Am J Blood Res 2018;8(4):57-72
www.AJBlood.us /ISSN:2160-1992/AJBR0086441

Review Article

Use of direct oral anticoagulants in daily practice

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Received October 8, 2018; Accepted October 19, 2018; Epub December 10, 2018; Published December 20, 2018

Abstract: In recent years, the options for anticoagulant therapy have examined new direct oral anticoagulants (DOACs) comprising direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). These agents represent further progress towards the ideal anticoagulant drug and thus towards a safe and effective antithrombotic therapy. The ideal anticoagulant is oral and has a wide therapeutic range, predictable pharmacokinetics and pharmacodynamics, a rapid onset of action, an available antidote, minimal side effects, and minimal interactions with other drugs or food. This review addresses the practical considerations for physicians in DOAC use, including indication, dosage, monitoring, pharmacokinetic profile, drug-drug interaction, and reversal of direct anticoagulation effects in case of bleeding.

Keywords: DOACs, dabigatran, rivaroxaban, apixaban, edoxaban, reversal

Introduction

Direct oral anticoagulants (DOACs) are oral medications that specifically inhibit factors IIa or Xa. They are also known as new oral anticoagulants (NOACs) or target-specific oral anticoagulants (TSOACs). DOACs are the preferred name according to the International Society of Thrombosis and Haemostasis [1].

The availability of DOACs has significantly changed the perspective of anticoagulation. Despite some limitations, these agents may displace conventional VTE treatment with a rapid-acting parenteral anticoagulant overlapped with a vitamin K antagonist (e.g., warfarin) in appropriate patients [2]. DOACs are preferred for their ease of use, favorable pharmacokinetics with fixed dosing, fewer drug interactions, and lack of monitoring requirements [2]. DOACs exhibit comparable efficacy and significantly lower bleeding risk compared to warfarin [3]. It is imperative that physicians be able to manage patients on these medications. This review discusses the current evidence on uses of DOACs.

DOACS phase III clinical trials in approved indications

VTE Treatment

VTE is the third most common cause of vascular death after myocardial infarction and stroke [4]. Anticoagulation is essential to prevent recurrence and complications from VTE [5]. The RE-COVER I trial compared 150 mg of dabigatrantwice daily to warfarin after an initial treatment with parenteral anticoagulation in preventing recurrent symptomatic VTE. Dabigatran was not inferior to conventional therapy ($P < 0.001$) [4]. Dabigatran has significantly lower rates of major bleeding and clinically relevant rates of non-major bleeding and any other bleeding however. Major bleeding was similar in both groups. The RE-COVER II trial was carried out to confirm the results of RE-COVER I and included 2568 patients with acute VTE [6]. The study confirmed the non-inferiority of dabigatran in terms of the prevention of VTE recurrence ($P < 0.001$) and lower risk of any bleeding events (**Table 1**).

EINSTEIN-DVT was an open-label randomized controlled trial (RCT) comparing 15 mg of rivar-

Table 1. A summary of DOAC phase-III trials on the treatment and prevention of VTE

Trial	Drug	Comparator	Recurrent VTE Absoluterate (%) HR (95% CI)	Major bleeding Absoluterate (%) HR (95% CI)	Major or CRNM bleeding Absoluterate (%) HR (95% CI)
RE-COVER II, 2013	Dabigatran 150 mg BD for 6 months	Heparin/VKA	2.3 vs. 2.2	1.2 vs. 1.7	5.3 vs. 8.5
			1.08 (0.64-1.80)	0.69 (0.36-1.32)	0.62 (0.50-0.76)
			P < 0.001 for NI	P < 0.001 for NI	
AMPLIFY, 2013	Apixaban: 10 mg, BD (one week), then 5 mg for 6 months	LMWH/VKA	2.3 vs. 2.7	0.6 vs. 1.8	4.3 vs. 9.7
			RR 0.84 (0.60-1.18)	RR 0.31 (0.17-0.55)	RR 0.44 (0.36-0.55)
			P < 0.001 for NI	P < 0.001 for superiority	P < 0.001
HOKUSAI-VTE, 2013	Edoxaban 60 mg or 30 mg OD for 3-12 months	Enoxaparin or UFH/VKA	3.2 vs. 3.5	1.4 vs. 1.6	8.5 vs. 10.3
			0.89 (0.70-1.13)	0.84 (0.59-1.21)	0.81 (0.71-0.94)
			P < 0.001 for NI	P=0.35 for superiority	P=0.004 for superiority
EINSTEIN-PE, 2012	Rivaroxaban15 mg BD (3 weeks), then 20 mg OD for 3,6 & 12 months	LMWH/VKA	2.1 vs. 1.8	1.1 vs. 2.2	10.3 vs. 11.4
			1.12 (0.75-1.68)	0.49 (0.31-0.79)	0.90 (0.76-1.07)
			P=0.003 for NI	P=0.003	P=0.23
EINSTEIN-DVT, 2010	Rivaroxaban15 mg BD (3 weeks), then 20 mg, OD for 3,6 & 12 months	LMWH/VKA	2.1 vs. 3.0	0.8 vs. 1.2	8.1 vs. 8.1
			0.68 (0.44-1.04)	0.65 (0.33-1.30)	0.97 (0.76-1.22)
			P < 0.001 for NI	P=0.21	P=0.77
RE-COVER I, 2009	Dabigatran 150 mg BD for 6 months	Heparin/VKA	2.4 vs. 2.1	1.6 vs. 1.9	5.6 vs. 8.8
			1.10 (0.65-1.84)	0.82 (0.45-1.48)	0.63 (0.47-0.84)
			P < 0.001 for NI		

Abbreviations: VTE: venous thromboembolism; HR: Hazard ratio; CI: confidence interval; CRNMB: clinically relevant non-major bleeding; RR: Relative risk; DVT: Deep venous thrombosis; BD: Twice daily; OD: once daily; LMWH: low molecular weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonist; NI: non-inferiority.

Table 2. A summary of DOACs phase-III trials on the long-term prevention of VTE

Trial	Drug	Comparator	Recurrent VTE Absolute rate (%) HR (95% CI)	Major Bleeding Absolute rate (%) HR (95% CI)	Major or CRNM bleeding Absolute rate (%) HR (95% CI)
AMPLIFY-EXT, 2013	Apixaban: 5 mg or 2.5 mg BD	Placebo	Apixaban 5 mg: 1.7 vs. 8.8 ARR 7% (4.9-9.1) Apixaban 2 mg: 1.7 vs. 8.8 ARR 7.2% (5.0-9.3) P < 0.001 for both comparisons	Apixaban 5 mg: 0.1 vs. 0.5 RR 0.25 (0.03-2.24) Apixaban 2.5 mg: 0.2 vs. 0.5 RR 0.49 (0.09-2.64)	Apixaban 5 mg: 4.3 vs. 2.7 RR 1.62 (0.96-2.73) Apixaban 2.5 mg: 3.2 vs. 2.7 RR 1.20 (0.69-2.10)
RE-MEDY, 2011	Dabigatran: 150 mg BD	VKA	1.8 vs. 1.3 1.44 (0.78-2.64) P=0.01 for NI	0.9 vs. 1.8 0.52 (0.27-1.02) P=0.06	5.6 vs. 10.2 0.54 (0.41-0.71) P < 0.001
RE-SONATE, 2011	Dabigatran: 150 mg BD	Placebo	0.4 vs. 5.6 0.08 (0.02-0.25) P < 0.001 for superiority	0.3 vs. 0 HR not estimable P=1	5.3 vs. 1.8 2.92 (1.52-5.60) P=0.001
EINSTEIN-EXT, 2010	Rivaroxaban: 20 mg OD	Placebo	1.3 vs. 7.1 0.18 (0.09-0.39) P < 0.001	0.7 vs. 0 HR not estimable P=0.11	6 vs. 1.2 5.19 (2.3-11.7) P < 0.001

Abbreviations: VTE: venous thromboembolism; HR: Hazard ratio; RR: Relative risk; BD: Twice daily; OD: Once daily; ARR: absolute risk reduction; NI: non-inferiority; RR: relative risk; HR: Hazard ratio; CI: confidence interval; clinically relevant non-major bleeding: clinically relevant non-major bleeding.

oxaban taken orally twice daily for three weeks followed by 20 mg once daily with enoxaparin/vitamin K antagonist (VKA) for the treatment of acute symptomatic deep vein thrombosis (DVT) [7]. Rivaroxaban was non-inferior to enoxaparin/VKA (P < 0.001) in preventing recurrent symptomatic VTE with comparable bleeding rates. EINSTEIN-PE was another trial that compared rivaroxaban with enoxaparin/VKA in patients suffering from acute pulmonary embolism (PE) [8]. Rivaroxaban was non-inferior to conventional therapy (P=0.003) in preventing recurrent symptomatic VTE. Major bleeding was lower in the rivaroxaban group (P=0.003), but clinically relevant non-major bleeding and any other bleeding were comparable in both groups.

HOKUSAI-VTE was a double-blind RCT including 8292 patients with DVT or PE that examined 60 mg of edoxaban once daily (or 30 mg if creatinine clearance (CrCl) was 30-50 ml/min or body weight was below 60 kg), which was compared to warfarin after at least 5 days of parenteral anticoagulation [9]. Edoxaban was non-inferior to standard therapy in preventing recurrent VTE (P < 0.001) and showed significantly lower rates of major bleeding or clinically relevant non-major bleeding (P=0.004). The AMPLIFY trial was a double-blind RCT at comparing 10 mg of apixaban twice daily for one week followed by 5 mg twice daily to a standard treatment in 5395 patients with acute VTE [10]. Apixaban was non-inferior to standard therapy in preventing recurrent VTE or related deaths (P < 0.001). Additionally, it showed significantly lower rates of major or clinically relevant non-major bleeding. In a meta-analysis of six RCTs comparing treatments, DOACs were as effective as standard therapy in preventing symptomatic recurrent VTE (RR 0.89, 95% CI 0.75-1.05). However, the risk of major bleeding was significantly lower (1.08% vs. 1.73% for VKAs, RR 0.63, 95% CI 0.51-0.77) [11].

Long-term prevention of VTE

Anticoagulation plays key roles in the long-term prevention of recurrent VTE. DOACs show promise for overcoming the limitations of conventional anticoagulation, such as delayed onset, the need for parenteral anticoagulation overlap, and drug interactions [12]. EINSTEIN-EXT was an extended placebo-controlled RCT comparing 20 mg of rivaroxaban once daily to a placebo for 6 or 12 months in preventing recurrent VTE [7]. Rivaroxaban showed superior efficacy to the placebo (HR, 0.18; 95% CI, 0.09 to 0.39; P < 0.001) with similar bleeding risk (**Table 2**).

The RE-MEDY and RE-SONATE trials compared 150 mg of dabigatran twice daily to warfarin (6-36 months) and a placebo (6 months) in patients treated for three months for VTE [13]. Dabigatran was as effective as warfarin (P=0.01) in the long-term prevention of VTE. Major bleeding was similar between groups, but major or clinically relevant non-major bleeding was significantly lower in the dabigatran group (P < 0.001). The RE-SONATE trial demonstrated that dabigatran significantly reduced recurrent events of VTE (P < 0.001), but it significantly increased the frequency of bleeding events compared to a placebo.

AMPLIFY-EXT was a double-blinded RCT comparing two doses of apixaban (2.5 mg and 5 mg twice daily) with a placebo in patients who completed at least 6 months of initial VTE treatment [14]. For both dose regimens, apixaban significantly reduced the risk of recurrent VTE and related deaths (P < 0.001) with similar rates of bleeding in both apixaban groups compared to the placebo.

Prevention of stroke and embolization in non-valvularatrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with significant morbidity and mortality due to the occurrence of stroke or thromboembolism [15]. In the United States, AF occurs in ≥ 15% of all strokes, of which > 20% are fatal. It makes patients chronically disabled, bed-bound, and requires constant nursing care [16]. Thromboembolic events can be prevented with anticoagulation therapy, and warfarin has been the gold standard for over 50 years [5]. DOACs were introduced for preventing stroke and thromboembolism. This review summarizes four phase-III RCTs assessing DOACs in patients with AF (**Table 3**).

ROCKET-AF was a prospective, double-blinded, double-dummy trial on 14264 patients with AF (mean CHADS2 score =3.5) [17]. Compared to warfarin, 20 mg of rivaroxaban daily was non-inferior in preventing stroke or systemic embolism (P < 0.001). Moreover, patients on rivaroxaban showed significantly fewer intracranial hemorrhages but similar rates of major and clinically relevant non-major bleeding. The RE-LY trial was a partially blinded RCT with 18113 non-valvular AF patients (mean CHADS2

Table 3. DOAC phase-III trials in patients with AF

Trial	Drug	Comparator	Stroke and systemic embolism Absoluterate (%) HR (95% CI)	Major bleeding Absoluterate (%) HR (95% CI)	Major or CRNM bleeding Absoluterate (%) HR (95% CI)
ENGAGE-AF-TIMI 48, 2013	Edoxaban: 30 mg or 60 mg OD	Warfarin	Edoxaban 60 mg: 1.18 vs. 1.50 0.79 (0.63-0.99)* P < 0.001 for NI	Edoxaban 60 mg: 2.75 vs. 3.43 0.80 (0.71-0.91) P < 0.001	Edoxaban 60 mg: 11.10 vs. 13.02 0.86 (0.80-0.92) P < 0.001
			Edoxaban 30 mg: 1.61 vs. 1.50 1.07 (0.87-1.31)* P=0.005 for NI	Edoxaban 30 mg: 1.61 vs. 3.43 0.47 (0.41-0.55) P < 0.001	Edoxaban 30 mg: 7.97 vs. 13.02 0.62 (0.57-0.67) P < 0.001
ARISTOTLE, 2011	Apixaban 5 mg BD	Warfarin	1.28 vs. 1.60 0.79 (0.66-0.95) P=0.01 for superiority	2.13 vs. 3.09 0.69 (0.60-0.80) P < 0.001	4.07 vs. 6.01 0.68 (0.61-0.75) P < 0.001
ROCKET-AF, 2011	Rivaroxaban: 20 mg, OD	Warfarin	1.7 vs. 2.2 0.79 (0.66-0.96) P < 0.001 for NI	3.6 vs. 3.4 1.04 (0.90-1.20) P=0.58	14.9 vs. 14.5 1.03 (0.96-1.11) P=0.44
RE-LY, 2009	Dabigatran: 110 mg or 150 mg BD	Warfarin	Dabigatran 150 mg: 1.11 vs. 1.69 RR 0.66 (0.53-0.82) P < 0.001 for superiority	Dabigatran 150 mg: 3.11 vs. 3.36 RR 0.93 (0.81-1.07) P=0.31	Not reported
			Dabigatran 110 mg: 1.53 vs. 1.69 RR 0.91 (0.74-1.11) P < 0.001 for NI	Dabigatran 110 mg: 2.71 vs. 3.36 RR 0.80 (0.69-0.93) P=0.003	

Abbreviations: HR: Hazard ratio; RR: Relative risk; BD: Twice daily; OD: once daily; CI: confidence interval; clinically relevant non-major bleeding: clinically relevant non-major bleeding; *A 97.5% Confidence interval was used.

=2.1) comparing dabigatran (110 mg or 150 mg twice daily) to dose-adjusted warfarin [18]. The 110-mg dose of dabigatran was as effective as warfarin in preventing stroke and systemic embolism, but major bleeding was significantly reduced. Stroke and systemic embolisms were significantly lower in patients receiving 150 mg of dabigatran twice daily with similar rates of major bleeding compared to warfarin.

ARISTOTLE was a double-blinded RCT involving 18201 patients with AF (mean CHADS2=2.1) [19]. Compared with warfarin, 5 mg of apixaban twice daily was superior in preventing stroke and systemic embolism with significantly reduced bleeding rate. ENGAGE-AF-TIMI 48 was a double-blinded, double-dummy RCT with 21105 non-valvular AF patients comparing edoxaban (30 mg and 60 mg, once daily) to warfarin in terms of stroke and embolic events [20]. Both edoxaban regimens were as effective as warfarin in the prevention of stroke or systemic embolism with significantly lower bleeding risk. A meta-analysis by Rong et al. included the mentioned RCTs and showed that DOACs are comparable safety with to warfarin in patients with AF and have lower risk of intracranial bleeding (ICB) [21]. The efficacy and safety of DOACs in AF were compared in another meta-analysis that included three RCTs, which showed similar efficacy with a lower risk of ICB [22].

Thromboprophylaxis

The estimated incidence of DVT after elective arthroplasty is 40-60% [23]. Dabigatran, apixaban, and rivaroxaban are approved for VTE prevention after elective arthroplasty based on clinical trials comparing each drug with conventional thromboprophylaxis. In the ADVANCE-1 RCT, 2.5 mg of apixaban twice daily was compared to 30 mg of enoxaparin twice daily for preventing VTE after total knee arthroplasty (TKA) [24]. Apixaban did not reach statistical criteria for non-inferiority for the primary outcome. However, apixaban had similar efficacy in preventing VTE after TKA with lower risk of bleeding. In the ADVANCE-2 RCT, 2.5 mg of apixaban twice daily was as effective as 40 mg of enoxaparin in VTE prevention after TKA. In the ADVANCE-3 trial, it was superior to enoxaparin after total hip arthroplasty (THA), and there was no increased bleeding risk in either trial [25, 26].

RE-MODEL and RE-NOVATE I and II reported that 150 mg or 220 mg of dabigatran daily was non-inferior to 40 mg of enoxaparin for thromboprophylaxis after TKA and THA, respectively, and bleeding risk was comparable [27-29]. In the RE-MOBILIZE trial, 150 mg or 220 mg of dabigatran did not meet the criteria for statistical non-inferiority compared to 30 mg of enoxaparin twice daily [30]. The RE-CORD-1 and 2 trials compared 10 mg of rivaroxaban with 40 mg of enoxaparin. Rivaroxaban was superior to enoxaparin in terms of VTE prevention and all-cause mortality after THA without differences in bleeding events [31, 32]. The RE-CORD-3 and 4 trials compared 10 mg of rivaroxaban to 40 mg of enoxaparin daily or 30 mg twice daily [33, 34]. Rivaroxaban was superior to both regimens of enoxaparin in total VTE prevention after TKA with similar rates of bleeding.

A pooled analysis of four rivaroxaban trials showed a significant reduction of symptomatic VTE and all-cause mortality with rivaroxaban compared to enoxaparin (40 mg or 30 mg twice) after TKA or THA with comparable safety profiles [35]. In another meta-analysis, enoxaparin and dabigatran had similar efficacy and bleeding rates. However, rivaroxaban was more effective in VTE prevention after TKA or THA but had an increased bleeding rate [36].

Dosing

Different DOAC doses from phase III clinical trials are summarized in **Table 4**. Notably, apixaban and rivaroxaban were started without initial parenteral anticoagulation. However, higher doses were used for apixaban (10 mg BD) for the first 7 days and for rivaroxaban (15 mg BD) for the first 21 days [7, 10]. Furthermore, parenteral anticoagulation was used for at least 5 days before introducing dabigatran and edoxaban [4, 9]. Renal impairment is a limitation of using DOACs. All phase III trials excluded patients with severe renal impairment. This exclusion was based on creatinine clearance (CrCl) calculated using the Cockroft-Gault equation [37]. Generally, all patients with CrCl < 30 mL/min were excluded from clinical trials, although the ARISTOTLE trial used 25 mL/min as a cut off [20].

Limitations

Patients needing anticoagulants for indications not considered in clinical trials are not eligible for DOAC treatment. Patients who are pregnant,

lactating, pediatric, hepatically impaired, and have severe renal failure were excluded from phase III clinical trials, thus limiting their prescription for these populations. Optimal dosing in obese patients is also unknown since this population was underrepresented in clinical trials [38]. Several studies concluded that the treatments are ineffective in patients with mechanical heart valves [39] and acute coronary syndrome [40, 41]. Inadequate safety and efficacy data constrain utilization in thromboembolism with complications of anti-phospholipid syndrome and in unstable cancer patients [2]. As novel anticoagulants, DOACs lack specific antidotes, but idarucizumab was recently approved for dabigatran reversal, while and exanetalpha and ciraparantag are under development [42-44].

Perioperative management

Generally, anticoagulants should be thoroughly managed before invasive procedures to minimize bleeding and thrombotic risks. Unlike VKAs, the rapid onset of action and short half-life of DOACs limit perioperative bridging to parenteral anticoagulation. However, bridging with heparin should be considered in patients with high thrombotic risk, such as patients with recent VTE or AF with recent stroke.

DOACs are mainly eliminated by the kidney, and the washout period before intervention should be based on the bleeding risk of the procedure and renal clearance. **Table 5** summarizes the perioperative management of DOACs based on bleeding risk and creatinine clearance. Procedures with low bleeding risk include treatment for cataracts, minor dermatological and dental procedures, pacemaker implantation, arthroscopy, coronary angiography, endoscopy, bronchoscopy, and hernia repair. High-risk procedures include all other interventions [45].

Monitoring

DOACs are eliminated via renal clearance; therefore, creatinine clearance based on the Cockcroft-Gault equation should be used to adjust the dosing indication to the formula used during phase III trials. Liver function tests may also be indicated before starting DOACs in patients with suspected liver diseases. The baseline haemoglobin level, platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should be tested before initiating DOACs, as for all anticoagulants.

Patients on DOACs do not necessarily require routine coagulation monitoring, but specific clinical scenarios may necessitate coagulation testing, such as renal or hepatic impairment, suspected overdose, serious bleeding or thrombotic events, and emergency perioperative management. Unfortunately, DOACs may interfere with the results of some coagulation assays, depending on the coagulation endpoint. The magnitude of interference depends on the plasma concentration of the drug; therefore, interpreting the results should be based on the interval between sampling and the last dose of the DOAC agent [46]. Regarding dabigatran, thrombin time (TT) and ecarin clotting time (ECT) tests are linear and sensitive enough to measure its anticoagulant activity [47]. In the case of rivaroxaban and apixaban, modified chromogenic anti-Xa assays with drug-specific calibrators could provide sensitive and quantitative results [48]. **Table 6** illustrates the effects of DOACs on common coagulation tests [48].

Switching to or from DOACs

Switching among drugs with similar pharmacokinetic profiles is more straightforward than among those with dissimilar pharmacokinetic profiles. Since LMWH has similar pharmacokinetics to DOACs, the first DOAC dose is given when the next dose of LMWH would have been given, and vice versa. When shifting from unfractionated heparin, the DOACs should commence after ceasing unfractionated heparin infusion [49]. In the reverse situation, the parenteral anticoagulant should start when the DOAC dose is scheduled.

Upon switching from VKAs to DOACs, the first dose of DOACs may be started as soon as the prothrombin-time INR is ≤ 2. When switching from DOACs, VKA can be administrated concomitantly until therapeutic INR [49]. However, INR should be checked before the next scheduled DOACS dose and at 24 hours after the last dose, as the DOACs may have an impact on INR. An alternative approach is to start parenteral anticoagulation with VKA at the next scheduled dose of DOACs.

Pharmacokinetics

DOACs are direct and specific inhibitors of a single coagulation factor, and the two main targets are FIIa (dabigatran) and FXa (apixaban, rivaroxaban, and edoxaban) [50, 51]. DOACs have a rapid onset of action after oral inges-

Table 4. A Summary of DOACs dosing based on indications and creatinine clearance

Drug	Condition	Renal function (CrCl)			
CrCl		> 50 mL/min	30-50 mL/min (α)	15-29 mL/min (β)	< 15 mL/min
Dabigatran	AF	150 mg, BD-©1	150 mg, BD-©1	CI	
	VTE treatment*	150 mg, BD	150 mg, BD		
	VTE long-term prevention	150 mg, BD	150 mg, BD		
	Thromboprophylaxis§	220 mg, OD	220 mg, OD		
Rivaroxaban	AF	20 mg, OD	15 mg, OD	NR for AF	CI
	VTE treatment	15 mg, BD for 21 days, then 20 mg OD	15 mg, BD for 21 days, then 20 mg OD	CI	
	VTE long term prevention	20 mg, OD	20 mg, OD	CI	
	Thromboprophylaxis§§	10 mg, OD	10 mg, OD	CI	
Edoxaban	AF	60 mg, OD-©2, ©3	30 mg, OD	CI	
	VTE treatment*	60 mg, OD-©2	30 mg, OD	CI	
	VTE long term prevention	60 mg, OD	30 mg, OD	CI	
	Thromboprophylaxis	Not approved-©4			
Apixaban	AF	5 mg, BD	5 mg BD-©5	CI	
	VTE treatment	10 mg, BD for 7 days, then 5 mg BD	10 mg, BD for 7 days, then 5 mg BD	CI	
	VTE long term prevention	2.5 mg BD	2.5 mg BD	CI	
	Thromboprophylaxis	2.5 mg BD	2.5 mg BD		

Abbreviations: AF: Atrial fibrillation; VTE: Venous thromboembolism; BD: Twice daily; NR: not reported; OD: Once daily; CI: Contraindications. α: 30-49 mL/min for rivaroxaban. β: 15-24 mL/min for apixaban. ©1-110 mg if ≥ 75 years with any risk factor for bleeding or aged 80 years and older. ©2-30 mg if weight ≤ to 60 kg or concomitant use of strong gp inhibitors. ©3-Edoxaban is not recommended if CrCl > 95 mL/min. ©4-Approved in Japan only. ©5-Apixaban 2.5 mg BD if age ≥ 80 years or weight < 60 kg or creatinine ≥ 1.5 mg/dl. *, Parenteral anticoagulation for at least 5 days. §, Initial 110 mg 1-4 hours after surgery and then 220 mg. §§, First dose 6-10 hours after surgery.

Table 5. Perioperative management of direct oral anticoagulants based on creatinine (CrCl) clearance and bleeding risk

Drugs / Preoperative	Dabigatran Crcl > 50 mL/min	Dabigatran Crcl 30-50 mL/min	Apixaban, rivaroxaban and edoxaban
Low bleeding risk	Last dose 48 hours before procedure	Last dose 72 hours before procedure	Last dose 48 hours before procedure
High bleeding risk*	Last dose 72 hours before procedure	Last dose 96-120 hours before procedure	Last dose 72 hours before procedure
Postoperative	Resume 24 hours after low bleeding risk surgery and 48-72 hours after high bleeding risk surgery.		

*Includes procedures requiring neuroaxial anesthesia.

Table 6. Effect of DOACs on common coagulation tests

Assay test	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
APTT	++	+	Little to no effect	+
PT/INR	+	++	++	++
TT	+++	No effect	No effect	No effect
Anti-Xa	No effect	Overestimation	Overestimation	Overestimation
Anti-IIa	overestimation	No effect	No effect	No effect

+, Slight increase in clotting time; ++, Moderate increase in clotting time; +++, Marked increase in clotting time.

tion, and peak plasma levels occur in 2 to 4 hours. All have rather short half-lives of approximately 8 to 12 hours. As opposed to VKAs, they are not subject to food interactions, although some must be taken with food to enhance absorption. Drug interactions are minimal compared with VKAs.

Dabigatran has low oral bioavailability, and as a hydrophilic molecule, it cannot be absorbed in the intestinal tract. Therefore, it must be administered as a pro-drug, dabigatran etexilate, which has less than 10% oral availability. Another important pharmacokinetic difference between FXa inhibitors and FIIa inhibitors is the metabolic pathway. Absorption of all DOACs is influenced by intestinal P-glycoprotein. However, whereas the metabolism of dabigatran does not depend on the cytochrome P450 pathways, the FXa inhibitors are all metabolized by the cytochrome CYP3A4 to varying extents. Finally, renal impairment has a different influence on the pharmacokinetics of FXa inhibitors and FIIa inhibitors [51-53].

Dabigatran is mainly eliminated by the kidneys, but not FXa inhibitors. The subtle differences between FXa inhibitors in the percentages of renal elimination do not seem relevant, especially when considering the wide interindividual variation of the pharmacokinetic profile [54]. Their pharmacology is well characterized (**Table 7**). Direct FXa inhibitors have good oral bioavailability (> 50%) and lower renal clearance than dabigatran, although still significant (54-73% of absorbed doses is excreted through the kidneys). They also undergo extensive metabolism by mainly CYP3A4 (rivaroxaban), CYP3A4/5 (apixaban), or hydrolysis (edoxaban), as shown in **Table 7** [55-61].

Relevant drug-drug interactions and criteria for dose reduction

Most DOACs are substrates of P-glycoprotein resulting in potential risk of drug-drug interactions. Relevant interactions are known for antiarrhythmics (dronedarone, amiodarone, digoxin, chinidin, propafenone, verapamil), antihypertensives (carvedilol, felodipine, nifedipine, timolol, propranolol, labetalol, diltiazem, aliskiren), antiplatelet drugs (clopidogrel, ticagrelor, dipyridamole), statins (atorvastatin, lovastatin), antibiotics (erythromycin, clarithromycin, rifampicin, fluconazole, ketoconazole), and HIV protease inhibitors (ritonavir) [62].

Dabigatran

Dabigatran is metabolized by P-glycoprotein and should be avoided in conjunction with P-glycoprotein inducers (e.g., rifampicin). Furthermore, the co-administration of P-glycoprotein inhibitors (e.g., dronedarone, ketokonazole) should be avoided when creatinine clearance (CrCl) is < 30 mL/min. Dose adjustment is generally required, depending on the degree of renal impairment [62].

Rivaroxaban

Rivaroxaban is metabolized by CYP3A4 and P-glycoprotein and should be avoided in conjunction with P-glycoprotein and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir). Furthermore, the co-administration of

Table 7. Pharmacokinetic profile of DOACs

Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Inhibition factor II	Inhibition of factor X	Inhibition of factor X	Inhibition of factor X
Half-life	7-9 h after first dose, 12-14 h after multiple doses	9 h in young & adults, 12 h in elderly over 75 years	12 h	8-10 h
Time to reach plasma peak	0.5-2 h	2-4 h	3 h	1-2 h
Bioavailability	6.5 %	> 80%	> 50%	> 45%
Excretion	Kidney 80%	Kidney 66%, of which 33% unmodified biliary-fecal system 35%	Kidney 25%, biliary-fecal system 75%	Kidney 35%, biliary-fecal system 65%
Plasma protein binding	35%	90%	85%	55%
Substrate of cytochrome P3A4	No	Yes	Yes	Yes
Substrate of P-glycoprotein	Yes	Yes	Yes	Yes

PCC: prothrombin complex concentrate; FFP: fresh frozen plasma; FEIBA: Factor VIII inhibitor by-passing activity; raFVII: recombinant activated Factor VII; INR: international normalized ratio; ECT: ecarin clotting time; TT: thrombin time; aPTT: activated partial thromboplastin time; PT: prothrombin time.

P-glycoprotein and strong CYP3A4 inducers should be avoided (e.g., carbamazepin, phenytoin, phenobarbital, and rifampicin). Dose adjustment is generally required depending on renal impairment [62].

Apixaban

Apixaban is a substrate for P-gp and is metabolized mainly by CYP3A4/5, although other enzymes, particularly CYP1A2 and CYP2J2, play minor roles. Consequently, a potential for drug-drug interactions exists. The use of the drug is not recommended in those receiving simultaneous treatment with strong inhibitors of both CYP3A4 and P-gp (itraconazole, ketoconazole, and others). Rifampicin, phenytoin, carbamazepine, phenobarbital, and other strong CYP3A4 and P-gp inducers may also reduce plasma concentration of apixaban. Therefore, the concomitant use of apixaban and these drugs should be done with caution [63].

Edoxaban

Co-administration of ketoconazole, erythromycin, or cyclosporine increased total edoxaban exposure by 87%, 85% and 73%, respectively, and the peak concentration was increased by 89%, 68% and 74%, respectively, compared with edoxaban alone. The half-life did not change appreciably. Administration of dual inhibitors of P-gp and CYP3A4 increased edoxaban exposure by less than twofold. This effect appears to be primarily due to the inhibition of P-gp. The impact of CYP3A4 inhibition appears to be less pronounced, and its contribution to total clearance appears limited in healthy subjects [64].

Reversal of direct anticoagulation effect in case of bleeding

DOACs are associated with reduced risk of major bleeding, fatal bleeding, ICB, clinically relevant non-major bleeding, and no increased risk of gastrointestinal bleeding compared with warfarin [65]. Bleeding is a concern with DOACs because specific reversal agents for some of them are not yet approved for clinical use. Reversal of the anticoagulant effects may be needed for patients with major bleeding or patients at risk for bleeding, including patients undergoing emergent surgery.

In patients experiencing a DOAC-induced major bleeding event, withholding the anticoagulant and administering oral charcoal (if within two hours of DOAC ingestion) should be considered [66]. The use of prothrombin complex concentrate (PCC) at a dose of 25-50 U/kg (with an additional 25 U/kg if clinically needed), activated prothrombin complex concentrate (aPCC; factor eight inhibitor bypassing agent) at a dose of 50 U/kg (max 200 U/kg/day), or recombinant factor VIIa may be considered [49, 68-72]. There are limited available data supporting the efficacy of these non-specific drugs in the reversal of DOAC-induced bleeding events [49]. Hemodialysis may also be considered to reverse the anticoagulant effect for dabigatran-associated bleeding [67, 72]. The European Heart Rhythm Association (EHRA) has provided guidance for clinicians managing bleeding events in patients with nonvalvular AF treated with DOACs [49]. The approach for bleeding in patient using DOAC is described in **Figure 1**.

Currently, the only specific reversal agent approved for clinical use is idarucizumab, which is specific for dabigatran only. Other reversal agents are still under development, and data are mostly limited to in vitro studies, animal models, and trials with healthy volunteers. Idarucizumab is a monoclonal antibody fragment that binds and neutralizes dabigatran. In the RE-VERSE AD study, dabigatran-treated patients who had serious bleeding or who required an emergent procedure were treated with idarucizumab. The first 90 patients (51 with bleeding, 39 requiring a procedure) showed normalization of coagulation tests within minutes of infusion. Among patients requiring an emergent procedure, 92 percent were judged to have normal surgical hemostasis. Idarucizumab was well tolerated. One patient had a thrombotic event within 72 hours of administration [42].

Andexanet alpha is recombinant modified human factor Xa decoy protein that is catalytically inactive but retains the ability to bind factor Xa inhibitors. In the ANNEXA-A and ANNEXA-R trials [44], healthy volunteers taking apixaban and rivaroxaban were randomly received andexanet or a placebo. Rapid and profound reduction in anti-Xa activity was observed within minutes of a bolus administration of andexanet. Anongoing phase IIIb-IV study will provide data

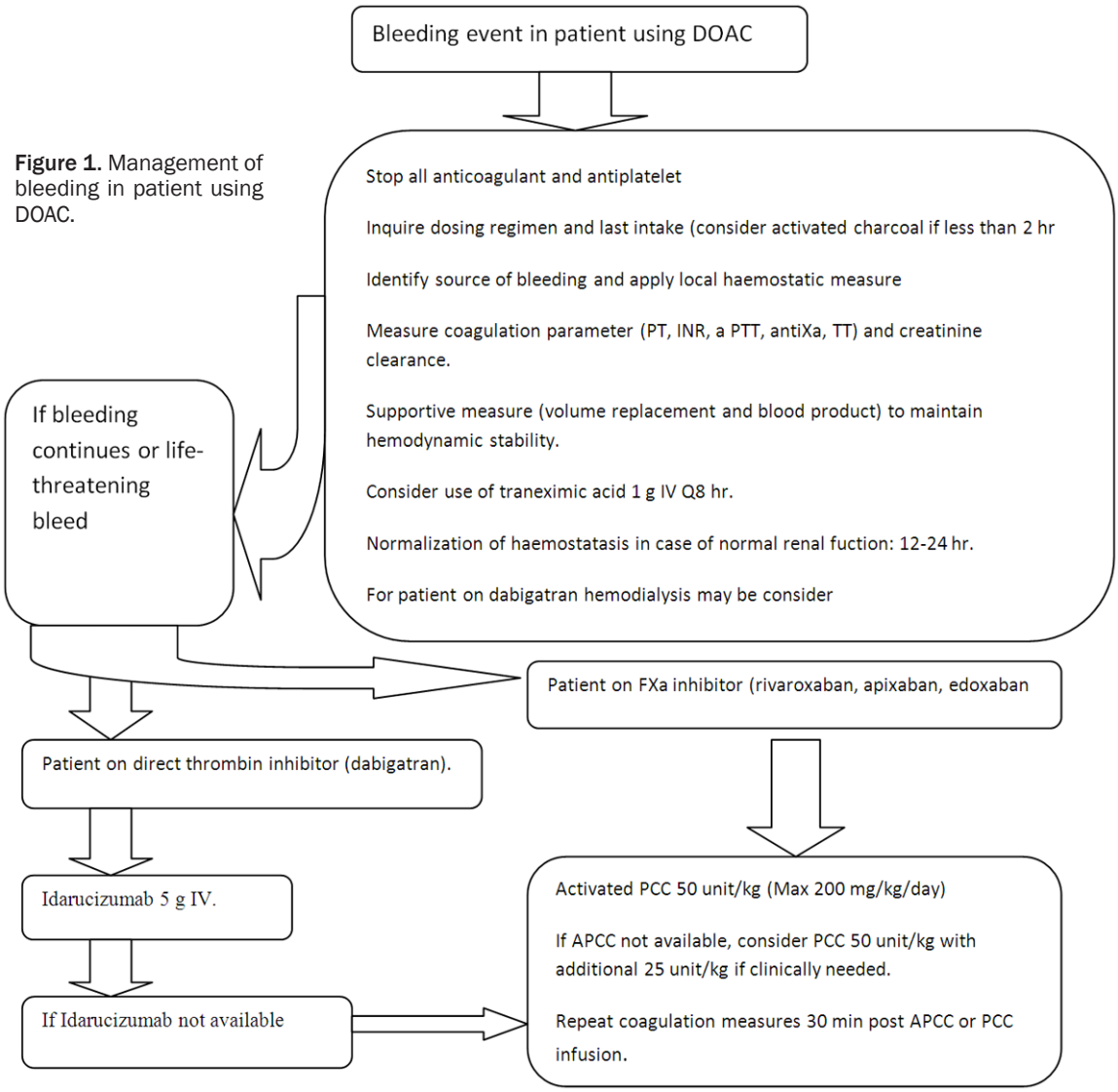

Figure 1. Management of bleeding in patient using DOAC.

on the efficacy and safety of andexanet in patients taking a factor Xa inhibitor who have serious bleeding [44].

Ciraparantag is a compound that binds directly to several anticoagulants, such as unfractionated heparin, LMWH, and DOACs (anti-FXa and anti-FIIa), thus removing them or preventing them from binding to their targets [43]. Ciraparantag could be considered as a potential universal antidote for several different classes of anticoagulant drugs. However, a phase III trial is still needed.

Conclusion

DOACs represent a major development in treating venous thromboembolic diseases and AF. Their main advantages include no need for laboratory monitoring, less drug and food interaction, and lower risk of ICB. Their short half-life is an important advantage, particularly in preoperative management and helps to avoid bridging with parenteral anticoagulation. However, it is a concern in poorly compliant patients. Appropriate doses of all DOACs for each indication are essential for safe and efficient outcomes.

Disclosure of conflict of interest

None.

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