≥75 years)*	20 once daily *(CrCl≥50mL/min)* **OR** 15 once daily *(CrCl 30-50mL/min)*	5 twice daily **OR** 2.5 twice daily *(Age≥80 or weight≤60 kg or serum Cr≥133 umol/L)*	60 daily **OR** 30 daily *(CrCl 15-50mL/min or weight≤60kg)*
Mechanism of action	Direct thrombin inhibition of bound and fibrin free	Direct factor Xa inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition
T_{max} (Time to peak concentration, hr)	2	2.5-4	1-3	1-2
$T_{1/2}$ (Half-life, hr)	12-17	5-9	8-15	10-14
Plasma protein binding (%)	35	95	87	55
Cellular efflux protein P-glycoprotein ligand	Yes	Yes	Yes	Yes (but no inhibition of pump function)
Hepatic cytochrome binding	No effect on plasma levels in moderate hepatic impairment	CYP3A4, CYP 2J2 and non-cytochrome dependent pathways	CYP3A4, CYP3A5	Minimal metabolism by CYP3A4
Metabolism and excretion	Renal 85% unchanged excretion	66% metabolised and renal 33% unchanged excretion	25% metabolised, 27% renal clearance, gastrointestinal excretion	Renal 50% unchanged excretion, 50% unchanged gastrointestinal excretion
Effects of renal impairment	Increase in AUC, T_{max} and $T_{1/2}$ with decreased in CrCL*	Inverse relationship between CrCL and AUC, anti-factor Xa activity and PT*	Inverse relationship between CrCL and AUC, however no correlation with anti-factor Xa activity*	Inverse relationship between CrCL and AUC§
Weight impact on trough levels	50% greater trough levels in <50 kg compared to >100kg	Negligible effect. No dose adjustment necessary	<50 kg associated with 30% increase in AUC and >120 kg associated with 30% decrease in AUC‡	13% greater AUC in <55 kg compared to >84kg
Impact of age	Compared to <65yrs, 28% higher trough levels in 65-75yrs, 68% higher in >75yrs	AUC 1.5-fold higher in elderly but no dose adjustment necessary	AUC 32% higher in >65yrs compared to <65yrs‡	No impact independent of age-related changes in body weight and renal function

‡ No dose adjustment required unless weight ≤60 kg, age ≥80yrs or renal impairment (creatinine ≥133umol/L). * Contraindicated in severe renal impairment (CrCL < 30 mL/min). § Absolute contraindication in non-valvular atrial fibrillation patients with CrCl >95 mL/min., based on clinical trial data. AUC denotes area under curve. CrCL denotes creatinine clearance.

algorithms incorporating ancillary demographic, vascular and other cardiometabolic risk factors. Recent large international surveys of patients undergoing catheter ablation of AF, estimate a periprocedural risk of cerebral thromboembolism and cardiac tamponade at 0.94% and 1.31%, respectively [1]. Mitigating these risks requires a systematic approach to pre-, intra- and post-procedural management of NOAC therapy. Current areas of significant uncertainty are:

- The safety and efficacy of peri-procedural NOAC therapy. Specifically, the impact on minor bleeding, major bleeding and thromboembolic complications, including ''silent'' cerebral ischaemia.
- A unified definition of ''uninterrupted therapy'' and ''minimally interrupted therapy'', the latter implying dose omission or modification pre-procedure.
- The role of pre-procedural transoesophageal echocardiography to evaluate for LA thrombus.
- The effect of OACs on intra-procedural in vivo anticoagulation and/or potential interference with various coagulation assays in vitro, in particular the activated clotting time (ACT).
- The optimal NOAC resumption strategy post-procedure.
- The management of bleeding complications and potential clinical use of ligand-specific reversal agents.

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