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# Safety and Efficacy of Direct Oral Anticoagulants vs Warfarin in Patients With Obesity and Venous Thromboembolism: A Retrospective Analysis

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## Abstract

**Background:** Current venous thromboembolism guidelines recommend using direct oral anticoagulants (DOACs) over warfarin regardless of obesity status; however, evidence remains limited for the safety and efficacy of DOAC use in patients with obesity. This retrospective analysis sought to demonstrate the safety and efficacy of DOACs compared with warfarin in a diverse population of patients with obesity in light of current prescribing practices.

**Methods:** A retrospective cohort study was conducted at a large academic health system between July 2014 and September 2019. Adults with an admission diagnosis of deep vein thrombosis (DVT) or pulmonary embolism, with weight greater than 120 kg or a body mass index greater than 40, and who were discharged on an oral anticoagulant were included. Outcomes included occurrence of a thromboembolic event (DVT, pulmonary embolism, or ischemic stroke), bleeding event requiring hospitalization, and all-cause mortality within 12 months following index admission.

**Results:** Out of 787 patients included, 520 were in the DOAC group and 267 were in the warfarin group. Within 12 months of index hospitalization, thromboembolic events occurred in 4.23% of patients in the DOAC group vs 7.12% of patients in the warfarin group (hazard ratio, 0.6 [95% CI, 0.32-1.1]; $P = .082$). Bleeding events requiring hospitalization occurred in 8.85% of DOAC patients vs 10.1% of warfarin patients (hazard ratio, 0.93 [95% CI, 0.57-1.5]; $P = .82$). A DVT occurred in 1.7% and 4.9% of patients in the DOAC and warfarin groups, respectively (hazard ratio, 0.35 [95% CI, 0.15-0.84]; $P = .046$).

**Conclusion:** No significant differences could be determined between DOACs and warfarin for cumulative thromboembolic or bleeding events, pulmonary embolism, ischemic stroke, or all-cause mortality. The risk of DVT was lower with apixaban and rivaroxaban. Regardless of patient weight or body mass index, physicians prescribed DOACs more commonly than warfarin.

**Keywords:** Anticoagulants; obesity; warfarin; venous thromboembolism; venous thrombosis; factor Xa inhibitors

## Introduction

Patients with obesity, classified as those with a body mass index (BMI) of 30 or greater, have up to a 6-fold greater risk of developing venous thromboembolisms (VTEs), an incidence that rises when coupled with other risk factors.[1-8] Though current VTE guidelines recommend the use of direct oral anticoagulants (DOACs) over vitamin K antagonists in patients without obesity because of these drugs' comparable efficacy and improved safety,[9] no large randomized controlled trials have provided guidance for DOAC use in patients with obesity. The

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most recent International Society on Thrombosis and Haemostasis guidance, however, suggests that apixaban and rivaroxaban may be safe to use in this patient population.[10]

In the few studies that have suggested evidence of safe and efficacious use of DOACs in patients with obesity, apixaban and rivaroxaban have the most abundant and promising data. Though limited by their retrospective nature, data from 10 studies have sought to provide evidence of DOACs in patients with obesity to fill this knowledge gap. These studies in patients with obesity often included patients with a BMI of at least 40 and found either no difference or notable reductions in the occurrence of thromboembolic or bleeding events between DOACs and warfarin, providing evidence for a similar or superior safety and efficacy profile.[11-20] Of these studies, Costa et al[14] was the largest, with a total study population of more than 13,000 patients. This study found a reduced risk of recurrent VTE in the DOAC group 1 year after initial VTE, with no significant difference in risk of major bleeding events; however, this study included patients with a lower BMI cutoff (at least 30), and only 26.25% of those patients had a BMI of at least 40. Two studies collected data for patients with obesity receiving a DOAC vs warfarin for either VTE treatment or stroke prevention with atrial fibrillation (AF). One of these studies found similar incidences of stroke and major bleeding events between groups[11]; the other study found a higher percentage of bleeding complications but lower rates of clinical failure (defined as ischemic stroke, VTE recurrence, or mortality within 12 months) in the DOAC group, though this percentage did not meet statistical significance.[20] One study assessed the safety and efficacy of DOACs without a warfarin comparison in patients with AF and a BMI of at least 50 compared with patients with a BMI between 18 and 30 and found numerically similar ischemic stroke and bleeding outcomes between the BMI groups.[21]

Though available data appear to favor the use of DOACs for both VTE and stroke prevention in patients with obesity, the data remain limited, particularly for patients with a BMI of at least 50. This retrospective analysis aimed to contribute to the growing literature on this topic, with the twin goals of demonstrating the noninferiority of DOACs compared with warfarin in this patient population and of influencing the direction of future anticoagulation guidelines.

### Key Points

- No statistically significant difference was seen between the 2 groups for cumulative thromboembolic events or clinically significant bleeding events.
- Statistically significantly fewer DVT events occurred in patients taking apixaban or rivaroxaban than in patients taking warfarin.
- The majority of patients in this study were discharged on a DOAC—specifically, apixaban—which reflects current clinical practice.
- A considerably greater portion of patients had a baseline BMI of at least 50 than in previous studies.

### Abbreviations and Acronyms

| | |
|---|---|
| AF | atrial fibrillation |
| BMI | body mass index |
| DOAC | direct oral anticoagulant |
| DVT | deep vein thrombosis |
| HR | hazard ratio |
| PE | pulmonary embolism |
| VTE | venous thromboembolism |

## Patients and Methods

This retrospective cohort study consisted of patients treated at University of North Carolina Health, an integrated system of 11 academic and community hospitals, between July 2014 and September 2019. Patients were identified using *International Classification of Diseases, Tenth Revision,* codes through the Carolina Data Warehouse for Health, an electronic data repository for the University of North Carolina Health system. The university's institutional review board approved this study.

Patients were included if they were at least 18 years of age and had an admission diagnosis of acute VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]), had a BMI of at least 40 or a weight of at least 120 kg upon admission, and were discharged from the index hospital encounter on an oral anticoagulant. Patients were excluded if they had a diagnosis of AF or atrial flutter, were pregnant, or were incarcerated. Included patients were allocated to 1 of 2 cohorts based on discharge anticoagulation selection (DOAC or warfarin).

The primary efficacy outcome was the occurrence of a thromboembolic event (DVT, PE, or ischemic stroke) within 12 months of index hospitalization. The primary safety outcome was occurrence of a bleeding event

requiring hospitalization. Secondary outcomes included recurrence or occurrence of DVT, PE, or ischemic stroke as separate events and all-cause mortality, all within 12 months of the index admission. Bleeding was defined as any bleeding event leading to a hospital encounter (including emergency department, observation, or admission), and all primary and secondary outcomes were identified by manual review of individual patient charts.

### Statistical Analysis

A Cox proportional hazards regression model was used for the primary and secondary outcomes in this study, as appropriate. The proportional hazards assumption was checked using the score of the scaled Schoenfeld residuals. In addition to discharge medication (DOAC or warfarin), models were adjusted for patient age, sex, chronic kidney disease status, BMI, and history of VTE before index hospitalization. Adjusted hazard ratios (HRs) and corresponding 95% CIs were determined for the primary and secondary outcomes. As a sensitivity analysis, propensity scores were estimated for exposure to warfarin, matching patients in the DOAC group were found by propensity score, and the analyses were re-run using the Cox models for the primary efficacy and primary safety outcomes. The same covariates were used in the propensity score models as in the covariate-adjusted models. All statistical analyses were performed using the *survival* package in R, version 3.3-1.2 (R Foundation for Statistical Computing). $P \leq .05$ was considered statistically significant.

## Results

Between July 2014 and September 2019, electronic health records for 787 patients who met inclusion criteria were analyzed in this study. Among these patients, 520 were discharged on a DOAC and 267 were discharged on warfarin. Of the patients discharged on a DOAC, 334 (64.2%) were discharged on apixaban,

**TABLE I. Baseline Demographics**

| Characteristic | DOAC (n = 520) | Warfarin (n = 267) | *P* value |
|---|---|---|---|
| Age, median (IQR), y | 56 (45-65) | 56 (44-65) | .60 |
| Male sex, No. (%) | 230 (44.2) | 120 (44.9) | .80 |
| Race, No. (%) | | | |
| White or Caucasian | 332 (63.8) | 152 (57) | – |
| Minority racial or ethnic group[a] | 188 (36.2) | 115 (43) | – |
| **Medical history** | | | |
| BMI, median (IQR) | 42.8 (40.2-47.2) | 44.8 (40.8-50.9) | <.001 |
| Weight, median (IQR), kg | 124.9 (120-136.4) | 129.7 (121-146.8) | <.001 |
| Chronic kidney disease, No. (%) | 75 (14.4) | 46 (17.2) | .30 |
| History of VTE, No. (%) | 119 (22.9) | 67 (25.1) | .50 |
| Index event type, No. (%) | | | |
| DVT | 237 (45.6) | 139 (52.1) | .11 |
| PE | 294 (56.5) | 128 (47.9) | .60 |
| **Specific DOAC given, No. (%)** | | | |
| Apixaban | 334 (64.2) | – | – |
| Rivaroxaban | 178 (34.2) | – | – |
| Dabigatran | 7 (1.3) | – | – |
| Edoxaban | 1 (0.2) | – | – |

BMI, body mass index; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Patients in the "Minority racial or ethnic group" category were Black or African American, American Indian or Alaska Native, other race, or unknown.

$P \leq .05$ was considered statistically significant.

178 (34.2%) on rivaroxaban, 7 (1.3%) on dabigatran, and 1 (0.2%) on edoxaban. Baseline characteristic data collected during electronic health record review included age, sex, race, weight, BMI, chronic kidney disease status, and history of VTE before index admission. These characteristics were similar in both groups, with a slighly higher BMI and weight in the warfarin group (Table I). The median BMI of the total study population was 43.1, and 157 patients (19.9%) had a BMI of at least 50.

Within 12 months of each patient's index hospitalization, a thromboembolic event (DVT, PE, or ischemic stroke) occurred in 4.23% of patients in the DOAC group and 7.12% of patients in the warfarin group (HR, 0.6 [95% CI, 0.32-1.1]; $P = .082$]. Bleeding events requiring hospitalization occurred in 8.85% of patients in the DOAC group and 10.1% of patients in the warfarin group (HR, 0.93 [95% CI, 0.57-1.5]; $P = .82$). The complete results can be found in Table II. The plots of the tests for proportional hazards can be found in Supplemental Figure 1 (thromboembolic events) and Supplemental Figure 2 (bleeding events requiring hospitalization). The HRs for the primary efficacy and safety outcomes across all patient covariates are presented visually in Supplemental Figure 3 and Supplemental Figure 4.

No significant difference was found between the DOAC group and the warfarin group for the occurrence of a PE, ischemic stroke, or all-cause mortality at 12 months, but there was a difference regarding DVT occurrence at 12 months. Deep vein thrombosis occurred in 1.7% of patients in the DOAC group and 4.9% of patients in the warfarin group (HR, 0.35 [95% CI, 0.15-0.84]; $P = .046$). The complete results for the secondary outcomes can be found in Table II.

In the sensitivity analysis using propensity score matching, a match was found for each patient in both groups.

**TABLE II. Thromboembolic and Bleeding Event Outcomes**

| Event | DOAC, No. (%) (n = 520) | Warfarin, No. (%) (n = 267) | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| Any thromboembolic event | 22 (4.23) | 19 (7.12) | 0.60 | 0.32-1.10 | .074 |
| DVT | 9 (1.7) | 13 (4.9) | 0.35 | 0.15-0.84 | .046 |
| PE | 8 (1.5) | 6 (2.2) | 0.70 | 0.24-2 | .46 |
| Ischemic stroke | 5 (1) | 1 (0.4) | 1.70 | 0.19-15 | .75 |
| Bleeding event requiring hospitalization | 46 (8.85) | 27 (10.1) | 0.93 | 0.57-1.50 | .82 |
| All-cause mortality | 43 (8.3) | 27 (10.1) | 0.79 | 0.48-1.30 | .85 |

DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism.

$P \leq .05$ was considered statistically significant.

**TABLE III. Thromboembolic and Bleeding Event Outcomes After Propensity Score Matching**

| Outcome | DOAC, No. (%) (n = 267) | Warfarin, No. (%) (n = 267) | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| Any thromboembolic event | 10 (3.7) | 19 (7.1) | 0.53 | 0.25-1.14 | .16 |
| Bleeding event requiring hospitalization | 27 (10.1) | 27 (10.1) | 1.03 | 0.60-1.75 | .15 |

DOAC, direct oral anticoagulant; HR, hazard ratio.

$P \leq .05$ was considered statistically significant.

Baseline demographics and clinical characteristics were similar across both groups after matching (Supplemental Table I). The results of the analysis were similar to those of the primary analysis regarding risk of a thromboembolic event (HR, 0.53 [95% CI, 0.25-1.14]; $P$ = .16) and risk of a bleeding event requiring hospitalization (HR, 1.03 [95% CI, 0.6-1.75]; $P$ = .15) between DOACs and warfarin. These results can be found in Table III.

## Discussion

Results from this retrospective cohort analysis show that treatment of VTE with apixaban or rivaroxaban displays a similar safety and efficacy profile to treatment with warfarin within 12 months of initial treatment in patients with obesity. Direct oral anticoagulants were also associated with a reduced risk of DVT. The results from this study were comparable with those of previous retrospective studies exploring similar outcomes in similar patient populations. Recent guidance issued by the International Society on Thrombosis and Haemostasis suggests that apixaban and rivaroxaban are appropriate anticoagulant options for VTE treatment, regardless of high BMI or weight.[10] This study adds to the existing evidence to support that recommendation.

In a retrospective study analyzing patients with a BMI of at least 40, Kushnir et al[11] compared the safety and efficacy of rivaroxaban and apixaban with the safety and efficacy of warfarin in patients with VTE or AF. This study was most similar to the current investigation in terms of design and outcomes. Both patient groups had numerically similar rates of recurrent VTEs and bleeding events without statistical significance, which is in concordance with the present study's results.

Compared with other studies relating to this topic, the present study demonstrated similar efficacy and safety results, but it is unique in that it included a higher proportion of patients on DOACs than on warfarin. A higher percentage of its patient population was also on apixaban than on other DOACs, while rivaroxaban use had been more prevalent in previous studies.[11,17-19] The present study is also unique in that it included 4 DOACs (several previous studies had assessed a single DOAC agent vs warfarin).[12-16,20] Among these studies, 3 found a reduced HR or risk of recurrent VTE with apixaban or rivaroxaban[13-15] and 2 found a reduced HR or risk of major bleeding with apixaban.[15,16] Notably, the present study used propensity score matching, which may reduce selection bias and other confounding variables. Its patient population was diverse, with a similar number of male and female patients, and more than one-third of its patients reported belonging to a marginalized racial or ethnic group. Nearly one-fifth of the current study's patient population also had a BMI of at least 50, which is a higher proportion than that seen in most previous studies. Based on a 2018 analysis of DOAC public interest and drug use, current clinical practice has been trending toward the increased use of apixaban over other DOACs, particularly for nonvalvular AF.[22] The present study is therefore more reflective of clinical practice, exemplified by its greater percentage of patients on DOACs being discharged on apixaban rather than on rivaroxaban, dabigatran, or edoxaban. Given the small proportion of patients discharged on dabigatran or edoxaban, the apprpriateness of these particular agents for this patient population is unclear.

### Limitations

As with any observational study, only association (not causality) can be inferred from the data. As the present study's data track well with those of previous retrospective studies conducted in this patient population at other US centers, the data add to the existing literature, which supports the use of DOACs in patients with class III obesity (ie, a BMI of at least 40). As the present study only included patients from a single regional health system, though, there are inherent limitations to its generalizability.

Another limitation of this study is that active cancer or a history of hypercoagulopathy (eg, factor V Leiden, antiphospholipid syndrome)—conditions that may put patients at higher risk of developing recurrent VTE at baseline—were not included as regression variables. More broadly, the study did not investigate why certain patients were prescribed 1 agent over another. It is unclear whether confounding demographic factors favored the selection of a DOAC over warfarin or vice versa.

The study also did not differentiate in its safety outcomes between whether patients experienced a major bleeding event or a clinically significant but nonmajor bleeding event. Moreover, data collection was limited to patient follow-up appointments within

the University of North Carolina Health system. Results may not be comprehensive if patients sought care elsewhere.

Finally, adherence to or any alteration of anticoagulation therapy during the study period was not assessed as part of this study. It is possible that some patients switched agents after discharge without the authors' knowledge. Duration of anticoagulation therapy was also not assessed. Major differences between the 2 study groups are not anticipated in terms of adherence to or duration of treatment, and thus these factors should not confound the study's results. Indeed, they may more accurately reflect real-world practice when treating VTE.

## Conclusion

This study could not determine a statistically significant difference in the rate of composite thromboembolic events or bleeding events requiring hospitalization when comparing apixaban and rivaroxaban with warfarin in patients with obesity (a weight of at least 120 kg or a BMI of at least 40). This study showed that regardless of weight or BMI, the practicing physicians for this population tend to prescribe DOACs more commonly than warfarin. These findings support recent International Society on Thrombosis and Haemostasis guidance that suggests that apixaban and rivaroxaban are safe and effective options for VTE treatment, regardless of patient BMI and weight. Further research with a prospective study is warranted to confirm these findings.

## Article Information

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## References

1. Yang G, de Staercke C, Hooper WC. The effects of obesity on venous thromboembolism: a review. *Open J Prev Med.* 2012;2(4):499-509. doi:10.4236/ojpm.2012.24069
2. Purdy JC, Shatzel JJ. The hematologic consequences of obesity. *Eur J Haematol.* 2021;106(3):306-319. doi:10.1111/ejh.13560
3. Willenberg T, Schumacher A, Amann-Vesti B, et al. Impact of obesity on venous hemodynamics of the lower limbs. *J Vasc Surg.* 2010;52(3):664-668. doi:10.1016/j.jvs.2010.04.023
4. Rosito GA, D'Agostino RB, Massaro J, et al. Association between obesity and a prothrombotic state: the Framingham Offspring Study. *Thromb Haemost.* 2004;91(4):683-689. doi:10.1160/th03-01-0014
5. Puurunen MK, Gona PN, Larson MG, Murabito JM, Magnani JW, O'Donnell CJ. Epidemiology of venous thromboembolism in the Framingham Heart Study. *Thromb Res.* 2016;145:27-33. doi:10.1016/j.thromres.2016.06.033
6. Hotoleanu C. Association between obesity and venous thromboembolism. *Med Pharm Rep.* 2020;93(2):162-168. doi:10.15386/mpr-1372
7. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. *J Intern Med.* 2015;277(5):573-584. doi:10.1111/joim.12299
8. Eichinger S, Hron G, Bialonczyk C, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med.* 2008;168(15):1678-1683. doi:10.1001/archinte.168.15.1678
9. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest.* 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055
10. 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.* 2021;19(8):1874-1882. doi:10.1111/jth.15358
11. 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
12. 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
13. Crouch A, Ng TH, Kelley D, Knight T, Edwin S, Giuliano C; ASCEND-HIGHER. 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
14. 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
15. Cohen A, Sah J, Lee T, et al. Effectiveness and safety of apixaban vs. warfarin in venous thromboembolism patients with obesity and morbid obesity. *J Clin Med.* 2021;10(2):200. doi:10.3390/jcm10020200
16. 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
17. 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
18. Quan S, Smith J, Wu C, Koshman SL, Nguyen B, Bungard TJ. Anticoagulant therapies and outcomes in obese patients with acute venous thromboembolism. *Thromb Res.* 2020;187:56-62. doi:10.1016/j.thromres.2020.01.011
19. Sa RA, Al-Ani F, Lazo-Langner A, Louzada ML. Efficacy and safety of direct oral anticoagulants in obese patients with venous thromboembolism. *Blood.* 2019;134(suppl_1):3675. doi:10.1182/blood-2019-121765
20. 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
21. O'Kane CP, Avalon JCO, Lacoste JL, et al. Apixaban and rivaroxaban use for atrial fibrillation in patients with obesity and BMI ≥50 kg/m$^2$. *Pharmacotherapy.* 2022;42(2):112-118. doi:10.1002/phar.2651
22. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. *Pharmacotherapy.* 2018;38(9):907-920. doi:10.1002/phar.2158