ORIGINAL ARTICLE

The Growing Potential of Direct Oral Anticoagulants in Hypercoagulable States

Julianne M Fallon[1], Surabhi Palkimas[1], Paul R Kunk[2], Hillary S Maitland[2]

[1]Department of Pharmacy, University of Virginia Health System, Virginia, USA, [2]Department of Medicine, University of Virginia Health System, Virginia, USA

ABSTRACT

The direct oral anticoagulants are being increasingly used as alternatives to warfarin in patients with venous thromboembolism and atrial fibrillation. The role of these agents in Hypercoagulable states, such as heparin induced thrombocytopenia and antiphospholipid syndrome has not yet been proven in randomized controlled trials. In addition, the lack of clinical experience with DOACs in these Hypercoagulable states raises questions on the safety and efficacy of these agents for treatment. However, a growing multitude of clinical reports provides some insight into the utility of DOACs in Hypercoagulable disease states. A keyword search utilizing PubMed was performed to identify reports of DOAC use in HIT and APS. Direct oral anticoagulants possess their own unique advantages and limitations when compared to standard therapy for these disease states. This review was conducted to compile the current evidence for the direct oral anticoagulants in heparin induced thrombocytopenia and antiphospholipid syndrome along with the potential advantages and disadvantages of these medications compared to the current standard treatment.

Key words: Apixaban, dabigatran, rivaroxaban, direct oral anticoagulants, direct thrombin inhibitor, factor Xa inhibitor, antiphospholipidsyndrome, heparin-induced thrombocytopenia, hypercoagulablestate

Correspondence:
Julianne M Fallon,
Department of Pharmacy, University of Virginia Health System, Charlottesville, Virginia, USA.
E-mail: jfallon@virginia.edu

Access this article online
Website: www.jbclinpharm.org
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INTRODUCTION

Patients with Hypercoagulable states such as antiphospholipid syndrome (APS), heparin induced thrombocytopenia (HIT), factor V Leiden (FVL), and prothrombin deficiency require therapeutic anticoagulation due to the high risk of recurrent thromboembolism. While some patients require anticoagulation for a defined duration, many patients require indefinite anticoagulation. To date, evidence supports use of parenteral anticoagulants or vitamin K antagonists (VKA), such as warfarin for the treatment of thromboembolism in patients with APS or FVL. Patients with HIT have even more limited options.

There is a striking need for safe, reliable, effective, and easy to administer alternatives to warfarin for patients who may require short or long-term anticoagulation. The successful introduction of the direct oral anticoagulants (DOACs), apixaban, rivaroxaban, dabigatran, and edoxaban, for the treatment and prevention of venous thromboembolism (VTE) has triggered an interest in utilizing these agents in other settings. DOACs have reliable pharmacokinetic characteristics, limited interactions, and do not require routine monitoring. The landmark clinical trials of rivaroxaban and apixaban (EINSTEIN and AMPLIFY) established their role as alternatives to the combination of low molecular weight heparin (LMWH) and warfarin in the treatment of acute VTE, but included only a small number of patients with unspecified known thrombophilia (6.2% vs 2.8%, respectively).[1,2] The trials for dabigatran in the treatment of VTE (RE-COVER/RE-COVER II and RE-MEDY) also included patients with known thrombophilia (8% and 18%, respectively), including APS (1.7% and 2.7%, respectively).[3-5] A post-hoc analysis of pooled data from RE-COVER/RE-COVER II and RE-MEDY showed no significant difference in efficacy or safety of dabigatran in the presence of thrombophilia, though there was a lack of statistical power.[6] The Hokusai-VTE trial of edoxaban for the treatment of symptomatic VTE did not report any patients with known thrombophilia and excluded patients with an indication for anticoagulation other than deep vein thrombosis (DVT) and/or pulmonary embolism (PE).[7] These data limitations translate into a poor characterization of the safety and efficacy of DOACs in Hypercoagulable states.

Past and present trials studying DOACs in thrombophilic patients have encountered significant challenges in enrollment given the low prevalence of many hypercoagulable states.[8] Current evidence for the use of DOACs in Hypercoagulable states relies heavily on clinical experiences described in case reports, case series, and limited prospective trials. The clinical significance of these will be discussed in this review.

METHODS

A keyword search utilizing PubMed was performed to identify reports of DOAC use in HIT and APS. Keywords included DOACs, apixaban, rivaroxaban, edoxaban, dabigatran, APS, and HIT. All identified studies in English that included a report of the use of a DOAC in the treatment of patients with HIT or APS were included in this review.

Heparin induced thrombocytopenia

Background

Use of heparin containing products such as unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) places patients at risk for the immune-mediated adverse event known as HIT. Though this condition only occurs in approximately 1 to 5% of patients receiving UFH and 0.1 to 1% of patients receiving LMWH, HIT carries a significant risk of mortality and precludes the use of any heparin-containing product in future treatment.[9-11] In HIT or patients with a history of HIT, heparin exposure results in formation of immune complexes leading to platelet depletion through platelet activation, aggregation, and formation of procoagulant platelet-derived microparticles.[12] These procoagulant mic roparticles activate the coagulation cascade at Factor VII, leading to subsequent activation of Factor Xa (FXa) and thrombin generation.[11,12] Activation of the coagulation cascade places

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patients at risk for both arterial and venous thrombotic events. The hallmark signs of HIT are thrombocytopenia (platelets <150,000/μL or a 50% reduction) and formation of anti-platelet factor 4-heparin (PF4-heparin) antibodies. When HIT is suspected, the 4T score is used to determine the pretest probability of a patient having HIT by taking into account the severity and timing of thrombocytopenia, thrombosis, and other potential causes of thrombocytopenia.[13,14] A low 4T score is associated with a high-negative predictive value ruling out HIT, whereas a patient with an intermediate or high score should undergo therapeutic intervention and heparin antibody testing.

The American College of Chest Physicians recommends acute treatment of HIT with a non-heparin parenteral anticoagulant (e.g., fondaparinux, argatroban, or bivalirudin) followed by a vitamin K antagonist (VKA), such as warfarin, once the platelet count starts to recover.[10] Transition to warfarin therapy should include at least 5 days of a parenteral non-heparin anticoagulant to prevent complications associated with a fall in protein C leading to skin necrosis or venous limb gangrene.[10] HIT is considered a transient risk factor for thrombosis and treatment duration of at least 3 months is recommended, though this may vary based on patient-specific risk factors.[10] The current limited options for treatment combined with the inconvenience of parenteral agents and warfarin, lead to increased interest in using DOACs for HIT. These agents are structurally dissimilar to heparin and in-vitro studies have shown that rivaroxaban, dabigatran, and apixaban do not interact with PF4, anti-PF4-heparin antibodies, or cause platelet activation mediated by anti-PF4/heparin.[15,16]

Clinical use

A summary of the clinical reports of DOACs in HIT is shown in Table 1. Patients were diagnosed based on clinical suspicion of HIT or laboratory confirmation of HIT using an assay to assess presence of anti-PF4 antibodies, positive SRA, platelet aggregation, or heparin-induced platelet activation (HIPA). Clinical suspicion of HIT was usually based on presence of profound thrombocytopenia after heparin exposure with or without a thrombotic complication.

Several case reports have described the safe and effective use of dabigatran, rivaroxaban, and apixaban as alternatives to VKA in HIT.[9,17-21] These reports have been echoed by larger case series. Kunk *et al.* performed a retrospective analysis of 12 adult patients with definite HIT and acute thrombocytopenia who were initially treated with argatroban or bivalirudin until platelets recovered to at least 50-150,000/μL.[22] They were then transitioned to either apixaban (n=10) or rivaroxaban (n=2) for a treatment duration ranging from 1 to 6 months.[22] Three patients were anticoagulated with a DOAC for longer than 13 months for reasons other than HIT, such as PE or malignancy. No recurrent thrombotic events and two episodes of major bleeding were reported in the 12 patients. The first bleeding event was gastrointestinal bleed from known gastric varices while on concomitant therapy with clopidogrel.[22] The second bleeding event was hemoptysis likely secondary locally advanced to squamous cell lung cancer.[22]

Sharifi *et al.* reported a retrospective analysis of 22 patients with suspicion

Table 1: Reports of DOAC Utilization in Patients with HIT

Reference	Study Type	N	Indication for heparin product	HIT Dx	DOAC Treatment Regimen	Treatment duration	Outcomes
Linkins *et al.*[8]	Prospective cohort study	12	Cardiovascular surgery (n=4) DVT prophylaxis (n=5) VTE treatment (n=2) CVA prophylaxis (n=1)	SRA+ (n=12)	Rivaroxaban 15 mg BID until platelet recovery, then 20 mg daily	NR	Events reported after 30 days of follow-up: Recurrent VTE (n=1) BKA (n=1)
Hantson *et al.*[9]	Case report	1	DVT prophylaxis	Clinical diagnosis	Rivaroxaban 15 mg BID for 21 days, then 20 mg daily	NR	No recurrent VTE or bleeding events reported after two months of follow-up
Ng *et al.*[17]	Case series	3	Hemodialysis (n=1) Post-embolectomy for critical limb ischemia (n=1) PE and DVT (n=1)	Anti-PF4 and SRA + (n=1) Anti-PF4 + (n=2)	Rivaroxaban: 10 mg daily (n=1) 15 mg BID x 3 weeks, then 20 mg daily (n=1) 15 mg BID (n=1)	22 days* (n=1) 15 months (n=1) 10 weeks (n=1)	No recurrent VTE or bleeding events reported after 6 months (n=1), 15 months (n=1), and 4 months (n=1) of follow-up
Abouchakra *et al.*[18]	Case report	1	Cardiovascular surgery	Anti-PF4 +	Rivaroxaban 20 mg BID	NR	No recurrent bleeding or thrombotic events reported after 1 month of follow-up
Larsen *et al.*[19]	Case report	1	PE	Anti-PF4 and HIPA +	Apixaban 5 mg BID	6 months	No recurrent VTE or bleeding events reported after 3.5 months of follow-up
Mirdamadi *et al.*[20]	Case report	1	Orthopedic DVT prophylaxis	Clinical diagnosis	Dabigatran 110 mg BID	NR (at least 10 days)	No recurrent VTE or bleeding events reported
Sartori *et al.*[21]	Case report	1	DVT treatment	ELISA and platelet aggregation test +	Rivaroxaban 20 mg daily	3 months	No recurrent VTE or bleeding events reported after three months of follow-up

Kunk *et al.*[22]	Retrospective analysis	12	Cardiovascular surgery (n=3); VTE prophylaxis (n=3); VTE treatment (n=5) Afib (n=1)	SRA+ (n=12)	Apixaban (n=10) Rivaroxaban (n=2)	1 to 2 months (n=5) 3 to 6 months (n=4)	No recurrent VTE events reported Serious bleeding (n=2; GI and hemoptysis)
Sharifi *et al.*[23]	Case series**	22	VTE prophylaxis (n=6); VTE suspicion (n=5); VTE treatment (n=4); Afib (n=3); Cardiovascular surgery (n=2); Other surgery (n=2)	ELISA/SRA + (n=20) Clinical dx (n=2)	Dabigatran 150 mg BID (n=6) Rivaroxaban 20 mg daily (n=11) Apixaban 5 mg BID (n=5)	>12 months (n=3) 3 to 6 months (n=12) Indefinite (n=10)	No recurrent VTE or bleeding events reported after a mean 19 months of follow-up

N=total number of HIT positive patients; CABG: coronary artery bypass graft; PE: pulmonary embolism; DVT: Deep vein thrombosis; Afib: atrial fibrillation; VTE: venous thromboembolism; GI: gastrointestinal; NR: not reported; Platelet recovery: ≥ 150 x 10^9/L (or baseline) * Then switched to warfarin to complete 6 month course due to severe renal impairment; BKA: below-knee amputation **Retrospective cohort followed prospectively HIPA: heparin-induced platelet activation; BID: twice per da

of or definite HIT who received argatroban (0.3-0.5 mcg/kg/min) dose adjusted to maintain an activated thromboplastin time (aPTT) between 50-90 seconds for approximately 32 hours.[23] Dabigatran, apixaban, or rivaroxaban were started two hours after discontinuation of argatroban and continued for 3 to 6 months.[23] At the end of 6 months, 18 patients were still receiving a DOAC and 10 of these patients were recommended to continue an anticoagulant indefinitely.[23] No recurrent VTE, limb loss, death related to thrombosis, or bleeding events were reported after an average 19 months of follow-up.[23] However, at the end of the follow-up time frame 6 deaths had occurred due to non-thrombotic causes, such as cancer, heart failure, systemic sclerosis, or renal failure.[23] It remains unclear if all these patients truly had HIT or simply the suspicion of HIT as two patients did not receive laboratory testing to confirm HIT.

In a Canadian prospective multi-center study, Linkins *et al.* treated twelve HIT positive patients with therapeutic rivaroxaban.[8] Nine of the ten patients with thrombocytopenia recovered their platelet counts. There were no reports of major bleeding, however one patient developed recurrent VTE while on rivaroxaban and there was one episode of arterial thrombosis requiring limb amputation. Unfortunately, this study was discontinued in the setting of low enrollment but the available data suggests that rivaroxaban in safe and effective in the treatment of HIT.

These reports of utilizing DOACs for the treatment of acute HIT indicate that apixaban, rivaroxaban, and dabigatran may offer an attractive alternative to warfarin. At the time of this publication there have been no reports of the use of edoxaban in the treatment of HIT. The safety and efficacy of these agents in the treatment of HIT appear to be supported by the low rate of reported thrombosis and limited bleeding events in these studies. Further evidence is required to provide definitive guidance concerning dosage, use of non-heparin parenteral anticoagulation prior to transitioning to DOAC, and optimal duration of anticoagulation.

Anti-phospholipid syndrome

Background

APS is a systemic autoimmune disorder characterized by venous or arterial thromboembolism and pregnancy morbidity. It may occur as a primary condition or secondary to another autoimmune disease, such as systemic lupus erythematosus (SLE), and is more commonly diagnosed in females. The hallmark sign of APS is the presence of antiphospholipid (aPL) antibodies (lupus anticoagulant (LA), anticardiolipin (aCL), and anti-β2-glycoprotein-1). The classification criteria traditionally used is the Sydney criteria, which considers a definite diagnosis of APS if at least one of the antiphospholipid antibodies is present on two successive occasions at least 12 weeks apart plus the presence of vascular thrombosis or pregnancy morbidity.[24] While treated, the syndrome carries a significant mortality rate, found to be as high as 9.3% over 10 years in a prospective multi-center study of 1,000 patients with APS.[25] The most common cause of death in patients with APS is thrombotic events, such as myocardial infarction, strokes, and PE.[25]

Treatment of thromboembolism associated with APS is similar to the initial treatment for VTE or PE. The 14th International Congress on Antiphospholipid Antibodies Task Force (ICAATF) recommends standard treatment with UFH or LMWH with transition to warfarin for long-term therapy.[26] Anticoagulation should generally continue indefinitely in these patients due to the high rate of recurrence of thrombosis, particularly during the first 6 months after stopping anticoagulation.[26-28] Factors that increase the risk for recurrent thrombosis include prior arterial thrombosis, autoimmune disease, and triple aPL positivity.[28,29] Furthermore, triple positive APS patients have been observed to have a recurrent thrombosis event rate of 12.2% per year even while on an anticoagulant.[30]

Impediments to warfarin use specific to APS include a variable response of thromboplastin reagents due to aPL, particularly LA, resulting in uncertain elevations of prothrombin time (PT) and international

normalized ratio (INR).[26] The goal INR for patients with APS is generally considered to be 2 to 3, as this maximizes efficacy without increasing the risk of bleeding. Prospective controlled trials of APS patients randomized to receive warfarin at either high-intensity (INR goal 3 to 4) or moderate-intensity (INR goal 2 to 3) have reported lower incidence of recurrent VTE and major or minor bleeding associated with moderate-intensity therapy.[31,32] However, some clinicians consider a higher therapeutic goal INR of 3 to 4 when APS patients experience recurrent thromboembolism while on warfarin or have a history of arterial thrombosis.[33] This approach is supported by historical observational studies that suggested the use of high-intensity warfarin therapy was associated with decreased risk of recurrent thrombosis compared to lower intensity.[27,34]

As an autoimmune disorder, the dysregulation of complement systems promotes the pro-coagulant state in APS.[35,36] Factor Xa is involved in the process of complement activation and theoretically the use of Factor Xa inhibitors could decrease complement activation compared to treatment with warfarin.[37] Decreased complement activation with rivaroxaban compared to warfarin was shown in a translational research study of patients enrolled in the Rivaroxaban in Antiphospholipid Syndrome (RAPS) study.[37] This finding suggests a potential advantage to using DOACs over warfarin in APS that will need to be confirmed with clinical outcomes data.

Clinical use

The safety and efficacy of DOACs in APS has not been established in randomized controlled trials and clinical experience using DOACs in APS patients has been limited to case series. Clinical reports for the use of DOACs in APS are summarized in Table 2. The most common rationale for the use of a DOAC in these patients was labile INR.

None of the case series included in this review reported major bleeding. Minor bleeding, such as worsening menorrhagia or rectal bleeding, was reported in three patients.[33,38] Six case series reported complications ranging from recurrent arterial or venous thrombotic

Table 2: Reports of DOAC Utilization in Patients with APS

Reference	N	Reason for switch to DOAC	DOAC Treatment Regimen	Triple Positive Patients	Outcomes
Kunk *et al.*[22]	11	Recurrent thrombosis with previous therapy (n=6); Labile INR (n=2); First line (n=2) Injection difficulties (n=1);	Apixaban dose NR (n=6) Rivaroxaban dose NR (n=5)	n=4	No serious bleeding or thrombotic complications reported
Signorelli *et al.*[29]	8	Labile INR (n=2) Patient preference (n=2) NR (n=4)	Rivaroxaban 20 mg once daily (n=2); dose NR (n=6)	n=3	Stroke (n=2); DVT (n=2); Neurological symptoms (n=2); Acute MI (n=1); Arterial ischemia (n=1)
Savino *et al.*[33]	35	Labile INR (n=29); Sub-therapeutic INR (n=6)	Rivaroxaban 20 mg daily (n=35)	NR	No recurrent VTE or major bleeding was reported; Worsening menorrhagia (n=2)
Noel *et al.*[38]	26	INR lability (n=16); Physician's choice (n=6); Bleeding (n=1); Therapeutic simplification (n=1); Associated Afib (n=1); Recurrent DVT, poor adherence to monitoring, INR lability (n=1)	Dabigatran 150 mg BID (n=11) Rivaroxaban: 20 mg daily (n=13); 15 mg daily (n=1); 15 mg BID (n=1)	n=7	Microthrombotic recurrence (n=1) Neurological symptoms (n=1) Minor bleeding: - Hypermenorrhea (n=1) - Rectal bleeding (n=1)
Win *et al.*[39]	3	Recurrent DVT, TIA, and stroke (n=1); Labile INR (n=2)	Rivaroxaban 20 mg daily (n=2) Dabigatran 150 mg BID (n=1)	NR	Superficial venous thrombosis (n=2); Neurological symptoms (n=1)
Schaefer *et al.*[40]	3	Bleeding complications & subtherapeutic INR (n=1); Atraumatic subdural hematoma (n=1); Inconvenience of INR monitoring (n=1)	Dabigatran 150 mg daily (n=1) Rivaroxaban 20 mg daily (n=2)	n=2	Recurrent thromboembolism (n=3): - Thrombotic endocarditis (n=1) - Recurrent strokes (n=1) - Portal vein, splenic, and mesenteric thrombus (n=1)
Son *et al.*[41]	12	Labile INR or difficulty monitoring (n=12)	Rivaroxaban 20 mg daily (n=12)	n=5	DVT (n=2)
Haladyj *et al.*[42]	23	INR lability/ therapeutic simplification (n=7); Patient preference (n=8); Recurrent thrombosis (n=6); PE (n=2)	Rivaroxaban dose NR (n=23)	n=4	PE (n=1) No reports of major or minor bleeding
Betancur *et al.*[43]	8	Labile INR & recurrence despite therapy (n=4); Labile INR (n= 2); Recurrence despite therapy (n=1); Bleeding (n=1)	Rivaroxaban: 20 mg daily (n=6); dose NR (n=1) Apixaban 5 mg BID (n=1)	n=1	No recurrent thrombosis or bleeding complications reported

ASA: aspirin; CS: corticosteroids; AFib: atrial fibrillation; PE: pulmonary embolism; DVT: deep vein thrombosis; INR: International normalized ratio; CrCl: creatinine clearance; CKD: chronic kidney disease; NR: not reported; aPL: antiphospholipid antibody; MI: myocardial infarction; TIA: transient ischemic attack; BID: twice per day

events to neurological symptoms. Out of the 129 APS patients receiving DOAC (rivaroxaban, dabigatran, or apixaban) adverse events included recurrent arterial or venous thrombotic events (n=15;11.6%) and neurological symptoms (n=4; 3.1%). The majority of the reports of failure of DOACs to prevent recurrent thrombosis were made by Schaefer *et al*., Win *et al*. and Signorelli *et al*.[29,39,40] They reported failure of dabigatran (n=2) or rivaroxaban (n=12) to prevent recurrent thrombosis in eleven out of fourteen patients.[26,31,32] Some of these patients were at high-risk of recurrent thrombosis with risk factors including multiple prior venous or arterial thrombosis, autoimmune disease, and triple antibody positivity.[29,39,40] Additionally, Schaefer *et al*. reported an individual with poor renal function who received dabigatran 150 mg once/day which may have lead to treatment failure.[40] These results suggest that certain patient populations, such as those at high risk for recurrent thrombosis and those with poor renal function, may have a higher risk of treatment failure with DOACs.

To contrast this seemingly high rate of treatment failure, Haladyj *et al.* and Son *et al*. saw PE or DVT in only three patients out of the 35 patients they followed.[41,42] Similarly, Noel *et al.* reported recurrent migraine and microthrombotic recurrence that lead to DOAC discontinuation, but no other recurrent thrombotic events in 26 APS patients after 19 months (range 8 to 29 months) of follow-up.[38] Several other series have reported an absence of thrombotic events in their APS patients on DOACs. Kunk *et al*. reported 11 patients with confirmed APS and normal renal function receiving either apixaban (n=6) or rivaroxaban (n=5).[22] Of these patients, 4 were reported to be triple positive based on two positive serum IgG antiphospholipid antibodies and a positive lupus anticoagulant.[22] There were no reported bleeding or thrombotic complications during the average 11 months (range 5-39 months) of follow-up.[22] Savino *et al*. reported 35 patients fulfilling APS criteria who were switched from VKA (goal INR 2 to 3) to rivaroxaban due to patients' INR time in therapeutic range being 65% or lower.[33] There were no reported thrombotic events or serious side effects after a median follow up time of 10 months (range 6-24 months).[33] Betancur *et al*. reported 8 patients with confirmed APS who were switched from VKA (goal INR 2 to 3) to rivaroxaban or apixaban.[43] Five of the patients were switched to DOAC due to recurrent thrombosis on warfarin treatment.[43] In the average 19 months (range 2 to 36 months) of follow up there were no reports of recurrent thrombosis.[43]

While there have been some reports of treatment failure, reviewing all of these reports suggests the potential safety and efficacy of DOACs in APS. The risk of recurrence of thrombotic events in APS patients on DOACs appears similar to that seen with warfarin. These reports suggest that DOACs may be considered for patients who have difficulty maintaining a therapeutic INR or those with a known VKA allergy or intolerance. Similar to the clinical reports for HIT, the low number of patients reported and the risk of publication bias prevents determinative conclusions from the current published evidence in the absence of randomized controlled prospective clinical trials. There are three currently ongoing clinical trials that will be assessing the safety and efficacy of apixaban and rivaroxaban in APS. These include apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome (ASTRO-APS), rivaroxaban in antiphospholipid syndrome (RAPS), and trial on rivaroxaban in high risk patients (TRAPS).[44-46]

Advantages of DOACs

DOACs are promising compared to warfarin therapy, as these agents are easy to administer, have fewer drug interactions, offer reliable inter-individual efficacy, standardized dosing, and do not require routine monitoring. In addition, these agents have been found to be just as effective as warfarin for the treatment of VTE with similar rates of bleeding. The DOACs do not alter the body's natural anticoagulant proteins C or S, eliminating the need for a bridge with a parenteral anticoagulant. The DOACs are structurally unique compared to heparin, offering a promising anticoagulant alternative for patients with HIT.

Limitations of DOACs

DOACs have fewer considerations when starting therapy in terms of worrying about drug-drug or drug-food interactions, frequent monitoring, or route of administration compared to warfarin and parenteral agents. However, there are several factors should be considered prior to starting a patient on a DOAC. These factors include cost, need for strict adherence, lack of established monitoring parameters, reversibility, and less clinical experience in HIT and APS.

Cost and adherence

In terms of cost, these agents are more expensive than warfarin. To offset this, manufacturers provide discount cards that allow patients to receive the first month free and lower co-pay on refills for patients with commercial insurance. While patients with government-sponsored insurance, such as Medicare and Medicaid are unable to take advantage of manufacturer sponsored discounts, if they demonstrate financial need they can enroll in patient assistance programs. Ensuring patient access to the prescribed DOAC through prior authorization or providing a discount cards is of paramount importance to treatment success. Additionally, medical cost differences between warfarin and the DOACs in non-valvular atrial fibrillation and VTE favors the use of DOACs.[47] Estimated medical cost savings based on reported clinical event rates in phase 3 trials are -$495, -$340, -$204, and -$140 per patient for apixaban, edoxaban, dabigatran, and rivaroxaban, respectively.[47] The projected cost savings were primarily driven by the decreased incidence of major bleeding.[47] Though this data was projected for patients with atrial fibrillation or VTE, this data may hold true in other patient populations as well.

The DOACs all possess much shorter half-lives than warfarin, meaning that missing a single dose or two will put the patient at increased risk for thromboembolism. Ensuring that a patient being started on a DOAC will be adherent to the treatment regimen is key to successful treatment. Decreased adherence to DOACs has been correlated to increased mortality and stroke.[48] Adherence to DOACs, such as dabigatran, has been shown to improve as a result of pharmacist led education and monitoring.[49] Pharmacist led DOAC patient education offers a promising option to increase education touch points during transitions of care.[49,50]

Monitoring

Interference in monitoring of aPL testing has been reported with rivaroxaban. Specifically, false positivity with Russell's viper venom time (RVVT) for detecting LA has been reported with rivaroxaban.[51] It is unclear if this interaction is present for the other factor Xa inhibitors. Options to overcome this interaction include discontinuing factor Xa inhibitor for 24 hours prior to performing the test or utilizing another aPL test, such as the Taipan snake venom time test.[33]

Difficulty of monitoring therapeutic anticoagulation with DOACs presents a problem for patients in extreme weight classes (over 120 kg or below 60 kg), those facing critical illness, recurrent thrombus, or bleeding events. While monitoring for DOAC therapeutic effect is not routine, methods such as mass spectrometry or calibrated anti-Xa levels have been used in patients weighing over 120 kg and may be useful in other populations.[52]

Reversibility

Only idarucizumab (Praxbind; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) has been approved for the reversal of dabigatran in the setting of emergent surgery/procedure or life-threatening and uncontrolled bleeding.[53] Idarucizumab is a monoclonal antibody fragment that binds dabigatran with an affinity 350 times that of thrombin, leading to rapid reversal of anticoagulant effect within minutes.[54] No current FDA approved reversal agent exists for apixaban, rivaroxaban, or edoxaban, though two potential candidates are currently undergoing clinical trials.

Emerging options for reversal include andexanet alfa and ciraparantag. Andexanet alfa is a decoy FXa decoy molecule currently undergoing phase 3 clinical trials that has been shown to provide rapid and sustained reversal of FXa activity.[55] Phase 2 clinical trials are currently underway for ciraparantag, a synthetic, water-soluble, cationic molecule designed to be a broad spectrum anticoagulant reversal agent that binds through charge-charge interactions specifically to anticoagulants including, UFH, LMWH, apixaban, rivaroxaban, edoxaban, and dabigatran.[56] Until these investigative reversal agents are approved, prothrombin complex concentrate (PCC), or activated prothrombin complex concentrate (aPCC) can be considered as hemostatic agents for patients taking rivaroxaban or apixaban.[57,58]

Dosing

In the absence of randomized trials, the appropriate DOAC dosing in HIT and APS is unclear. Tables 1 and 2 summarize the treatment regimen chosen for patients with HIT and APS. Most clinicians selected a dose equivalent to the VTE treatment dose with or without a loading dose dependent on the risk of thromboembolism. The dosing of DOACs in their respective VTE approval trials used a comparator group of warfarin dosed to an INR of 2 to 3. While an INR goal of 2 to 3 is commonly accepted, in patients with APS a higher goal of 3 to 4 is sometimes used. In this case, there is insufficient evidence to compare the efficacy of regular DOAC treatment dosing to warfarin dosed to a higher INR goal.

Renal dysfunction poses another challenge in DOAC dosing, particularly for patients on the threshold of lowered dosing. It is unclear whether patients receiving dose-adjusted anticoagulation are being under anticoagulated and whether choosing to not dose-adjust would lead to over anticoagulation. In addition, all of the DOACs with the exception of apixaban, are recommended to be dose adjusted based on creatinine clearance and may not be ideal for patients with poor renal function. The renal function of all of the patients in the reports in Tables 1 and 2 and whether the regimen was dose adjusted is not known. The results of the ASTRO-APS, RAPS, and TRAPS trials may provide some guidance on dosing.

Limited evidence

While the initial evidence for the use of DOACs in Hypercoagulable states such as HIT and APS appears positive, there remains a need for further evidence of the safety and efficacy of these agents. The evidence to date has been with a small number of retrospective studies and case series employing small sample sizes. These reports are subject to publication bias, as authors are more likely to report negative outcomes. These studies have only reported the use of apixaban, rivaroxaban, and dabigatran, with no reports of edoxaban. Due to the low prevalence of Hypercoagulable states, it is difficult to perform high-quality, well-powered clinical trials to provide sufficient comparison between anticoagulants. Further research and clinical experience will be required before these agents can be used with full confidence.

CONCLUSION

DOACs offer a promising alternative to traditional parenteral anticoagulants and VKA therapy for Hypercoagulable states. There is growing evidence that these agents may offer a safe and effective alternative to warfarin in the treatment of patients with HIT and APS. This may particularly be true for patients who cannot tolerate warfarin due to variable INRs or convenience and those who experience recurrent VTE while on warfarin therapy (i.e., warfarin failure). The limitations of therapy include cost, need for strict adherence, interference with aPL monitoring, lack of reliable reversal agents, inconsistent dosing in case reports, and sparse evidence in the thrombophilic population. For now, it appears that patients with high risk of recurrent thrombosis, such as triple positive APS, may be at higher risk for treatment failure with DOACs. While more experience is needed with these agents they do offer many advantages over warfarin, including lack of dietary restrictions, no need for routine drug monitoring, fewer drug-drug, and drug-food interactions. The ongoing ASTRO-APS, RAPS, and TRAPS trials should provide further guidance on the use of DOACs in APS.

Contribution details

All authors participated in manuscript editing and review. JF performed literature search and manuscript preparation. SP and PK contributed to the concept leading to the writing of this review. JF and SP are guarantors of the article.

Conflict of interest

All authors, none.

Abbreviations

aCL: Anticardiolipin; aPCC: Activated prothrombin complex concentrate; aPL: Antiphospholipid antibodies; APS: Antiphospholipid syndrome; APTT: Activated thromboplastin time; CI: Confidence interval; DOACs: Direct oral anticoagulants; DVT: Deep vein thrombosis; FVL: Factor V Leiden; FXa: Factor Xa; HIPA: Heparin-induced platelet activation; HIT: Heparin induced thrombocytopenia; ICAATF: International Congress on Antiphospholipid Antibodies Task Force; INR: International normalized ratio; LA: Lupus anticoagulant; LMWH: Low molecular weight heparin; PCC: Prothrombin complex concentrate; PE: Pulmonary embolism; PF4-heparin: anti-platelet factor 4-heparin; PT: Prothrombin time; RR: Relative risk; RVVT: Russell's viper venom time; SLE: Systemic lupus erythematosus; UFH: Unfractionated heparin; VTE: Venous thromboembolism; VKA: Vitamin K antagonists.

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