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Review Article

Use of Oral Anticoagulants in Obese Patients

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Abstract

The prevalence of obesity is increasing worldwide, and obesity is a known risk factor for venous thromboembolism (VTE) and the development of atrial fibrillation. While warfarin remains the most commonly prescribed oral anticoagulant worldwide, direct oral anticoagulants (DOACs) offer fewer drug and dietary interactions and do not require routine lab monitoring, making them enticing options for many patients. Obese patients are underrepresented in the majority of the pharmacologic and clinical trials for these medications, leaving uncertainty regarding the safety and efficacy of DOACs in this patient population. The adequacy of their fixed dosing regimens in patients with a body mass index (BMI) of 40 kg/m2 or greater, or a body weight of more than 120 kg remains in question, leading to concerns of under dosing, with resultant increased risk of thromboembolic events. Herein we review the available literature on the use of warfarin and DOACs in obese patients for the treatment of acute VTE and prevention of stroke and systemic embolization in atrial fibrillation.

ABBREVIATIONS

VTE: Venous Thromboembolism; DOAC: Direct Oral Anticoagulant; BMI: Body Mass Index; WHO: World Health Organization; PK: Pharmacokinetics; PD: Pharmacodynamics; VKA: Vitamin k Antagonist; ISTH: International Society on Thrombosis and Haemostasis; CL: Clearance; VD: Volume of Distribution; T1/2: Elimination Half-Life; GFR: Glomerular Filtration Rate; PT: Prothrombin Time; INR: International Normalized Ratio; C_{max}: Maximum Concentration; FDA: Food Drug Administration; FXa: Factor Xa; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; AUC: Area Under the Curve; ECT: Ecarin Clotting Time; APTT: Activated Partial Thromboplastin Time; D-TT: Dilute Thrombin Time.

INTRODUCTION

The global prevalence of obesity continues to rise, with 13% of the world's adult population categorized as obese in 2014 [1]. Obesity is defined by the World Health Organization (WHO) as a BMI of more than 30 kg/m^2, and obesity is stratified into three classes. Obese class I includes persons with BMI of 30 to 34.99 kg/m^2, obese class II includes BMI 35 to 39.99 kg/m^2, and obese class III includes BMI of 40 kg/m^2 and greater. Obesity is a known risk factor for the development of both atrial fibrillation and venous thromboembolism [2,3]. Thus, understanding the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of the available oral anticoagulants in this patient population is essential for appropriate use.

Currently, the available evidence on the use of oral anticoagulants in obese patients is limited. While DOACs offer increased convenience to patients compared to warfarin, the safety and efficacy of these medications in obese patients is far from certain. Much of the available clinical outcomes data in obese patients comes from the pre-specified subgroup analyses of the phase 3 trials that demonstrated the safety and efficacy of DOACs compared to vitamin K antagonists (VKAs). None of these studies excluded patients based on weight or BMI, and all included obese patients, although the details of included patients are variable between studies. None of these studies reported the absolute weights of patients, or the number of obese class III patients and their specific outcomes. The major concern about use of DOACs in this patient population is that fixed dosing schedules in patients who are above the average weight in the clinical trials may lead to unintentional underdosing, thus increasing a patient's risk for developing a thrombotic complication.

Based on this concern and the lack of robust data in this subset of patients, various expert groups have published recommendations for management of anticoagulation in obese patients [4,5]. In a guidance statement initiated by the Anticoagulation Forum, it was advised that until further evidence is available, DOACs should be avoided in patients > 120 kg or BMI ≥ 35 kg/m^2 unless VKAs cannot be used [5]. The International Society on Thrombosis and Haemostasis (ISTH) guidance statement recommends standard dosing for patients with BMI ≤ 40 kg/m^2 or weight ≤ 120 kg, suggests not using DOACs in patients with BMI > 40 kg/m^2 or weight > 120 kg, and suggests checking drug-specific peak and trough levels if using DOACs in a patient with BMI > 40 kg/m^2 or weight > 120 kg [4]. None of the prescribing information from the drug manufacturers provides dose-adjustments for obesity [6-10].

In the absence of randomized controlled trials evaluating the safety and efficacy of DOACs in obese patients, clinicians are left extrapolating data from PK/PD studies, and subgroup analysis from the phase 3 clinical trials. This review aims to summarize the literature surrounding the use of oral anticoagulants in obese patients, for the indications of stroke and systemic embolization prevention in atrial fibrillation and treatment of VTE. Each medication will be discussed, with a summary of the medication's mechanism of action, PK, PD, as well as safety and efficacy data in obese patients, as available in the medical literature.

The effect of obesity on pharmacokinetics

A basic understanding of the key pharmacokinetic principles is imperative to the interpretation of the oral anticoagulant PK and PD studies, and understanding some of the uncertainties of their use in obese patients. Relevant factors in drug dosing decisions are absorption, pharmacokinetic properties, clearance (CL), and volume of distribution (VD). Although oral drug absorption is thought to be unchanged in obesity, both CL and VD likely are altered in increased body weight [11]. The VD of a drug reflects the extent to which it distributes into extravascular tissues and is related to the lipid solubility of the drug as well as other chemical properties of the drug. Since obesity increases adipose tissue, the VD for lipophilic drugs increases in obesity, but it is unlikely to affect more water-soluble drugs [11].

Clearance, or elimination of the drug from tissues, is the major determinant of the steady state concentration of a drug, and is defined as the volume of blood from which a drug is removed in a given amount of time. It is estimated by the equation: CL = (0.7 * VD) / t1/2, where t1/2 is the elimination half- life of a drug. CL is inversely proportional to the steady-state plasma concentration of a drug, and is primarily the result of renal and hepatic physiology. Thus, CL depends on the blood flow to the organs responsible for clearing the drug as well as the ability of those organs to remove the drug from the blood [11]. It is the key PK parameter when determining maintenance dosing. Glomerular filtration rate (GFR) and renal plasma flow have been shown to be significantly increased in extremely obese patients, which can lead to increased renal clearance of drugs [12]. The t1/2 is dependent on both the CL and VD of a drug, thus, changes in t1/2 that occur with obesity could be due to changes in either the CL or VD.

Warfarin

Despite the introduction of DOACs, warfarin is still the most commonly prescribed oral anticoagulant globally [13]. Warfarin works by competitively inhibiting subunit 1 of the vitamin K epoxide reductase complex in the liver, thereby functionally depleting vitamin K dependent coagulation factors. Multiple factors contribute to the variability of warfarin dose requirements; including age, gender, comorbid conditions, nutritional status, concurrent medication or herbal supplement use, and genetic polymorphisms of CYP2C9 and/or VKORC1 [2].

Early PK and PD studies of warfarin demonstrated that it is nearly completely bio available and plasma protein bound. The half-life is highly variable among individuals, ranging from 20-70 hours. The apparent volume of distribution (VD) depends on the R or S enantiomer, and is related to a patient's body weight [14]. The patients included in this study were eleven healthy men, with body weights ranging from 65 to 96 kilograms [14]. It is important to consider that obese patients are likely underrepresented in PK/PD studies for warfarin, as the prevalence of obesity was lower in the 1970s than it is today.

Warfarin therapy is monitored by the prothrombin time (PT), where commercially prepared thromboplastin is added to anticoagulated plasma, the mixture is recalcified, and the first formation of thrombin is counted as the "prothrombin time." [15]. The international normalized ratio (INR), a standardized method of reporting the PT has been used to monitor warfarin therapy since the 1980s [16]. The ability to monitor the anticoagulant effect of warfarin using the PT/INR mitigates the risk of under dosing and overdosing. Although obesity influences the PK of warfarin, this effect is felt to be minimally clinically significant, due to the ability to monitor the drug and tailor dosing specific to individual patients [2].

There are several studies of warfarin use in obese patients. One study of 211 patients evaluated the initial response to warfarin between obese and non-obese patients. When compared to normal weight patients, those with BMI > 30 kg/m^2 took longer to achieve the therapeutic range and required higher doses of warfarin [17]. Another study of 831 patients with a BMI ranging from < 19 to > 40 kg/m^2 demonstrated that for each 1 kg/m^2 -unit increase in BMI, the weekly warfarin dose increased by 0.69 mg. This finding was true even after controlling for age and gender [18].

In regards to the effect of obesity on warfarin-associated bleeding risk, a study of 863 patients in an outpatient anticoagulation clinic found that obese class II and III (BMI ≥ 35 kg/m^2) had a significantly increased risk of major bleeding (HR 1.84) when compared to normal weight individuals [19]. However, a more recent study measuring the incidence of major bleeding amongst obese patients on warfarin found that obese patients (BMI ≥ 30 kg/m^2) actually had a lower rate of bleeding than non-obese patients (BMI <30 kg/m^2) [20]. These discrepancies may be due to the limitations of their retrospective study designs and residual confounding. Thus, clinical equipoise remains with respect to obesity and warfarin-associated bleeding risk.

Direct oral anticoagulants (DOACs)

Oral direct thrombin inhibitors:

Dabigatran: Dabigatran etexilate is a prodrug that is orally administered and converted to the active drug, dabigatran. The use of the prodrug is necessary as dabigatran is highly lipophilic and poorly absorbed. Dabigatran is a rapid, direct and competitive inhibitor of thrombin that works in a concentration dependent manner. Peak plasma concentration (Cmax) is reached approximately 2hours after drug administration, t1/2 is 12 to 17hours, and steady state is reached after 2-3days. Dabigatran is 35% protein-bound, 80% renally-cleared, and has a VD of 50-70L. A phase 2 dose-

Table 1: Comparison of the pharmacokinetic and pharmacodynamic principles of the available oral anticoagulants.

Drug	Dose	Indication	Mechanism of Action	Bio-availability	Onset	Half life (hr)	Volume of distribution	Clearance	Lab measurement
Warfarin [6]	Varies	AF, VTE	Vitamin K antagonist	Near complete	>24 hours	19.9 to 69.8 hr	0.14 L/kg	Metabolized by liver, metabolites renally cleared	PT/INR
Dabigatran [7]	110 mg bid	AF	Direct thrombin inhibitor	3-7%	2 hours	12 to 17 hr in healthy subjects	50-70 L	80% renal clearance (L/hr not reported in prescribing summary)	Linear correlation between TT, ECT and plasma dabigatran concentration*
	150 mg bid	VTE							
Rivaroxaban [8]	15 mg BID for 21 days, then 20 mg daily with food	VTE	Factor Xa inhibitor	Near complete	2-4 hours	5-9 hours in healthy subjects (11-13 in patients aged 60-76 years)	50 L	2/3 liver 1/3 directly excreted by the kidneys (10L/hr in healthy subjects)	Anti-Xa activity (linear relationship between plasma concentration and anti-FXa activity level). Absence of anti-FXa activity indicates no relevant drug effect **
	20 mg daily with food	AF							
Apixaban [9]	5 mg BID***	VTE AF	Factor Xa inhibitor	50%	3-4 hours	12 hours	21 L	25-27% renal-excretion (3.3 L/h in healthy subjects) [38]	Anti-Xa activity (linear relationship between plasma concentration and anti-FXa activity level)**
Edoxaban [10]	60 mg daily if	VTE	Factor Xa inhibitor	62%	1-2 hours	10-14 hours	107 L	50% renal clearance	Anti-Xa activity (linear relationship between
	CrCl >50-≤95 mL/min ****	AF						22 L/hr	plasma concentration and anti-FXa activity level) absence of anti-FXa activity indicates no relevant drug effect**

Abbreviations: AF: Atrial Fibrillation; VTE: Venous Thromboembolism; TT: Thrombinclotting Time; ECT: Ecarinclotting Time; Crcl: Creatinine Clearance

*Not widely studied or recommended for clinical use

**PT maybehelpfulasqualitativeassessmentofthepresenceofanticoagulanteffect.IfPTisnormal, suggests little anticoagulant effect. Anticoagulant effect cannot be monitored with standard laboratory testing.

***Reduce dose of apixaban to 2.5 mg bid if ≥ 2 of the following: age ≥80, body weight ≤60 kg, serum Cr ≥1.5)

****Reduce dose of edoxaban to 30 mg daily if patient's CrCl 15-50 mL/min or body weight ≤60 kg or P-glycoprotein inhibitors). Don't use ifCrCl ≥95 mL/min

finding study of 289 patients investigating dabigatran for VTE prophylaxis following orthopedic surgery concluded that "weight, gender…. could not be shown to influence significantly dabigatran pharmacokinetics." However, patient weights ranged from 49-130 kg with few patients weighing more than 100 kg, limiting the conclusions in obese patients [21]. In addition, in a PK study of dabigatran in 289 patients with atrial fibrillation, increasing body weight was found to significantly increase the VD, but the effect was concluded to be small to moderate, and not require dose adjustment [22].

The phase 3 clinical trials comparing dabigatran to VKA for stroke prevention in atrial fibrillation (RE- LY) and acute VTE treatment (RE-COVER) performed subgroup analyses assessing the effect of weight on clinical outcomes. Of the 18,113 patients in the RE-LY trial, 3,099 (17.1%) had a weight ≥100 kg. The subgroup analyses by weight (<50 kg, 50-99 kg, and ≥ 100 kg), and BMI (<28 and ≥ 28) failed to demonstrate significant differences in efficacy or safety outcomes between the subgroups [23]. Similarly, in the re-cover trial 19.8% of patients weighed ≥ 100 kg and 12.1% had a BMI ≥ 35 mg/m^2. In the subgroup analyses, outcomes were consistent with the overall trial results, suggesting a negligible difference in obese patients [24].

Although patients were not excluded from these trials based on weight, the number of severely obese patients enrolled is small, and clinically meaningful differences may exist in the severely obese population. Following the Food and Drug Administration (FDA) approval of dabigatran, treatment failures have been reported in severely obese patients. For example, a 48-year-old male weighing 153 kg (BMI 44.7 kg/m^2) presenting with an ischemic stroke was found to have undetectable dabigatran levels despite adherence with therapy. Repeat dabigatran administration in the hospital demonstrated peak levels to be less than the 25th percentile of the therapeutic trough level, suggesting a weight-dependent increase in drug clearance [25]. A similar case of a 124 kg

Table 2: Summary of clinical studies for available oral anticoagulants.

Study name or citation	Drug	Indication	Average weight studied	Maximum weight or BMI studied	Proportion of obese patients receiving drug	Key finding
Wallace 2013	Warfarin	AF, VTE, stroke, valve	89.4 kg	BMI ≥ 40 kg/m2	50.2% with BMI ≥30 kg/m2	Obese patients require higher dose and more time to achieve therapeutic INR
Mueller 2014	Warfarin	AF, VTE, valve, HF	28.4 kg/m2	BMI=30 kg/m2	27.4% with BMI ≥ 31 kg/m2	Obese patients require higher dose of warfarin
Ogunsua 2015	Warfarin	AF, VTE, valve	N/A	BMI = 39.99 kg/m2	21/71 cases with BMI ≥ 30 kg/m2	Case series; BMI >30 kg/m2 associated with higher bleeding risk
Hart 2017	Warfarin	AF, stroke, VTE, valve, other*	N/A	BMI >30 kg/m2	125/265 cases with BMI ≥ 30 kg/m2	Case-control study; OR 0.6 bleeding risk in obese patients
RE-LY	Dabigatran etexilate	AF	82.9 ±19.9 kg	≥100 kg	17.1%	Non-inferiority to warfarin for patients in subgroup analysis of <50 kg, 50-99 kg, >100 kg and BMI <28 and ≥28 kg/m2
RE-COVER	Dabigatran etexilate	VTE	85.5 ±19.2 kg	175 kg	19.8% >100 kg 12.1% BMI ≥ 35	Non-inferiority to warfarin for patients in subgroup analysis of <50 kg, 50-100 kg, ≥100 kg and BMI <25, 25-30, 30-35, >35 kg/m2
EINSTEIN-DVT	Rivaroxaban	DVT	NR	>100 kg	14.2%	Non-inferiority to warfarin for patients ≤70 kg, 70-90 kg, >90 kg
EINSTEIN-PE	Rivaroxaban	PE	NR	>100 kg	14.3%	Non-inferiority to warfarin for patients between≤70 kg 70-90 kg, >90 kg
ROCKET-AF	Rivaroxaban	NVAF	BMI 28.2	>90 kg BMI >35	28.5% 13.6%	Non-inferiority to warfarin for patients with BMI ≤25, 25-35, >35 kg/m2
AMPLIFY	Apixaban	Acute VTE	84.6±19.8 kg	>100 kg BMI >35	19.4% 13.6%	Safety and efficacy consistent across weight subgroups; major bleeding was lower in patients with BMI >35 kg/m2
ARISTOTLE	Apixaban	NVAF	82 kg	BMI >30 [39]	40%	Reduction in bleeding rates with apixaban compared to warfarin smaller in obese patients versus normal BMI
Hokusai-VTE	Edoxaban	Acute VTE	NR	>100 kg (14.8%)	14.8%	No difference in safety or efficacy or drug for groups with body weight <100kg versus>100 kg
ENGAGE AF-TIMI 48	Edoxaban	NVAF	NR	NR	NR	Non-inferiority to warfarin for prevention of stroke/SE. No subgroup analysis for weight reported.

Abbreviations: BMI: Body Mass Index; AF: Atrial Fibrillation; NVAF: Non-valvular AF; VTE: Venous Thromboembolism; OR: Odds Ratio; HF; Heart Failure; PE: Pulmonary Embolus; DVT: Deep Vein Thrombosis; NR: Not Reported; SE: Systemic Embolism
*Other: coronary artery bypass graft, myocardial infarction, joint replacement

patient (BMI 39.6 kg/m^2) started on dabigatran following an ischemic stroke was found to have low peak and trough levels. After a therapeutic interchange to rivaroxaban, therapeutic peak and trough levels of rivaroxaban were easily achieved, further highlight in a weight-dependent alteration in drug clearance for dabigatran [26]. These reports raise concerns that obese patients may be undertreated with standard dabigatran doses. A possible explanation for this may be related to the high renal clearance of dabigatran, as GFR is known to be increased in severe obesity [12]. Further studies are needed to determine whether dabigatran use is safe and effective in obese patients, especially those weighing >120kg, or with a BMI ≥ 35kg/m^2.

Oral factor Xa inhibitors: Three oral direct Factor Xa (FXa) inhibitors (rivaroxaban, apixaban, and edoxaban) are approved by the FDA for the management of VTE and stroke prevention in atrial fibrillation in the United States. FXa plays a central role in the coagulation cascade, linking the intrinsic and extrinsic pathways to the common pathway resulting in thrombin generation. Unlike heparins or the pentasaccharide fondaparinux, which exert their anticoagulant effects indirectly through potentiation of anti-thrombin, the FXa inhibitors exert their anticoagulant effect through direct FXa inhibition.

Rivaroxaban: Rivaroxaban was the first oral FXa inhibitor approved for use in the United States and is administered in fixed-dose regimens for stroke prevention in atrial fibrillation and VTE treatment. Rivaroxaban is highly protein-bound (90%) and its elimination occurs predominantly in the liver (~66%), with the remainder directly excreted by the kidneys [27,28].

Rivaroxaban was assessed in a small PK/PD study of 36 healthy volunteers divided into 3 weight categories (< 50 kg,

70-80 kg, >120 kg). The apparent VD was small and seemed to decrease proportionally as body weight increased (<50 kg: VD = 2.44 L/kg; 70-80 kg: VD = 1.36 L/kg; >120 kg: VD = 0.69 L/kg). Keeping these VD alterations in mind, it was also noted that among patients weighing ≤ 50 kg, the t1/2 of rivaroxaban was 9.60 hours, compared to 7.20 and 7.39 hours for patients weighing 70-80 kg and > 120 kg, respectively [28]. Renal elimination appeared relatively constant across weight categories. Considering the VD differed nearly 50% between patients weighing 70-80 kg and those >120 kg while the half-life remained relatively constant, these findings suggest a substantial weight-dependent alteration in drug clearance, not attributable to renal elimination. Although the authors of this study repeatedly state the observed differences were "not considered clinically relevant," their study was underpowered to draw definitive conclusions. Ultimately, they recommended confirmation of their findings in phase 3 studies.

In a separate study designed to evaluate the effect of demographics (age, sex, weight, renal function) on rivaroxaban PK/PD in patients with acute deep vein thrombosis (DVT) using pooled data from the EINSTEIN-DVT and ODIXa-DVT phase 2 studies, the VD directly correlated with weight, increasing by 0.8% per kg above the median lean body weight of 56 kg [29]. These findings support the previous PK/PD study, which demonstrated a similar relationship between VD and body weight [30]. Although the authors concluded the increase in VD was not clinically significant, it remains concerning that this degree of change has the potential to become clinically meaningful in patients who are extremely obese.

The phase 3 clinical trials comparing rivaroxaban to enoxaparin/VKA for treatment of DVT, pulmonary embolism (PE), and stroke prevention in atrial fibrillation were EINSTEIN-DVT, EINSTEIN-PE, and ROCKET-AF, respectively [31-33]. These studies included a moderate number of obese patients, although the weight categories were not uniform across the trials. The EINSTEIN-DVT and EINSTEIN-PE trials used a weight cutoff of >100 kg to classify patients into the uppermost weight category, with approximately 14% of patients >100 kg [31,32]. ROCKET-AF used a weight cutoff of >90 kg (28.5% of patients) to define the uppermost weight category, in addition to a BMI >35 kg/m^2 (13.6% of patients) [33]. All three trials performed pre-specified subgroup analyses stratified by weight for efficacy and safety outcomes. The EINSTEIN-DVT and EINSTEIN-PE subgroup analyses demonstrated the primary outcomes were similar across weight groups (≤ 70 kg, 70-90 kg and >90 kg) [31,32]. Similarly, in the ROCKET-AF trial the primary outcomes were consistent across weight (≤ 70 kg, 71-90 kg, ≥ 90 kg) and BMI groups (≤ 25 kg/m^2, 25-≤ 35 kg/m^2, >35 kg/m^2) [33].

A posthoc analysis of over 8,000 patients pooled from the EINSTEIN studies assessing the risk of major bleeding and recurrent VTE relative to body weight found that fixed-dose rivaroxaban was not associated with increased risk of recurrent VTE, major bleeding, or clinically relevant bleeding in patients with high body weight. Although 1,393 patients (16.8%) had a body weight of >100 kg, very few (n = 81) weighed >140 kg, limiting the generalize ability of the results to extremely obese patients [34]. Based on the available evidence, the use of rivaroxaban in obese patients appears safe. However, due to the observed changes in VD and CL with increasing weight, caution must be used in extremely obese patients.

Apixaban: Apixaban is an oral, FXa inhibitor that is administered twice-daily in fixed doses dependent upon the clinical indication. It has a bioavailability of 50%, is estimated to be 87% protein-bound, and is approximately 25% renally cleared [35]. The effect of body weight on apixaban pharmacokinetics has been assessed in a small phase 1 PK/PD study of healthy adults. The high body weight group (18 patients with weight ≥ 120 kg and BMI ≥ 30 kg/m^2) had a 31% lower apixaban peak plasma concentration and 23% lower area under the curve (AUC) (0,∞) compared to the reference body weight group (65-85 kg) [36]. Thus, overall drug exposure decreased while drug clearance increased in obese patients. The apparent VD was 24% larger and t1/2 was 27% shorter (8.8 hours vs. 12 hours) in the high body weight group compared to the reference group [36]. The effects of body weight on the peak plasma concentration, AUC, VD, and t1/2 were concluded to have unlikely clinical significance, not requiring dose adjustment for body weight [36].

The phase 3 clinical trials evaluating apixaban versus VKA therapy for VTE treatment and stroke prevention in atrial fibrillation are AMPLIFY and ARISTOTLE, respectively [37,38]. In the AMPLIFY trial, 522 (19.4%) patients who received apixaban weighed > 100 kg and 349 (13.6%) had a BMI >35 kg/m^2. Although the reported safety and efficacy of apixaban were consistent across weight (≤ 60kg, >60-<100 kg, ≥ 100 kg) and BMI (≤ 25 kg/m^2, >25-30 kg/m^2, >30-35 kg/m^2, >35 kg/m^2) subgroups, major bleeding was significantly lower in patients with BMI > 35 kg/m^2 receiving apixaban; potentially related to the lower peak concentrations and drug exposure noted in the PK/PD study. The ARISTOTLE trial did not initially report the proportion of obese patients in the weight-based analysis (≤ 60 kg vs. >60 kg) of safety and efficacy outcomes. A subsequently published analysis showed that 40% of the study population was categorized as obese (BMI ≥ 30 kg/m^2) [39]. No significant interaction between BMI and efficacy outcomes was noted. However, there was an interaction with BMI and major bleeding. The reduction in bleeding rates with apixaban compared to warfarin was smaller in obese patients as compared to those with a normal BMI, contrary to the findings of the AMPLIFY trial. Whether the increased bleeding noted in obese patients in ARISTOTLE compared to AMPLIFY is related to decreased drug clearance or patient-specific factors such as older age, remains uncertain.

Edoxaban: Edoxaban is the most recently FDA-approved FXa inhibitor. PK data have shown predictable and consistent effects on the peak plasma concentration (Cmax) and AUC (0,∞), that are proportional to dose [40]. Oral bioavailability is approximately 50%, plasma protein binding is modest at 40-59%, and renal excretion is approximately 35% [40]. In a phase 2 study comparing edoxaban to warfarin for stroke prevention in atrial fibrillation, once-daily edoxaban had similar bleeding as warfarin, whereas twice- daily

administration was associated with increased bleeding [41]. In a pooled analysis of 11 edoxaban trials evaluating population PK, low body weight was found to significantly decrease the non-renal clearance of edoxaban [42].

Minimal information is available regarding edoxaban safety and efficacy in obese patients. Two phase 3 trials comparing edoxaban to VKA for prevention of stroke in atrial fibrillation and VTE treatment have been performed. In the Hokusai-VTE trial, 611 (14.8%) patients receiving edoxaban weighed >100 kg. In the pre-specified subgroup analysis by body weight, the primary efficacy and safety outcomes remained consistent across weight groups [43]. The ENGAGE AF-TIMI 48 trial did not report the proportion of obese patients, and subgroup analysis of body weight was not performed [44].

As part of its approval process by the FDA, edoxaban carries a warning against its use in atrial fibrillation in patients with a CrCl of >95 mL/min due to decreased efficacy. This was due to a subgroup analysis from the ENGAGEAF-TIMI 48 that showed patients with a CrCl of >95mL/min had a higher risk of ischemic stroke when treated with edoxaban than warfarin (HR [95% CI]: 2.16 [1.17, 3.97]) [10]. Although weight is not specifically mentioned as a caution or contraindication, prescribers should remain mindful of this warning, since in the absence of significant renal dysfunction, very few obese patients are likely to have CrCl<95mL/min.

Laboratory monitoring of direct oral anticoagulants: A limitation of DOAC use remains the lack of standardized and widely available coagulation tests to monitor an individual patient's anticoagulant response. Although routine laboratory monitoring of the anticoagulant effect is typically not warranted, there are clinical scenarios (e.g., extremely obese patients) where the ability to monitor the anticoagulant effect would be desirable. Direct measurement of the peak and trough plasma concentrations may be the best assessment of an individual patient's response to DOAC therapy [35]. Liquid chromatography-tandem mass spectrometry methods have been developed and were used in the DOAC PK/PD studies, and are considered the reference standard method, however they are not widely available nor FDA-approved for routine clinical use.

In situations where knowledge of an anticoagulant effect is necessary, such as in hemorrhage or emergent surgery, the use of existing coagulation assays may be helpful. For example, the ecarin clotting time (ECT) provides a quantitative assessment of the anticoagulant effect from dabigatran, but is not widely available. The activated partial thromboplastin time (aPTT) is sensitive to dabigatran and shows a curvilinear concentration-response relationship. The aPTT is a widely available method for determining the presence of dabigatran, but is not useful for determining the plasma drug level [45]. The dilute thrombin time (d-TT) is a sensitive dabigatran-calibrated thrombin clotting time that can estimate drug concentration at levels <300 ng/mL. In the United States, plasma reagents for calibration of the thrombin time to dabigatran are not FDA-approved for clinical use, thereby limiting their role to research purposes [46]. The prothrombin time (PT) and anti-FXa activity levels are not reliable surrogates for dabigatran activity [47].

Anti-FXa activity assays have been shown to have better sensitivity and less variability than PT/INR for determining FXa inhibitor drug levels [48]. However, the accuracy of anti-FXa activity assays requires drug-specific calibration, which is not widely performed [49]. Liquid anti-Xa calibrators are available for research use in the United States, but are not clinically available [50,51]. Although rivaroxaban and edoxaban, and to a lesser extent apixaban, prolong the PT, many PT reagents are not sensitive enough to make this a reliable means of excluding the presence of drug. The aPTT is less sensitive to FXa inhibitors than PT, and is not helpful in the laboratory assessment of these medications [49].

DISCUSSION

The direct oral anticoagulants offer advantages over warfarin, including convenience to patients due to lack of frequent lab monitoring, and fewer drug-drug and drug-food interactions. Drug-specific prescribing information does not recommend dose adjustments for obese patients. However, these medications have not been widely studied in obese patients, especially patients weighing >120 kg. While none of the clinical trials comparing DOACs to VKA therapy specifically excluded patients based on high body weight, most of the trials enrolled low numbers of obese and extremely obese patients. In the studies that performed subgroup analyses by weight categories, several different weight or BMI cutoffs were used (e.g., >90 kg, >100 kg, or BMI > 35 kg/m^2), and although significant differences in clinical outcomes were not observed, the PK/PD studies of the individual drugs raise concerns regarding substantial weight-dependent alterations in drug clearance. The risk of drug failure in a patient who weighs 110 kg may be very different than a patient who weighs 200 kg. The case reports of treatment failure in obese patients on dabigatran raise concerns that obese patients may be under dosed, thereby increasing the thrombotic risk, unbeknownst to prescribing clinicians. It remains undetermined if the increased number of reported dabigatran failures compared to FXa inhibitors is due to the fact that dabigatran was the first DOAC used clinically, or because dabigatran is more reliant on renal-clearance than FXa inhibitors, leading to increased drug clearance and decreased overall drug exposure in obesity. In spite of the favorable characteristics associated with the DOACs, the uncertainty of achieving adequate drug levels and desired anticoagulant effect in severely obese patients makes warfarin a more appealing agent based on the accessibility of INR monitoring to ensure therapeutic levels.

SUGGESTIONS FOR CLINICAL PRACTICE

Based upon the available evidence reviewed above, we attempt to make suggestions regarding the use of oral anticoagulants in obese patients. These recommendations are similar to those issued in the ISTH guidance statement, with minor distinctions [4]. First, extrapolating from the PK/PD studies of apixaban and rivaroxaban in patients with body weight >120 kg and the demonstrated differences in drug exposure, CL, VD, and t1/2 when compared to patients with

normal body weight, clinically significant differences in drug safety and efficacy may exist in severely obese patients.

The low numbers of severely obese patients enrolled in phase 3 trials, and the non-uniform, arbitrary weight cut-offs used in subgroup analyses may be insufficient to detect meaningful differences in outcomes. Hence, we suggest against DOAC use in severely obese patients (e.g. > 120 kg), unless drug-specific peak and trough levels are able to measured and found to be in the reported therapeutic dose ranges. The decades of clinical experience and ease of monitoring warfarin make it the preferred agent in severely obese patients, especially when DOAC-specific testing is unavailable. Lastly, we acknowledge there may be clinical scenarios when warfarin cannot be safely used. Therefore, we agree with the Anticoagulation Forum guidance statement limiting DOAC use to situations where vitamin K antagonists cannot be used for patients with body weight >120 kg or BMI $\geq$ 35 kg/m^2 [5]. In these situations, we suggest measuring peak and trough drug levels for all obese patients initiating DOACs, acknowledging the evidence supporting this approach is limited. We believe hospitals and clinical laboratories should develop drug-specific tests to measure DOAC plasma concentrations, with reference ranges adapted from clinical trials. If peak and trough levels for DOACs are performed in obese patients and are found to be low, we suggest transitioning therapy to a vitamin K antagonist.

CONCLUSION

Obese patients are at increased risk of thromboembolism and atrial fibrillation, and may require larger doses of oral anticoagulants than non-obese patients. Available evidence suggests substantial weight- dependent alterations in drug clearance may exist. The use of fixed-dose regimens with the DOACs may lead to sub-therapeutic drug levels in severely obese patients, putting obese patients at risk for thromboembolism. Until further studies are completed, severely obese patients should be treated with warfarin.

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