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## RECOMMENDATIONS AND GUIDELINES

# Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

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### Abstract

Although direct-acting oral anticoagulants (DOACs) have widespread first-line use for treatment and prevention of venous thromboembolism (VTE), uncertainty remains regarding their efficacy and safety in patients with obesity. We reviewed available data for use of DOACs for VTE treatment and prevention in patients with obesity, including phase 3, phase 4, meta-analyses, and pharmacokinetic and pharmacodynamics studies. In addition, we reviewed available data regarding DOACs in bariatric surgery. We provide updated guidance recommendations on using DOACs in patients with obesity for treatment and prevention of VTE, as well as following bariatric surgery.

### KEYWORDS

anticoagulant, bariatric surgery, direct oral anticoagulant, obesity, venous thromboembolism

## 1 | INTRODUCTION

As the prevalence of obesity continues to rise, with recent estimates of more than 650 million adults affected worldwide,<sup>1</sup> clinicians must frequently make treatment decisions in obese patients. One such decision involves anticoagulation for treatment and prevention of

venous thromboembolism (VTE). Direct-acting oral anticoagulants (DOACs) have first-line use for many patients needing anticoagulation for VTE.<sup>2</sup> In 2016, the ISTH SSC published guidance that suggested not using DOACs in patients with extreme obesity (body mass index [BMI] >40 kg/m<sup>2</sup> or weight >120 kg), and if DOACs nevertheless are used in these patients, to obtain peak and trough drug levels.<sup>3</sup> These suggestions were made due to the lack of clinical evidence available regarding the efficacy and safety in the extremely

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obese population because phase 3 trials comparing individual DOACs with warfarin for treatment of VTE included relatively few patients with obesity and extreme obesity, and pharmacokinetic (PK) and pharmacodynamics (PD) data that suggested alternations in the setting of obesity.<sup>3</sup>

We provide an updated review of available data and update recommendations for the use of DOACs for VTE treatment and prevention in patients with severe obesity. As atrial fibrillation (AF) is a different disease affecting a different patient population,<sup>4</sup> we limited this current literature review and guidance to VTE.

## 2 | METHODS

We conducted a literature review by searching PubMed with the following strategy: (DOAC or novel oral anticoagulant [NOAC] or apixaban or betrixaban or dabigatran or edoxaban or rivaroxaban) and (obese weight or obesity) and (VTE treatment or VTE prevention or VTE prophylaxis) or (bariatric surgery) or (pharmacokinetic or pharmacodynamic or drug level) through August 1, 2020. We held multiple video conference discussions with all authors to review data and discuss consensus recommendations.

## 3 | SUMMARY OF DATA REVIEW

### 3.1 | Clinical data for VTE treatment

Available clinical data for the use of DOAC treatment of VTE in obese patients consisted of phase 3, phase 4 (including retrospective and prospective observational studies and comparisons within claims databases), and systematic review/meta-analysis. Studies compared efficacy and safety of DOAC in two broad approaches: (1) DOAC versus vitamin K antagonist (VKA) within a given weight category, or (2) DOAC across weight categories (Table 1). In addition,

some studies considered a given DOAC drug individually, whereas others pooled all DOAC drugs in the analysis.

#### 3.1.1 | Apixaban

Data analyzing apixaban individually are limited. There has been no post hoc analysis of a phase 3 clinical trial of apixaban for treatment of VTE. In a small single-center, retrospective study of DOACs in patients with BMI  $\geq 40$  kg/m<sup>2</sup>, of whom 47 were on apixaban, similar incidences of VTE recurrence occurred compared with warfarin (1/47 [2.1%; 95% CI, 0.0–6.3] vs. 2/167 [1.2%; 0.0–2.9], respectively), with similar incidences of major bleeding (1/47 [2.1%, 0–6.3] vs. 4/167 [2.4%, 0–4.7], respectively).<sup>5</sup> Patients with BMI  $\geq 50$  kg/m<sup>2</sup> had similar rates of VTE recurrence (0/10 on apixaban and 2/52 on warfarin;  $p = .53$ ) and major bleeding (0/10 on apixaban and 2/52 on warfarin). In an observational study of combined data from US insurance claims databases, apixaban, compared with warfarin, was associated with lower risk of recurrent VTE (5.3 vs. 8.1 per 100 person-years [HR 0.63; 0.52–0.78]) and major bleeding (4.5 vs. 6.2 per 100 person-years [hazard ratio (HR) 0.70; 0.56–0.89]) in morbidly obese patients. Of note, this study was published in the final stages of peer-review, after the initial planned study period.<sup>6</sup>

#### 3.1.2 | Rivaroxaban

A post hoc analysis of the EINSTEIN deep vein thrombosis (DVT) and pulmonary embolism (PE) trials, which included 861 patients with BMI  $\geq 35$  kg/m<sup>2</sup>, found no significant difference in recurrent VTE in patients taking rivaroxaban compared with those taking warfarin at both 21 days (9/427 [2.1%] vs. 4/434 [0.9%], respectively; HR 2.22; 0.68–7.26) and 12 months (13/427 [3%] vs. 9/434 [2.1%], respectively; HR 1.45; 0.62–3.39), and no difference in major bleeding (5/426 [1.2%] vs. 7/432 [1.6%]; HR 0.71; 0.22–2.24).<sup>7</sup> When analyzed

**TABLE 1** Summary of efficacy and safety outcomes in VTE treatment clinical studies comparing DOACs with VKA in patients with obesity

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes <sup>6</sup>	Similar outcomes <sup>5,6</sup>
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes <sup>7</sup>	X	Similar outcomes <sup>5,8-10</sup>	Similar outcomes <sup>5,9</sup>
Pooled DOAC	Similar outcomes <sup>11</sup>	X	Similar outcomes <sup>12-16</sup>	Similar outcomes <sup>12</sup>

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m<sup>2</sup>; BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

by body weight, no difference in VTE recurrence was found between rivaroxaban and warfarin, including those  $\geq 120$  to 140 kg (2/119 [1.7%] vs. 3/103 [2.9%], respectively) and  $\geq 140$  kg (1/40 [2.5%] vs. 1/41 [2.4%], respectively). Notably, event rates were low.

Several observational studies presented data for rivaroxaban in obese patients. A study using individual-level, electronic health record data for a propensity-matched cohort of more than 6700 patients with BMI  $\geq 30$  kg/m<sup>2</sup> found that rivaroxaban reduced recurrent VTE compared with warfarin at 3, 6, and 12 months (HR 0.61 [0.51–0.72]; HR 0.65 [0.55–0.77]; HR 0.63 [0.54–0.74], respectively) with no difference in major bleeding (HR 0.99 [0.68–1.44] and HR 1.00 [0.73–1.36] at 3 and 12 months, respectively). Limiting the analysis to patients with BMI  $\geq 35$  kg/m<sup>2</sup> demonstrated similar results with reduced risk of VTE recurrence with rivaroxaban compared with warfarin (HR at 3, 6, and 12 months of 0.60 [0.48–0.76]; HR 0.64 [0.51–0.81]; HR 0.63 [0.51–0.78], respectively) and reduced risk of major bleeding (HR at 3, 6, and 12 months of 0.99 [0.61–1.63], 0.85 [0.54–1.36], and 0.95 [0.64–1.43], respectively).<sup>8</sup> A single-center retrospective study of patients with BMI  $\geq 40$  kg/m<sup>2</sup> or weight  $\geq 120$  kg had similar 12-month rates of VTE recurrence (2/47 vs. 4/62;  $p = 0.61$ ) and composite of major and clinically relevant non-major bleeding (3/47 vs. 2/62;  $p = .26$ , respectively) in those taking rivaroxaban compared with warfarin, respectively.<sup>9</sup> A second single-center retrospective study comparing outcomes for patients with BMI  $\geq 40$  kg/m<sup>2</sup> found similar rates of recurrent VTE (3/152 [2.0%, 0.0–4.2] and 2/167 [1.2%, 0.0–2.9]) and major bleeding (2/152 [1.3%, 0.0–3.1] and 4/167 [2.4%, 0.1–4.7]) in those taking rivaroxaban vs. warfarin for VTE, respectively.<sup>5</sup> When limited to patients with BMI  $\geq 50$  kg/m<sup>2</sup>, 0/30 on rivaroxaban and 2/52 on VKA had recurrent VTE ( $p = .50$ ). Another study analyzing administrative claims data found similar risks of recurrent VTE (OR 0.99; 0.85–1.14) and major bleeding (OR 0.75; 0.47–1.19) for patients with obesity treated with rivaroxaban compared with VKA, though notably used International Classification of Disease codes to identify obesity, rather than individual weight or BMI.<sup>10</sup> Overall, data from observational studies demonstrate at least similar efficacy and bleeding outcomes with rivaroxaban in patients with obesity.

### 3.1.3 | Betrixaban, dabigatran, and edoxaban

We did not identify studies limiting analysis to betrixaban, dabigatran, or edoxaban individually for treatment of VTE.

### 3.1.4 | Pooled DOAC

Most studies pooled DOAC drugs for comparison, rather than considering each individually. We identified two meta-analyses of DOACs for VTE indication that analyzed by weight categories. One included a randomized clinical trial (RCT) of DOAC vs. VKA for VTE treatment and stratified body weight into low, normal, and high categories as defined by the individual trials. The lower end of weight for the high

body weight (HBW) category was 90–100 kg and included more than 5400 patients. The study found similar risks of recurrent VTE and VTE-related death (RR 0.98, 95% CI 0.72–1.35) and major and clinically relevant non-major bleeding (RR 0.93; CI 0.65–1.32) for DOAC compared with VKA in HBW group.<sup>11</sup> A second meta-analysis of five observational studies with more than 6500 patients with extreme obesity (BMI  $\geq 40$  kg/m<sup>2</sup> or weight  $>120$  kg) compared DOACs (rivaroxaban, apixaban, and dabigatran) with warfarin for treatment of VTE and found similar efficacy of DOAC (recurrent VTE OR 1.07; 0.93–1.23) and a nonsignificant trend toward reduced risk of major bleeding (OR 0.80; 0.54–1.17); notably, however, 88% of patients in the study came from one previously referenced administrative claims-based study that used International Classification of Disease qualitative coding rather than a quantitative definition for obesity.<sup>12</sup>

Several observational studies have compared pooled DOAC. Using a prospective registry of patients on DOAC, one study found patients with BMI  $\geq 30$  kg/m<sup>2</sup> compared with BMI  $<30$  kg/m<sup>2</sup> taking DOAC for VTE treatment had similar rates of stroke/TIA/recurrent VTE (6/285 [2.1%] vs. 24/770 [3.1%], respectively) and similar rates of major bleeding (9/285 [3.2%] vs. 24/770 [3.1%], respectively).<sup>13</sup> A prospective single-institutional observational study of patients treated with DOACs (rivaroxaban and apixaban) compared outcomes in those with body weight of  $>120$  kg (HBW,  $N = 230$ ) to those with reference body weight (RBW) of 60–120 kg ( $n = 2123$ ) and found similar cumulative rates of VTE in HBW group (4.91 per 100 patient-years [0.1–9.7]) compared with RBW (3.19 per 100 patient-years [1.94–4.44]), with similar rates of major bleeding. Additionally, 3-month VTE recurrence rates were similar between HBW and RBW groups (2.2% vs. 1.7%;  $p = .6$ ).<sup>14</sup> A retrospective matched cohort study conducted at more than 40 institutions, which included 1840 patients weighing 100–300 kg, found no difference in VTE recurrence rates at 1 year (6.5% vs. 6.4% in DOAC vs. VKA respectively,  $p = .93$ ) nor bleeding (1.7% vs. 1.2%;  $p = .31$ ).<sup>15</sup> A separate retrospective study comparing outcomes of 133 patients weighing  $\geq 120$  kg compared with  $\geq 1000$  patients weighing  $<120$  kg, taking apixaban, dabigatran, or rivaroxaban for treatment of VTE, had similar rates of recurrent VTE (0.8% vs. 1.1%, OR 0.66; 0.09–5.14).<sup>16</sup> In summary, available studies pooling DOACs show similar rates of efficacy and safety outcomes either compared with VKA or across weight categories.

### 3.1.5 | Dose reduction for extended VTE treatment

Prespecified subgroup analyses provided in the EINSTEIN CHOICE trial comparing rivaroxaban 10 mg daily, rivaroxaban 20 mg daily, and aspirin 100 mg daily showed similar rates of primary outcome of composite of fatal and nonfatal VTE in patients with BMI  $\geq 30$  kg/m<sup>2</sup> (1.6% for rivaroxaban 10 mg daily and 1.3% for rivaroxaban 20 mg daily).<sup>17</sup> In a prespecified subgroup analysis of the AMPLIFY EXTENSION trial, similar rates of composite secondary outcome of recurrent VTE or death related to VTE occurred with apixaban 5 mg twice daily (1.5%) and 2.5 mg twice daily (1.7%) for weight  $>60$  kg.<sup>18</sup> However, given the thresholds of BMI  $>30$  kg/m<sup>2</sup> for lower-dose rivaroxaban and weight  $>60$  kg for lower dose apixaban, and no

dedicated analysis or data for severely obese patients with any DOAC, data are insufficient to provide evidence-based guidance regarding DOAC dose reduction for obese patients after the initial 6 months of full dose for extended treatment of VTE.

### 3.2 | Clinical data for VTE prevention

Data for VTE prevention come primarily from studies in orthopedic patients.

#### 3.2.1 | Apixaban

One study analyzed pooled data from the ADVANCE-2 and ADVANCE-3 trials (which compared apixaban 2.5 mg twice daily to enoxaparin for postoperative prevention of VTE in knee and hip arthroplasty, respectively) and analyzed by weight.<sup>19</sup> In the highest BMI category of  $\geq 30$  kg/m<sup>2</sup>, similar rates of the primary VTE outcome of proximal DVT, nonfatal PE or VTE related death occurred in the in patients receiving apixaban compared with enoxaparin (11/1149 [0.96%] vs. 23/1239 [1.9%] respectively; RR 0.52; 0.25–1.07), with similar rates of major bleeding (7/1483 [0.5%] versus 11/1552 [0.7%]; absolute risk difference 0.24; CI 0.79–0.30).

#### 3.2.2 | Betrixaban

No data were identified analyzing betrixaban by weight.

#### 3.2.3 | Dabigatran

A post hoc analysis of pooled data from three phase 3 trials comparing dabigatran with enoxaparin 40 mg daily for prophylaxis following orthopedic surgeries (RE-MODEL, RE-NOVATE, and RE-NOVATE II), found that, for BMI of  $\geq 35$  kg/m<sup>2</sup>, similar rates of VTE and VTE-related mortality occurred with dabigatran and enoxaparin (3.5% vs. 2.8%, respectively, OR 1.25; 0.33–4.75), with similar rates of major bleeding (1.0% vs. 1.1%, respectively; OR 0.95; 0.13–6.80).<sup>20</sup> Limiting to BMI  $\geq 40$  kg/m<sup>2</sup>, 3/42 (7.1%) of patients on dabigatran and 1/43 (2.3%) on enoxaparin had VTE and VTE-related mortality, while none had major bleeding.

#### 3.2.4 | Rivaroxaban

A pooled analysis of four phase 3 studies of rivaroxaban versus enoxaparin for thromboprophylaxis following orthopedic surgery (RECORD-1, RECORD-2, RECORD-3, and RECORD-4) stratified by weight (but not BMI), and found that in the highest weight category of  $>90$  kg, similar rates of symptomatic VTE and all-cause mortality occurred in each treatment group (0.6% in patients receiving rivaroxaban vs. 1.3% in patients receiving enoxaparin; HR 0.49; 0.2–1.1),

with a significant increase in composite of major bleeding and clinically relevant non-major bleeding for those receiving rivaroxaban compared with enoxaparin (4.4% vs. 2.7%; HR 1.6; 1.1–2.4).<sup>21</sup>

#### 3.2.5 | Pooled DOAC

A meta-analysis of five phase 3 RCT comparing apixaban or dabigatran with enoxaparin for postarthroplasty thromboprophylaxis found that, for patients with BMI  $\geq 30$  kg/m<sup>2</sup>, similar rates of VTE or VTE-related deaths occurred for DOAC and enoxaparin (2.19 vs. 2.24%, respectively; OR 0.88, 95% CI 0.32–2.37), with similar rates of major and CRNB bleeding (0.58 vs. 0.86%, respectively; OR 0.67, 95% CI 0.35–1.28) (revised data, personal communication with Dr. Pathak).<sup>22</sup>

### 3.3 | Pharmacokinetic/pharmacodynamic data

The PK/PD data evaluation was limited to studies derived from VTE patients and those that reported PK/PD data for both VTE and AF indication given the paucity of data (Table S1).

#### 3.3.1 | Apixaban

Two PK studies demonstrate alteration of apixaban levels in patients of higher weight. Upreti et al. compared apixaban levels after a single dose in 54 healthy subjects divided into three weight categories ( $<50$  kg, 65–85 kg,  $\geq 120$  kg), and found 31% lower mean peak apixaban concentration (144 vs. 207 ng/ml), 24% higher volume of distribution (75.6 vs. 61.0 L), and 23% lower area under the curve (AUC) in the higher compared with the reference weight group.<sup>23</sup> A second study compared apixaban levels in a group of 23 patients (three with VTE indication) with mean BMI 31 kg/m<sup>2</sup> and weight  $\leq 120$  kg with a group of 23 patients (five with VTE indication) with mean BMI 49 kg/m<sup>2</sup> and weight  $>120$  kg. They showed that the higher weight patients had significantly lower peak apixaban anti-Xa levels at 2 h, nonsignificantly lower levels at 4 h, and lower AUC.<sup>24</sup> On the other hand, Martin et al.<sup>25</sup> studied a population of 100 patients weighing  $\geq 120$  kg taking apixaban or rivaroxaban for AF and VTE (84% of whom had BMI  $\geq 40$  kg/m<sup>2</sup>), and found all 19 peak apixaban levels (including all VTE patients) and 89% of 18 trough levels to be in the expected range.

#### 3.3.2 | Betrixaban

We did not identify PK/PD studies of betrixaban analyzing by weight.

#### 3.3.3 | Dabigatran

One study measured peak DOAC levels in 38 patients weighing  $>120$  kg (for all indications). Of 10 patients taking dabigatran, 20%

had peak plasma concentrations below the usual on-treatment range and below the median trough level reported in the literature (no subanalysis by indication was performed).<sup>26</sup>

### 3.3.4 | Edoxaban

In a PK model developed from data of 11 edoxaban clinical studies that included body weights ranging from 31 kg to 165 kg, nonrenal clearance decreased significantly with lower body weight.<sup>27</sup>

### 3.3.5 | Rivaroxaban

In a study of rivaroxaban in 48 healthy volunteers, similar PK measures were found in subjects weighing >120 kg compared with those weighing 70–80 kg, including similar peak plasma concentration (149.0 ng/ml [percentage coefficient of variation (CV) 20.4%] vs. 143.4 ng/ml [CV 26.5%]), AUC (1155 g.h/L [CV 15.6%] vs. 1029 g.h/L [CV 20.1%]) and half-life (7.30 h [CV 25.4%] vs. 7.20 h [CV 42.1%]), suggesting that obesity does not significantly affect the peak concentration, distribution or half-life of rivaroxaban.<sup>28</sup> In another study of 219 patients taking rivaroxaban for VTE, there were no significant differences in peak levels of rivaroxaban levels for patients weighing >120 kg ( $n = 44$ ) compared with those 50–120 kg ( $n = 135$ ).<sup>29</sup> In a study measuring DOAC levels for all indications, of 21 patients >120 kg, six (28%) had rivaroxaban peak levels below the fifth percentile of peak concentrations reported as usual on-treatment range.<sup>26</sup> In the previously referenced study by Martin et al.,<sup>25</sup> of the 58 rivaroxaban levels, 26 (45%) peak levels were below expected ranges (11/22 for AF and 15/36 for VTE), and all 21 trough levels were within expected ranges.

Other studies have developed PK models of rivaroxaban and investigated the influence of weight. In a PK model developed using pooled data from two phase 2 studies of rivaroxaban in acute DVT (EINSTEIN-DVT and ODIXa-DVT trials), body weight did not significantly affect maximum serum concentration ( $C_{max}$ ), but volume of distribution decreased 0.8% per kilogram below the median low body weight of 56 kg, although the clinical significance of this is unknown.<sup>30</sup> Another study developed a PK model from 101 patients taking rivaroxaban for VTE, including 17 with weight >100 kg and six with BMI  $\geq 40$  kg/m<sup>2</sup>, and found that creatinine clearance but not weight best predicted rivaroxaban exposure.<sup>31</sup> In a population PK model derived from 913 patients (including 86 with weight >120 kg and 74 with BMI >40 kg/m<sup>2</sup>, the majority of whom had AF indication), simulated patients of 200 kg and 150 kg had lower median AUC and  $C_{max}$  compared with a 70-kg simulated patient; however, the prediction intervals overlapped across body weight and the authors concluded that weight had a minor influence on PK of rivaroxaban.<sup>32</sup> Finally, an integrated population PK model using pooled data from 4918 patients in seven clinical trials across all approved indications again found that BMI had a minor influence on the PK of rivaroxaban.<sup>33</sup>

### 3.3.6 | PK/PD summary

In summary, several studies have shown little impact of body weight on the PK/PD of rivaroxaban. Although some peak rivaroxaban levels were reported in the low range, most peak and trough have been within previously reported ranges. PK changes resulting from obesity have been demonstrated in apixaban; however, a study of apixaban drug levels in obese patients showed all peak and most trough within range.<sup>25</sup> PK and drug-level data for dabigatran are limited but that which exists shows a considerable proportion of levels below expected ranges, which is concerning for use in obesity. Although PK studies showed impact of body weight on edoxaban, a large post hoc RCT analysis did not show a significant impact of increasing weight on PK of edoxaban.

Important limitations to DOAC levels must be acknowledged. First, therapeutic targets for DOACs remain unknown. Although it is reasonable to assume that levels matter, as they do for other anticoagulants (e.g., International Normalized Ratio for VKA, anti-Xa/partial thromboplastin time for heparin), and two studies - DOAC drug levels have generally not been reported nor correlated with risk for clinical outcomes. One showed an inverse relationship between trough concentration of dabigatran and the probability of an ischemic event<sup>34</sup> and another demonstrated risk of major bleeding increases as plasma edoxaban levels rise.<sup>35</sup> Instead, currently available reference DOAC levels represent “expected” or “on-therapy ranges,” rather than therapeutic targets. In addition, interpretation of levels may be limited by large inter- and intra-patient variability.<sup>36–38</sup> Therefore, although levels within “expected” ranges can be reassuring, currently there are not sufficient data to make clinical decisions based on drug-specific levels.

## 3.4 | Bariatric surgery

Bariatric surgeries may alter bioavailability of oral drugs by decreasing absorptive surfaces and/ or reducing caloric intake. Apixaban absorption occurs primarily in the upper gastrointestinal tract (stomach and jejunum) with more limited absorption throughout, with reduction of  $C_{max}$  by about 60% when apixaban was released into distal small bowel.<sup>39,40</sup> Dabigatran appears to be absorbed in the lower stomach and duodenum.<sup>41,42</sup> Edoxaban is absorbed in the proximal small intestine and is dependent on acidic solubility.<sup>43,44</sup> Rivaroxaban appears to be absorbed to a significant degree in the stomach, as absorption is reduced (29% decrease in AUC and 56% decrease in  $C_{max}$ ) when the drug is released into the proximal small intestine.<sup>45</sup> Anticipated effects of bariatric surgeries, including sleeve gastrectomy, gastric banding, Roux-en-Y-gastric bypass (RYGB) on alteration of DOAC absorption are summarized in Table 2.<sup>41,43</sup> In addition, the reduced oral caloric intake immediately following bariatric surgery may impact bioavailability in the acute setting of the 15- and 20-mg dosages of rivaroxaban used for VTE treatment.<sup>45</sup> However, data specific to the use of DOAC after bariatric surgery are sparse and limited to PK/PD studies with small numbers of patients or case reports. One study investigated rivaroxaban

TABLE 2 Expected impact of bariatric surgery procedures on absorption of DOACs

DOAC	Site of Absorption in Gastrointestinal Tract	Surgical Intervention and Anticipated Effect on Absorption		
		Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration <sup>39</sup>	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine <sup>41,42,49</sup>	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment <sup>43,44</sup>	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach <sup>43-45</sup>	Possibly reduced	Possibly reduced	Possibly reduced

Abbreviations: DOAC, direct oral anticoagulant; RYGB, Roux-en-Y gastric bypass.

anti-Xa levels in 12 patients given a single dose of prophylactic rivaroxaban before and 6–8 months after sleeve gastrectomy and RYGB and found no difference in rivaroxaban anti-Xa levels.<sup>46</sup> Another study investigated DOAC levels in 18 patients on chronic anticoagulation, who had undergone bariatric surgery a median of median of 4.9 years before study enrollment. The study showed that median peak rivaroxaban level in the bariatric surgery group was significantly lower than that in the control group (159 ng/ml in surgery vs. 249 ng/ml in the control group;  $p = .02$ ), whereas peak plasma drug levels of apixaban were within the expected range.<sup>47</sup> Finally, a case report of a patient with BMI 61 kg/m<sup>2</sup> (181 kg), who had widely variable VKA for several months after RYGB, was subsequently treated with rivaroxaban 20 mg and found to have peak and trough levels within expected ranges.<sup>48</sup> These data suggest that DOACs may be appropriate to prescribe after at least 6–12 months following bariatric surgery. However, in the early/acute setting after bariatric surgery, prescribers should consider alterations in the gastrointestinal tract that may lead to malabsorption as well as altered and reduced oral intake. A cautious approach would include early treatment with a parenteral anticoagulant (e.g., low molecular weight heparin [LMWH], fondaparinux) followed by a switch to VKA or DOAC in the stable postacute phase. If switch to DOAC is made for long-term anticoagulation, prescribers may consider obtaining trough levels, which, if within expected ranges, suggest adequate absorption.

### 3.5 | Limitations

Limitations to conclusions regarding DOAC use in patients with obesity include the paucity of data at extremes of weight (BMI  $\geq 50$  kg/m<sup>2</sup> and weight  $>150$  kg), as most studies consider “high weight” as BMI  $>30$  kg/m<sup>2</sup> and weight  $>120$  kg. In addition, studies are inconsistent in comparisons, with some comparing DOAC with VKA, and others comparing a given drug across weight categories. Furthermore, although each DOAC should be considered individually, rather than grouped together, data on individual DOAC are limited. Although PK/PD data can provide assistance in predicting changes, the clinical

impact is uncertain and cannot serve as a replacement for clinical data; moreover, no DOAC has a clinically validated therapeutic range, neither for VTE prophylaxis nor treatment. At present, however, the main limitation is the lack of prospective randomized trials to evaluate individual DOAC against LMWH/VKA in the acute and long-term treatment of VTE in severely obese patients. Neither post hoc analyses of phase 3 trials nor observational data can replace adequately powered prospective RCTs with clinical endpoints. Until then, current conclusions should be regarded as preliminary.

### 3.6 | Guidance statements

The guidance statements are meant to provide practical guidance for clinicians (Table 3). “Recommend” indicates a strong guidance statement based on existing literature, whereby the clinician should consider adopting the practice in most cases, whereas “suggest” reflects a weak guidance statement because of limited existing literature whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients. As for all cases, our statements may provide guidance but do not replace clinical judgment for the management of an individual patient.

#### 3.6.1 | DOAC use in patients with obesity

1. Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m<sup>2</sup> or weight 120 kg. For patients with BMI  $>40$  kg/m<sup>2</sup> or weight  $>120$  kg, we recommend that the individual DOACs should be used as follows:
2. For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.

TABLE 3 Summary guidance statements

**Summary Guidance Statements for use of DOACs in Patients with Obesity**

- 1). Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m<sup>2</sup> or weight 120 kg. For patients with BMI >40 kg/m<sup>2</sup> or weight >120 kg, we recommend that the individual DOACs should be used as follows:
- 2). For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
- 3). For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
- 4). We suggest not to use dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m<sup>2</sup> or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
- 5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
- 6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

Abbreviations: BMI, body mass index; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

3. For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
4. We suggest not using dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m<sup>2</sup> or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
5. We suggest not regularly following peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.

### 3.6.2 | DOAC use in patients who have undergone bariatric surgery

1. We suggest not using DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of

concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

## 4 | CONCLUSIONS

Available data suggest that rivaroxaban and apixaban can be adequate for treatment of VTE in patients with obesity regardless of body weight and BMI. We acknowledge that plasma DOAC levels within published ranges may provide reassurance for the treating clinician, but in view of absent correlating clinical outcome data as to what constitutes therapeutic target values, they are currently insufficient to influence management. Studies should be undertaken to establish therapeutic ranges for individual DOACs. Because clinical data remain limited for DOACs in the treatment of VTE in patients with obesity, and particularly with extreme obesity, we encourage future randomized controlled trials to be conducted in this population.

### CONFLICT OF INTEREST

Dr. Martin reports funding from Janssen Scientific Affairs for an investigator-initiated study. Dr. Huisman reports grants from ZonMW Dutch Healthcare Fund, and grants and fees for presentations to the hospital from Boehringer-Ingelheim, Pfizer-BMS, Bayer Health Care, Aspen, and Daiichi-Sankyo, outside the submitted work. Dr. Beyer-Westendorf reports grants and personal fees from Boehringer-Ingelheim, Pfizer-BMS, Bayer, Daiichi-Sankyo, DOASENSE, and Portola, outside the submitted work. Drs. Davidson and Sandset declare no conflicts. Dr. Moll reports consulting fees from Bristol-Myers-Squibb.

### AUTHOR CONTRIBUTIONS

Karlyn A. Martin contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version. Jan Beyer-Westendorf contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version. Bruce L. Davidson contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version. Menno V. Huisman contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version. Per M. Sandset contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version. Stephan Moll contributed to the development and review of guidance document, the writing of the manuscript, and final approval of the submitted version.



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## REFERENCES

- World Health Organization. "Obesity and overweight," 2018. Available at <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>.:~:text=Some%20recent%20WHO%20global%20estimates,years%20and%20older%20were%20overweight.&text=In%202016%2C%2039%25%20of%20adults,women%20were%20obese%20in%202016. Accessed 28 Oct 2020.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
- Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(6):1308-1313.
- Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*. 2019;92:98-107.
- Kushnir M, Choi Y, Eisenberg R, et al. Efficacy and safety of direct oral factor Xa inhibitors compared with warfarin in patients with morbid obesity: a single-centre, retrospective analysis of chart data. *Lancet Haematol*. 2019;6(7):e359-e365.
- Cohen A, Sah J, Lee T, et al. Effectiveness and safety of apixaban vs. warfarin in venous thromboembolism patients with obesity and morbid obesity. *J Clin Med*. 2021;10(2):200.
- Di Nisio M, Vedovati MC, Riera-Mestre A, et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. *Thromb Haemost*. 2016;116(4):739-746.
- Costa OS, Beyer-Westendorf J, Ashton V, et al. Effectiveness and safety of rivaroxaban versus warfarin in obese patients with acute venous thromboembolism: analysis of electronic health record data. *J Thromb Thrombolysis*. 2021;51(2):349-358. <https://doi.org/10.1007/s11239-020-02199-0>
- Perales IJ, San Agustín K, DeAngelo J, Campbell AM. Rivaroxaban versus warfarin for stroke prevention and venous thromboembolism treatment in extreme obesity and high body weight. *Ann Pharmacother*. 2020;54(4):344-350.
- Spyropoulos AC, Ashton V, Chen YW, Wu B, Peterson ED. Rivaroxaban versus warfarin treatment among morbidly obese patients with venous thromboembolism: comparative effectiveness, safety, and costs. *Thromb Res*. 2019;182:159-166.
- Di Minno MN, Lupoli R, Di Minno A, Ambrosino P, Scalera A, Dentali F. Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: a meta-analysis of randomized controlled trials. *Ann Med*. 2015;47(1):61-68.
- 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*. 2020;51(2):388-396.
- Tittl L, Endig S, Marten S, Reitter A, Beyer-Westendorf I, Beyer-Westendorf J. Impact of BMI on clinical outcomes of NOAC therapy in daily care - results of the prospective Dresden NOAC Registry (NCT01588119). *Int J Cardiol*. 2018;262:85-91.
- Wysockinski WE, Froehling DA, Houghton DE, et al. Effectiveness and safety of apixaban and rivaroxaban for acute venous thromboembolism therapy in patients with extremes in body weight. *Eur J Haematol*. 2020;105(4):484-494.
- Coons JC, Albert L, Bejjani A, Isabella CJ. Effectiveness and safety of direct oral anticoagulants versus warfarin in obese patients with acute venous thromboembolism. *Pharmacotherapy*. 2020;40(3):204-210.
- Aloi KG, Fierro JJ, Stein BJ, Lynch SM, Shapiro RJ. Investigation of direct-acting oral anticoagulants and the incidence of venous thromboembolism in patients weighing  $\geq 120$  kg compared to patients weighing  $< 120$  kg. *J Pharm Pract*. 2019;34(1):64-69.
- Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222.
- Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708.
- Pineo GF, Gallus AS, Raskob GE, et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. *J Thromb Haemost*. 2013;11(3):444-451.
- Eriksson BI, Dahl OE, Feuring M, et al. Dabigatran is effective with a favourable safety profile in normal and overweight patients undergoing major orthopaedic surgery: a pooled analysis. *Thromb Res*. 2012;130(5):818-820.
- Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost*. 2011;105(3):444-453.
- Pathak R, Karmacharya P, Giri S, et al. Meta-analysis on efficacy and safety of new oral anticoagulants for venous thromboembolism prophylaxis in overweight and obese postarthroplasty patients. *Blood Coagul Fibrinolysis*. 2015;26(6):635-642.
- 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(6):908-916.
- Wasan SM, Feland N, Grant R, Aston CE. Validation of apixaban anti-factor Xa assay and impact of body weight. *Thromb Res*. 2019;182:51-55.
- Martin AC, Thomas W, Mahir Z, et al. Direct oral anticoagulant concentrations in obese and high body weight patients: a cohort study. *Thromb Haemost*. 2021;121(02):224-233. <https://doi.org/10.1055/s-0040-1715834>
- Piran S, Traquair H, Chan N, Bhagirath V, Schulman S. Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kilograms: a retrospective study. *Res Pract Thromb Haemost*. 2018;2(4):684-688.
- Yin OQ, Miller R. Population pharmacokinetics and dose-exposure proportionality of edoxaban in healthy volunteers. *Clin Drug Invest*. 2014;34(10):743-752.
- 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(2):218-226.
- Arachchilage D, Reynolds R, Devey T, Maclean R, Kitchen S, van Veen JJ. Effect of extremes of body weight on drug level in patient treated with standard dose of rivaroxaban for venous thromboembolism; real life experience. *Thromb Res*. 2016;147:32-35.
- Mueck W, Eriksson BI, Bauer KA, et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct factor Xa inhibitor—in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet*. 2008;47(3):203-216.
- Barsam SJ, Patel JP, Roberts LN, et al. The impact of body weight on rivaroxaban pharmacokinetics. *Res Pract Thromb Haemost*. 2017;1(2):180-187.
- 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(9):2296-2307.

33. Willmann S, Zhang L, Frede M, et al. Integrated population pharmacokinetic analysis of rivaroxaban across multiple patient populations. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(5):309-320.
34. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol*. 2014;63(4):321-328.
35. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet*. 2015;385(9984):2288-2295.
36. Chan NC, Hirsh J, Ginsberg JS, Eikelboom JW. Real-world variability in dabigatran levels in patients with atrial fibrillation: reply. *J Thromb Haemost*. 2015;13(6):1168-1169.
37. Hawes EM, Deal AM, Funk-Adcock D, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. *J Thromb Haemost*. 2013;11(8):1493-1502.
38. Testa S, Tripodi A, Legnani C, et al. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: results observed in four anticoagulation clinics. *Thromb Res*. 2016;137:178-183.
39. Byon W, Nepal S, Schuster AE, Shenker A, Frost CE. Regional gastrointestinal absorption of apixaban in healthy subjects. *J Clin Pharmacol*. 2018;58(7):965-971.
40. Apixaban FDA package insert. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/202155s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf). Accessed 12 Dec 2020.
41. Martin KA, Lee CR, Farrell TM, Moll S. Oral anticoagulant use after bariatric surgery: a literature review and clinical guidance. *Am J Med*. 2017;130(5):517-524.
42. Douros A, Schlemm L, Bolbrinker J, Ebinger M, Kreutz R. Insufficient anticoagulation with dabigatran in a patient with short bowel syndrome. *Thromb Haemost*. 2014;112(2):419-420.
43. Hakeam HA, Al-Sanea N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). *J Thromb Thrombolysis*. 2017;43(3):343-351.
44. Parasrampur DA, Kanamaru T, Connor A, et al. Evaluation of regional gastrointestinal absorption of edoxaban using the enterion capsule. *J Clin Pharmacol*. 2015;55(11):1286-1292.
45. Xarelto FDA package insert. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/202439s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf). Accessed 11 Dec 2020.
46. Kröll D, Nett PC, Borbély YM, et al. The effect of bariatric surgery on the direct oral anticoagulant rivaroxaban: the extension study. *Surg Obes Relat Dis*. 2018;14(12):1890-1896.
47. Rottenstreich A, Barkai A, Arad A, Raccach BH, Kalish Y. The effect of bariatric surgery on direct-acting oral anticoagulant drug levels. *Thromb Res*. 2018;163:190-195.
48. Mahlmann A, Gehrisch S, Beyer-Westendorf J. Pharmacokinetics of rivaroxaban after bariatric surgery: a case report. *J Thromb Thrombolysis*. 2013;36(4):533-535.
49. Grainger B, Holloway R, Merriman E, et al. Evidence of impaired dabigatran absorption following laparoscopic Roux-en-Y gastric bypass surgery: the Auckland regional experience (2011-2018). *Br J Haematol*. 2020;191(2):e67-e69.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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