A review of the fixed dose use of new oral anticoagulants in obese patients: Is it really enough?

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Abstract

Obesity is a significant cause of morbidity and mortality, and it is becoming increasingly prevalent worldwide. Altered pharmacodynamics and pharmacokinetics of drugs in obese patients require dose adjustment according to body weight. New oral anticoagulants (NOACs), which are more frequently used for anticoagulation, are recommended to be used at a fixed dose based on data derived from phase 2 and 3 studies. However, the representation of obese patients [>100 kg or a body mass index (BMI) of >30 kg/m^2] in subgroups with a small sample size and reports of various emboli cases under drug treatment have raised suspicions about the adequacy of fixed dose use. To address this issue, we analyzed several patients with a body weight of >100 kg or BMI of >30 kg/m^2 participating in NOAC studies and evaluated whether these numbers were sufficient to enable an accurate recommendation of fixed dose use in obese patients. *(Anatol J Cardiol 2015; 15: 1020-9)*

Keywords: obesity, anticoagulants, Factor Xa inhibitor, dabigatran, oral, fixed dose

Introduction

Fixed dose new oral anticoagulants (NOACs) are recommended for patients with non-valvular atrial fibrillation (AF) and an eligible CHA_2DS_2-VASc score according to the current guidelines (1). Under the guidance of the current literature, we aimed to discuss the following: a) the pharmacodynamics of these drugs in obese patients, b) the demographic characteristics of the patients included in NOAC studies and evaluation of the number of patients with a body weight of >100 kg or body mass index (BMI) of >30 kg/m^2 who were enrolled in the study, and c) the efficacy of a fixed dose of NOACs in obese and extremely obese patients.

Modern cardiology practice requires specific treatment approaches in selected conditions. Patients have been categorized into groups such as the elderly, pregnant women, and patients with renal disease or obesity according to the guidelines because there are certain differences in their management compared with the management of general population. Nevertheless, the sample sizes of subgroups that include obese or morbidly obese patients in phase 3 trials of NOACs are not large enough for extrapolation.

Obesity is a comorbid condition with an increasing prevalence worldwide. In the United States, the prevalence rates of obesity and extreme obesity are 34.9% (78.6 million) and 6.4%, respectively (2). Each year, approximately 300,000 deaths occur because of obesity-related health problems; it is estimated that if prompt intervention is not provided, the obesity prevalence will increase to approximately 58% by 2030 (3). Obesity is associated with hypertension, diabetes, metabolic syndrome, AF, venous thromboembolism (VTE), coronary artery disease, stroke, malignancy, decreased functional capacity, and heart failure (4).

The adjustment of drug dose based on a patient's body weight is a matter of debate with regard to many drugs. In particular, the use of adjusted-dose chemotherapy and antibiotic agents has provided great experience in this field. Drug absorption, pharmacokinetic parameters, renal clearance, and volume of distribution (Vd) are major relevant factors. It is assumed that drug absorption does not differ significantly in obese patients (5), whereas clearance is inversely correlated with plasma concentration and varies according to the route of excretion. The glomerular filtration rate and renal plasma flow were shown to be increased in non-diabetic extremely obese patients (6). The total amount of drug in the body/plasma concentration of the

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Table 1. Mean body weight and BMI values of the patients enrolled in the dabigatran trials

Dabigatran							
Trial	**Method**	**Number of patients**	**Mean/ median in trial follow-up**	**Weight median/ range, kg**	**BMI, kg/m²**	**Efficacy**	**Safety**
RE-NOVATE (9) Tromboprophylaxis after orthopedic surgery	Dabigatran 220 mg or 150 mg once a day vs. enoxaparin 40 mg once a day	1146–1163 vs. 1154	28–35 days	Median: 79 kg		Total VTE and all-cause mortality Dabigatran 220 mg 6% vs. 6.7%; *P*<0.0001 non-inferior Dabigatran 150 mg 8.6% vs. 6.7%; *P*<0.0001 non-inferior	Major bleeding Dabigatran 220 mg 2.0% vs. 1.6%; *P*=0.44 Dabigatran 150 mg 1.3% vs. 1.6%; *P*=0.60
RE-NOVATE II (10)	Dabigatran 220 mg once a day vs. enoxaparin 40 SC once a day	1010 vs. 1003	28-35 days	Mean: 79±17 vs. 80±17	mean: 27.8±4.8 vs. 27.8±4.8 8.8%	Total VTE and all cause mortality Dabigatran 220 mg 7.7% vs. *P*<0.0005 non-inferior	Major bleeding Dabigatran 220 mg 1.4% vs. 0.9% *P*=0.28 150 mg *P*=0.40
RE-MODEL (11) Tromboprophylaxis after orthopedic surgery	Dabigatran 220 mg or 150 mg once a day vs. enoxaparin 40 mg once a day	679 -703 vs. 694	6-10 days	Mean: 82±15 - 83±15 vs. 82±15		Total VTE and all-cause mortality Dabigatran 220 mg 36.4% vs. 37.7% *P*<0.0005 non- inferior	Major bleeding Dabigatran 220 mg 1.5% vs. 1.3% *P*=0.28
RE-MOBILIZE (12) Tromboprophylaxis after orthopedic surgery	Dabigatran 220 mg once a day vs. enoxaparin 40 mg once a day	857 -871 vs. 868	12-15 days	Mean: 88.4±19.1 - 87.6±20.0 vs. 88.0±19.2	mean: 27.8±4.8 vs. 27.8±4.8	Total VTE and all-cause mortality Dabigatran 220 mg 31.1%; vs 25.3% *P*<0.05 Dabigatran 150 mg 33.7% vs. 25.3% *P*<0.005	Major bleeding Dabigatran 220 mg 0.6% vs. 1.4% Dabigatran 150 mg 0.6% vs. 1.4%
RE-COVER (13) Prevention of acut VTE and related death	Heparin/dabigatran 150 mg BID vs. Heparin/warfarin (INR 2-3)	1274 vs. 1265	6 months	median: 84 vs. 82 range: 38–175 vs. 39–161	28.9±5.7 vs. 28.4±5.5 *P*<0.05	Recurrent VTE or related death Dabigatran 150 mg 2.4% vs. 2.1%; *P*<0.05 non-inferior	Major bleeding Dabigatran 150 mg 1.6% vs. 1.9%
RE-COVER II (14) Prevention of acut VTE and related death	Heparin/dabigatran 150 mg BID vs. Heparin/warfarin (INR 2-3)	1280 vs. 1288	6 months	median: 80 vs. 81 range: 36–184 vs. 35–210	28.4±5.8 vs. 28.4±5.8 *P*=0.89	Recurrent VTE or related death Dabigatran 150 mg 2.3% vs. 2.2%; *P*<0.05 non-inferior	Major bleeding Dabigatran 150 mg 1.2% vs. 1.7%
RE-MEDY (15) Extended treatment of VTE	Dabigatran 150 mg BID vs. warfarin (INR 2-3)	1430 vs. 1426	3–12 months + 6–36 months	mean: 86.1±19.3 vs. 86±18.9 range:40–188 vs. 41–182		Recurrent VTE Dabigatran 150 mg 1.8% vs. 1.3%; *P*<0.05 non-inferior	Major bleeding Dabigatran 150 mg 0.9% vs. 1.8%
RE-SONATE (15) Extended treatment of VTE	Dabigatran 150 mg BID vs. placebo	681 vs. 662	6-18 months + 6-18 months	mean: 83.7±18 vs. 84±18.6 range:40–151 vs. 40–206		Recurrent VTE or death Dabigatran 150 mg 0.4% vs. 5.6; *P*<0.05	Major bleeding Dabigatran 150 mg 0.3% vs. 0%
RE-LY (16)	Dabigatran 110 mg BID – dabigatran 150 mg BID vs. warfarin (INR 2-3)	6015 vs. 6075 vs. 6022	24 months	mean: 82.9±19.9 –82.5±19.4 vs. 82.7±19.7		Stroke or systemic embolism Dabigatran 150 mg 1.11% vs. 1.69% *P*<0.05 non-inferior; *P*<0.05 superior Dabigatran 110 mg 1.53% vs. 1.69% *P*<0.05 non-inferior	Major bleeding Dabigatran 150 mg 3.11% vs. 3.36%; *P*=0.31 Dabigatran 110 mg 2.71% vs. 3.36% *P*=0.052
RELY-ABLE (17) Extended treatment of AF	Dabigatran 150 mg BID vs. dabigatran 110 mg BID	5851	mean: 4.3 years median: 2.3 years	NR		Stroke or systemic embolism Dabigatran 150 mg 1.46% vs. 1.60%	Major bleeding Dabigatran 150 mg 3.74% vs. 2.99%

AF - atrial fibrillation; BMI - body mass index; BID - twice daily; INR - international normalized ratio; NR - not reported; SC - subcutaneous; VTE - venous thromboembolism

drug (Vd) provides an estimate of its distribution in extravascular tissues.

Vd=total amount of drug in the body/ plasma concentration of the drug

Vd is affected by the molecular size, ionization level, lipid solubility, and membrane transport characteristics; a reduced Vd indicates an increased plasma concentration of a given drug (7). However, it is not yet clear how obesity affects these parameters. Therefore, as with any other drug, the pharmacodynamics and pharmacokinetics of each NOACs in obese patients should be investigated to gain a better understanding of the drug's efficacy and safety profile.

We reviewed the current literature and, in particular, we addressed the data related to body weight and the BMI of participants in major NOAC trials. Specifically, dabigatran, rivaroxaban, apixaban, and edoxaban trials for VTE, AF, and acute coronary syndrome were examined.

Dabigatran

Dabigatran, a direct thrombin inhibitor, is excreted up to 85% via the kidneys. However, there is insufficient data about dabigatran use in obese or morbidly obese patients in terms of efficacy and safety (8). Current trials have included few patients with a body weight of >100 kg or a BMI of >30 kg/m^2. Dabigatran was compared with conventional treatment for VTE prophylaxis after total hip or knee replacement surgery in RE-NOVATE (2007), RE-MODEL (2007), RE-MOBILIZE (2009), and RE-NOVATE II (2011) trials. The mean body weight of the patients on dabigatran (220 mg and 150 mg) was 79 kg in the RE-NOVATE trial (9), whereas in the RE-NOVATE II trial, the mean body weights and BMI of the patients in the dabigatran and enoxaparine groups were 79±17 kg vs. 80±17 kg and 27.8±4.8 kg/m^2 vs. 27.8±4.8 kg/m^2, respectively (10). The mean body weight of the patients was 79 kg in the RE-MODEL trial (11), while the mean body weight of the patients in the dabigatran 220 mg and 150 mg groups were 88.4±19.1 kg and 87.6±20.0 kg, respectively, in the RE-MOBILIZE trial (12). The efficacy of dabigatran for the prevention and treatment of VTE was investigated in RECOVER (2009), RECOVER II (2014), RE-MEDY, and RE-SONATE (2013) trials. Dabigatran was compared with warfarin in the RECOVER trial in which the median body weight and BMI of the study population were 85.5±19.2 kg and 28.9±5.7 kg/m^2, respectively (13). The RECOVER II trial included 2589 patients with acute VTE, and long-term follow-up were conducted. The mean body weight of the population was 83.2±19.7 kg, while the BMI was 28.4±5.8 kg/m^2 (14). The mean body weights of patients receiving dabigatran in the RE-MEDY and RE-SONATE trials were 86.1±19.3 kg and 83.7±18.0 kg, respectively (15).

The RE-LY trial (2009) compared dabigatran 110 mg, 150 mg, and warfarin in 18.113 patients with AF. The proportion of patients with a body weight of >100 kg was 17% of the total study population, and the mean body weights in dabigatran (110 mg and 150 mg) and warfarin groups were 82.9±19.9 kg, 82.5±19.4 kg, and 82.7±19.7 kg, respectively. Furthermore, a subgroup analysis showed that patients with a body weight of <50 kg, 50–99 kg, or a BMI of <28 kg/m^2 obtained more benefit with 150 mg dabigatran than patients with a body weight of >100 kg (16). RELY-ABLE, the long-term follow-up study of the RE-LY trial, was designed to obtain information through an additional 2.8-year follow-up but no data regarding body weight or BMI were provided (Table 1) (17).

Apixaban

Apixaban, an oral Factor Xa inhibitor, is recommended for use in a fixed dose for all body weights similar to the other NOACs. Apixaban has a bioavailability of 50%, and its renal elimination rate is 25% (18). Women have 18% more exposure rate, and the area under the curve (AUC) increases by 32% in patients older than 65 years (19). In the phase 1 study investigating apixaban efficacy in patients with extreme body weight, three groups of patients with body weights of ≤50 kg, 65–85 kg, and ≥120 kg were evaluated (18 patients in each group) (20). It was reported that anti-Xa activity had a linear relationship with the apixaban dose regardless of body weight. However, when compared with the reference group, the group of patients with a body weight of ≤50 kg had a 30% higher Cmax and 20% higher AUC as well as the group of patients with a body weight of ≥120 kg had a 30% lower Cmax and 20% lower AUC. Because different body weights resulted in slight alterations in plasma apixaban levels, fixed dose use, and caution for renal dysfunction were recommended (20).

The efficacy and safety of apixaban after orthopedic surgery were investigated in the ADVANCE 1 (2009), ADVANCE 2 (2010), and ADVANCE 3 (2010) trials. The mean body weight in ADVANCE 1 was 86.7 (range, 41–163.7) kg, and the mean BMI was 31.2 (18.1–54.7) kg/m^2 (21) the mean body weights and BMIs in the ADVANCE 2 and ADVANCE 3 trials were 78 kg vs. 79.9 kg (22) and 29.1 kg/m^2 vs. 28.2 kg/m^2, respectively (23).

The AMPLIFY trial (2011) compared apixaban with conventional therapy and placebo in patients with acute deep-venous thrombosis (DVT) in which 19.4% of the study population weighed up to >100 kg (24). In the AMPLIFY EXTENDED trial, apixaban was compared with the placebo for VTE recurrence. The average weight in 5 mg apixaban, 2.5 mg apixaban, and the placebo groups were 85.7±19.8 kg, 85.7±19.1 kg, and 84.7±18.6 kg, respectively (25). Patients with a BMI of >30 kg/m^2 constituted 44.5% of the study population in ADOPT (2011), which evaluated apixaban for VTE prophylaxis. In this study, which enrolled the highest number of obese patients, apixaban was not superior to enoxaparine; furthermore, it was also associated with increased bleeding frequency. However, data about safety and efficacy in the obese subgroup were not provided (26). APPRAISE (2009), a phase 2 trial, investigated apixaban for the prevention of ischemic events in acute coronary syndrome, and the mean body weight was 81 kg (27). APPRAISE 2 (2011) did not provide any

Table 2. Mean body weight and BMI values of the patients enrolled in the apixaban trials

Trial	Method	Number of patients	Mean/median in trial follow-up	Weight median/ range, kg	BMI, kg/m^2	Weight, %	Efficacy	Safety
ADVANCE 1 (21) Thromboprophylaxis after orthopedic surgery	Apixaban 2.5 mg BID vs. Enoxaparin 30 mg BID	1599 vs. 1596	10–14 days	Mean: 86.7 vs. 86.7 Range: 41.0–163.7 vs. 40.5–163.3	Mean: 31.2 vs. 31.1 Range: 18.1–54.7 vs. 17.7–57.6		DVT, non-fatal PE, or all-cause mortality Apixaban 2.5 mg: 9.0% vs. 8.8%; *P* = 0.06 non-inferior	Major bleeding on-treatment Apixaban 2.5 mg: 0.7% vs. 1.4%; *P*<0.05
ADVANCE 2 (22) Thromboprophylaxis after orthopedic surgery	Apixaban 2.5 mg BID vs. Enoxaparin 30 mg BID	1528 vs. 1529	10–14 days	Mean: 78.7 vs. 78.3 Range: 68–89 vs. 68–88	Mean: 29.1 vs. 29.3 Range: 25.8–32.4 vs. 26.1–32.7		DVT, non-fatal PE, or all -cause mortality Apixaban 2.5 mg: 15.1% vs. 24.4%; *P*<0.005	Major bleeding on-treatment Apixaban 2.5 mg: 0.6% vs. 0.9%; *P* = 0.314
ADVANCE 3 (23) Thromboprophylaxis after orthopedic surgery	Apixaban 2.5 mg BID vs. Enoxaparin 30 mg BID	2708 vs. 2699	35 days	Mean: 79.9 vs. 79.5 Range: 37–179.9 vs. 28–152.4	Mean: 28.2 vs. 28.1 Range: 15.4–58.5 vs. 12.5–48.7		DVT, non-fatal PE or all-cause mortality Apixaban 2.5 mg: 1.4% vs. 3.9%; *P*<0.05 non-inferior; *P*<0.05 superior	Major bleeding on-treatment Apixaban 2.5 mg: 0.8% vs. 0.7%; *P* = 0.54
AMPLIFY (24) Recurrent VTE or related death	Apixaban 10 mg BID, after 7 days 5 mg BID vs. Enoxaparin 1 mg/kg SC/ warfarin (INR 2-3)	2691 vs. 2704	6 months	mean: 84.6±19.8 vs. 84.6±19.8		≤60 kg 8.6% vs. 9.1% >60 to <100 71.8% vs. 71.6% ≥100 kg 19.4% vs. 19.2%	Recurrent VTE or related death Apixaban 10 mg 2.3% vs. 2.7%; *P*<0.001 non -inferior	Major bleeding Apixaban 10 mg 0.6% vs. 1.8%; *P*<0.001 superior
AMPLIFY-Extension (25) Extended treatment of recurrent VTE or death	Apixaban 5 mg BID or apixaban 2.5 mg BID vs. placebo	840 vs. 813 vs. 829	6–12 + 12 months	mean: 85.7±19.8 vs. 85.7±19.1 vs. 84.7±18.6		≤60 kg 6.9% vs. 7.3% vs. 5.8% >60 kg 92.9% vs. 92.4% vs. 93.8%	Recurrent VTE or related death Apixaban 5 mg 1.7% vs. 8.8%; *P*<0.001 superior Apixaban 2.5 mg 1.7% vs. 8.8%; *P*<0.001 superior	Major bleeding Apixaban 5mg 0.1% vs 0.5% Apixaban 2.5 mg 0.2% vs. 0.5%
ADOPT (26) Prevention of VTE, medically ill patients	Apixaban 2.5 mg BID (30 days) vs. Enoxaparin 40 mg once a day (6–14 days)	3255 vs. 3273	30 days		BMI≥30: 44.5% vs. 44.3%		VTE-related death, PE, symptomatic DVT or asymptomatic DVT Apixaban 2.5 mg: 2.71% vs. 3.06%; *P*=0.44	Major bleeding Apixaban 2.5 mg: 0.47% vs. 0.19%; *P*<0.05
APPRAISE (27) Prevention of acute ischemic events after recent ACS and risk of bleeding	Apixaban 2.5 mg BID, 10 mg once a day, 10 mg BID, 20 mg once a day vs. placebo	317, 318, 248, 221 vs. 611	26 weeks	Median: 80, 81, 82, 82 vs. 81			CVS death, MI, recurrent ischemia or ischemic stroke Apixaban 2.5 mg, 10 mg 7.6%, 6% vs. 8.7%	Major or CRNM bleeding Apixaban 2.5 mg, 10 mg 5.7%, 7.9% vs. 3.0%
APPRAISE 2 (28) Prevention of acute ischemic events after recent ACS	Apixaban 5 mg BID vs. placebo	3705 vs. 3687	241 days	NR			CV death, MI or ischemic stroke Apixaban 5 mg: 7.5% vs. 7.9%; *P*=0.51	Major bleeding Apixaban 5 mg: 1.3% vs. 0.5%; *P*<0.001

Table 2. Mean body weight and BMI values of the patients enrolled in the apixaban trials (continued)

Trial	Method	Number of patients	Mean/median in trial follow-up	Weight median/ range, kg	BMI, kg/m²	Weight, %	Efficacy	Safety
APPRAISE-J (29), phase 2 Prevention of acute ischemic events after recent ACS and risk of bleeding	Apixaban 2.5 mg BID, 5 mg BID vs. placebo	49,50 vs. 52	24 weeks	Mean: 65.5±11.2	Mean: 24.5±3.1			Major or clinically relevant nonmajor bleeding Apixaban 2.5 mg: 10 mg 4.1% vs. 2.0%
AVERROS (30)	Apixaban 5 mg BID vs. Aspirin 84-324 mg/day	2808 vs. 2791	mean: 1.1 years		Mean: 28±5 vs. 28±5		Stroke or systemic embolism Apixaban 5 mg 1.6% vs. 3.7% *P*<0.001	Major bleeding Apixaban 5 mg 1.4% vs. 1.2% *P*=0.57
ARISTOTLE (31)	Apixaban 5 mg BID vs. Warfarin (INR 2-3)	9120 vs. 9081	median: 1.8 years	median: 82 vs. 82 Range: 70–96 vs. 70–95			Stroke or systemic embolism Apixaban 5 mg 1.27% vs. 1.6% *P*<0.001 non-inferior	Major bleeding Apixaban 5 mg 2.13% vs. 3.09% *P*<0.001;

ACS - acut coronary syndrome; BMI - body mass index; BID - twice daily; CRNM - clinically relevant non-major; CV - cardiovascular; DVT - deep-vein thrombosis; INR - international normalized ratio; MI - myocardial infarction; NR - not reported; PE - pulmonary emboli; SC - subcutaneous; VTE - venous thromboembolism.

data regarding body weight or BMI (28). The APPRAISE-J (2013) trial was conducted with Japanese patients suffering from ACS, and the mean body weight and BMI were 65.6±11.4 kg and 24.3±2.9 kg/m², respectively (29). Apixaban was compared with aspirin in patients with AF and with those who were not suitable or unwilling to take vitamin K antagonists in the AVERROES trial (2011). It was stopped at an early stage because of a clear benefit in favor of apixaban. BMI was 28±5 kg/m² in the apixaban group (30). In the ARISTOTLE trial, registry apixaban was compared with warfarin in 18,201 patients with AF; their average weight was 82 kg, and the primary outcome in the ≤60 kg subgroup was better than that in the >60 kg subgroup (Table 2) (31).

Rivaroxaban

Rivaroxaban is an oral Factor Xa inhibitor, and food increases the mean AUC by 39% (32). In the phase II trial of rivaroxaban, the mean body weight of the >120 kg group (n=12) was 132.2±9.9 kg and the mean BMI was 43.5±4.2 kg/m². Cmax levels of the drug were similar in the reference and in the >120 kg groups but up to 24% higher in the <50 kg group than in the reference group. According to the study results, it was concluded that 10 mg rivaroxaban had the same efficacy and safety profile in healthy individuals regardless of age, gender, and body weight (33).

In the RECORD trial (1-4), rivaroxaban was compared with enoxaparin for VTE prevention after elective total hip and knee arthroplasty. The mean body weight of patients on rivaroxaban was 79.4 kg, and the mean BMI was 28.7 kg/m². A subgroup analysis revealed that rivaroxaban was superior in patients with a body weight of ≤70 kg than in patients weighing >70 kg and >90 kg with regard to symptomatic VTE prevention and all-cause mortality (34).

In the EINSTEIN trial (2010), rivaroxaban was compared with enoxaparin plus warfarin in acute DVT, and the percentage of patients with a body weight of >100 kg in the rivaroxaban group was 14.2% (35). The EINSTEIN-PE trial (2012) enrolled patients with symptomatic VTE and pulmonary embolism, and patients with a weight of >100 kg constituted 14.3% of the study population (36). The mean body weight and BMI were 77.5 kg and 28.2 kg/m², respectively, in the MAGELLAN trial (2013), which evaluated rivaroxaban for VTE prophylaxis in acutely ill medical patients (37).

In the ROCKET-AF trial (2011), rivaroxaban was compared with warfarin, and the mean BMI of the study population was 28.2 (25.1–32.0) kg/m² (38). Japanese patients were not included in the global ROCKET-AF trial. In the phase 1 trial, Japanese patients receiving 15 mg rivaroxaban had either Cmax (median: 259.48 µg/L) or AUC0-24 (median: 3,193.89 µgh/L) values similar to Caucasian patients receiving 20 mg rivaroxaban (Cmax median: 289.05 µg/L and AUC0–24 median: 3.243.04 µgh/L); hence, they were not included in the global trial. Additionally, Japanese guidelines recommend lower INR values for patients taking warfarin for AF stroke prophylaxis (39). Alternatively, in the J-ROCKET AF (2012) trial, 15 mg rivaroxaban was compared with warfarin for the primary endpoint of stroke and ischemic embolism and was reported to be non-inferior. The body weight or BMI was provided in the demographic characteristics (40). Nevertheless, it was emphasized that the rivaroxaban and warfarin groups did not differ when patients with BMIs of ≤25 or ≥25 were compared in terms of the primary safety endpoint incidence (Table 3) (41).

Table 3. Mean body weight and BMI values of the patients enrolled in the rivaroxaban trials

Trial	Method	Number of patients	Mean/median in trial follow-up	Weight median/ range, kg	BMI, kg/m^2	Weight, %	Efficacy	Safety
RECORD 1-4 (34) Symptomatic VTE + all-cause mortality after THA or TKA	Rivaroxaban 10 mg vs. enoxaparin sc 30/40 mg	6183 vs. 6200	30-35 days	mean: 79.4 vs. 79.8 range: 37 -190 vs. 33.2-171.5	mean: 28.7 vs. 28.8 range:15-74.2 vs. 13.7-62.4		Symptomatic VTE + all-cause mortality Rivaroxaban 0.5% vs. 1.0% *P*<0.001	Major bleeding or CRNM bleeding Rivaroxaban 10 mg 0.3% vs. 0.2% *P*=0.23; *P*=0.19
EINSTEIN-DVT (35) Acute symptomatic deep-VTE	Rivaroxaban 15 mg BID, after 3 weeks 20 mg once a day vs. Enoxaparin 1.0 mg/kg followed by VKA (INR 2-3)	1731 vs. 1718	3, 6, 12 months			≤50 kg 2.1% vs. 2.9% >50-100 kg 83.4% vs. 82.8% >100 kg 14.1% vs. 14.3%	Recurrent VTE Rivaroxaban 20 mg 2.1% vs. 3.0%; *P*<0.001 non-inferior	Major bleeding or CRNM bleeding Rivaroxaban 20 mg 8.1% vs. 8.1%; *P*=0.77
EINSTEIN-PE (36) symptomatic recurrent VTE	Rivaroxaban 15 mg BID, after 3 weeks 20 mg once a day vs. Enoxaparin 1.0 mg/kg followed VKA (INR 2-3)	2419 vs. 2413	3, 6, 12 months			≤50 kg 1.6% vs. 1.8% >50-100 kg 84.1% vs. 83.3% >100 kg 14.3% vs. 14.9%	Recurrent VTE Day 10: Rivaroxaban 20 mg 2.1% vs. 1.8% *P*<0.005 non-inferior	Major bleeding or CRNM bleeding Rivaroxaban 20 mg 10.3% vs. 11.4% *P*=0.23
MAGELLAN (37) Prevention of VTE, medically ill patients	Rivaroxaban 10 mg once a day vs. Enoxaparin 40 mg once a day	4050 vs. 4051	35 days	Median: 77.5 vs. 77.3	mean: 28.2 vs. 28.2		VTE and death Day 10: rivaroxaban 10 mg 2.7% vs. 2.7% *P*<0.005 non-inferior Day 35: rivaroxaban 10 mg 4.4% vs. 5.7% *P*<0.05 superior	Major bleeding or CRNM bleeding Day 10: Rivaroxaban 10 mg 2.8% vs. 1.2% *P*<0.001 Day 35: Rivaroxaban 10 mg 4.1% vs. 1.7% *P*<0.001
ROCKET-AF (38)	Rivaroxaban 20 mg once a day vs. Warfarin (INR 2-3)	7131 vs. 7133	707 days	median: 28.3 vs. 28.1 range: 25.2–32.1 vs. 25.1-31.8			Stroke or systemic embolism Rivaroxaban 20 mg 1.7% vs. 2.2%; *P*<0.001	Major bleeding or CRNM bleeding Rivaroxaban 20 mg 14.9% vs. 14.5%; *P*=0.44
J-ROCKET AF (40)	Rivaroxaban 15 mg once a day vs. Warfarin (INR 2-3)	639 vs. 639	30 days	NR			Stroke or systemic embolism Rivaroxaban 20 mg 1.26% vs. 2.61% *P*<0.05 non-inferior	Major bleeding or CRNM bleeding Rivaroxaban 20 mg 18.04% vs. 16.42% *P*<0.001 non-inferior; CRNM bleeding *P*<0.05 superior

BMI - body mass index; BID - twice daily; CRNM - clinically relevant non-major; INR - international normalized ratio; NR - not reported; PE - pulmonary embolism; SC - subcutaneous; THA - total hip artroplasty; TKA - total knee artroplasty; VKA - vitamin K antagonist; VTE - venous thromboembolism.

Edoxaban

Edoxaban is a novel oral anticoagulant and is highly specific and directly inhibits Factor Xa. Thirty-five percent of an administered edoxaban dose is eliminated by renal excretion, while exposure increases in patients weighing ≤60 kg (42). The mean body weight was 59.6±11.2 kg in the STARS E-3 trial (2010) and

Table 4. Mean body weight and BMI values of the patients enrolled in the edoxaban trials

Trial	Method	Number of patients	Mean/median in trial follow-up	Weight median/ range, kg	BMI, kg/m^2	Weight, %	Efficacy	Safety
STARS E-3 (43) Thromboprophylaxis after orthopedic surgery	Edoxaban 30 mg once a day vs. Enoxaparin 20 mg BID	299 vs. 295	11–14 days	Mean: 59.6±11.2 vs. 60.7±10.4			Symptomatic PE, and symptomatic and asymptomatic DVT Edoxaban 30 mg: 7.4% vs. 13.9%; *P*<0.001 non-inferior; *P*<0.01 superior	Major and CRNM bleeding Edoxaban 30 mg: 6.2% vs. 3.7%; *P*=0.129
STARS J-4 (44) Thromboprophylaxis after orthopedic surgery	Edoxaban 30 mg once a day vs. enoxaparin 20 mg BID	59 vs. 29	11–14 days	Mean: 52.3±8.4 vs. 55.1±10.0			Thromboembolic events Edoxaban 30 mg: 6.5% vs. 3.7%	Major and CRNM bleeding (primary study endpoint) Edoxaban 30 mg: 3.4% vs. 6.9%
Hokusai-VTE (45) Symptomatic VTE	Enoxaparin or UFH/ edoxaban 60 mg once a day vs. Enoxaparin or UFH/warfarin (INR 2.0–3.0)	4118 vs. 4122	3–12 months			≤60 kg 12.7% vs. 12.6% >100 kg 14.8% vs. 15.9%	Recurrent VTE Edoxaban 60 mg 3.2% vs. 3.5%; *P*<0.001 non-inferior	Major bleeding or CRNM bleeding Edoxaban 60 mg 8.5% vs. 10.3%; *P*<0.004 superior
Weitz et al, phase 2 (46)	Edoxaban 30 mg once a day vs. 30 mg BID vs. 60 mg once a day vs. 60 mg BID warfarin	235 vs. 244 vs. 234 vs. 180 vs. 250	12 weeks	89.0±17.6 vs. 87.8±18.0 vs. 87.8±17.9 vs. 88.6±18.2 vs. 88.0±18.6	30.5±5.0 vs. 30.4±5.6 vs. 30.1±6.1 vs. 30.3±5.4 vs. 30.4±5.6		Major + CRNM bleeding Edoxaban 3.0% vs. 7.8%; *P*<0.05 vs. 3.8% vs. 10.6%; *P*<0.002 vs. warfarin 3.2%	Any stroke, TIA and/or SEE 0.4% vs. 1.2% vs. 0.4% vs. 1.1% vs. 1.6%
ENGAGE AF-TIMI 48 (47)	Edoxaban 60 mg once a day or edoxaban 30 mg once a day vs. warfarin (INR 2.0–3.0)	7035 vs. 7034 vs. 7036	median: 2.8 years			≤60 kg 9.7% vs. 9.9%	Stroke or systemic embolism Edoxaban 60 mg 1.18% vs. 1.5%; *P*<0.001 non-inferior Edoxaban 30 mg 1.61% vs. 1.5%; *P*<0.005 non-inferior	Major bleeding Edoxaban 60 mg 2.75% vs. 3.43%; *P*<0.001 Edoxaban 30 mg 1.61% vs. 3.43%; *P*<0.001

BMI - body mass index; BID - twice daily; CRNM - clinically relevant non-major; DVT - deep-vein thrombosis; INR - international normalized ratio; PE - pulmonary embolism; SEE - systemic embolic event; TIA - transient ischemic attack; UFH - unfractionated heparin; VTE - venous thromboembolism.

52.3±8.4 kg in the STARS J-4 trial (2014), and both trials evaluated edoxaban efficacy and safety for VTE prophylaxis after orthopedic surgery (43, 44). Raskob et al. (42) compared different doses of edoxaban with dalteparin for thromboprophylaxis after elective total hip replacement in 903 patients and found that edoxaban was effective in all dose groups. The mean BMI in the study population was 28±4.8 kg. The percentage of patients weighing >100 kg was 14.8 in the Hokusai-VTE trial (2013), which was designed for patients with acute VTE (45).

Weitz et al. (46) enrolled 1146 patients in the phase 2 trial of edoxaban to compare it with warfarin for stroke prevention in patients with AF. Single dose edoxaban was similar with warfarin in terms of the safety endpoint. The mean body weight and BMI of the study population were 89±17.6 kg and 30.4±5.6 kg/m^2, respectively. ENGAGE AF-TIMI (2013), a phase 3 trial, compared edoxaban and warfarin in 21 105 patients with AF. Patients weighing <60 kg constituted 9.7% of the study population, but data for patients with a body weight of >100 kg were not provided (Table 4) (47).

Discussion

The current recommendation for NOACs implies a fixed dose use for obese patients. However, when the relevant trials are investigated, it can be clearly seen that the plasma levels of drugs show a great diversity according to body weight. Because this diversity was not translated into statistical significance, fixed dose use is recommended. When the study populations are inspected, the frequencies of patients with a body weight of >100 kg for NOACs drugs ranged between 14.3% and 19.4%. The numbers of obese and morbid obese patients were even lower in these trials. Furthermore, subgroup analyses showed that the primary endpoint results were better in patients weighing <50 kg than in patients weighing >50 kg. For a lower dose of rivaroxaban (15 mg), a similar efficacy was reported in Japanese patients who had relatively lower BMIs than patients of other nationalities. Therefore, it is likely that using higher doses of NOACs in more obese populations may be more effective.

Breuer et al. (48) reported a case of an acute stroke in an obese patient (BMI 44.7 kg/m^2, weight 153 kg) who was on dabigatran treatment. They decided to replace dabigatran with vitamin K antagonist because the peak plasma level of dabigatran was 50 ng/mL and this value was below the 25th percentile of the therapeutic levels. Decreased creatinine clearance and the concomitant use of a proton pump inhibitor were considered as possible causes for the stroke episode (48). Rafferty et al. (49) reported a case of acute pulmonary embolism in an obese patient with AF using dabigatran (150 mg twice), and they commented that the possible reason was the increased creatinine clearance. In another case report by Safourisa et al. (50), an obese non-diabetic patient (124 kg, BMI 39.6 kg/m^2) using dabigatran 150 mg twice a day with the indication of non-valvular AF experienced a stroke episode. The creatinine clearance of this patient was calculated to be 132 mL/min and the dabigatran levels detected using Hemoclot® thrombin inhibitor assay were lower than the therapeutic levels. The drug was substituted with rivaroxaban and the rivaroxaban plasma levels were evaluated with Direct factor Xa Inhibitor (DiXaL®) and found to be in the therapeutic range. They also addressed that rivaroxaban had a stronger pharmacotherapeutic effect than dabigatran in obese non-diabetic patients (50). Such case reports with dabigatran are more extensive but this may be a consequence of its earlier introduction into the market. However, it may be rational to use drugs with lower renal clearance (Rivaroxaban 66%, Apixaban 27%, Edoxaban 35%) (45) in these patients because of increased creatinine clearance. Recent reports of patients with stroke or systemic embolism during NOACs treatment have raised concerns about the efficacy of these agents in obese and morbidly obese patients. A comparison of fixed and high doses of NOACs, for safety and efficacy, in a specific obese study population would provide appropriate knowledge about the adequate dosage in these patients.

Conclusion

NOACs have emerged as popular agents marking a new era in anticoagulant therapy and have set many patients free from the dependence on vitamin K antagonists. However, it should be kept in mind that effective doses of these agents may require refinement in specific patient subgroups. Therefore, further studies are required to determine and establish the effective dose in this growing subgroup of obese patients.

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References

1. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. ESC Committee for Practice Guidelines (CPG). Focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-27. [CrossRef]
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. JAMA 2014; 311: 806-14. [CrossRef]
3. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes 2008; 32: 1431-7. [CrossRef]
4. Haslam D, James P. Obesity. Lancet 2005; 366: 1197-209. [CrossRef]
5. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010; 49: 71-87. [CrossRef]
6. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 2000; 278: 817-22.
7. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 2004; 58: 119-33. [CrossRef]
8. Weitz JI. Expanding use of new oral anticoagulants. F1000Prime Rep 2014; 1: 6: 93.
9. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007; 15: 370: 949-56. [CrossRef]
10. Eriksson BI, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). Thromb Haemost 2011; 105: 721-9. [CrossRef]
11. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Dabigatran etexilate vs. enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL Randomized Trial. J Thromb Haemost 2007; 5: 2178-85. [CrossRef]

12. Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, et al. RE-MOBILIZE Writing Committee. Oral thrombin inhibitör dabigatran etexilate vs. North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009; 24: 1-9. [CrossRef]
13. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 10: 361: 2342-52. [CrossRef]
14. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 18: 129: 764-72. [CrossRef]
15. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013; 368: 709-18. [CrossRef]
16. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. RE-LY Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009; 361: 1139-51. [CrossRef]
17. Connolly SJ, Wallentin L, Ezekowitz MD, Eikelboom J, Oldgren J, Reilly PA, et al. The Long Term Multi-Center Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation: (RELY-ABLE) Study. Circulation 2013; 16: 128: 237-43. [CrossRef]
18. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol 2013; 29: S24-33. [CrossRef]
19. Frost CE, Song Y, Shenker A, Wang J, Barrett YC, Schuster A, et al. Effects of age and sex on the single-dose pharmacokinetics and pharmacodynamics of apixaban. Clin Pharmacokinet 2015; 54: 651-62. [CrossRef]
20. Upreti VV, Wang J, Barrett YC, Byon W, Boyd RA, Pursley J, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013; 76: 908-16. [CrossRef]
21. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009; 361: 594-604. [CrossRef]
22. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010; 375: 807-15. [CrossRef]
23. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010; 363: 2487-98. [CrossRef]
24. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 29: 369: 799-808. [CrossRef]
25. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. PLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013; 21: 368: 699-708. [CrossRef]
26. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med 2011; 8: 365: 2167-77. [CrossRef]
27. Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009; 9: 119: 2877-85.
28. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011; 25: 365: 699-708. [CrossRef]
29. Ogawa H, Goto S, Matsuzaki M, Hiro S, Shima D; APPRAISE-J investigators. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients (APPRAISE-J). Circ J 2013; 77: 2341-8. [CrossRef]
30. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 3: 364: 806-17. [CrossRef]
31. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 15: 365: 981-92. [CrossRef]
32. Stampfuss J, Kubitza D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. Int J Clin Pharmacol Ther 2013; 51: 549-61. [CrossRef]
33. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinectics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in health subjects. J Clin Pharmacol 2007; 47: 218-26. [CrossRef]
34. Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. Thromb Haemost 2011; 105: 444-53. [CrossRef]
35. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 23: 363: 2499-510.
36. Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 5: 366: 1287-97.
37. Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, et al. MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013; 7: 368: 513-23. [CrossRef]
38. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. ROCKET AF Investigators. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 2011; 365: 883-91. [CrossRef]
39. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation. Circ J 2011; 75: 1328-33. [CrossRef]
40. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. J-ROCKET AF study investigators. Rivaroxaban vs. Warfarin in Japanese Patients With Atrial Fibrillation – The J-ROCKET AF Study. Circ J 2012; 76: 2104-11. [CrossRef]
41. Hori M, Kajikawa M. The J-ROCKET AF Study: A Matter of Ethnicity or a Matter of Weight? – Reply. Circ J 2013; 77: 2637. [CrossRef]
42. Raskob G, Cohen AT, Eriksson BI, Puskas D, Shi M, Bocanegra T, et al. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double blind dose response study. Thromb Haemost 2010; 104: 642-9. [CrossRef]
43. Fuji T, Wang CJ, Fujita S, Kawai Y, Nakamura M, Kimura T, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxapa-

rin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res 2014; 134: 1198-204. [CrossRef]

44. Fuji T, Fujita S, Kawai Y, Nakamura M, Kimura T, Kiuchi Y, et al. Safety and efficacy of edoxaban in patients undergoing hip fracture surgery. Thromb Res 2014; 133: 1016-22. [CrossRef]
45. Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369: 1406-15. [CrossRef]
46. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost 2010; 104: 633-41. [CrossRef]
47. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation N Engl J Med 2013; 369: 2093-104. [CrossRef]
48. Breuer L, Ringwald J, Schwab S, Köhrmann M. Ischemic stroke in an obese patient receiving dabigatran. N Engl J Med 2013; 368: 2440-2. [CrossRef]
49. Rafferty JA, Prom R, Kujawski SZ. Acute pulmonary emboli in a patient on long-term dabigatran therapy. Ann Pharmacother 2013; 47: e20. [CrossRef]
50. Safouris A, Demulder A, Triantafyllou N, Tsivgoulis G. Rivaroxaban presents a better pharmacokinetic profile than dabigatran in an obese non-diabetic stroke patient. J Neurol Sci 2014; 346: 366-7. [CrossRef]