DOACs and Obesity Virtual Resource Guide

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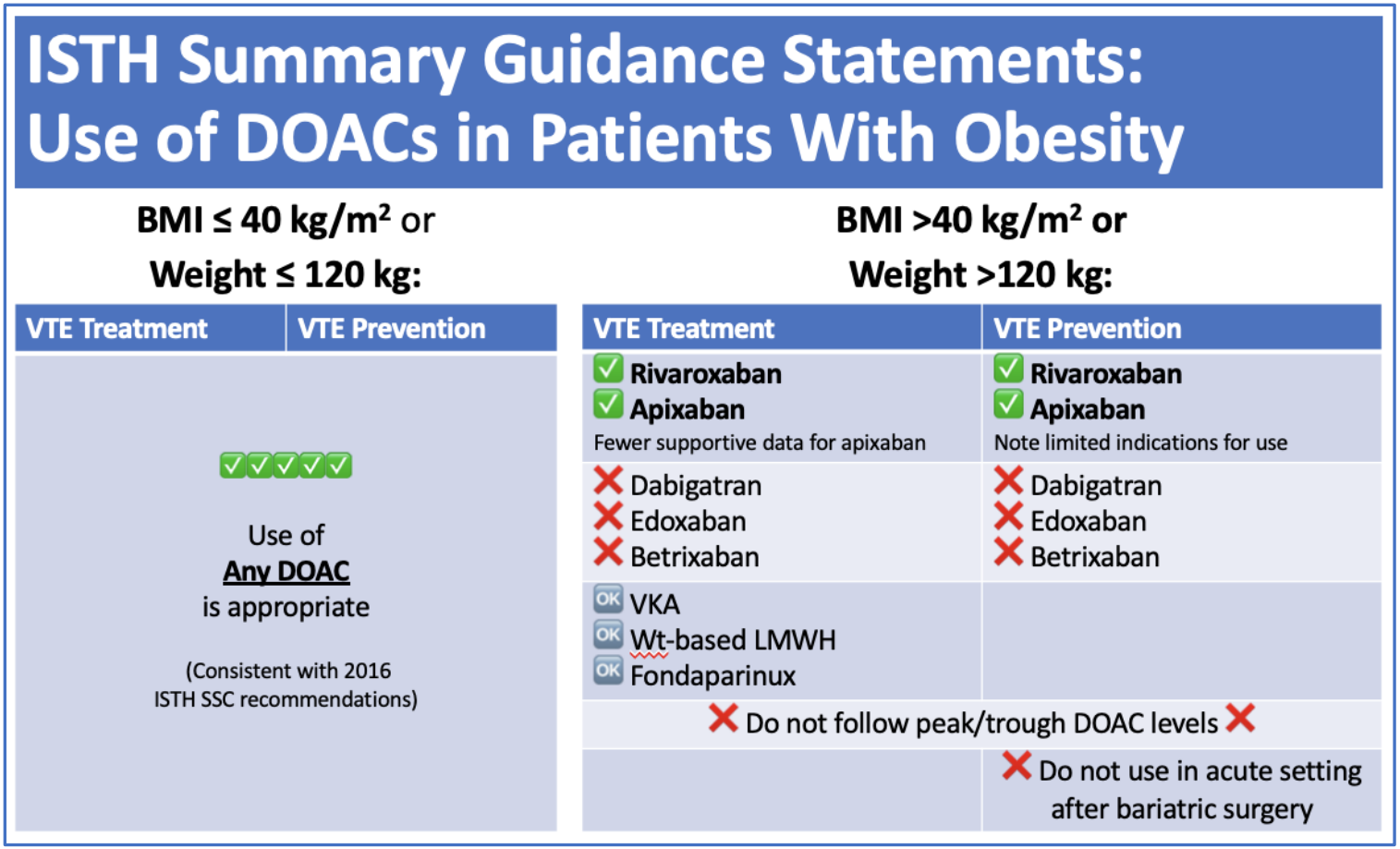
This activity is supported by an educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC.

ISTH Summary Guidance Statements: Use of DOACs in Patients With Obesity



Notes: The ISTH SSC 2021 guidance indicates that use of any DOAC is appropriate for patients with BMI ≤ 40 kg/m^2 and weight ≤ 120 kg (left). Guidance is more detailed for extremely obese patients, i.e., BMI > 40 kg/m^2 or weight > 120 kg (right). For VTE treatment, standard doses of rivaroxaban or apixaban are suggested. For VTE primary prevention, rivaroxaban or apixaban are options, recognizing that drug approvals are generally limited to elective hip and knee arthroplasties and in some countries, to extended VTE prevention in acutely ill medical patients. By contrast, it is suggested not to using other available DOACs in extremely obese patients based on unconvincing or missing data. It is suggested that drug-specific peak and trough levels not be routinely followed, given insufficient data to guide clinical management. It is also suggested not to use DOACs for treatment or prevention of VTE right after bariatric surgery due to concerns regarding decreased absorption. Instead, patients be started on parenteral anticoagulation after surgery, with a switch to VKA or DOAC considered after at least 4 weeks. (Adapted from Martin et al, *J Thromb Haemost.* 2021[1])

Recent Studies of the Efficacy and Safety of VTE Treatment with DOACs in Patients with Obesity

Study	Objective	Design	Patients	Outcomes
Di Nisio et al (2016)[2]	Treatment of VTE with rivaroxaban in relation to body weight	Sub-analysis of the EINSTEIN DVT/PE studies	Patients (>8,000) with DVT or PE receiving rivaroxaban or enoxaparin/VKA therapy	Rivaroxaban recipients: no association between risk of recurrent VTE and weight (P = 0.87) or BMI (P = 0.62) Also, no associations between major bleeding or clinically relevant bleeding and weight/BMI MB events numerically lower in rivaroxaban patients across all weight and BMI categories
Kushnir et al (2019)[3]	DOACs vs warfarin for VTE in patients with morbid obesity	Single-center retrospective analysis of chart data	Adult patients prescribed apixaban, rivaroxaban, or warfarin for VTE (N = 366) or AF BMI ≥ 40 kg/m^2	Incidence of recurrent VTE similar (P = 0.74) between apixaban (2.1%; 95% CI, 0.0-6.3), rivaroxaban (2.0%; 95% CI, 0.0-4.2), and warfarin (1.2%, 95% CI, 0.0-2.9) cohorts MB incidence also similar (P = 0.77) between apixaban (2.1%, 95% CI, 0.0-6.3), rivaroxaban (1.3%; 95% CI, 0.0-3.1), and warfarin (2.4%; 95% CI, 0.1-4.7) cohorts
Spyropoulos et al (2019)[4]	Rivaroxaban vs warfarin in morbidly obese patients with VTE	Retrospective 1:1 propensity score-matched cohort study	2890 matched pairs of morbidly obese VTE patients initiating rivaroxaban or warfarin	Similar risks between cohorts for recurrent VTE (OR, 0.99; 95% CI; 0.85-1.14) and MB (OR, 0.75; 95% CI: 0.47-1.19) Rivaroxaban associated with fewer hospitalizations (OR, 0.86; 95% CI, 0.77-0.96) and fewer outpatient visits (OR, 0.23; 95% CI, 0.10-0.56) vs warfarin Average total medical costs per patient per year were $2829 lower with rivaroxaban versus warfarin; total healthcare costs (including pharmacy) were similar
Coons et al (2020)[5]	DOACs vs warfarin in obese patients with acute VTE	Retrospective matched cohort study	Patients with acute VTE who received apixaban (N = 580), dabigatran (N = 19), or rivaroxaban (N = 33) or warfarin (N = 1208) while hospitalized Weight >100 kg, <300 kg	Recurrence of VTE within 12 months of index admission date: 6.5% DOAC; 6.4% warfarin (P= 0.93) No significant differences in occurrence of PE and DVT No difference in bleeding: 1.7% in DOAC and 1.2% in warfarin group (p=0.31)

Study	Objective	Design	Patients	Outcomes
Perales et al (2020)[6]	Rivaroxaban vs warfarin for stroke prevention and VTE treatment in severe obesity and high body weight	Retrospective chart review at 2 academic medical centers	Adult patients with BMI >40 kg/m^2 or weight >120 kg newly initiated on warfarin (N = 92) or rivaroxaban (N = 84) for VTE treatment or AF	Clinical failure numerically lower for rivaroxaban vs warfarin (5% vs 13%; P = 0.06) LOS was significantly shorter for rivaroxaban vs warfarin (2 days vs 4 days; P < 0.0001). Bleeding complications numerically higher in the rivaroxaban arm (8% vs 2%, P = 0.06)
Ballerie et al (2021)[7]	Apixaban and rivaroxaban in obese patients treated for VTE	Observational study of drug levels and clinical outcomes	Obese patients followed at a thrombosis center and treated for VTE (N = 146)	22 patients (15%) had DOAC concentrations outside the on-therapy ranges; associated with younger age, rivaroxaban use, and shorter time since last intake In median follow-up of 16 mos, 2 patients (1%) receiving apixaban had recurrent VTE; no major bleeding; minor bleeding in 11 patients (8%)
Costa et al (2021)[8]	Rivaroxaban versus warfarin in obese VTE patients	Cohort analysis of HER data	Patients with incident VTE receiving rivaroxaban (N = 6,755) or warfarin (N = 6,755) BMI ≥ 30 kg/m^2	Rivaroxaban associated with reduced hazard of recurrent VTE vs warfarin at 3 months (HR 0.61, 95% CI 0.51-0.72); 6 mo (HR 0.65, 95%CI 0.55-0.77); and 12 months (HR 0.63, 95% CI 0.54-0.74) No difference in major bleeding at 3 months (HR 0.99; 95% CI, 0.68-1.44), 6 mo (HR, 0.90; 95% CI, 0.64-1.26), and 12 months (HR, 1.00, 95% CI, 0.73-1.36) No significant differences across BMI categories for recurrent VTE or major bleeding
Cohen et al (2021)[9]	Apixaban vs. warfarin in VTE patients with obesity and morbid obesity	Integrated study of 5 US claims databases	112,024 non-obese and 43,095 obese patients (of whom 19,751 were morbidly obese)	No significant effect of weight or BMI on recurrent VTE and MB when stratified by obesity status (interaction p > 0.10) Apixaban associated with significantly lower risk of recurrent VTE (obese: 0.73 [0.64-0.84]; morbidly obese: 0.65 [0.53-0.80]) and MB (obese: 0.73 [0.62-0.85]; morbidly obese: 0.68 [0.54-0.86]) vs warfarin

Study	Objective	Design	Patients	Outcomes
Cohen et al (2021)[10]	Apixaban in patients with high body weight or obesity and VTE	Post hoc analysis of the AMPLIFY trial	Patients in the AMPLIFY safety population who had recorded body weight (n = 5384) and/or BMI (n = 5359)	For apixaban vs enoxaparin/warfarin: Recurrent VTE/VTE-related death rates were similar (P= 0.44) across body weight subgroups, with RR (95% CI) of 0.63 (0.23, 1.72) for ≤ 60 kg, 0.99 (0.65, 1.50) >60 to <100 kg, 0.77 (0.34, 1.72) for ≥ 100 to < 120 kg, and 0.20 (0.02, 1.72) for ≥ 120 kg Composite of MB/CRNMB rates significantly lower, with RRs (95% CI) of 0.46 (0.24, 0.89), 0.49 (0.38, 0.63), 0.30 (0.16, 0.58), and 0.28 (0.12, 0.66), respectively
Perino et al (2021)[19]	Bleeding and recurrent VTE across spectrum weights in patients taking warfarin vs DOACs (all DOACs)	Retrospective cohort	N = 51,871 ≥120 kg - <140 kg: warfarin, N = 2829; DOAC, N = 1938 ≥140 kg: warfarin N = 1442; DOAC, N = 725 (apixaban, N = 221; dabigatran, N = 38; edoxaban, N = 2; rivaroxaban, N 464)	**Pts ≥120 to <140 kg** Major bleeding, DOAC vs warfarin; IRs: (33.2 [95% CI, 21.7–51.0] versus 60.0 [95% CI, 45.1–79.8], P=0.0217) CRNM bleeds, DOAC vs warfarin; IRs (164.3 [95% CI, 135.2–199.6] versus 239.2 [95% CI, 206.6–276.9], P=0.0022), Numerically less recurrent VTE **Pts ≥140kg** No significant differences in outcome incidence rates; numerically fewer major bleeds
Samaranayake et al (2021)[20]	Rate of recurrent VTE within 6 months of starting anticoagulation in newly diagnosed PE taking DOAC vs warfarin	Multisite propensity scores matched case-control study	>120kg or BMI >40 receiving DOACs (apixaban, N = 13; rivaroxaban, N = 141) or warfarin (N = 46)	BMI >40 or body weight >120 kg, the rate of recurrent VTE was 5.8% (n=6) in the DOAC group compared to 6.8% (n=3) in the warfarin group, bleeding events occurred in 9.6% (n=10) in the DOAC group compared to 15.2% (n=7) in the warfarin group.
Scott et al (2022)[21]	Compare DOACs and VKA use in morbidly obese patients with VTE	Single center retrospective cohort study	Patients with BMI ≥40 kg/m^2 admitted with acute VTE and initiated on a DOAC (N = 129) or VKA (N = 118)	Similar risks of recurrent VTE for DOAC and VKA Hazard of recurrent thrombosis not statistically, significantly different in patients treated with a DOAC compared with VKA (HR, 0.28; CI, 0.07-1.11; P=0.07)

Study	Objective	Design	Patients	Outcomes
Crouch et al (2022)[11]	Apixaban vs warfarin for treatment of VTE in patients with severe obesity	Multi-center retrospective study	Patients with acute VTE receiving apixaban (N = 314) or warfarin (N = 785) Weight ≥120 kg or BMI ≥40 kg/m^2	Time to recurrent VTE significantly longer for apixaban vs warfarin (P = 0.018) Apixaban use associated with a reduced risk of recurrent VTE vs warfarin (HR, 0.54, 95% CI, 0.29-0.97; P = 0.04) No significant differences in MB, CRNMB, or all-cause mortality
Anusim et al (2022)[12]	Safety and efficacy of apixaban and rivaroxaban in obese patients with acute thrombosis/embolism	Retrospective single-center study	Patients (N = 499) with BMI ≥ 40 kg/m^2 admitted from January 2013 to January 2020 with acute VTE and treated with either rivaroxaban (n=296) or apixaban (n=203)	Neither apixaban nor rivaroxaban are associated with an increase in VTE recurrence in the morbidly obese No statistically significant differences in bleeding rates or mortality between the rivaroxaban and apixaban groups
Berger et al (2022)[17]	VTE recurrence, major bleeding, healthcare resource utilization, and healthcare costs among VTE patients with obesity who received rivaroxaban versus warfarin	Retrospective, observational cohort study	Patients with BMI >40 (rivaroxaban, N = 3565; warfarin, N = 2493) 9.6-month mean observation period	Rivaroxaban associated with lower risk of VTE recurrence [7.0% vs. 8.2%, HR(95% CI)=0.85(0.75;0.97)] and a similar risk of major bleeding [4.1% vs. 3.6%, HR(95% CI)=1.11(0.89;1.37)] relative to warfarin users at 12 months Higher pharmacy costs incurred by rivaroxaban recipients (cost difference=$1252) were offset by lower medical costs (cost difference=– $2515, all p<0.05) compared with warfarin recipients
Lorenz M (2022)[18]	Safety and efficacy of DOACs in pts >140kg or BMI >50. Primary: any bleed Secondary: thrombotic events	Retrospective chart review	Patients aged 18-89 years and weight ≥140 kg or BMI ≥50 kg/m^2 receiving DOACs (apixaban, N = 43; rivaroxaban, N = 23; dabigatran, N = 13) or warfarin (N = 205)	Bleeding event rates comparable in DOAC and warfarin groups (17.5% vs 17.1%, *P*>.05) Bleeding events in the DOAC group: apixaban, 7 patients (16.3%); rivaroxaban, 11 patients (45.8%), dabigatran, 1 patient (7.7%) No significant difference in rates of minor, nonmajor clinically relevant, or major bleeding events Thrombotic events: 2 in the warfarin group, 0 in the DOAC group

Study	Objective	Design	Patients	Outcomes
Watson et al (2022)[22]	Examine effectiveness (stroke and VTE) of DOACs compared to warfarin in a population (Afib and VTE) with obesity (composite primary outcome)	Retrospective cohort study	Patients with a diagnosis of VTE or AF and BMI ≥35 kg/m^2 receiving DOACS (apixaban, N = 35; rivaroxaban, N = 19) or warfarin (N = 108)	Primary outcome (composite of stroke or recurrent VTE): 1 patient (1.9%) in the DOAC group; 2 patients (1.9%) in the warfarin group Incidence of bleeding nonsignificantly higher in DOAC group (5.6% vs 0.9% for warfarin, *P* = 0.11) No difference between groups in incidence of DVT, PE, or stroke in patients with a BMI ≥40 kg/m^2.
Weaver et al (2022)[23]	Rates of thrombosis and bleeding in morbidly obese VTE patients receiving rivaroxaban or warfarin	Multicenter, retrospective cohort study	Patients identified for acute VTE with BMI >40 kg/m^2 or weight >120 kg Treated with rivaroxaban (N = 487) or warfarin (N = 785)	No difference in hazard of VTE HR = 0.69, 95% CI, 0.42-1.08; P = 0.12 No difference in major bleeding HR = 1.29; 95% CI, 0.66-2.30; P = 0.52

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; CRNMB = clinically relevant non-major bleeding; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; HR = hazard ratio; MB = major bleeding; NE = not estimable; OR = odds ratio; PE = pulmonary embolism; RR = relative risk; VTE = venous thromboembolism

Efficacy and Safety of DOACs vs Other Anticoagulants in Very Obese Patients with VTE: Systematic Reviews and Meta-analyses

Study	Objective	Studies/Patients Included	BMI/Weight	Outcomes
Martin et al (2021 ISTH Guidance)[1]	**Review and update 2016 ISTH recommendations[13] on use of DOACs for VTE treatment and prevention in patients with severe obesity**	**Available data for use of DOACs for VTE treatment and prevention in patients with obesity, including phase 3, phase 4, meta-analyses, and PK/PD studies**	**Literature review through August 1, 2020 including terms "obese weight" or "obesity", along with relevant terms for DOACs and VTE treatment/prevention**	**See Graphical Abstract on page 2 of this Resource Guide**
Elshafei et al (2021)[14]	DOACs vs warfarin in morbidly obese patients with acute VTE	5 observational studies of DOACs compared to warfarin (N = 6585)	BMI > 40 kg/m^2 or weight > 120 kg	DOACs non-inferior to warfarin in reducing VTE recurrence (OR, 1.07; 95% CI, 0.93–1.23) DOACs non-inferior to warfarin in MB events (OR 0.80; 95% CI, 0.54–1.17)
Katel et al (2021)[15]	DOACs vs traditional anticoagulants in VTE in morbidly obese patients	5 studies comparing DOACs to VKAs or LMWH (N = 6,575)	Various, depending on study 1. BMI ≥40 kg/m^2 2. BMI>40 kg/m^2, >120 kg 3. ICD 9/ICD 10 diagnosis code for morbid obesity 4. BMI ≥ 30 kg/m^2 vs < 30 kg/m^2; weight ≥120 kg vs. <120 kg** 5. Weight >120kg	Recurrent VTE: 2.96% DOAC, vs 2.54% VKA/LMWH (OR, 1.17; 95% CI, 0.87 to 1.59; P = 0.30) MB: 1.89% DOAC, vs 2.54% VKA/LMWH (OR, 0.74; 95% CI: 0.53-1.03, P = 0.08)
Mai et al (2021)[16]	DOACs in the treatment of acute VTE in patients with obesity	21 studies (N = 50,360) including 22,593 with obesity	BMI ≥30 kg/m^2: 16,150 pts; BMI ≥40 kg/m^2: 6443 pts	VTE recurrence*; Obese: RR 1.03; 95% CI 0.93-1.15); Morbidly obese: RR 1.06; 95% CI 0.94-1.19 MB*, Obese: RR 0.57; 95% CI 0.34-0.94; Morbidly obese: RR 0.71; 95% CI 0.50-1.00

*Comparisons are for DOAC vs VKA/LMWH.
**Only data from weight ≥120 kg included.
BMI = body mass index; CI = confidence interval; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; HR = hazard ratio; MB = major bleeding; OR = odds ratio; RR = relative risk; VKA = vitamin K antagonist; VTE = venous thromboembolism

References

1. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. 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. *J Thromb Haemost JTH*. 2021;19(8):1874-1882. doi:10.1111/jth.15358
2. 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. doi:10.1160/TH16-02-0087
3. 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. doi:10.1016/S2352-3026(19)30086-9
4. 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. doi:10.1016/j.thromres.2019.08.021
5. Coons JC, Albert L, Bejjani A, Iasella CJ. Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Obese Patients with Acute Venous Thromboembolism. *Pharmacotherapy*. 2020;40(3):204-210. doi:10.1002/phar.2369
6. Perales IJ, San Agustin 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. doi:10.1177/1060028019886092
7. Ballerie A, Nguyen Van R, Lacut K, et al. Apixaban and rivaroxaban in obese patients treated for venous thromboembolism: Drug levels and clinical outcomes. *Thromb Res*. 2021;208:39-44. doi:10.1016/j.thromres.2021.10.009
8. 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. doi:10.1007/s11239-020-02199-0
9. 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):E200. doi:10.3390/jcm10020200
10. Cohen AT, Pan S, Byon W, Ilyas BS, Taylor T, Lee TC. Efficacy, Safety, and Exposure of Apixaban in Patients with High Body Weight or Obesity and Venous Thromboembolism: Insights from AMPLIFY. *Adv Ther*. 2021;38(6):3003-3018. doi:10.1007/s12325-021-01716-8
11. Crouch A, Ng TH, Kelley D, et al. Multi-center retrospective study evaluating the efficacy and safety of apixaban versus warfarin for treatment of venous thromboembolism in patients with severe obesity. *Pharmacotherapy*. 2022;42(2):119-133. doi:10.1002/phar.2655
12. Anusim N, Ghimire B, Smalley M, Jaiyesimi I, Gaikazian S. Safety and efficacy of Apixaban and Rivaroxaban in obese patients with acute thrombosis/embolism. *Eur J Haematol*. Published online June 23, 2022. doi:10.1111/ejh.13817
13. 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 JTH*. 2016;14(6):1308-1313. doi:10.1111/jth.13323
14. Elshafei MN, Mohamed MFH, El-Bardissy A, et al. Comparative effectiveness and safety of direct oral anticoagulants compared to warfarin in morbidly obese patients with acute venous thromboembolism: systematic review and a meta-analysis. *J Thromb Thrombolysis*. 2021;51(2):388-396. doi:10.1007/s11239-020-02179-4
15. Katel A, Aryal M, Neupane A, et al. Efficacy and Safety of Direct Oral Anticoagulants in Venous Thromboembolism Compared to Traditional Anticoagulants in Morbidly Obese Patients: A Systematic Review and Meta-Analysis. *Cureus*. 2021;13(4):e14572. doi:10.7759/cureus.14572
16. Mai V, Marceau-Ferron E, Bertoletti L, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism in patients with obesity: A systematic review with meta-analysis. *Pharmacol Res*. 2021;163:105317. doi:10.1016/j.phrs.2020.10531717.

17. Berger JS, Laliberté F, Kharat A, et al. Effectiveness, safety, and healthcare costs associated with rivaroxaban versus warfarin among venous thromboembolism patients with obesity: a real-world study in the United States. *J Thromb Thrombolysis*. Published online May 13, 2022. doi:10.1007/s11239-022-02661-1
18. Lorenz MA, Linneman TW. Comparing Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin in Extreme Obesity. *J Pharm Pract*. Published online August 8, 2022:8971900221116809. doi:10.1177/08971900221116809
19. Perino AC, Fan J, Schmitt S, et al. Anticoagulation Treatment and Outcomes of Venous Thromboembolism by Weight and Body Mass Index: Insights From the Veterans Health Administration. *Circ Cardiovasc Qual Outcomes*. 2021;14(11):e008005. doi:10.1161/CIRCOUTCOMES.121.008005
20. Samaranayake CB, Keir G, Slader SAA, et al. Use of direct oral anticoagulants for acute pulmonary embolisms in obesity: a propensity-matched, multicentre case-control study. *ERJ Open Res*. 2021;7(3):00379-02021. doi:10.1183/23120541.00379-2021
21. Scott LC, Li J, Cafuir LA, Gaddh M, Kempton CL. Comparing direct oral anticoagulants and vitamin K antagonist use in morbidly obese patients with venous thromboembolism: A single center retrospective cohort study. *EJHaem*. 2022;3(2):457-462. doi:10.1002/jha2.418
22. Watson RM, Smith CB, Crannage EF, Challen LM. Examination of the Effectiveness of Direct Oral Anticoagulants in Comparison to Warfarin in an Obese Population. *J Pharm Technol*. 2022;38(1):26-30. doi:10.1177/87551225211064113
23. Weaver P, Ng TH, Breeden T, et al. Management of Venous Thromboembolism in Morbid Obesity With Rivaroxaban or Warfarin. *Ann Pharmacother*. Published online May 3, 2022:10600280221089008. doi:10.1177/10600280221089008