



# Efficacy, Safety, and Exposure of Apixaban in Patients with High Body Weight or Obesity and Venous Thromboembolism: Insights from AMPLIFY

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## ABSTRACT

**Introduction:** As a result of limited clinical data, guidelines do not recommend the use of non-vitamin K antagonist oral anticoagulants in patients who weigh > 120 kg or have a body mass index (BMI) > 40 kg/m<sup>2</sup>.

**Methods:** This post hoc analysis of the AMPLIFY trial evaluated the efficacy (venous thromboembolism [VTE]/VTE-related death), safety (major and composite of major and clinically relevant non-major [CRNM] bleeding), and exposure of apixaban compared with enoxaparin followed by warfarin for the treatment of VTE by body weight ( $\leq 60$ , > 60 to < 100,  $\geq 100$  to < 120,  $\geq 120$  kg) and BMI ( $\leq 25$ , > 25 to 30, > 30 to 35, > 35 to 40, > 40 kg/m<sup>2</sup>).

**Results:** Among the AMPLIFY safety population, 5384 and 5359 patients had recorded body weight (range 28.9 to 222.0 kg;  $\geq 120$  kg,  $n = 290$ ) and BMI (range 12.5–71.8 kg/m<sup>2</sup>;

> 40 kg/m<sup>2</sup>,  $n = 263$ ), respectively. The rates of recurrent VTE/VTE-related death for apixaban versus enoxaparin/warfarin were similar across body weight subgroups: relative risks (RR; 95% confidence intervals [CI]) were 0.63 (0.23, 1.72), 0.99 (0.65, 1.50), 0.77 (0.34, 1.72), and 0.20 (0.02, 1.72) for the  $\leq 60$ , > 60 to < 100,  $\geq 100$  to < 120, and  $\geq 120$  kg groups, respectively ( $P_{\text{interaction}} = 0.44$ ). The rates of major bleeding were lower with apixaban versus enoxaparin/warfarin; RRs (95% CI) were 0.15 (0.02, 1.15), 0.41 (0.21, 0.77), not estimable, and 0.34 (0.04, 3.22), respectively ( $P_{\text{interaction}} = \text{not estimable}$ ). The rates of major/CRNM bleeding were significantly lower for apixaban versus enoxaparin/warfarin; RRs (95% CI) were 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 ( $P_{\text{interaction}} = 0.36$ ). Similar trends were seen in the BMI subgroups. There was a modest, not clinically meaningful, decrease (< 30%) in the median predicted exposure with increasing body weight ( $n = 281$ ).  
**Conclusions:** The findings of this post hoc analysis support the use of apixaban in patients with body weight  $\geq 120$  kg or BMI > 40 kg/m<sup>2</sup>.  
**Trial Registration Number:** NCT00643201

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12325-021-01716-8>.

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**Graphic Abstract:****Comparing apixaban with other blood thinners used to treat blood clots in patients who are obese**

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The purpose of this plain language summary is to help make clear the findings from a recently published research article. The title of the research article is *Efficacy, safety, and exposure of apixaban in high body weight and obese patients with venous thromboembolism: Insights from AMPLIFY*.

The results of this study may differ from those of other studies. Treatment decisions should be based on all available evidence, not on the results of a single study.

This graphical plain language summary represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC 2021.

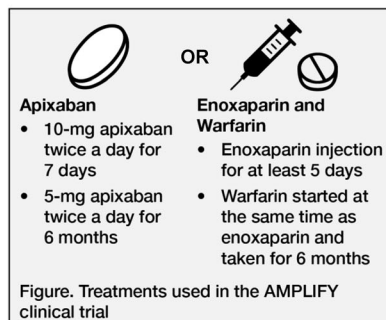
**What did this study look at?**

Patients who are obese have a higher risk of developing blood clots in their veins, known as venous thromboembolism (VTE). Blood thinners lower the risk of VTE by slowing down or stopping clots from forming.

However, blood thinners can also increase the risk of bleeding. Finding the balance between thinning the blood to reduce the risk of having a

blood clot without increasing the risk of bleeding is important.

The authors of this study looked at data from patients in the AMPLIFY clinical trial (NCT00643201; [clinicaltrials.gov/ct2/show/NCT00643201](https://clinicaltrials.gov/ct2/show/NCT00643201)) who were obese. Previously, data from all patients in AMPLIFY (obese and not obese) showed that a blood thinner called apixaban worked as well as and caused less bleeding than a combination of two blood thinners called enoxaparin and warfarin for treating VTE (Figure).

**What were the results of the study?**

The authors found that apixaban worked as well as enoxaparin and warfarin in reducing the risk of having another VTE or VTE-related death and lowered the risk of bleeding in patients with VTE who were obese.

They also found that as a patient's body weight increased, the amount of apixaban in their bloodstream decreased. But this did not affect how well the drug worked.

**What do the authors think these results mean?**

Overall, these findings support treating VTE with apixaban in patients who are obese.

More research is needed to confirm these findings.

Apixaban is a prescription medicine used to treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) and reduce the risk of them occurring again.

Approval of apixaban varies by country; please check with your local provider for more details.

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**Keywords:** Apixaban; Body mass index; Body weight; Enoxaparin; Venous thromboembolism; Warfarin

**Key Summary Points****Why carry out this study?**

Obesity, which has a rising worldwide prevalence, is associated with an increased risk of venous thromboembolism (VTE) and recurrent VTE. Current guidelines do not recommend the use of non-vitamin K antagonist oral anticoagulants in patients who weigh > 120 kg or have a body mass index (BMI) > 40 kg/m<sup>2</sup> because of limited clinical data in this population.

This post hoc analysis of the AMPLIFY trial extends previous subgroup analyses to explore the efficacy, safety, and exposure of apixaban for the treatment of VTE in patients with a body weight ≥ 120 kg or BMI > 40 kg/m<sup>2</sup>.

**What was learned from the study?**

The efficacy and safety of apixaban in patients with body weight ≥ 120 kg or BMI > 40 kg/m<sup>2</sup> were consistent with the main results of the AMPLIFY trial.

Across the different body weight and BMI categories, including body weight ≥ 120 kg and BMI > 40 kg/m<sup>2</sup>, apixaban had similar rates of recurrent VTE or VTE-related death and lower rates of bleeding compared with enoxaparin/warfarin.

There were no clinically meaningful differences in apixaban exposure between patients with body weight ≥ 120 kg and those in lower body weight groups.

**DIGITAL FEATURES**

This article is published with digital features, including a summary slide and graphical plain language summary, to facilitate understanding

of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13705642>.

## INTRODUCTION

Obesity affects over 650 million adults worldwide; between 1975 and 2016, the worldwide prevalence of obesity nearly tripled and continues to increase [1]. Obesity is a risk factor for thrombotic disorders, including venous thromboembolism (VTE), due to disruption of the balance between prothrombotic and anti-thrombotic adipokines, which leads to chronic inflammation, impaired fibrinolysis, and enhanced platelet activation inducing the coagulation cascade [2, 3]. Studies have reported up to a 6.2-fold increase in the risk of VTE due to obesity [4–6].

The International Society on Thrombosis and Haemostasis guidelines for the treatment of VTE do not recommend the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients who weigh > 120 kg or have a body mass index (BMI) > 40 kg/m<sup>2</sup> because of limited clinical data in this population [7]. In addition, there is some concern regarding underdosing with NOACs in patients in this body weight or BMI category with VTE because of decreased drug exposures, reduced peak concentrations, and shorter half-lives with increasing weight [7].

Apixaban, a factor Xa (FXa) inhibitor, is approved for the treatment and secondary prevention of VTE, the prophylaxis of VTE after hip or knee surgery, and the prevention of stroke in patients with non-valvular atrial fibrillation [8]. It is administered in fixed doses with no dose adjustment for body weight alone [8]. A population pharmacokinetic (PK) analysis showed that apixaban PK characteristics in patients with VTE were generally consistent with observations in healthy subjects [9]. Additionally, no statistically significant relationship was found between apixaban exposure and clinical endpoints in an exposure–response analysis [9]. A PK study in healthy subjects, using a single dose of apixaban (10 mg), showed that apixaban exposure (AUC) was approximately 23%

lower in the high body weight ( $\geq 120$  kg) group and approximately 20% higher in the low body weight ( $\leq 50$  kg) group compared with the reference group (65–85 kg) [10]. These modest changes in exposure were not considered to be clinically meaningful.

The AMPLIFY trial (NCT00643201), an active-controlled, parallel-group, double-blind, triple-dummy, randomized study, showed that a 6-month treatment course of oral apixaban monotherapy was non-inferior to enoxaparin followed by warfarin in reducing the rate of recurrent VTE or VTE-related death and was associated with less major bleeding [11]. Consistent results were demonstrated in subgroup analyses of VTE or VTE-related death and major bleeding by body weight ( $\leq 60$ ,  $> 60$  to  $< 100$ , and  $\geq 100$  kg) and BMI ( $\leq 25$ ,  $> 25$  to  $30$ ,  $> 30$  to  $35$ , and  $> 35$  kg/m<sup>2</sup>) [11]. However, the efficacy and safety of apixaban in patients with body weight  $\geq 120$  kg and BMI  $> 40$  kg/m<sup>2</sup> remain unknown. The objective of this post hoc analysis of the AMPLIFY trial was to extend the previous subgroup analyses to explore the efficacy, safety, and exposure of apixaban for the treatment of VTE in patients with a body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup>.

## METHODS

### Study Design and Population

The study design, methods, and primary results of the AMPLIFY trial have been published previously [11]. Briefly, patients were eligible for inclusion in the study if they were aged 18 years or older with an objectively confirmed, symptomatic proximal deep vein thrombosis (DVT) involving the popliteal, femoral, or iliac veins, or acute symptomatic pulmonary embolism (PE) with or without DVT. Exclusion criteria were active bleeding, a high risk of bleeding, or other contraindications to treatment with enoxaparin and warfarin. Patients with cancer whose VTE was to be treated for 6 months or more with low molecular weight heparin were excluded. Patients were also excluded if their DVT or PE was provoked in the absence of a persistent risk factor for recurrence; if less than

6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin at a dosage of more than 165 mg daily, or treatment with potent inhibitors of cytochrome P450 3A4.

The protocol was approved by the institutional review board of each participating study center (full list of institutional review boards that approved the study is included as supplementary material). All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki. An independent committee unaware of study group assignments adjudicated all suspected outcomes. No patients were involved in the design of the study or the dissemination of the results.

Randomization was stratified by the qualifying index event (DVT alone or PE with or without DVT). Eligible patients were randomized 1:1 to apixaban (10 mg twice daily) for the first 7 days followed by 5 mg twice daily for 6 months, or to subcutaneous enoxaparin (1 mg/kg of body weight every 12 h) for at least 5 days and warfarin initiated concomitantly and continued for 6 months. The warfarin dosage was adjusted to an international normalized ratio (INR) of 2.0–3.0. Enoxaparin was discontinued when a blinded INR of 2.0 or more was achieved. To measure apixaban plasma concentrations, blood samples were collected at steady state at – 2 h (ca. 2 h prior to dosing), 0 h (pre-dose), and 2 and 4 h post-dose [9].

## Outcomes

In this post hoc analysis, patients were analyzed according to body weight ( $\leq 60$ ,  $> 60$  to  $< 100$ ,  $\geq 100$  to  $< 120$ , and  $\geq 120$  kg) and BMI categories ( $\leq 25$ ,  $> 25$  to  $30$ ,  $> 30$  to  $35$ ,  $> 35$  to  $40$ , and  $> 40$  kg/m<sup>2</sup>).

The primary efficacy outcome was the incidence of the adjudicated composite of recurrent symptomatic VTE or VTE-related death. Recurrent VTE included fatal or nonfatal PE and DVT. Causes of death were classified as related to VTE, cardiovascular disease, bleeding, or other causes. PE was considered the cause of death if

there was objective documentation, or if death could not be attributed to another documented cause and PE could not be ruled out.

The primary safety outcome was adjudicated major bleeding and the secondary safety outcome was the composite of major bleeding and clinically relevant non-major (CRNM) bleeding. Major bleeding was defined as overt bleeding associated with a decrease in the hemoglobin level of  $\geq 2$  g/dL, requiring the transfusion of  $\geq 2$  units of blood, occurring into a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or contributing to death. CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life. The criteria for the diagnosis and adjudication of all outcomes have been previously reported [11].

Finally, a population PK analysis was conducted to characterize apixaban exposure in patients treated for VTE as published previously [9].

## Statistical Analysis

All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented. Patients with missing endpoint events were excluded from the efficacy analysis. All safety analyses included data obtained from treated patients during the study treatment period, defined as the time from the administration of the first dose until 48 h after the last dose was administered.

For each subgroup, the relative risk (RR) and 95% confidence intervals (CIs) were calculated using the Cochran–Mantel–Haenszel test, stratified by index event strata. The 95% CIs for single event rates were calculated on the basis of the Wald asymptotic confidence limits. *P* values for interaction were based on a logistic model using Wald's chi-square test.



Using the published population PK analysis of apixaban in patients undergoing VTE treatment, steady-state daily (0–24 h) exposure was predicted for each patient using the empirical Bayes' prediction of their oral clearance value from the final population PK model and total daily dosage of apixaban, and was summarized by body weight category [9].

## RESULTS

### Patient Population and Baseline Characteristics

Of the 5395 patients who were randomized and included in the safety population of AMPLIFY, 5384 and 5359 patients had recorded body weight and BMI, respectively. The ranges of body weight and BMI for the trial were 28.9–222.0 kg and 12.5–71.8 kg/m<sup>2</sup>, respectively. Among these patients, 290 had a body weight  $\geq 120$  kg and 263 had a BMI  $> 40$  kg/m<sup>2</sup>. The baseline demographics and clinical characteristics of patients by body weight group are shown in Table 1. Patients in the  $\geq 120$  kg group were younger than those in lower body weight groups and were less likely to be female than those in the  $\leq 60$  and  $> 60$  to  $< 100$  kg body weight groups. As expected, mean BMI increased across body weight groups. Creatinine clearance was normal in most patients who weighed  $\geq 100$  to  $< 120$  or  $\geq 120$  kg. The clinical presentation of VTE did not differ by body weight group; however, patients weighing  $\geq 100$  to  $< 120$  or  $\geq 120$  kg were more likely to have had a previous VTE than those in lower weight groups. There was an increase in the percentage of patients with diabetes, hypercholesterolemia, and hypertension with increasing body weight.

The baseline demographic and clinical characteristics of patients by BMI category are shown in Table 2. Similar trends were seen across BMI groups as for body weight groups with some exceptions: age was similar among BMI groups and patients were more likely to be female in higher BMI groups.

### Efficacy and Safety Outcomes

The rates of recurrent VTE or VTE-related death were similar between apixaban-treated and enoxaparin/warfarin-treated patients across body weight groups (Fig. 1a). The RRs (95% CI) for the  $\leq 60$ ,  $> 60$  to  $< 100$ , and  $\geq 100$  to  $< 120$  kg groups were 0.63 (0.23, 1.72), 0.99 (0.65, 1.50), and 0.77 (0.34, 1.72), respectively. The  $\geq 120$  kg group had the lowest RR: 0.20 (95% CI 0.02, 1.72). No treatment by body weight interaction was observed ( $P_{\text{interaction}} = 0.44$ ).

Major bleeding rates were numerically lower with apixaban compared with enoxaparin/warfarin across body weight groups with point estimates of RR of 0.15 to 0.41 (Fig. 1b). The RR (95% CI) of major bleeding for the  $\geq 120$  kg group was 0.34 (0.04, 3.22). No major bleeding episodes were reported in the  $\geq 100$  to  $< 120$  kg group receiving apixaban; thus, the  $P_{\text{interaction}}$  for treatment by body weight was not estimable.

The rates of major or CRNM bleeding were significantly lower in apixaban-treated patients compared with enoxaparin/warfarin-treated patients across all body weight groups (Fig. 1c). The RRs (95% CI) for the  $\leq 60$ ,  $> 60$  to  $< 100$ ,  $\geq 100$  to  $< 120$ , and  $\geq 120$  kg groups were 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. No treatment by body weight interaction was observed ( $P_{\text{interaction}} = 0.36$ ).

The efficacy and safety results by BMI group were similar to those seen across body weight groups (Fig. 2).

### Exposure Outcomes

Apixaban plasma concentrations were measured for 281 patients: 16, 199, 45, and 21 patients in the  $\leq 60$ ,  $> 60$  to  $< 100$ ,  $\geq 100$  to  $< 120$ , and  $\geq 120$  kg body weight groups, respectively. There was a modest decrease ( $< 30\%$ ) in the median predicted exposure with increasing body weight (Fig. 3). The exposure range was similar among body weight categories with overlapping quartiles.

**Table 1** Baseline demographic and clinical characteristics by body weight category (*n* = 5384)

	Weight ≤ 60 kg		Weight > 60 to < 100 kg		Weight ≥ 100 to < 120 kg		Weight ≥ 120 kg		
	Total <i>n</i> = 476	Apix <i>n</i> = 231	Total <i>n</i> = 3868	Apix <i>n</i> = 1932	Total <i>n</i> = 750	Apix <i>n</i> = 378	Total <i>n</i> = 290	Apix <i>n</i> = 144	E/W <i>n</i> = 146
<b>Demographic characteristics</b>									
Age, years, mean (SD)	55.5 (20.1)	56.5 (20.2)	58.0 (15.9)	58.2 (15.9)	55.5 (13.6)	55.8 (13.6)	49.2 (12.1)	49.2 (11.8)	49.3 (12.5)
Female sex, <i>n</i> (%)	371 (77.9)	179 (77.5)	1585 (41.0)	816 (42.2)	179 (23.9)	85 (22.5)	87 (30.0)	38 (26.4)	49 (33.6)
<b>Physical characteristics</b>									
BMI, kg/m <sup>2</sup> , mean (SD)	21.4 (2.4)	21.4 (2.4)	27.7 (3.8)	27.6 (3.8)	34.2 (4.3)	34.2 (4.3)	42.4 (7.1)	42.2 (7.1)	42.7 (7.2)
BMI category, kg/m <sup>2</sup> , <i>n</i> (%)									
≤ 25	455 (95.6)	221 (95.7)	987 (25.5)	507 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 25 to 30	17 (3.6)	10 (4.3)	1933 (50.0)	946 (49.0)	93 (12.4)	48 (12.7)	2 (0.7)	1 (0.7)	1 (0.7)
> 30 to 35	0 (0.0)	0 (0.0)	750 (19.4)	374 (19.4)	390 (52.0)	191 (50.5)	27 (9.3)	15 (10.4)	12 (8.2)
> 35	0 (0.0)	0 (0.0)	182 (4.7)	97 (5.0)	264 (35.2)	137 (36.2)	259 (89.3)	128 (88.9)	131 (89.7)
Not reported	4 (0.8)	0 (0.0)	16 (0.4)	8 (0.4)	3 (0.4)	2 (0.5)	2 (0.7)	0 (0.0)	2 (1.4)
<b>Clinical characteristics</b>									
Creatinine clearance, mL/min, <i>n</i> (%)									
≤ 30	13 (2.7)	5 (2.2)	16 (0.4)	9 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 30 to ≤ 50	81 (17.0)	46 (19.9)	223 (5.8)	112 (5.8)	5 (0.7)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
> 50 to ≤ 80	148 (31.1)	75 (32.5)	872 (22.5)	440 (22.8)	71 (9.5)	33 (8.7)	2 (0.7)	1 (0.7)	1 (0.7)
> 80	182 (38.2)	86 (37.2)	2408 (62.3)	1193 (61.7)	633 (84.4)	315 (83.3)	255 (87.9)	127 (88.2)	128 (87.7)
Not reported	52 (10.9)	19 (8.2)	349 (9.0)	178 (9.2)	41 (5.5)	27 (7.1)	33 (11.4)	16 (11.1)	17 (11.6)

Table 1 continued

	Weight ≤ 60 kg		Weight > 60 to < 100 kg		Weight ≥ 100 to < 120 kg		Weight ≥ 120 kg	
	Total n = 476	Apix n = 231	Total n = 3868	Apix n = 1932	Total n = 750	Apix n = 378	Total n = 290	Apix n = 144
Clinical presentation of VTE, n (%)								
Provoked	67 (14.1)	34 (14.7)	368 (9.5)	188 (9.7)	80 (10.7)	42 (11.1)	27 (9.3)	8 (5.6)
Unprovoked	409 (85.9)	197 (85.3)	3497 (90.4)	1744 (90.3)	668 (89.1)	334 (88.4)	262 (90.3)	135 (93.8)
Not reported	0 (0.0)	0 (0.0)	3 (< 0.1)	0 (0.0)	2 (0.3)	2 (0.5)	1 (0.3)	0 (0.0)
Risk factors, n (%)								
Active cancer	18 (3.8)	9 (3.9)	104 (2.7)	47 (2.4)	14 (1.9)	6 (1.6)	7 (2.4)	4 (2.8)
Persistent or permanent immobility	33 (6.9)	18 (7.8)	246 (6.4)	138 (7.1)	46 (6.1)	23 (6.1)	21 (7.3)	8 (5.6)
Previous VTE	42 (8.8)	22 (9.5)	620 (16.0)	327 (16.9)	149 (19.9)	81 (21.5)	59 (20.4)	32 (22.4)
Known thrombophilia	8 (1.7)	5 (2.2)	96 (2.5)	55 (2.8)	21 (2.8)	10 (2.7)	7 (2.4)	4 (2.8)
Cigarette smoking, n (%)	103 (21.6)	48 (20.8)	893 (23.1)	452 (23.4)	195 (26.1)	93 (24.7)	86 (29.8)	38 (26.6)
Diabetes mellitus, n (%)	27 (5.7)	17 (7.4)	435 (11.3)	224 (11.6)	128 (17.1)	58 (15.4)	73 (25.3)	44 (30.8)
Hypercholesterolemia, n (%)	78 (16.4)	45 (19.5)	937 (24.2)	484 (25.1)	205 (27.4)	103 (27.4)	81 (28.0)	42 (29.4)
Hypertension, n (%)	130 (27.3)	67 (29.0)	1601 (41.4)	787 (40.7)	378 (50.5)	204 (54.3)	169 (58.5)	89 (62.2)

Apix apixaban, BMI body mass index, E/W enoxaparin/warfarin, SD standard deviation, VTE venous thromboembolism

**Table 2** Baseline demographic and clinical characteristics by BMI category ( $n = 5359$ )

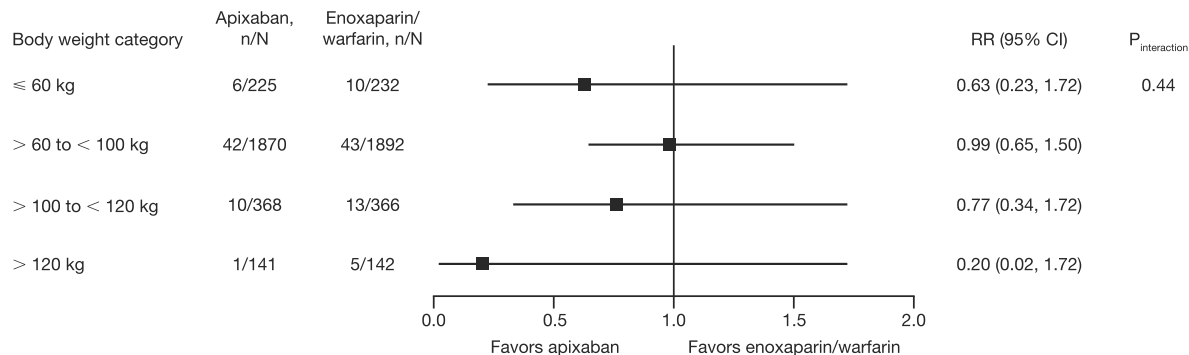
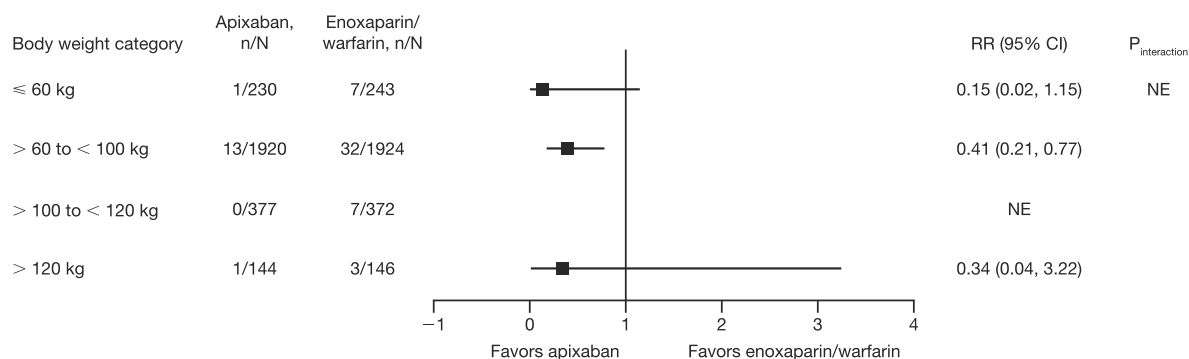
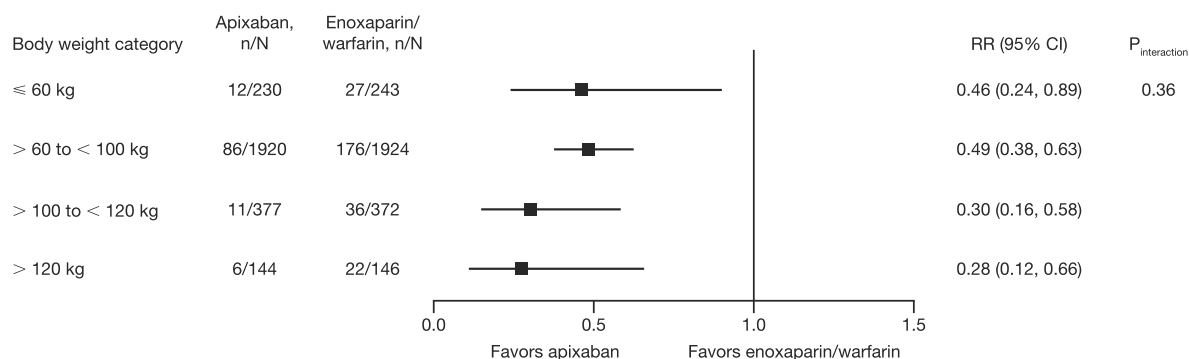
	BMI $\leq 25$ kg/m <sup>2</sup>			BMI > 25 to 30 kg/m <sup>2</sup>			BMI > 30 to 35 kg/m <sup>2</sup>			BMI > 35 to 40 kg/m <sup>2</sup>			BMI > 40 kg/m <sup>2</sup>		
	Total $n = 1442$	Apix $n = 728$	E/W $n = 714$	Total $n = 2045$	Apix $n = 1005$	E/W $n = 1040$	Total $n = 1167$	Apix $n = 580$	E/W $n = 587$	Total $n = 442$	Apix $n = 236$	E/W $n = 206$	Total $n = 263$	Apix $n = 126$	E/W $n = 137$
<b>Demographic characteristics</b>															
Age, years, mean (SD)	54.9 (18.4)	55.3 (18.5)	54.6 (18.4)	58.7 (15.4)	58.9 (15.4)	58.5 (15.5)	57.6 (14.3)	57.8 (14.4)	57.5 (14.3)	56.3 (14.3)	54.7 (14.2)	53.4 (13.3)	53.7 (13.4)	53.2 (13.2)	
Female sex, $n$ (%)	658 (45.6)	338 (46.4)	320 (44.8)	665 (32.5)	323 (32.1)	342 (32.9)	483 (41.4)	255 (44.0)	228 (38.8)	237 (53.6)	122 (51.7)	115 (55.8)	172 (65.4)	79 (62.7)	93 (67.9)
<b>Physical characteristics</b>															
BMI, kg/m <sup>2</sup> , mean (SD)	22.6 (1.9)	22.7 (1.9)	22.6 (1.9)	27.4 (1.4)	27.4 (1.4)	27.4 (1.4)	32.0 (1.4)	32.0 (1.4)	32.0 (1.4)	37.0 (1.4)	37.0 (1.4)	37.0 (1.4)	45.2 (5.5)	45.3 (5.5)	45.3 (5.5)
<b>Clinical characteristics</b>															
Creatinine clearance, mL/min, $n$ (%)															
$\leq 30$	20 (1.4)	8 (1.1)	12 (1.7)	8 (0.4)	5 (0.5)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 30 to $\leq 50$	135 (9.4)	72 (9.9)	63 (8.8)	126 (6.2)	64 (6.4)	62 (6.0)	37 (3.2)	20 (3.4)	17 (2.9)	7 (1.6)	3 (1.3)	4 (1.9)	3 (1.1)	2 (1.6)	1 (0.7)
50 to $\leq 80$	379 (26.3)	198 (27.2)	181 (25.4)	441 (21.6)	223 (22.2)	218 (21.0)	194 (16.6)	88 (15.2)	106 (18.1)	56 (12.7)	30 (12.7)	26 (12.6)	13 (4.9)	7 (5.6)	6 (4.4)
> 80	784 (54.4)	390 (53.6)	394 (55.2)	1268 (62.0)	613 (61.0)	655 (63.0)	846 (72.5)	425 (73.3)	421 (71.7)	349 (79.0)	182 (77.1)	167 (81.1)	220 (83.7)	105 (83.3)	115 (83.9)
Not reported	124 (8.6)	60 (8.2)	64 (9.0)	202 (9.9)	100 (10.0)	102 (9.8)	90 (7.7)	47 (8.1)	43 (7.3)	29 (6.6)	20 (8.5)	9 (4.4)	27 (10.3)	12 (9.5)	15 (10.9)
<b>Clinical presentation of VTE, <math>n</math> (%)</b>															
Provoked	161 (11.2)	81 (11.1)	80 (11.2)	189 (9.2)	101 (10.0)	88 (8.5)	111 (9.5)	57 (9.8)	54 (9.2)	50 (11.3)	22 (9.3)	28 (13.6)	29 (11.0)	11 (8.7)	18 (13.1)
Unprovoked	1280 (88.8)	647 (88.9)	633 (88.7)	1854 (90.7)	903 (89.9)	951 (91.4)	1055 (90.4)	522 (90.0)	533 (90.8)	392 (88.7)	214 (90.7)	178 (86.4)	232 (88.2)	114 (90.5)	118 (86.1)
Not reported	1 (< 0.1)	0 (0.0)	1 (0.1)	2 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	1 (0.7)
<b>Risk factors, <math>n</math> (%)</b>															



Table 2 continued

	BMI ≤ 25 kg/m <sup>2</sup>			BMI > 25 to 30 kg/m <sup>2</sup>			BMI > 30 to 35 kg/m <sup>2</sup>			BMI > 35 to 40 kg/m <sup>2</sup>			BMI > 40 kg/m <sup>2</sup>		
	Total <i>n</i> = 1442	Apix <i>n</i> = 728	E/W <i>n</i> = 714	Total <i>n</i> = 2045	Apix <i>n</i> = 1005	E/W <i>n</i> = 1040	Total <i>n</i> = 1167	Apix <i>n</i> = 580	E/W <i>n</i> = 587	Total <i>n</i> = 442	Apix <i>n</i> = 236	E/W <i>n</i> = 206	Total <i>n</i> = 263	Apix <i>n</i> = 126	E/W <i>n</i> = 137
Active cancer	51 (3.5)	24 (3.3)	27 (3.8)	45 (2.2)	24 (2.4)	21 (2.0)	25 (2.1)	7 (1.2)	18 (3.1)	13 (2.9)	7 (3.0)	6 (2.9)	7 (2.7)	4 (3.2)	3 (2.2)
Persistent or permanent immobility	94 (6.5)	54 (7.4)	40 (5.6)	118 (5.8)	65 (6.5)	53 (5.1)	73 (6.3)	40 (6.9)	33 (5.6)	35 (7.9)	17 (7.2)	18 (8.7)	25 (9.6)	11 (8.8)	14 (10.3)
Previous VTE	179 (12.4)	92 (12.6)	87 (12.2)	334 (16.3)	164 (16.3)	170 (16.4)	208 (17.8)	123 (21.2)	85 (14.5)	84 (19.0)	50 (21.2)	34 (16.5)	58 (22.2)	28 (22.4)	30 (22.1)
Known thrombophilia	41 (2.8)	24 (3.3)	17 (2.4)	52 (2.5)	28 (2.8)	24 (2.3)	31 (2.7)	17 (2.9)	14 (2.4)	6 (1.4)	3 (1.3)	3 (1.5)	2 (0.8)	2 (1.6)	0 (0.0)
Cigarette smoking, <i>n</i> (%)	383 (26.6)	194 (26.6)	189 (26.5)	476 (23.3)	226 (22.5)	250 (24.1)	259 (22.2)	128 (22.1)	131 (22.3)	97 (21.9)	54 (22.9)	43 (20.9)	60 (23.0)	28 (22.4)	32 (23.5)
Diabetes mellitus, <i>n</i> (%)	95 (6.6)	59 (8.1)	36 (5.0)	214 (10.5)	99 (9.9)	115 (11.1)	188 (16.1)	94 (16.2)	94 (16.0)	98 (22.2)	56 (23.7)	42 (20.4)	64 (24.5)	34 (27.2)	30 (22.1)
Hypercholesterolemia, <i>n</i> (%)	245 (17.0)	129 (17.7)	116 (16.3)	494 (24.2)	244 (24.3)	250 (24.1)	330 (28.3)	173 (29.9)	157 (26.7)	146 (33.0)	81 (34.3)	65 (31.6)	83 (31.8)	45 (36.0)	38 (27.9)
Hypertension, <i>n</i> (%)	399 (27.7)	206 (28.3)	193 (27.1)	839 (41.1)	416 (41.4)	423 (40.7)	597 (51.2)	293 (50.6)	304 (51.8)	263 (59.5)	139 (58.9)	124 (60.2)	171 (65.5)	90 (72.0)	81 (59.6)

Apix apixaban, BMI body mass index, E/W enoxaparin/warfarin, SD standard deviation, VTE venous thromboembolism

**VTE or VTE-related death****Major bleeding****Major or CRNM bleeding**

**Fig. 1** Recurrent VTE or VTE-related death, major bleeding, and composite of major or CRNM bleeding during the treatment period by body weight category. *CI* confidence interval, *CRNM* clinically relevant non-major, *NE* not estimable, *RR* relative risk, *VTE* venous thromboembolism

## DISCUSSION

The presumed decrease in NOAC exposure in patients with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup> has raised concern regarding potential underdosing and associated lack of efficacy in patients with VTE. Therefore, this post hoc analysis focused on patients with body weight  $\geq 120$  kg or BMI of  $> 40$  kg/m<sup>2</sup> with VTE who participated in the AMPLIFY trial. Compared with enoxaparin/warfarin, fixed-dose apixaban without any dose adjustments was not associated with a higher risk of recurrent VTE or VTE-related death in patients with VTE, including those with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup>. Consistent with the overall results of the AMPLIFY trial [11], the rates of recurrent VTE or VTE-related death were similar between treatments, with lower rates of bleeding (major and composite of major and CRNM bleeding) occurring with apixaban compared with enoxaparin/warfarin across increasing body weight and BMI groups, including in those with obesity and high body weight.

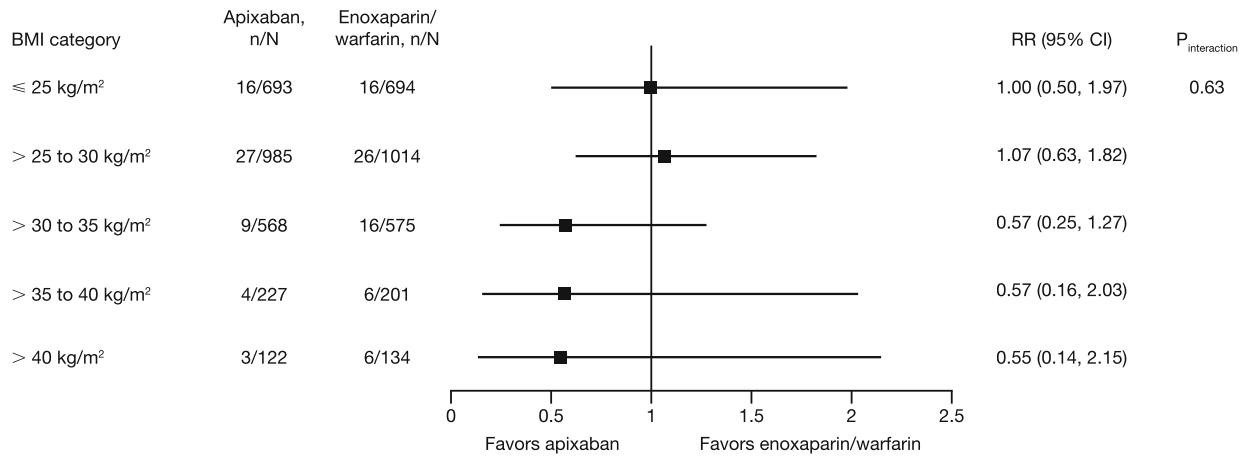
Apixaban exposures by body weight category were consistent with the overall population PK analysis [9]. Among the subset of AMPLIFY patients in whom apixaban plasma concentrations were measured, there was a modest decrease of  $< 30\%$  in apixaban exposure in the  $\geq 120$  kg group compared with the  $> 60$  to  $< 100$  kg group, which had the most patients. The magnitude of this decrease is consistent with the results of a study of apixaban exposure in healthy subjects with extremes of body weight [10]. This is not considered clinically meaningful because similar magnitudes of changes have been observed in male individuals, or patients with moderate renal impairment, or patients receiving concomitant diltiazem, a moderate inhibitor of CYP3A4, without altering the benefit–risk profile of apixaban or requiring dose adjustment [10, 12–14]. This is supported by the observed relative risk of recurrent VTE or VTE-related death in apixaban-treated patients in the  $\geq 120$  kg and  $> 40$  kg/m<sup>2</sup> groups being no greater than that in lower body weight or BMI groups. Additionally, an observational study in

100 patients with a median BMI of 45 kg/m<sup>2</sup> found that obese or high body weight patients typically achieve therapeutic FXa inhibitor concentrations, with no relationship between FXa inhibitor concentrations at peak or trough and body weight or BMI [15]. Thus, despite the modest decrease in apixaban exposure in the  $\geq 120$  kg group, our analysis does not suggest that high body weight or obesity unfavorably affect the efficacy of apixaban for the treatment of VTE.

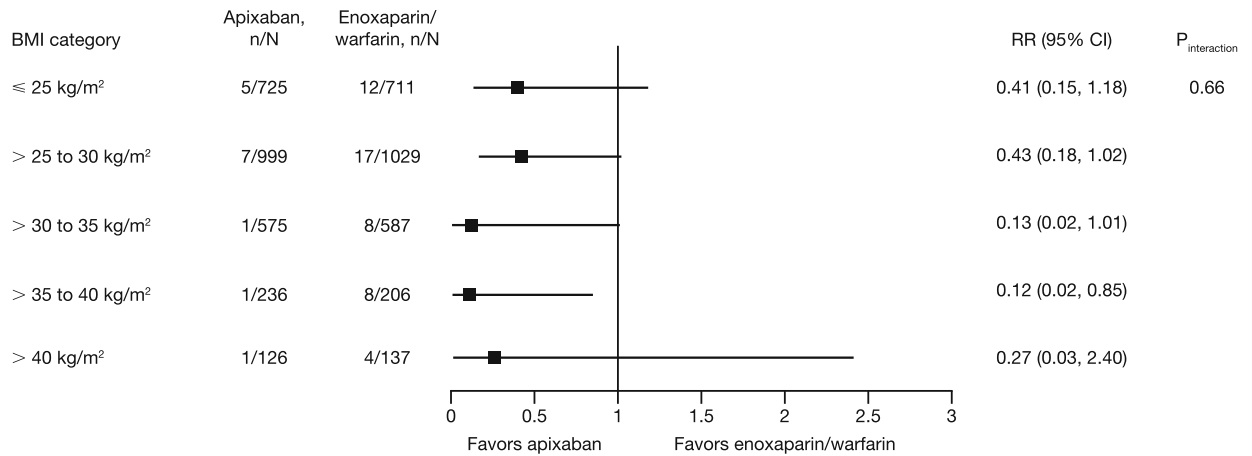
Evidence for NOAC use in patients with extremes of body weight is sparse, both for the treatment of VTE and the prevention of stroke in patients with non-valvular atrial fibrillation; however, apixaban and rivaroxaban appear to have the most favorable efficacy and safety profiles [16, 17]. The EINSTEIN DVT/PE studies showed no association between body weight ( $\leq 50$ ,  $> 50$  to  $< 100$ ,  $\geq 100$  kg) or BMI ( $< 25$ ,  $\geq 25$  to  $< 30$ ,  $\geq 30$  to  $< 35$ , and  $\geq 35$  kg/m<sup>2</sup>) and risk of recurrent VTE ( $P_{\text{trend}} = 0.87$  and  $0.62$ , respectively), major bleeding ( $P_{\text{trend}} = 0.24$  and  $0.36$ , respectively), or clinically relevant bleeding ( $P_{\text{trend}} = 0.17$  and  $0.63$ , respectively) in rivaroxaban-treated patients. Major bleeding events were numerically lower in rivaroxaban-treated patients across all body weight and BMI categories [18]. The pre-specified subgroup analysis of the AMPLIFY trial by body weight ( $\leq 60$ ,  $> 60$  to  $< 100$ , and  $\geq 100$  kg) showed no significant differences between apixaban and enoxaparin/warfarin for the outcome of recurrent VTE; furthermore, apixaban-treated patients had a lower rate of major bleeding [11]. Similar results were shown for BMI groups ( $\leq 25$ ,  $> 25$  to  $30$ ,  $> 30$  to  $35$ , and  $> 35$  kg/m<sup>2</sup>). The current analysis confirms and extends these results in obese patients with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup>.

Several observational studies have shown that NOACs have a similar effectiveness and similar rates of bleeding compared with warfarin in obese patients treated for VTE; however, most of these studies did not differentiate between individual NOACs. A meta-analysis of five observational studies showed that the use of NOACs in obese patients with body weight  $> 120$  kg or BMI  $> 40$  kg/m<sup>2</sup> was non-inferior to warfarin with regard to effectiveness (VTE

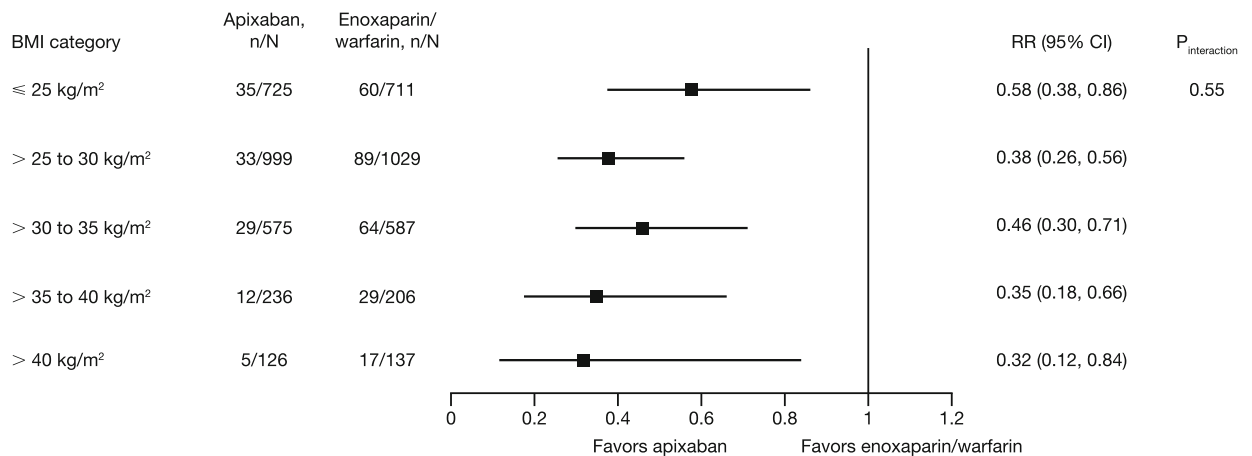
**VTE or VTE-related death**



**Major bleeding**



**Major or CRNM bleeding**

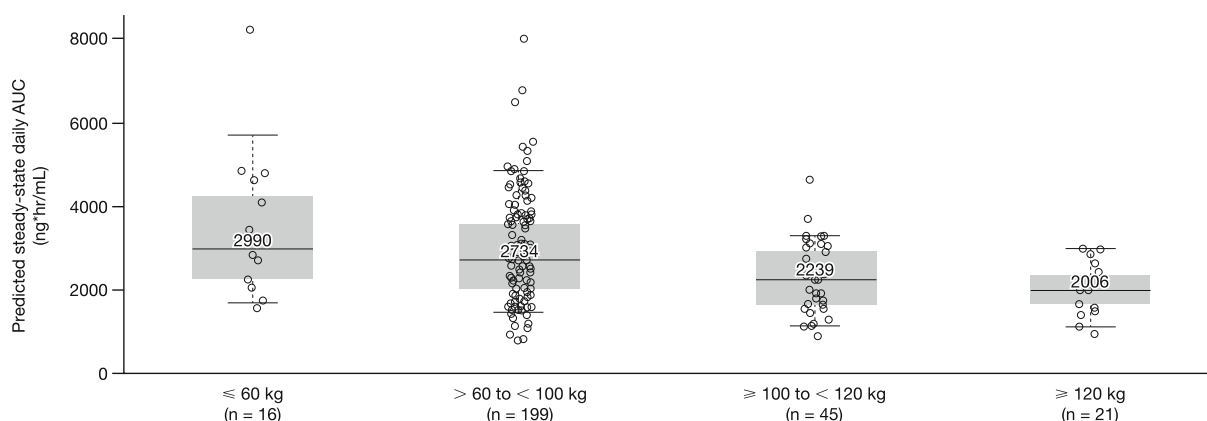


**Fig. 2** Recurrent VTE or VTE-related death, major bleeding, and composite of major or CRNM bleeding during the treatment period by BMI category. *BMI* body mass index, *CI* confidence interval, *CRNM* clinically relevant non-major, *RR* relative risk, *VTE* venous thromboembolism

recurrence) and safety (major bleeding) [19]. Further observational studies have shown consistent results. A retrospective cohort study in 1840 obese patients (> 100 and < 300 kg) with acute VTE treated at an integrated delivery system of 40 academic, community, and specialty hospitals in the USA found that NOACs and warfarin had similar effectiveness and safety (no significant differences in the rates of VTE recurrence or bleeding, respectively) [20]. Another study in 366 patients with a BMI ≥ 40 kg/m<sup>2</sup> prescribed an anticoagulant for venous thromboembolism (apixaban, *n* = 47; rivaroxaban, *n* = 152; warfarin, *n* = 167) found the incidences of recurrent VTE and major bleeding to be similar between each NOAC and warfarin [21]. An analysis of the Mayo Clinic VTE Registry consisting of 2577 patients with VTE receiving anticoagulant treatment (apixaban, *n* = 772; rivaroxaban, *n* = 502) found similar rates of recurrent VTE and major bleeding between apixaban-treated and rivaroxaban-treated patients across body weight groups (< 60, 60 to 120, and > 120 kg) [22]. Observational data comparing rivaroxaban with

warfarin are available from a propensity score-matched analysis using pooled data from two US claims databases. Results showed that morbidly obese patients (based on ICD-9/10 codes) with VTE treated with rivaroxaban had similar risks of recurrent VTE and major bleeding compared with those treated with warfarin [23].

Because our analysis was performed in the setting of a randomized, double-blind, active-controlled clinical trial, the possibility of treatment selection bias and treatment-related management decisions are minimized. Other strengths of this analysis are the inclusion of patients with extremes of body weight, particularly ≥ 120 kg and BMI > 40 kg/m<sup>2</sup>; central adjudication of all VTE and bleeding events by an independent committee blinded to treatment assignment; and assessment of apixaban exposure from a representative set of study patients which spanned across all body weight and BMI categories. However, the results of this post hoc analysis are only hypothesis-generating. As body weight and BMI were assessed only at baseline, clinical outcomes may have been impacted by any body weight and BMI changes among patients during the trial. In addition, because patients in a clinical trial tend to have fewer comorbidities and concomitant medications, apixaban exposure may be different in a real-world population, and this could be further pronounced in the obese population. Other limitations of this analysis include the low



**Fig. 3** Predicted steady-state daily AUC by body weight category. Boxes indicate 25th to 75th percentiles, whiskers indicate 5th to 95th percentiles, and black horizontal lines represent the median. Numbers inside boxes are median values. Circles are individual predicted values. *AUC* area under the plasma concentration–time curve



numbers of patients in the  $\geq 120$  kg body weight and BMI  $> 40$  kg/m<sup>2</sup> groups, a small number of patients (approximately 5% of patients in AMPLIFY) in the population PK analysis, and a relatively short follow-up duration.

## CONCLUSIONS

In this post hoc analysis, the efficacy and safety of apixaban in patients with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup> were consistent with the main results of the AMPLIFY trial. Across different body weight or BMI categories, compared with enoxaparin/warfarin, apixaban had similar rates of recurrent VTE or VTE-related death and lower rates of major bleeding (significant for body weight  $> 60$  to  $< 100$  kg and BMI  $> 35$  to  $40$  kg/m<sup>2</sup> groups) and the composite of major or CRNM bleeding (significant for all groups). There were no clinically meaningful differences in apixaban exposure between patients in the high and low body weight groups. Taken together, the findings of this post hoc analysis support the use of apixaban in patients with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup>.

Prospective studies evaluating the efficacy and safety of apixaban for the treatment of VTE in obese patients with body weight  $\geq 120$  kg or BMI  $> 40$  kg/m<sup>2</sup> are needed to confirm these findings and inform clinical decisions.

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**Compliance with Ethics Guidelines.** The protocol was approved by the institutional review board of each participating study center (full list of institutional review boards that approved the study is included as supplementary material). All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

**Data Availability.** All data generated or analyzed during this study are included in this published article as supplementary information files. The datasets generated during and/or analyzed during the current study are available

from the corresponding author on reasonable request.

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