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 body mass index (BMI) of >30 kg/m²) 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/m² 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 CHA₂DS₂-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/m² 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
### Table 1. Mean body weight and BMI values of the patients enrolled in the dabigatran trials

| Trial Description | Method | Method Details | Number of patients | Efficacy | Safety |
|-------------------|--------|----------------|-------------------|----------|--------|
| RE-NOVATE (9) Tomboprophylaxis 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 | Major bleeding Dabigatran 220 mg 2.0% vs. 1.6%; P=0.04 |
| RE-NOVATE II (10) | Dabigatran 220 mg once a day vs. enoxaparin 40 mg SC once a day | 1010 vs. 1003 | 28–35 days | Mean: 79±17 vs. 80±17 | Total VTE and all-cause mortality Dabigatran 220 mg 7.7% vs. 8.8% | Major bleeding Dabigatran 220 mg 1.4% vs. 0.9%; P=0.28 |
| RE-MODEL (11) | 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 - 82±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) | Dabigatran 220 mg once a day vs. enoxaparin 40 mg once a day | 857–871 vs. 868 | 12–15 days | Mean: 88.4±19 - 88.4±19 vs. 88.0±19.2 | Total VTE and all-cause mortality Dabigatran 220 mg 27.8±4.8 vs. 27.8±4.8 | Major bleeding Dabigatran 220 mg 0.6% vs. 0.4%; P=0.40 |
| 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 | 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. 1.3% |
| 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 | 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±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. 0.6%; 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 |
| RELY-ABLE (17) Extended treatment of AF | Dabigatran 150 mg BID – dabigatran 110 mg BID | 5851 | median: 4.3 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.

\[ V_d = \frac{\text{total amount of drug in the body}}{\text{plasma concentration of the drug}} \]

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/m². 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/m² vs. 27.8±4.8 kg/m², 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 RECOVERY (2009), RECOVERY II (2014), RE-MEDY, and RE-SONATE (2013) trials. Dabigatran was compared with warfarin in the RECOVERY 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/m², respectively (13). The RECOVERY 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/m² (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/m² obtained more benefit with 150 mg dabigatran than patients with a body weight of >100 kg (16). RE-LY-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, 41–187.4) kg, and the mean BMI was 31.2 (18.1–54.7) kg/m² (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/m² vs. 28.2 kg/m², 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/m² 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 enoxaparin; 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...
| Trial | Method | Number of patients | Mean/median in trial follow-up | Weight median/ range, kg | BMI, kg/m² | 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% vs. 60 to <100 71.8% vs. 71.6% ≥100 kg 19.4% vs. 19.2% | ≤60 kg 6.9% vs. 7.3% vs. 60 kg 92.9% vs. 92.4% vs. 93.8% | 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. 60 kg 92.9% vs. 92.4% vs. 93.8% | ≤60 kg 6.9% vs. 7.3% vs. 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 5 mg 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%; \(P = 0.44\) | 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, 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% | 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%; \(P = 0.51\) | 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%; \(P < 0.001\) |
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 and BMI were 65.6±11.4 kg and 24.3±2.9 kg/m², respectively (29). Rivaroxaban 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).

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).
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

| Trial | Method | Number of patients | Mean/median in trial follow-up | Weight median/range, kg | BMI, kg/m² | Weight, % | Efficacy | Safety |
|-------|--------|--------------------|-------------------------------|-------------------------|------------|-----------|----------|--------|
| RECORD 1-4 (34) | 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 by 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 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 arthroplasty; TKA - total knee arthroplasty; VKA - vitamin K antagonist; 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 30.5±5.0 kg/m², 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).

### 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/m² | 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 | Edoxaban 30 mg: Symptomatic PE, and symptomatic and asymptomatic DVT 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 | 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% | Edoxaban 60 mg: 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 (INR 2.0–3.0) | 235 vs. 244 vs. 30 vs. 250 | 12 weeks                        | 89.0±17.6 vs. 87.8±18.0 vs. 87.8±18.0 vs. 88.6±18.2 vs. 88.0±18.6 | Edoxaban 30 mg: Major + CRNM bleeding Edoxaban 30.0% 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. 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% | Edoxaban 60 mg 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.
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/m², 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/m²) 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 of this patient 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/m²) 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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