

Direct-acting oral anticoagulant use at extremes of body weight: Literature review and recommendations

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Purpose. To review the literature on treatment of venous thromboembolism (VTE) and prevention of cardioembolic stroke with direct-acting oral anticoagulants (DOACs) in low- and high-body-weight patients and to make recommendations regarding agent selection and dosing in these patient populations.

Summary. The selection and optimal dosing of DOACs in low- and high-body-weight patients has not yet been fully elucidated by clinical trials; however, evidence suggests that issues of both safety and efficacy in patients at the extremes of body weight may warrant careful consideration when selecting a DOAC for such patients. This review provides a thorough discussion of the use of DOACs in the treatment of VTE and prevention of cardioembolic stroke in patients at the extremes of body weight and provides guidance regarding agent selection.

Conclusion. While the published evidence on use of DOACs in patients at extremes of body weight is sparse, apixaban and rivaroxaban appear to have the most favorable safety and efficacy profiles. Edoxaban and dabigatran should be avoided.

Keywords: anticoagulants, atrial fibrillation, factor Xa inhibitors, obesity, thromboembolism

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Since Food and Drug Administration (FDA) approval of dabigatran in 2010, the direct-acting oral anticoagulants (DOACs) have become an increasingly utilized medication class in the treatment of venous thromboembolism (VTE) and for the prevention of cardioembolic stroke in patients with nonvalvular atrial fibrillation (NVAF). Each DOAC has been compared to warfarin and was found to be noninferior for treatment of VTE and prevention of cardioembolic stroke, and DOACs' ease of administration, fixed dosing, and lack of monitoring requirements make them appealing alternatives.¹⁻⁹ In the majority of the landmark DOAC trials, patients with low (<60 kg) or high (>120 kg) body weight were underrepresented. The most recent American College of Chest Physicians guidelines clearly recommend DOACs over vitamin K antagonist (VKA) therapy for VTE and cardioembolic stroke prophylaxis;

however, neither guidance document discusses nuances of DOAC use in patients at the extremes of body weight.^{10,11} The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has recommended avoidance of DOACs in patients with a body mass index (BMI) of >40 kg/m² or a weight of >120 kg due to a lack of supportive clinical data, and the committee has advocated for drug-specific peak and trough levels if these agents are used in such patients.¹² Guidance detailing monitoring of DOACs suggests that direct thrombin inhibitors may be monitored using activated partial thromboplastin time (APTT) or thrombin time (TT) and that factor Xa inhibitors may be monitored using anti-factor Xa activity.¹³ However, use of factor Xa monitoring requires drug plasma calibrants, which are not widely available. As such, there is currently no reliable way to monitor DOAC

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effectiveness that is widely available. Furthermore, conflicting pharmacokinetic and pharmacodynamic analyses have detailed the impact of body weight on DOAC efficacy.^{14,15} There are currently no guidance documents pertaining to DOAC use in low-body-weight patients.

The obesity epidemic has been well documented in recent years, and according to the Centers for Disease Control and Prevention, 39.8% of US adults were obese in 2015-2016.¹⁶ Obesity is a well-established risk factor for deep vein thrombosis (DVT), pulmonary embolism (PE), and heart failure and NVAF.¹⁷ Furthermore, obesity causes significant pharmacokinetic changes via alterations in volume of distribution, protein binding, and clearance. Since elimination of all DOACs relies at least partially on renal clearance, alterations in renal function may significantly impact drug removal. Obese patients may have increased kidney size or increased cardiac output, each of which may increase renal clearance; however, obese patients also have a higher incidence of kidney disease secondary to type 2 diabetes mellitus, which reduces DOAC clearance.^{18,19}

While a significantly smaller proportion of the population is underweight (1.5% in 2015-2016), this population also presents significant challenges in anticoagulation management.²⁰ Underweight patients typically have reduced adipose tissue, which may alter volume of distribution as well as renal clearance. Given the paucity of data and potential for significant pharmacokinetic changes, dosing guidance for DOAC use in patients at the extremes of body weight is needed.

The purpose of this review is to provide an overview of the available literature concerning DOAC use in patients with high or low body weights and to make recommendations for drug selection in these populations. A critical assessment of the thromboembolic and bleeding risk of each patient should also be considered when selecting a DOAC for treatment of NVAF or VTE.

KEY POINTS

- The utility of direct-acting oral anticoagulants (DOACs) in under- or overweight patients continues to be a topic of clinical debate.
- If a DOAC is to be used in an overweight patient, use of apixaban or rivaroxaban is supported by the most robust data, and dabigatran and edoxaban should be avoided.
- A thorough evaluation of embolic and bleeding risk, as well as a discussion with the patient, should be undertaken prior to initiation of a DOAC in these patient populations.

Methods

A PubMed search covering the period 2010 to January 2019 was conducted using the following keywords or search terms: dabigatran, rivaroxaban, apixaban, edoxaban, body weight, obesity AND venous thromboembolism, and obesity AND atrial fibrillation. Additional references were identified from a review of citations.

Retrieved articles and references were evaluated for content, and articles that evaluated the use of DOACs for VTE treatment or cardioembolic stroke prevention in patients of low or high body weight were included. High body weight was defined as a BMI of ≥ 30 kg/m² or a body weight of >120 kg, and low body weight was defined as a body weight of <60 kg. Articles evaluating triple therapy (dual antiplatelet therapy plus an anticoagulant) or the utility of DOACs for VTE prophylaxis in medically ill or bariatric surgery patients were excluded, as were studies involving pediatric patients (<18 years of age) or pregnant patients. Given the paucity of data, all study designs were considered.

Results

Use of DOACs for VTE and NVAF in overweight adults. Tittl and colleagues²¹ used data from a DOAC registry to evaluate the impact of BMI on DOAC effectiveness in 3,432 patients, 731 of whom had a BMI of 30.0 to 34.9 kg/m² and 346 of whom had a BMI of ≥ 35 kg/m². All DOACs were included, and indications for both VTE and NVAF were evaluated. In total, 2,104 patients (61.3%) were prescribed rivaroxaban, 685 (20%) were prescribed apixaban, 348 (10.1%) were prescribed dabigatran, and 295 (8.6%) were prescribed edoxaban. Ultimately, the authors found no significant differences in DOAC safety or effectiveness between patients with a BMI of <30 kg/m² and those with a BMI of ≥ 30 kg/m². This study provided evidence to support the overall effectiveness of DOACs in patients with a BMI of >30 kg/m² but did little to define the role in therapy of individual DOACs.

Piran and colleagues¹⁵ completed a pharmacokinetic study in 38 obese patients (weight of >120 kg) taking a DOAC for any indication to evaluate peak DOAC plasma concentrations. Twenty-one patients (55%) were prescribed rivaroxaban, 10 (26%) were prescribed dabigatran, and 7 (18%) were prescribed apixaban. Within the dabigatran cohort, 20% of patients had peak plasma concentrations below the 10th percentile and 2 patients had peak plasma concentrations below the median trough level from previous pharmacokinetic studies. Within the rivaroxaban group, 6 patients (29%) had peak plasma concentrations below the fifth percentile. Patients with a lower peak plasma concentration tended to be younger (mean age, 55 years vs 66 years; $P = 0.06$); however, there was no significant difference in body weight in patients with low peak concentrations vs patients with appropriate peak concentrations. There were no patients in the apixaban group who had low peak drug levels. While this study shed light on key pharmacokinetic differences between DOACs,

there is currently no clinical correlation between drug levels and effectiveness or safety in the populations of interest.

Kushnir and colleagues²² published a retrospective analysis of outcomes in 795 patients with a BMI of ≥ 40 kg/m² receiving anticoagulation with apixaban, rivaroxaban, or warfarin for NVAF or VTE. In total, 366 patients were prescribed anticoagulation for VTE treatment. In this group, 152 patients (41.5%) were anticoagulated with rivaroxaban, 47 (12.8%) with apixaban, and 167 (45.7%) with warfarin. Ultimately, there was no difference in rates of recurrent VTE and cardioembolic stroke between patients anticoagulated with rivaroxaban, apixaban, or warfarin (2% vs 2.1% vs 1.2% [$P = 0.74$] and 2.3% vs 1% vs 1.3% [$P = 0.71$], respectively). A subgroup analysis of all patients with a BMI of ≥ 50 kg/m² was also completed, and there were no VTEs reported in the DOAC group. Finally, rates of bleeding were not significantly different between groups; however, in the NVAF cohort DOAC use was associated with significantly lower rate of major bleeds than warfarin use (2.9% vs 7.9%, $P = 0.02$). While the sample size in this study was small, the data are encouraging in that they indicate that rivaroxaban and apixaban are as effective as warfarin for VTE and cardioembolic stroke prevention in an obese patient population and have a more favorable safety profile.²²

Finally, Talamo and colleagues²³ published a retrospective analysis of patients of low (<60 kg, $n = 27$), normal (61-120 kg, $n = 26$), or high body weight (>120 kg, $n = 26$) taking either rivaroxaban or apixaban for any indication and found no significant difference in the rate of major bleeding between reference-weight and high-body-weight patients (11.54% vs 0%, $P = 0.0744$), although no bleeding events were noted in the reference-weight population.²³

DOAC use for VTE treatment in overweight adults. Table 1 displays comparative data from clinical trials that evaluated the effectiveness of DOAC use for the treatment of VTE in high-body-weight patients.

Dabigatran. After the RE-COVER and RE-COVER II trials, dabigatran was approved by FDA for the treatment of VTE disease in 2014. The RE-COVER trial was a randomized, double-blind, noninferiority trial comparing dabigatran to dose-adjusted warfarin for preventing 6-month recurrence of symptomatic VTE or related death.¹ Dabigatran was noninferior to warfarin for VTE prophylaxis (rate of VTE recurrence and/or death, 2.7% vs 2.5%; hazard ratio [HR], 1.05, with a 95% confidence interval [CI] of 0.65-1.70), with similar rates of major bleeding in the dabigatran and warfarin groups (1.6% and 1.9%, respectively; HR, 0.82 [95% CI, 0.45-1.48]). The mean (SD) BMI and weight in the dabigatran group were 28.9 (5.7) kg/m² and 85.5 (19.2) kg, respectively. In total, 502 study patients (20%) weighed more than 100 kg, 538 (21%) had a BMI of 30.0-34.9 kg/m², and 306 (12%) had a BMI of ≥ 35 kg/m². The study was underpowered to detect differences between BMI groups. The RE-COVER II trial aimed to confirm the results of the RE-COVER trial and (given the low event rate in the first trial) perform a pooled analysis.²⁴ No significant safety or efficacy differences were found between the dabigatran and warfarin groups. Within the dabigatran analysis, 438 patients (34.2%) weighed 100 kg or more, 544 (43%) had a BMI of 30.0-34.9 kg/m², and 302 (23.6%) had a BMI of ≥ 35 kg/m². The RE-COVER and RE-COVER II trials included more obese patients than many of the landmark DOAC studies, but they were not powered to detect outcome differences in high-body-weight patients.

The RE-MEDY trial was designed to test the efficacy of dabigatran vs warfarin for long-term VTE prophylaxis.²⁵ This trial confirmed the noninferiority of dabigatran to warfarin and found that dabigatran had a better safety profile. A subgroup analysis conducted in patients weighing 100 kg or more found no significant between-group difference in the rate of recurrent VTE (2.6% vs 1%, $P = 0.55$); however, the study was underpowered to detect a difference between the weight subgroups, as there were only 299 patients (21%) in the

dabigatran group who weighed 100 kg or more. These findings lent further credence to the notion that dabigatran is likely as effective as warfarin in patients weighing more than 100 kg, but given the lack of stratification by BMI, the results are less applicable to patients with a BMI of >40 kg/m².

The safety and efficacy data on dabigatran use in obese patients is sparse. While the RE-COVER, RE-COVER II, and RE-MEDY trials included more obese patients than later landmark trials, they were still underpowered to truly evaluate the safety and efficacy of dabigatran in this population. None of the studies reported outcomes in patients with a BMI of ≥ 40 kg/m²; therefore, warfarin remains the anticoagulant of choice in these patients.

Rivaroxaban. Based on the results of the EINSTEIN and EINSTEIN-PE trials, rivaroxaban was approved by FDA for the treatment of acute DVT and PE in 2012.^{3,5} The first phase of the EINSTEIN trial compared rivaroxaban to warfarin or low-molecular-weight heparin (LMWH) in an open-label, randomized, event-driven, noninferiority trial involving patients with acute VTE. The continuation phase of the EINSTEIN trial included patients who completed 6 to 12 months of treatment for acute VTE. In these 2 studies, 245 of 1,731 (14.2%) and 85 of 602 (14.1%) patients in the respective rivaroxaban groups weighed greater than 100 kg.³ The investigators did not complete any analyses evaluating the safety and efficacy of rivaroxaban in patients weighing more than 100 kg. Similarly, the EINSTEIN-PE trial was a randomized, open-label, event-driven, noninferiority trial that compared rivaroxaban against standard therapy in patients with symptomatic PE.⁵ In the rivaroxaban group, 345 of 2,419 patients (14.3%) weighed more than 100 kg, but no analyses of high-body-weight patients were conducted. Ultimately, no conclusions can be drawn from the EINSTEIN or EINSTEIN-PE trials regarding the utility of rivaroxaban in obese patients.

Kubitza and colleagues²⁶ completed a single-dose pharmacokinetic

Table 1. Summary of Clinical Trials of DOAC Use for VTE Treatment in Overweight Patients

Reference	Study Design	Weight Categories	Obese Patients, No. (% of Total)	Intervention	Results
Studies of Dabigatran					
Schulman et al ¹ (2009) ^a	Randomized, double-blind, noninferiority	≥100 kg BMI of 30.0–34.9 kg/m ² BMI of ≥35 kg/m ²	502 (20) 538 (21) 306 (12)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in obese patient population: no significant difference in rate of primary outcome in patients ≥100 kg (4.4% vs 3%, <i>P</i> = 0.76 for interaction), patients with BMI of 30.0–34.9 kg/m² (2.6% vs 1.8%, <i>P</i> = 0.89 for interaction), and patients with BMI of ≥35 kg/m² (3.5% vs 2.3%, <i>P</i> = 0.89 for interaction)
Schulman et al ²⁴ (2014) ^a	Randomized, double-blind, noninferiority	≥100 kg BMI of 30.0–34.9 kg/m ² BMI of ≥35 kg/m ²	438 (34) 544 (43) 302 (24)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in obese patient population: no significant difference in rate of primary outcome in patients with BMI of ≥100 kg (4.1% vs 3.6%, <i>P</i> = 0.99 for interaction), patients with BMI of 30.0–34.9 kg/m² (2.9% vs 2.8%, <i>P</i> = 0.48 for interaction), and patients with BMI of ≥35 kg/m² (3.3% vs 2.2%, <i>P</i> = 0.48 for interaction)
Schulman et al ²⁵ (2013) ^a	Double-blind, randomized	≥100 kg	299 (21)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in obese patient population: no significant difference in rate of recurrence of VTE between groups (2.6% vs 1%, <i>P</i> = 0.555 for interaction)
Study of Rivaroxaban					
Kushnir et al ²² (2018)	Retrospective, cohort	BMI of ≥40 kg/m ² BMI of ≥50 kg/m ²	152 (100) 30 (19.7)	Rivaroxaban vs VKA vs apixaban	<ul style="list-style-type: none"> No difference in rate of VTE recurrence (2% vs 1.2%, vs 2.1%, <i>P</i> = 0.45); no difference in rate of major bleeding (1.3% vs 2.4% vs 2.1%, <i>P</i> = 0.77); no recurrence of VTE in patients with BMI of >50 kg/m²
Studies of Apixaban					
Agnelli et al ⁷ (2013) ^a	Randomized, double-blind, prospective	≥100 kg BMI of >35 kg/m ²	522 (19.4) 349 (13)	Apixaban vs LMWH plus VKA	<ul style="list-style-type: none"> Findings in obese patient population: in patients with weight ≥100 kg, apixaban noninferior for acute VTE treatment (rate of recurrent VTE, 2.2% vs 3.5%; <i>P</i> = 0.43) and patients with BMI of >35 kg/m² (rate of recurrent VTE, 2% vs 3.56%; <i>P</i> = 0.06)
Choi et al ²⁸ (2017) ^a	Retrospective, cohort	BMI of ≥30 kg/m ²	58 (100)	Apixaban vs VKA	<ul style="list-style-type: none"> No difference in rate of VTE recurrence (1.7% vs 1.1%, <i>P</i> = 0.76); no difference in overall bleeding rate (8.3% vs 12%, <i>P</i> = 0.23) Less major bleeding with apixaban (0.6% vs 4.3%, <i>P</i> = 0.02)
Kushnir et al ²² (2018)	Retrospective, cohort	BMI of ≥40 kg/m ² BMI of ≥50 kg/m ²	47 (100) 10 (21.3)	Apixaban vs VKA vs rivaroxaban	<ul style="list-style-type: none"> No difference in rate of VTE recurrence (2.1% vs 1.2% vs 2%, <i>P</i> = 0.45); no difference in rate of major bleeding (2.1% vs 2.4% vs 1.3%, <i>P</i> = 0.77); no recurrence of VTE in patients with BMI of >50 kg/m²

Abbreviations: CRNM, clinically relevant nonmajor; DOAC, direct-acting oral coagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aStudy was underpowered to detect a difference in patients at weight extremes.

crossover study in 48 patients, 12 of whom weighed more than 120 kg, with an average BMI of 43.5 kg/m². Rivaroxaban was dosed at 10 mg daily, and plasma and urine drug concentrations were used to calculate area under the curve (AUC). Pharmacodynamic efficacy was measured by measuring anti-factor Xa activity. The researchers found no significant difference in rivaroxaban maximum concentration (C_{max}) in patients weighing more than 120 kg compared to patients weighing 70 to 80 kg (149 µg/L vs 143.4 µg/L); however, the maximum anti-factor Xa activity was slightly, although not significantly, reduced in the high-body-weight group.²⁶ This study had several limitations worth noting. First, the dose of rivaroxaban used was subtherapeutic for the treatment of VTE, and the clinical utility of anti-factor Xa monitoring to determine the effectiveness of DOACs is poorly understood. Additionally, the single-dose nature of this study could not accurately account for the long-term influence of renal clearance on rivaroxaban levels.

The efficacy data for rivaroxaban in the treatment of VTE in obese patients is sparse. Given the heterogeneity of the studies that included rivaroxaban, as well as a lack of head-to-head studies of rivaroxaban vs warfarin in an obese patient population, it is difficult to argue that a recommendation to use rivaroxaban for anticoagulation in this patient population is evidence based. Furthermore, the available pharmacokinetic data indicate mixed results.^{26,27} With regard to safety, the available data suggest that rivaroxaban is comparable to warfarin in terms of bleeding events. Rivaroxaban may be considered in patients who have a BMI of ≥ 30 kg/m² or a contraindication to warfarin.

Apixaban. Apixaban was approved for the treatment of acute VTE in 2012 after the results of the AMPLIFY trial, which demonstrated the noninferior efficacy of apixaban relative to LMWH plus warfarin as well as its more favorable safety profile.⁷ Only 19.4% of patients in the apixaban group weighed 100 kg or more, and only 13% had a BMI of >30 kg/m².

The investigators completed a subgroup analysis of patients by weight and BMI, and the noninferior effectiveness of apixaban was maintained in these subgroups; however, the study was underpowered for this analysis.

Upreti and colleagues¹⁴ published results of an open-label, single-dose, parallel-group pharmacokinetic study to assess the impact of body weight extremes on the pharmacokinetics and pharmacodynamics of apixaban. Nineteen patients were enrolled in the high-body-weight group (weight of ≥ 120 kg and BMI of ≥ 30 kg/m²). The researchers found 31% (90% CI, 18%-41%) and 23% (90% CI, 9%-35%) lower mean C_{max} and AUC values, respectively, in the high-body-weight group relative to the reference group. Furthermore, the half-life of apixaban was approximately 3 hours shorter in the high-body-weight group (8.8 hours vs 12.0 hours), and the mean volume of distribution was approximately 24% higher (75.6 L vs 61.0 L). Pharmacodynamically, the authors measured anti-factor Xa activity to assess apixaban effectiveness and found a trend toward lower anti-factor Xa activity in the high-body-weight group 3 hours after dosing (mean activity, 1.85 IU/mL vs 2.79 IU/mL) but no significant between-group difference 12 hours after dosing (0.70 IU/mL vs 0.77 IU/mL). Ultimately, the researchers concluded that the pharmacokinetics and pharmacodynamics of apixaban are modestly impacted by high body weight but that this impact is not clinically significant. There were, however, several limitations of this study. First, the study's single-dose nature did not fully realize the impact of long-term alterations in renal clearance that are common in obese patients. Second, the relationship between anti-factor Xa activity and apixaban efficacy is not well established. Finally, the patient population represented in this study was younger, with a mean age of 29 years; therefore, these results should not be extrapolated to an older population.

Choi and colleagues²⁸ completed a retrospective analysis of 390 patients

with a BMI of ≥ 40 kg/m² who were anticoagulated with warfarin or apixaban for NVAF or VTE. In total, 58 and 88 patients with VTE were anticoagulated with apixaban and warfarin, respectively. The investigators found no significant differences in rates of VTE recurrence (1.7% vs 1.1%, $P = 0.76$) or overall bleeding (8.3% vs 12%, $P = 0.23$); however, the study was underpowered to detect these differences given the estimated rates of embolism and bleeding. The researchers noted a significant reduction in major bleeding in the apixaban group vs the warfarin group (0.6% vs 4.3%, $P = 0.02$), which suggests that the favorable safety profile of apixaban found in the AMPLIFY trial may extend to obese patients.

High-quality evidence endorsing the efficacy of apixaban for the acute treatment of VTE in an obese patient population is sparse. Apixaban should be considered in this population only if patients cannot tolerate warfarin. Apixaban appears to maintain a favorable safety profile and may be an appealing anticoagulant in patients at higher bleeding risk.^{7,28}

Edoxaban. In 2013, Büller and colleagues⁹ published results of the HOKUSAI VTE noninferiority trial, in which 4,921 patients were randomly assigned to receive either the standard of care (warfarin) or edoxaban (30-60 mg daily). Only 611 patients (14.8%) in the edoxaban group weighed more than 100 kg, and the investigators did not evaluate the impact of body weight on safety or efficacy outcomes.⁹ There have been no pharmacokinetic studies evaluating edoxaban in an obese population. Given the lack of data, edoxaban should be avoided for VTE treatment in obese patients.

DOACs for cardioembolic stroke prophylaxis in overweight adults with NVAF. Table 2 displays comparative data from clinical trials that evaluated the efficacy of each DOAC in the treatment of NVAF in high-body-weight patients.

Studies evaluating multiple DOACs. Kido and colleagues²⁹ published results of a retrospective, single-center cohort study comparing the efficacy of DOACs with warfarin in obese patients with NVAF.

Table 2. Summary of Studies of DOAC Use for Cardioembolic Stroke Prevention in Overweight Patients With Nonvalvular Atrial Fibrillation

Reference	Study Design	Weight Categories	Obese Patients, No. (% of Total)	Intervention	Results
Study Evaluating Multiple DOACs					
Kido et al ²⁹ (2019) ^a	Retrospective, single-center cohort	BMI of >40 kg/m ² or weight >120 kg	128 (100)	DOACs (dabigatran, n = 20; rivaroxaban, n = 25; apixaban, n = 19) vs VKA	<ul style="list-style-type: none"> No difference in incidence of stroke or TIA (1.75% vs 1.24%, P = 0.66) No difference in rate of major bleeding (2.18% vs 4.97%, P = 0.11) Numerically higher incidence of TIA in the dabigatran group vs rivaroxaban and apixaban groups (4.03% vs 1.07% vs 0%)
Study of Dabigatran					
Connolly et al ² (2009) ^a	Randomized, noninferiority	≥100 kg	3,099 (17)	Dabigatran 110 mg vs dabigatran 150 mg vs VKA	<p>Findings in obese population:</p> <ul style="list-style-type: none"> No difference in incidence of stroke or systemic embolism (0.8% vs 0.87% vs 0.94%, P = 0.48 for dabigatran 110 mg, P = 0.42 for dabigatran 150 mg)
Study of Rivaroxaban					
Kushnir et al ²² (2018)	Retrospective, cohort	BMI of ≥40 kg/m ² BMI of ≥50 kg/m ²	174 (100) 37 (21)	Rivaroxaban (n = 174), apixaban (n = 103) vs VKA (n = 152)	<ul style="list-style-type: none"> No difference in rate of stroke (2.3% vs 1% vs 1.3%, P = 0.71) Trend toward reduction in rate of major bleeding with rivaroxaban and apixaban vs VKA (2.9% vs 2.9% vs 7.9%, P = 0.06)
Studies of Apixaban					
Sandhu et al ³¹ (2016)	Post hoc analysis of randomized, double-blind trial	BMI of ≥30 kg/m ²	7,159 (40)	Apixaban vs VKA	<p>Results in patients with BMI of ≥30 kg/m²</p> <ul style="list-style-type: none"> No significant difference in rate of stroke or systemic embolism (0.97% vs 1.28%, 95% CI, 0.55-1.05) Apixaban significantly reduced occurrence of composite outcome of stroke, systemic embolism, MI, and death (3.78% vs 4.51%; HR, 0.84 [95% CI, 0.71-0.99]) No significant difference in rate of major bleeding (2.21% vs 2.51%; HR, 0.84 [95% CI, 0.67-1.07])
Choi et al ²⁸ (2017) ^a	Retrospective, cohort	BMI of ≥30 kg/m ²	124 (100)	Apixaban vs VKA	<ul style="list-style-type: none"> No difference in incidence of stroke (0.8% vs 2.4%, P = 0.31) No difference in rate of bleeding (8.3% vs 12%, P = 0.23) Lower rate of major bleeding with apixaban (0.6% vs 4.3%, P = 0.02)
Kushnir et al ²² (2018)	Retrospective, cohort	BMI of ≥40 kg/m ² BMI of ≥50 kg/m ²	103 (100) 19 (100)	Apixaban (n = 103) vs VKA (n = 152) vs rivaroxaban (n = 174)	<ul style="list-style-type: none"> No difference in rate of stroke (1% vs 1.3% vs 2.3%, P = 0.71) Trend toward reduction in rate of major bleeding with apixaban and with rivaroxaban vs VKA (2.9% vs 2.9% vs 7.9%, P = 0.06)

Abbreviations: CI, confidence interval; DOAC, direct-acting oral coagulant; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.
^aStudy was underpowered to detect a difference in patients at weight extremes.

In total, 128 patients were included, 64 (50%) of whom were anticoagulated with warfarin, 25 (39.1%) with rivaroxaban, 20 (31.1%) with dabigatran, and 19 (29.7%) with apixaban. All patients had a BMI of >40 kg/m² or weighed more than 120 kg. There were no significant differences in rates of stroke and/or transient ischemic attack (TIA) and major bleeding between the DOAC and warfarin groups (1.75% vs 2.07% [$P = 0.8$] and 2.18% vs 4.97% [$P = 0.11$], respectively); however, dabigatran-treated patients had a numerically higher annual rate of TIA than patients who received rivaroxaban or apixaban (4.03% vs 1.07% vs 0%). Of note, this study was underpowered to detect significant between-group differences due to small sample size. Globally, this study outlined the utility of DOACs as a reasonable treatment modality for NVAF; however, it did little to differentiate between DOACs.

Dabigatran. Based on the results of the RE-LY trial, dabigatran was approved by FDA for stroke prevention in NVAF in 2010. The RE-LY trial was a randomized noninferiority trial comparing blinded dabigatran use (110 or 150 mg by mouth twice daily) vs open-label warfarin use, and the primary outcome of interest was the rate of stroke or systemic embolism.² Both doses of dabigatran were found to be noninferior to warfarin for the primary outcome (1.53% vs 1.11% vs 1.69%, $P < 0.001$), with the 150-mg dose found superior to warfarin (relative risk [RR], 0.66; 95% CI, 0.53-0.82; $P < 0.001$). Low-dose dabigatran was demonstrated to be associated with a lower rate of major bleeding (2.71% vs 3.36%, $P = 0.003$); however, there was no significant difference in bleeding rates with use of high-dose dabigatran vs either low-dose dabigatran (3.11% vs 2.71%, $P = 0.052$) or warfarin (3.11% vs 3.36%, $P = 0.31$). The RE-LY trial included 3,099 patients (17%) who weighed 100 kg or more. There were no significant differences in rates of stroke or systemic embolism with use of low-dose dabigatran, high-dose dabigatran, or warfarin in the higher-body-weight population (0.8% vs 0.87% vs 0.94% [$P = 0.49$ for comparison of dabigatran 110 mg with warfarin;

$P = 0.42$ for comparison of dabigatran 150 mg with warfarin]); however, the study was not powered to detect a significant difference in this subgroup.

Reilly and colleagues³⁰ completed a pharmacokinetic analysis of the RE-LY trial to evaluate the association between dabigatran serum concentrations and safety and efficacy outcomes. The investigators compared drug levels in patients weighing less than 50 kg, 50 to 99.9 kg, or 100 kg or more and found peak concentrations in these weight groups of 2.63, 1.94, and 1.56 ng/mL/mg, respectively. Median trough concentrations were 1.01, 0.84, and 0.66 ng/mL/mg, respectively. The utility of drug level monitoring and correlation of drug levels to clinical outcomes of DOAC use is unclear; however, there is certainly a trend of lower concentrations in high-body-weight patients. Reilly et al noted an inverse relationship between dabigatran trough levels and the probability of a symptomatic embolic event (C statistic, 0.657; 95% CI, 0.61-0.71). The results of this pharmacokinetic analysis raise questions regarding the impact of weight on dabigatran serum levels and the drug's effectiveness.

Given the unfavorable pharmacokinetic profile of dabigatran in obese patients as well as a lack of strong clinical data, dabigatran should likely be avoided in this patient population.

Rivaroxaban. In 2011, based on results of the ROCKET-AF trial, rivaroxaban received FDA approval for prevention of cardioembolic stroke in patients with NVAF.⁴ This trial was a double-blind, randomized noninferiority trial comparing rivaroxaban to warfarin in over 14,000 patients. Safety and efficacy outcomes were reported for body weight and BMI subgroups. Only 2.46% and 2.88% of patients in the rivaroxaban group weighed more than 90 kg and had a BMI of >35 kg/m², respectively. There were no differences noted in safety or thromboembolic outcomes in obese patients; however, the study was underpowered to detect a difference within these subgroups.

It is difficult to draw strong conclusions on the use of rivaroxaban in the

treatment of NVAF in an obese patient population given low cardioembolic stroke rates and a tendency toward analysis of combined event rates in DOAC trials. Additionally, the data for the use of rivaroxaban in patients with a BMI of >30 kg/m² is even more sparse. Rivaroxaban may be considered in patients with a BMI of 30.0 to 34.9 kg/m² who are poor candidates for warfarin therapy.

Apixaban. Results of the ARISTOTLE trial prompted FDA approval of apixaban for NVAF in 2013 based on superior efficacy results and a significant reduction in bleeding events.⁶ A 2015 post hoc analysis of the trial, which included 7,159 patients (40%) with a BMI of ≥ 30 kg/m², aimed to explore the impact of adiposity on stroke incidence in patients with NVAF.³¹ When comparing apixaban to warfarin among patients with a BMI of ≥ 30 kg/m², the authors found no significant difference in rates of stroke or systemic embolism (0.97% vs 1.28%; HR, 0.76 [95% CI, 0.55-1.05]) but did find a significant difference in the composite outcome of stroke, systemic embolism, MI, and death (3.78% vs 4.51%; HR, 0.84 [95% CI, 0.71-0.99]). There was no significant difference in rates of major bleeding between groups (2.12% vs 2.51%; HR, 0.84 [95% CI, 0.67-1.07]). When evaluating the impact of high waist circumference (>102 cm for men, >88 cm for women) on outcomes, the authors found no efficacy difference between the 2 drugs (rate of recurrent VTE, 1.29% vs 1.22%; 95% CI, 0.82-1.36), but patients taking apixaban had a significantly lower rate of major bleeding (2.14% vs 2.96%; 95% CI, 0.6-0.87). This study, in addition to the study by Choi and colleagues, suggested that apixaban is at least as effective as warfarin at preventing stroke and systemic embolism and has a favorable safety profile.^{28,31}

As with the data for high-body-weight patients with VTE, the evidence for apixaban for NVAF in high-body-weight patients is sparse and heterogeneous. However, it appears that apixaban maintains a favorable safety and efficacy profile when compared to warfarin. Like the other DOACs,

the evidence supporting apixaban use in patients with a BMI of >35 kg/m² is sparse, and warfarin should remain the preferred anticoagulant in that population.

Edoxaban. In 2015, FDA approved edoxaban for the prevention of stroke and systemic embolization in patients with NVAF based on the results of the ENGAGE-AF TIMI 48 trial.⁸ Edoxaban was noninferior to warfarin for the prevention of stroke or systemic embolism; however, no analysis in overweight patients was conducted, and outcomes were not stratified by body weight. The majority of studies that compared DOACs to warfarin for NVAF either did not include patients taking edoxaban or had such small numbers of edoxaban-prescribed patients that little can be inferred from the results.^{21,23,29} Given the paucity of data regarding the safety and efficacy of edoxaban in obese patients with NVAF, an alternative DOAC should be selected in this population.

DOACs for VTE treatment in underweight adults. Table 3 displays comparative data from clinical trials that evaluated the efficacy of dabigatran for the treatment of VTE in low-body-weight patients.

Dabigatran. The RE-COVER, RE-COVER II, and RE-MEDY studies included very few low-body-weight patients and did not provide significant insight into the utility of dabigatran for the treatment of acute VTE in underweight patients.^{1,24,25} Additionally, there are currently no pharmacokinetic studies evaluating dabigatran use in low-body weight patients to guide clinician decision making. Dabigatran should be avoided in low-body-weight patients with VTE disease unless significant contraindications to warfarin exist.

Rivaroxaban. Both the EINSTEIN and EINSTEIN-PE trials included low-body-weight patients; however, the percentage of underweight patients (≤50 kg) included was low in both trials (1.6% and 2.1%, respectively).^{3,5} Safety and efficacy outcomes were not evaluated in relation to weight in these studies, so minimal conclusions can be drawn.

Table 3. Summary of Studies of DOAC Use for VTE Treatment in Underweight Patients

Reference	Study Design	Weight Categories	Obese Patients, No. (% of Total)	Intervention	Results
Studies of Dabigatran					
Schulman et al ¹ (2009) ^a	Randomized, double-blind, noninferiority	<50 kg	18 (0.7)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in underweight population: no VTE events occurred in either group
Schulman et al ²⁴ (2014) ^a	Randomized, double-blind, noninferiority	<50 kg	57 (2.2)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in underweight population: 1 VTE event in warfarin group
Schulman et al ²⁵ (2013) ^a	Double-blind, randomized	<50 kg	10 (0.7)	Dabigatran vs VKA	<ul style="list-style-type: none"> Findings in underweight population: no VTE events recorded in either group
Study of Rivaroxaban					
Prins et al ²⁷ (2013)	Pooled analysis of data from EINSTEIN-DVT and EINSTEIN-PE trials	≤50 kg	107 (7)	Rivaroxaban vs LMWH plus VKA	<ul style="list-style-type: none"> Findings in fragile patients: lower rate of major bleeding with rivaroxaban (1.3% vs 4.5%; HR, 0.27 [95% CI, 0.13-0.54])
Study of Apixaban					
Agnelli et al ⁷ (2013) ^a	Randomized, double-blind, prospective	≤60 kg	225 (9)	Apixaban vs LMWH plus VKA	<ul style="list-style-type: none"> Findings in underweight population: in patients with weight ≤60 kg, apixaban noninferior to VKA for acute VTE treatment (rate of recurrent VTE, 2.7 % vs 4.3%; P = 0.43)

Abbreviations: CI, confidence interval; DOAC, direct-acting oral coagulant; HR, hazard ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
^aStudy was underpowered to detect a difference in patients at weight extremes.

Prins and colleagues²⁷ performed a pooled data analysis of the EINSTEIN trials that included fragile patients (age of >75 years, creatinine clearance of <50 mL/min, or weight of ≤50 kg). In total, 1,573 patients (19%) were classified as fragile; however, the majority (1,279, or 81%) were deemed fragile secondary to advanced age. There was no difference in rates of recurrent VTE in fragile patients treated with rivaroxaban vs a LMWH plus warfarin, but there was a significantly lower incidence of major bleeding with rivaroxaban (1.3% vs 4.5%; HR, 0.27 [95% CI, 0.13–0.54]). These results are difficult to apply to patients of low body weight but suggest that rivaroxaban may be a safer option in older patients.

A study by Kubitz et al²⁶ found significantly higher peak rivaroxaban plasma concentrations in low-body-weight (≤50 kg) patients when compared to standard-body-weight patients (1.24 µg/L vs 1.00 µg/L, $P = 0.04$); however, there was no significant difference in AUC, half-life, or anti-factor Xa activity between groups. The clinical implications of peak plasma concentrations of rivaroxaban are currently unknown, making these data difficult to utilize in a clinical setting.

Ultimately, there is evidence suggesting that rivaroxaban may be a safer alternative to warfarin in the treatment of VTE in low-body-weight patients; however, there are currently no comparative data on the safety and efficacy of rivaroxaban and other DOACs in this patient population.

Apixaban. While there is a partially weight-based recommendation for apixaban in NVAf, there is less guidance on use of the drug in VTE treatment, and the available evidence on this topic is sparse.³²

The AMPLIFY trial included 225 patients (9% of the total) with a body weight of ≤60 kg and was not powered to detect safety or efficacy differences in this population.⁷ The study by Upreti and colleagues¹⁴ demonstrated 27% and 20% higher mean apixaban C_{max} and AUC values, respectively, in patients weighing 50 kg or less. Additionally,

underweight patients had a 14% lower volume of distribution than heavier patients (52.7 L vs 61 L), and the apixaban half-life was 4 hours longer (15.8 hour vs 12 hours). These pharmacokinetic differences did not translate to differences in 12-hour postdose anti-factor Xa activity, but they do beg the question as to whether underweight patients are overanticoagulated with the standard 10-mg starting dose of apixaban.

Apixaban appears to be an efficacious option for anticoagulation in a low-body-weight population; however, the safety profile is less well established. There are studies demonstrating a higher risk of bleeding with DOAC use in low-body-weight patients, and apixaban concentrations appear to be higher in a low-body-weight population. It is, however, well established that apixaban is safer than either rivaroxaban or dabigatran in a normal-body-weight population.^{14,33} Apixaban use may be considered in low-body-weight patients who cannot tolerate warfarin.

Edoxaban. The HOKUSAI VTE trial enrolled 524 patients (12.7% of the total population) who weighed less than 60 kg, but a safety or efficacy analysis within weight categories was not completed.⁸ The dose of edoxaban for patients with a weight of <60 kg was halved in the study secondary to prior knowledge of higher bleeding risk in patients with a low body weight.³⁴ This reduction in edoxaban dose is reflected in the drug's package insert, as 30 mg daily is recommended for patients with a weight of ≤60 kg (after 5 days of parenteral anticoagulant therapy).³⁵ Based solely on the HOKUSAI VTE trial results, it is difficult to draw strong conclusions on the utility of edoxaban for VTE treatment in low-body-weight patients.

DOAC use for cardioembolic stroke prophylaxis in underweight adults. Table 4 displays comparative data from clinical trials evaluating the efficacy of DOACs for the treatment of NVAf in low-body-weight patients.

Dabigatran. The RE-LY trial included 376 patients (2% of the total population)

who weighed less than 50 kg but was not powered to detect safety or efficacy differences within a low-body-weight subgroup.² The previously discussed pharmacokinetic analysis by Reilly and colleagues³⁰ noted 21% and 53% higher geometric mean drug concentrations in patients weighing less than 50 kg compared to patients weighing 50 to 100 kg and patients weighing 100 kg or more, respectively. Those investigators also noted a positive correlation between drug concentrations and bleeding events. As such, dabigatran should be used with caution in patients with a low body weight given their higher risk of bleeding relative to that of their normal-weight counterparts.

Rivaroxaban. The ROCKET-AF trial included 93 patients (4.62% of the total population) and 72 patients (4.25% of the total) with a weight of ≤70 kg or a BMI of ≤25 kg/m², respectively; however, no specific analyses focused on low-body-weight patients were conducted.⁴ Additionally, pharmacokinetic data suggest insignificant changes in rivaroxaban pharmacokinetics and pharmacodynamics in low-body-weight patients.²⁶ Rivaroxaban may be considered for NVAf in low-body-weight patients.

Apixaban. The apixaban package insert provides a recommendation for a 2.5-mg reduction of the dose (given by mouth twice daily) in patients with 2 or more of the following risk factors: body weight of ≤60 kg, age of ≥80 years, and serum creatinine concentration of ≥1.5 mg/dL. This recommendation is based on documented pharmacokinetic changes as well as an increased risk of bleeding in such patients; however, the impact of body weight alone on apixaban safety is unclear.^{32,33}

In the ARISTOTLE trial, 1,985 of patients (11%) in the apixaban group weighed 60 kg or less, and improved safety and efficacy outcomes observed with use of apixaban vs VKA persisted in this group.⁶ However, it is unclear how many of these patients were on reduced-dose apixaban. Alexander and colleagues³⁶ published a secondary analysis of the ARISTOTLE trial to evaluate the impact of each dose-reduction

Table 4. Summary of Studies of DOAC Use for Cardioembolic Stroke Prevention in in Underweight Patients With Nonvalvular Atrial Fibrillation

Reference	Study Design	Weight Category	Obese Patients, No. (% of Total)	Intervention	Results
Study of Dabigatran					
Connolly et al ² (2009) ^a	Randomized, noninferiority	<50 kg	376 (2)	Dabigatran 110 mg vs dabigatran 150 mg vs VKA	Findings in underweight population: no difference in incidence of stroke or systemic embolism (2.6% vs 2.2% vs 5.0%, <i>P</i> = 0.48 for dabigatran 110 mg, <i>P</i> = 0.42 for dabigatran 150 mg)
Studies of Apixaban					
Granger et al ⁶ (2011) ^a	Randomized, double-blind	≤60 kg	1,985 (11)	Apixaban vs VKA	Findings in underweight population: <ul style="list-style-type: none"> No difference in incidence of stroke or systemic embolism (2.0% vs 3.2%, <i>P</i> = 0.26)
Alexander et al ³⁶ (2016)	Secondary analysis of a randomized, double-blind trial	≤60 kg	1,426 (36)	Apixaban vs VKA	<ul style="list-style-type: none"> Lower rate of major bleeding with apixaban (2.3% vs 4.0%; HR, 0.69 [0.4-0.9])

Abbreviations: DOAC, direct-acting oral coagulant; HR, hazard ratio; VKA, vitamin K antagonist.
^aStudy was underpowered to detect a difference in patients at weight extremes.

criteria on bleeding risk. Of the 13,356 patients in the ARISTOTLE trial who met only 1 dose-reduction criteria, 1,426 (36%) weighed 60 kg or less. There was a significantly lower rate of major bleeding events in the apixaban group compared to the warfarin group (2.3% vs 4.0%; HR, 0.69 [95% CI, 0.4-0.9]) in patients with a weight of ≤60 kg. The researchers concluded that the 5-mg dose of apixaban maintained the efficacy and safety benefit in patients with isolated advanced age, low body weight, or renal dysfunction.

While the safety data on use of apixaban in low-body-weight patients appears promising, several studies have found an increased risk of bleeding with DOAC use in low-body-weight patients compared to standard-weight patients.^{23,34,37} Notably, these studies did not compare individual DOACs to warfarin but rather combined all DOACs for analysis. As such, it is difficult to form any conclusions regarding apixaban specifically from these studies. Ultimately, apixaban appears to be both safe and efficacious for patients with low body weights. A dose reduction based on low body weight alone is not warranted.

Edoxaban. The ENGAGE-AF TIMI 48 trial included 2,083 patients who weighed 60 kg or less. Of these patients, 684 (9.7%) received edoxaban 60 mg daily and 698 (9.9%) received edoxaban 30 mg daily.⁸ Edoxaban was deemed noninferior to warfarin for the prevention of stroke or systemic embolism; however, the lower edoxaban dose was associated with a significantly higher incidence of ischemic stroke (HR for comparison with 60-mg dose, 1.41; 95% CI, 1.19-1.67; *P* < 0.001), which is reflected in the edoxaban labeling.³⁵ No analyses focused specifically on patients with low body weight were conducted; therefore, if edoxaban is selected for stroke prevention in NVAf in a low-body-weight patient, a dosage of 60 mg daily should be used.

Discussion

A lack of high-quality, randomized trials evaluating optimal DOAC

selection and dosing in high- and low-body-weight patients makes optimal drug selection difficult. Dabigatran and edoxaban should likely be avoided on the basis of negative pharmacokinetic data and minimal efficacy data. In the context of VTE and NVAE, safety and efficacy data support for use of rivaroxaban is comparable to that for warfarin, while apixaban has a more favorable safety profile. Ultimately, if warfarin cannot be used, both rivaroxaban and apixaban appear to be reasonable options for high-body-weight patients, and apixaban may be the most appropriate DOAC for low-body-weight patients.

Conclusion

While the evidence on DOAC use in patients at extremes of body weight is sparse, apixaban and rivaroxaban appear to have the most favorable safety and efficacy profiles. Edoxaban and dabigatran should be avoided.

Disclosures

The authors have declared no potential conflicts of interest.

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