Published in final edited form as:

J Thromb Haemost. 2016 June ; 14(6): 1308–1313. doi:10.1111/jth.13323.

Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH

K. MARTIN[*], **J. BEYER-WESTENDORF**[†], **B. L. DAVIDSON**[‡], **M. V. HUISMAN**[§], **P. M. SANDSET**[¶], and **S. MOLL**[*]

[*]Department of Medicine, Division of Hematology-Oncology, University of North Carolina, Chapel Hill, NC, USA [†]Thrombosis Research Unit, Center for Vascular Diseases, University Hospital, Technische Universität Dresden, Dresden, Germany [‡]Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle, WA, USA [§]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands [¶]Department of Hematology, Oslo University Hospital and University of Oslo, Oslo, Norway

Introduction

Four direct-acting oral anticoagulants (DOACs) – the thrombin inhibitor dabigatran, and the activated factor X (FXa) inhibitors apixaban, edoxaban, and rivaroxaban –are approved in many countries for the treatment of venous thromboembolism (VTE), the prevention of VTE after hip and knee arthroplasty, and ischemic stroke prevention in patients with non-valvular atrial fibrillation (AF). Because of their fixed dosing – without the need for routine monitoring – and limited dietary interactions, they are used as a convenient anticoagulant alternative to vitamin K antagonists (VKAs). In the product labeling (package inserts) of the approved DOACs, none has a dose adjustment for high weight or body mass index (BMI) in obese categories. However, there is uncertainty about their efficacy and safety in the obese population, with 'obese' defined by the National Institutes of Health as a BMI between 30 kg m^{-2} and 40 kg m^{-2}, and 'extreme obesity' as a BMI of > 40 kg m^{-2}. Although a recent publication has suggested recommendations for use of DOACs in the obese population [1], data from clinical outcomes studies and pharmacokinetic (PK)/pharmacodynamic (PD) studies regarding the efficacy and safety of DOACs in obese patients are limited. We reviewed the available data on the use of DOACs in obese patients through a PubMed search

Correspondence: Karlyn Martin, University of North Carolina at Chapel Hill, 170 Manning Drive, Campus Box 7305, Chapel Hill, NC 27599, USA. Tel.: +1 919 966 1996; fax: +1 919 966 6735. karlyn.martin@unchealth.unc.edu.

Addendum

K. Martin and S. Moll were responsible for concept and design. K. Martin, S. Moll, J. Beyer-Westendorf, B. L. Davidson, M. V. Huisman, and P. M. Sandset were responsible for interpretation of data, critical writing or revision of the intellectual content, and final approval of the version to be published.

Disclosure of Conflict of Interests

J. Beyer-Westendorf reports grants and personal fees from Bayer HealthCare, Boehringer Ingelheim, Pfizer, and Daiichi Sankyo, outside the submitted work. B. L. Davidson reports personal fees from Bayer, outside the submitted work. M. Huisman reports grants from Boehringer Ingelheim, GlaxoSmithKline, and Actelion, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

of key terms, including each DOAC in combination with the terms ‘pharmacokinetic’, ‘pharmacodynamic’, ‘drug level’, ‘VTE’, ‘VTE prophylaxis’, and ‘atrial fibrillation’. Data on obese patients in phase III clinical trials were pooled by anticoagulation indication to obtain risk ratios for DOACs versus VKAs. Guidance statements were then developed to provide practical guidance for clinicians regarding the use of DOACs in obese patients.

Evidence on the efficacy of VTE treatment and stroke prevention in AF

No large randomized controlled trial has specifically investigated the efficacy and safety of DOACs in the obese population. However, phase III clinical trials that demonstrated the efficacy and safety of DOACs as compared with VKAs included a moderate number of obese patients, and most included a subgroup analysis of efficacy by weight [2–11]. The conclusions are limited, however, by inconsistencies across studies, as shown in Table 1: the absolute weight cut-offs vary, and BMI stratification is found in only some analyses. Moreover, published data on the absolute weight of patients and the number of patients at the far extreme of weight in the trials are limited; none of the phase III clinical trials reported the number of patients enrolled with a BMI of > 40 kg m^{-2} or their clinical outcomes.

The weight category and number of obese patients in the phase III trials for each DOAC are listed in Table 1. All trials except ARISTOTLE and ENGAGE had a weight-based analysis for efficacy. Thus, two of four AF trials did not have a subanalysis by weight, and one AF trial (RE-LY) that analyzed by weight reported only an outcome rate per year and a total number of obese patients, without a breakdown of the number of patients in each treatment group. The major phase III trials that reported weight-based analyses demonstrated that the DOACs appeared to be equivalent to VKAs in the prevention of recurrent VTE and stroke in the highest-weight category of each of the trials, with a calculated risk ratio (RR) and a 95% confidence interval (CI) that crosses 1 (Figs S1 and S2). Additionally, the direct-acting oral anti-FXa agents appeared to be non-inferior in efficacy in obese patients as compared with normal-weight patients, with an equivalent calculated RR (Fig. S3). Notably, this did not hold true for a pooled analysis by weight of the use of dabigatran in VTE patients [10], in which the risk of the primary efficacy outcome was significantly higher for patients weighing > 100 kg than for patient of normal weight (50–100 kg) taking dabigatran (Fig. S3; RR 2.04, 95% CI 1.2–3.5). In addition to primary trial publications, two abstracts have published weight-based analyses. The first analyzed the RE-LY trial by BMI subgroups categorized into an upper 10% (BMI of > 36 kg m^{-2}), a middle 80% (BMI of 22.5 to ≤ 36 kg m^{-2}), and a bottom 10% (BMI of ≤ 22.5 kg m^{-2}), and found that the 1-year stroke/systemic embolism (S/SE) rate did not significantly differ in the highest BMI category among treatment groups of dabigatran 110 mg (1.2%, 95% CI 0.3–2.0), dabigatran 150 mg (0.9%, 95% CI 0.1–1.6), and warfarin (1.3%, 95% CI 0.4–2.3) [12]. Furthermore, the BMI category had comparable rates of S/SE to the middle BMI category, although both the middle and upper BMI categories tended to have higher rates of S/SE than the lowest BMI category [12]. The second abstract analyzed data from the EINSTEIN deep vein thrombosis (DVT) and pulmonary embolism (PE) studies divided into three weight categories of 50 kg, 50–100 kg, and > 100 kg, and found no association between body weight and risk of

recurrent VTE, and similar rates of recurrent VTE by treatment group in the highest weight category of > 100 kg (2.3% receiving DOACs versus 2.0% receiving VKAs) [13].

Evidence on the safety of VTE treatment and stroke prevention in AF

The evidence surrounding the safety of DOACs in obese patients is more limited. Only half of the major phase III trials (including only one of the AF trials) included a safety subgroup analysis by weight, namely AMPLIFY, Hokusai-VTE, EINSTEIN-DVT, EINSTEIN-PE, and ROCKET-AF [2,5,7–9]. As in the primary efficacy analysis, the weight divisions were inconsistent, with differences in absolute kilograms and BMI cut-offs. Furthermore, primary safety outcomes differed among trials: all but one reported the composite outcome of major bleeding and clinically relevant non-major bleeding as the primary outcome, whereas AMPLIFY reported only major bleeding (Table S2). Overall, the subgroup analyses by weight suggest that DOACs are safe in obese patients with calculated RRs with a 95% CI crossing 1 (Fig. S4). Notably, in one trial (AMPLIFY), the major bleeding rate for patients with a BMI of > 35 kg m^{-2} receiving apixaban was significantly lower than that for obese patients receiving a VKA (apixaban 0.6% versus VKA 3.5%, RR 0.16, 95% CI 0.04–0.70). Additionally, a published abstract of a subanalysis of the RE-LY data by BMI found that 1-year major bleeding rates were comparable across treatment groups for patients in the upper 10% of BMI (> 36 kg m^{-2}), with major bleeding rates for dabigatran 110 mg, dabigatran 150 mg and warfarin of 3% (95% CI 1.6–4.4), 4.4% (95% CI 2.7–6.1), and 3.7% (95% CI 2.2–5.2), respectively [12].

Evidence on the efficacy and safety of thromboprophylaxis following joint arthroplasty

Although large trials investigating the DOACs for thromboprophylaxis in orthopedic surgeries also included moderate numbers of obese patients, none of the initial publications included a subgroup analysis by weight. Subsequently, however, pooled analyses that include a subanalysis by weight have been published for each of the four DOACs. First, a pooled analysis of three phase III trials comparing dabigatran with enoxaparin 40 mg daily for prophylaxis in orthopedic surgeries (RE-MODEL, RE-NOVATE, and RE-NOVATE II) found similar rates of VTE (2.7% in patients receiving dabigatran versus 2.9% in patients receiving enoxaparin; odds ratio [OR] 0.92, 95% CI 0.5–1.7), major bleeding (1.3% in patients receiving dabigatran versus 1.1% in patients receiving enoxaparin; OR 1.25, 95% CI 0.5–2.9) and a composite outcome of major plus clinically relevant non-major bleeding (CRNMB) (5.4% in patients receiving dabigatran versus 4.6% in patients receiving enoxaparin; OR 1.17, 95% CI 0.8–1.8) in the highest BMI category (> 30 kg m^{-2}) [14]. Furthermore, the rates of efficacy and safety were similar in each treatment group across obesity subgroups of BMI 30–35 kg m^{-2}, 35–40 kg m^{-2}, and > 40 kg m^{-2} [14].

A pooled analysis of two apixaban studies, ADVANCE-2 and ADVANCE-3, comparing 2.5 mg of apixaban to 40 mg daily of enoxaparin, also included an analysis by body weight and BMI, and found a similar primary VTE outcome rate between treatment groups in the highest BMI category (≥ 30 kg m^{-2}) (1.0% in patients receiving apixaban versus 1.9% in patients receiving enoxaparin; RR 0.52, 95% CI 0.25–1.07), as well as similar rates of major

bleeding (0.5% in patients receiving apixaban versus 0.7% in patients receiving enoxaparin; absolute risk difference − 0.24, 95% CI − 0.79 to 0.30) and CRNMB (3.6% in patients receiving apixaban versus 4.9% in patients receiving enoxaparin; absolute risk difference 1.34, 95% CI − 2.8 to 0.1) [15].

Similarly, a pooled analysis of four phase III studies (RECORD-1, RECORD-2, RECORD-3, and RECORD-4) of rivaroxaban for thromboprophylaxis following orthopedic surgeries demonstrated similar rates of symptomatic VTE and all-cause mortality in each treatment group for patients weighing > 90 kg (0.6% in patients receiving rivaroxaban versus 1.3% in patients receiving enoxaparin; hazard ratio [HR] 0.49, 95% CI 0.2–1.1). In the safety analysis of the composite of major bleeding and CRNMB within the same highest weight subgroup, rivaroxaban was associated with an insignificant increase in bleeding as compared with enoxaparin (4.4% versus 2.7%; HR 1.6, 95% CI 1.1–2.4) [16].

Evidence on efficacy and safety from PK/PD data

In the absence of randomized controlled trials, PK/PD studies supplement data by providing insights into the effects of body weight on plasma drug concentrations, expected drug exposure, and half-lives. The available PK/PD data for each DOAC are summarized below.

A subgroup analysis of dabigatran peak and trough concentrations within the RELY trial demonstrated an inverse relationship between trough concentration and weight, with dose-normalized trough concentrations that were 21% lower for the high body weight group (> 100 kg) than for the reference body weight group (50–100 kg) [17]. A multivariate analysis showed an inverse relationship between trough concentration and the probability of an ischemic event; however, weight was not found to be a significant covariate for stroke in logistic regression of events [17].

A study of the pharmacokinetics of apixaban in healthy volunteers at the extremes of body weight included a comparison of a high body weight group (weight of > 120 kg and BMI of ≥ 30 kg m^{-2}) and a reference group (weight of 65–85 kg), and found a 31% lower mean peak apixaban concentration (144 ng mL^{-1} [coefficient of variation (CV) of 28%] versus 207 ng mL^{-1} [CV 24%]), a 24% higher volume of distribution ($\boldsymbol{V}_d$) (75.6 L [standard deviation (SD) 28] versus 61.0 L [SD 22]) and a 23% lower drug exposure (area under the curve [AUC] of 1561 ng h mL^{-1} [CV 31%] versus 2024 ng h mL^{-1} [CV 24%]) in the high body weight group than in the reference body weight group[18]. The 20% lower apixaban exposure in the high body weight group resulted in a statistically significant inverse relationship between apixaban exposure and body weight ($\boldsymbol{P} < 0.001$); however, the authors concluded that, because the effect was modest, there was no need to adjust the dose of apixaban in patients weighing > 120 kg. Additionally, the mean half-life of apixaban was found to be 8.8 h (SD 3.2) in the high body weight group as compared with 12.0 h (SD 5.4) in the reference weight group, but this was interpreted as unlikely to be clinically significant [18].

Although no studies examining the effects of body weight on the pharmacokinetics of edoxaban have been published to date, one study analyzed pooled data from 11 clinical

studies of edoxaban, and included body weight as a covariate [19]. The analysis included subjects with body weights ranging from 31 kg to 165 kg, with a mean of 81.8 kg. On the basis of the developed model, body weight significantly affected the non-renal clearance of edoxaban, with non-renal clearance decreasing with lower body weight [19].

Two studies have examined the effects of obesity on the pharmacokinetics of rivaroxaban. The first examined the pharmacokinetics of rivaroxaban at the extremes of body weight in a small study of healthy volunteers, and demonstrated similar peak plasma concentrations (149.0 ng mL^{-1} [CV 20.4%] versus 143.4 ng mL^{-1} [CV 26.5%]), AUCs (1155 μg h L^{-1} [CV 15.6%] versus 1029 μg h L^{-1} [CV 20.1%]) and half-lives (7.30 h [CV 25.4%] versus 7.20 h [CV 42.1%]) for rivaroxaban in a group of subjects weighing > 120 kg and in a group of subjects weighing 70–80 kg, respectively, suggesting that obesity does not significantly affect the peak concentration, distribution or half-life of rivaroxaban [20]. The second study developed a PK model for rivaroxaban by using pooled data of patients with acute DVT from two phase II studies (EINSTEIN-DVT and ODIXa-DVT trials), and did not find maximum plasma drug levels to be significantly influenced by body weight [21]. $\boldsymbol{V}_d$, however, directly correlated with body weight, with a decrease in $\boldsymbol{V}_d$ of 0.8% per kg below the median low body weight of 56 kg [21]. Therefore, on the basis of this model, higher-weight individuals may have increased $\boldsymbol{V}_d$ levels, although the clinical significance of this is unknown.

Discussion

As no randomized controlled trials of DOACs administered to large numbers of obese patients exist, decisions regarding the use of DOACs in this population must, instead, rely on the available evidence. Subgroup analyses of obese patients that were included in the large phase III DOAC trials suggest that DOACs are efficacious and safe in these patients. However, this conclusion must be tempered by the lack of available data on the extremes of weight and the numbers of patients in these extremes. PK/PD studies indicate that increasing body weight has a modest overall effect on PK parameters of the DOACs at the ranges tested, but suggest reduced drug exposure, lower peak concentrations and shorter half-lives of the drugs with higher body weights. The clinical implications of such changes are unknown, but they raise concerns about underdosing of DOACs in patients at the extremes of obesity. Checking DOAC-specific anticoagulant blood levels to attempt to assess anticoagulant effects in obese patients is problematic, for logistic and interpretative reasons. First, there are currently no defined therapeutic ranges for DOAC drug levels. Furthermore, the published levels show high interpatient variability among subjects for a given dose, and among populations with different indications for anticoagulation [22–25]. In addition to between-subject variability, there is high variability of dabigatran levels in the same patient; hence, one level may not be sufficient to reliably identify a patient with extreme values [23]. Currently, it is not known whether the other DOACs also have pronounced intraindividual variability. Therefore, although a DOAC-specific level may suggest that a patient is within an ‘on-therapy’ range, the interpretation of testing and its use in clinical management continue to be extremely challenging.

The guidance statements are meant to provide practical guidance for clinicians regarding the use of DOACs in obese patients. ‘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 due to 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 judgement for the management of individual patients.

Guidance statements

1. We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^{-2} and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.
2. We suggest that DOACs should not be used in patients with a BMI of > 40 kg m^{-2} or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about underdosing in the population at the extreme of weight.
3. If DOACs are used in a patient with a BMI of > 40 kg m^{-2} or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level (anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs). If the level falls within the expected range, continuation of the DOAC seems reasonable. However, if the drug-specific level is found to be below the expected range (Table S1) [17,24,26–29], we suggest changing to a VKA rather than adjusting the dose of the DOAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank D. Zeng and W. Zhong for their statistical analysis of the data. The manuscript was reviewed by the Chair and Vice-Chair of the Guidelines and Guidance Committee of the ISTH. K. Martin is supported by NIH grant T32 HL007149.

References

1. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016; 41:206–32. [PubMed: 26780747]
2. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369:799–808. [PubMed: 23808982]

3. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369:2093–104. [PubMed: 24251359]

4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365:981–92. [PubMed: 21870978]

5. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369:1406–15. [PubMed: 23991658]

6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361:1139–51. [PubMed: 19717844]

7. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363:2499–510. [PubMed: 21128814]

8. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012; 366:1287–97. [PubMed: 22449293]

9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365:883–91. [PubMed: 21830957]

10. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014; 129:764–72. [PubMed: 24344086]

11. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361:2342–52. [PubMed: 19966341]

12. Ezekowitz ME, Parise H, Connolly SJ, Brueckmann M, Kleine E, Clemens A, Parvataneni R, Yusuf S, Wallentin L. The use of dabigatran according to body mass index: the RE-LY experience. Eur Heart J. 2014; 35:1111.

13. Prins MH, Nisio MD, Vedovati MC, Riera-Mestre A, Mueller K, Cohen AT, Wells PS, Beyer-Westendorf J, Brighton TA, Bounameaux H, Schneider J, Lensing AW. Fixed-dose rivaroxaban is not associated with increased recurrent venous thromboembolism or major bleeding in patients with a high or low body weight. J Thromb Haemost. 2015; 13:35–6.

14. Eriksson BI, Dahl OE, Feuring M, Clemens A, Noack H, Hantel S, Friedman RJ, Huo M. Dabigatran is effective with a favourable safety profile in normal and overweight patients undergoing major orthopaedic surgery: a pooled analysis. Thromb Res. 2012; 130:818–20. [PubMed: 22840686]

15. Pineo GF, Gallus AS, Raskob GE, Chen D, Ramirez LM, Ramacciotti E, Lassen MR, Wang L. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. J Thromb Haemost. 2013; 11:444–51. [PubMed: 23279103]

16. Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, Bandel TJ, Homering M, Westermeier T, Kakkar AK. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. Thromb Haemost. 2011; 105:444–53. [PubMed: 21136019]

17. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L. RE-LY Investigators. 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; 63:321–8. [PubMed: 24076487]

18. Upreti VV, Wang J, Barrett YC, Byon W, Boyd RA, Pursley J, LaCreta FP, Frost CE. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol. 2013; 76:908–16. [PubMed: 23488672]
19. Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure–response analysis in patients with nonvalvular atrial fibrillation. Eur J Clin Pharmacol. 2014; 70:1339–51. [PubMed: 25168620]
20. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol. 2007; 47:218–26. [PubMed: 17244773]
21. Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. Clin Pharmacokinet. 2011; 50:675–86. [PubMed: 21895039]
22. Hawes EM, Deal AM, Funk-Adcock D, Gosselin R, Jeanneret C, Cook AM, Taylor JM, Whinna HC, Winkler AM, Moll S. 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; 11:1493–502. [PubMed: 23718677]
23. Chan NC, Coppens M, Hirsh J, Ginsberg JS, Weitz JI, Vanassche T, Douketis JD, Schulman S, Eikelboom JW. Real-world variability in dabigatran levels in patients with atrial fibrillation. J Thromb Haemost. 2015; 13:353–9. [PubMed: 25523236]
24. Skeppholm M, Al-Aieshy F, Berndtsson M, Al-Khalili F, Ronquist-Nii Y, Soderblom L, Ostlund AY, Pohanka A, Antovic J, Malmstrom RE. Clinical evaluation of laboratory methods to monitor apixaban treatment in patients with atrial fibrillation. Thromb Res. 2015; 136:148–53. [PubMed: 25981142]
25. Francart SJ, Hawes EM, Deal AM, Adcock DM, Gosselin R, Jeanneret C, Friedman KD, Moll S. Performance of coagulation tests in patients on therapeutic doses of rivaroxaban. A cross-sectional pharmacodynamic study based on peak and trough plasma levels. Thromb Haemost. 2014; 111:1133–40. [PubMed: 24401946]
26. Frost C, Nepal S, Wang J, Schuster A, Byon W, Boyd RA, Yu Z, Shenker A, Barrett YC, Mosqueda-Garcia R, Lacreta F. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol. 2013; 76:776–86. [PubMed: 23451769]
27. Mueck W, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Kalebo P, Muelhofer E, Misselwitz F, Eriksson BI. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Haemost. 2008; 100:453–61. [PubMed: 18766262]
28. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N, Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. 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; 385:2288–95. [PubMed: 25769361]
29. Song S, Kang D, Halim AB, Miller R. Population pharmacokinetic–pharmacodynamic modeling analysis of intrinsic FXa and bleeding from edoxaban treatment. J Clin Pharmacol. 2014; 54:910–16. [PubMed: 24706516]

Table 1

Weight categories and number of obese patients in major phase III trials

Drug	Trial	Weight categories	Number of obese patients (%)
Dabigatran	RE-COVER I	≥ 100 kg	502/2539 (20)
		BMI ≥ 35	306/2539 (12)
	RE-COVER II	> 100 kg	438/1280 (34.2)
		BMI > 35	302/1280 (23.6)
	RE-LY	≥ 100 kg	3099/18 113 (17.1)
	RE-MEDY	≥ 100 kg	299/1430 (20.9)
	RE-SONATE	≥ 100 kg	122/681 (17.9)
Rivaroxaban	EINSTEIN DVT	> 100 kg	245/1731 (14.2)
	EINSTEIN PE	> 100 kg	345/2419 (14.3)
	EINSTEIN EXTENSION	> 100 kg	85/602 (14.1)
	ROCKET-AF	> 90 kg	2035/7131 (28.5)
		BMI > 35	972/7131 (13.6)
Apixaban	AMPLIFY	≥ 100 kg	522/2691 (19.4)
		BMI > 35	349/2691 (13.0)
	ARISTOTLE	None	
Edoxaban	ENGAGE AF TIMI 48	None	
	HOKUSAI VTE >	100 kg	611/4118 (14.8)

BMI, body mass index.