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REVIEW ARTICLE

The Pharmacology, Efficacy, and Safety of Rivaroxaban in Obese Patient Populations

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Abstract

Cardiovascular disease (CVD) remains the leading cause of death in the USA. Several risk factors have been identified, and obesity has become one of prominent concern. Excessive weight is considered a risk factor for CVD based on evidence linking it to a hypercoagulable state. Considering the prevalence of CVD and obesity in the USA, along with the increased risk for thrombus-related events, anticoagulation plays a significant role in prevention and treatment. Direct oral anticoagulants have taken the place of many traditional anticoagulants. Considering the recently approved indications and continued postmarketing studies conducted with rivaroxaban, this updated review provides data on the overall impact of obesity on this compound. This includes data obtained from both healthy obese volunteers and obese patients with various CVD conditions enrolled in rivaroxaban clinical trials, along with data obtained from postmarketing real-world evidence studies. Assessment of the clinical pharmacology and population pharmacokinetics in obese individuals revealed no clinically relevant effects of increased weight. Additionally, subgroup analyses from each of the pivotal phase III trials supporting the current approved labeling also demonstrated consistent efficacy and safety results in obese patients. Lastly, these findings are further supported by several recent real-world evidence studies assessing the continued effectiveness and safety of rivaroxaban. In conclusion, rivaroxaban's overall pharmacological and clinical profile remained consistent in obese adults when assessed in both drug development and postmarketing studies, supporting the premise that higher weight does not necessitate adjustment in either dose strength or regimen.

Key Points

Obesity is a prominent risk factor for cardiovascular disease (CVD) in the USA, and anticoagulation plays a significant role in the prevention and treatment of cardiovascular conditions.

Obesity may also affect the pharmacological profile of drugs, including anticoagulants. This may ultimately increase or decrease systemic plasma concentrations, impacting a drug's efficacy and safety.

Rivaroxaban is a Factor Xa inhibitor approved for use in various cardiovascular-related conditions. Obesity does not appear to affect the clinical pharmacology, safety, efficacy, or effectiveness of this anticoagulant.

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1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the USA [1]. While several risk factors that lead to CVD have been identified, obesity (body mass index [BMI] ≥ 30 kg/m^2) is of prominent concern, particularly in the USA, where approximately 40% of adults are diagnosed with obesity [2, 3]. The management of this disease and its cardiovascular effects poses a significant challenge, so optimizing treatment in this population is crucial. Obesity is identified as an independent risk factor, as substantial evidence shows that excessive weight gain or elevated BMI is strongly associated with a hypercoagulable state, through mechanisms that include chronic inflammation and impaired fibrinolysis [4].

Based on this risk, anticoagulation is generally warranted in obese patients with comorbid CVD and where therapy is indicated (e.g., atrial fibrillation [AF] [5], venous thromboembolism [VTE] [6], hip/knee arthroplasty [7], coronary artery disease [CAD] [8], peripheral artery disease [PAD] [9]). However, such treatment can be complicated because obesity may also affect the pharmacology of anticoagulants, potentially changing the absorption, distribution, metabolism, and elimination characteristics and resulting in under- or over-anticoagulation. This potential change is generally assessed during drug development, within both small clinical pharmacology and large clinical efficacy and safety studies.

Treatment with direct oral anticoagulants (DOACs) has increased substantially in the past 5 years. This is primarily because of their comparable (if not better) safety and efficacy profiles, simplified treatment regimens, limited drug interactions, and lack of strict dietary restrictions when compared with vitamin K antagonists. Current labeling indicates that the use of DOACs in obese patients with CVD is not restricted. However, it is generally understood that experience with these compounds in obese individuals enrolled in randomized controlled trials (RCTs) is limited. This is evident in the 2016 International Society on Thrombosis and Haemostasis (ISTH) guidelines, which recommend against the use of DOACs in patients with a BMI > 40 kg/m^2 or a weight > 120 kg because of the lack of available clinical data [10]. Hence, it is important to expand our knowledge through real-world evidence (RWE) studies based on medical claims databases, electronic healthcare records (EHRs), and prospective registries. The combination of all three data sources (clinical pharmacology, subpopulation analyses from RCTs, and RWE studies) should provide greater understanding of these compounds in the treatment of CVD in obese individuals.

Another consideration when treating individuals with CVD and obesity is the increasing use of bariatric surgery among patients who do not reduce their weight through lifestyle modifications. According to the American Society for Metabolic and Bariatric Surgery, approximately 250,000 individuals in the USA underwent bariatric surgery in 2018, compared with 158,000 in 2011 [11]. The two most common types of bariatric surgery were sleeve gastrectomy (~ 61%) and Roux-en-Y gastric bypass (~ 17%), both of which may lead to malabsorption following surgery [11]. Consequently, this can affect the pharmacokinetic profile of drugs, specifically concerning bioavailability and volume of distribution [12–14]. Based on the physiologic changes that occur following bariatric surgery and the increased risk of thrombotic events, it is important to assess both the potential for changes in the pharmacological profile and the overall safety and efficacy of the drug in question.

Rivaroxaban was chosen for this review because of its breadth of indications, which include (1) reducing the risk of stroke and systemic embolism in patients with nonvalvular AF (NVAF), (2) treating deep vein thrombosis (DVT), (3) treating pulmonary embolism (PE), (4) reducing the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting ≥ 6 months, (5) prophylaxis of DVT that may lead to PE in patients undergoing knee- or hip-replacement surgery, (6) prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications and not at high risk of bleeding, and (7) in combination with aspirin, reducing the risk of major adverse cardiovascular events [MACE; cardiovascular death, myocardial infarction (MI), and stroke] in patients with chronic CAD or PAD [15]. Additionally, rivaroxaban is the only DOAC for which both the short- and long-term (6–8 months) pharmacological profile after bariatric surgery has been studied [16, 17], with an ongoing clinical trial (BARIVA; NCT03522259) assessing its long-term safety and efficacy [18].

2 Objective

This is a targeted review of the DOAC rivaroxaban in patients with various CVD states and comorbid obesity. Our objectives were to review the pharmacological profile, RCT efficacy and safety data, and RWE postmarketing effectiveness and safety of rivaroxaban in patients with obesity (BMI ≥ 30 kg/m^2). The pharmacological and RCT publications referenced in this review are those that support the current drug labeling for the (1) prophylaxis of DVT after hip or knee arthroplasty, (2) treatment of VTE (DVT and PE), (3) reduction of the risk of stroke and systemic embolism in AF, and (4) reduction of the risk of MACE (cardiovascular death, MI, and stroke) in chronic CAD or PAD. While an indication based on the data obtained from VOYAGER-PAD is still

pending regulatory review and approval (hence it was not included in the rivaroxaban label as of July 2020), the data from this recent trial are felt to be relevant for this review to better inform the medical community of the latest research in this important patient population. The included RWE studies were identified in PubMed and Ovid MEDLINE searches focusing on real-world use of rivaroxaban compared with standard of care among patients with either AF or VTE and comorbid obesity.

3 The Effects of Obesity on the Pharmacology of Rivaroxaban

Based on the pathophysiology of obesity, evidence indicates it may affect the pharmacological profile of various drugs, so dose adjustments may be required. However, the extent and clinical significance of this effect is drug specific [19]. Rivaroxaban has been assessed in phase I clinical pharmacology studies, population-pharmacokinetic (Pop-PK) models, various phase II and III clinical trials, and phase IV RWE studies to provide further information on its use in patients with CVD and obesity.

The first study to formally assess the effects of body weight on rivaroxaban was a clinical pharmacology study conducted by Kubitza et al. [20]. This study assessed the effects of extreme weights (≤ 50 and > 120 kg) on the pharmacokinetics and pharmacodynamics of rivaroxaban compared with those of normal weight (70–80 kg). The study enrolled 48 otherwise healthy individuals who were then randomized to receive either a single 10-mg dose of rivaroxaban or placebo in a 3:1 ratio. This allowed 12 participants in each weight group to receive rivaroxaban and four to receive placebo.

Rivaroxaban was well-tolerated and mean maximum concentrations (C_{max}) were unaffected in participants weighing > 120 kg. Participants weighing ≤ 50 kg had an approximately 24% increase in C_{max} that resulted in a 15% increase in expected prolongation of prothrombin time, which was not considered clinically relevant. Systemic exposure, as measured by the area under the curve (AUC), was unaffected by body weight [20]. The authors speculated that this limited effect may be due to rivaroxaban's low volume of distribution and the theory that rivaroxaban may be limited mainly to the vascular bed and interstitial space [20]. This study supported the current rivaroxaban prescribing information, which suggests that dose adjustment based on weight is not necessary.

Phase I clinical pharmacology studies are generally limited to collecting data in healthy volunteers. However, these data do provide a firm foundation of the different pharmacological attributes a compound displays across subpopulations. To further understand these attributes, the influence of body weight was assessed in diverse patient populations using Pop-PK modeling. Studies in which the model was applied included (1) phase IIb clinical trials for the prevention of VTE after hip- or knee-replacement surgery [21, 22], (2) phase II clinical trials for acute DVT [23], (3) phase III clinical trial in NVAF [24], and (4) the phase II trial in acute coronary syndrome [25].

The purpose of this modeling was to allow for a broader understanding of the potential effects of different intrinsic patient characteristics on the pharmacology of rivaroxaban, beyond that assessed in the initial phase I study. When assessing the totality of these data, increased body weight was determined not to have a clinically meaningful impact on rivaroxaban pharmacology. Volume of distribution was the parameter most influenced by high weight/BMI, although it is important to note that this difference was within the range of interpatient variability and did not support the need for dose reduction.

4 Efficacy and Safety of Rivaroxaban in Patients with Obesity

While large efficacy and safety studies that comprise phase III drug development were not conducted solely within an obese patient population, each of the rivaroxaban trials that led to an approved treatment indication allowed for a rich analysis based on participant body weight and/or BMI. It should be noted that no weight or BMI restrictions were placed on participation in these studies. Table 1 summarizes the design of each of the phase III trials.

4.1 Prophylaxis of Deep Vein Thrombosis (DVT) After Hip or Knee Arthroplasty

The RECORD series was a group of four phase III clinical trials that looked at the efficacy and safety of rivaroxaban compared with enoxaparin for the prevention of VTE in patients undergoing total hip or knee arthroplasty [26–29]. The primary efficacy endpoints in these studies was a composite of any symptomatic VTE (DVT and PE) and all-cause mortality. The primary safety endpoint was the incidence of major bleeding. Turpie et al. [30] completed a pooled analysis of these four trials, which included an assessment of the various intrinsic factors, including weight, on the safety and efficacy of rivaroxaban. The 12,729 patients enrolled into these four studies were randomized to receive either rivaroxaban 10 mg once daily or enoxaparin 40 mg once daily (or 30 mg twice daily) following surgery. For this pooled analysis, 12,383 of these patients were included. Given the slight differences in each of the four trials, the authors provided three different grouped analyses of the data. When assessing the

Table 1 Summary of phase III rivaroxaban trial designs

Characteristic	RECORD [26–30]	EINSTEIN [32–35]	ROCKET AF [36]	COMPASS [38]	VOYAGER-PAD [39]
Study population	Adults undergoing elective THA or TKA	Adults with VTE (PE, DVT)	Adults with NVAF at increased risk for stroke	Adults with stable atherosclerotic vascular disease	Adults with PAD undergoing revascularization
Treatment comparators	Rivaroxaban vs. SC enoxaparin	Rivaroxaban vs. SC enoxaparin and dose-adjusted VKA	Rivaroxaban vs. warfarin	Rivaroxaban + ASA vs. rivaroxaban alone vs. ASA alone	Rivaroxaban + ASA vs. placebo + ASA
Overall sample size	RECORD I: 4541 RECORD II: 2509 RECORD III: 2531 RECORD IV: 3148	EINSTEIN DVT:3449 EINSTEIN PE: 4832 EINSTEIN CHOICE: 3365	Rivaroxaban: 7131 Warfarin: 7133	Rivaroxaban plus ASA: 9152 Rivaroxaban alone: 9117 ASA alone: 9126	Rivaroxaban: 3286 Placebo: 3278
Study design	Double-blind RCTs	Open-label, randomized, event-driven, noninferiority study [32–34]; double-blind RCT [35]	Double-blind, noninferiority RCT	Double-blind RCT	Double-blind, RCT
Proportion of patients with excess bodyweight/BMI included (total study population)	Body weight > 90 kg: 2883/12,365 (23.3%)	EINSTEIN DVT/PE Body weight ≥ 100 kg: 1393/8271 (16.8%) BMI ≥ 30 kg/m^2: 2491/8230 (30.3%) EINSTEIN CHOICE Body weight > 90 kg: 1070/3365 (31.8%) BMI ≥ 30 kg/m^2: 1145/3365 (34.0%)	Body weight > 90 kg: 3977/14,168 (28.1%) BMI ≥ 30 kg/m^2: 1891/14,162 (13.4%)	Body weight > 60 kg (for rivaroxaban plus ASA vs. ASA alone): 16,526/18,263 (90.5%) Body weight > 90 kg (for rivaroxaban plus ASA vs. ASA alone): 4612/18,278 (25.2%)	BMI ≥ median (26 kg/m^2): 3250/6491 (50.1%)

ASA acetylsalicylic acid (aspirin), *BMI* body mass index, *DVT* deep vein thrombosis, *NVAF* nonvalvular atrial fibrillation, *PAD* peripheral artery disease, *PE* pulmonary embolism, *SC* subcutaneous, *THA* total hip arthroplasty, *TKA* total knee arthroplasty, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

effects of weight on the primary outcomes across the four trials, the "total treatment duration pool" was used. From this pool, the safety population, which excluded patients who were randomized but did not receive any study medication, included 12,383 patients (6183 in the rivaroxaban group and 6200 in the enoxaparin group) and was used for this analysis [30].

When assessing the overall safety population across these trials, the primary efficacy endpoint occurred less frequently for patients treated with rivaroxaban than for those receiving enoxaparin (0.6 and 1.3%, respectively; hazard ratio [HR]

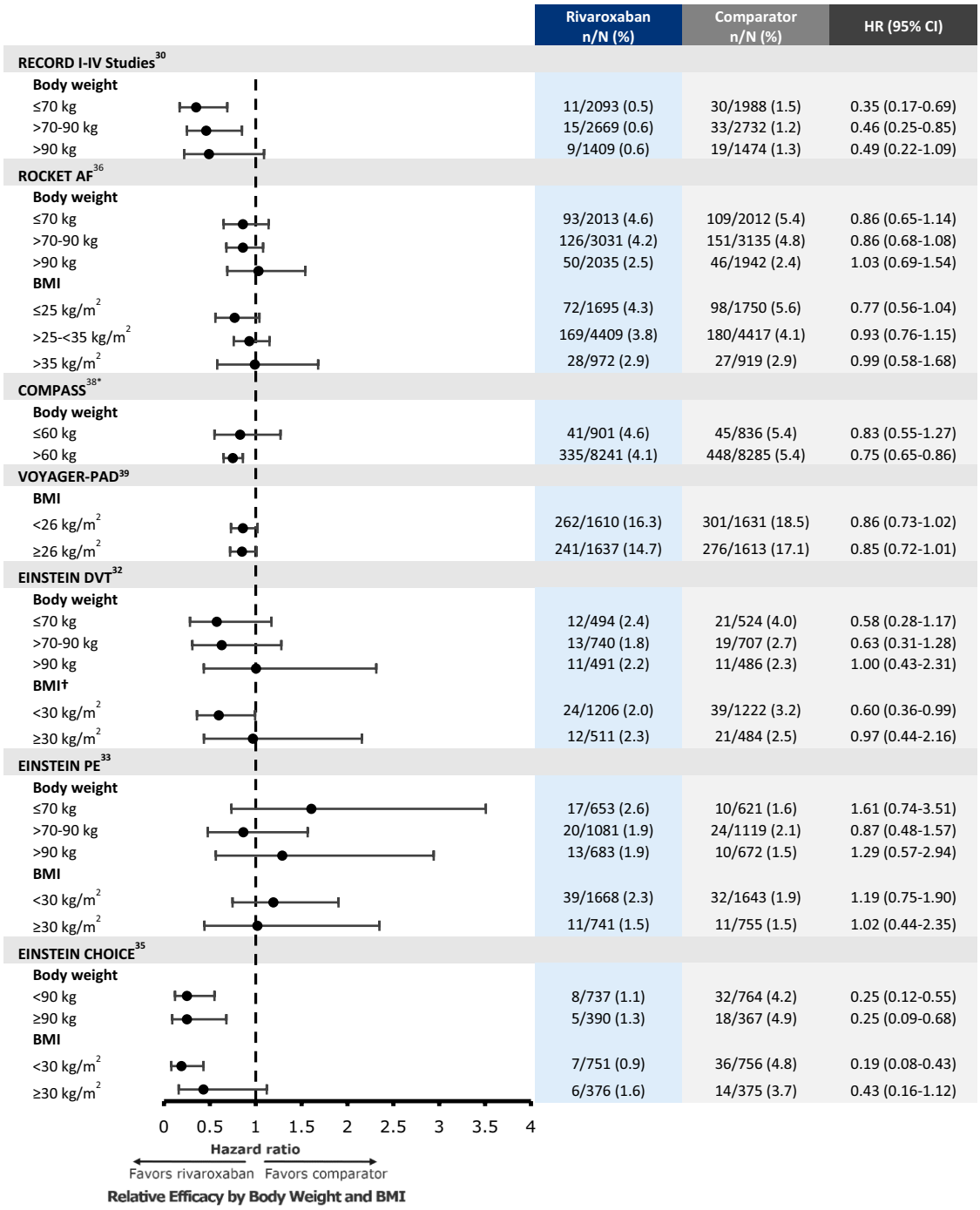

Fig. 1 Rivaroxaban relative efficacy by body weight and BMI. *AF* atrial fibrillation, *ASA* acetylsalicylic acid (aspirin), *BID* twice daily, *BMI* body mass index, *CI* confidence interval, *DVT* deep vein thrombosis, *HR* hazard ratio, *PAD* peripheral artery disease, *PE* pulmonary embolism. *COMPASS efficacy results shown for rivaroxaban 2.5 mg BID + ASA vs. ASA alone. †Data on file

0.42; 95% confidence interval CI 0.29–0.63). These reductions were consistent when analyzed by weight subgroup (≤ 70, 70–90, > 90 kg) (Fig. 1) [29]. The primary safety endpoint, major bleeding, occurred in 24 (0.4%) patients receiving rivaroxaban and 13 (0.2%) receiving enoxaparin (HR 1.84; 95% CI 0.94–3.62). Major plus clinically relevant nonmajor bleeding rates were similar among the patient subgroups weighing ≤ 70 and 70–90 kg. However, an increase was observed in patients weighing > 90 kg receiving rivaroxaban when compared with enoxaparin (Fig. 2) [30].

A post-hoc observational analysis was also completed in patients from the RECORD series to examine the early postoperative (up to 6–8 weeks) efficacy and safety [31]. The analysis specifically focused on morbidly obese patients (BMI ≥ 40 kg/m^2; $n = 445$) compared with those with BMI < 40 kg/m^2 ($n = 11{,}910$). Results showed similar rates in both primary efficacy and safety outcomes between the two BMI groups [31].

4.2 Treatment of Venous Thromboembolism (VTE) [DVT and Pulmonary Embolism (PE)]

The EINSTEIN trials were two phase III noninferiority studies that assessed the safety and efficacy of rivaroxaban used in the treatment of acute symptomatic DVT (EINSTEIN DVT) [32] and PE (EINSTEIN PE) [33]. The primary

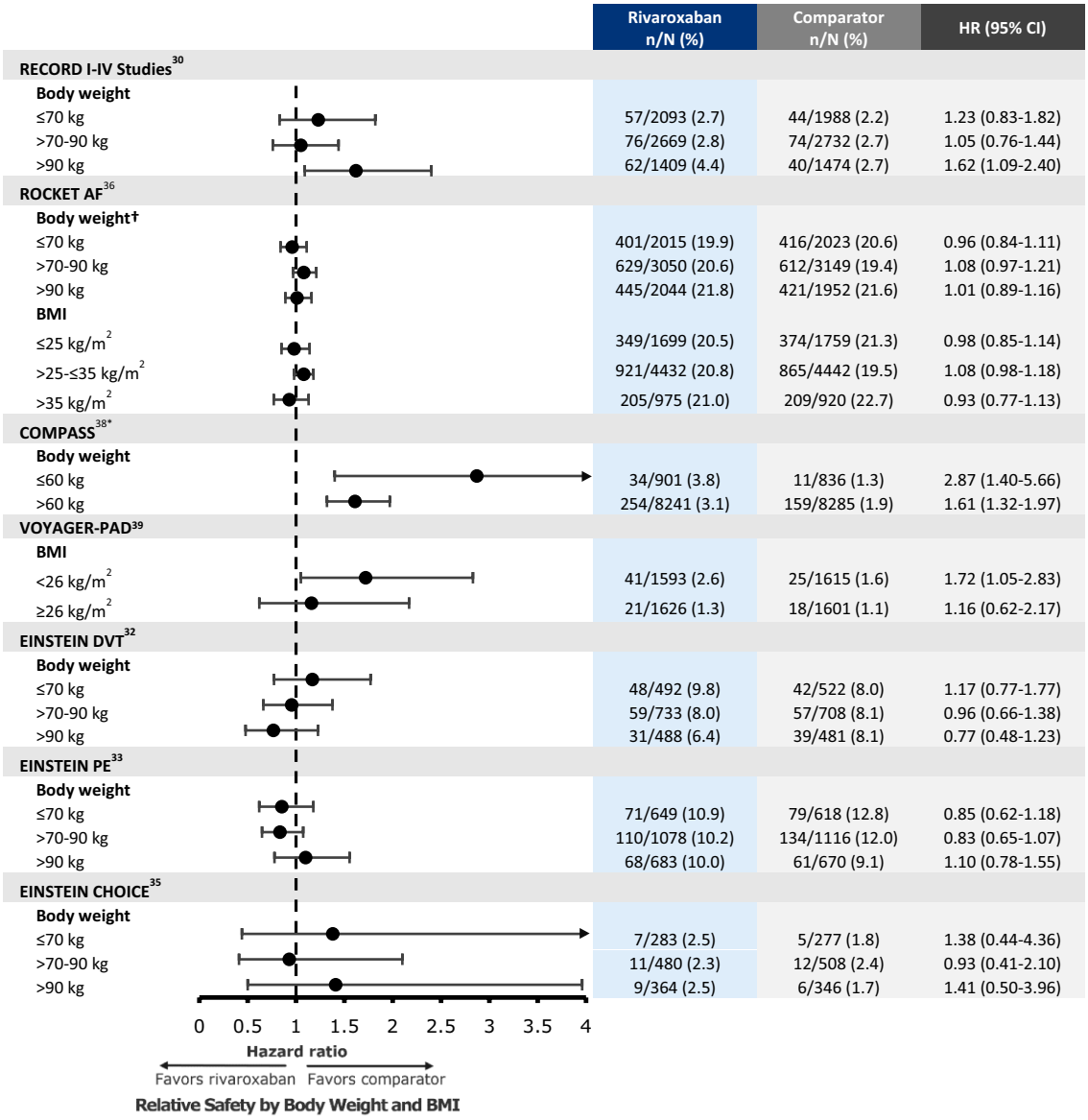

Fig. 2 Rivaroxaban relative safety by body weight and BMI. *AF* atrial fibrillation, *ASA* acetylsalicylic acid (aspirin), *BID* twice daily, *BMI* body mass index, *CI* confidence interval, *DVT* deep vein thrombosis, *HR* hazard ratio, *PAD* peripheral artery disease, *PE* pulmonary embolism. *COMPASS safety results shown for rivaroxaban 2.5 mg BID + ASA vs. ASA alone. †Data on file

efficacy outcome for both studies was recurrent VTE. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding. In both studies, patients received either rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or subcutaneous enoxaparin and a dose-adjusted vitamin K antagonist (VKA) for 3, 6, or 12 months [32, 33]. An extension study (EINSTEIN Extension) assessed the continued use of rivaroxaban 20 mg once daily versus placebo over an additional 6 or 12 months of treatment for those who had already completed 6–12 months of initial VTE treatment [32].

In both trials, rivaroxaban was noninferior to enoxaparin/VKA therapy for the primary efficacy endpoint of recurrent VTE (EINSTEIN DVT, HR 0.68; 95% CI 0.44–1.04; $P < 0.001$; EINSTEIN PE, HR 1.12; 95% CI 0.75–1.68; $P = 0.003$) [32, 33]. In the EINSTEIN Extension study, rivaroxaban had superior efficacy (8 [1.3%] vs. 42 [7.1%] events with rivaroxaban vs. placebo, respectively; HR 0.18; 95% CI 0.09–0.39; $P < 0.001$) [32]. In the EINSTEIN DVT study, rivaroxaban had the same principal safety outcome results (8.1% of patients) as enoxaparin/VKA therapy. Within the EINSTEIN PE study, rivaroxaban displayed a principal safety outcome comparable to that of enoxaparin/VKA therapy (10.3 vs. 11.4%, respectively) [32, 33]. In the EINSTEIN Extension study, four patients in the rivaroxaban group had nonfatal major bleeding (0.7%) versus none in the placebo group [32].

Approximately 14% of the total enrolled patients randomized to rivaroxaban weighed > 100 kg in EINSTEIN DVT ($N = 245/1731$ [14.2%]) and EINSTEIN PE ($N = 345/2419$ [14.3%]) [32, 33]. When assessing the primary efficacy and safety endpoints for the EINSTEIN DVT and EINSTEIN PE trials across predetermined weight groups (≤ 70, > 70–90, > 90 kg), both endpoints displayed similar results regardless of weight, with those weighing > 90 kg displaying a trend of lower occurrence (Figs. 1, 2) [32, 33]. The same consistent efficacy across weight was also observed in the EINSTEIN Extension portion of the trial. However, a higher incidence of bleeding occurred in the rivaroxaban treatment group when compared with placebo.

A follow-up analysis by Di Nisio et al. [34] combining both EINSTEIN DVT and PE studies further assessed the potential risk for different efficacy and safety profiles in subjects with either very low weight (≤ 50 kg) or very high weight (≥ 100 kg) [34]. The trials enrolled 8282 patients. When accounting for patients who did not sign an informed consent form or did not provide a baseline body weight, the total number of patients included in the analysis was reduced to 8271. The mean body weight of the entire population was 82.5 kg and ranged from 33 to 220 kg. From this population, 166 (2.0%) patients had a body weight ≤ 50 kg and 1393 (16.8%) a body weight ≥ 100 kg. This analysis further supported the results obtained from the initial studies. Specifically, there was no association between body weight and risk of recurrent VTE or risk of major bleeding for either rivaroxaban or the standard of care (enoxaparin/warfarin) [34].

A fourth study, EINSTEIN CHOICE, was conducted to ascertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin for patients with VTE requiring extended treatment [35]. This randomized, double-blind, phase III study was conducted in 3396 patients with a VTE. Patients were randomized to receive either once-daily rivaroxaban 20 or 10 mg or acetylsalicylic acid (aspirin) 100 mg. Patients were required to first complete 6–12 months of anticoagulation therapy and be in equipoise regarding the need for continued anticoagulation, at which time therapy was administered for an additional up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal VTE, and the principal safety outcome was major bleeding [35].

A total of 3365 patients were included in the final analyses. The primary efficacy outcome occurred in 1.5% of patients receiving rivaroxaban 20 mg, in 1.2% receiving rivaroxaban 10 mg, and in 4.4% receiving aspirin. Rates of major bleeding were 0.5% with rivaroxaban 20 mg, 0.4% with rivaroxaban 10 mg, and 0.3% with aspirin. Ultimately, the lower 10 mg dose of rivaroxaban was approved for use. Subgroup analyses by both body weight and BMI showed a result for both primary efficacy and safety endpoints consistent with that in the overall study population (Figs. 1, 2) [35].

4.3 Reduction in the Risk of Stroke and Systemic Embolism in Atrial Fibrillation (AF)

ROCKET AF was a phase III, randomized noninferiority trial that assessed the efficacy and safety of rivaroxaban versus warfarin in stroke prevention for patients with NVAF. The study included approximately 14,000 patients who received either rivaroxaban 20 mg once daily (15 mg once daily in moderate renal impairment) or dose-adjusted warfarin. Primary endpoints included the composite of stroke and systemic embolism and the composite of major bleeding and nonmajor clinically relevant bleeding. While weight was not an enrollment criterion, approximately 2000 patients weighing > 90 kg and 1000 patients with a BMI > 35 kg/m^2 were enrolled [36].

The overall results from this study support the noninferiority of rivaroxaban when compared with warfarin for both primary endpoints. The primary efficacy endpoint (composite of stroke [ischemic or hemorrhagic] and systemic embolism) occurred in 188 patients in the rivaroxaban group and in 241 patients in the warfarin group (HR 0.79; 95% CI 0.66–0.96; $P < 0.001$ for noninferiority) [36]. When assessing the intent-to-treat (ITT) population, the primary endpoint occurred in 269 patients in the rivaroxaban group

and in 306 patients in the warfarin group (HR 0.88; 95% CI 0.74–1.03; $P<0.001$ for noninferiority; $P=0.12$ for superiority). The primary safety endpoint (major and nonmajor clinically relevant bleeding) occurred in 1475 patients in the rivaroxaban group and in 1449 in the warfarin group (HR 1.03; 95% CI 0.96–1.11; $P=0.44$), with significant reductions in intracranial hemorrhage (0.5 vs. 0.7%; $P=0.02$) and fatal bleeding (0.2 vs. 0.5%; $P=0.003$) in the rivaroxaban group [36].

When assessing both the primary efficacy and the safety endpoints for this trial across the predetermined weight groups ($\leq 70, > 70$–$90, > 90$ kg), both endpoints displayed similar results regardless of weight or BMI (Figs. 1, 2) [36]. These results were reiterated in a post-hoc analysis of the trial that further classified patients into three BMI categories: normal (BMI 18.50–24.99 kg/m^2; reference group), overweight (BMI 25.00–29.99 kg/m^2), and obese (BMI ≥ 30 kg/m^2) [37]. In this analysis, Balla et al. [37] compared the incidence of stroke and systemic embolic events as well as bleeding events in normal ($N=3289$), overweight ($N=5535$), and obese ($N=5206$) patients.

The incidence of stroke and systemic embolic event rates per 100 patient-years was 2.93 in the normal (reference), 2.28 in the overweight (adjusted HR 0.81; 95% CI 0.66–0.99; $P=0.04$), and 1.88 in the obese (adjusted HR 0.69; 95% CI 0.55–0.86; $P<0.001$) groups. Bleeding event rates were similar among all three weight groups; no statistically significant associations were found. Further grouping patients into more severe categories of obesity (BMI ≥ 35 kg/m^2), stroke risk was significantly lower for patients when compared with normal weight patients in both the rivaroxaban (HR 0.62; 95% CI 0.40–0.96; $P=0.03$) and the warfarin (HR 0.48; 95% CI 0.31–0.74; $P<0.001$) groups [37].

4.4 Reduction of Risk of Major Adverse Cardiovascular Events (MACE) in Chronic Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD)

The COMPASS phase III trial assessed the use of rivaroxaban, with and without concomitant aspirin, for the prevention of MACE and major bleeding events (using a modified ISTH criteria) in patients with a history of stable atherosclerotic vascular disease (CAD and/or PAD) [38]. MACE was defined as a composite of cardiovascular death, stroke, and MI. A total of 27,395 patients were enrolled in the trial and randomized to receive either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily alone, or aspirin 100 mg once daily. The study was stopped early by the independent data safety and monitoring board for evidence of superiority for the rivaroxaban + aspirin regimen after a mean follow-up of 23 months.

Patients randomized to the rivaroxaban + aspirin group had fewer primary outcome events ($N=379$ [4.1%] patients) than the aspirin-alone group ($N=496$ [5.4%] patients) and rivaroxaban-alone group ($N=448$ [4.9%] patients). When comparing the rivaroxaban + aspirin and aspirin-alone groups, rivaroxaban displayed a significant reduction in events (HR 0.76; 95% CI 0.66–0.86; $P<0.001$) [38]. Major bleeding events occurred more frequently in the rivaroxaban + aspirin group ($N=288$ [3.1%] patients) than in the aspirin-alone group ($N=170$ [1.9%] patients; HR 1.70; 95% CI 1.40–2.05; $P<0.001$). Importantly, there was no significant difference in intracranial or fatal bleeding between these two groups.

To assess the effects of weight, patients were placed into the following two weight categories at baseline: ≤ 60 or > 60 kg. Consistent with the overall study outcomes, patients in the rivaroxaban + aspirin group experienced fewer MACE than those in the aspirin-alone group for both weight categories (Fig. 1). Consistent with the overall study outcomes, the incidence of major bleeding was greater in the rivaroxaban + aspirin group than in the aspirin-alone group across both weight categories (Fig. 2) [38].

Further expanding the knowledge of rivaroxaban use in PAD, another phase III study assessed the use of rivaroxaban in patients with PAD who underwent lower-extremity revascularization [39]. VOYAGER-PAD was a randomized, double-blind clinical trial in which 6564 patients received either rivaroxaban 2.5 mg twice daily plus aspirin ($N=3286$) or placebo plus aspirin ($N=3278$). The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding, defined according to the thrombolysis in myocardial infarction (TIMI) classification. Additionally, major bleeding as defined by the ISTH was assessed as a secondary safety outcome [39].

Patients randomized to rivaroxaban + aspirin had fewer primary composite outcome events than those randomized to placebo + aspirin (rivaroxaban 508 vs. placebo 584). The Kaplan–Meier estimates of the incidence at 3 years were 17.3% for rivaroxaban and 19.9% for placebo (HR 0.85; 95% CI 0.76–0.96; $P=0.009$). The primary safety endpoint (TIMI major bleeding) occurred in 62 (2.65%) versus 44 (1.87%) patients, randomized to the rivaroxaban and placebo groups, respectively (HR 1.43; 95% CI 0.97–2.10; $P=0.07$). The secondary safety outcome (ISTH major bleeding) occurred in 140 (5.94%) patients in the rivaroxaban group compared with 100 (1.42%) in the placebo group (HR 1.42; 95% CI 1.10–1.84; $P=0.007$) [39].

A subgroup analysis by treatment group and BMI was conducted, with the median BMI for both groups being 26 kg/m^2. Within each group, patients were separated into two BMI categories, either (1) < median BMI or (2) ≥ median

BMI. The primary efficacy and safety results were consistent with the main trial results. Those randomized to the rivaroxaban + aspirin group with a BMI < 26 kg/m^2 had fewer primary composite outcome events than those randomized to the placebo group (Fig. 1). Similar outcomes were also observed in those with a BMI ≥ 26 kg/m^2, with the rivaroxaban + aspirin group displaying fewer primary composite outcomes (Fig. 1). Again consistent with the overall study outcomes, the incidence of major bleeding (both primary TIMI major and secondary ISTH major bleeding) was greater in the rivaroxaban + aspirin group than in the placebo group across both BMI categories (Fig. 2) [39].

As with all clinical research trials, there were limitations to each. While those specific to the study can be found in the respective primary publications, some common limitations found across these randomized trials include a limited diversity in patient demographics (sex, ethnicity, etc.), unequal patient enrollment per country or region, and limited assessment of different doses and regimens, to highlight a few. However, as mentioned, these limitations are found in all large clinical trials and are not necessarily unique to those mentioned in this review.

5 Real-World Evidence (RWE) Studies

Until recently, RWE studies focusing on the effectiveness and safety of rivaroxaban in obese and morbidly obese patients have been scarce. Findings from retrospective claims databases, EHRs, single-center studies, and prospective anticoagulation registries are helping fill this evidence gap.

One of the first studies to analyze the effectiveness and safety of rivaroxaban compared with warfarin among patients with NVAF who were morbidly obese was published by Peterson et al. [40]. Using retrospective data (December 2011–September 2016) from the US Truven MarketScan Commercial and Medicare supplemental databases, these authors identified 7126 patients with NVAF with an International Classification of Diseases, Ninth/Tenth Revision (ICD-9/ICD-10) diagnosis code for morbid obesity and initiating rivaroxaban or warfarin treatment, with a minimum of 12 months continuous plan enrollment prior to and 3 months post treatment initiation. Given the lack of BMI, height, and weight in the claims databases, morbid obesity was identified via ICD-9/ICD-10 codes, which may underestimate the morbidly obese population but have been validated as being accurate when coded in claims databases (i.e., high specificity) [41–44]. Patients with mitral stenosis, a heart valve procedure, organ/tissue transplant, or oral anticoagulation use during the baseline

Table 2 Rivaroxaban effectiveness outcomes among obese patients in real-world evidence studies

Outcomes	Rivaroxaban	Comparator	OR/HR (95% CI)
Peterson et al. [40]			
Ischemic stroke/systemic embolism	52/3563 (1.5)	59/3563 (1.7)	OR 0.88 (0.60–1.28)
Spyropoulos et al. [45]			
Recurrent VTE			
Intent to treat	485/2890 (16.8)	459/2890 (15.9)	OR 0.99 (0.85–1.14)
On treatment	418/2832 (14.8)	380/2832 (13.4)	OR 1.02 (0.87–1.20)
Kushnir et al. [46]			
Stroke	4/174 (2.3)	2/152 (1.3)	HR NR
Recurrent VTE	3/152 (2.0)	2/167 (1.2)	HR NR
Perales et al. [47]			
Composite of clinical failure (i.e., VTE recurrence, stroke, all-cause mortality)	4/84 (4.8)	12/92 (13.0)	HR NR
Costa et al. [48]			
Stroke/systemic embolism	429/35,613 (1.2)	668/35,613 (1.9)	HR 0.83 (0.73–0.94)
Ischemic stroke alone	399/35,613 (1.1)	586/35,613 (1.7)	HR 0.89 (0.78–1.01)
Ageno et al. [52]			
Weight ≥ 90 kg subgroup			
Recurrent VTE	11/599 (1.8)	12/482 (2.5)	HR 0.91 (0.35–2.35)

Data are presented as *n*/*N* (%) unless otherwise indicated

CI confidence interval, *HR* hazard ratio, *NR* not reported, *OR* odds ratio, *VTE* venous thromboembolism

Table 3 Rivaroxaban safety outcomes among obese patients in real-world evidence studies

Outcomes	Rivaroxaban	Comparator	OR/HR (95% CI)
Peterson et al. [40]			
Major bleeding	77/3563 (2.2)	96/3563 (2.7)	OR 0.80 (0.59–1.08)
Spyropoulos et al. [45]			
Major bleeding			
Intent to treat	52/2890 (1.8)	73/2890 (2.5)	OR 0.66 (0.45–0.98)
On treatment	40/2832 (1.4)	50/2832 (1.8)	OR 0.75 (0.47–1.19)
Kushnir et al. [46]			
Major bleeding (AF)	5/174 (2.9)	12/152 (7.9)	HR 0.39 (0.13–1.17)
Composite bleeding (AF)	17/174 (9.8)	25/152 (16.4)	HR 0.55 (0.29–1.06)
Major bleeding (VTE)	2/152 (1.3)	4/167 (2.4)	HR NR
Composite bleeding (VTE)	14/152 (9.2)	17/167 (10.2)	HR NR
Perales et al. [47]			
Bleeding complications (i.e., major bleeding or clinically relevant nonmajor bleeding)	7/84 (8.3)	2/92 (2.2)	HR NR
Costa et al. [48]			
Major bleeding	877/35,613 (2.5)	1382/35,613 (3.9)	HR 0.82 (0.75–0.89)
Intracranial hemorrhage	79/35,613 (0.2)	164/35,613 (0.5)	HR 0.62 (0.47–0.81)
Extracranial bleeding	809/35,613 (2.3)	1232/35,613 (3.5)	HR 0.85 (0.78–0.93)
Ageno et al. [52]			
Weight ≥ 90 kg subgroup			
Major bleeding	6/599 (1.0)	12/482 (2.5)	HR 0.91 (0.31–2.68)

Data are presented as *n*/*N* (%) unless otherwise indicated

AF atrial fibrillation, *CI* confidence interval, *HR* hazard ratio, *NR* not reported, *OR* odds ratio, *VTE* venous thromboembolism

period were excluded from the study. Propensity score matching (1:1) was used to minimize potential confounding between the treatment cohorts. Among the rivaroxaban cohort, most patients (81.4%) received the 20-mg dose. During an average follow-up period of 10.27 ± 2.89 months for rivaroxaban users and 10.56 ± 2.70 months for warfarin users, no significant differences were identified in the risk of ischemic stroke/systemic embolism (Table 2) or major bleeding (Table 3).

A second retrospective 1:1 propensity score-matched analysis assessed the effectiveness and safety of rivaroxaban versus warfarin among morbidly obese patients who experienced a VTE in the US Truven MarketScan Commercial and Medicare supplemental databases from December 2012 to September 2016 [45]. A total of 5780 morbidly obese patients (identified via ICD-9/ICD-10 diagnosis codes) with VTE and initiating rivaroxaban or warfarin treatment, with a minimum of 12 months continuous plan enrollment prior to and 3 months post treatment initiation, were included in the ITT analysis. The average follow-up period in the ITT analysis was 10.04 ± 3.01 months among rivaroxaban users and 10.51 ± 2.77 months among warfarin users. An on-treatment analysis included 5664 patients during an average follow-up of approximately 6 months. No significant differences were found in the risk of recurrent VTE in both the ITT and the on-treatment analyses (Table 2). The risk of major bleeding for rivaroxaban was also similar to that with warfarin (Table 3).

Researchers from Montefiore Medical Center conducted a single-center retrospective chart analysis among patients with AF or VTE from March 2013 to March 2017 to determine whether DOACs (rivaroxaban and apixaban) were as effective and well-tolerated as warfarin among patients with a BMI ≥ 40 kg/m^2 [46]. Note, the focus of this review is on rivaroxaban, so the results for other DOACs are not summarized. Patients were excluded from the analysis if they were diagnosed with both AF and VTE, had another indication for anticoagulation treatment, were unable to confirm actual treatment start date, or were missing follow-up after treatment initiation. A total of 174 patients receiving rivaroxaban and 152 receiving warfarin were included in the AF analysis, with median follow-up times being 412.9 (interquartile range [IQR] 187.3–675.2) days and 293.6 (IQR 81.6–671.8) days for rivaroxaban and warfarin, respectively.

Stroke incidence was relatively low and similar for patients receiving rivaroxaban (Table 2). Major bleeding occurred in five (2.9%; 95% CI 0.4–5.4) patients receiving rivaroxaban and 12 (7.9%; 95% CI 3.6–12.2; $P = 0.0419$) receiving warfarin. The incidence of composite bleeding was similar for rivaroxaban and warfarin (Table 3).

Time-to-event analysis found no significant difference in composite bleeding and major bleeding (Table 3) between rivaroxaban and warfarin. The VTE analysis included 152 patients receiving rivaroxaban and 167 receiving warfarin, with median follow-up times of 217.4 (IQR 94.4–514.1) days and 206.3 (IQR 64.4–540.3) days for rivaroxaban and warfarin, respectively. Recurrent VTE incidence was low and similar for patients receiving rivaroxaban or warfarin (Table 2). Major bleeding occurred in two (1.3%; 95% CI 0.0–3.1) patients receiving rivaroxaban and four (2.4%; 95% CI 0.1–4.7) receiving warfarin. The incidence of the composite of major bleeding and clinically relevant nonmajor bleeding was also similar among those receiving rivaroxaban or warfarin (Table 3).

In another retrospective chart review study conducted in two academic medical centers in southern Arizona, Perales et al. [47] compared rivaroxaban and warfarin among patients identified as extremely obese (BMI ≥ 40 kg/m^2) or having high body weight (> 120 kg). Adult patients initiating rivaroxaban or warfarin treatment during hospitalization for AF or VTE with a BMI ≥ 40 kg/m^2 or body weight > 120 kg were identified between November 2013 and September 2017. Patients who were on rivaroxaban or warfarin prior to admission, had a bioprosthetic or mechanical heart valve, or were on hemodialysis were excluded from the study. The primary endpoint was the composite of clinical failure during anticoagulation therapy, which was defined as VTE recurrence, stroke incidence, or mortality (from any cause) within the first 12 months of treatment initiation. A total of 176 patients were included (84 on rivaroxaban and 92 on warfarin) in the analysis. Clinical failure was not significantly different with rivaroxaban compared with warfarin (Table 2; $P = 0.06$). Bleeding complications, defined as a major bleed or clinically relevant nonmajor bleed, were also not significantly different (Table 3; $P = 0.06$).

A recent 1:1 propensity score-matched retrospective analysis using the Optum® De-identified EHR database from November 2011 to September 2018 evaluated the effectiveness and safety of rivaroxaban versus warfarin among obese patients with NVAF, including analyses by obesity classes as defined by the National Heart, Lung, and Blood Institute based on BMI (obesity class I = 30–34.9 kg/m^2; class II = 35–39.9 kg/m^2; and class III = ≥ 40 kg/m^2) [48]. Patients with NVAF with a BMI ≥ 30 kg/m^2 who had been newly prescribed rivaroxaban or warfarin and who had ≥ 1 year of EHR activity and one or more healthcare encounter prior to treatment initiation were included. Patients with valvular heart disease or evidence of oral anticoagulation use during the baseline period were excluded. Given that the analysis was based on EHR data, an ITT approach was followed based on the physicians' prescription of rivaroxaban or warfarin. Pharmacy claims data were not available in the database. A total of 71,226 patients were included in the matched analysis (35,613 in each treatment cohort) and followed for a median of 2.6 (IQR 1.2–4.1) years. The majority of patients were categorized as class I obese (48%), followed by class II (27%) and class III (25%). Patients prescribed rivaroxaban had a significant reduction in stroke/systemic embolism compared with patients prescribed warfarin among the overall obese group (HR 0.83; 95% CI 0.73–0.94; Table 2) and the class I obese subgroup (HR 0.78; 95% CI 0.66–0.93). No significant differences were identified in the class II and class III subgroups for stroke/systemic embolism, although the numerically lower trend for rivaroxaban was present. When ischemic stroke was assessed alone, the findings were not significantly different (Table 2). Safety analysis showed reductions in major bleeding with rivaroxaban in the overall obese group (HR 0.82; 95% CI 0.75–0.89; Table 3) and the obesity class subgroups (class I HR 0.85; 95% CI 0.75–0.96; class II HR 0.85; 95% CI 0.72–1.00; class III HR 0.75; 95% CI 0.64–0.89). Significant reductions were also noted with rivaroxaban when the safety outcome was assessed separately by intracranial hemorrhage and extracranial bleeds (Table 3). Exploratory analysis did not find a significant interaction across the BMI categories for stroke/systemic embolism (P interaction = 0.58) or major bleeding (P interaction = 0.44).

It is important to note that RWE studies have inherent limitations. Multiple biases, such as misclassification, sampling, and confounding, are possible in nonrandomized studies and could impact a study's internal validity [49]. Residual confounding is also possible because of unobserved or unmeasured covariates. For several of the real-world studies summarized, calculation of time in therapeutic international normalized ratio (INR) range for the patients treated with warfarin was not possible because of missing laboratory data [40, 45, 47, 48]. Studies utilizing administrative claims data and/or EHR data cannot confirm a patient took the medication as prescribed.

In addition to retrospective claims, EHRs, and chart reviews, several prospective registries are investigating the real-world utilization and outcomes of DOACs in patients with NVAF and VTE [50–53], with some prospective studies focused specifically on rivaroxaban [54, 55]. XALIA was a multicenter, international, prospective, noninterventional study that took place in hospitals and community centers in 21 countries to assess the effectiveness and safety of rivaroxaban compared with the standard of care among 5142 patients between 26 June 2012 and 31 March 2014 [54]. Propensity score-adjusted analysis was used to control for potential imbalances between the treatment groups. Approximately one-quarter of the enrolled patients had a body weight ≥ 90 kg, with subgroup analysis in this body weight group finding a similar risk of recurrent VTE (Table 2) and major bleeding (Table 3).

RIVER is an ongoing international, prospective registry that recruited 5072 patients with newly diagnosed NVAF with one or more investigator-determined risk factor for stroke who received rivaroxaban as their initial treatment between January 2014 and June 2017 from 309 centers in 17 countries [55]. Each patient will be followed for a minimum of 2 years, and the registry will capture details on the rate and nature of stroke/systemic embolism, bleeding complications, all-cause mortality, and other major cardiovascular events. Baseline characteristics show that approximately 20% of patients are obese. Findings from the RIVER registry will help add to the growing body of RWE for rivaroxaban.

The pharmacokinetics of rivaroxaban and bodyweight have also been studied in real-world settings. Researchers from King's College developed a pharmacokinetic model for rivaroxaban and included 101 patients prescribed rivaroxaban (prophylactic or treatment doses) for the prevention of VTE from a London teaching hospital [56]. After full covariate analysis, creatinine clearance was the significant covariate impacting rivaroxaban's pharmacokinetic profile, whereas weight alone had little effect. Study authors concluded that weight on its own was not a good predictor of rivaroxaban exposure. A second study included 21 morbidly obese patients (body weight > 120 kg) taking rivaroxaban from anticoagulation clinics in Ontario, Canada, and found a median peak concentration of 215 ng/mL (IQR 181–249). Six of the 21 patients had a peak concentration below the fifth percentile peak rivaroxaban concentration [57].

6 Rivaroxaban and Bariatric Surgery

Based on the limited data, it is difficult to predict how bariatric surgery will influence the pharmacology, efficacy, and safety of rivaroxaban in this patient population. Additionally, the complexity of the bariatric procedure and the downstream physiological changes that follow are highly dependent on the type of surgery taking place. Most of the surgical options currently available bypass portions of the small intestine, where nutrients and pharmaceutical products are absorbed. Hence, malabsorption is a significant postoperative concern. Bariatric surgery can lead to delayed gastric emptying, decreased time of mucosal exposure, and changes in gastric pH, all of which can impact drug pharmacokinetics. However, these changes are procedure specific [12–14].

Specific to anticoagulant therapies, most of the data available to date in this population are from the use of VKAs. A review paper including data on the use of anticoagulants in post-bariatric surgery patients noted that, possibly due to a physiologic decrease in vitamin K absorption, patients using warfarin experienced fluctuations in INR [58, 59]. This in turn, can lead to decreased control over drug levels and keeping warfarin concentrations within predefined therapeutic ranges, thus leading to clinical complications [60].

Rivaroxaban was the first of the DOACs for which the effects of bariatric surgery on its pharmacological profile were assessed. Kröll et al. [16] assessed the pharmacological profile of rivaroxaban in obese patients prior to and after bariatric surgery. This study assessed 12 patients undergoing gastric bypass (six Roux-en-Y procedures and six sleeve gastrectomy procedures). Each patient received a single oral dose of rivaroxaban 10 mg 1 day prior to and 3 days following bariatric surgery. At both times, serial pharmacokinetic and pharmacodynamic plasma samples were taken before and after drug administration.

Overall, the pharmacokinetic and pharmacodynamic parameters were within expected ranges and interpatient variability both before and after surgery. Preoperative values were consistent with those obtained from previous rivaroxaban studies conducted in healthy volunteers and patients following hip-replacement surgery. Following surgery, there was a small increase in systemic exposure (measured by AUC) for both postbariatric surgery procedures, with a slightly more notable difference in patients who underwent the sleeve gastrectomy procedure. Regardless, the plasma concentration–time curves prior to and after surgery were largely superimposable for both procedures. The pharmacodynamic effects of rivaroxaban, as measured by thrombin–antithrombin complexes, prothrombin activation fragments F1 + 2, and D-dimer concentrations, followed the same trend as the pharmacokinetic parameters. Ultimately, these results show the minimal effect of bariatric surgery on the pharmacology of rivaroxaban. The latter was further confirmed in an extension study completed 6–8 months following the procedure [17]. Despite a changed physiology following bariatric surgery, pharmacology parameters months later were comparable to those at baseline prior to the procedure.

7 Summary

Pharmaceutical research is a complex scientific paradigm that is highly regulated. Even with the immense amount of data collected during the drug development stage and used for drug approval, some gaps in our knowledge that require further evaluation will always remain. Appropriately, some of these gaps are recognized in various medical guidelines as areas in need of further data. Regarding the use of DOACs, one such area is their use in patients with CVD who are also obese. This can be seen in the ISTH guidelines, published in 2016.

These guidelines currently recommend against the use of DOACs in patients with a BMI > 40 kg/m^2 or a weight

of > 120 kg [10]. This recommendation, which is for the DOAC class as a whole, was based on the limited clinical data available at that time and on the basis that the pharmacology of these agents may differ with varying weight, based on limited data in otherwise healthy individuals. Now, when examining all the available data on rivaroxaban, specifically that related to high weight/obese individuals, the preponderance of data collected during both drug development and after its marketed use supports the premise that weight/obesity does not have a significant influence on the pharmacology, efficacy, and safety of rivaroxaban.

This understanding is based on patient data obtained from large phase II and III clinical trials across rivaroxaban's various indications. It is further supported by a dedicated clinical pharmacology study, Pop-PK modeling, and several RWE studies. In totality, all outcomes were comparable, if not favorable, in obese patients relative to those with normal weight.

One area that may still benefit from further clinical research is the use of DOACs in bariatric surgery patients, as the data in this patient population are more limited. At the time of writing, most of the data available were on the utilization of VKAs, showing that fluctuation in plasma concentration and drug levels may ultimately complicate their use. Fortunately, the use of rivaroxaban in this population continues to be investigated. The currently available evidence, albeit limited, shows a comparable pharmacokinetic/pharmacodynamic profile before and after surgery, both initially and after 6 months. Lastly, the previously mentioned ongoing BARIVA study will hopefully provide greater understanding of both the safety and the efficacy of rivaroxaban use in this important patient population.

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Declarations

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Conflict of Interest V. Ashton and K.T. Moore are employed by Janssen Pharmaceuticals Inc. L. Mudarris was a graduate student intern at Janssen Pharmaceuticals at the time of writing this manuscript.

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