Direct oral anticoagulant use in special populations

Michelle C. Lamarche[a], *Eman Alrajhi*[b] *and Philip S. Wells*[c]

Purpose of review
The pivotal phase III trials demonstrating efficacy and safety of direct oral anticoagulants (DOACs) in the treatment of venous thromboembolism (VTE) or nonvalvular atrial fibrillation (NVAF) excluded patients with important and common comorbidities, including obesity, advanced chronic kidney disease, cirrhosis, cancer and antiphospholipid antibody syndrome. Despite the lack of large prospective randomized control trials in these patient populations, the use of DOACs has led to a wealth of efficacy and safety data within these groups.

Recent findings
Retrospective studies, meta-analyses, national databases and pharmacokinetic data have shed light on the efficacy and safety of DOACs in these patient populations. Although DOACs should be avoided in those with high-risk triple positive antiphospholipid antibody syndrome, advanced cirrhosis, advanced kidney disease and intact gastrointestinal cancers, and used with caution in genitourinary cancers, their use extends beyond the inclusion criteria of the initial randomized control trials.

Summary
DOACs have revolutionized anticoagulant management and have become the cornerstone for VTE treatment and stroke prevention in NVAF. The decision to use DOACs must be individualized. Patient preference, underlying comorbidities and informed consent must always be considered when selecting the most appropriate anticoagulant.

Keywords
antiphospholipid antibody syndrome, cancer, chronic kidney disease, cirrhosis, direct oral anticoagulants, obesity

INTRODUCTION

Direct oral anticoagulants (DOACs) have been approved for multiple indications, including treatment of nonvalvular atrial fibrillation/flutter (NVAF) and venous thromboembolism (VTE). Due to their ease of use (oral and no need for monitoring) and fewer drug-food interactions, DOACs have largely replaced vitamin K antagonists (VKAs), most notably warfarin, and low molecular weight heparin (LMWH) as first-line treatment. The initial phase III NVAF and VTE randomized control trials (RCTs) comparing specific DOACs with warfarin excluded many patients, notably those with obesity, cirrhosis, chronic kidney disease (CKD), cancer and antiphospholipid antibody syndrome (APS). We performed a comprehensive, algorithm-based literature review to evaluate DOAC use in these specific populations to provide our recommendations.

OBESITY

The 2016 International Society of Thrombosis and Haemostasis (ISTH) guidance statement recommended against use of DOACs for VTE or NVAF in patients with weight more than 120 kg or BMI more than 40 kg/m^2 (herein defined as morbid obesity) due to limited evidence since the initial RCTs of DOACs excluded these patients. If used, they suggested drug-specific serum monitoring [1,2]. However, the following year a meta-analysis assessing patients with weight above the predefined obesity thresholds, from these studies, found no difference in rate of VTE recurrence, stroke or systemic embolism, nor major bleeding when comparing DOACs to

[a]Department of Medicine, University of Alberta, Clinical Sciences Building, Edmonton, Alberta, [b]Department of Medicine, Division of Hematology, Ottawa Research Hospital Institute and [c]Department of Medicine, University of Ottawa, The Ottawa Research Hospital Institute, The Ottawa Hospital General Campus, Ottawa, Ontario, Canada

Correspondence to Philip S. Wells, Department of Medicine, University of Ottawa, and the Ottawa Research Hospital Institute, The Ottawa Hospital General Campus, 501, Smyth Road, Ottawa, ON K1H 8L6, Canada. Tel: +1 613 798 5555 x78755; e-mail: pwells@toh.ca

Curr Opin Pulm Med 2021, 27:311–318
DOI:10.1097/MCP.0000000000000787

KEY POINTS

- DOACs appear well tolerated for use in patients with weight more than 120 kg or BMI more than 40 kg/m^2.
- Apixaban and rivaroxaban appear well tolerated to use in patients with nonvalvular atrial fibrillation and chronic kidney disease down to a CrCl more than 15 ml/min.
- DOACs should be used with caution to treat venous thromboembolism in patients with chronic kidney disease and CrCl less than 25–30 ml/min.
- DOACs should be avoided in patients with cirrhosis-associated coagulopathy or with Child-Pugh C cirrhosis and only apixaban or dabigatran should be considered for those with Child-Pugh B.
- DOACs are recommended for patients with cancer-associated thrombosis, but require caution in those with intact gastrointestinal or genitourinary malignancy.
- DOACs should be avoided in patients with triple-positive antiphospholipid antibody syndrome (APS), but can be continued in those with low-risk APS.
- Any off-label use of a DOAC should occur only after an informed discussion with the patient.

warfarin. Interestingly, in the NVAF subgroup, DOACs were more effective at preventing systemic embolism compared with warfarin [3].

Obesity may affect drug pharmacokinetics, most notably changes in absorption, volume of distribution and clearance [4]. Given that rivaroxaban and apixaban have the smallest volumes of distribution, lowest dependence on renal clearance, and are the most protein bound (Table 1) [5–8], they are conceivably less likely to be influenced by weight than dabigatran. Single-dose studies in healthy morbidly obese volunteers demonstrated lower maximum concentration of apixaban compared with patients weighing 65–85 kg, but these values were deemed clinically irrelevant [9]; similar findings occurred with rivaroxaban 10 mg [10]. A pharmacokinetic modelling study, derived from 913 patients weighing between 39 and 176 kg determined renal function, not weight, was the most significant factor influencing drug levels and concluded rivaroxaban can be used at extremes of weight if renal function is satisfactory [11▪].

Two United States (US) retrospective database studies comparing rivaroxaban with warfarin provide clinical data supportive of this assessment. In 3563 matched pairs treated for NVAF, there was no difference in rates of stroke, systemic embolism or major bleed [12]. In 2890 propensity matched pairs of patients treated for VTE, there was no statistical difference in rate of VTE recurrence but significantly lower rates of major bleeding in the rivaroxaban group, 1.8 versus 2.5% ($P = 0.0038$). Rivaroxaban plasma levels were tested in less than 1% of patients, highlighting that serum drug monitoring is likely unnecessary [13]. Meta-analyses of DOAC use compared with warfarin in NVAF found no difference in stroke or systemic embolism but fewer major bleeds [14], and in VTE patients, no differences in VTE recurrence or major bleeding [15▪▪,16]. Similar results were seen in patients with morbid obesity compared with reference weight in those treated with a DOAC for intermediate-to-high risk pulmonary embolism [17].

In summary, most evidence supporting the use of DOACs in patients with morbid obesity comes from retrospective data and hospital databases. Limitations include reliance on ICD codes for diagnosis, no data for warfarin time in therapeutic range and possible selection bias. Regardless, studies show an increase in safe prescribing rates for morbidly obese patients [18]. Therefore, despite a lack of high-quality prospective data, given that the existing data highlight DOACs as being at least noninferior for both efficacy and safety, it is reasonable to use DOACs in patients with morbid obesity after an informed discussion with the patient. We suggest rivaroxaban or apixaban given the preferred

Table 1. Pharmacokinetic and metabolic parameters of DOACs [5–8]

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Mechanism of action	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Thrombin inhibitor
Renal clearance	36%	27%	50%	80%
Hepatic clearance	64%	73%	50%	20%
Protein bound	95%	87%	55%	35%
Volume of distribution	50L	21L	107L	50–70L
Interactions	CYP3A4/5, CYP2J2	CYP3A4	–	–
	P-gp	P-gp	P-gp	P-gp

CYP, cytochrome P; P-gp, P-glycoprotein inhibitors.

pharmacokinetic profiles and most of the published data utilized these drugs.

CIRRHOSIS

Cirrhosis-related hepatic synthetic dysfunction affects the production of procoagulant and anticoagulant factors, leading to both increased bleeding and thrombotic complications [19]. Patients with cirrhosis were excluded from the initial DOAC studies due to baseline coagulopathy, risk of variceal bleeds, variable hepatic metabolism of DOACs and hypoalbuminemia in the setting of a highly protein bound drug (Table 1) [20].

Despite their increased bleed risk, patients with cirrhosis have better outcomes with anticoagulation, when indicated [21]. In a retrospective review of 2694 propensity-matched patients from the National US Veterans database, patients with Child-Pugh A, B or rarely C (1%) cirrhosis and NVAF had statistically significant improved all-cause mortality and no difference in bleeding when treated with either warfarin or a DOAC compared with no anticoagulation [22]. DOACs were associated with less bleeding compared with warfarin; however, patients with Child-Pugh B cirrhosis were more often treated with warfarin (29.5 versus 10%), thereby limiting the direct comparison of bleeding risk.

In a meta-analysis of four studies including 3483 patients with advanced liver fibrosis or cirrhosis and NVAF treated with either a DOAC (1936) or warfarin (1547), DOACs had a statistically significant reduced risk of both major bleeding and gastrointestinal bleeding and nonstatistically significant reduction in stroke [23▪]. Only one of the included studies had subgroups for the Child-Pugh classes, with warfarin used predominantly in more severe dysfunction [24]. More recently, two retrospective studies of DOACs compared with warfarin in patients with cirrhosis found at least equal efficacy and safety [25,26]. In one of these studies, warfarin was used preferentially in those with more advanced cirrhosis and there were more patients (not statistically significant) with varices in the warfarin arm (25.5 versus 12.3%), again preventing direct comparisons of the two treatments [26].

Patients with cirrhosis are at increased risk of VTE, with portal vein thrombosis (PVT) occurring most frequently [19]. Compared with those left untreated, patients receiving anticoagulation have significantly higher rates of portal vein recanalization, significantly lower rates of variceal bleeds and overall no difference in bleeding [27]. An RCT of 80 patients, comparing rivaroxaban 10 mg twice daily with warfarin for the treatment of PVT in cirrhosis, found those treated with rivaroxaban had improved survival (20.4 versus 10.6 months), and a significantly higher degree of complete recanalization (85% within 2.6 months versus 45% within 4.3 months, $P = 0.001$), without any episodes of upper gastrointestinal bleeding (0 versus 43.3%) [28]. Overall, the small sample size makes interpretation of these low event rates difficult, and no patients with Child-Pugh C cirrhosis were treated with a DOAC.

Most evidence of DOAC use in cirrhosis stems from retrospective studies, which are predominantly small, have limited patients with advanced disease and were not matched regarding degree of Child-Pugh class or presence of varices. Given these limitations, our recommendations for DOAC use in cirrhosis align with the current Food and Drug Administration (FDA) recommendations (Table 2). In those with Child-Pugh A or B cirrhosis, and without a history of variceal bleed or current untreated varices, we will consider a DOAC after an informed discussion with the patient.

CHRONIC KIDNEY DISEASE

As renal function declines, patients are at an increasing risk of thrombosis, bleeding and death [29,30]. From the pivotal phase III DOAC trials in VTE and NVAF, DOACs have been deemed safe and effective in patients with CKD stages 1–3; however, these RCTs excluded patients with creatinine clearance (CrCl) less than 25–30 ml/min [31]. Currently, the FDA has approved apixaban and rivaroxaban for use

Table 2. US Food and Drug Administration recommendations for DOAC use in cirrhosis [5–8]

	Child-Pugh Class			Hepatic disease associated coagulopathy
	A	B	C	
Rivaroxaban	usual dose	not recommended	not recommended	not recommended
Apixaban	usual dose	use with caution	not recommended	not recommended
Edoxaban	usual dose	not recommended	not recommended	not recommended
Dabigatran	usual dose	use with caution	not recommended	not recommended

in advanced CKD (CrCl 15–29 mL/min) and end-stage kidney disease (ESKD, CrCl < 15 ml/min or requiring dialysis) (Table 3), predominantly based on retrospective studies and small pharmacokinetic studies [32,33]. However, due to a lack of clinical data, the 2019 American Heart Association guideline for the management of NVAF does not recommend rivaroxaban in ESKD [34]. In addition, the 2020 Canadian Cardiovascular Society guideline for management of NVAF questions the safety of all DOACs in advanced CKD and does not recommend their use in ESKD [35▪▪]. There has been conflicting evidence in overall net benefit of any anticoagulation in patients with ESKD and NVAF [36,37], with an RCT underway comparing apixaban, VKA and no anticoagulation in patients requiring dialysis (ClinicalTrials.gov, NCT03987711).

Studies of DOACs in patients with advanced CKD or ESKD suggest at least equal efficacy and often improved safety compared with warfarin [38,39], with the most supporting evidence for apixaban [40–42], aligning with its preferred pharmacokinetic properties in the setting of renal dysfunction (Table 1). In a meta-analysis of five studies with 43 850 patients with advanced CKD/ESKD and NVAF, apixaban was associated with significantly less bleeding and no difference in rates of thromboembolic events compared with warfarin [43]. In a retrospective review of patients with NVAF on dialysis anticoagulated with apixaban ($n = 2351$) or warfarin (prognostic score matched 1 : 3), there was no difference in rate of thromboembolic events but significantly lower risk of major bleeding in those treated with apixaban, with apixaban 5 mg twice daily associated with significantly lower rates of stroke/systemic embolism and mortality compared with either reduced-dose apixaban or warfarin [44]. Evidence supporting the use of other DOACs in advanced CKD or ESKD is less robust, with conflicting evidence on the safety profiles of rivaroxaban [45–47] and evidence of potential harm with dabigatran [47,48].

Most data of DOAC use in advanced CKD are in the setting of NVAF. Given this, we feel it is reasonable to continue DOACs, preferentially apixaban and possibly rivaroxaban, in those with advanced CKD, particularly if they were started on it prior to renal function decline and after an informed discussion with the patient. There is insufficient evidence of net clinical benefit of anticoagulation in ESKD and we currently approach this on a case-by-case basis. Due to the relative paucity of data in VTE treatment, we tend to use the renal function thresholds from the initial phase III trials and generally avoid DOAC use in those with CrCl less than 30 ml/min (25 ml/min for apixaban). In calculating CrCl in patients with CKD, we use the Cockroft-Gault equation to align with the renal function definitions in

Table 3. US Food and Drug Administration recommended dosing of DOACs based on renal function and indication [5–8]

	Creatinine Clearance Categories (ml/min)			
	>50	30–50	15–29	<15 or dialysis
Treatment of venous thromboembolism (for the first 3–6 months)				
Rivaroxaban	15 mg b.i.d. x 21 days then 20 mg daily	15 mg b.i.d. x 21 days then 20 mg daily	15 mg b.i.d. x 21 days then 20 mg daily	not recommended
Apixaban	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.
Edoxaban	LMWH[a] 5–10 days then 60 mg or 30 mg daily based on weight[b]	LMWH[a] 5–10 days then 30 mg daily	LMWH[a] 5–10 days then 30 mg daily	not recommended
Dabigatran	LMWH[a] 5–10 days then 150 mg b.i.d.	LMWH[a] 5–10 days then 150 mg b.i.d.	not recommended	not recommended
Treatment of atrial fibrillation				
Rivaroxaban	20 mg daily	15 mg daily	15 mg daily	15 mg daily
Apixaban	5 mg b.i.d.[c]	5 mg b.i.d.[c]	5 mg b.i.d.*	5 mg b.i.d.[c]
Edoxaban	60 mg daily[b,d]	30 mg daily	30 mg daily	not recommended
Dabigatran	150 mg b.i.d.	150 mg BID	75 mg b.i.d.	not recommended

b.i.d., twice daily; LMWH, low molecular weight heparin.
[a]LMWH or alternate parenteral anticoagulant.
[b]Use 30 mg daily if patient's weight ≤60 kg.
[c]Dose reduce to 2.5 mg b.i.d. if patient has at least two of the following 3: weight ≤60 kg, age ≥80 years, or serum creatinine ≥1.5 mg/dl (133 μmol/l).
[d]Do not use if CrCl > 95 ml/min.

the initial RCTs. An RCT comparing low-dose apixaban or rivaroxaban in patients with advanced CKD and VTE will provide much-needed prospective clinical data in this population (ClinicalTrials.gov, NCT02664155).

CANCER

The use of DOACs in patients with cancer is complicated by malabsorption in those with vomiting, diarrhoea or mucositis; safety in those with thrombocytopenia, or hepatic or renal impairment; or drug-drug interactions with systemic chemotherapies (Table 1) [49]. Most data of DOAC use in cancer stem from trials comparing DOACs with the standard treatment, LMWH, in cancer-associated thrombosis (CAT). Recent trials have highlighted the efficacy of rivaroxaban, edoxaban and apixaban in patients with CAT compared with LMWH [50▪▪].

Hokusai-VTE, an RCT of edoxaban compared with LMWH, and the CARAVAGGIO RCT, comparing apixaban to LMWH, both determined these DOACs were noninferior regarding VTE recurrence at 6 months but with edoxaban there were more major bleeds, with a gastrointestinal source accounting for 61% of events [51,52]. Similar findings were reported in the SELECT-D RCT comparison of rivaroxaban to LMWH [53]. However, the CARAVAGGIO study found no difference in major bleeding or gastrointestinal bleeding [52].

Current guidelines recommend DOACs for treatment of CAT, but caution against their use in those with gastrointestinal [54] and possibly genitourinary cancers [55]. However, subgroup analyses of patients with major bleeds in the Hokusai-VTE and CARAVAGGIO studies found relatively equal rates of major bleeding in patients with gastrointestinal cancer in both DOAC and LMWH treated patients. In addition, no patients in CARAVAGGIO with resected colorectal or upper gastrointestinal cancer developed major bleeds with either apixaban or LMWH [56▪], with similar findings in the Hokusai-VTE trial [57].

Currently, we treat CAT patients with an approved DOAC in all patients, except those with active in situ gastrointestinal tumours, provided swallowing is not an issue. We use LMWH if there are concerns regarding the patient's ability to absorb the medication, impending thrombocytopenia (to titrate LMWH dosing) or proven drug-drug interactions exist. Note the latter is less often an issue with edoxaban, as it is only influenced by P-glycoprotein interactions. Informed discussions with the patient are always indicated. We are also cautious in starting DOACs in patients with an existing genitourinary malignancy due to increased risk of mucosal bleeding but, as haematuria is easily noted, starting with a DOAC is not unreasonable.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid antibody syndrome is characterized by thrombotic events (arterial or venous) and/or obstetric morbidity and persistently positive antiphospholipid (aPL) serum markers (Table 4) [58]. Patients with thrombotic-related APS are at an increased risk of recurrent events and warrant extended anticoagulation. Generally, persistently high titres of lupus anticoagulant and triple-positive aPL (positive for lupus anticoagulant, anticardiolipin antibody and antiβ2-glycoprotein antibody) portend the highest risk, with isolated, positive low-medium titres of anticardiolipin or antiβ2-glycoprotein having the lowest risk, particularly the IgM subtype [59,60]. The mainstay of treatment has been VKAs, but recent studies have compared rivaroxaban to warfarin for secondary prevention of thromboembolic events [61–64].

Patients with low and moderate risk VTE-related APS seem to have similar clinical outcomes when treated with rivaroxaban or warfarin for secondary prevention. In a single-arm feasibility study of 82 such patients with APS and prior VTE, patients were treated with full-dose rivaroxaban and followed for a mean of 19 months. There were four recurrent events (two strokes and two VTE), similar to the recurrence rates seen in patients treated with warfarin [61]. In a noninferiority trial of 116 patients with predominantly low and moderate-risk thrombotic APS (28% of patients were triple positive), patients were randomized to warfarin versus rivaroxaban for secondary prevention. There was no recurrent thrombosis in either group after seven months [62]. However, these studies included no or very few (6%) patients with arterial events and two recent studies assessing high-risk patients included those with arterial events and found different results. In the first, enrolling 190 patients, rivaroxaban had a nonstatistically significant increased risk of recurrent thrombotic events with 12 (12.6%) events in the rivaroxaban group, nine of which were stroke, versus six (6.3%) in the warfarin arm, with zero strokes over a 3-year period. Posthoc analyses identified an increased risk of recurrent thromboembolism in rivaroxaban-treated patients with previous arterial thromboses, livedo reticularis, or APS-related cardiac valvular disease [63]. A study of 120 patients with triple-positive thrombotic APS, randomized to rivaroxaban or warfarin, was stopped prematurely due to excess events in the rivaroxaban group. Over a mean follow-up of 1.5 years, there

Table 4. Revised classification criteria for the antiphospholipid syndrome

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met[a]
Clinical criteria
1. Vascular thrombosis[b]
One or more clinical episodes[c] of arterial, venous, or small vessel thrombosis[d], in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
(a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or
(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia defined according to standard definitions [11▪], or (ii) recognized features of placental insufficiency[e], or
(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b or c above.
Laboratory criteria[f]
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
3. Antib2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

[a]Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.
[b]Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, BMI 30 kg/m^2), microalbuminuria, estimated GFR < 60 ml/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis.
[c]A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.
[d]Superficial venous thrombosis is not included in the clinical criteria.
[e]Generally accepted features of placental insufficiency include (i) abnormal or nonreassuring foetal surveillance test(s), for example a nonreactive nonstress test, suggestive of foetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of foetal hypoxemia, for example absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, for example an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.
[f]Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, antib2 glycoprotein-I antibody present alone.
Table is reproduced from original publication by Miyakis *et al.* [58].

were seven arterial events (four stroke, three MI) in the rivaroxaban arm and zero in the warfarin arm [64].

Diagnosis of APS is complicated in the setting of acute VTE, as there is no consensus on who should be tested and because the lupus anticoagulant assay is inaccurate when anticoagulants have been initiated. If testing is warranted and patients are triple positive, we recommend VKAs. In patients with arterial events, we recommend testing for aPL early and avoiding DOACs in those with high titre single or double positive IgG aPLs. In those with low titres, or IgM antibodies, it is reasonable to continue a DOAC at full dose [65].

CONCLUSION

DOACs have become the mainstay of treatment for NVAF and most VTE indications. Patient comorbidities, bleed and thrombotic risk, and patient preference should help guide therapy. Retrospective data, subgroup analyses and hospital databases have provided insight into the efficacy and safety of DOACs in patients with morbid obesity, cirrhosis and CKD; however, high-quality, prospective and randomized data would provide more robust evidence and guidance for use in these populations.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Drs Lamarche and Alrajhi have no conflicts of interest or financial disclosures. Dr Wells has received honoraria for speaking engagements from Bayer Healthcare, Medscape and BMS/Pfizer.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Martin K, Beyer-Westendorf J, Davidson BL, *et al.* Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016; 14:1308–1313.
2. Wang TF, Carrier M. How I treat obese patients with oral anticoagulants. Blood 2020; 135:904–911.
3. Boonyawat K, Caron F, Li A, *et al.* Association of body weight with efficacy and safety outcomes in phase III randomized controlled trials of direct oral anticoagulants: a systematic review and meta-analysis. J Thromb Haemost 2017; 15:1322–1333.
4. Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. Expert Opin Drug Metab Toxicol 2011; 7:697–706.
5. Apixaban. New York, NY: Pfizer Inc; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202155s021lbl.pdf. [Accessed 20 February 2021]
6. Rivaroxaban. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202439s031,022406s035lbl.pdf. [Accessed 20 February 2021]
7. Edoxaban. Tokyo, Japan: Daiichi Sankyo Co.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206316s016lbl.pdf. [Accessed 20 February 2021]
8. Dabigatran. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022512s039lbl.pdf. [Accessed 20 February 2021]
9. Upreti VV, Wang J, Barrett YC, *et al.* Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013; 76:908–916.
10. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59–7939) in healthy subjects. J Clin Pharmacol 2007; 47:218–226.
11. ■ Speed V, Green B, Roberts LN, *et al.* Fixed dose rivaroxaban can be used in extremes of bodyweight: a population pharmacokinetic analysis. J Thromb Haemost 2020; 18:2296–2307.

A pharmacokinetic model assessing the association between body weight and serum concentrations of rivaroxaban.

12. Peterson ED, Ashton V, Chen YW, *et al.* Comparative effectiveness, safety, and costs of rivaroxaban and warfarin among morbidly obese patients with atrial fibrillation. Am Heart J 2019; 212:113–119.
13. Spyropoulos AC, Ashton V, Chen YW, *et al.* Rivaroxaban versus warfarin treatment among morbidly obese patients with venous thromboembolism: comparative effectiveness, safety, and costs. Thromb Res 2019; 182:159–166.
14. Kido K, Shimizu M, Shiga T, Hashiguchi M. Meta-analysis comparing direct oral anticoagulants versus warfarin in morbidly obese patients with atrial fibrillation. Am J Cardiol 2020; 126:23–28.
15. ■■ Mai V, Marceau-Ferron E, Bertoletti L, *et al.* Direct oral anticoagulants in the treatment of acute venous thromboembolism in patients with obesity: a systematic review with meta-analysis. Pharmacol Res 2021; 163:105317.

Most recent and comprehensive review of studies assessing safety and efficacy of DOACs in patients with obesity and venous thromboembolism.

16. Elshafei MN, Mohamed MFH, El-Bardissy A, *et al.* Comparative effectiveness and safety of direct oral anticoagulants compared to warfarin in morbidly obese patients with acute venous thromboembolism: systematic review and a meta-analysis. J Thromb Thrombolysis 2021; 51:388–396.
17. Lachant DJ, Bach C, Fe A, *et al.* Direct oral anticoagulant therapy in patients with morbid obesity after intermediate- or high-risk pulmonary emboli. ERJ Open Res 2021; 7:00554-2020.
18. Falk K, McComb MN, Shapiro NL, Uppuluri EM. Prescribing pattern of oral anticoagulants in patients with obesity. J Pharm Pract 2020. [Epub ahead of print]
19. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: coagulation in cirrhosis. Gastroenterology 2019; 157:34–43e1.
20. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. J Am Coll Cardiol 2018; 71:2162–2175.
21. Chokesuwattanaskul R, Thongprayoon C, Bathini T, Torres-Ortiz A, *et al.* Efficacy and safety of anticoagulation for atrial fibrillation in patients with cirrhosis: a systematic review and meta-analysis. Dig Liver Dis 2019; 51:489–495.
22. Serper M, Weinberg EM, Cohen JB, *et al.* Mortality and hepatic decompensation in patients with cirrhosis and atrial fibrillation treated with anticoagulation. Hepatology 2021; 73:219–232.
23. ■ Violi F, Vestri A, Menichelli D, *et al.* Direct oral anticoagulants in patients with atrial fibrillation and advanced liver disease: an exploratory meta-analysis. Hepatol Commun 2020; 4:1034–1040.

A large meta-analysis of DOAC use in patients with cirrhosis and nonvalvular atrial fibrillation.

24. Goriacko P, Veltri KT. Safety of direct oral anticoagulants vs warfarin in patients with chronic liver disease and atrial fibrillation. Eur J Haematol 2018; 100:488–493.
25. Davis KA, Joseph J, Nisly SA. Direct oral anticoagulants and warfarin in patients with cirrhosis: a comparison of outcomes. J Thromb Thrombolysis 2020; 50:457–461.
26. Jones K, Pham C, Aguilar C, Sheth S. Retrospective review on the safety and efficacy of direct oral anticoagulants compared with warfarin in patients with cirrhosis. Fed Pract 2020; 37:479–485.
27. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology 2017; 153:480–487e1.
28. Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute nonneoplastic portal vein thrombosis. Vascul Pharmacol 2019; 113:86–91.
29. Goto S, Haas S, Ageno W, *et al.* Assessment of outcomes among patients with venous thromboembolism with and without chronic kidney disease. JAMA Netw Open 2020; 3:e2022886.
30. Yuzawa Y, Kuronuma K, Okumura Y, *et al.* Relationship between the renal function and adverse clinical events in patients with atrial fibrillation: a Japanese Multicenter Registry Substudy. J Clin Med 2020; 9:167.
31. Lega JC, Bertoletti L, Gremillet C, *et al.* Consistency of safety profile of new oral anticoagulants in patients with renal failure. J Thromb Haemost 2014; 12:337–343.
32. Wang X, Tirucherai G, Marbury TC, *et al.* Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol 2016; 56:628–636.
33. De Vriese AS, Caluwé R, Bailleul E, *et al.* Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis 2015; 66:91–98.
34. January CT, Wann LS, Calkins H, *et al.* 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019; 140:e125–e151.
35. ■■ Andrade JG, Aguilar M, Atzema C, *et al.* The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol 2020; 36:1847–1948.

Comprehensive updated review of anticoagulation in atrial fibrillation, including recommendations in chronic kidney disease, liver disease and cirrhosis, and obesity.

36. Chang SH, Wu CV, Yeh YH, *et al.* Efficacy and safety of oral anticoagulants in patients with atrial fibrillation and stages 4 or 5 chronic kidney disease. Am J Med 2019; 132:1335–1343e6.
37. Randhawa MS, Vishwanath R, Rai MP, *et al.* Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. JAMA Netw Open 2020; 3:e202175.
38. Malhotra K, Ishfaq MF, Goyal N, *et al.* Oral anticoagulation in patients with chronic kidney disease: a systematic review and meta-analysis. Neurology 2019; 92:e2421–e2431.
39. Laugesen EK, Staerk L, Carlson N, *et al.* Nonvitamin K antagonist oral anticoagulants vs. vitamin-K antagonists in patients with atrial fibrillation and chronic kidney disease: a nationwide cohort study. Thromb J 2019; 17:21.
40. Reed D, Palkimas S, Hockman R, *et al.* Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Res Pract Thromb Haemost 2018; 2:291–298.
41. Schafer JH, Casey AL, Dupre KA, Staubes BA. Safety and efficacy of apixaban versus warfarin in patients with advanced chronic kidney disease. Ann Pharmacother 2018; 52:1078–1084.
42. Heleniak Z, Papuga-Szela E, Krzysztof P, Anetta U. Efficacy and safety of non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and chronic kidney disease stage G4: a single-center experience. J Cardiovasc Pharmacol 2020; 76:671–677.
43. Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, *et al.* Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: meta-analysis. Pacing Clin Electrophysiol 2018; 41:627–634.

44. Siontis KC, Zhang X, Eckard A, *et al.* Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation 2018; 138:1519–1529.
45. Godino C, Melillo F, Rubino F, *et al.* Real-world 2-year outcome of atrial fibrillation treatment with dabigatran, apixaban, and rivaroxaban in patients with and without chronic kidney disease. Intern Emerg Med 2019; 14:1259–1270.
46. Coleman CI, Kreutz R, Sood NA, *et al.* Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med 2019; 132:1078–1083.
47. Feldberg J, Patel P, Farrell A, *et al.* A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrol Dial Transplant 2019; 34:265–277.
48. Jang SM, Bahjri K, Tran H. Safety and efficacy of direct oral anticoagulants for atrial fibrillation in patients with renal impairment. Pharmacy (Basel) 2020; 8:30.
49. Gelosa P, Castiglioni L, Tenconi M, *et al.* Pharmacokinetic drug interactions of the nonvitamin K antagonist oral anticoagulants (NOACs). Pharmacol Res 2018; 135:60–79.
50. ■■ Mulder FI, Bosch FTM, Young AM, *et al.* Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood 2020; 136:1433–1441.

A systematic review and meta-analysis of the randomized control trials of DOACs compared with low molecular weight heparin for the treatment of cancer-associated thrombosis.

51. Raskob GE, van Es N, Verhamme P, *et al.* Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018; 378:615–624.
52. Agnelli G, Becattini C, Meyer G, *et al.* Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020; 382:1599–1607.
53. Young AM, Marshall A, Thirlwall J, *et al.* Comparison of an oral Factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018; 36:2017–2023.
54. Lyman GH, Carrier M, Ay C, *et al.* American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021; 5:927–974.
55. Key NS, Khorana AA, Kuderer NM, *et al.* Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2020; 38:496–520.
56. ■ Ageno W, Vedovati MC, Cohen A, *et al.* Bleeding with apixaban and dalteparin in patients with cancer-associated venous thromboembolism: results from the Caravaggio Study. Thromb Haemost 2020; 121:616–624.

A subgroup analysis of patients of the CARAVAGGIO study assessing bleeding outcomes based on location of bleed and type of cancer.

57. Kraaijpoel N, Di Nisio M, Mulder FI, *et al.* Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE Cancer Study. Thromb Haemost 2018; 118:1439–1449.
58. Miyakis S, Lockshin MD, Atsumi T, *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295–306.
59. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, *et al.* Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus 2011; 20:206–218.
60. Tektonidou MG, Andreoli L, Limper M, *et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019; 78:1296–1304.
61. Legault K, Blostein M, Carrier M, *et al.* A single-arm feasibility cohort study of rivaroxaban in antiphospholipid syndrome. Pilot Feasibility Stud 2020; 6:1–7.
62. Cohen H, Hunt BJ, Efthymiou M, *et al.* Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, noninferiority trial. Lancet Haematol 2016; 3:e426–e436.
63. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, *et al.* Rivaroxaban versus Vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. Ann Intern Med 2019; 171:685–694.
64. Pengo V, Denas G, Zoppellaro G, *et al.* Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018; 132:1365–1371.
65. Chayoua W, Kelchtermans H, Gris JC, *et al.* The (non)sense of detecting anticardiolipin and antiβ2glycoprotein I IgM antibodies in the antiphospholipid syndrome. J Thromb Haemost 2020; 18:169–179.