# 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

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## Summary

**Background** Because studies of direct oral anticoagulants in patients with venous thromboembolism and non-valvular atrial fibrillation have had minimal representation of morbidly obese patients (ie, body-mass index [BMI] ≥40 kg/m²), their efficacy and safety in this population are unclear. We investigated whether apixaban and rivaroxaban are as effective and safe as warfarin in morbidly obese patients.

**Methods** We did a single-centre, retrospective analysis of chart data for all adult patients aged at least 18 years at Montefiore Medical Center (Bronx, NY, USA) with a BMI of at least 40 kg/m² who were prescribed apixaban, rivaroxaban, or warfarin for either venous thromboembolism or atrial fibrillation between March 1, 2013, and March 1, 2017. Patients who had both venous thromboembolism and atrial fibrillation were excluded, as were patients with indications other than atrial fibrillation and venous thromboembolism. Outcomes of recurrent venous thromboembolism, stroke, and bleeding were measured from the first prescription date to the earliest of a thrombotic event, medication discontinuation, death, or end of study on June 30, 2017. Analyses were stratified by anticoagulation indication and adjusted for comorbidities, $CHA_2DS_2$-VASc score, and age where appropriate. Outcome rates were compared using Pearson's $\chi^2$ or Fisher's exact test. Time-to-event analyses accounting for length of follow-up were used to compare risks of outcomes.

**Findings** We obtained data for 795 patients: 150 prescribed apixaban, 326 rivaroxaban, and 319 warfarin. In 366 patients prescribed an anticoagulant for venous thromboembolism, the incidence of recurrent venous thromboembolism was similar between the apixaban, rivaroxaban, and warfarin cohorts (1/47 [2·1%, 95% CI 0·0–6·3], 3/152 [2·0%, 0·0–4·2], and 2/167 [1·2%, 0·0–2·9], respectively; p=0·74). Incidence of major bleeding in this patient group was also similar between the treatment cohorts (1/47 patients on apixaban [2·1%, 95% CI 0·0–6·3], 2/152 on rivaroxaban [1·3%, 0·0–3·1], and 4/167 on warfarin [2·4%, 0·1–4·7]; p=0·77). In 429 patients prescribed an anticoagulant for atrial fibrillation, incidence of stroke was similar between the treatment cohorts (1/103 patients on apixaban [1·0%, 95% CI 0·0–2·9], 4/174 on rivaroxaban [2·3%, 0·1–4·5], and 2/152 on warfarin [1·3%, 0·0–3·1], p=0·71). In this patient group, major bleeding occurred in 3/103 patients on apixaban (2·9%, 95% CI 0·0–6·2), 5/174 on rivaroxaban (2·9%, 0·4–5·4), and 12/152 on warfarin (7·9%, 3·6–12·2); p=0·063. Time-to-event analyses showed that risk of all outcomes in patients with venous thromboembolism, and stroke and composite bleeding in patients with atrial fibrillation, were similar between the anticoagulant cohorts.

**Interpretation** Our retrospective study provides further evidence of similar efficacy and safety between the direct oral anticoagulants apixaban and rivaroxaban, and warfarin in morbidly obese patients with atrial fibrillation and venous thromboembolism. These data, if confirmed in prospective studies, might enable patients with a BMI of at least 40 kg/m² to benefit from more convenient, and possibly safer, anticoagulants.

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See Comment page e341

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## Introduction

Direct oral anticoagulants have been increasingly replacing vitamin K antagonists in patients with venous thromboembolism and atrial fibrillation. The advantages of direct oral anticoagulants over vitamin K antagonists include fewer food and drug interactions, fixed dosing, and no requirements for routine monitoring. Findings from some clinical trials[1–7] in patients with acute venous thromboembolism and non-valvular atrial fibrillation have shown that direct oral anticoagulants have similar efficacy compared with vitamin K antagonists in prevention of venous thromboembolism recurrence and systemic embolism, and similar or lower bleeding risk. However, the low representation of obese patients in these studies has raised questions about the efficacy, adequacy of fixed dosing, and safety of direct oral anticoagulants in these patients.[8–9] This is an important consideration because obesity is a major problem in many countries and might affect drug pharmacokinetics and pharmacodynamics.[10–13]

## Research in context

### Evidence before this study

We searched Google Scholar and PubMed from database inception to March 15, 2019, without language restrictions, using the terms "rivaroxaban in obesity," "apixaban in obesity," "warfarin in obesity," "DOACs in obesity,"and "thrombosis in obesity." Further studies were identified in reference lists. Although pivotal clinical trials of acute venous thromboembolism and non-valvular atrial fibrillation have shown similar therapeutic efficacy and similar or lower bleeding risk for direct oral anticoagulants compared with warfarin, minimal representation of morbidly obese patients in these studies raises concern for the efficacy and safety of direct oral anticoagulants in this population. Additionally, some pharmacodynamics studies showed that the volume of distribution of factor Xa inhibitors was higher in obese patients and the mean peak concentration was lower. Because of the little evidence and absence of randomised controlled trials on direct oral anticoagulants in obese patients, the US Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis in its guidance statements issued in 2016 recommended against use of direct oral anticoagulants in patients with a body-mass index (BMI) of more than 40 kg/m² or weighing more than 120 kg.

### Added value of this study

We showed that the incidence of recurrent venous thromboembolism was low and similar between patients with morbid obesity on direct factor Xa inhibitors and those on warfarin. The incidence of stroke in patients with atrial fibrillation was also similar between the cohorts. There was no difference in the incidence of bleeding, including major bleeding, between patients on direct factor Xa inhibitors and warfarin. Findings were similar in patients with a BMI of 50 kg/m² or more.

### Implications of all the available evidence

Our investigation is the largest cohort study to date examining the efficacy and safety of direct oral anticoagulants in morbidly obese patients. It provides further evidence of efficacy and safety of direct factor Xa inhibitors in patients with a BMI of 40 kg/m² or more, and might enable more than 19 million people with morbid obesity in the USA alone to access these more convenient and potentially safer anticoagulants.

In a 2013 study[12] of apixaban, a high bodyweight (>120 kg and body-mass index [BMI] ≥30 kg/m²) was associated with a lower mean peak concentration, a higher volume of distribution, lower drug exposure, and shorter mean half-life compared with normal weight (ie, 65–85 kg and BMI ≤30 kg/m²). When the pharmacokinetics of rivaroxaban were assessed in a few patients in another study,[13] the peak concentration, distribution and half-life were similar between patients who weighed more than 120 kg and those who weighed 70–80 kg. An analysis of pooled data[14] from two rivaroxaban studies suggested that patients of greater weight have a higher volume of distribution.

The clinical implications of these pharmacokinetic differences in obese patients are unknown. Most outcome data on direct oral anticoagulants in obesity were derived from phase 3 clinical trials that led to their approval after they were compared with vitamin K antagonists. There have been no randomised controlled trials specifically done with morbidly obese patients. In a 2015 study,[8] investigators pooled data for obese patients from pivotal clinical trials and showed similar efficacy between direct oral anticoagulants and vitamin K antagonists. However, cutoffs for high bodyweight and BMI were low: only 100 kg or more for bodyweight and 35 kg/m² or more for BMI in most studies in this meta-analysis. Additionally, none of the major trials reported separately about patients with morbid obesity (BMI ≥40 kg/m²). Another investigation[15] also did not show evidence of decreased efficacy with direct oral anticoagulants but included only 98 patients with a BMI of 40 kg/m² or higher. A study[16] of 64 morbidly obese patients did not note any differences in efficacy between direct oral anticoagulants and vitamin K antagonists, but this study only included patients with atrial fibrillation. Although clinical evidence for the use of direct oral anticoagulants in morbidly obese patients is sparse, we could not find any data on patients with extreme obesity (ie, BMI ≥50 kg/m²).

Because of the little evidence and absence of trials investigating direct oral anticoagulants in obese patients, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis in its guidance statements issued in 2016 recommended against use of direct oral anticoagulants in patients with a BMI of more than 40 kg/m² or weighing more than 120 kg.[17] This restriction translates into an increased therapeutic burden for this population, a growing segment in many parts of the USA, essentially depriving them of a major medical advance. Therefore in this study, we investigated the efficacy and safety of the direct oral anticoagulants apixaban and rivaroxaban in comparison with warfarin in morbidly obese patients.

## Methods

### Study design and participants

We did a single-centre, retrospective analysis of chart data for all adult patients (aged ≥18 years) at Montefiore Medical Center (Bronx, NY, USA) with a BMI of at least 40 kg/m² who were started on anticoagulation treatment with apixaban, rivaroxaban, or warfarin, for atrial fibrillation or venous thromboembolism between March 1, 2013, and March 1, 2017. Patients who had both venous thromboembolism and atrial fibrillation were

excluded, as were patients with indications other than atrial fibrillation and venous thromboembolism. We also excluded patients if we were unable to confirm that they actually started the drug (despite the prescription) and those that had no follow-up after initiation of anticoagulation.

### Data collection

Data were obtained from Clinical Looking Glass, an interactive database software application developed at Montefiore Medical Center that integrates demographic, clinical, and administrative datasets for the purpose of clinical research. The initiation date of anticoagulation was based on the first prescription of warfarin, rivaroxaban, or apixaban. We did a retrospective review of charts to obtain detailed information on patient demographic characteristics and to document clinical outcomes of recurrent venous thromboembolism, ischaemic stroke, and bleeding from the first prescription date to the earliest of a thrombotic event, discontinuation of medication, death, or the end of study period on June 30, 2017. BMI, the Charlson Comorbidity Index, and $CHA_2DS_2$-VASc scores (congestive heart failure, hypertension, age [≥75 years=2 points], diabetes, and stroke or transient ischaemic attack [2 points]-vascular disease [peripheral arterial disease, previous myocardial infarction, aortic atheroma, and female sex]) were also recorded. For patients on warfarin, the International Normalized Ratio (INR) at the time of clinical events was documented. The INR for patients on warfarin, where available, was recorded for the day of a thrombotic and a first bleeding event (or the day before if no INR was recorded on the day of event). An INR value over 20 was captured in our system as greater than 20 without an actual value. Venous thromboembolism and stroke events were confirmed by a review of imaging studies (compression ultrasonography, ventilation-perfusion scans, CT scans, and MRIs). Bleeding events were included if they met criteria for clinically relevant non-major bleeding or major bleeding according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[18,19] Safety outcomes included major bleeding and a composite of major bleeding and clinically relevant non-major bleeding.

### Statistical analysis

All analyses were done in samples stratified by indication (venous thromboembolism or atrial fibrillation) separately and adjusted for comorbidities, $CHA_2DS_2$-VASc score, and age where appropriate. Means and SDs, medians and IQRs, or counts and percentages of baseline demographic and clinical characteristics (age, sex, race, BMI, BMI ≥50 kg/m², $CHA_2DS_2$-VASc score, Charlson comorbidity index, and follow-up in days) were tabulated by anticoagulant cohorts (apixaban *vs* rivaroxaban *vs* warfarin). Each variable was compared among the three cohorts using ANOVA or Kruskal-Wallis tests for continuous variables and Pearson's $\chi^2$ or Fisher's exact test for categorical variables. Pairwise comparisons were done for variables that differed significantly among the three anticoagulant cohorts. Baseline characteristics were also compared between the combined direct oral anticoagulant cohort (apixaban plus rivaroxaban) and warfarin.

Incidences and 95% CIs of recurrent venous thromboembolism (for patients with venous thromboembolism), stroke (for patients with atrial fibrillation), major bleeding and composite major bleeding and clinically relevant non-major bleeding (for each indication) were compared among the anticoagulant cohorts using $\chi^2$ tests or Fisher's exact tests. Rates were also calculated as events per 100 patient-years. For comparisons that were statistically significant, logistic regression models were used to estimate odds ratios (OR) and 95% CIs for pairwise comparisons and to adjust for potential confounding factors.

Additionally, to account for differing durations of follow-up among patients, time-to-event analyses were done for all outcomes including recurrent venous thromboembolism, stroke, major bleeding, and composite major bleeding and clinically relevant non-major bleeding separately. Time to event was defined as the time from first prescription date to venous thromboembolism recurrence, ischaemic stroke, or bleeding event. Patients who did not have a specific event were censored at the time of death, last confirmed date on the anticoagulant, or the end of the study period of June 30, 2017. Kaplan-Meier curves were examined for the apixaban, rivaroxaban, and warfarin cohorts and compared using log-rank tests. If these unadjusted time-to-event comparisons were statistically significant, Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% CIs for pairwise comparisons and to adjust for potential confounding factors. Sensitivity analyses included additional analyses that compared the combined direct anticoagulant cohort (apixaban plus rivaroxaban) with the warfarin cohort. All analyses were repeated in the respective subgroups of patients with a BMI of at least 50 kg/m². A two-tailed $\alpha$ of 0·05 was used to denote significance. All analyses were done with SAS 9.4.

### Role of the funding source

There was no funding source for this study. All authors had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

We identified 2699 patients who were aged at least 18 years, with a BMI of at least 40 kg/m² and were started on anticoagulation with apixaban, rivaroxaban, or warfarin. After applying exclusion criteria, 795 patients qualified for the study (150 on apixaban, 326 on rivaroxaban, and 319 on warfarin). BMI ranged from

| | Venous thromboembolism | | | | | Atrial fibrillation | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban (n=47) | Rivaroxaban (n=152) | Apixaban and rivaroxaban combined (n=199) | Warfarin (n=167) | Total (n=366) | Apixaban (n=103) | Rivaroxaban (n=174) | Apixaban and rivaroxaban combined (277) | Warfarin (n=152) | Total (n=429) |
| Age at prescription (years) | 53·3 (13·9) | 52·4 (14·7) | 52·6 (14·5)* | 58·1 (15·1) | 55·1 (15·0) | 65·9 (10·7) | 60·9 (12·6) | 62·7 (12·1)† | 66·8 (13·6) | 64·2 (12·8) |
| BMI (kg/m²) | 43·3 (41·2–49·4) | 43·7 (41·1–48·8) | 43·7 (41·2–49·0)* | 45·3 (41·4–52·5) | 44·7 (41·3–50·1) | 43·8 (41·0–48·1) | 44·6 (41·8–48·6) | 44·4 (41·5–48·3) | 44·5 (41·7–52·3) | 44·4 (41·6–49·4) |
| ≥50 | 10 (21%) | 30 (20%) | 40 (20%)* | 52 (31%) | 92 (25%) | 19 (18%) | 37 (21%) | 56 (20%)† | 44 (29%) | 100 (23%) |
| Female | 35 (75%) | 100 (66%) | 135 (68%) | 118 (71%) | 253 (69%) | 58 (56%) | 95 (55%) | 153 (55%) | 90 (59%) | 243 (57%) |
| Male | 312 (25%) | 52 (34%) | 64 (32%) | 49 (29%) | 113 (31%) | 45 (44%) | 79 (45%) | 124 (45%) | 62 (41%) | 186 (43%) |
| Ethnic origin | | | | | | | | | | |
| White | 3 (6%) | 26 (17%) | 29 (15%) | 31 (19%) | 60 (16%) | 33 (32%) | 40 (23%) | 73 (26%) | 49 (32%) | 122 (28%) |
| Black | 26 (55%) | 66 (43%) | 92 (46%) | 80 (48%) | 172 (47%) | 37 (36%) | 62 (36%) | 99 (36%) | 42 (28%) | 141 (33%) |
| Other or unknown | 18 (38%) | 60 (40%) | 78 (39%) | 56 (34%) | 134 (37%) | 33 (32%) | 72 (41%) | 105 (38%) | 61 (40%) | 166 (39%) |
| Charlson score | 0·0 (0·0–2·0) | 1·0 (0·0–2·5) | 1·0 (0·0–2·0) | 2·0 (0·0–4·0) | 1·0 (0·0–3·0) | 0·0 (0·0–2·0) | 1·0 (0·0–2·0) | 1·0 (0·0–2·0)† | 2.0 (1·0–4·0) | 1·0 (0·0–3·0) |
| $CHA_2DS_2$-VASc | NA | NA | NA | NA | NA | 3·5 (1·6) | 3·1 (1·5) | 3·3 (1·6)† | 4.1 (1·8) | 3·6 (1·7) |
| Follow-up (days) | 163·3 (90·0–233·3) | 217·4 (94·4–514·1) | 191·5 (91·5–425·3) | 206·3 (64·4–540·3) | 196·0 (89·4–457·3) | 331·5 (181·5–577·0) | 412·9 (187·3–675·2) | 402·2 (183·3–648·4) | 293·6 (81·6–671·8) | 359·4 (159·5–654·0) |

Data are mean (SD), median (IQR), or n (%). BMI=body-mass index. NA=not applicable. *Among patients with venous thromboembolism, the combined apixaban and rivaroxaban group differed significantly from the warfarin group in age (p=0·00045), median BMI (p=0·035), and proportion of patients with BMI ≥50 kg/m² (p=0·015). †Among patients with atrial fibrillation, the combined apixaban and rivaroxaban group differed significantly from the warfarin group in age (p=0·0016), proportion of patients with BMI ≥50 kg/m² (p=0·041), Charlson score (p<0·0001), $CHA_2DS_2$-VASc score (p<0·0001), and median follow-up (p=0·031).

***Table:*** **Baseline characteristics**

40 to 88 kg/m² in our total sample. There were 366 patients in the venous thromboembolism group and 429 patients in the atrial fibrillation group (table). BMIs at initial prescription, sex, race, and duration of follow-up were similar between the three anticoagulant cohorts within each indication group. Among patients with venous thromboembolism, the cohorts differed significantly in age (p=0·0020) and Charlson score (p=0·015; table). Pairwise comparisons showed that warfarin patients were older than rivaroxaban patients (p=0·00072), and that apixaban patients had lower Charlson scores compared to warfarin patients (p=0·0068) and rivaroxaban patients (p=0·015). Among atrial fibrillation patients, the cohorts differed significantly in age (p<0·0001), $CHA_2DS_2$-VASc score (p<0·0001), and Charlson score (p<0·0001). Further pairwise comparisons show that rivaroxaban patients were younger than warfarin patients (p<0·0001) and apixaban patients (p=0·00078), and that warfarin patients had higher Charlson scores and $CHA_2DS_2$-VASc scores compared with the other two cohorts (all p-values <0·0001, except for $CHA_2DS_2$-VASc scores for apixaban *vs* warfarin, for which p=0·0029).

See Online for appendix

In the venous thromboembolism group, the incidence of recurrent venous thromboembolism was low and similar among the apixaban, rivaroxaban, and warfarin cohorts (1/47 [2·1%, 95% CI 0·0–6·3], 3/152 (2·0%, 0·0–4·2), and 2/167 (1·2%, 0·0–2·9), respectively, p=0·74; figure). The incidence of major bleeding in venous thromboembolism group was similar between the cohorts: 1/47 (2·1%, 0·0–6·3) for patients on apixaban, 2/152 (1·3%, 0·0–3·1) on rivaroxaban, and 4/167 (2·4, 0·1–4·7) on warfarin (p=0·77). There was also no difference in the incidence of composite major bleeding and clinically relevant non-major bleeding among patients with venous thromboembolism on apixaban (2/47 [4·3%, 95% CI 0·0–10·0]), on rivaroxaban (14/152 [9·2%, 4·6–13·8]), and on warfarin (17/167 [10·2%, 5·6–14·8]; p=0·45). Time-to-event analyses for risks of recurrent venous thromboembolism, major bleeding, and composite major bleeding and clinically relevant non-major bleeding similarly showed no significant differences between the three anticoagulant cohorts among the venous thromboembolism patients (appendix p 3). Kaplan-Meier curves for recurrent venous thromboembolism, major bleeding, and composite major bleeding and clinically relevant non-major bleeding (including events per 100 patient-years) are in the appendix (pp 3, 7–9).

Among the 429 patients with atrial fibrillation, incidence of stroke was low and similar among anticoagulant cohorts for apixaban (1/103 [1·0%, 95% CI 0·0–2·9]), rivaroxaban (4/174 [2·3%, 0·1–4·5]), and warfarin (2/152 [1·3%, 0·0–3·1]); p=0·71. Major bleeding occurred in 3/103 (2·9%, 95% CI 0·0–6·2) on apixaban, 5/174 (2·9%, 0·4–5·4) on rivaroxaban, and 12/152 (7·9%, 3·6–12·2) on warfarin; p=0·063. This translated to 2·5 events per 100 patient-years on apixaban, 2·2 events per 100 patient-years on rivaroxaban, and 6·9 events per 100 patient-years on warfarin. There was no difference

in the incidence of composite bleeding among cohorts (11/103 [10·71%, 95% CI 4·7–16·6] on apixaban, 17/174 [9·8%, 5·4–14·2] on rivaroxaban, and 25/152 [16·4%, 10·6–22·3%] on warfarin; p=0·16]. Time-to-event analyses for stroke and composite bleeding among patients with atrial fibrillation showed no differences between the three anticoagulant cohorts (appendix pp 3–5), but the log-rank test showed that time from prescription to major bleeding differed among the three cohorts (p=0·035), driven by the significant pairwise comparison between the rivaroxaban and warfarin cohorts (p=0·025; appendix p 4). Cox regression showed that patients on rivaroxaban had a lower risk of major bleeding than patients on warfarin (HR=0·32, 95% CI 0·11–0·91, p=0·032), a finding that became non-significant when adjusted for age, Charlson score, and $CHA_2DS_2$-VASc score (p=0·093). Median time from prescription to major bleeding or censoring was 331·5 days (IQR 181·5–577·0) on apixaban, 409·3 days (183·0–675·2) on rivaroxaban, and 276·1 days (78·5–655·3) on warfarin. Kaplan-Meier curves for stroke, major bleeding, and composite major bleeding and clinically relevant non-major bleeding in patients with atrial fibrillation are in the appendix (pp 10–12).

The incidence of recurrent venous thromboembolism among patients with venous thromboembolism and incidence of stroke among patients with atrial fibrillation in the combined direct oral anticoagulant cohort (apixaban plus rivaroxaban) were still low and similar to those in the warfarin cohort (appendix p 3). In patients with venous thromboembolism, the incidence of major bleeding and composite bleeding was similar between the combined DOAC and warfarin cohorts (appendix p 3). Among patients with atrial fibrillation, the incidence of composite bleeding did not differ between the combined cohort versus warfarin (p=0·056; appendix p 4). There was a lower incidence of major bleeding events in patients with atrial fibrillation for the combined cohort than for the warfarin cohort (8/277, [3%, 95% CI 0·9–4·9] *vs* 12/152 [8%, 3·6–12·2]; OR 0·35, 95% CI 0·14–0·87, p=0·024), but again, this finding lost significance when adjusted for age, Charlson score, and $CHA_2DS_2$-VASc score (p=0·087; appendix p 4).

Time-to-event analyses showed that the risks of recurrent venous thromboembolism were similar between the combined cohort and the warfarin cohort among patients with venous thromboembolism and risks of stroke were similar between the combined cohort and the warfarin cohort among patients with atrial fibrillation (appendix p 3). Among patients with venous thromboembolism, time-to-event analysis showed that risks of composite and major bleeding were similar between the combined and warfarin cohorts (appendix p 3). However, among patients with atrial fibrillation, time-to-event analyses showed lower risks of composite bleeding (HR 0·55, 95% CI 0·32–0·95; p=0·032) and major bleeding (HR 0·32, 0·13–0·80; p=0·014) for the combined cohort compared with the warfarin cohort (appendix p 5). As in the other analyses, these time-to-event findings became non-significant when adjusted for age, $CHA_2DS_2$-VASc, and Charlson score (p=0·079 for composite bleeding and p=0·060 for major bleeding; appendix p 5).

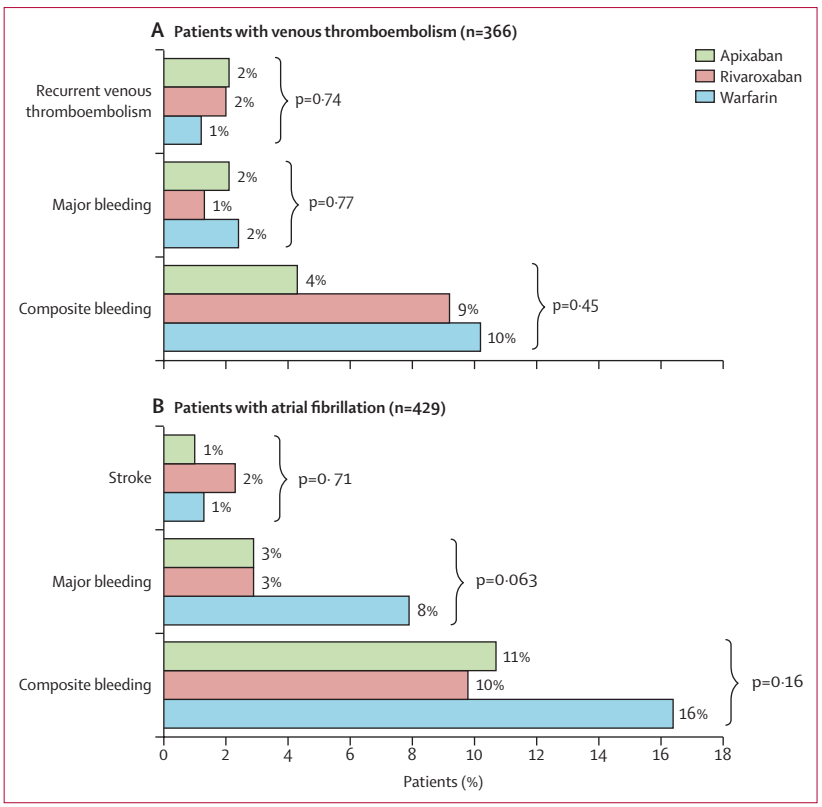


***Figure:*** **Outcomes in patients with venous thromboembolism and atrial fibrillationby anticoagulant, BMI >40 kg/m²**

(A) Histogram plot shows the proportion of patients with venous thromboembolism with outcomes of recurrent venous thromboembolism, major bleeding, and a composite of clinically relevant major and non-major bleeding. (B) Histogram plot shows the proportion of patients with atrial fibrillation with outcomes of stroke, major bleeding, and a composite of clinically relevant major and non-major bleeding. p values for all were derived from three-way comparisons of the anticoagulant cohorts. BMI=body-mass index.

In a subgroup of 92 patients with venous thromboembolism and a BMI of at least 50 kg/m² none of ten patients on apixaban and none of 30 patients on rivaroxaban had recurrent venous thromboembolism; two of 52 patients on warfarin (4%, 95% CI 0·0–9·1) had a recurrence (p=0·63). In a subgroup of 100 patients with atrial fibrillation and a BMI of at least 50 kg/m², strokes were similarly rare: 1/19 (5·3%, 95% CI 0·0–15·3) patients on apixaban, none of 37 on rivaroxaban and 1/44 (2·3%, 0·0–6·7) patients on warfarin; p=0·48. The incidence of both major bleeding and composite bleeding was comparable among the three anticoagulants in the venous thromboembolism cohort (0/10 for major and composite bleeding with apixaban; 0/30 for major bleeding and 6/30 [20·0%, 95% CI 5·7–34·3] for composite bleeding with rivaroxaban; 2/52 [3·9%, 0·0–9·1] for major bleeding and 8/52 [15·4%, 5·6–25·2]

for composite bleeding with warfarin; p=0·63 and 0·44 for major bleeding and composite bleeding, respectively). For patients with a BMI of at least 50 kg/m² and atrial fibrillation, the incidence of bleeding was similar between cohorts (1/19 [5·3%, 95% CI 0·0–15·3] for major bleeding and composite bleeding with apixaban; 2/37 [5·4%, 0·0–12·7] for major bleeding and 6/37 [16·2%, 4·3–28·1) for composite bleeding with rivaroxaban; 5/44 (11·4%, 2·0–20·7) for major bleeding and 10/44 [22·7%, 10·3–35·1] for composite bleeding with warfarin; p=0·63 and 0·24 for major and composite bleeding, respectively). Time-to-event analyses of patients with a BMI of at least 50 kg/m² showed no difference between the three anticoagulant cohorts in risks of recurrent venous thromboembolism in patients with venous thromboembolism, stroke in patients with atrial fibrillation, and major and composite bleeding (for patients with venous thromboembolism and atrial fibrillation, separately; appendix pp 5, 6).

In patients on warfarin, three of four patients who had thrombotic events had INRs recorded, with a mean INR of 2·3 (range 1·9–2·6). INRs were available at the time of events in 37 of 42 patients with clinically significant bleeding, with a mean INR 2·7 (1·2–5·7). At the time of bleeding events, 16/37 (43%) were therapeutic (INR 2–3), ten of 37 (27%) were supratherapeutic, and 11/37 (30%) were subtherapeutic. For major bleeding events, the mean INR was 2·9 (1·3–5·7); 43% were therapeutic, 29% were supratherapeutic, and 29% were subtherapeutic. Time in therapeutic range of patients on warfarin could not be calculated due to missing long-term INR data.

## Discussion

The substantial advantages of direct oral anticoagulants over warfarin have made the choice of anticoagulation easy in most circumstances. However, a large portion of the US population, a group at a particularly high risk of thrombosis, cannot benefit from these drugs as the representation of obese patients in previous studies was minimal.[1–7,14,20–27] This absence of evidence has led many authors to conclude that further studies are needed to establish the efficacy or the effective dose of direct oral anticoagulants in obese patients before their use can be recommended.[9,28,29–30]

Our study showed an overall low incidence of recurrent venous thromboembolism and stroke in morbidly obese patients, even those with a BMI of at least 50 kg/m², treated with apixaban, rivaroxaban, or warfarin. We showed no differences in bleeding events, including major bleeding, between the direct oral anticoagulant and warfarin cohorts in patients with venous thromboembolism. In patients with atrial fibrillation, we observed a higher risk of major bleeding in patients on warfarin compared with rivaroxaban but this difference became non-significant when adjusting for age, Charlson score, and $CHA_2DS_2$-VASc score. We interpret this to mean that there was a selection bias, which caused physicians to put sicker, older patients on a drug with which they were more familiar and perhaps trusted more. The data show that there does not appear to be support for these biases and, indeed, they might not be benefitting our sicker, older patients.

There were limitations to our study. Because of its retrospective nature, there was no randomisation to anticoagulation cohorts. We compensated for a potential bias in anticoagulation choice by adjusting significant associations in the unadjusted analyses (for $CHA_2DS_2$-VASc score for the atrial fibrillation patients and age and Charlson score for all patients), although residual confounding is likely and over adjustment is possible. Our sample size and low number of clinical events limited us in our ability to do more extensive adjustments. Additionally, the Bronx population is somewhat unique in its high proportion of African-American and Hispanic patients, and findings may not be generalisable to other morbidly obese populations. We did not obtain data on thrombotic risk factors that might have been important, such as presence of malignancy and history of bariatric surgery. We used outcomes from our medical records and therefore could not identify any events that were not noted in our system. Although patients might have had unrecorded events if they were treated at another hospital, our institution covers most of the Bronx and, once patients returned for follow-up to our primary care clinics, the event was likely to be documented. Furthermore, we have a Bronx Regional Health Information Organization Network, which feeds its events into our database. Moreover, this limitation would have affected all cohorts, further reducing its effect on the study.

Due to missing long-term INR data, the time in therapeutic range of patients on warfarin could not be calculated. The INRs for patients on warfarin who had events were generally within the accepted variance that is seen with warfarin and therefore the INR could not predict bad outcomes. Because this was a retrospective study, we could not measure the concentrations of direct oral anticoagulants (and they were not available on chart review) but this study represented typical care for this population. Absence of warfarin time in therapeutic range, concentrations of direct oral anticoagulants, and reliable adherence data were further limitations to our investigation.

Studies investigating obesity have often used its classic definition of BMI at least 30 kg/m². This threshold is likely to over-represent patients with milder forms of obesity such as obese class I (BMI 30–34·9) and under-represent the true effect of more substantial forms of obesity. We therefore decided that including only morbidly obese patients in this study would enable us to elucidate the effect of extreme weight on the efficacy of direct oral anticoagulants more definitively.

In summary, this is the largest study to date examining morbidly obese patients on direct oral anticoagulants and

provides further evidence of similar efficacy and safety between direct oral anti-Xa inhibitors and warfarin in morbidly obese patients with atrial fibrillation and venous thromboembolism. Although the overall low incidence of events in our study population was reassuring, a randomised controlled trial is needed to enable patients with morbid obesity to benefit from more convenient therapies, which might also offer a net clinical benefit.

#### Contributors

MK was responsible for the study design, data acquisition and interpretation, and writing of the manuscript. YC did the data acquisition, chart review, and contributed to the manuscript. DR, ST, and JG were responsible for chart review. RE did the statistical analysis and data interpretation, and contributed to the manuscript. WM was responsible for the statistical analysis plan and interpretation of the results, and contributed to the manuscript. HHB was responsible for the study design, data interpretation, and writing and final approval of the manuscript. All authors had full access to the study data.

#### Declaration of interests

HHB has received research or advisory funding from Janssen Pharmaceuticals, Bayer, and Kedrion Pharmaceuticals. MK has received research funding from Janssen Pharmaceuticals. All other authors declare no competing interests.

#### Data sharing

For original data, please contact mkushnir@montefiore.org.

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