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Review article

A review of the use of direct oral anticoagulant use in orthotopic heart transplantation recipients

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1. Introduction

Over 60 years ago, the vitamin K antagonist (VKA) warfarin was approved and remained the only oral anticoagulation agent until recently [1]. Currently, within North America and Europe there are four DOACs available. Dabigatran, first approved in Europe and Canada in 2008, then in the United States of America in 2010, followed by rivaroxaban, apixaban, and most recently edoxaban. The introduction of direct oral anticoagulants (DOACs) has been a major advancement and these agents are the preferred to VKAs for many indications [2–5], including stroke prevention in nonvalvular atrial fibrillation (NVAF), acute treatment and prevention of venous thromboembolism (VTE), and VTE prophylaxis post elective hip and knee arthroplasty [6–9]. Of note, rivaroxaban also has an indication in Europe for the prevention of atherothrombotic events after an acute coronary syndrome (ACS) with elevated cardiac biomarkers [10].

Despite the wide global availability of DOACs and increasing use in the general population, randomized controlled trials (RCTs) with these agents have not been conducted in orthotopic heart transplantation (OHT) patients and the safety of their use within this population is largely unknown. As such, warfarin has remained the standard of care in OHT patients, despite its many limitations with its use. Estimates of the percentage of warfarin time in therapeutic range (TTR) for OHT patients on warfarin is unknown but expected to be worse than the general population real-world TTR reports of ~58% [11,12]. Lower TTR in the OHT population may be expected due to the increased risk of warfarin-

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drug interactions (ie: concomitant use of azole antifungal agents, sulfamethoxazole/trimethoprim, etc.), gastrointestinal adverse effects of immunosuppressants causing loss of vitamin K via vomiting and diarrhea, and frequent anticoagulation interruptions for invasive procedures such as endomyocardial biopsies. A low TTR is problematic and puts patients at an increased risk of thrombotic events or increased risk of major bleeding [13]. Furthermore, the need for both short term and extended duration anticoagulation therapy remains a relevant clinical issue for OHT patients. Among the OHT population, estimates of the overall incidence of atrial fibrillation are ~13%, and rates of venous thromboembolism are ~8.5% [14,15]. Given the ongoing need for anticoagulation for a significant portion of OHT patients, and advantages of DOACs compared to warfarin, the potential use of DOACs in OHT patients is an inviting option. In this article we provide a review of DOACs and the unique considerations for their potential use in OHT patients, based on the currently available published evidence.

2. Efficacy and safety of DOACs compared to warfarin in general population

When compared to warfarin, a recent meta-analysis in over 70,000 NVAF patients demonstrated that DOACs significantly reduced the risk of stroke or systemic embolic events, intracranial hemorrhage (ICH), and all-cause mortality [13]. DOACs had similar rates of major bleeding but were associated with an overall increased rate of gastrointestinal bleeding (GIB) compared to warfarin [13]. In a pooled analysis of 6 phase 3 RCTs for VTE treatment, DOACs were found to be non-inferior to warfarin and were associated with significantly less major bleeding, including ICH, fatal bleeding, and clinically relevant non-major bleeding [16]. The warfarin TTR in these landmark NVAF and VTE trials ranged from 58%–68% [13,16]. It is notable that clinical trials with edoxaban specifically excluded patients taking cyclosporine for an organ transplant, and it is unclear from the study inclusion/exclusion criteria for the dabigatran, rivaroxaban, or apixaban trials if any OHT patients were included.

3. Pharmacokinetic considerations of DOACs

The pharmacokinetic advantages of DOACs compared to VKAs are numerous and include: rapid onset of action, short offset, predictable anticoagulant effect, lack of dietary vitamin K effects, lack of frequent blood monitoring, decreased risk of intracranial bleeding, and fewer drug interactions [2]. The four available DOACs differ in their mechanism of action, with dabigatran acting as a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban acting as factor Xa inhibitors. A detailed comparison of pharmacologic properties of available DOACs is summarized in Table 1. It is also important to highlight that dosing of each DOAC differs according to indication (i.e.: NVAF, treatment of acute VTE). Dosing selection may also depend on the patient's age (dabigatran, apixaban), weight (apixaban, edoxaban), and renal function (all DOACs). Given this complexity, clinicians must be diligent to ensure selection of appropriate dosing is made according to the approved product monographs.

All four DOACs are substrates of P-glycoprotein (P-gp), an efflux transporter pump present in the intestine and liver; therefore, potent inhibitors of P-gp can increase plasma concentrations of DOACs significantly [17]. Rivaroxaban and apixaban are both metabolized in the liver via the cytochrome P450 system, primarily through isoenzymes 3A4; therefore, they are subject to increased or decreased serum concentrations with inhibitors or inducers of this enzyme. Comparatively, dabigatran and edoxaban undergo minimal CYP450 metabolism. Based on these properties, dabigatran and edoxaban should generally be avoided in combination with potent P-gp inhibitors or inducers, whereas rivaroxaban and apixaban should be avoided with combined potent inhibitors or inducers of both CYP3A4 and P-gp.

When considering DOACs in the OHT population, the potential for drug interactions with commonly used post-transplant medications exist, specifically with the calcineurin inhibitors (CNIs) cyclosporine (CsA) and tacrolimus (Tac). Refer to Table 2 for a summary of DOAC drug interaction considerations for commonly used post-transplant medications. Both CsA and Tac are substrates and inhibitors of CYP3A4 and P-gp pathways [18]. Importantly, Tac is considered to be a weaker inhibitor of CYP3A4 and P-gp, with inhibition being much more pronounced and likely only clinically relevant for CsA, which is both a potent P-gp inhibitor and moderate CYP3A4 inhibitor [17,18]. The Food and Drug Administration (FDA), Health Canada, and European Medicines Agency (EMA) monographs differ for DOAC use and dosing recommendations with concomitant use of CsA or Tac. The FDA drug monographs for DOACs do not comment specifically on CsA or Tac interactions [6–9]. In Canada, the dabigatran product monograph recommends caution for use with CsA due to potential for increased dabigatran concentrations, and the edoxaban product monograph recommends a reduced dose of 30 mg once daily when combined with CsA [19,20]. In Europe only, the dabigatran monograph addresses CsA and Tac specifically, with the combination of dabigatran with CsA being contraindicated, and use with Tac was originally contraindicated but in 2013 this recommendation was modified to not recommended [20].

While the renal clearance varies between the DOACs, all four agents have the potential to accumulate in patients with renal impairment, which is a pertinent issue for OHT patients whom renal function can be highly variable. Recommendations for DOAC dosing in renal impairment are vary between the FDA [6–9], Health Canada [19,21–23], and EMA [10,20,24,25] approved drug product monographs, as well as the 2015 Updated European Heart Rhythm Association (EHRA) Practical

Table 1
Comparisons of DOACs.[a]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Anticoagulation mechanism	Direct thrombin inhibitor (prodrug)	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability %	6–7	10 mg dose: 80–100% 20 mg dose: 66% fasting state, higher with food.	50	62
Protein binding	35%	92% to 95%	87%	55%
Half-life (hours)	12–14	9–13	8–15	9–14
Metabolism via cytochrome P450%	<2	57	<32	<5
Renal elimination %	>80	33	25	50
Drug interactions	P-gp inhibitors and inducers	Strong inhibitors or inducers of both CYP3A4 P-gp	Strong inhibitors or inducers of both CYP3A4 P-gp	P-gp inhibitors and inducers
P-glycoprotein substrate	Yes	Yes	Yes	Yes
Cytochrome P450 3A4 substrate	No	Yes	Yes	No

[a] Adapted from Ref. [2].

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