QATAR UNIVERSITY

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THE EFFECT OF OBESITY ON RIVAROXABAN PHARMACOKINETICS AND

PHARMACODYNAMICS

BY

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ABSTRACT

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Title: The Effect of Obesity on Rivaroxaban Pharmacokinetics and Pharmacodynamics

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent condition that is associated with high rates of morbidity and mortality worldwide. Similarly, atrial fibrillation (AF) is one of the most common sustained heart arrhythmias, with an increased prevalence over the last two decades. Anticoagulation therapy is the cornerstone in the treatment and prevention of VTE, and the prevention of stroke in patients with non-valvular AF. Direct oral anticoagulants (DOACs) - including rivaroxaban - are a novel class of anticoagulants which have overcome the limitations of the traditional anticoagulants (warfarin and heparins) and have demonstrated superior safety and efficacy in general population. Rivaroxaban is a selective and direct inhibitor of factor Xa in the coagulation process.

Despite the fact that obesity is a risk factor for VTE onset and recurrence and that a large proportion of obese patients who have VTE or AF need to use DOACs for anticoagulation, there is a conflicting evidence in terms of rivaroxaban pharmacokinetics (PK) and dosing in the obese population.

We have conducted a three-phase research project to investigate the effect of obesity on the PK and the pharmacodynamics (PD) of rivaroxaban. Phase One was a systematic review that aimed to compile the available evidence regarding rivaroxaban PK in obese vs. non-obese populations, and it revealed that obesity has a variable impact on rivaroxaban PK parameters. Phase Two was a pharmacoepidemiologic retrospective cohort study that investigated prescribing trends and clinical outcomes

based on BMI categorization in patients who received rivaroxaban. The findings revealed that rivaroxaban prescribing trend had increased significantly from 2015 to 2020. Furthermore, morbidly obese patients receiving rivaroxaban therapy were at a significantly higher risk of all-cause mortality compared with lower BMI categories. Finally, Phase Three was a prospective, parallel-group, single-dose, fed-state controlled clinical PK and PD study that included healthy male subjects who were assigned in one of two groups: obese subjects with BMI $\geq$35 kg/m^2 and normal-weight control subjects with BMI of 18.5 to <25 kg/m^2. After administration of a single oral dose of rivaroxaban 20 mg, nine blood samples and multiple urine samples were collected over 48 hr, and the samples were analyzed using ultra-performance liquid chromatography coupled with tandem mass spectrometer to obtain rivaroxaban concentrations. The findings revealed that the pharmacokinetic parameters, including, maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration vs. time curve from zero to 48 hr (AUC_{0-48}) and from zero to infinity (AUC_{0-inf}), elimination rate constant (k_e), half-life ($t_{1/2}$), mean residence time (MRT), apparent volume of distribution (V_d/F), apparent clearance (Cl/F), and fraction of dose recovered unchanged in urine over the urine collection period (f_e), as well as the pharmacodynamic parameters (prothrombin time [PT], international normalized ratio [INR], and activated partial thromboplastin clotting time [aPTT]) were mostly similar in obese compared to non-obese subjects.

Overall, the results suggest that the standard dosing regimen of rivaroxaban may be applied uniformly across both obese and non-obese subjects, eliminating the need for rivaroxaban dose adjustments based on body weight. The findings of the last phase can be complemented by robust PK studies in diseased populations and using multiple doses of rivaroxaban.

DEDICATION

I dedicate this work to my cherished husband Osama, to my loving parents (Entisar

and Omar), and to my adorable children (Lujain, Tamim, Juman, and Joud) whose

support, understanding, kindness, unwavering sacrifices and care have been my

steadfast anchor during these challenging years.

Finally, to the brave souls who made the ultimate sacrifice in Gaza Strip, this is for

you!

"إِنْ أُرِيدُ إِلَّا الْإِصْلَاحَ مَا اسْتَطَعْتُ ۚ وَمَا تَوْفِيقِي إِلَّا بِاللَّهِ ۚ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ" سورة هود, 88

I only intend reform as much as I am able. And my success is not but through
Allah. Upon him I have relied, and to Him I return. (Hud, 88)

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with high rates of morbidity and mortality, and poses a considerable burden on healthcare systems globally [1-3]. VTE is a leading cause of hospital admission and mortality [4, 5], with 10 million hospital-associated incidences of VTE reported every year [2, 6]. The huge cost and burden that VTE causes globally cannot be underestimated. For example, the cost of VTE treatment in the United States of America (USA) was estimated to be approximately US$10 billion (US$9,407 to US$28,353 for single VTE episode) between 2012 and 2016 [7]. Similarly, atrial fibrillation (AF) is the most common sustained heart arrhythmia and is highly prevalent [8, 9]. According to a recent report by the European Society of Cardiology, AF affects an estimated 100 million people worldwide, resulting in a significant increase from previous estimates [10, 11].

On the other hand, obesity is a growing burden on healthcare systems worldwide. In 2016, an estimated 650 million adults worldwide were obese, representing approximately 13% of the global adult population [12], and the next decade is likely to witness a considerable rise in obesity, as it is estimated that 50% of the population would be obese/overweight by the 2030 (10% would fall under the category of morbid obesity) [13]. Moreover, many studies have reported that obesity is a risk factor for VTE [14-17], and suggested that the prevalence of VTE and AF is increasing, partly due to an aging population and an increase in certain risk factors such as obesity and others [18-22].

The risk of VTE recurrence is also high, especially in the absence of secondary preventive therapies [23, 24]; thus, the treatment of patients at risk with appropriate

anticoagulants is the optimal way to decrease morbidity and mortality [4].

In 2010, the direct oral anticoagulants (DOACs) were introduced as therapeutic alternatives to vitamin K antagonists such as warfarin, and were indicated for the prevention and treatment of several thromboembolic conditions [25, 26]. The choice of DOACs is favored largely due to their superior safety profile and other advantages, including, limited interactions with food and other drugs, predictable pharmacokinetics (PK) and pharmacodynamics (PD), which allow for fixed dosing, and therefore less required monitoring and follow-up [27-32]. Clinical studies suggest that these agents were associated with lower mortality and less severe intracranial hemorrhage when compared with warfarin [33-35]. Accordingly, over the last decade, the prescription of DOACs has surpassed other long-standing anticoagulants [36]. DOACs are indicated for the prevention/treatment of DVT and PE [37], as well as for lowering the risk of stroke and embolism in non-valvular atrial fibrillation (NVAF) [38, 39]. Due to similar efficacy and lower bleeding risks, the current clinical practice guidelines recommend the use of DOACs over warfarin in patients with NVAF for stroke and thromboembolism prevention [40].

Rivaroxaban is one of the DOACs and it directly inhibits factor Xa, which is a key factor in the coagulation pathway [41]. The use of rivaroxaban, as an alternative anticoagulant, is rapidly increasing in clinical practice and has rapidly become one of the drugs of choice for anticoagulation therapy in secondary care [42]. Rivaroxaban is administered orally, in fixed doses, with a few documented drug-drug and drug-food interactions, and possesses predictable PK and PD profiles [43]. Although the PK of rivaroxaban is well-established in healthy and diseased individuals with normal body weight, prospective controlled studies to establish the PK profile and thus its effective dosing regimen in extreme obesity patients (BMI >40 kg/m^2 or weight >120 kg) are

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still lacking [44, 45]. During rivaroxaban drug development, several studies were conducted to investigate the PD profile of rivaroxaban [46, 47]; however, only a few studies were published with a focus to its PK profile [48, 49]. The PD studies found that rivaroxaban was an effective anticoagulant among obese/morbidly obese patients, with no signs of stroke or systemic embolism reported [50-53]. However, studies investigating the effect of obesity on rivaroxaban PK and its potential adverse effects in long-term therapy among the obese population are still limited [53]. Some case reports have documented that obese patients developed stroke or PE during their long-term dabigatran anticoagulation therapy [54, 55]. This has raised a serious concern about the efficacy of DOACs, including rivaroxaban, as they may fail to achieve the desired anticoagulant activity in obese patients. Moreover, the fact that some old anticoagulants such as heparin are given in weight-adjusted manner for patients, has increased the uncertainty about whether this should also be the case for DOACs when treating obese patients or not [53, 56].

The PK of rivaroxaban following administration of a single 10 mg oral dose in healthy individuals has been described [57]. A maximum plasma rivaroxaban concentration ($C_{max,}$) was reached after 4 hours (t_{max}) [57]. An increase in the C_{max} and the area under plasma concentration vs. time curve (AUC) values was proportional to rivaroxaban doses of $\leq$10 mg (but not with higher doses, where the increase was reported to be less than proportional) [57]. While the absorption of rivaroxaban was not affected by the fed and fast states at $\leq$10 mg doses (~90%), the bioavailability at higher doses decreased to 66% under fasting conditions -due to the limited aqueous solubility of rivaroxaban- [58] and increased to $\geq$80% under fed states [58]. Rivaroxaban has high (95%) and reversible plasma protein binding, mainly with albumin [59, 60]. Furthermore, PK modelling studies showed that rivaroxaban had low-to-moderate

affinity to peripheral tissues, with a volume of distribution (V_d) of 50 L (0.62 L/kg) [61]. Around 50% of rivaroxaban dose undergoes hepatic metabolism [28], 66% of the resulted metabolites are excreted renally mainly by active secretion via P-glycoprotein and breast cancer resistance protein (BCRP) [62, 63], and 28% of which are excreted through feces [28, 64]. The systemic clearance (Cl) of rivaroxaban is 10 L.h^{-1} (0.14 L.h^{-1}.kg^{-1}) [28], while its elimination half-life ($t_{1/2}$) is around 8.3 h [65].

Rivaroxaban is typically prescribed at standardized fixed doses for general population as the marketing authorization of rivaroxaban does not specify any dose adjustment for obese subjects. Nevertheless, abundant evidence from previous studies showed that this practice would end up with sub therapeutic anticoagulation, and thus recurrency of the thromboembolic event in obese subjects [54, 55, 66, 67]. This substantiates the low anti-factor Xa levels which have been observed in symptomatic VTE and asymptomatic DVT cases in previous studies [66, 68-70], emphasizing the need of a potential dosage optimization in the context of obesity. In obese individuals, PK parameters of some medications - including rivaroxaban [71-73] - could be affected and thus under-dosing or over-dosing would be expected due to changes in the drug exposure and PK profile [74]. Changes in plasma concentrations, however, were less than 25% upon using 10 mg tablet of rivaroxaban in subjects with extreme weights (<50 kg or >120 kg), as reported in the Canadian product monograph of rivaroxaban, and thus no dosage adjustment is recommended [60]. In a meta-analysis that evaluated the impact of body weight on efficacy and safety of DOACs and warfarin, the results suggested that DOACs showed a similar efficacy to warfarin in obese patients [75]. In 2017, a study meta-analyzed 11 randomized control trials (RCTs), aiming to investigate the impact of body weight on outcomes in patients who were receiving fixed doses of DOACs [76]. The study demonstrated that dose adjustment of DOACs, according to

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patients' body weights, was unlikely to improve the safety or efficacy of these agents [76]. Moreover, many attempts have been made to investigate the pharmacokinetics of rivaroxaban in the obese population [77-79]. In their randomized controlled PK study, Kubitza et al. revealed that rivaroxaban PK parameters were comparable between obese and non-obese populations and thus, no weight-based dose adjustments were recommended for extreme weight populations (>120 kg and ≤50 kg) [49]. Similarly, Barsam et al. suggested that body weight has only little impact on rivaroxaban PK profile [48]. On the other hand, Mueck et al. examined the PK profile of rivaroxaban in patients undergoing hip and knee replacement surgeries, and demonstrated that body weight has affected the V_d of rivaroxaban [80]. Furthermore, in a retrospective study, 28% of the morbidly obese patients had their rivaroxaban peak concentration below the 5th percentile of the peak concentration [81]. Several other recent studies aimed to determine rivaroxaban's PK parameters in obese subjects, supporting the theory under clinical dilemma that "the body weight may have an impact on rivaroxaban's PK profile, suggesting a need for dosing adjustment" [78, 79, 82, 83].

1.2 Rationale of the Study

The American College of Chest Physicians (CHEST) guidelines recommended that DOACs can be used effectively and safely in patients with extreme body weights for VTE prevention and treatment; however, these guidelines suggested that larger studies are necessary to confirm the safety and efficacy profiles of DOACs in such population [84-86]. Furthermore, the International Society of Thrombosis and Haemostasis (ISTH) 2016 guidance does not support the use of DOACs in patients with a body mass index (BMI) of >40 kg/m^2 or weight of >120 kg due to the weak evidence driven by lack of adequate clinical data for these specific populations [87]. However,

ISTH has updated its guideline recommendations on DOACs use in extreme obesity in 2021 [88], in which the term 'suggest' reflects a weak guidance statement because of limited existing literature. The statement reads: '*For treatment (or primary prevention) of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight*'. Such controversy among RCTs and guidelines can explain, in part, the physicians' hesitancy in prescribing rivaroxaban for overweight/obese patients for the treatment and prevention of VTE and for stroke and thromboembolism prevention in NVAF [53].

This lack of clinical consensus regarding rivaroxaban dosing in the obese population is largely based on the fact that most of the reported studies on rivaroxaban PK in obese subjects suffer one or more of the following drawbacks: studies performed based on retrospective data [78, 79, 81, 89], based on single time-point concentration measurement which does not allow for full PK profiling [82, 83, 89], conducted using low doses of rivaroxaban [49], based on a small number of obese subjects in the sample [48, 77, 79], missed to report distinctive results [48, 80, 90], had variable dose regimen of rivaroxaban [48, 77, 80, 81, 90], lack a control or comparison group in the study design [48, 77-83, 89], or missed to have PK and the corresponding PD profiles for the same study sample [48, 77, 79, 81-83, 89]. These limitations of the previous PK studies have collectively resulted in an inconclusive evidence about the rivaroxaban PK and PD profiles and dosing regimens in the obese population. Hence, uncertainty remains in clinical practice and standard dosing of rivaroxaban among obese patients is still an area of clinical controversy and therapeutic challenge [48, 71, 73, 88, 91].

To sum up, despite the fact that obesity is one of the risk factors for VTE onset and recurrence in both men and women [15, 92-95] and a large proportion of obese patients who have VTE or AF need to use DOACs for anticoagulation, dosing of

rivaroxaban in obese subjects is yet an area of therapeutic dilemma due to the scarcity of PK clinical studies in this population [96]. Therefore, robust evidence is warranted to guarantee the dose adequacy and to optimize the risk within the obese population [44, 52, 66, 88, 97-100].

Accordingly, we conducted this project to investigate the effect of obesity on the PK and PD of rivaroxaban. We approached this in three distinct phases in this thesis, each building on the previous one and refining our understanding.

Phase 1: A systematic literature review that provided a critical overview of existing knowledge about rivaroxaban dosing in obese patients. This identified data gaps and helped us to compile the available evidence, paving the way for further investigation.

Phase 2: A retrospective cohort study that explored the prescribing pattern and clinical outcomes of rivaroxaban across different BMI categories - including obese patients - in a real-world setting. This phase revealed the practical complexities of using rivaroxaban in obese patients and informed the design of the next phase.

Phase 3: A prospective clinical PK study that investigated the PK and PD of rivaroxaban in obese subjects with BMI $\geq$35 kg/m^2 compared to normal-weight control subjects with BMI of 18.5 to <25 kg/m^2, providing robust evidence for the clinical practice.

1.3 Aim and Objectives

The study aim is to investigate the effect of obesity on rivaroxaban PK and PD profiles. To achieve this aim, the following objectives were designed.

The specific objectives of the research project (based on the phases) were:

- *Phase 1 (Systematic review of rivaroxaban's PK in obese subjects) objectives:*

o   To compile the available evidence and identify the gaps in the literature about rivaroxaban PK in obese subjects.

- *Phase 2 (Pharmacoepidemiologic study of rivaroxaban prescribing and clinical outcomes in different BMI categories) objectives:*

   o   To examine the prescribing trends of rivaroxaban in Qatar, among real-world patients based on BMI categorization.

   o   To evaluate/compare the clinical outcomes of rivaroxaban therapy based on different BMI categories, using real-world data.

- *Phase 3 (Clinical PK study of rivaroxaban in obese subjects) objectives:*

   o   To determine the PK and PD profiles of rivaroxaban in obese subjects with BMI ≥ 35 kg/m^2 compared to normal-weight control participants with BMI of 18.5 to <25 kg/m^2.

1.4 Significance of the Study

This study is significant as it contributed to addressing a critical gap in the current clinical practice regarding the dosing of rivaroxaban in obese population, which remains uncertain due to limited and inconclusive data from previous PK studies. This study has provided robust evidence on the PK and the PD of rivaroxaban in obese subjects compared to normal-weight control subjects, as it is the first clinical PK study that provided a full PK profile of rivaroxaban among obese subjects using a well-designed controlled multiple sampling design and a high therapeutic dose of rivaroxaban (20 mg) -which has not been investigated among obese in the literature- and utilizing the UPLC/MS-MS instrument for rivaroxaban concentration determination.

The pharmacokinetic data generated from this study will enrich the

understanding of the PK of rivaroxaban and thus will facilitate tracking the efficacy changes in obese population that were previously argued in the literature [52, 101]. The study findings are expected to supplement the clinical guidelines [88] which have recommended conducting further controlled studies of rivaroxaban (among other DOACs) in extremely obese population. This would significantly impact the clinical practice, guide the clinicians in the appropriate dosing of rivaroxaban in obese subjects with VTE or AF, and ultimately improve clinical outcomes, including reducing the burden of thrombotic complications in obese individuals.

CHAPTER 2: LITERATURE REVIEW

2.1 Venous Thromboembolism and Atrial Fibrillation

2.1.1 Epidemiology of venous thromboembolism and atrial fibrillation

The development of clots (thrombi) within veins is known as venous thromboembolism (VTE), and it comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is among the leading causes of cardiovascular death globally [3, 102-105], as it has been suggested that the VTE-related death incidences are approximately 60,000-100,000 in USA and 544,000 in Europe annually [106, 107]. Additionally, it has been reported that sudden death occurs as a first symptom in 25% of PE patients [106, 108]. These conditions are highly prevalent as it has been found that VTE affects as many as 1,220,000 individuals annually in the USA [109]. The lowest average VTE incidences has reached 122 per 100 000 patient-years in Asian patients, followed by whites (191 per 100 000 patient-years) and blacks (203 per 100 000 patient-years) [110]. Other studies revealed an occurrence of approximately 762,000 VTE incidences in six countries in Europe (which their total population was 310.4 million) [111].

Studies suggest that the prevalence of VTE is increasing, partly due to the aging population and the increase in certain risk factors such as obesity, hypertension, diabetes, and cancer [18-21]. The annual estimation of VTE incidences in the USA is 1 to 2 per 1000 per year in adults, and this number increases dramatically with age [112]. According to a study which was conducted on two large cohorts, the lifetime risk of VTE after the age of 45 years was 8.1 overall and 10.9 in obese subjects [113]. From clinical point of view, the key demographic risk factors for VTE are age [114], female gender [110, 115], and obesity [116]. Other illness-related risk factors are: acute stroke [117], inflammatory bowel disease [118], hospitalization for acute infection [119],

cancers (which accounts for 20% of all VTE events) [120], surgical procedures (which accounts for another 20% of all VTE events) [121, 122]. After first VTE incidence, recurrence of another VTE incidence or death probabilities are 25%, and this percentage is highly dependent on the existence of underlying risk factors (modifiable vs. non-modifiable factors) [123-125]. VTE and its complications are considered a serious problem that imposes a huge financial burden on the healthcare sector in most countries. It was recently reported that the cost of VTE treatment is around $12,000 to $15,000 per patient per year (VTE-related complications are excluded from this cost) [126]. The cost of patients' readmission (which comprises 18% of the total patients) is about $10 000 per patient [126]. It is evident that VTE is a preventable condition, and thus risk assessment and optimum prophylaxis are crucial for patients [127]. Evidence suggests that the VTE-associated morbidity and mortality are preventable, and that the appropriate use of prophylactic anticoagulants in high-risk patients improves clinical outcomes, reduces hospitalization, and reduces the economic burden [128-130].

Atrial fibrillation (AF) is a prolonged cardiac rhythm abnormality, and it is associated with significant mortality and morbidity from heart failure, stroke, thromboembolism, and quality of life deterioration [131, 132]. It is highly prevalent [10], as it affects an estimated 100 million people worldwide, resulting in a significant increase from previous estimates [10, 11]. Studies have assessed the risk of developing AF. The overall prevalence was found to be 6% (ranging from 1% in individuals aged around 57 years old, to 18% in individuals aged 85 years old) [133], and lifetime risks were found to be one in four for males and females aged 40 years and above [134]. A recent study reported that the worldwide incidence rate of AF has increased by 31% between 1997 and 2017 (37.574 million cases globally), with middle socio-demographic index countries being the most countries which were affected from this

increased burden [135]. Scientific expectations suggest that AF future burden might increase by 60% in 2050 [135]. Multiple risk factors have been shown to contribute to the development and recurrence of VTE, one of which is obesity [136].

2.1.2 Obesity as a risk factor for venous thromboembolism and atrial fibrillation

According to the World Health Organization (WHO), obesity is defined as abnormal or excessive fat accumulation that may impair health [12]. Since 1975, both children's and adults' obesity rates have dramatically increased, and obesity has reached now global pandemic status [12, 137, 138]. Recently, obesity is described as a low-degree chronic inflammation state of adipose tissue [139], which increases mortality and morbidity rates [140]. Obesity has emerged as a significant public health problem that drives up health and economic burdens [141], and has detrimental effects on one's physical and mental well-being [142]. WHO statistics in 2016 indicated that around 1.9 billion adults were considered overweight, of which 650 million were obese [12]. According to the WHO statistics, the current prevalence of obesity is estimated to be 40% [143], 27.8% [144], 35.1% [144], 32% [144] in the USA, United Kingdom (UK), State of Qatar, and in Egypt, respectively. Given the current exponential increasing trend, we would end up with 57% of the adults considered as overweight or obese by 2030 globally [145]. Moreover, the highest level of obesity is expected to be reached by 2054 in the USA and UK, followed by the European countries [146]. Obesity has been identified as being a risk factor for numerous numbers of comorbidities such as: type 2 diabetes mellitus [147], hypertension [148], hyperlipidemia [149], cardiovascular disorders [150], several types of cancer [151]. Furthermore, studies have found that obesity can contribute in the development of many other diseases such as: non-alcoholic fatty liver disease [152], gallbladder disease [153], gout [154], and

others.

In the last few decades, much more information on obesity and its role in cardiovascular disease morbidity and mortality has become available [155]. The association between obesity and VTE is evident from multiple previous studies [14-16]. Hotoleanu 2020 has assessed the risk of VTE associated with obesity, and has demonstrated that obesity is an independent moderate risk factor for VTE [17]. Moreover, obesity/overweight in adulthood has been acknowledged as an important risk factor for developing VTE later in life [156].

For comparison, surveillance, and classifying obesity, body mass index (BMI) is the most accepted and commonly used parameter in clinical practice among adults and children [12, 157]. BMI can be defined as the metric which is used to interpret the height to weight ratio, and thereby measuring the index of fatness for adults and children [158]. An individual with BMI 18.5 - <25 kg/m^2 falls within normal healthy range. Other BMI-based categories of overweight and obesity are shown in Table 2.1.

Table 2.1 Classification of Obesity by Body Mass Index*

BMI (Kg/m^2)	Category
<18.5	Underweight
18.5 to <25	Normal weight
25.0 to <30	Overweight
30 to <35	Obese Class 1
35 to <40	Obese Class 2
≥40	Obese Class 3

* [159, 160]

2.2 Anticoagulants in the Management of Venous Thromboembolism and Atrial Fibrillation

The management of VTE and AF involves pharmacologic and non-pharmacologic therapy, including, but not limited to, anticoagulants, thrombolytics, surgical procedures such as thrombectomy, and other medications such as beta blockers, amiodarone, and anti-arrhythmic agents in the case of AF. The focus of this section is to discuss the anticoagulant management of VTE and AF.

Anticoagulation therapy is a cornerstone and mainstay in the therapeutic management of VTE and AF. Utilizing the appropriate anticoagulation therapy for the prevention and treatment of VTE and AF is the optimal strategy to decrease their associated morbidity and mortality [4]. Historically, unfractionated heparin (UFH) was the first proper anticoagulant that was successfully introduced into clinical use and hence, its efficacy in thromboembolic disorders has long been established [161]. However, UFH dose could be greatly different between patients due to its unpredictable pharmacodynamic effect in response to standard dosing [162], activated platelet and protein binding neutralization of the given dose [163, 164], and rebound coagulation incidences that follow the discontinuation of the drug [165]. A derivative of heparin is the low molecular weight heparin (LMWH), which has several advantages over UFH. It possesses longer-lasting effect, and has better anticoagulation dose-response profile compared to UFH [166], thereby requiring less frequent monitoring of the anticoagulation effect [163, 164]. Remarkably, LMWHs have partially obviated a fatal heparin-induced side effect, thrombocytopenia [167]. Both types of heparins are exclusively injectable medications [168].

For oral anticoagulants, warfarin was the first to be discovered and approved for clinical use, and it is still among the most used 100-medication list globally [169, 170].

Warfarin needs careful dose adjustment and close monitoring to achieve the needed coagulation level due to inter-patient pharmacogenetic variability in metabolism, significant drug-drug and drug-food interactions [171, 172], and narrow therapeutic index [173]. Notwithstanding the aforementioned disadvantages of warfarin, it is the drug of choice in many clinical situations where other anticoagulants cannot be used [174].

Due to their considerable effectiveness and safety, the aforementioned conventional anticoagulants have been incorporated into guidelines and adopted as a standard of care for VTE and AF management over a very long time. However, due to their unpredictable PK and PD and other drawbacks listed above [163, 173, 175, 176], the development of novel classes of anticoagulants was deemed necessary.

Direct oral anticoagulants (DOACs), also called non-vitamin K oral anticoagulants and/or novel oral anticoagulants, have been introduced for clinical use since 2010. DOACs can be categorized into direct factor Xa inhibitors (i.e., rivaroxaban, apixaban, edoxaban, and betrixaban) and direct thrombin inhibitors (i.e., dabigatran). Due to their advantages, DOACs have overcome many of the limitations of the conventional anticoagulant. Such advantages include: the predictable PK and PD profiles which allow for fixed dosing with a limited need for monitoring, minimum drug-drug and drug-food interactions, and rapid onset and offset of actions. Compared to conventional anticoagulants, DOACs have proven superior efficacy enhanced outcomes, lower mortality, and lower bleeding risks [33, 35, 40, 177-179]. Consequently, DOACs are widely replacing the standard therapy of anticoagulation in clinical practice.

2.3 Rivaroxaban

Rivaroxaban is one of the most widely used DOACs in clinical practice [180]. Rivaroxaban is 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide (Figure 2.1), with a molecular formula $C_{19}H_{18}ClN_3O_5S$ [181]. The active rivaroxaban which exhibits a strong inhibitory activity against factor Xa is the pure (S)-enantiomer (Xarelto®), and the (R)-enantiomer is almost inactive. Rivaroxaban is odorless, non-hygroscopic, and white to yellowish powder. It has low lipophilicity when compared to other DOACs (apixaban, betrixaban and dabigatran), with a computed log P value equals to 1.5 (P is the partition coefficient of the molecule in octanol/water system) [28]. According to the biopharmaceutical classification system (BCS), rivaroxaban is classified as class 2, which includes low solubility and high permeability drugs [182]. In addition, rivaroxaban has a topological polar surface area of 116 $Å^2$, molecular weight of 435.89 g/mole, six hydrogen bond acceptor and one hydrogen bond donor, which collectively contribute to its favorable membrane permeability and thus an enhanced bioavailability [60, 183, 184]. The drug is practically insoluble in water/aqueous solutions (10 mg/L at 25 °C), very slightly soluble in some organic solvents (such as acetone), and freely soluble in other organic solvents (such as dimethyl sulfoxide, dimethylformamide, acetonitrile, chloroform) [183, 185, 186].

Rivaroxaban is a potent anticoagulant, which exerts its action by direct, selective, and reversible inhibition of free, prothrombinase-bound, and clot-associated activated factor Xa, which is generated by both intrinsic and extrinsic coagulation pathways and thus plays a central role in the coagulation process [187, 188]. By inhibiting factor Xa, thrombin generation will be prevented, which will stop the coagulation process completion [187] (Figure 2.2). Inhibition of factor Xa by

rivaroxaban is highly selective, dose-proportional, and concentration-dependent [28, 187, 189].
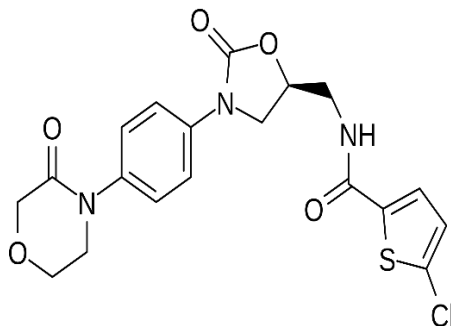
Figure 2.1. Rivaroxaban chemical structure [181]

Since 2011 onwards, rivaroxaban has been approved by the USA's Food and Drug Administration (FDA) with different doses (2.5 mg, 10 mg, 15 mg, and 20 mg) for the following indications [60, 190, 191]):

- Treatment of VTE (DVT and PE) and prevention of their recurrence in patients at continued risk.

- Prophylaxis for DVT incidences (which might cause PE) following elective total hip or knee replacement surgery (it was the first oral direct Xa inhibitor approved for this purpose).

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), in whom anticoagulation is appropriate.

- Treatment and prevention of VTE incidences in pediatric patients (from birth to less than 18 years).

- Prevention of VTE in hospitalized acutely-ill patients, who are at risk for thromboembolic complications.

- As an add-on to clopidogrel or acetylsalicylic acid, rivaroxaban is used for:

- o prevention of stroke, myocardial infarction, cardiovascular death, and acute limb ischemia in patients with coronary artery disease with or without peripheral artery disease.
- o prevention of major thrombotic vascular events in patients with peripheral artery disease who are at high risk of major adverse limb events or major adverse cardiovascular and/or cerebrovascular events.

The efficacy and safety of rivaroxaban have been extensively investigated during the last decade. A study was conducted to compare efficacy and safety of rivaroxaban with warfarin for stroke prevention in NVAF patients, and the findings have revealed that rivaroxaban was non-inferior to warfarin for the prevention of systemic embolism or stroke ($p < 0.001$) [192]. Moreover, the study has shown that the rates of intracranial bleeding and fatal bleeding were significantly lower in those who received rivaroxaban therapy. However, there was a significant increase in major gastrointestinal (GI) bleeding in the rivaroxaban arm ($p < 0.001$), although there was no difference in all-cause mortality [192]. Furthermore, findings from a study which was conducted to assess the use of 2.5 or 5 mg twice daily of rivaroxaban in acute coronary syndrome, showed a significant reduction in death rates from cardiovascular causes, as well as higher rates of major bleeding incidences in rivaroxaban group; however, no statistically significant differences in fatal bleeding [193]. A large recent study has highlighted the superior efficacy and safety of rivaroxaban compared to warfarin in NVAF cohort [194]. It was found that patients in the rivaroxaban arm had less ischemic stroke/systemic embolism, less major bleeding, and less all-cause mortality risks compared to the warfarin arm [194]. In addition, one retrospective study had investigated the associated effectiveness, safety and persistence of rivaroxaban vs. warfarin among real-world patients [195]. The study demonstrated a significant VTE

events reduction among patients who received rivaroxaban therapy compared to those on warfarin ($p < 0.0001$) [195].

The major side effect of rivaroxaban is bleeding that can be managed by Andexanet (a recombinant factor Xa molecule that binds to rivaroxaban), which is the clinically approved antidote to be used to reverse rivaroxaban action in such emergency medical circumstances [196, 197]. Before starting rivaroxaban therapy for a particular patient, baseline coagulation status must be determined [198]. In addition, liver and kidney function at baseline must be assessed and documented for any future potential dose adjustment due to liver or kidney impairment [60]. Regular monitoring for coagulation level is not required during rivaroxaban therapy [198]. However, assessing the achieved anti-coagulation effect is still necessary in some cases and/or populations such as in case of urgent surgery, uncontrolled or life-threatening bleeding, recurrence of thrombosis while the patient is on-therapy, patients who are extreme in age or weight, and patients with impaired liver or kidney functions [60, 199-201]. At present, the therapeutic range of rivaroxaban is not proven, and the anti-Xa drug-level assay is not yet calibrated against rivaroxaban [197]. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests are not the gold standard tests to assess the anticoagulation activity of rivaroxaban as they are not reliably sensitive for rivaroxaban presence. Nevertheless, they are used in clinical practice to confirm the presence of anticoagulation effect and/or patient adherence, which can both inform medical decisions [201, 202]. The preferred approach to determine the anticoagulation activity of rivaroxaban is to conduct the commercially available chromogenic anti-Xa assay that is calibrated specifically for rivaroxaban using rivaroxaban calibrators [203, 204]. One accurate technique to quantify rivaroxaban reliably and accurately in patients' blood or urine samples are mentioned in the coming sections.
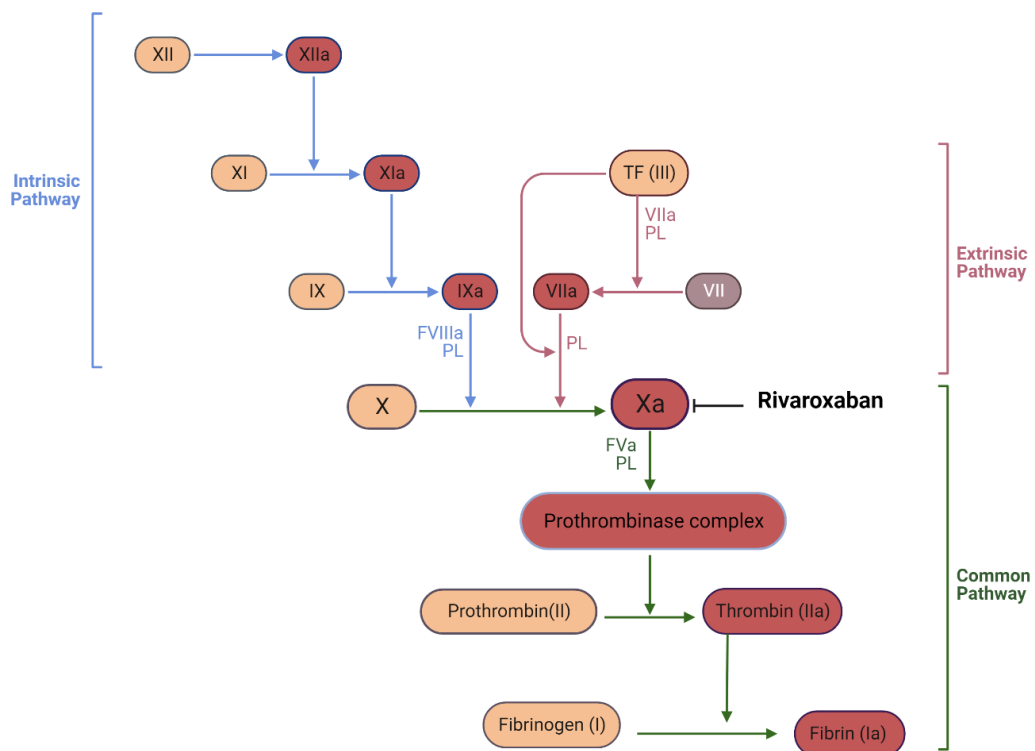
Figure 2.2. Site of rivaroxaban action in the coagulation cascade; Figure created in BioRender.com by Majdoleen Alalawneh

2.4 Pharmacokinetic Profile of Rivaroxaban in Normal Subjects

The pharmacokinetic profile of rivaroxaban in healthy subjects has been widely investigated during the early clinical phases of rivaroxaban development [205]. Rivaroxaban has predictable (dose-proportional) pharmacokinetic as well as pharmacodynamic profiles [57, 206]. It is absorbed rapidly from stomach after oral dose administration to achieve its maximum plasma concentration (C_{max}) in 2-4 hrs (t_{max}), and its half-life ($t_{1/2}$) ranges from 7 to 11 hrs in young subjects, and 11–13 hrs in elderly subjects [60, 207]. Rivaroxaban bioavailability is reported to be dose-dependent, and it varies according to the given dose. After administration of low doses of rivaroxaban (10 mg or lower), the attained bioavailability is high and can be complete (ranges from

20

80 to 100 %), with no effect of food intake [57]. However, a lower bioavailability (~66%) is reported after the administration of higher doses of 15 or 20 mg under fasting state [28]. For higher therapeutic doses of rivaroxaban (15 mg or 20 mg), fed state was found to enhance the bioavailability by 39% and thus, rivaroxaban therapeutic doses should be administered with food [28]. Bioavailability of rivaroxaban varies according to the site in which it is released within the gastrointestinal tract (GIT), and this is largely due to the changes in PH across the GIT which will affect rivaroxaban ionization [58, 60]. A reduction of 29% in exposure - indicated by AUC - was reported when rivaroxaban was released in the proximal small intestine, and a higher reduction was reported when rivaroxaban was released in the distal small intestine [60, 208].

Rivaroxaban binds reversibly and extensively (up to 95%) to plasma albumin which is the main binding component, and it has relatively low-to-moderate affinity to peripheral tissues, which explains the moderate steady state volume of distribution (V_d) value of 50 L (0.62 L/kg) for rivaroxaban [28]. About one-third (36%) of an administered rivaroxaban dose is recovered as unchanged drug in the urine. The unchanged drug is excreted mainly via active urinary secretion by P-glycoprotein (P-gp) and breast cancer resistance protein (ABCG2), and to a lesser extent by glomerular filtration [28, 209, 210]. The remaining two-thirds of the administered rivaroxaban dose undergoes hepatic metabolism; either via oxidative degradation of the morpholinone moiety by cytochrome P450 enzymes - particularly CYP3A4 and CYP2J2 - or through non-CYP-mediated amide bond hydrolysis [28, 60]. Half of the total resulted metabolites are excreted in urine, half by the hepatobiliary route, and no active circulating metabolites have been detected for rivaroxaban (Figure 2.3) [28, 60]. In summary, about 66% of rivaroxaban administered dose is excreted in urine (36% as active unchanged drug and 30% as inactive metabolites), while about 28% is eliminated

in feces (7% as unchanged active drug and 21% as inactive metabolites). As rivaroxaban is a substrate for P-gp and CYP3A4 enzymes, the co-administration of both CYP3A4 and P-gp strong inhibitors (e.g. cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir) is contraindicated while using rivaroxaban [28, 189, 210]. Regarding clearance, rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration [28, 189]. The aforementioned pharmacokinetic properties are for general population, and thus caution must be exercised when it comes to special populations pharmacokinetics (e.g. elderly patients, obese patients, and patients with renal or hepatic impairment) [211, 212].
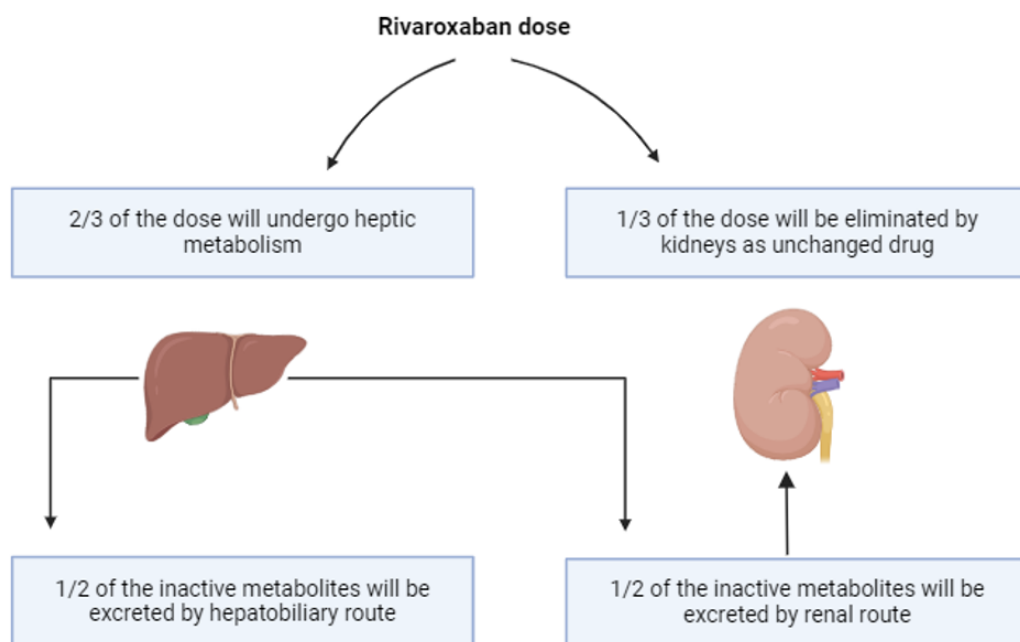
Figure 2.3. Elimination routes of rivaroxaban. Figure created in BioRender.com by Majdoleen Alalawneh

2.5 Pharmacokinetic Profile of Rivaroxaban in Obese Individuals

Some physiological processes are known to be influenced by obesity, including

gut permeability and gastric emptying time [213, 214]. In addition, cardiac output, the entire blood volume, and capillary flow are increased to provide nutrients and oxygen to the excess fat tissue in obese patients [215]. Based on the increase in the cardiac output, the blood flow to the liver will be increased too, and this is noted as ''short-term'' effect [216]. However, blood flow to the liver was noted to decline over long-term due to non-alcoholic fatty liver disease, which is a characteristic of morbidly obese individuals [217]. Similarly, glomerular filtration rate (renal clearance) is noted to be elevated initially due to the increased hyperfiltration of kidneys, and to be decreased at later stages due to the prolonged increase in the intra-glomerular pressure [218, 219]. An increasing number of studies have reported the potential changes in the PK processes - and thus PK parameters - in obesity. The following are examples of the potential impact of obesity on pharmacokinetic processes.

Although the evidence of obesity effect on *absorption* is inconsistent across the literature, the overall absorption process is affected by obesity by increasing the gut permeability and gastric emptying time [213, 214, 220-222]. Similarly, drug *distribution* is dependent on its physicochemical properties, ionization status, and protein binding [223, 224], which might be influenced by the obesity (excessive fat tissue in the body). Theoretically, as the fat tissues increase in the body, the V_d for a lipophilic drug would be increase. Although this idea has been emphasized previously for certain medications [225], many studies have shown that lipophilicity does not necessarily predict the change of V_d in obese subjects [226, 227]. Across the literature, tissue penetration for drugs, which is reflected by lipophilicity, has been investigated; For instance, peak and trough plasma concentrations of ciprofloxacin – which was given intravenously- were measured among 12 obese and 12 matched normal-weight subjects, aiming to investigate the need for dose-adjustment in obese subjects [228].

The results showed that trough plasma concentrations were higher significantly in obese compared to normal-weight subjects. However, the tissue penetration (indicated as AUC tissue/AUC plasma) was lower significantly in the obese subject, while interstitial fluid concentrations were similar for both groups, implying the need for ciprofloxacin dose adjustment according to body weight [228]. Brill, Houwink et al. (2014) has shared similar findings for cefazolin in morbidly obese patients, as the penetration ratio has found to be lower in obese subjects compared to non-obese [229]. Moreover, previous studies have extensively assessed the impact of obesity on total plasma protein concentration, and the fraction of bound to unbound drug [230-232]. One study has demonstrated that alpha 1-acid glycoprotein concentration was doubled among the morbidly obese compared to control non-obese female subjects [233]. On contrary, a reduction in albumin concentration has been observed in a study of propranolol in obese subjects [234]. Furthermore, an elevation of albumin and alpha 1-acid glycoprotein were reported in a study that has assessed the plasma protein alteration in obese children [235].

It is a well-known fact that drug elimination impacts drug dosage regimens [236, 237] and thus, the impact of obesity on liver and kidney, which are the main eliminating organs [236], was investigated thoroughly across the literature, and the findings varied among different drugs. For drugs that are metabolized in the liver, it is difficult to predict the changes in metabolism rate/extent due to other confounding factors that might affect the metabolism process, i.e., blood flow, liver size, extraction ratio of the drug, and duration of obesity [238]. Regarding renal excretion, the influence of obesity is also complex and bear opposite effects, i.e., enhancing the renal elimination function, and contributing into renal chronic conditions that may progress with time [239, 240].

Considering the earlier points, potential changes in rivaroxaban PK might be

observed in obese population. Although some PD studies found that rivaroxaban was an effective anticoagulant agent among obese/morbidly obese patients, with no signs of stroke or systemic embolism reported [50, 52, 53], studies investigating the effect of obesity on rivaroxaban PK and its potential adverse effects in long-term therapy among the obese population are still limited [53]. A study by Kubitza et al. in 2007 was one of the first studies which investigated the PK of rivaroxaban in extreme weight subjects [49]. The study concluded that rivaroxaban was tolerated by extreme weight subjects (>120 kg and ≤50 kg), compared to normal weight subjects, and the PK and PD were not influenced by body weight to an extent considered likely to be clinically relevant [49].

Another study was carried out in 2008 to generate a population PK model for rivaroxaban and the results reported a minor effect of BMI on the PK parameters of rivaroxaban [80]. In 2017, Barsam et al. developed a PK model for rivaroxaban based on real-world data, and the model had shown that weight and creatinine clearance were the two significant covariates affecting the model, although weight has only a slight effect [48]. Afterwards, Piran et al. in their retrospective study in 2018 found that 28% of the obese subjects (>120 kg) in the study had C_{max} values below the 5th percentile of the peak concentration [81], which might be clinically relevant in long-term therapy. In addition, a global population PK model study by Willmann et al. in 2018 involving data pooled from 27 countries, concluded that renal function (mainly), age, body weight, and use of comedication have affected the total exposure of rivaroxaban [90].

The aforementioned rivaroxaban PK studies in obese population have suffered one or more of the following drawbacks: (1) performed based on retrospective data [78, 79, 81, 89], (2) based on single time-point concentration measurement, which does not allow for full PK profiling [82, 83, 89], (3) conducted using rivaroxaban sub-therapeutic

doses [49], (4) based on a small number of obese subjects in the sample [48, 77, 79], (5) missed to report distinctive results [48, 80, 90], (6) used variable rivaroxaban dosing regimen [48, 77, 80, 81, 90], (7) lack a control or comparison group in the study design [48, 77-83, 89], or (8) missed to have PK and the corresponding PD profiles for the same study sample [48, 77, 79, 81-83, 89]. The divergent PK profiles exhibited by these studies, and the absence of a strong evidence from well-designed controlled prospective clinical PK studies on this topic have led to a lack of consensus on this matter and contribute to the variability of recommendations in different clinical practice guidelines [40, 88, 98, 241].

CHAPTER 3: METHODS

3.1 Methods for Phase One – Rivaroxaban Pharmacokinetics in Obese Subjects: A Systematic Review

A systematic review was conducted in an effort to compile the available evidence on rivaroxaban PK in obese population relative to non-obese population and to identify the existing gaps in knowledge. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for conducting and reporting this systematic review [242, 243]. The review protocol was registered in PROSPERO database (CRD42020177770).

3.1.1 Data sources and search strategy

Five electronic bibliographic databases and systematic review applications (PubMed, Embase, ScienceDirect, Cochrane Library, and Rayyan) were systematically searched by the authors from 1 May 2021 to 28 February 2022 [244, 245]. The following keywords were used to search the databases: "rivaroxaban" or "BAY 59-7939" or "anticoagulant" AND "pharmacokinetics" or "half-life" or "concentration" or "volume of distribution" or "bioavailability" or "clearance" AND "obesity" or "obese" or "overweight" or "extreme weight" or "BMI" or "body mass index" (Table 3.1). The keywords and search strategies were customized according to each bibliographic database and using specific indexing terms as appropriate. Limits and filters such as language and human studies were applied according to the functionalities and features of each database. The reference lists of the identified studies were manually reviewed to identify any potentially missed studies from the aforementioned electronic search. Furthermore, the grey literature was searched for any missing non-indexed or unpublished studies.

The search results from the targeted databases were combined, duplicates were

removed, and the reminder of the identified studies were screened based on their titles and abstracts. The pre-specified eligibility criteria were used to assess the identified studies from the databases. Any doubt about a study during title/abstract screening was resolved by conducting a full-text reading by the authors. Articles that were potentially eligible underwent full-text screening. This was achieved by two independent reviewers (MA and OR) and discrepancies were resolved through consensus and adjudication by a third reviewer (AA), whenever necessary. Finally, studies that fulfilled the eligibility criteria were included in the systematic review.

Table 3.1 Detailed Keyword Search in Each Database

Database	Keywords used for search
PubMed	(Rivaroxaban) OR (BAY 59-7939) OR (anticoagulant) AND (Pharmacokinetics) OR (half-lfe) OR (concentration) OR (volume of distribution) OR (bioavailability) OR (clearance) AND (Obesity) OR (obese) OR (overweight) OR (extreme weight) OR (BMI) OR (body mass index)
Embase	'rivaroxaban'/exp OR rivaroxaban OR (bay AND '59 7939') OR anticoagulant AND 'pharmacokinetics'/exp OR pharmacokinetics OR 'half life' OR 'concentration'/exp OR concentration OR 'volume of distribution' OR (('volume'/exp OR volume) AND ('distribution'/exp OR distribution)) OR bioavailability OR clearance AND 'obesity'/exp OR obesity OR obese OR 'overweight'/exp OR overweight OR 'extreme weight' OR (extreme AND ('weight'/exp OR weight)) OR bmi OR (body AND mass AND index)
ScienceDirect	((Rivaroxaban) OR (BAY 59-7939)) AND ((Pharmacokinetics) OR (half-lfe) OR (concentration) OR (volume of distribution)) AND ((Obesity) OR (obese) OR (body mass index))

Database	Keywords used for search
Cochrane Library	Rivaroxaban OR BAY 59 7939 OR anticoagulant AND Pharmacokinetics OR half-life OR concentration OR volume of distribution OR bioavailability OR clearance AND Obesity OR obese OR overweight OR extreme weight OR BMI OR body mass index

3.1.2 Eligibility criteria and studies selection

This review included studies that investigated rivaroxaban PK in obese subjects who were healthy or diseased. Studies were included in the review if they fulfilled the following criteria: investigating rivaroxaban PK in obese (with BMI ≥30 kg/m^2 or body weight >120 kg) and/or overweight (with BMI 25-29.9 kg/m^2) subjects (including those studies that included mixed obese/overweight and normal weight subjects, referred as general population in this systematic review), being an original investigation, and involving subjects aged 18 years or older. Studies were excluded if they involved non-human subjects (e.g., animal studies), or were case studies, commentaries, reviews, expert opinions or topic discussions, guidelines, editorials, conference abstracts, or were written in non-English language.

3.1.3 Methodological quality assessment

Two reviewers (MA and AA or OR) independently conducted the risk of bias assessment, and any differences were resolved through consensus by the research team. Two different appraisal tools were used to assess the methodological quality of the selected studies: the Crowe Critical Appraisal Tool (CCAT) and the Critical Appraisal of Clinical Pharmacokinetic Studies (CACPK) tool [246-248]. The CCAT tool was chosen to be used as it was designed to assess the quality of varying types of research

designs. It consists of two main parts: the CCAT checklist which was filled for each included study, and the CCAT user guide that was used along with the checklist to ensure consistency of the scoring [246, 247]. The CCAT is a score-based instrument that provides a composite quantitative score of a study's quality. It consists of eight categories: preliminaries, introduction, design, sampling, data collection, ethical matters, results, and discussion. Each category contains multiple items that are scored as present, absent, or not applicable, while the overall category is scored on a scale of $0-5$ (0, no evidence; 5, high evidence). Consequently, the total maximum obtainable quality score is 40, which can be converted to a percentage score.

On the other hand, the CACPK tool is specifically designed to assess the quality of clinical pharmacokinetic studies. It consists of 21 questions, which assess the background (2 questions), study design and experimental methods (15 questions), applied statistics (1 question), and results (3 questions) of a study. In addition to the tool, two appendices were used to guide in answering some specific questions within the 'study design and experimental methods' section of the CACPK tool. Each question has a rating scale of yes, no, I do not know, and not applicable [248].

3.1.4 Data extraction and synthesis

The data extraction was performed by one reviewer (MA) and independently verified by one other reviewer (OR or AA). A final reconciled version of the extracted data was achieved. From each included study, relevant data were extracted, including: first author's name, publication year, country of the study, study design, study groups (if any), sample size, general demographics (e.g., baseline age and gender distribution of the study population), clinical conditions, anthropometric parameters (body weight and/or BMI), rivaroxaban dosage regimen, PK model and parameters, and outcomes of

the study.

The included studies were observed in terms of their characteristics. Due to heterogeneity in terms of study design, PK model, population studied, and variability in the type of PK parameters determined, meta-analyses of the PK parameters was not feasible. Consequently, we applied a narrative approach to data synthesis. We compared between different studies in terms of PK parameters reported and other important key variables.

3.2 Methods for Phase Two – Trends in Prescribing and Outcomes in Obese Versus Non-Obese Patients Receiving Rivaroxaban Therapy: A Retrospective Observational Study Using Real-world Data

A pharmacoepidemiologic study was conducted to examine the prescribing trends of rivaroxaban in patients of different BMI categories (i.e. obese vs. non-obese) and to compare the clinical outcomes of the rivaroxaban therapy in these patients, using real-world data.

3.2.1 Study design and setting

This was a retrospective cohort study involving patients of different BMI categories who were prescribed rivaroxaban therapy at Hamad Medical Corporation (HMC) from 2015 to 2020. HMC is the principal public healthcare provider in the State of Qatar and consists of 12 general and specialized hospitals. HMC facilities deliver medical services to more than 80% of the population in Qatar [249]. The study data were obtained from all of the HMC facilities where patients received rivaroxaban therapy.

3.2.2 Study subjects

All adult patients (aged ≥18 years) who were prescribed rivaroxaban therapy, either as in-patients or outpatients from 1 January 2015 to 31 December 2020, were eligible for inclusion in the study. Patients were stratified by two dimensions: BMI and year of rivaroxaban therapy prescription. For BMI stratification, patients were classified into six categories: under-weight (<18.5 kg/m^2), normal weight (18.5 to 24.99 kg/m^2), overweight (25 to 29.99 kg/m^2), obese class 1 (30 to 34.99 kg/m^2), obese class 2 (BMI of 35 to 39.99 kg/m^2), and obese class 3 (≥40 kg/m^2). Per calendar year, patients who had multiple refill prescriptions were counted only once.

3.2.3 Sample size and sampling technique

For the study sample analyses, universal sampling (i.e. whole population sampling) was used. Thus, all eligible patients (adult patients at HMC who received rivaroxaban therapy from 1 January 2015 to 31 December 2020) were included in the study. Consequently, sample size determination and sampling technique were not warranted in this study.

3.2.4 Data collection procedures

Data were collected from 5 August 2022 to 9 February 2023. The following data were extracted from HMC's electronic medical record system, CERNER: patient demographics, baseline clinical characteristics, rivaroxaban-related data (i.e. clinical indication for rivaroxaban use, rivaroxaban dosage regimen, rivaroxaban starting and discontinuation/switching dates), and clinical outcomes of interest (i.e. bleeding, occurrence/recurrence of DVT, PE, stroke, and all-cause mortality). The data were collected by reviewing all prescription records of rivaroxaban and associated clinical notes documented during hospitalization, outpatient clinic visits, or emergency visits to

any HMC facility, since all facilities within HMC have an integrated electronic system (i.e. CERNER). All relevant data were manually extracted using a pre-tested data collection form. All missing data were indicated in the results section and relevant tables.

3.2.5 Outcomes measures

The study's outcome measures include the following: the number of annual rivaroxaban prescriptions from 2015 to 2020; major/minor bleeding events according to International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria [250, 251]; thrombotic events (stroke, DVT and PE) and; all-cause mortality. Each patient was retrospectively followed for at least one year after initiation of rivaroxaban therapy, or until mortality occurred. Furthermore, retrospective follow-up was continued until determination of lost to follow-up, or until the end of the study (i.e. end of data collection from the electronic system in February 2023). All outcomes were calculated for the total study sample and compared according to the different BMI groups.

3.2.6 Study covariates

The results of safety and effectiveness outcomes of rivaroxaban therapy based on BMI categorization were adjusted for clinically relevant demographic-related, disease-related and medication-related variables that were associated with thromboembolic diseases, including: gender, nationality of origin, age, BMI, smoking status, number of co-medications, diabetes, hypertension, dyslipidemia, coronary artery disease (CAD), anemia, liver disease, kidney disease, and duration on rivaroxaban therapy [252-257].

3.2.7 Statistical analyses

Data analyses were performed using IBM Statistical Package for Social Sciences (IBM SPSS Statistics for Windows) version 28 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean±SD, while categorical variables were expressed as proportions and percentages. Descriptive statistics were applied to explore the trends of annual rivaroxaban prescribing and across the BMI subgroups. The rivaroxaban prescribing trends between BMI groups were compared using Chi-square test. Similarly, clinical outcomes (incidences of bleeding, DVT, PE, stroke, or all-cause mortality) were compared between BMI groups using Chi-square test.

Multivariate and univariate analyses were conducted to examine the effect of BMI on outcomes of therapy (bleeding, DVT, PE, stroke, and all-cause mortality incidences), while controlling for predetermined confounding variables (gender, nationality, age, BMI, smoking status, number of co-medications, diabetes, hypertension, hyperlipidemia, coronary artery diseases, anemia, liver disease, kidney disease, duration on rivaroxaban therapy). All the study variables (gender, nationality, age, BMI, smoking status, number of co-medications, diabetes, hypertension, hyperlipidemia, coronary artery diseases, anemia, liver disease, kidney disease, duration on rivaroxaban therapy) were first tested for association with clinical outcomes using univariate analysis. Variables with p-value of less than 0.2 were included into multivariate logistic regression models to investigate the predictors of the study outcomes (bleeding, DVT incidence, PE incidence, stroke incidence, and all-cause mortality). For all analyses, $p < 0.05$ was considered statistically significant.

3.3 Methods for Phase Three – Pharmacokinetics and Pharmacodynamics of Single Dose Rivaroxaban under Fed State in Obese vs. Non-Obese Subjects: An Open-Label Controlled Clinical Trial (RIVOBESE-PK)

A prospective clinical PK study was conducted in order to provide robust evidence for clinical practice. The study investigated the PK and PD of rivaroxaban in obese subjects with BMI ≥ 35 kg/m^2 compared to normal-weight control subjects with BMI of 18.5 to <25 kg/m^2.

3.3.1 Study design and setting

RIVOBESE-PK is a non-randomized, controlled, open-label, parallel-group, single-dose, fed-state clinical trial. Healthy volunteers who met the study's eligibility criteria were assigned into one of the two study groups based on their BMI: (1) obese group (healthy volunteers with BMI ≥ 35 kg/m^2) or; (2) non-obese group (healthy volunteers with BMI 18.5–24.9 kg/m^2). The study was conducted at the International Centre for Bioavailability, Pharmaceutical and Clinical Research (ICBR) in Cairo, Egypt. This trial was registered under the International Standard Randomized Controlled Trial Number (ISRCTN) registry (ISRCTN identifier:12520248) [258].

3.3.2 Study population

Healthy male subjects with BMI 18.5 to 24.9 kg/m^2 or ≥ 35 kg/m^2 and aged between 18 and 60 years were enrolled into the study after passing the screening examinations which took place three weeks before the commencement of the study. Subjects were excluded if they had any of the following: coagulation disorder, known increased bleeding risk, diagnosed chronic medical condition, or severe renal/hepatic impairment. Detailed screening procedures and examinations, inclusion criteria, and exclusion criteria are listed in Appendix 1.

A sample size of 36 in total (i.e., 18 subjects in each group) was calculated using independent-sample t-test to reliably (with probability greater than 0.8) detect a moderate effect size, δ of 1.0, assuming a two-sided criterion of detection that allows for a maximum Type I error rate, α of 0.05 [259].

Upon signing an informed consent form (Appendix 2), each enrolled participant received a badge with a unique code that indicates his group (obese vs. non-obese) and his sequence in that group. Participants were admitted to the clinical facility in ICBR at 8:00 PM, on the day prior to rivaroxaban administration. All participants were assessed for their body temperature, vital signs, and drug abuse. The recruited participants remained in the clinical facility under protocol conditions until the collection of the 18-hr post-dose blood and urine samples. All food and fluid intake during the study was standardized for all participants 12 hr prior to dosing, and up to 18 hr post-dosing. Adverse events and serious adverse drug reactions were assessed during the study for all participants (study protocol is shown in Appendix 3).

3.3.3 Study intervention and samples collection and processing

After an overnight fast of at least 10 hours, a single 20 mg film-coated rivaroxaban tablet (Xarelto® Bayer, batch number: BXJLLK1, expiry date: 08/03/2024) was orally administered with 240 mL water after a high-fat and high-calorie standardized breakfast [191, 260] to each participant in the two groups (maximum variability in rivaroxaban administration time between the participants was 12 minutes). Under direct supervision of the principal investigator and the clinical trial administrator, a total of 19 blood samples (78 ml) were withdrawn from each subject by certified nurses, pre-dosing and then at 1, 2, 4, 8, 12, 18, 36, and 48 hr post-dosing (Appendix 3). Blood samples for rivaroxaban quantifications were centrifuged at 4000

rpm for 8 minutes, and the plasma was aliquoted and stored at -86 °C until analysis. Actual blood sampling time points were recorded in each participant's case report form (Appendix 4).

Furthermore, multiple urine samples were obtained from each participant within the following time intervals: -2 to 0 hr (pre-dosing), and 0 to 3 hr, 3 to 6 hr, 6 to 9 hr, 9 to 12 hr, 12 to 15 hr, 15 to 18 hr post-dosing. All urine samples collected during each time interval were pooled, and the total volume of the pooled urine in each interval was recorded. Out of the pooled urine, 10 mL of each interval was stored at -86 °C until analysis. Actual urine collection time points and volumes were recorded in the urine samples collection form (Appendix 5).

3.3.4 Rivaroxaban analysis using UPLC-MS/MS

Full validation of the analytical method of rivaroxaban in both matrices (plasma and urine) was performed following the accepted international parameters for chromatographic methodologies [261, 262]. Rivaroxaban extraction from plasma and urine samples was conducted by spiking the samples with a known concentration of rivaroxaban–d4 (internal standard). The procedure was carried out using acetonitrile for protein precipitation [263-269]. Rivaroxaban concentrations in the processed samples were analyzed using a fully validated ultra-performance liquid chromatography coupled with tandem mass spectrometer (UPLC-MS/MS, ACQUITY H-Class system, Waters, USA). The stationary phase consisted of C18 reversed phase column (Acquity UPLC BEH, 2.1X50 mm, 1.7 µm particle size) kept at 45°C. For plasma samples analysis, a mobile phase of 50% acetonitrile and 50% of a mixture of 10 mM ammonium acetate and 0.1% formic acid was delivered at a flow rate of 0.3 mL/min for a run time of 1.0 min. Similarly, for urine samples analysis, a mobile phase

of 50% acetonitrile and 50% of 0.1% ammonia was delivered at a flow rate of 0.3 mL/min for a run time of 1.6 min.

The mass spectrometer was operated using an electrospray ionization source on positive mode. A 3.0 µL of the extracted samples was injected into the UPLC-MS/MS and quantification was performed using transitions of m/z 436.14→144.96 for rivaroxaban, and at 440.24→145.02 for rivaroxaban-d4. The established range was linear over a rivaroxaban concentration range of 2.5–1000.0 and 10.0–30000.0 ng/mL, with a lower limit of quantification (LLOQ) of 2.5 and 10.0 ng/mL in plasma and urine, respectively. MassLynx version 4.1 software (Waters, Milford, MA, USA) was used for chromatographic data acquisition and integration. The bioanalytical method validation is shown in Appendix 6.

3.3.5 Pharmacokinetic assessment

The PK parameters were calculated by using Phoenix WinNonlin version 8.1 software using non-compartmental model analysis, model 200 for plasma and 210 for urine (Certara Inc., Princeton, NJ, USA). The primary pharmacokinetic parameters estimated were: (1) maximum plasma concentration (C_{max}), (2) time to reach C_{max} (t_{max}), (3) area under the plasma concentration vs. time curve from zero to 48 hr (AUC_{0-48}) and from zero to infinity (AUC_{0-inf}), (4) elimination rate constant (k_e), (5) half-life ($t_{1/2}$), (6) mean residence time from zero to infinity (MRT), (7) apparent volume of distribution (V_d/F), (8) apparent clearance (Cl/F) and, (9) fraction of dose recovered unchanged in urine over the urine collection period (f_e).

Using the linear regression curve of log concentration vs. time of at least three time points in the terminal phase of the curve, k_e was obtained, and accordingly $t_{1/2}$ was calculated as $0.693/k_e$, assuming linear terminal phase of the PK profiles. The AUC was

calculated from the concentration vs. time curve using linear trapezoidal rule [270]. By extrapolating the curve to infinity, the $AUC_{0\text{-inf}}$ was calculated using equation [1] below (Eq. 1). Apparent total body clearance (Cl/F) and volume of distribution (V_d/F) were calculated using equations [2] (Eq. 2) and [3] (Eq. 3), respectively.

$$AUC_{0\text{-inf}} = AUC_{0\text{-}48} + (C^{48}/k_e) \qquad \text{Eq. 1}$$

$$Cl/F = Dose/AUC_{0\text{-inf}} \qquad \text{Eq. 2}$$

$$V_d/F = (Cl/F)/k_e = Dose/(AUC_{0\text{-inf}} \times k_e) \qquad \text{Eq. 3}$$

Rivaroxaban amount excreted in urine during each of the collection periods over 18 hr post-dose administration was estimated based on the measured rivaroxaban concentration in urine and the voided urine volume; and this was expressed as a fraction of the administered dose recovered unchanged in urine over the urine collection period, i.e., 18 hr (f_e).

3.3.6 Pharmacodynamic assessment

The primary pharmacodynamic parameters measured for all participants included the following: (1) prothrombin time (PT), (2) the corresponding international normalized ratio (INR) and, (3) activated partial thromboplastin clotting time (aPTT) . Two mL of blood was withdrawn pre-dosing and at 1, 2, 4, 8, 12, 18, 36 and 48 hr post-dosing in sodium citrate tubes (total 18 mL) to perform these coagulation assays (PT and aPTT).

3.3.7 Statistical analysis

Statistical analyses were performed utilizing Statistical Package for the Social

Sciences (SPSS, version 28). The independent samples t-test was used to compare C_{max}, AUC_{0-48}, AUC_{0-inf}, $t_{1/2}$, Cl/F, and f_e in obese (BMI $\geq$35 kg/m^2, n=18) vs. non-obese subjects (BMI 18.5–24.9 kg/m^2; n=18). Mann-Whitney U test was used to compare t_{max}, k_e, MRT, V_d/F between the two groups. Furthermore, a subgroup analysis which included only class III obese participants with BMI >40 kg/m^2 and/or body weight >120 kg (n=6) -compared to non-obese participants (n=18)- was performed and used the same statistical analysis tests for comparison. Simple linear and multiple linear regressions were used to detect any potential associations between the variables (to account for any confounding factors). The level of significance was set at 0.05 for all statistical analyses, except for simple linear regression, which was set at 0.2.

3.3.8 Ethical approvals

The study was conducted in accordance with ICH-GCP and the Declaration of Helsinki ethical principles. The study protocol was approved by independent ethics committee of the ICBR (FORM04/SOP: QA-034 – RESH-012); Appendix 7. Moreover, ethical approvals were obtained from Egypt Drug Authority, the Evaluation Unit of Bioavailability and Bioequivalence Studies for Human Pharmaceuticals (Appendix 8), and from the Qatar University Institutional Review Board (approval number: QU-IRB 1741-E/22); Appendix 9.

CHAPTER 4: RESULTS

4.1 Results for Phase One – Rivaroxaban Pharmacokinetics in Obese Subjects: A Systematic Review

4.1.1 Literature search findings

Using the systematic search strategy described earlier (Chapter 3, section 3.1.1), 2,918 articles were identified, of which 28 articles were duplicates and thus excluded. Of the remaining 2890 studies, 2,844 were excluded based on title and abstract screening. Uncertainty of the eligibility of any study was resolved by further reading and confirmation by a second reviewer. A full-text reading of the remaining 46 potentially eligible studies was performed, of which 35 studies were excluded for different reasons, including study type and study outcomes. Finally, 11 studies were included in the review [48, 49, 77-83, 89, 90]. The detailed PRISMA flow diagram that summarizes the search results and the studies' selection process is shown in Figure 4.1.
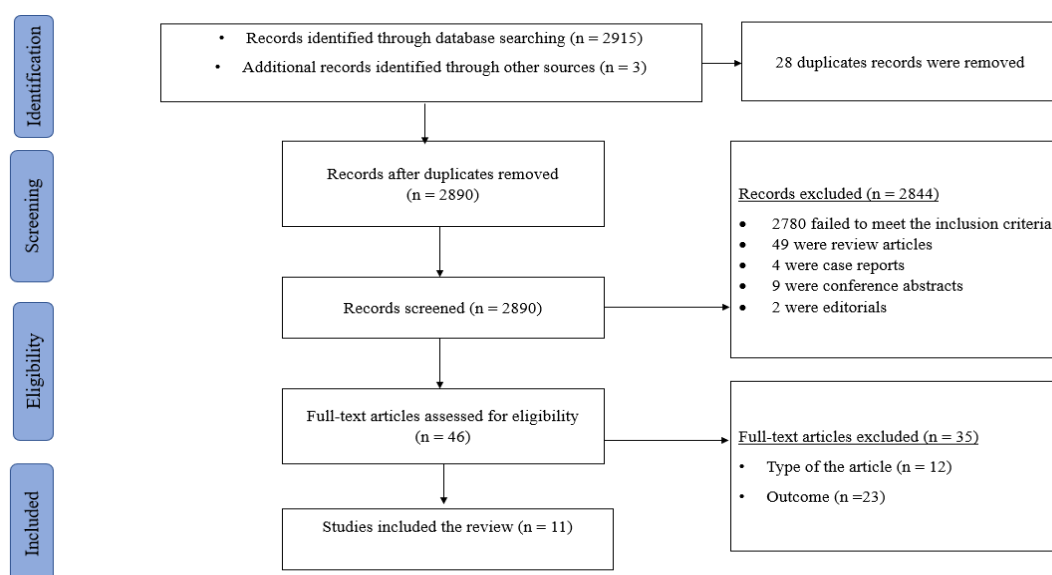
Figure 4.1. PRISMA flow diagram for literature search and studies selection process

4.1.2 Characteristics and key pharmacokinetics-related findings of the included studies

The characteristics and key PK-related findings of the included studies are presented in Table 4.1 and Table 4.2. The 11 studies included in this systematic review were published between 2007 and 2022. Four of the studies were retrospective cohort studies [78, 79, 81, 89], one was randomized controlled trial (RCTs) [49], two were observational prospective studies [82, 83], and the remaining four were PK modelling studies [48, 77, 80, 90], one of which was pooled from seven RCTs [90]. Two studies were multinational and multicenter [80, 90], while the remaining nine studies were conducted in the United Kingdom (three studies), Canada (two studies), Germany, France, Italy, and the Netherlands (one each) [48, 49, 77-79, 81-83, 89]. In the 11 studies included, around 7,140 healthy and diseased subjects received rivaroxaban therapy (sample size ranged from 12 to 4,918). The two multinational and multicenter clinical trials contributed to the majority of the subjects (5,927) [80, 90]. Except for one RCT and one PK modelling study, which both lacked any clear indication of categorization of subjects based on body weight or BMI [80, 90], 351 out of the 1488 subjects in the remaining studies (~23.6 %) were obese (detailed categorization can be found in Table 4.2).

Except in one study which included healthy subjects [49], most subjects were taking rivaroxaban for one or more of the following clinical indications: treatment or prevention of VTE, prevention of VTE in patients undergoing elective hip or knee replacement surgeries, and prevention of stroke and systemic embolism in patients with NVAF. Rivaroxaban dose across the studies ranged between 2.5 mg once daily and 30 mg twice daily.

The studies' characteristics [author(s), year of publication, country of the study, sample size, study design, general population demographics, clinical condition of the

subjects, rivaroxaban dosage regimen, PK parameters that were reported in the studies, and the studies' outcomes] are presented in Table 4.2 and Table 4.3. A one-compartment model or non-compartmental model analysis was reported in some studies. Seven PK parameters were extracted from the included studies: C_{max}, t_{max}, AUC, absorption rate constant (k_a), V_d, Cl, and $t_{1/2}$. Overall, the systematic review results showed that rivaroxaban PK parameters changed slightly or considerably in the extreme body weight groups.

Drug exposure (AUC and C_{max}) in all included studies, except in one [49], was measured during steady state. The mean C_{max} of rivaroxaban in obese subjects was reported in one study to be 149 $\mu g.L^{-1}$ following 10 mg dose [49], and was reported in another study to be 305 $\mu g.L^{-1}$ following 20 mg dose [77]. These reported values fall within the range of reported C_{max} values in the general population 143-180 $\mu g.L^{-1}$ following 10 mg dose [49, 80, 209] and 299-360 $\mu g.L^{-1}$ following 20 mg dose [77, 80, 209]. However, in other studies, the reported C_{max} values of 214 $\mu g.L^{-1}$, 215 $\mu g.L^{-1}$ and 222 $\mu g.L^{-1}$ following 20 mg rivaroxaban dose was slightly lower than anticipated [81, 83, 89]. The AUC of rivaroxaban following 10 mg dose was reported to be 1155 $\mu g.h.L^{-1}$ (AUC from time zero to infinity [$AUC_{0-\infty}$]) in obese subjects [49] compared to 864-1029 ($AUC_{0-\infty}$) $\mu g.h.L^{-1}$ in the general population [49]. Similarly, the AUC of rivaroxaban following 20 mg dose was found to be 1204-2800 $\mu g.h.L^{-1}$ (AUC from time zero to 24 h [AUC_{0-24}]) in obese subjects [77, 78] compared to 1764-3200 (AUC_{0-24}) in the general population [77].

The reported/calculated clearance value in obese subjects was 7.86-16.8 $L.h^{-1}$ [49, 78] compared to 5.57-11.3 $L.h^{-1}$ in the general population [48, 77, 271, 272], i.e., some of the values in obese subjects did not fall within the clearance value range reported in the general population. Furthermore, the reported/calculated value of V_d

was 73.4-82.8 L in the obese population [49, 78] and was 59.4-104 L [48, 49, 77, 90] in the general population, indicating a wide range in the reported/calculated values in the general population, and therefore the effect of obesity on the V_d is yet to be investigated. A comparison among the PK parameters in the general vs. obese populations is shown in Table 4.3.

The studies had variable methodological quality characteristics. The CCAT total scores for the studies ranged from 31 to 39 out of 40, with an average of 35.4 out of 40. Average percentage scores of the studies were 88.4% (range 78-98%), with individual study CCAT scores of 78% [83], 80% [82], 83% [80], 85% [81, 89], 90% [49, 79], 93% [77], 95% [48, 78], and 98% [90]. For example, one included study lacked the explanatory diagrams, secondary questions among its objective, and it did not account for inter-individual variability or potential bias [81]. Another study lacked important criteria in its title, and its sample size was questionable for a PK model development purposes [48]. The reporting of study design/intervention description, as well as information about ethical considerations were lacking in some studies [80, 83, 89]. The CACPK tool rating trend was consistent with the scoring trend of CCAT in a number of the included studies. The three most highly rated studies using the CACPK tool have scored >90% in the CCAT tool [48, 77, 90]. Similarly, the three least rated studies by CACPK have scored ≤85% in the CCAT tool [81, 83, 89]. A number of questions within the 'study design and experimental methods' domain in the CACPK tool were not applicable in six of the 11 included studies. This is expected as the CACPK tool is not designed specifically for retrospective studies. More details of all the score categories are shown in Table 4.4 and Table 4.5.

Table 4.1 Overview of the General Study Characteristics in the Included Studies

Study reference	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
[81]	Piran, S., et al., 2018	Canada	38, of which 21 subjects receiving rivaroxaban had weight >120 kg	Retrospective cohort study which included subjects treated between June 2017 and February 2018	-Age mean (±SD) = 64 (±11) years old -Males = 79%	-AF 22 subjects (58%) -VTE 14 subjects (37%) -AF + VTE 1 subject (3%) -Others 1 subject (3%)	Three groups: -On apixaban = 7 (18%) -On dabigatran = 10 (26%) -On rivaroxaban = 21 (55%)	85%	10
[48]	Barsam, S.J., et al., 2017	United Kingdom	101, of which, 41 subjects had BMI ≥30 kg/m^2	PK model development study, which was based on real-world subjects	-Age mean (range) = 52 (20-86) years old -Males = 58% -White 74%, Afro-Caribbean 21% -Other 5%	-Acute VTE first event (58%) -Acute recurrent event (26%) -Prevention of VTE (12%) -Elective orthopaedic VTE prophylaxis (4%)	One group: all were taking rivaroxaban prophylactic or treatment doses for the prevention or treatment of VTE	95%	16
[49]	Kubitza, D., et al., 2007	Germany	48, of which 12	Single-center, randomized,	-Age mean (range) =	-The subjects are all healthy	Three groups	90%	15

45

Study reference[a]	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
			subjects receiving rivaroxaban had weight >120 kg	single-blind, placebo-controlled, parallel-group study	34.75 (20-54) years old -Males = 33.3% -Caucasian healthy		based on weight: a] ≤50 kg b] 70 to 80 kg c] >120 kg In each group, 12 healthy subjects were receiving rivaroxaban and 4 healthy subjects were receiving placebo		
[90]	Willmann, S., et al., 2018	Data from >27 countries, multi-national and multi-centre	4918, data for subgroups based on weight or BMI categories	Integrated population PK model, pooled data from seven randomized controlled trials.	-Age mean (±SD) = 60.53 (±11.82) years old -Males = 60.7%	-Prevention of VTE in subjects undergoing elective hip or knee replacement surgery	Seven global clinical trials, all subjects were on rivaroxaban therapy for	98%	17

Study reference[a]	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
			were not available			-Treatment of acute symptomatic VTE -Prevention of cardiovascular events in subjects with ACS -Stroke prevention in subjects with AF	different indications		
[80]	Mueck, W., et al., 2008	Multi-national subjects	1009, data for subgroups based on weight or BMI categories was not available	PK modelling study; Randomized, double-blind, double-dummy, active comparator -controlled	-Age median (range) = 65 (26–87) years old in the hip study and 67 (39–92) years old in the knee study	-Prevention of VTE in subjects undergoing elective total hip or knee replacement	Two groups: -Hip study (n=517) -Knee study (n=492)	83%	16
[89]	Abdulrehman, J., et al., 2021	Canada, in a single center	43, all had weight of >120 kg	Retrospective study which reviewed patient records between 2014 and 2019.	-Age mean = 54.2 years old -Males = 60.5%	-Treatment or secondary prevention of VTE	One group: all were on rivaroxaban treatment. Peak rivaroxaban plasma levels were measured 2-	85%	13

Study reference[a]	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
							4 hrs after rivaroxaban ingestion		
[77]	Speed, V., et al., 2020	United Kingdom	913, of which 86 were >120 kg and 74 had BMI >40 kg/m^2	PK model generation/development	-Age mean (±SD) = 67.03 (±15) years old -Males = 57.2%	-AF 110 subjects (68.9%) -VTE 47 subjects (29.4%) -Other 3 subjects (1.9%)	One group: all were on fixed doses of rivaroxaban, according to their indication	93%	17
[82]	Ballerie, A., et al., 2021	France	146, of which 77 patients were receiving rivaroxaban and had BMI ≥30 kg/m^2	Observational prospective	-Age median (min-max) = 61 (19–86) years -Males = 52%	-All patients were treated for VTE	Two groups: -On rivaroxaban = 77 (53%) -On apixaban = 69 (47%)	80%	14
[79]	Kok, T., et al., 2021	The Netherlands	41, of which 12 patients were on rivaroxaban and had	Retrospective, cross-sectional, and longitudinal study	-Age mean (SD) = 57.9 (8.4) years old	-AF 8 subjects (66.7 %) -VTE 4 subjects (33.3 %)	Two groups: -On rivaroxaban = 12 (29%)	90%	13

Study reference[a]	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
			BMI mean of 42.6±5.9 kg/m²		-Males = 33.3 %		-On apixaban = 29 (71%)		
[83]	Martin, A., et al., 2021	United Kingdom	100, all are ≥120 kg -Peak rivaroxaban concentrations obtained from 58 subjects -Trough rivaroxaban concentrations obtained from 21 subjects	Prospective observational study	-Age median (range) = 58 (23–78) years old -Males = 69%	-AF 58 subjects (58%) -VTE 42 subjects (42%)	Two groups: -On rivaroxaban -On apixaban *The number of patients on each group was not reported.*	78%	12
[78]	Russo, V., et al., 2021	Italy	58, with BMI of ≥40 kg/m², of which 9 subjects receiving rivaroxaban	Retrospective observational design	-Age mean (±SD) = 70.93 (±98.73) years -Male = 60%	-All patients were treated for AF	Four groups: - Rivaroxaban = 9 (15.5%)	95%	15

Study reference[a]	Authors and publication years	Country	Sample size	Study design	Population	Clinical condition	Groups	CCAT quality scores	CACPK 'yes' number[a]
							- Apixaban = 24 (41.4%) - Dabigatran = 12 (20.7%) - Edoxaban = 13 (22.4%)		

SD standard deviation, *AF* atrial fibrillation, *VTE* venous thromboembolism, *ACS* acute coronary syndromes, *CCAT* Crowe critical appraisal tool,

CACPK critical appraisal of clinical pharmacokinetic studies, *BMI* body mass index, *PK* pharmacokinetics, *min* minimum, *max* maximum

[a]The number of questions in the CACPK tool with 'yes' responses.

Table 4.2 Overview of the Pharmacokinetic Models, Parameters and Outcome Measures in the Included Studies

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
[81]	Median weight: 132.5 kg BMI (IQR): 41 (37.6-47.6) kg/m^2	Every patient received their medication as prescribed for their condition. Generally, it was ≥15 mg/day	Not reported	Median peak plasma concentration after >15 mg rivaroxaban = 249 µg.L^{-1}	No obese subjects on rivaroxaban therapy had C_{max} below the median trough. However, 28% of the obese subjects on rivaroxaban had a C_{max} that was below the 5th percentile peak concentration.
[48]	Mean weight (±SD) for the whole sample: 88.0 (±23.4) kg BMI, kg/m^2 (%) 16-18.49 1 18.5-24.9 27 25-29.9 32 30-34.9 21 35-39.9 14	-15 mg twice/day 57% -20 mg once/day 38% -10 mg once/day 4% -15 mg once/day 1%	One-compartment model	Value (%SD): CL = 8.59 (7%) L.h^{-1} V_d = 104 (13%) L K_a = 1.32 (24%) h^{-1}	The findings suggest that rivaroxaban behaves differently from other traditional anticoagulants, in the extremes of weight population and that the dose does not need to be increased with weight. The results suggest that the most important covariate impacting rivaroxaban PK is creatinine clearance and the weight has only little effect. The study showed that the weight did not feature a significant covariant in the study.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
	≥40 6				
[49]	Mean BMI (±SD) kg/m^2: 28.5 (±10.4) for placebo group 19.3 (±1.1) for intervention group who are ≤50 kg 24.3 (±2.3) for intervention group who are 70-80 kg 43.5 (±4.2) for intervention group who are >120 kg	10 mg/day or placebo in a 3:1 ratio, so that 12 subjects in each weight group received rivaroxaban and 4 received placebo	Non-compartmental analysis	Values expressed as means (coefficient of variation), except the t_{max} which was expressed as median (range) after a 10 mg dose of rivaroxaban: *For subjects >120 kg:* $AUC_\infty = 1155$ (15.60%) µg.hr.L^{-1} $AUC_{\infty, norm} = 15,230$ (18.50%) g.h.L^{-1} $C_{max} = 149$ (20.40%) µg.L^{-1} $C_{max, norm} = 1964$ (23.10%) g.L^{-1} $t_{max} = 4.00$ (2.00-4.00) h $t\frac{1}{2} = 7.30$ (25.40%) h $Vz/F = 0.69$ (35.80%) L.kg^{-1} *For subjects 70-80 kg:* $AUC_\infty = 1029$ (20.10%) µg.h.L^{-1} $AUC_{\infty, norm} = 7611$ (19.20%) g.h.L^{-1}	Rivaroxaban was well tolerated in subjects with extremes of body weight as in subjects with normal body weight, and its PK and PD were not influenced by body weight to an extent considered likely to be clinically relevant.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
				C_{max} = 143 (26.50%) $\mu g.L^{-1}$ $C_{max, norm}$ = 1061 (25.90%) $g.L^{-1}$ t_{max} = 3.50 (1.00-4.00) h $t\frac{1}{2}$ = 7.20 (42.10%) h Vz/F = 1.36 (37.40%) $L.kg^{-1}$	
[90]	Mean weight (±SD) for the whole sample: 82.48 (±16.87) kg BMI (kg/m^2) <18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40	Ranged from 2.5 mg once daily to 30 mg twice daily	One-compartment model	Value (% SE): Ka = 0.821 h^{-1} CL/F = 6.58 (2.33) $L.h^{-1}$ V/F = 62.5 (2.04) L Population medians varied for AUC, C_{max}, and C_{trough} by 7.5%, 7.6%, and 44%, respectively, among the BMI categories compared with the reference groups	The influence of body weight on rivaroxaban PK was minor, demonstrating that fixed doses of rivaroxaban can be prescribed in adult subjects without adjustment for body weight. The study showed that the BMI had a minor influence on exposure of rivaroxaban.
[80]	Median weight (range):	2.5, 5, 10, 20 or 30 mg every 12 ± 1 hours (5, 10, 20, 40 or	One-compartment model	Values expressed as geometric means (except t_{max} which was	Rivaroxaban has predictable PK and PD in subjects undergoing major orthopaedic surgery.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
	-76 (45–125) kg in the hip study -86 (50–173) kg in the knee study	60 mg total daily dose)		expressed as median (range)): *After a 10 mg dose of rivaroxaban:* $AUC_{12} = 974\ (63.0)\ \mu g.h.L^{-1}$ $AUC_{12,\ norm} = 7817\ (57.4)\ g.h.L^{-1}$ $C_{max} = 180\ (74.1)\ \mu g.L^{-1}$ $C_{max,\ norm} = 1423\ (62.1)\ g.L^{-1}$ $t_{max} = 1\ (1\text{-}12)\ h$ $CL/F = 9.80\ (59.5)\ L.hr^{-1}$ *After a 20 mg dose of rivaroxaban:* $AUC_{12} = 1764\ (53.4)\ \mu g.h.L^{-1}$ $AUC_{12,\ norm} = 7267\ (61.2)\ g.h.L^{-1}$ $C_{max} = 299\ (45.6)\ \mu g.L^{-1}$ $C_{max,\ norm} = 1234\ (49.8)\ g.L^{-1}$ $t_{max} = 2\ (1\text{-}4)\ h$	Body weight affected the volume of distribution of rivaroxaban in hip and knee studies. However, the effects of covariates on the PK of rivaroxaban were generally small.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
				$CL/F = 11.3$ (53.4) L.hr^{-1}	
[89]	Mean weight ($\pm$SD): 140.9 ($\pm$16.9) kg, with range 120-181 kg	20 mg daily	Not reported	Value (IQR): 222 (186-313) µg.L^{-1}	There was no significant correlation between body weight and peak plasma concentration of rivaroxaban. The peak rivaroxaban concentration are largely unaffected in subjects weighing 120 kg or greater.
[77]	Weight (kg) (%) <50 3.3 50-100 73.2 100-120 14.1 >120 9.4 BMI (kg/m^2) (%) <18.5 2.1 18.5-25 25.3 25-30 30.9	Ranged from 10 mg once daily to 30 mg once daily	One-compartment model	*After a 20 mg dose of rivaroxaban in patients with weight 125 kg[a]:* AUC$_{24}$ = 2800 µg.h.L^{-1} C$_{max}$ = 305 µg.L^{-1} *After a 20 mg dose of rivaroxaban in patients with normal weight[a]:* AUC$_{24}$ = 3200 µg.h.L^{-1} C$_{max}$ = 360 µg.L^{-1}	Creatinine clearance was the single best predictor of rivaroxaban exposure. Weight alone was not the most significant factor influencing rivaroxaban PK. To conclusively answer the question of whether rivaroxaban is as safe and as effective as warfarin at extremes of bodyweight, a large randomized control trial would be required. However, conducting a prospective analysis of patients weighing <50 kg or >120 kg, or with a BMI >40 kg/m^2 would be challenging.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
	30-35 20.3 35-40 13.4 >40 8.1				
[82]	Median weight (range):100 (73–178) kg BMI (kg/m^2) n (%) 30-34.9 79 (54) 35-39.9 38 (26) ≥40 29 (20)	20 mg once daily	Not reported	The median (min-max) of rivaroxaban concentration reported at a median time of 7 hr after dose intake = 108 (20-453) µg.L^{-1}	DOAC use in obese patients treated for VTE at fixed doses led to concentrations similar to those of the general population in a high proportion of patients, without a noticed BMI effect.
[79]	Mean weight (±SD): 134.9 (±16.7) kg of apixaban group 133.2 (±21.9) kg of rivaroxaban group Mean BMI (±SD):	20 mg once daily	Not reported	*For subjects' weight from 120 to 130 kg[a]:* Peak range of anti-Xa level = 200-380 µg.L^{-1} *For subjects' weight >130 to 150 kg[a]:* Peak range of anti-Xa level = 320-350 µg.L^{-1}	Plasma anti-Xa level measurements were predominantly within the therapeutic range in morbidly obese patients. In patients using rivaroxaban, no statistically significant relation between plasma anti-Xa levels and body weight was found.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes
	44.5 (±5.1) kg/m^2 of apixaban group 42.3 (±5.9) kg/m^2 of rivaroxaban group				
[83]	BMI (kg/m^2) n (%) 30–34.99 3 (3.2) 35–39.99 12 (12.7) ≥40 54 (57.5) ≥50 16 (17) ≥60 9 (9.6)	20 mg once daily	Not reported	*In AF cohort, values expressed as mean (5th–95th):* C_{max} = 214 (61–672) C_{trough} = 59 (14–148) *In VTE cohort, values expressed as mean (5th–95th):* C_{max} = 220 (99–474) C_{trough} = 98 (20–299)	Subjects with high body weight or morbid obesity receiving factor Xa inhibitors for AF or VTE were unlikely to be underexposed to anticoagulant therapy when administered in standard doses.
[78]	Mean BMI (±SD) for the whole sample: 44.43 (±3.54) kg/m^2	20 mg once daily	One-compartment model	Values expressed as median (IQR): AUC = 1204 (861–1390) (AUC_{0-24}) $\mu g.h.L^{-1}$ Cl/F = 16.8 (14.4–23.3) $L.h^{-1}$ V_d = 73.4 (63.5–97.9) L	Subjects with extreme obesity, receiving DOAC therapy for AF had a DOAC plasma concentration in the expected range. The inappropriate DOAC underdosing seems to be the only independent factor associated with the drugs' plasma concentration out of the expected range.

Study reference	Weight/BMI	Rivaroxaban dosing regimen	PK model	PK parameter	Outcomes

BMI body mass index, *PK* pharmacokinetics, *PD* pharmacodynamics, *IQR* interquartile range, C_{max} maximum plasma concentration, *SD* standard deviation, *CL* clearance, V_d volume of distribution, K_a absorption rate constant, AUC_∞ area under the plasma-concentration time curve from time 0 to infinity, t_{max} time needed to reach the C_{max}, $t^{1/2}$ elimination half-life, *Vz/F* apparent volume of distribution during the terminal phase, *SE* standard error, *CL/F* apparent clearance, *V/F* apparent volume of distribution, C_{trough} trough concentration, AUC_X area under the plasma concentration time curve from time zero to time x h, min minimum, max maximum, *DOAC* direct oral anticoagulant, $AUC_{12(norm)}$ dose-normalized AUC_{12} (AUC_{12} divided by the dose per kg of bodyweight), $C_{max(norm)}$ dose-normalized Cmax (Cmax divided by the dose per kg of bodyweight).

[a]Values were visually extracted from study graphs

Table 4.3 A Comparison Between the Values of Selected Pharmacokinetic Parameters in the Included Studies[a]

Parameter (units)	Obese				General Population									
	Kubitza et al. 2007 [49]	Piran et al. 2018 [81]	Speed et al. 2020 [77]	Abdulrehman et al. 2021 [89]	Ballerie et al. 2021 [82]	Kok et al. 2021 [79]	Martin et al. 2021 [83]	Russo et al. 2021 [78]	Speed et al. 2020 [77]	Barsam et al. 2017 [48]	Willmann et al. 2018 [90]	Mueck et al. 2008 [80]	Kubitza et al. 2005[b] [209]	Kubitza et al. 2007 [61]
AUC after 10 mg dose ($\mu g.h.L^{-1}$)	1155 (AUC_∞) (16%)	-	-	-	-	-	-	-	-	-	-	974 (AUC_{12}) (63.0)	864 (AUC_{12}) (18.6)	1029 (AUC_∞) (20%)
AUC after 20 mg dose ($\mu g.h.L^{-1}$)	-	-	2800[d] (AUC_{24}) in a 125 kg subject	-	-	-	-	1204[e] (AUC_{0-24})	3200[d] (AUC_{0-24})	-	-	1764 (AUC_{12}) (53)	1903 (AUC_{12}) (25)	-
C_{max} after 10 mg dose ($\mu g.L^{-1}$)	149 (20%)	-	-	-	-	-	-	-	-	-	-	180 (74)	158 (19)	143 (27%)
C_{max} after 20 mg dose ($\mu g.L^{-1}$)	-	215[f]	305[d] in a 125 kg subject	222	-	200-380[d] in 120-130 kg subjects	214 (in AF) 220 (in VTE)	-	360[d]	-	-	299 (46)	318.1 (19)	-

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	Obese						General Population							
	Kubitza et al. 2007 [49]	**Piran et al. 2018** [81]	**Speed et al. 2020** [77]	**Abdulrehman et al. 2021** [89]	**Ballerie et al. 2021** [82]	**Kok et al. 2021** [79]	**Martin et al. 2021** [83]	**Russo et al. 2021** [78]	**Speed et al. 2020** [77]	**Barsam et al. 2017** [48]	**Willmann et al. 2018** [90]	**Mueck et al. 2008** [80]	**Kubitza et al. 2005b** [209]	**Kubitza et al. 2007** [61]
Parameter (units)														
						320-350[a] *in 130-150 kg subjects*								
C^{7hr} after 20 mg dose (µg.L^{-1})	-	-	-	-	108[e]	-	-	-	-	-	-	-	-	-
CL/F (L.h^{-1})	7.86[g]	-	-	-	-	-	-	16.8[e] *expressed as Cl/F*	5.57 (5.34-5.82) *expressed as Cl/F*	8.59 (7%)	6.58 (2.33) *expressed as Cl/F*	9.80 (59.5) *after 10 mg dose* 11.3 (53.4) *after 20 mg dose express*	-	-

	Obese						General Population							
	Kubitza et al. 2007 [49]	Piran et al. 2018 [81]	Speed et al. 2020 [77]	Abdulrehman et al. 2021 [89]	Ballerie et al. 2021 [82]	Kok et al. 2021 [79]	Martin et al. 2021 [83]	Russo et al. 2021 [78]	Speed et al. 2020 [77]	Barsam et al. 2017 [48]	Willmann et al. 2018 [90]	Mueck et al. 2008 [80]	Kubitza et al. 2005[b] [209]	Kubitza et al. 2007 [61]
Parameter (units)														
											ed as Cl/F			
V_d/F (L)[***]	82.8[h] expressed as V_z/F or 0.69 (36%) $L.kg^{-1}$	-	-	-	-	-	-	73.4[e]	59.4 (55-64) expressed as V_d/F	104 (13%)[f]	62.5 (2) expressed as V/F	-	-	95.2[h] expressed as V_z/F or 1.36 (37%) $L.kg^{-1}$

AUC area under the plasma concentration-time curve, *AUC$_\infty$* AUC from time zero to infinity, *AUC$_x$* AUC from time zero to time x h, *C$_{max}$* maximum plasma concentration. *CL* clearance. *V$_d$* apparent volume of distribution, *PK* pharmacokinetic, *AF* atrial fibrillation, *VTE* venous thromboembolism, *CL/F* apparent clearance, *Vd/F* apparent volume of distribution during the terminal phase

[a]Values expressed as geometric means (percentage coefficient of variation) unless otherwise stated

[b]This study was not included in this systematic review but was used in Table 4.3 to extract further PK parameters from the general population for comparison purposes

[c]Assuming bioavailability of 100% for the whole range of rivaroxaban doses under fed condition [58]

	Obese						General Population							
	Kubitza et al. 2007 [49]	Piran et al. 2018 [81]	Speed et al. 2020 [77]	Abdulrehman et al. 2021 [89]	Ballerie et al. 2021 [82]	Kok et al. 2021 [79]	Martin et al. 2021 [83]	Russo et al. 2021 [78]	Speed et al. 2020 [77]	Barsam et al. 2017 [48]	Willmann et al. 2018 [90]	Mueck et al. 2008 [80]	Kubitza et al. 2005^b [209]	Kubitza et al. 2007 [61]

Parameter

(units)

^dAUC and C_{max} values were visually extracted from the study graphs

^eMedian (range)

^fMedian C_{max} after an unspecified dose of rivaroxaban ($\geq$15 mg)

^gCL was calculated using other available PK parameters

^hV_d (L.kg^{-1})×weight of the corresponding category

^IPercentage standard error.

Table 4.4 Quality Assessment of the 11 Included Studies Using CCAT

Study No.	Reference	Preliminary	Introduction	Design	Sampling	Data collection	Ethical matters	Results	Discussion	Total	Total Percentage
1	[81]	5	4	4	4	4	5	4	4	34	85%
2	[48]	5	5	4	4	5	5	5	5	38	95%
3	[49]	5	5	4	5	5	3	5	4	36	90%
4	[90]	5	5	5	4	5	5	5	5	39	98%
5	[80]	5	5	5	4	4	2	4	4	33	83%
6	[89]	3	4	4	5	5	5	4	4	34	85%
7	[77]	5	5	5	4	5	5	4	4	37	93%
8	[82]	4	5	4	4	4	4	3	4	32	80%

Study No.	Reference	Preliminary	Introduction	Design	Sampling	Data collection	Ethical matters	Results	Discussion	Total	Total Percentage
9	[79]	5	5	4	5	5	5	4	4	36	90%
10	[83]	5	4	3	3	5	2	5	4	31	78%
11	[78]	5	5	5	5	5	5	4	4	38	95%

The CCAT tool is based on a rating score on an overall scale of 0 – 5 (0, no evidence; 5, high evidence) in each of eight categories

CCAT Crowe Critical Appraisal Tool

Table 4.5 Quality Assessment of the 11 Included Studies Using CACPK

Study No.	Reference	Background (2 questions)			Study design and experimental methods (15 questions)			Applied statistics (1 question)			Results (3 questions)			Total Number of 'Yes' Responses
		Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA	
1	[81]	2	-	-	4	2	9	1	-	-	3	-	-	10
2	[48]	2	-	-	11	4	-	1	-	-	2	1	-	16
3	[49]	2	-	-	9	4	2	1	-	-	3	-	-	15
4	[90]	2	-	-	11	4	-	1	-	-	3	-	-	17
5	[80]	2	-	-	11	4	-	1	-	-	2	1	-	16
6	[89]	2	-	-	7	5	3	1	-	-	3	-	-	13
7	[77]	2	-	-	11	4	-	1	-	-	3	-	-	17

Study No.	Reference	Background (2 questions)			Study design and experimental methods (15 questions)			Applied statistics (1 question)			Results (3 questions)			Total Number of 'Yes' Responses
		Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA	
8	[82]	2	-	-	10	5	-	1	-	-	1	2	-	14
9	[79]	2	-	-	8	5	2	1	-	-	2	1	-	13
10	[83]	2	-	-	7	5	3	1	-	-	2	1	-	12
11	[78]	2	-	-	10	3	2	1	-	-	2	1	-	15

The CACPK tool is based on a rating scale of 'yes, no, I do not know, and not applicable' in each of the 21 questions in four categories.

As there was no 'I do no know' answer, this was not included as an option in this table

CACPK Critical Appraisal of Clinical Pharmacokinetic Studies, *NA* not applicable

4.2 Results for Phase Two – Trends in Prescribing and Outcomes in Obese Versus Non-Obese Patients Receiving Rivaroxaban Therapy: A Retrospective Observational Study Using Real-world Data

4.2.1 Subjects' selection and baseline characteristics

From 1 January 2015 to 31 December 2020, 4663 electronic medical records of patients who received rivaroxaban therapy were identified. Twenty-five records were for patients below 18 years, and thus were excluded from the study. The remaining 4638 patients' records were included in the analyses. The mean±SD age and BMI for the study cohort were 51.84±16.8 years and 30.56±7.4 kg/m^2, respectively. The majority of the study subjects were male (60%) and non-smokers (90.9%).

Stratifying the study subjects by BMI, the overweight group (BMI 25 – 29.99 kg/m^2) had the highest number of patients [1411 patients (32.2%)], followed by obese class 1 category (BMI 30 – 34.99 kg/m^2) [1098 patients (25%)]. The rest of the groups were shown in Table 4.6. Obesity classes 1, 2, and 3 were found to be most common among non-Qatari Arab populations (42.9%, 48.0%, and 52.2%, respectively) compared to Qatari and non-Arab populations (p<0.001). For the baseline clinical characteristics, diabetes, hypertension, dyslipidemia, and coronary artery disease (CAD) were highly prevalent in the studied population with proportions of 40.1%, 33%, 15.8%, and 11.4%, respectively; with a significant increase in the proportions of patients with these comorbidities as the BMI increases (p <0.001). The mean±SD number of co-medications per patient was 2.3±2.1, with a significant increase in this number as the BMI increases (p<0.001). Table 4.6 presents details on other demographic and baseline clinical characteristics for the overall study subjects based on BMI categories.

Table 4.6 Demographics and Baseline Clinical Characteristics of Patients on Rivaroxaban From 2015 to 2020 According to BMI Classification (n = 4638)

Parameter	Total (n=4638)	BMI (kg/m^2)						p-value
		<18.5 (n=64)	18.5 to 24.99 (n=886)	25 to 29.99 (n=1411)	30 to 34.99 (n=1098)	35 to 39.99 (n=535)	≥40 (n=391)	
Gender, n (%)								
Male	2783 (60)	44 (68.8)	625 (70.5)	972 (68.9)	642 (58.5)	221 (41.3)	114 (29.2)	<0.001[b]
Female	1855 (40)	20 (31.2)	261 (29.5)	439 (31.1)	456 (41.5)	314 (58.7)	277 (70.8)	
Age (years), n (%)								
18 to <55	2566 (55.3)	38 (59.4)	539 (60.8)	832 (59)	603 (54.9)	230 (43)	150 (38.4)	
55–75	1665 (35.9)	14 (21.9)	242 (27.3)	456 (32.3)	414 (37.7)	260 (48.6)	213 (54.5)	<0.001[b]
>75	407 (8.8)	12 (18.7)	105 (11.9)	123 (8.7)	81 (7.4)	45 (8.4)	28 (7.2)	
Nationality, n (%)								
Qatari Arab	1105 (23.8)	22 (34.4)	164 (18.6)	277 (19.6)	285 (26)	181 (33.8)	145 (37.1)	
Non-Qatari Arab	1790 (38.6)	15 (23.4)	269 (30.3)	489 (34.7)	471 (42.9)	257 (48.0)	204 (52.2)	<0.001[b]
Non-Arab	1743 (37.6)	27 (42.2)	453 (51.1)	645 (45.7)	342 (31.1)	97 (18.1)	42 (10.7)	
Smoking history, n (%)								
Smokers	391 (8.4)	4 (6.3)	94 (10.6)	138 (9.8)	92 (8.4)	38 (7.1)	20 (5.1)	
Non-smoker	4214 (90.9)	60 (93.7)	788 (88.9)	1263 (89.5)	996 (90.7)	492 (92.0)	369 (94.4)	0.003[b]
Ex-smoker	33 (0.7)	0 (0)	4 (0.5)	10 (0.7)	10 (0.9)	5 (0.9)	2 (0.5)	
Heart rate (bpm), mean (SD)	76.06 (10.99)	76.7 (9.8)	75.9 (10.9)	75.8 (11.2)	76.1 (11.2)	75.9 (10.6)	76.6 (10.3)	0.843[a]
SBP (mmHg), mean (SD)	126.63 (15.76)	122 (18.7)	124.3 (15.8)	126.2 (15.7)	127.5 (15.3)	127.9 (15.9)	128.9 (15.9)	<0.001[a]

Parameter	Total	BMI (kg/m^2)						p-value
		<18.5	18.5 to 24.99	25 to 29.99	30 to 34.99	35 to 39.99	≥40	
	(n=4638)	(n=64)	(n=886)	(n=1411)	(n=1098)	(n=535)	(n=391)	
DBP (mmHg), mean (SD)	76.04 (9.60)	74.4 (9.2)	74.7 (9.2)	76 (9.4)	76.3 (9.5)	76.2 (10.1)	76.9 (10.4)	<0.001[a]
ALT (U/L), mean (SD)	27.90 (37.70)	27.2 (27.6)	31.5 (71.6)	28.7 (25.7)	27.7 (23)	24.4 (19)	23.3 (19.7)	<0.001[a]
AST (U/L), mean (SD)	25.30 (28.00)	31 (20.8)	29.4 (56.5)	25.6 (15.4)	24.6 (16.7)	22 (10.7)	21.9 (13.2)	<0.001[a]
SCr. (μmol/L), mean (SD)	75.65 (29.88)	74.8 (29.6)	75.1 (36.4)	77.61 (30.9)	75.5 (28.4)	73.8 (23.7)	72.8 (24.6)	<0.001[a]
Diabetes mellitus, n (%)	1858 (40.1)	17 (26.6)	293 (33.1)	545 (38.6)	458 (41.7)	273 (51.0)	216 (55.2)	<0.001[b]
Hypertension, n (%)	1533 (33.0)	18 (28.1)	218 (24.6)	428 (30.3)	405 (36.9)	240 (44.9)	191 (48.8)	<0.001[b]
Dyslipidemia, n (%)	773 (15.8)	6 (9.4)	110 (12.4)	210 (14.9)	211 (19.2)	110 (20.6)	111 (28.4)	<0.001[b]
CAD, n (%)	528 (11.4)	5 (7.8)	97 (10.9)	155 (11.0)	139 (12.7)	64 (12.0)	60 (15.3)	0.158[b]
Kidney disease, n (%)	411 (8.9)	6 (9.4)	69 (7.8)	128 (9.1)	99 (9.0)	57 (10.7)	45 (11.5)	0.303[b]
Liver disease, n (%)	94 (2.0)	2 (3.1)	14 (1.6)	22 (1.6)	26 (2.4)	15 (2.8)	15 (3.8)	0.059[b]
Anemia, n (%)	266 (5.7)	3 (4.7)	42 (4.7)	85 (6.0)	64 (5.8)	29 (5.4)	37 (9.5)	0.043[b]
No. of co-medications per patient, mean (SD)	2.3 (2.1)	2.4 (2.1)	2.3 (2.1)	2.5 (2.1)	2.7 (2.1)	3.1 (2.1)	3.4 (2.0)	< 0.001[a]
Co-medications, n (%)								
0	1002 (21.6)	12 (18.8)	251 (28.3)	320 (22.7)	208 (18.9)	71 (13.3)	36 (9.2)	
1 to 4	2640 (56.9)	38 (59.4)	477 (53.8)	809 (57.3)	637 (58.0)	322 (60.2)	232 (59.3)	< 0.001[b]
5 to 10	996 (21.5)	14 (21.8)	158 (17.8)	282 (20.0)	253 (23.0)	142 (26.5)	123 (31.4)	

Total number of patients with known BMI is 4385 as some BMI data were missing from patients' records

			BMI (kg/m^2)					
Parameter	**Total**	**<18.5**	**18.5 to**	**25 to 29.99**	**30 to 34.99**	**35 to 39.99**	**≥40**	***p*-value**
	(n=4638)	**(n=64)**	**24.99**	**(n=1411)**	**(n=1098)**	**(n=535)**	**(n=391)**	
			(n=886)					

SBP Systolic blood pressure, *DBP* Diastolic blood pressure, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *SCr* Serum creatinine, *CAD* coronary artery disease

[a]Kruskal Wallis test; significant p-value indicates that the distribution of a parameter is significantly different across the BMI categories.

[b]chi-square test; significant p-value indicates significant association between a parameter and BMI categories.

4.2.2 Rivaroxaban prescribing trends among patients with thromboembolic diseases

There was an increasing trend in rivaroxaban prescribing across the study period for the entire study cohort: 152 patients (3.3%) in 2015, 505 patients (10.9%) in 2016, 646 patients (13.9%) in 2017, 810 patients (17.5%) in 2018, 1183 patients (25.5%) in 2019, and 1342 patients (28.9%) in 2020 (p <0.001) (Figure 4.2).
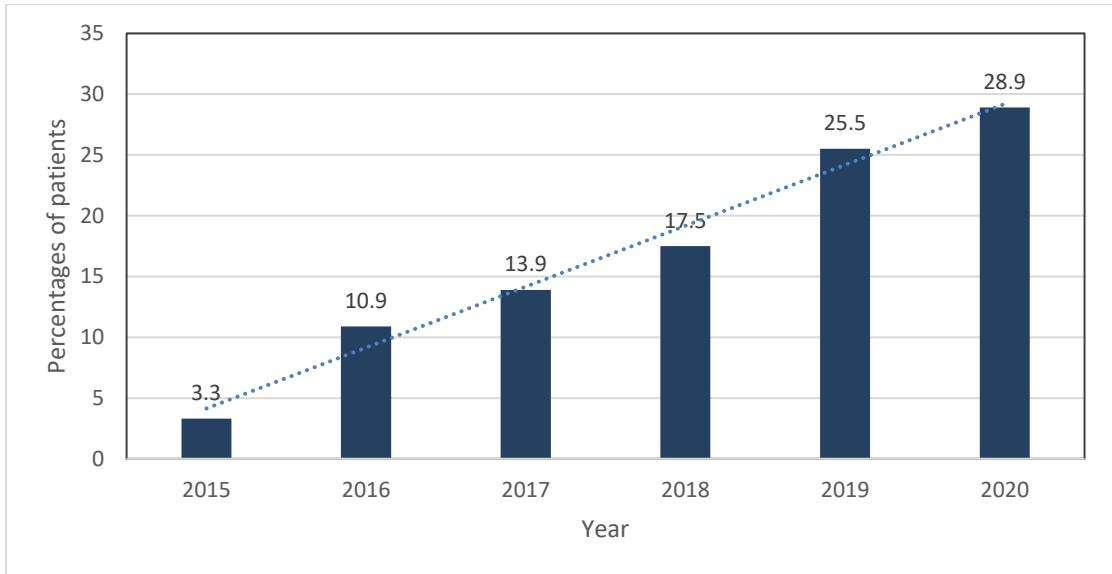
Figure 4.2. Trend of rivaroxaban utilization across the years from 2015 to 2020 (n=4638). This figure is Microsoft Excel-generated.

Interestingly, the increasing trend in rivaroxaban prescriptions was consistent among the lower BMI categories (underweight, normal, overweight), but not in the obese categories, where the trends (expressed as percentage of patients in each year) started to decline from 2018 to 2020 (i. e., declining percentages of 5%, 31%, and 36% were found in obese class 1, 2 and 3, respectively). Table 4.7 and Figure 4.3 demonstrate the trend in rivaroxaban prescription based on BMI categorization across the study years.

Table 4.7 Number of Patients on Rivaroxaban Therapy Over the Study Period According to Their BMI Classification (n = 4385)[a]

			BMI (Kg/m^2)			
	<18.5	**18.5-24.99**	**25.00-29.99**	**30.00-34.99**	**35.00-39.99**	**≥40**
2015 (n=146)	2 (1.4)	15 (10.3)	46 (31.5)	41 (28.1)	24 (16.4)	18 (12.3)
2016 (n=465)	5 (1.1)	66 (14.2)	130 (28.0)	129 (27.7)	77 (16.6)	58 (12.5)
2017 (n=607)	8 (1.3)	121 (19.9)	186 (30.6)	160 (26.4)	73 (12.0)	59 (9.7)
2018 (n=747)	11 (1.5)	146 (19.5)	227 (30.4)	185 (24.8)	102 (13.7)	76 (10.2)
2019 (n=1137)	17 (1.5)	228 (20.1)	377 (33.2)	280 (24.6)	138 (12.1)	97 (8.5)
2020 (n=1283)	21 (1.6)	310 (24.2)	445 (34.7)	303 (23.6)	121(9.4)	83 (6.5)

[a]Total number of patients with known BMI is 4385 as some BMI data were missing from records
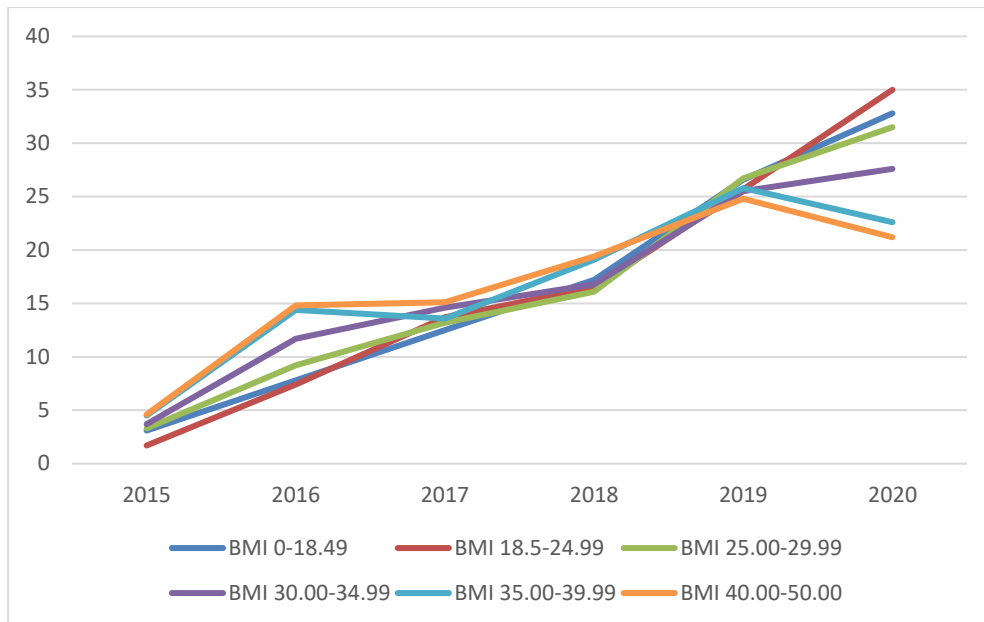
Figure 4.3. Percentages of patients on rivaroxaban therapy over the study period according to their BMI classification. This figure is Microsoft Excel-generated.

4.2.3 Rivaroxaban-related characteristics and clinical outcomes according to body mass index

Table 4.8 indicates the rivaroxaban dosing regimens and their distribution across the BMI-classified groups. The findings suggest that 20 mg rivaroxaban once daily was the most common dosing regimen across the study period [2866 patients, (61.9%)], followed by 10 mg rivaroxaban once daily [1310 patients, (28.3%)]. In addition, the prescribing of rivaroxaban 20 mg once daily was significantly higher as the BMI of patients increases [i.e., 50% among the underweight, 56.9% among normal weight, 59.5% among overweight, 65.1% among obese class 1, 63.9% among obese class 2, and 65.9% among obese class 3 ($p<0.001$)]. The duration of rivaroxaban therapy significantly increases as the BMI increases ($p<0.001$) (Table 4.8). The most common clinical indication for the use of rivaroxaban was NVAF (1351 patients, 29.1%), followed by DVT (402 patients, 8.7%). The mean follow-up period for study sample was 1.8 years.

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Table 4.8 Rivaroxaban Dosing Regimen Within the Study Sample According to Body Mass Index (n = 4633)[a]

	BMI (Kg/m^2)							
Dosing regimen, n (%)	Total (n=4633)[a]	<18.5 (n=64)	18.5 to 24.99 (n=885)	25 to 29.99 (n=1409)	30 to 34.99 (n=1097)	35 to 39.99 (n=535)	≥40 (n=390)	*p*-value
2.5 mg twice a day	1 (0.02)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	
10 mg once a day	1310 (28.3)	22 (34.4)	297 (33.6)	416 (29.5)	299 (27.2)	137 (25.6)	87 (22.3)	<0.001[b]
15 mg once a day	456 (9.8)	10 (15.6)	84 (9.5)	154 (11.0)	84 (7.7)	56 (10.5)	45 (11.5)	
20 mg once a day	2866 (61.9)	32 (50.0)	504 (56.9)	839 (59.5)	714 (65.1)	342 (63.9)	257 (65.9)	
Duration on rivaroxaban (days), mean (SD)	662.1 (650.9)	478.1 (528.2)	525 (544.2)	621.7 (627.9)	694 (683.2)	817.8 (714.3)	852.4 (732.1)	<0.001[c]

[a]Some data were missing (the total number of patients with known dosing regimen is 4633)

[b]Chi-square test, significant p-value indicates significant association between the dosage regimen and BMI categories.

[c]Kruskal Wallis, significant p-value indicates that the distribution of the dosage regimen is significantly different across the BMI categories.

For the total study sample (4638 patients), 1156 outcome events were identified during the follow-up. After adjustment for follow-up duration and number of patients, the incidence rates of clinical outcome events in the study sample were 1.01, 4.89, 4.44, 0.92, 2.38, and 4.14 per 100-person year for major bleeding, minor bleeding, DVT, PE, stroke, and all-cause mortality, respectively. Interestingly, there was a significant difference in all-cause mortality across the BMI groups ($p <0.001$), but not minor bleeding ($p=0.087$), major bleeding ($p=0.987$), DVT recurrence ($p=0.956$), PE recurrence ($p=0.170$), or stroke ($p=0.886$). Although the differences were not statistically significant regarding minor bleeding and DVT, the highest incidences of these cardiovascular events occurred among morbidly obese patients compared to the other BMI groups (11.8% and 6.9% respectively). Further analysis to compare the clinical outcomes in terms of different dosage regimens did not show statistical significance [major bleeding ($p= 0.759$), minor bleeding ($p=0.454$), DVT ($p=0.058$), PE ($p=0.063$), stroke ($p=0.780$), all-cause mortality ($p=0.076$)]. Table 4.9 represents more details about the clinical indications and the clinical outcomes of rivaroxaban therapy in the study sample.

Table 4.9 clinical Indication and Outcomes of Rivaroxaban Therapy Within the Study Sample

n (%)	Total (n = 4638)	<18.5 (n=64)	18.5-24.99 (n=886)	25.00-29.99 (n=1411)	30.00-34.99 (n=1098)	35.00-39.99 (n=535)	≥40 (n=391)	*p*-value[b]
linical indications[a]								
NVAF	1351 (29.1)	21 (32.8)	207 (23.4)	396 (28.1)	350 (31.9)	174 (32.5)	167 (42.7)	
PE	192 (4.1)	1 (1.6)	37 (4.2)	49 (3.5)	41 (3.7)	28 (5.2)	28 (7.2)	
DVT	402 (8.7)	3 (4.7)	60 (6.8)	120 (8.5)	107 (9.7)	54 (10.1)	23 (5.9)	
DVT + PE	69 (1.5)	0 (0.0)	8 (0.9)	15 (1.1)	19 (1.7)	13 (2.4)	10 (2.6)	<0.001
Hip and knee replacement	39 (0.8)	0 (0.0)	9 (1.0)	9 (0.6)	14 (1.3)	4 (0.7)	2 (0.5)	
Others[c]	140 (3.0)	3 (4.7)	25 (2.8)	53 (3.8)	31 (2.8)	14 (2.6)	10 (2.6)	
Unspecified	2445 (52.7)	36 (56.3)	540 (60.9)	769 (54.5)	536 (48.8)	248 (46.4)	151 (38.6)	
Clinical outcomes								
Major bleeding	72 (1.6)	1 (1.6)	21 (2.4)	21 (1.5)	18 (1.6)	9 (1.7)	8 (2.0)	0.987
Minor bleeding	372 (8.0)	5 (7.8)	61 (6.9)	107 (7.6)	96 (8.7)	50 (9.3)	45 (11.8)	0.087
DVT	270 (5.9)	3 (4.7)	50 (5.6)	82 (5.8)	64 (5.8)	30 (5.6)	27 (6.9)	0.956
PE	41 (0.9)	0 (0.0)	3 (0.3)	17 (1.2)	13 (1.2)	3 (0.6)	2 (0.5)	0.170
Stroke	138 (3.0)	1 (1.6)	29 (3.3)	46 (3.3)	31 (2.8)	13 (2.4)	12 (3.1)	0.886
All-cause mortality	263 (5.7)	12 (18.8)	71 (8.0)	63 (4.5)	52 (4.7)	27 (5.0)	33 (8.4)	< 0.001

NVAF Atrial fibrillation; *PE* Pulmonary embolism; *DVT* Deep vein thrombosis

n (%)	Total (n = 4638)	<18.5 (n=64)	18.5-24.99 (n=886)	25.00-29.99 (n=1411)	30.00-34.99 (n=1098)	35.00-39.99 (n=535)	≥40 (n=391)	*p-value*[b]
				BMI (Kg/m^2)				

[a]Some clinical indication data were missing (total number of patients with known clinical indication is 2193)

[b]Chi-square test, significant p-value indicates a significant association between the parameter and BMI categories.

[c]Include catheter-related thrombosis, case of antiphospholipid syndrome with right big toe ischemia, isolated great saphenous vein thrombosis, cerebral vein thrombosis, protein C deficiency, mesenteric or portal vein thrombosis, sagittal vein thrombosis, rectal clots with ulcer, portal vein thrombosis, protein S deficiency, splenic vein thrombosis, superficial venous thrombosis, brachial artery thrombosis, history of right ovarian vein thrombosis, rheumatic heart disease, mild to moderate mitral stenosis, intracardiac thrombosis

Multivariate logistic regression analyses showed that all-cause mortality was higher in different categories of obese patients as follows: being obese class 1 (OR: 5.4, 95% CI: 2.3–12.2, *p*<0.001); being obese class 2 (OR: 6.5, 95% CI: 2.7–15.6, *p*<0.001); being obese class 3 (OR: 3.7, 95% CI: 1.6–8.7, *p*=0.003) when compared to underweight BMI group mortality rates. Regression analysis did not show significance for DVT recurrence and stroke with any variables. More details about the regression analyses results are shown in Table 4.10.

Table 4.10 Multiple Logistic Regression for the Predictors of Clinical Outcomes Among Patients Receiving Rivaroxaban Therapy

Clinical outcomes	*p*-value	Odd ratios	95% CI for population odd ratio
Major bleeding [a]			
Female gender	0.015	1.9	1.138 – 3.323
Number of co-medications	<0.001	1.301	1.120 - 1.510
Diabetes	0.044	1.835	1.017 – 3.310
Hyperlipidaemias	0.037	1.989	1.043 – 3.796
Liver disease	0.025	0.345	0.136 – 0.876
Minor bleeding [a]			
Female gender	<0.001	1.569	1.223 – 2.013
Nationality (being Qatari)	0.003	1.622	1.178 – 2.233
HTN	<0.001	0.571	0.428 – 0.763
Anaemia	<0.001	0.486	0.343 – 0.691
Duration on rivaroxaban	<0.001	1.00	1.00 – 1.00
PE			
Age	0.009	1.035	1.009 – 1.062
Mortality			
Nationality (being Arabs, non-Qatari)	0.034	1.391	1.026 – 1.886
Nationality (being non-Arabs)	<0.001	2.166	1.445 – 3.249
Age	<0.001	0.944	0.934 – 0.954
BMI (obese class 1)	<0.001	5.354	2.352 – 12.191
BMI (obese class 2)	<0.001	6.536	2.739 – 15.600

Clinical outcomes	*p*-value	Odd ratios	95% CI for population odd ratio
BMI (obese class 3)	0.003	3.700	1.567 – 8.737
Number of medications	0.002	0.879	0.811 – 0.953
Diabetes	0.010	1.537	1.008 – 2.132
Hyperlipidaemia	<0.001	0.471	0.334 – 0.664
Anaemia	0.013	1.741	1.124 – 2.698
Kidney disease	0.025	1.488	1.051 – 2.107

[a]Reference group is NO bleeding; Only variables which have statistically significant *p* values in the multiple logistic regression model are displayed in this table

4.3 Results for Phase Three – Pharmacokinetics and Pharmacodynamics of Single Dose Rivaroxaban under Fed State in Obese vs. Non-Obese Subjects: An Open-Label Controlled Clinical Trial (RIVOBESE-PK)

4.3.1 Subject enrollment and baseline characteristics

Seventy volunteers were screened, of whom 36 have met the eligibility criteria and assigned to one of the two groups based on BMI: obese group (BMI $\geq$35 kg/m^2) and non-obese group (BMI 18.5–24.9 kg/m^2). All of the participants completed the study per protocol, with no dropouts (Figure 4.4). Recruitment of study participants took place in the period between 1 July to 31 July 2022.
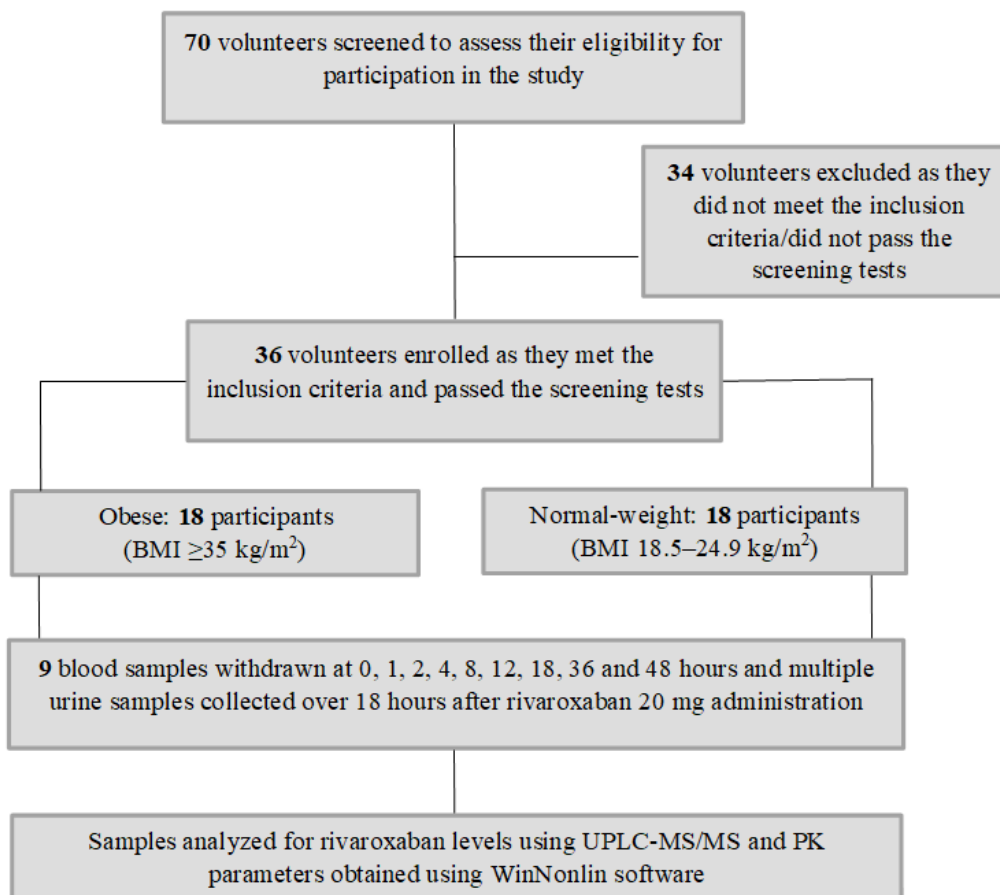
Figure 4.4. Flowchart diagram of the study workflow

Baseline demographic characteristics and laboratory examinations were similar between the two groups, except for age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and fasting plasma glucose level (p=0.007, 0.019, 0.034, and 0.005, respectively), which were significantly higher in the obese participants (Table 4.11). However, neither simple linear regression analysis (p=0.768, 0.254, 0.406, and 0.494; respectively) nor multiple linear regression analysis (p=0.419, 0.651, 0.783, and 0.515; respectively) has shown an association between these variables and the C_{max}, eliminating the probability of these variables' effect on the C_{max}. Rivaroxaban was well-tolerated and no deaths or adverse events were reported in the study participants of both groups.

Table 4.11 Participants' Demographic Characteristics and Laboratory Examinations

at Baseline (n = 36)

Characteristics[*]	Total (n=36)	Obese (n=18)	Non-obese (n=18)	*p*-value
Age (years)	31.1 (11.43)	35.6 (11.7)	26.6 (9.5)	0.007[a]
Body weight (kg)	89.5 (24.3)	111.5 (11.7)	67.4 (7.3)	<0.001[a]
BMI (kg/m^2)	29.6 (7.9)	37.0 (2.6)	22.2 (2.2)	<0.001[a]
Smokers, n (%)	17 (47.2)	6 (33.33)	11 (61.11)	0.095[b]
Total bilirubin (mg/dL)	0.733 (0.29)	0.731 (0.301)	0.736 (0.28)	0.995[c]
Direct bilirubin (mg/dL)	0.241 (0.088)	0.217 (0.061)	0.264 (0.105)	0.114[c]
Creatinine (mg/dL)	0.857 (0.104)	0.837 (0.096)	0.877 (0.111)	0.255[c]
Blood urea nitrogen (mg/dL)	27.92 (6.9)	27.1 (5.45)	28.7 (8.2)	0.491[c]
ALT (U/L)	24.28 (13.63)	30.33 (15.75)	18.2 (7.55)	0.019[a]
AST (U/L)	19.70 (7.6)	22.2 (8.04)	17.17 (6.37)	0.034[a]
Albumin (g/dL)	4.67 (0.2)	4.64 (0.17)	4.7 (0.22)	0.254[a]
Total cholesterol (mg/dL)	162.6 (36.2)	170.3 (38.98)	155.0 (32.5)	0.21[c]
Triglycerides (mg/dL)	104.78 (67.9)	123.7 (85.6)	85.9 (37.5)	0.097[a]
HDL (mg/dL)	43.2 (7.9)	41.8 (8.64)	44.67 (7.08)	0.280[c]
LDL (mg/dL)	98.5 (31.6)	103.78 (35.4)	93.2 (27.2)	0.320[c]
Fasting plasma glucose (mg/dL)	88.31 (8.3)	92.1 (7.97)	84.6 (6.96)	0.005[c]

*Values presented as mean (SD) unless otherwise indicated. [a]Mann-Whitney U test,

[b]Chi-square test; [c]Independent sample t test.

Characteristics[*]	Total	Obese	Non-obese	p-value
	(n=36)	(n=18)	(n=18)	

BMI body mass index; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein

4.3.2 Rivaroxaban PK parameters

The mean plasma concentration vs. time profiles of rivaroxaban after a single oral dose of 20 mg are shown in Figure 4.5 (A) and Appendix 10, and the PK parameters are summarized in Table 4.12. Insignificant decrease of 13.5% in the C_{max} was observed in obese compared to non-obese participants (339.7±84.2 vs. 392.9±78.9 ng/mL; p=0.059). Moreover, some PK parameters were observed to be lower for obese participants (i.e., AUC_{0-48}, AUC_{0-inf}, $t_{1/2}$), and others were observed to be higher for obese participants (i.e., V_d and Cl). However, no significant differences between the two groups were found regarding these PK parameters, i.e., t_{max}, AUC_{0-48}, AUC_{0-inf}, k_e, $t_{1/2}$, MRT, V_d/F, and Cl/F (p= 0.303, 0.490, 0.678, 0.569, 0.310, 0.176, 0.817, 0.614, respectively).

Furthermore, a subgroup analysis of only obese class III participants with BMI >40 kg/m^2 and/or body weight >120 kg - compared to non-obese participants - was performed. The C_{max}, t_{max}, AUC_{0-48}, AUC_{0-inf}, k_e, $t_{1/2}$, MRT, V_d/F, and Cl/F values revealed no statistically significant differences between the two groups (p=0.071, 0.310, 0.939, 0.599, 0.721, 0.614, 0.055, 0.587, 0.817, respectively); Figure 4.5 (B) and Table 4.13.
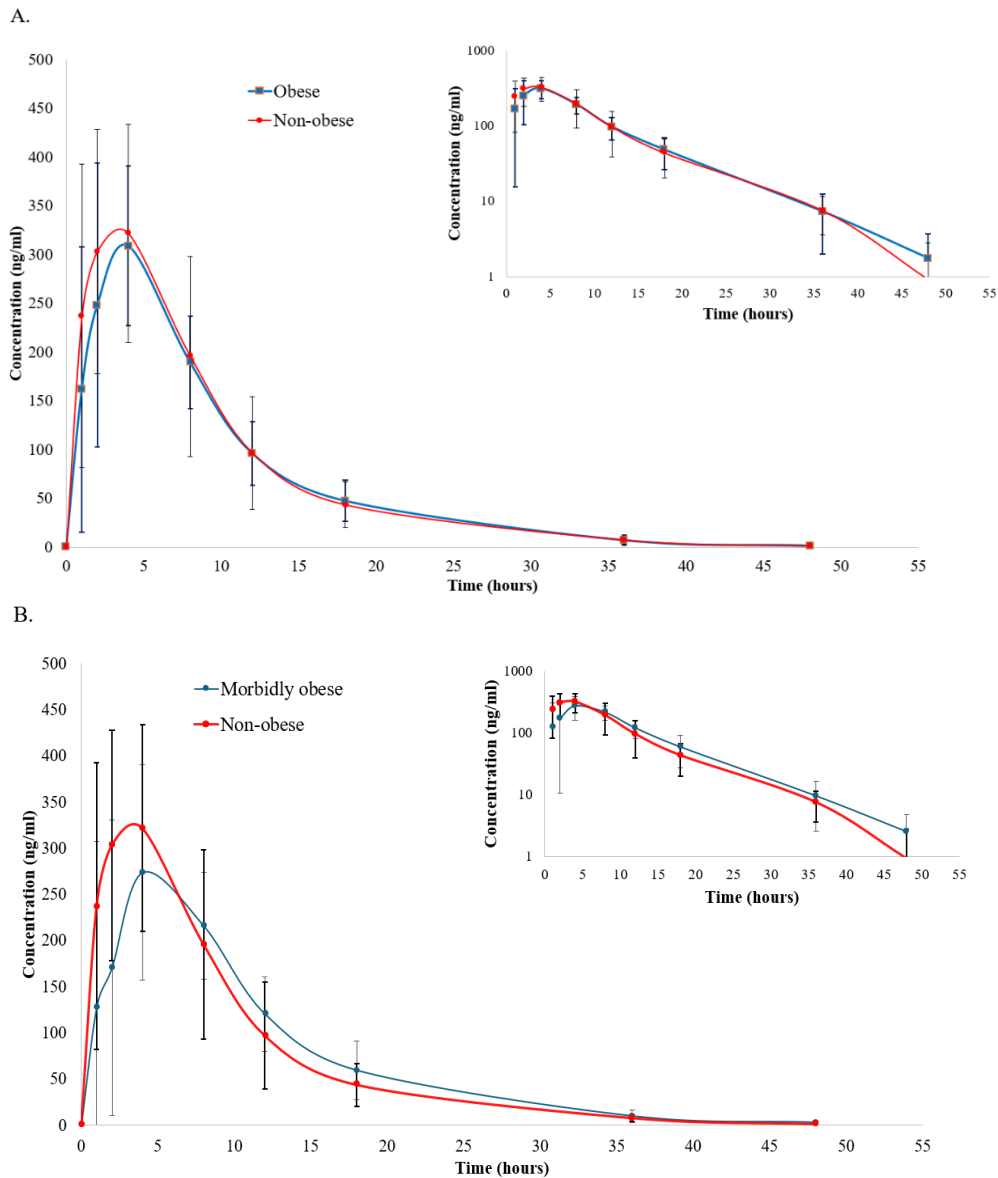
A.

B.

Figure 4.5. (A) Mean plasma concentrations of rivaroxaban versus time curves following a dose of rivaroxaban 20 mg [obese with BMI ≥35 kg/m² (n=18) vs. non-obese with BMI 18.5–24.9 kg/m² (n=18)]; (B) Mean plasma concentrations of rivaroxaban versus time curves following a dose of rivaroxaban 20 mg [morbidly obese with BMI >40 kg/m² and/or body weight >120 kg (n=6) vs. non-obese with BMI 18.5–24.9 kg/m² (n=18)]. The concentrations shown on the graphs are the averages of the individuals' concentrations at each sampling time point. Inlet figures presenting data on log-scale y-axis and showing a linear elimination terminal phase. These figures are Excel Microsoft-generated.

Table 4.12 Pharmacokinetic Parameters Estimated from Plasma Data in Obese and Non-Obese Subjects at Baseline and up to 48 Hours Following an Oral Administration of Rivaroxaban 20 mg (n = 36)

PK Parameter*	Obese (n=18)	Non-obese (n=18)	*p*-value
C_{max} (ng/mL)	339.7 (84.2)	392.9 (78.9)	0.059[a]
t_{max} (hr), median (25th –75th percentile)	4.00 (2-4)	2.00 (2-4)	0.303[b]
AUC_{0-48} (ng.hr/mL)	3339.2 (872.9)	3534.5 (805.3)	0.490[a]
AUC_{0-inf} (ng.hr/mL)	3481.1 (809.2)	3595.3 (805.7)	0.678[a]
k_e (1/hr), median (25th –75th percentile)	0.10 (0.09-0.13)	0.11 (0.08-0.12)	0.569[b]
$t_{1/2}$ (hr)	6.61 (1.4)	7.2 (1.77)	0.310[a]
MRT (hr), median (25th –75th percentile)	9.19 (8.12-10.64)	8.14 (7.64-9.91)	0.176[b]
V_d/F (L), median (25th –75th percentile)	60.38 (45.9-63.5)	56.88 (45.3-72.3)	0.817[b]
Cl/F (L/hr)	6.04 (1.38)	5.812 (1.22)	0.614[a]

*Values presented as mean (standard deviation) unless otherwise indicated. [a]Independent sample t-test; [b]Mann-Whitney U test.

C_{max}: mean±SD of maximum plasma concentration of each participant; t_{max}: mean±SD of the time at which maximum plasma rivaroxaban concentration was achieved for each participant; AUC_{0-48}: area under concentration-time curve from time zero to the last measurable concentration at 48 hr; AUC_{0-inf}: area under concentration-time curve from time zero to infinity; k_e: elimination rate constant; $t_{1/2}$: half-life; MRT: mean residence time. V_d/F: apparent volume of distribution; Cl/F: apparent clearance.

Table 4.13 Pharmacokinetic Parameters Estimated from Plasma Data in Obese (with BMI >40 kg/m^2 and/or body weight >120 kg) and Non-Obese Subjects at Baseline and Up to 48 Hours Following an Oral Administration of Rivaroxaban 20 mg (n = 24)

PK parameter*	Morbidly-obese (n=6)	Non-obese (n=18)	*p*-value
C_{max} (ng/mL)	317.3 (101.6)	392.9 (78.9)	0.071[a]
t_{max} (hr), median (25th –75th percentile)	4.00 (1.8-8)	2.00 (2-4)	0.310[b]
AUC_{0-48} (ng.hr/mL)	3500.7 (1271.2)	3534.5 (805.3)	0.939[a]
AUC_{0-inf} (ng.hr/mL)	3834.8 (1174.9)	3595.3 (805.7)	0.599[a]
k_e (1/hr), median (25th –75th percentile)	0.10 (0.09-0.27)	0.11 (0.08-0.12)	0.721[b]
$t_{1/2}$ (hr)	6.7 (0.9)	7.2 (1.77)	0.614[a]
MRT (hr), median (25th –75th percentile)	12.15 (9.0-12.4)	8.14 (7.64-9.91)	0.055[b]
V_d/F (L), median (25th –75th percentile)	46.68 (38.9-76.4)	56.88 (45.3-72.3)	0.587[b]
Cl/F (L/hr)	5.65 (1.8)	5.812 (1.22)	0.817[a]

*Values presented as mean (standard deviation) unless otherwise indicated. [a]Independent sample t-test; [b]Mann-Whitney U test.

C_{max}: mean±SD of maximum plasma concentration of each participant; t_{max}: mean±SD of the time at which maximum plasma rivaroxaban concentration was achieved for each participant; AUC_{0-48}: area under concentration-time curve from time zero to the last measurable concentration at 48 hr; AUC_{0-inf}: area under concentration-time curve from time zero to infinity; k_e: elimination rate constant; $t_{1/2}$: half-life; MRT: mean residence time. V_d/F: apparent volume of distribution; Cl/F: apparent clearance.

For urine data, no statistically significant difference was found between the two groups in terms of the mean f_e over the collection period (0.289±0.088 vs. 0.242±0.082; p= 0.105). Table 4.13 represents a detailed description of the urine data for both groups.

Table 4.14 Urine Data Obtained in Obese and Non-Obese Subjects During the Collection Period (18 hr) Following an Oral Administration of Rivaroxaban 20 mg (n = 36)

Interval No.	Interval Time Beginning	Interval Time Ending	Time period (hr)	Mid-point time (hr)	Mass recovered (mg), mean (SD)	Average excretion rate (mg/hr), mean (SD)	f_e over the collection period (18hr), mean (SD)
				Obese (n=18)			
1	0.00	3.32	3.32	1.66	1.32 (0.87)	0.40 (0.26)	
2	3.32	6.11	2.79	4.72	1.50 (0.57)	0.54 (0.21)	
3	6.11	9.22	3.11	7.67	1.36 (0.63)	0.44 (0.21)	0.289 (0.088)
4	9.22	12.21	2.99	10.72	0.87 (0.32)	0.29 (0.10)	
5	12.21	15.24	3.03	13.73	0.49 (0.23)	0.16 (0.79)	
6	15.24	18.28	3.05	16.76	0.25 (0.13)	0.07 (0.04)	
				Non-obese (n=18)			
1	0.00	3.30	3.38	1.692	1.41 (0.74)	0.42 (0.22)	
2	3.38	6.10	2.72	4.74	1.03 (0.47)	0.38 (0.17)	
3	6.10	9.21	3.09	7.65	1.14 (0.71)	0.37 (0.24)	
4	9.22	12.23	2.01	10.73	0.71 (0.47)	0.24 (0.15)	0.242 (0.082)
5	12.20	15.24	3.02	13.71	0.36 (0.17)	0.12 (0.06)	

Interval No.	Interval Time		Time period (hr)	Mid-point time (hr)	Mass recovered (mg), mean (SD)	Average excretion rate (mg/hr), mean (SD)	f_e over the collection period (18hr), mean (SD)
	Beginning	Ending					
6	15.22	18.21	2.99	15.88	0.20 (0.117)	0.07 (0.039)	

f_e: fraction of dose recovered unchanged in urine over 18 hr post-dosing

4.3.3 Rivaroxaban pharmacodynamic parameters

The mean plasma concentrations and PT vs. time profiles of rivaroxaban after a single dose of 20 mg are shown in Appendix 11. Statistical analysis of the pharmacodynamic parameters revealed a significant difference between obese and non-obese groups with respect to PT measurements at 1 hr (13.72 vs. 15.58, p=0.013) and 4 hr (13.64 vs. 16.47, p=0.008) (Table 4.15). Similarly, the corresponding INR measurements have shown significant difference between the two groups at 1 hr (1.10 vs. 1.25, p=0.013), and 4 hr (1.09 vs. 1.32, p=0.008). In contrast, no significant difference was found for the aPTT at any time point between the two groups.

Table 4.15 Pharmacodynamic Parameters at Baseline and up to 48 Hours Following an

Oral Administration of Rivaroxaban 20 mg (n = 36)

PD parameter, mean (SD)	Obese (n=18)	Non-obese (n=18)	*p*-value
Prothrombin time (PT)			
At baseline	12.77 (0.60)	12.94 (0.99)	0.501
At 1 hour	13.72 (1.39)	15.58 (2.65)	0.013*
At 2 hours	14.98 (3.57)	16.08 (4.05)	0.396
At 4 hours	13.64 (1.49)	16.47 (4.01)	0.008*
At 8 hours	13.13 (0.78)	13.09 (0.55)	0.883
At 12 hours	13.19 (1.08)	13.12 (0.91)	0.843
At 18 hours	12.75 (0.49)	12.69 (0.47)	0.731
At 36 hours	12.91 (0.84)	13.02 (0.86)	0.697
At 48 hours	12.70 (0.53)	12.76 (0.69)	0.768
International normalized ratio (INR)			
At baseline	1.02 (0.05)	1.04 (0.08)	0.514
At 1 hour	1.10 (0.11)	1.25 (0.21)	0.013*
At 2 hours	1.20 (0.29)	1.28 (0.32)	0.417
At 4 hours	1.09 (0.12)	1.32 (0.32)	0.008*
At 8 hours	1.05 (0.06)	1.05 (0.04)	0.806
At 12 hours	1.06 (0.09)	1.05 (0.07)	0.853
At 18 hours	1.01 (0.03)	1.02 (0.04)	0.963
At 36 hours	1.03 (0.07)	1.04 (0.06)	0.855
At 48 hours	1.02 (0.04)	1.02 (0.06)	0.793
Activated partial thromboplastin time (aPTT)			

PD parameter, mean (SD)	Obese (n=18)	Non-obese (n=18)	*p*-value
At baseline	35.09 (7.80)	40.3 (8.5)	0.067
At 1 hour	45.84 (10.61)	45.85 (17.00)	0.998
At 2 hours	40.57 (9.15)	45.93 (13.47)	0.172
At 4 hours	40.49 (12.34)	49.43 (15.55)	0.065
At 8 hours	38.32 (9.69)	42.01 (6.82)	0.195
At 12 hours	38.14 (6.13)	37.93 (7.11)	0.927
At 18 hours	31.07 (5.64)	32.31 (5.54)	0.745
At 36 hours	38.36 (16.49)	40.79 (20.10)	0.694
At 48 hours	31.98 (10.47)	31.97 (14.87)	0.997

*Indicates statistically significant difference

CHAPTER 5: DISCUSSION AND CONCLUSIONS

5.1 Summary of the Study Phases

Many studies have been conducted to investigate the use of rivaroxaban in obese population [46-49], and some have suggested that decreased drug exposure, reduced peak concentration and shorter half-life occur with increasing weight among obese population [79, 81-83, 91]. There is still a lack of clinical consensus regarding rivaroxaban dosing in obese population due to the limited PK data of rivaroxaban among obese population [71, 88, 99, 100] and thus, some of the current guidelines do not recommend the use of rivaroxaban in patients with BMI of >40 kg/m^2 or a weight of >120 kg [88]. Furthermore, several studies found that obesity is a significant risk factor for VTE [12, 94, 273], and a large proportion of patients who receive rivaroxaban are obese [15, 92]. The main goal of this project is to significantly contribute to resolving the aforementioned clinical controversy by generating a conclusive evidence pertaining to the PK - and thus the therapeutic dosing - of rivaroxaban in obese population.

5.2 Discussion and Interpretation

5.2.1 Discussion for Phase One – Rivaroxaban pharmacokinetics in obese subjects: a systematic review

The strength of the systematic literature review was that it focused exclusively on the PK of rivaroxaban, where all available PK parameters (AUC, C_{max}, t_{max}, V_d, CL, $t_{1/2}$) among obese subjects compared to the general population were pooled and extensively analyzed in order to assess the potential effect of obesity on the parameters. In contrast, previously published reviews have provided an overview of the effectiveness and safety of DOACs, including rivaroxaban, in obese population [99,

274, 275]. The findings reported in the systematic review provided an evidence that obesity has variable impact on some of the rivaroxaban's pharmacokinetic parameters (particularly C_{max}, AUC, CL and V_d). Obesity was found to lower the C_{max} of rivaroxaban following 20 mg dose [81, 83, 89], lower the AUC_{0-24} following 20 mg dose [77, 78], increase the clearance (the values were comparatively higher and have fallen outside the clearance range reported for general populations) [49, 78], while it has inconclusive effect on the V_d [49, 78].

To some extent, the data reported in the systematic review were consistent with previously published rivaroxaban PK studies in the general population. The findings regarding the C_{max} of 10 mg rivaroxaban in obese subjects were comparable to previous studies. For example, three studies [49, 80, 209] reported the C_{max} of rivaroxaban after 10 mg dose in the general population to be between 143-180 $\mu g.L^{-1}$, a range that covers the value in one of the included studies for obese subjects (149 $\mu g.L^{-1}$) [49]. However, the C_{max} following 20 mg dose was found to be within 214-305 $\mu g.L^{-1}$ in four of the included studies for obese subjects [77, 81, 83, 89], three of which were considerably lower than the values reported in the general population (299-360 $\mu g.L^{-1}$) [77, 80, 209], implying a possible effect of body weight on C_{max} after the 20 mg dose.

The AUC value following 10 mg rivaroxaban dose in one of the included studies was 1155 $\mu g.h.L^{-1}$ [49], which was higher than the reported values in the general population (range 864-1029 $\mu g.h.L^{-1}$) [49, 80, 209]. This is in agreement with guidelines recommendations which endorse that rivaroxaban could produce the desired exposure in obese subjects and thus could be prescribed without dose adjustment [60, 276]. A Cl value of 7.86 $L.hr^{-1}$ and a V_d value of 73.4-82.8 L in the obese population [49, 78] were interestingly falling in the middle of the ranges of values reported in the general population (Cl ranged from 5.57-11.3 L.hr-1 and V_d ranged from 59.4-104 L)

[48, 77, 80, 90], and thus the same trend was calculated for $t_{1/2}$ as well (using the equation: $t_{1/2}=0.693\frac{V_d}{Cl}$). As the indicated values of Cl and V_d in the obese population were extracted from two different studies [49, 78], and their corresponding values in the general population were extracted from five studies, such comparison is inconclusive in demonstrating the effect of obesity on Cl and V_d.

High body weight is known to significantly increase the V_d of many medications [277, 278]. Rivaroxaban moderate lipophilicity could partly explain the change in V_d that was observed in obese subjects in some of the included studies [48, 49]. A population PK model for rivaroxaban showed a positive correlation between V_d and body weight [279]. In addition, some other factors may affect the PK processes in obesity. For example, a change in albumin binding with an acidic drug (i.e., rivaroxaban) due to displacement by fatty acids, and thus changes in V_d, Cl and $t_{1/2}$, are expected in obese population. Moreover, the potential decrease in hepatic activity of cytochrome P450 (CYP) 3A4 in obesity may also explain partially any change in the PK parameters of rivaroxaban in obese population [220, 238]. Virtual subpopulations were simulated in the models developed in some of the included studies. For example, subpopulations with different weights and BMI categories, including the obese, were defined and the effects of these covariates on PK parameters such as the apparent Cl and V_d were simulated [90]. The covariate analysis revealed a minor effect of weight/BMI on rivaroxaban exposure [90]. On the other hand, another modelling study had demonstrated a greater effect of some covariates on the PK parameters such as V_d of rivaroxaban, emphasizing that the estimates of PK parameters may not reflect real-world populations and suggesting that larger datasets from real-world patients are warranted [48].

In the systematic review, the included studies were appraised for

methodological quality and data extraction, and thus some methodological issues were identified [280]. A comparatively short-term follow up of patients was noted, as two of the included studies were single-dosed and a third one was for about 10 days [82, 83, 89], all with only one time-point blood sampling. However, longer duration and multiple time points of follow-up and blood sampling may represent a better and clearer picture of rivaroxaban PK profile in obese population. Furthermore, in some of the included studies, the PK of rivaroxaban was examined retrospectively [78, 79, 81, 89], which made it difficult to ensure that the data were measured consistently, without confounding factors that could affect the results. Conducting the systematic literature review was challenging, as the data generated from the included studies have considerable heterogeneity in study designs, clinical indications, rivaroxaban dosing regimens, and the PK parameters that were evaluated and reported. Due to the heterogeneity of data in the included studies, the narrative approach was particularly selected for data synthesis, and thus the meta-analysis approach was deemed inappropriate. To accurately perform data synthesis utilizing the narrative approach, two reviewers systematically summarized the key points of each study's methodology and results to synthesize reliably the findings/conclusions of this systematic review.

Some limitations were identified for the systematic review as follows: different doses (ranged between 2.5-30 mg) of rivaroxaban were used in the included studies thus comparisons of parameters between obese and no-obese was challenging. Moreover, the selected studies lacked the reporting of the three related parameters (V_d, CL and $t_{1/2}$) in their results; thus, the comparison of these PK parameters between obese and general population subjects was based on values extracted from different studies or calculated using PK values from the same study. In other words, the missing link between the observed changes in V_d and Cl (and the calculated $t_{1/2}$) might be due to

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extracting the PK values from different studies. Another limitation is that the majority of the included studies were not specifically designed to investigate the impact of body weight on rivaroxaban PK parameters (except five study which included only obese/morbidly obese subjects to investigate the PK parameters [78, 79, 82, 83, 89]). Furthermore, the obese/morbidly obese subjects were accounting for unknown or small proportion of the whole sample size (as low as 18%) among the included studies, potentially skewing the results obtained from this systematic review [48, 49, 77, 80, 81, 89, 90]. In addition, some of the included studies have not analyzed their findings based on the BMI or weight categories, except in three studies which have covered, partially, the PK parameters in obese subjects [49, 77, 89]. Finally, despite that the systematic review has contributed to the understanding of rivaroxaban's PK parameters in the obese population, the included studies have not distinguished between large and obese subjects upon recruitment and thus have not examined the difference in PK parameters. There is a noteworthy difference in body fat composition between these two groups, which may significantly affect the PK parameters for lipophilic medications such as rivaroxaban, and consequently the interpretation of the findings and outcomes of the systematic review. These limitations highlight the challenges in analyzing the available data and deriving current outcomes regarding rivaroxaban PK in obese subjects.

By conducting the systematic review and analyzing the available evidence of rivaroxaban PK in obese population in the literature, it was found that the reviewed evidence is insufficient to conclude whether or not the differences in the reported PK parameter values would require dose adjustment of rivaroxaban in obese population. This has led us to the second phase of the project, in an attempt to examine the real-world prescribing trends and the clinical outcomes of rivaroxaban based on BMI categorization across six-year period in Qatar.

5.2.2 Discussion for Phase Two – Trends in prescribing and outcomes in obese versus non-obese patients receiving rivaroxaban therapy: a retrospective observational study using real-world data

This study was the first to be conducted locally or internationally to investigate the prescribing trends of rivaroxaban and the clinical outcomes based on BMI categorization.

Overall, the findings of the second phase of the study showed that rivaroxaban prescription has increased from 3.3% in 2015 to 28.9% in 2020 (i.e. more than 8-fold increase across the 6-year time span), which substantiates previous findings in the published literature [281-283]. Notably, an overall increase in rivaroxaban prescription was also reported among all BMI groups between 2015 and 2020 (i.e., 9.6, 19.6, 8.5, 6.5, 4, and 3.6 folds among underweight, normal weight, overweight, obese class 1, obese class 2, and obese class 3, respectively). This trend in rivaroxaban prescription reported in the study is consistent with the global rivaroxaban prescribing trends, the rank of which has increased from 132 in 2015 to 86 in 2020 [32]. The rank refers to the frequency that a given medication is prescribed within a calendar year compared to all other medications.

It is noteworthy that the increasing trend in the prescription of rivaroxaban remained steady in the lower BMI categories (underweight, normal weight, and overweight patients), while the utilization began to decline in all the obese categories in the last 2 years of the retrospective data analysis. This distinction in the trend of rivaroxaban prescribing in obese vs. non-obese populations may reflect clinicians' hesitance in prescribing rivaroxaban for obese population in light of the emerging and conflicting evidence and/or recommendations in recent years [49, 81, 284-286]. Such key recommendations were reported in the ISTH 2016 statement [87] '*We suggest that*

DOACs should not be used in patients with a BMI of >40 kg m² or a weight of >120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under dosing in the population at the extreme of weight', which emphasizes the usefulness of exploring such prescription trends of rivaroxaban in real-world practice [99, 287].

With regard to clinical outcomes, the findings suggest that morbidly obese patients had significantly higher numbers of all-cause mortality (8.4%) compared to other BMI groups (except underweight category). The all-cause mortality rate reported in the morbidly obese patients in this study was comparatively higher than the 6.2% and 5.6% reported in previous studies [288, 289], and fairly close to the 7.1% all-cause mortality reported in another study [290]. It should be highlighted that the higher mortality rate observed in underweight patients (18.8%) may be attributed to the large proportion of elderly patients (≥75 years old) in this group [291]. Conversely, DVT incidence was not significantly different between BMI groups; the finding that is in agreement with a previous study [292], and in contradiction with some earlier studies [293, 294] that have found a remarkable association between BMI and DVT during anticoagulation, and this might be due to the differences in study settings, designs, time span covered by the studies, and other confounding factors. On the other hand, our DVT results are almost indistinguishable from several previous studies which have raised the concern about thromboembolic events recurrence and the subclinical effect during rivaroxaban anticoagulation therapy among obese patients [87, 295]. For minor bleeding incidence in morbidly obese patients, the reported 11.8% in this study was considerably higher than what was reported in earlier studies [82, 289].

Multivariate logistic regression results showed that hypertension and number of medications have affected the bleeding outcome in the current study, the findings which were consistent with previous studies [296-298]. On the other hand, female gender effect on bleeding was not confirmed/found by previous studies in the literature as both genders were having the same bleeding risk upon rivaroxaban use [299]. Although our results that showed the effect of diabetes on bleeding outcome for patients on rivaroxaban were not found in earlier studies, the hemorheological changes that diabetes cause in general population (in the context of anticoagulation) have been extensively discussed in the literature [300-302]. Similarly, the effect of liver disease on bleeding is well-known [303, 304]; however, it was not investigated in the context of anticoagulation. As for the duration of rivaroxaban therapy effect on bleeding, and in accordance with our findings, many studies confirmed the increased risk of bleeding with increased therapy duration for oral anticoagulants [305-309]. Furthermore, our results regarding age as a risk factor for both pulmonary embolism and for all-cause mortality were in line with previous finding in the literature, respectively [310-313]. With regard to the effect of age, diabetes, and kidney disease on all-cause mortality outcome, our study results were consistent with the previous studies [314-318].

Some limitations, most of which are inherent to all retrospective studies, were identified in this phase of the study. First, the obtained results were based on HMC medical records only, and even though HMC is the principal public healthcare provider in the State of Qatar, it cannot be ruled out that the results would change if the private hospitals and centers were included. Second, including data from 2021 and 2022 records would be advisable, as it would provide a more complete picture of rivaroxaban prescription trends. However, this two-year gap was not included to allow for outcomes capturing among patients (i.e. clinical outcomes for rivaroxaban use were captured until

December 2021). Lastly, neither the effect of potential interacting co-medications nor the dose of rivaroxaban have been assessed in this study, which could possibly affect the current study findings and their interpretation.

5.2.3 Discussion for Phase Three – Pharmacokinetics and pharmacodynamics of single dose rivaroxaban under fed state in obese vs. non-obese subjects: an open-label controlled clinical trial (RIVOBESE-PK)

The culmination of this PhD research project is encapsulated in the third and final phase, which was constructed based on the preceding two phases. This clinical PK trial was conducted to investigate the PK and PD profiles of rivaroxaban in obese participants with BMI $\geq$35 kg/m^2 when compared to normal-weight participants with BMI of 18.5 to <25 kg/m^2. Two groups of participants were enrolled in the study and received a single dose of 20 mg rivaroxaban film-coated tablet as the study intervention. Rivaroxaban concentrations were measured in plasma and urine samples, and the PK parameters (i.e., C_{max}, t_{max}, AUC_{0-48}, AUC_{0-inf}, k_e, $t_{1/2}$, MRT, V_d/F, Cl/F, and f_e) and PD parameters (i.e., PT, INR, and APTT) were determined and compared between the two groups. The main analysis (n=36) revealed no significant difference between the two groups in terms of C_{max}, t_{max}, AUC_{0-48}, AUC_{0-inf}, k_e, $t_{1/2}$, MRT, V_d/F, Cl/F, and f_e (p=0.059, 0.303, 0.490, 0.678, 0.569, 0.310, 0.176, 0.817, 0.614,0.105 respectively). Moreover, subgroup analysis for participants with BMI >40 kg/m^2 and/or weight >120 kg (n=24) yielded similar results (p=0.071, 0.310, 0.939, 0.599, 0.721, 0.614, 0.137, 0.055, 0.587, 0.817, 0.457, respectively).

The results showed that C_{max} was comparable in obese and non-obese participants (p=0.059). In obese participants, the C_{max} was 339.7 ng/mL, which was well substantiated by the C_{max} value (305.0 ng/mL) following 20 mg rivaroxaban reported by Speed *et al.* in obese subjects with an average weight of 125 kg [77].

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Moreover, the C_{max} range for obese participants (207-485 ng/mL) in the current study was comparable to the C_{max} range (200-350 ng/mL) reported in a previous study [79]. On the other hand, one previous study has reported lower C_{max} of 214 and 220 ng/mL for AF and VTE cohorts with median body weight of 139 kg and BMI $\geq$40 kg/m^2 respectively [83]. This difference in C_{max} may be attributed to the difference in body weight and BMI (i.e., mean weight 111.5 kg and BMI 37.0 kg/m^2 in the current study), a different technique used for rivaroxaban concentration measurement (anti-Xa assays vs. UPLC-MS/MS), and to the fact that the C_{max} was determined using one sampling time point within 2-4 hr post rivaroxaban dosing in the previous study.

To be able to compare the AUC_{0-48} to the literature, median [range] value for obese participants in our study was calculated to be 3511 [2569-3745] ng.hr/mL, the value which was almost double the AUC_{0-24} reported by a previous study (1204 [861–1390] ng.hr/mL) which was conducted on AF patients who had a mean BMI of 44 kg/m^2, and utilized the anti-factor Xa assay for rivaroxaban level determination [91]. Another previous study, which retrospectively determined AUC_{0-24} via PK simulation from single time points in patients, reported the mean of AUC_{0-24} to be 2800 ng.hr/mL, which is lower than the reported value in the current study (3339.2 ng.hr/mL) [77]. These differences are clearly due to the partially estimated AUC (over 24 hr instead of 48 hr). Similarly, for AUC_{0-inf}, a higher value of 3481.1 ng.hr/mL was reported in the present study compared to 1155 ng.hr/mL reported in a prior study on subjects >120 kg [61]. This difference could be attributed to the different doses investigated in each study (20 mg vs. 10 mg).

A median V_d/F of 60.38 L in obese participants in this study was comparable to previously reported values of 73.40 and 82.80 L [61, 91]. To be able to compare our apparent clearance value to the literature, median value in obese participants was

calculated (5.63 L/hr), the value which was relatively lower than a previously reported median value of 16.80 L/hr [91], in which blood samples were obtained during steady-state which might be a possible reason for the differences in the clearance values [91]. On the other hand, the mean apparent clearance for obese subjects reported by a previous study [49] was 7.86 L/hr, which is comparable to the 6.04 L/hr reported in our study. It is noteworthy that the results obtained from the subgroup analysis (n=24) align with those of the main analysis (n=36), which emphasize that the conclusion of 'no difference in PK parameters of rivaroxaban' applies to the morbidly obese subjects, comprising 33% of the study sample.

Regarding the urine data, extrapolating the f_e values obtained in this study from the 18-hr urine collection period to 48-hr showed that f_e can reach up to 43% and 35% for obese and non-obese populations, respectively, which are in line with the 36% reported for the rivaroxaban dose excreted unchanged in urine for the general population [28]. To corroborate these points, the comparison of the PK parameters reported in our study with those reported previously was challenging due to substantial variations in study design, participants' characteristics, rivaroxaban dose, sampling time points, and rivaroxaban concentration measurement techniques.

Interestingly, despite the known differences between obese and non-obese subjects in terms of body fat composition and the consequent expected changes in the distribution and resulting PK profile and parameters of lipophilic drugs, the findings revealed no differences (obese or morbidly obese vs. non-obese). However, the results demonstrated a decreasing trend (although not significant) of C_{max} in the obese (339.7 ng/mL) and morbidly obese (317.3 ng/mL) compared to the non-obese (392.9 ng/mL) populations. Also, a longer t_{max} values (although not significant) were observed in the obese (4 hr) and morbidly obese (4 hr) populations compared to the non-obese (2 hr)

population. In addition, an increasing trend (although not significant) MRT in the obese (9.19 hr) and morbidly obese (12.15 hr) compared to the non-obese (8.14 hr) populations was observed. This could be attributed in part to rivaroxaban being in BCS II (low solubility and high permeability) with moderate lipophilicity ($logP = 1.5$) reflecting low-to-medium affinity to peripheral tissues [28], which might lead to distribution in the excess fat tissues within morbidly obese, although not supported by the current reported V_d data (56.88, 60.38, 46.68 L in the non-obese, obese, and morbidly obese populations, respectively) or the AUC_{0-inf} data (3595.3, 3481.1, and 3834.8 ng.hr/mL in the non-obese, obese, and morbidly obese populations, respectively).

Regarding the PD assessment of rivaroxaban, PT, INR, and aPTT coagulation tests were performed at baseline and up to 48 hr post-dosing. Comparisons with reported studies were not feasible due to the absence of any previous studies focusing on assessing the PD parameters of rivaroxaban in obese population. Although PT and aPTT have not been demonstrated to measure the anticoagulation activity of rivaroxaban, it is worth mentioning that these coagulation tests are prolonged by rivaroxaban in a dose-dependent manner and thus, would inform clinical decisions only in emergency cases, i. e., bleeding or urgent invasive therapy need [60, 201]. All PD parameters investigated in this study were used to compare between the obese and non-obese populations. However, the use of these tests in clinical practice settings for coagulation activity monitoring can lead to false interpretations [319]. Although in clinical practice, the use of the concentration-based anti-Xa assay is the gold standard for assessing the PD of rivaroxaban, in this study we did not measure it since we have already measured the plasma concentration using robust analytical techniques.

It is plausible that a few limitations in this study could have influenced our

results. Firstly, recruitment of female volunteers was not possible due to the hospitalization for over 18 hr, including an overnight stay, which was inconvenient to females in our setting and thus, only male volunteers were recruited. Secondly, this study included obese class II and III patients, but with a majority of a BMI < 40 kg/m^2, and therefore there is a likelihood that findings may have been skewed. Should obese class III only be recruited, significant differences in PK parameters are possible. Thirdly, urine samples were collected from participants for up to 18 hr (around 3 x $t_{1/2}$ only); therefore, partial capture of renal excretion was achieved and further urine samples for up to at least 5 x $t_{1/2}$ would be needed to determine accurately 95-99% of rivaroxaban excreted unchanged in urine. Fourthly, while the study exhibits a controlled, parallel-group design, it is worth noting that a single dose might, to some extent, not fully reflect the PK parameters that could be observed in a more comprehensive, long-term (multiple-dose) design. Lastly, the observed inter-subject variation (inferred by SD and interquartile range) might indicate the need for higher sample size, and may have contributed to the difficulty in identifying significant differences between obese and non-obese subjects regarding different PK parameters. All aforementioned limitation would affect the generalizability of the study.

5.3 Contribution to Knowledge

Due to its considerable effectiveness and safety, rivaroxaban, has been incorporated into guidelines as a standard of care for VTE and NVAF, and has largely replaced the conventional anticoagulants. Despite that obesity prevalence is increasing globally and that obese population constitute a large proportion of the population receiving rivaroxaban, guidelines have provided limited guidance on the optimal dosing of rivaroxaban in this population, leading to clinical uncertainty and potential

suboptimal anticoagulation therapy.

This three-phase research project advances the field by bridging the knowledge gap surrounding rivaroxaban dosing in obesity, and provides a significant contribution to the understanding of rivaroxaban therapy in obese subjects. Our findings represents the first comprehensive PK profiling of rivaroxaban in its therapeutic dose among obese population. Our findings shed light on the influence of obesity on rivaroxaban PK, which will inform future guidelines, enhance patient care, and empower healthcare providers to make informed decisions when managing rivaroxaban therapy in this high-risk population.

5.4 Recommendations for Future Research

Future research involves conducting a multiple dose study to capture any potential in PK parameter changes in the steady state. Moreover, recruiting both genders will be of benefit to confirm the observed PK changes based on the physiological differences between genders. In addition, recruiting real-world patients with multiple comorbidities would be more clinically relevant, as it mirrors the complexity of patient populations seen in practice and hence improves the generalizability of the results to real-world settings. Lastly, focusing on subjects with a BMI exceeding 40 kg/m^2 or a weight exceeding 120 kg solely will be a plus for any future study. We are currently extending the project to include phase 4, as we are developing a physiologically-based pharmacokinetic (PBPK) model of rivaroxaban to explore the effect of extreme BMI ($\geq$45 kg/m^2) on rivaroxaban PK parameters.

5.5 Conclusions

This project has set the foundation for clinical practice guidelines regarding

rivaroxaban dosing in obese population. Furthermore, it has succeeded in providing a full PK profile of rivaroxaban among obese subjects using a well-designed controlled multiple sampling approach and a therapeutic dose of rivaroxaban. The evidence from the prospective controlled clinical trial demonstrated that PK profile after oral rivaroxaban 20 mg were mostly similar in obese compared to non-obese participants. Maximum rivaroxaban concentration and exposure inferred by AUC were not affected in the obese participants. Taken together, dose adjustment of rivaroxaban is probably unwarranted in the obese population. Our findings will be constructive in helping to solve the clinical controversy and the therapeutic challenge regarding rivaroxaban use in the obese population. Further studies including real-world obese population, especially those with BMI $\geq$40 kg/m^2, are recommended to confirm the current findings. This population will have more excess fat accumulation which may cause different PK profile of rivaroxaban in the body.

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APPENDICES

Appendix 1: Participants Screening Procedures/Examinations, Inclusion

Criteria, and Exclusion Criteria

- **Screening Procedures/Examinations**

The following physical examination, and laboratory tests were carried out to assess that participants are healthy and thus they can participate in the study:

- o <u>Physical examination</u>: which was performed by the assigned physician; this included blood pressure, heart rate, respiratory rate, temperature, oxygen saturation measurements.

- o <u>Clinical chemistry tests:</u> which were performed in a certified lab; these included serum creatinine (and thus EGFR), blood urea, sodium, potassium, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate, total protein, albumin, fasting glucose, cholesterol, serum triglycerides, HDL, LDL

- o <u>Coagulation tests:</u> these included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT)

- o <u>Haematology tests:</u> these included red blood cells (RBC) count, haemoglobin (Hb), Hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV), platelets count, white blood cells (WBC), red blood cell distribution width (RDW), lymphocytes, monocytes, eosinophils, basophils.

- o <u>Virology tests:</u> these included hepatitis C virus antibodies, human immune deficiency virus 1 and 2 antibodies, hepatitis B surface antigen.

- Drugs of abuse: amphetamine; barbiturate; benzodiazepine; cocaine; morphine; tetrahydro cannabinol; tramadol traces were assessed in urine samples.

- electrocardiogram examination

- Urine analysis: this included physical test [color, appearance, specific gravity, PH], chemical test [albumin, glucose, ketone, bilirubin, urobilinogen, nitrite], and microscopic test [pus cells, RBCs, epithelial cells, crystals, amorphous, cast].

- **Inclusion Criteria**

  - Healthy participant from the Egyptian general population.

  - Age 18-60 years.

  - BMI for normal weight $18.5 – 24.9$ kg/m^2 vs. the obese subjects with BMI ≥ 35 kg/m^2.

  - The physical examination is done, assessed, and accepted by the assigned physician.

  - Oral body temperature within the normal range ($35.9 – 37.6$°C).

  - All screening procedures/examinations results within the normal range for normal weight volunteer and with some variation (not more than 20% from normal range) for the obese participants.

- **Exclusion Criteria**

  - History of hypersensitivity to rivaroxaban or similar compound.

  - Having any known coagulation conditions (i.e., von Willebrand disease, haemophilia).

  - Having any known increased bleeding risk (i.e., haemorrhoids, peptic ulcer, or frequent nasal bleeding).

- Having any chronic disease/condition (such as: diabetes type 2, cardiovascular disease, hypertension, and cancer).

- Known history or presence of food allergies or intolerabilities (e.g dairy product or gluten-containing food) or any condition which is known to interfere with the absorption, distribution, metabolism or excretion of rivaroxaban.

- Being vegetarian.

- Had an exhausting physical exercise in the last 24 hours.

- History of serious illness that can impact the fate of rivaroxaban or clinically significant illness 3 weeks before study.

- Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, musculoskeletal, endocrine disorders as evidenced by physical examination, and/or clinical laboratory tests.

- Being hepatitis B, hepatitis C, or human immunodeficiency viruses positive.

- History of drugs or alcohol abuse.

- Smoking more than 10 cigarettes or equivalent per day.

- Regular use of any medications.

- Use of any known enzyme inducers or inhibitors (e.g. barbiturates, phenytoin, rifampin) within 30 days prior to study entry.

- Use of any prescription or non-prescription medication within 3 weeks prior to study.

- Donation of ≥ 400 ml of blood within 60 days, or ≥ 150 ml of blood within 30 days, or ≥ 100 ml blood plasma or platelets within 14 days before study.

- o Participation in another study within 60 days prior to the start of this study.

- o Haemoglobin < 13 g/dl.

Appendix 2: The Informed Consent Form for Participants

Study Code: RESH-012

Participant ID: **Screening Random No.:**   **Study Random No.:**

اقرار الموافقة على المشاركة في دراسة الحركة الدوائية والمفعول الدوائي

نرجو منك أن تقضي وقتا كافيا لقراءة المعلومات التالية قبل أن تقرر المشاركة، وهي معلومات تتعلق بطبيعة وأهمية ، ونتائج الدراسة التى سوف يتم إجراؤها. ولك الحق و الحرية في توجيه أية أسئلة أو الاستفسار عن أية معلومة غير واضحة في أي وقت أثناء الدراسة. و من واجبنا الاجابة عن كل تساؤلاتك.

الهدف من هذه الدراسة:

- هو تقييم الحركة الدوائية (Pharmacokinetic) والمفعول الدوائي (Pharmacodynamic) للمستحضر المرجعي **زارلتو 20 ميللى جرام (الأقراص مغلفة)** (وهو مستحضر دوائي متداول منذ ما يزيد عن عشر سنوات) على مشاركين أصحاء و اخرين لديهم سمنة مفرطة.

- لا بد من الإشارة إلى أن الحاجة إلى الدراسات السريرية من اجل تطوير مستحضر دوائي لصالح الإنسان هو أمر لا بد منه.

- سيتم تنفيذ الدراسة طبقا للأنظمة الدولية المعتمدة في الممارسة السريرية الصحيحة وميثاق هلسنكي. وقد تم عرض الدراسة على لجنة أخلاقيات مستقلة، وقامت هذه اللجنة بإبداء رأي إيجابي بشأنها والموافقة على إجرائها. وقد أعطيت مسؤولية الدراسة للباحث **(مسؤول الدراسة)** الدكتور علاء الدين احمد **(01096897241)**.

- سوف يتم الحصول في سياق الدراسة السريرية على بيانات شخصية خاصة بك وعلى نتائج طبية. كما سوف يتم تقديم وعرض وحفظ ومعاينة هذه البيانات وفق مقتضيات القوانين والتعليمات المصرية. الأمر الذي يتطلب موافقتكم الطوعية على ذلك قبل المشاركة بالدراسة السريرية.

- إن توقيعي لهذا النموذج يثبت أنه كان لدي الوقت الكافي لقراءة واستيعاب المعلومات الموجهة إلى المشاركين بهذا المساق، وأنني حصلت على أجوبة واضحة لكل تساؤلاتي.

- أوافق على حفظ البيانات و البيانات الطبية التي يتم الحصول عليها في سياق الدراسة السريرية في وثائق كتابية وباستخدام الوسائط الإلكترونية، كما أوافق على تقديمها بدون تعيين هويتي الشخصية إلى راعي الدراسة و الجهات المسئولة لهدف التقييم السريري و النظر في صحة تنفيذ الدراسة.

- كما أوافق على معاينة البيانات الخاصة بي التي يقوم مسؤول الدراسة بالحصول عليها ، من قبل أشخاص يفوضهم الباحث تحت اتفاقية الحفاظ على سرية المعلومات، و مراجعتها من قبل السلطات المحليه والأجنبية ذات العلاقة، وذلك بالقدر الضروري لتقييم الدراسة. ونظرا لهذا الإجراء فإنني أعفي الجهة المسؤولة عن الدراسة التي أشارك فيها من مسؤولية الالتزام بالسرية الطبية.

موافق ☐   غير موافق ☐   غير لائق ☐

إسم المشارك الرباعي(Name): -------------------- تاريخ الميلاد: --------------------

الرقم القومى (National ID) --

العنوان (Address): --

التليفون (Mob) : --

توقيع المشارك: -------------------- التاريخ --------------------

	Title		
![ICBR logo]	**Title** **Consent Form**		
Form	Code: FORM01/ SOP:BEC-005	Version: 04	Status
Supersedes: 03	Page 2 of 7	Effective Date: 22/07/2020	

Study Code: RESH-012

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معلومات متعلقة بـ دراسة الحركة الدوائية والمفعول الدوائي

أ) عنوان راعي الدراسة :

كلية الصيدلة – جامعة قطر

العنوان: بناء رقم 106, الدور الاول كلية الصيدلة – جامعة قطر

رقم التليفون : 77654300-00974

البريد الالكتروني: malawneh@qu.edu.qa :

ب) مركز الدراسة :

المركز الدولي لاتاحة الحيوية و البحوث الصيدلية و الاكلينيكية (ICBR).

العنوان: PlotNo.10، بلوك رقم 12018 المنطقة الصناعية الشمالية، مدينة العبور، مصر

هاتف : 202/44652923+

فاكس: 202/44652922+

البريد الإلكتروني: info@icbr.info

ج) مادة الدراسة:

- **المستحضر المرجعي : زارلتو 20 ميللي جرام (أقراص مغلفة)** يستخدم كمضاد للتختر حيث يمنع تجلط الصفائح الدموية و ايضا يستخدم في علاج تجلط الاوردة العميقة و الانسداد الرئوي و للوقاية من السكتة الدماغية في المرضى الذين يعانون من الرجفان الاذيني وقد حصل هذا المستحضر على ترخيص لتسويقه عالمياً ومحلياً منذ ما يزيد عن عشر سنوات

- **المادة الفعالة: ريفاروكسابان (Rivaroxaban).**

- **الجرعة المعطاة: 20 ميللي جرام (قرص مغلف واحد).**

- **التأثيرات الجانبية للدواء:**
- وجع البطن.
- ألم الظهر.
- تشنج العضلات.
- ألم في الأطراف.
- الأرق.
- التعب.
- الاكتئاب.
- الدوخة.
- احتمال حدوث نزيف

د) شروط المشاركة:

هناك بعض الأمور يجب التأكيد عليها قبل توقيعك على هذا النموذج للموافقة على المشاركة في الدراسة.

</div>

	Title		
ICBR إسبر	**Consent Form**		
Form	Code: FORM01/ SOP:BEC-005	Version: 04	Status
Supersedes: 03	Page 3 of 7	Effective Date: 22/07/2020	

Study Code: RESH-012

أنا الموقع أدناه أقر وأوافق على ما يلي:

* أقر بأن عمري بين 18-55 عاما.
* أقر بأنني في حالة صحية جيدة و لست بحاجة الى اى علاج و أن جميع المعلومات التي سوف أخبرها عن تاريخي الطبي صحيحة و دقيقة.
* أقر بأنني لا أتناول اى أدوية قبل بداية الدراسة بثلاثة اسابيع وأني لا أعاني من أى أمراض مزمنة وفى حالة تناولى أى أدوية لأى سبب سوف اخبر مسؤلى الدراسة بالمركز.
* أقر بأنني لا أتبع نظام غذائى يتطلب تقليل تناول ملح الطعام أو يكون نظام غذائى نباتى.
* أقر بأنني لا أعاني من أى مرض في القلب أو الكلى.
* أقر بأنني لم أتبرع بالدم أو أشارك في دراسة تكافؤ حيوي خلال الشهرين الماضيين من تاريخ التوقيع.
* في حال ثبات صلاحية مشاركتي في الدراسة فانني أوافق على اعطاء **عينة** دم قبل تناول الجرعة الدوائية، و عينات دم عددها **8 عينات** بعد تناول الجرعة على أن مجموع كميات الدم المسحوبة قد يصل الى **78مللترا** طيلة الدراسة.
* في حال ثبات صلاحية مشاركتي في الدراسة فانني أوافق على اعطاء **عينة** بول قبل تناول الجرعة الدوائية، و عينات بول عددها **9 عينات** بعد تناول الجرعة.
* كما اوافق عل اعطاء عينات من البول في الاوقات المحدد للدراسة.
* أوافق على أن أخضع للفحص الطبي السريري و لعمل رسم للقلب الذي سيشرف عليه الطبيب المسؤول عن الدراسة.
* إنني على استعداد تام للالتزام بتعليمات مسؤول الدراسة ومساعديه.
* أوافق على الامتناع عن شرب الشاي، و القهوة، والكاكاو، و الكولا، وعصير الجريب فروت اثناء كل فترة من فترات الدراسة لحين سحب اخر عينة دم من الدراسة.
* أوافق على الامتناع عن القيام بأعمال شاقة و بمجهود عضلي كبير اثناء الدراسة و لحين سحب اخر عينة دم من الدراسة.
* أوافق على الامتناع عن التدخين خلال فترة تواجدي في مركز الدراسة و لحين سحب اخر عينة دم من الدراسة.
* **أقر بأنني قد استلمت نموذج التعليمات العامة من مسؤول الدراسة الذي يوضح جميع فعاليات الدراسة والواجبات الملقاة علي خلال الدراسة وإنني على استعداد تام للالتزام بها.**

هـ) إجراءات الدراسة :

* عدد المشاركين في هذه الدراسة **34 مشاركاً + 2 احتياطي** و سيتم اجراء الدراسة مع الامتناع عن تناول الطعام والشراب وفق التعليمات المعطاه. وسوف تستمر الدراسة لمدة لا تتجاوز **4 أسبوع** وتشمل فترة الفحص لاختيار المشاركين.

* **فترة فحص قدرة المشاركين في الدراسة:**
  * و تمتد لفترة **ثلاث اسابيع** في الحد الأقصى قبل أخذ جرعة الدواء في الفترة الأولى من الدراسة.
  * اذا وافقت على المشاركة في الدراسة و فقط بعد أن تكون قد قرأت بعناية و قمت بالتوقيع على هذا النموذج للموافقة على المشاركة في الدراسة ، سوف تخضع لفحص طبي شامل سيجريه / يشرف عليه الطبيب مسؤول الدراسة لمعرفة ما اذا كنت مؤهلا للمشاركة في الدراسة ويشمل (معرفة تاريخك الطبي، فحص بدني جسمي يتضمن قياس العلامات الحيوية من ضغط دم، و معدل نبض، و درجة حرارة الجسم، قياس الطول و الوزن، اجراء فحوصات مختبرية طبية على عينات دم و بول مأخوذة منك).

* **فترة الدراسة:**
  * تبدأ مرحلة أخذ جرعة الدواء الفعلية خلال فترة لا تتجاوز **ثلاثة اسابيع** بعد اختبار قدرة المشاركة.
  * يجب حضورك إلى مركز الدراسة في الساعة **السابعة مساءا** من يوم قبل تناول الجرعات الدوائية .
  * قبل المشاركة سيتم قياس العلامات الحيوية لديك (**ضغط الدم، النبض، درجة حرارة الجسم و معدل التنفس و مستوى الاكسجين في الدم**) و سؤالك عن شعورك بحدوث أي تعب أو تغيير في حالتك الصحية بعد خضوعك للفحص الطبي الشامل خلال فترة فحص صلاحية المشاركة.

Study Code: RESH-012

○ كما سيتم قبل المشاركة اجراء أختبار للكشف عن وجود المواد المخدرة فى البول، و عليك اعطاء عينة بول لاتمام الفحوصات اللازمة.

○ عند التأكد من صلاحيتك للمشاركة في الدراسة فانه سيتم تركيب ابرة وريدية (كانيولا) لسحب أو ادخال السوائل في وريد يدك لسحب عينات الدم منك و ذلك قبل تناول الجرعة بساعتين على الاقل.

○ و بعد فترة من الامتناع عن الطعام لمدة لا تقل عن عشرة ساعات سوف تبدأ بتعاطي الدواء الخاضع للدراسة في اليوم الأول للدراسة حسب تعليمات مسؤول الدراسة، ويتعين عليك تلقي جرعة واحدة مقدارها **20 ميللي جرام من زارلتو 20 ميللي جرام (أقراص مغلفة)** مع شرب كمية **240 مللتر من الماء وذلك بعد تناول وجبة الافطار** (والتى تشمل على الاتى: بيضتان مقليتان في الزبدة. قطعتان من النشون المقدد. شريحتان من الخبز بالزبدة. أربعة شرائح من البطاطس المقلية. ثمانى أوقيات من اللبن كامل الدسم) قبل اخذ الجرعه بنصف ساعة.

○ تناول الجرعة صباح يوم الاربعاء الساعة : **08:00**

○ سوف يتم سحب **عينة** دم منك قبل تناول الجرعة الدوائية، و عينات دم بعد عددها **8** عينات بعد تناول الجرعة في الاوقات الاتية :

صباح يوم الاربعاء: 09:00, 10:00
مساء يوم الاربعاء:12:00, 04:00, 08:00
صباح يوم الخميس: 02:00
مساء يوم الخميس: 08:00
صباح يوم الجمعة : 08:00

○ سوف يتم تجميع عينة بول قبل تناول الجرعة وعينات من البول عددها **8** بعد تناول الجرعة في الاوقات الاتية :

صباح يوم الاربعاء: 08:00 الى 10:59
مساء يوم الاربعاء: 11:00 الى 02:00 و 02:01 الى 05:00 و 05:01 الى 08:00 و 08:01 الى 11:00 و 11:01 مساءا الى02:00 (صباح يوم الخميس)
مساء يوم الخميس: 08:00
صباح يوم الجمعة : 08:00

○ سيوف يتم قياس **ضغط الدم، النبض، درجة حرارة الجسم و معدل التنفس و مستوى الاكسجين فى الدم** لديك وذلك قبل تناول الجرعة الدوائية و في أوقات محددة بعد تناول الجرعة، وسؤالك عن إحساسك بأية اثار جانبية اوتغير في حالتك الصحية.

○ عليك الامتناع عن الأكل و الشرب الا الوجبات المحددة في الأوقات المحددة.

○ يتعين عليك البقاء في مركز الدراسة طيلة الفترة المحددة من قبل الباحث وهي **36ساعة**. يمكنك مغادرة المركز بعد ذلك.

○ في حالة هبوط الضغط لديك بعد تناول الدواء فانه سيتم اعطاءك محلول ملحي عن طريق الوريد و ذلك للحفاظ على سلامتك.

• **الفحص النهائي:**

○ سوف تخضع في نهاية الدراسة لفحص بدني من قبل مسؤول الدراسة، و **ضغط الدم، النبض، درجة حرارة الجسم و معدل التنفس و مستوى الاكسجين فى الدم**. و اجراءات مراقبة السلامة متاحة خلال **3** أيام بعد انتهاء الدراسة.

○ مجموع كميات الدم المسحوبة في الدراسة قد يصل إلى **78 ميلليتر** طيلة الدراسة.

○ إن التزامك التام ببرنامج المواعيد والتوقيت الزمني للدراسة، فضلا عن تعليمات مسؤول الدراسة و الفريق المعاون له هو أمر في غاية الأهمية لنجاح الدراسة. ويعتمد تنفيذ الدراسة والوفاء بمتطلباتها على مقدار التعاون الذي تبديه.

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و) الرسم التالي يوضح نظرة عامة عن مسار الدراسة:

![ICBR logo] إسبر ICBR		**Title** **Consent Form**		
Form	Code: FORM01/ SOP:BEC-005	**Version:** 04		**Status**
Supersedes: 03	**Page 6 of 7**	**Effective Date:** 22/07/2020		

Study Code: RESH-012

ز) المخاطر و اجراءات السلامة:

- برجى ملاحظة أن كل مستحضر دوائي قد يسبب ، في أحوال استثنائية ، آثار جانبية لا يمكن توقعها ، أو لم يسبق ملاحظتها من قبل .

- وكما تعلم فان آلاما بسيطة و/أو تجمع دموي في أماكن تركيب الكانيولا قد تحدث أثناء سحب الدم . من ناحية ثانية ، في أحوال شديدة الندرة يمكن حدوث التهاب لأحد الأوردة.

- ومن أجل الحفاظ على سلامتك سيتم قياس النبض و ضغط الدم و درجة الحرارة الجسم و إجراء الفحص البدني إضافة إلى فحص التأثيرات الجانبية للعقار بانتظام أثناء سير الدراسة.

- إذا انتبهت ، في الفترات التي تفصل بين زياراتك لمركز الدراسة ، إلى أية ملاحظات يمكن ربطها بالدراسة فيجب إبلاغها إلى مسؤول الدراسة .

- في حالة معاناتك من أية آثار جانبية أثناء الدراسة ، وفي حالة عدم توقف هذه الآثار بعد انتهاء الدراسة ، فان مسؤول الدراسة سيقوم بزيارة تفقدية لك خلال ثلاثة ايام من وقت سحب آخر عينة دم.

- في حاله الضرورة برجى الاتصال بالدكتور علاء الدين احمد **(01096897241)**

ح) الانسحاب أو وقف مشاركتك من الدراسة:

- يحق لك التراجع عن موافقتك المشاركة في هذه الدراسة و الانسحاب من الدراسة في أي وقت بدون إبداء سبب لذلك وبدون التعرض لأية عواقب . إلا أنه من المهم للحفاظا على سلامتك ومصلحتك الشخصية ، الخضوع للفحص النهائي في حال أخذ جرعة الدواء.

- لمسؤول الدراسة الحرية في وقف مشاركتك في الدراسة في أي وقت إذا رأى ان مشاركتك سوف تضر بسلامة صحتك ، أو إذا لاحظ أن هناك خطرا يهدد الدراسة بسبب تقاعسك عن اتباع التعليمات بدقة ، ويمكن إنهاء الدراسة أيضا من قبل راعي الدراسة و/أو لجنة الأخلاقيات المستقلة .

ط) التأمين :

- إن جميع المشاركين مشمولين ببوليصة التأمين(رقم: P/GA/PA/01/2020/68648/R1 لدى المصرية للتأمين التكافلي) خلال فترات الدراسة في حال التعرض لأي إصابة صحية ناتجة عن الخضوع للدراسة. ولا يجوز أثناء سير الدراسة ، القيام بأية معالجة طبية أخرى ، باستثناء الحالات الطارئة ، إلا بعد استشارة مسؤول الدراسة ، ويجب إبلاغ مسؤول الدراسة فور القيام بمعالجة طارئة ، وفي حالة إصابتك بضرر صحي ، أثناء سير الدراسة ونتيجة لمشاركتك فيها ، فيجب عليك إبلاغ مسؤول الدراسة فورا. وبعكس ذلك يمكن أن تفقد تغطيتك التأمينية.

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	Title		
	Consent Form		
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Study Code: RESH-012

<div dir="rtl">

ى) المكافأة :

- في حال التزامك التام بجميع التعليمات المكتوبة والتي يحددها لك مسؤول الدراسة ، سيتم دفع الحافز المالي و مقداره **1300** جنيه مصرى.

- إذا قام الطبيب المسؤول عن الدراسة بإنهاء مشاركتك بناءا على المراقبة الطبية (اذا ثبت ذلك في صالحك) ، سوف تستلم الحافز المالي المقرر كاملا.

- في حالة عدم الالتزام بالتعليمات المكتوبة كما في حال التدخين ، الاكل بحرية أو المبيت خارج المركز خارج الدراسة ، فإنه يحق لمسؤول الدراسة أو من ينوب عنه انهاء مشاركتك بدون أن تستلم اي حافز مالي.

- تستطيع الانسحاب من الدراسة بملء ارادتك ودون ابداء اية اسباب دون الحصول على الحافز المالي المقرر .

• أوافق على المشاركة في هذه الدراسة طوعا و بمطلق اختياري و رغبتي، وذلك بعد الاطلاع على معلومات الدراسة و الحصول على أجوبة شافية لكل تساؤلاتي من قبل مسؤول الدراسة. • وأصرح بأنني تسلمت نسخة من المعلومات الموجهة إلى المشاركين، ويحق لي عند رغبتي الحصول على نسخة من نموذج الموافقة على المشاركة في دراسة التكافؤ الحيوي.	

التاريخ:	اسم و توقيع المشارك:

التاريخ:	اسم و توقيع شاهد أول:

التاريخ:	اسم و توقيع شاهد ثاني:

التاريخ:	اسم و توقيع مسؤول القسم السريري او ماينوب عنه :

التاريخ:	اسم و توقيع الطبيب المسؤول:

</div>

Appendix 3: Study Protocol and Samples Collection

The principal investigator (Ms. Majdoleen Alalawneh, Dr. Alaaldin Ahmed) and/ or the clinical trial administrator (Dr. Abdullah Rabee) have explained explicitly to all participants -in easily understood terms- the nature and objectives of the study, the effects of the drug, the possible risks and discomforts, study dates, drugs, diet, the number of harvested samples as well as the possibility of voluntary withdrawal from the study. It was made sure -by the principal investigators and/or clinical trial administrator- that all participants understood what they are signing by means of a verbal explanation using non-technical language and a written participant information sheet. All participants have had the opportunity to ask questions concerning the study, and the adequate time to decide on voluntary participation. The participants were asked to sign the consent form subsequently. Upon recruitment, each study participant received a badge identifying his study code. They were admitted to the clinical facility in the International Centre for Bioavailability, Pharmaceutical and Clinical Research (ICBR) at 8:00 PM, day prior to rivaroxaban dosing. At then, participants were checked for their vital signs, i.e., blood pressure (mmHg), heart rate (per minute), respiratory rate (per minute), temperature (C∘), oxygen saturation (%), and for drugs abuse (i.e., amphetamine, barbiturate, benzodiazepine, cocaine, morphine, tetra hydro cannabinol, tramadol). A standardized dinner meal was provided (12 hours before dosing), and participants fasting started directly after the dinner and lasts until half an hour prior to rivaroxaban administration (i.e., overnight fast of at least 10 hours). Participants remained under protocol conditions until the collection of the 18-hours post-dose blood samples. Throughout the stay in the clinical facility, vital signs and physical examination were measured/performed before dosing (at time zero) and at the scheduled time points after dosing (at 1, 2, 4, 8, 12, 18 hr from dosing). In addition,

adverse events were queried throughout the study period.

Before 30 minutes of rivaroxaban administration, participants started their standardized breakfast meal (7:30 AM). To provide the greatest effects on GI physiology and thus to maximize the systemic drug availability of rivaroxaban, a high-fat (approximately 50% of the total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal was given for the patients, prior rivaroxaban dosing. The meal contained two eggs fried in butter ($\approx$ 200 calories), two strips of meat (50 gm $\approx$ 140 calories), two slices of toast with butter ($\approx$ 250 calories), and 4 pieces of hash brown potatoes (100 gm $\approx$ 161 calories) and 200 gm of milk ($\approx$ 112 calories). This meal should derive approximately 150, 250, and 600 calories from protein, carbohydrate, and fat, respectively. In accordance with the standard operating procedures of ICBR, rivaroxaban dosing was performed by the assigned nurses and was supervised by the quality assurance principal (Dr. Amr Azzaz), principal investigator (Ms. Majdoleen Alalawneh, Dr. Alaaldin Ahmed), and the clinical trial administrator (Dr. Abdullah Rabee). Between 8:00 and 8:12 AM, rivaroxaban (one 20 mg film coated tablet) was administered orally at the indicated fed state to each participant with 240 mL of water (other water intake was not allowed 1 hour before and 2 hours after rivaroxaban dosing). Immediately after administration, each participant's oral cavity was checked with the aid of a flashlight and tongue depressant to confirm proper dosing and water intake. The time of administration of rivaroxaban was recorded in each participant's case report forms. Participants were not allowed to lie down or sleep for the first three hours after dosing (If dizziness or hypotension occurred/recorded, the participants were permitted to lie down, and normal saline were available for IV infusion at any time during the study). Food and fluid intake during the study was standardized for all participants. Next standardized meals (with 250 ml of apple juice) were provided at 4 hr (lunch), 8

hr (snack) and at 12 hr (dinner) after dosing. Participants will receive 170 ml of water at 2 hr after drug administration (details are in the table below). Alcohol, grapefruit, caffeine or xanthine-containing foods or beverages were not allowed to be consumed for 48 hours prior to dosing and 60 hours after the drug administration. Smoking was prohibited for 11 hours prior to rivaroxaban dosing and till study completion.

Food and fluid intake during hospitalization period		
Time in accordance to dosing	Food intake	Water intake
− 12 hr	Dinner	200 ml
− 30 min	Breakfast	200 ml
0 (Dosing)	-	240 ml
+ 2 hr	-	170 ml
+ 4 hr*	Lunch	200 ml
+ 8 hr*	Snack	200 ml
+ 12 hr*	Dinner	200 ml
*250 ml of apple juice was provided with the meal		

Case report form was the data collection document designated to record all the information for an individual study participant required by the study protocol. Each completed case report form was reviewed for accuracy and signed by the principal investigator (Ms. Majdoleen Alalawneh, Dr. Alaaldin Ahmed) and/ or the clinical trial administrator (Dr. Abdullah Rabee) who were responsible for ensuring the completeness and accuracy of the forms. Total of 19 blood samples (78 ml) were withdrawn from each participant for the study purpose as following:

- 10 ml for screening tests prior enrolment

- 10 ml pre-dosing (in heparinized tubes) for rivaroxaban assay

- 2 ml pre-dosing (in sodium citrate tube) for coagulation assay (PT and APTT)

- 5 ml post-dosing (in heparinized tubes) at 1, 2, 4, 8, 12, 18, 36 and 48 hr (total 40 ml) from rivaroxaban administration for rivaroxaban assay

- 2 ml post-dosing (in sodium citrate tube) at 1, 2, 4, 8, 12, 18, 36 and 48 hr (total 16 ml) from rivaroxaban administration for coagulation assay (PT and APTT)

After collecting the 18-hr sample the catheter were removed from a participant. There was a variability of 12 minute in blood collection times during participants' stay at ICBR. Blood samples were centrifuged (4000 rpm/8.00 minutes), and the plasma was aliquoted and stored at -86 °C until analysis.

Urine samples were obtained from each subject for the study purpose within the following time intervals: -2 to 0 h (pre-dosing), 0 to 3 h, 3 to 6 h, 6 to 9 h, 9 to 12 h, 12 to 15 h, 15 to 18 h. For the purpose of urine samples collection, the access for bathrooms were completely controlled, where for each participant all voided urine was collected, and the voiding time and volume was recorded. All urine were collected whenever the participant voided, and thus no urine was lost during the 18 hr post dosing of rivaroxaban. All urine samples collected during each interval were pooled, and total volume of the pooled urine in each interval was recorded. From the pooled urine, 10 ml of each interval was store at -86 °C until analysis.

Appendix 4: Case Report Form

ICBR	**Title** Case Report Form (Study Part)		
Form	Code: FORM02/ SOP:BEC-025	**Version:** 04	**Status**
Supersedes: 03	*Page 2 of 12*	**Effective Date:** 10/07/2019	

Study Code: RESH-012   **Study Random No.:**

(CRF) Filling and Completion
CRFs must be filled in with blue ink and corrections have to be made with a single line through, so that one can see what has been crossed out. Each correction or new entry must be signed and dated by the personnel who made that correction. The reason why the correction was made must be also provided, if applicable. Each completed CRF must be reviewed for accuracy and signed by the Principal Investigator/Co-Investigator and the Quality Assurance auditor. The Principal Investigator/Co-Investigator assumes responsibility for ensuring the completeness and of the forms, which confirms by signature in blue ink.

"I hereby confirm that the data required by the protocol are reported accurately on the Case Report Form (screening and study parts) and are consistent with the source documents".			
Principal Investigator	_____	Quality Assurance:	_____
Signature:	_____	Signature:	_____
Date:	_____/_____/_____	Date:	_____/____/_____

Study Code: RESH-012   **Study Random No.:**   [ ]

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ICBR إسـبر	**Title** **Case Report Form (Study Part)**		
Form	Code: FORM02/ SOP:BEC-025	Version: 04	Status
Supersedes: 03	*Page 4 of 12*	Effective Date: 10/07/2019	

Study Code: RESH-012 **Study Random No.:**

1. Admission screening tests:
*All Original tests and ECG sheets are attached.

A-Drugs of Abuse tests results.	☐ Positive	☐ Negative	☐ N/A
B-Alcohol test results	☐ Positive	☐ Negative	☐ N/A
C -ECG Examination	☐ Clinically normal	☐ Clinically abnormal	☐ N/A

Comments:_____
_____
_____

D- Conclusion   Is the participant eligible for inclusion in the study?

☐ YES   I confirm that the volunteer is eligible to participate in the study.

☐ NO   Describe the reasons:

_____
_____

Principal Investigator/Co-Investigator: _____

Study Code: RESH-012　　　　　　　　**Study Random No.:** 　　

2. Vital Signs Monitoring

A- Pre-Trial Monitoring (at admission to clinical site):

Normal range	Blood pressure.* Systolic: 90-140 mmHg Diastolic: 60-90 mmHg	Heart rate 60-100 (beat/min.)	Oral Body Temperature 35.9 – 37.6 °C
Present reading	Sys./Dia. _____ / _____	_____	_____
Signature:			

• Any change in the health status since screening?		☐YES	☐NO
Describe in case of any change: _____			
• Do you feel fit for the trial?		☐YES	☐NO
Describe why participant does not fit: _____			
• Conclusion: Volunteer is eligible to participate in the study?		☐YES	☐NO
Principal Investigator/Co-Investigator: _____			

B- During-Trial Monitoring (before dosing, -2 hours):

Normal range	Blood pressure.* Systolic: 90-140 mmHg Diastolic: 60-90 mmHg	Heart rate 60-100 (beat/min.)	Blood Glucose 70-110 mg/dL	Oral Body Temperature 35.9 – 37.6 °C
Present reading	Sys./Dia. _____ / _____	_____	_____	_____
Signature:				

• Any change in the health status since admission?		☐YES	☐NO
Describe in case of any change: _____			
• Do you feel fit for the trial?		☐YES	☐NO
Describe why participant does not fit: _____			
• Conclusion: Volunteer is eligible to participate in the study?		☐YES	☐NO
Principal Investigator/Co-Investigator: _____			

	Title			
ICBR إسبر	**Case Report Form (Study Part)**			
Form	Code: FORM02/ SOP:BEC-025	**Version:** 04	**Status**	
Supersedes: 03	*Page 6 of 12*	**Effective Date:** 10/07/2019		

Study Code: RESH-012　　　　　　　**Study Random No.:**

C- Scheduled time (post dosing)

Blood pressure	Normal range: Systolic: 90-140, Diastolic: 60-90 (mmHg)
Heart Rate	Normal range: 60-100 (beat/min.)
Body Temperature	Normal range: 35.9 – 37.6 ºC
Fasting Blood glucose	Normal range: 70 - 110 mg/dL
Random Blood glucose	Normal range: Less than 180 mg/dL after meals

Interval	Actual time	Blood pressure (mmHg)*	Heart rate (Beat/min.)	Body Temp.	Blood glucose**	Signature	Comments
1.00	09:00	/					
2.00	10:00	/					
4.00	11:00	/					
8.00	13:00	/					
12.00	16:00	/					
18.00	02:00	/					
Principal Investigator/Co-Investigator: _____							

*Normal saline will be infused intravenously at any time after drug intake to participants who become hypotensive.
**Glucose 5% will be infused intravenously at any time after drug intake to participants who become hypoglycemic.

ICBR	Title
	Case Report Form (Study Part)

Form	Code: FORM02/ SOP:BEC-025	Version: 04	Status
Supersedes: 03	*Page 7 of 12*	Effective Date: 10/07/2019	

Study Code: RESH-012   **Study Random No.:**

3. Blood samples harvesting time points during Study

Protocol time	Planned time (hh:mm)	Actual time (hh:mm)	(Date: / /)		
			Participant signature	Nurse Signature	Comments
Pre dosing	07:00				
Dosing	08:00				
1.00	09:00				
2.00	10:00				
4.00	12:00				
8.00	16:00				
12.00	20:00				
18.00	02:00				
36.00	20:00				
48.00	08:00				

*I: Volunteers incompliance,   T: Technical problems, L: Sample loss
*Incase of the actual time and the planned time are the same Check True (√) But in case of any difference write the actual time. (Actual Time Column)

Participant signature: _____

Study Code: RESH-012   **Study Random No.:**

4. . Drug Administration Record

(Here attach a copy of the single dose label that shows the actual administration time)

Study Code: RESH-012   **Study Random No.:**

5. **Adverse Event / Serious Adverse Event Registration**
   Date: -- / -- / 2022

Did Adverse Event (AE) occur?
 ☐NO   ☐YES

  If YES please proceed with the following

   ☐ NOT Serious AE

   If the adverse event has occurred complete the **Adverse Event Report** and attach it to the Case Report Form.

   ☐ Serious AE

   If the adverse event is serious or unexpected complete the **Serious Adverse Event Report** and attach it to the Case Report Form.

Principal Investigator/Co-Investigator: _____

Confidential

CRF (RESH-012)   *Page (9 of 12)*

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Study Code: RESH-012   **Study Random No.:**

6. Premature Termination

6.1   Study termination

Study has been terminated by:

- ❑ Investigator
- ❑ Sponsor
- ❑ IRB/IEC
- ❑ Other reasons, specify _____

6.2   Participant withdrawal

The participant completed this clinical Trial?

❑ **YES**

❑ **NO**   *If No please proceed with the following*

⬇

Study Participant freely decided to withdraw from the study (withdrawal of consent)

❑ **YES**

❑ **NO**   *If No please proceed with the following*

⬇

The Principal Investigator/Co-Investigator terminate the participant from the study (premature termination), for the following reason:

- ❑   Adverse events or serious adverse events.
- ❑   Failure to comply with study protocol
- ❑   Non-compliance with study instruction.

Comments:_____

_____

_____

Principal Investigator/Co-Investigator: _____ Date: ____/____/____

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Study Code: RESH-012   **Study Random No.:**

7. **Close out Examination**

   7.1 Physical Examination

Normal range Present reading	Blood pressure. Systolic: 90-140 mmHg Diastolic: 60-90 mmHg Sys./Dia._____/_____	Heart rate 60-100 (beat/min.) _____	Oral Body Temperature 35.9 – 37.6 ℃ _____
Normal Physical Examination	**Abnormal / clinically not significant**	**Abnormal / clinically significant**	
Nutrition status ☐ Yes , ☐ No	_____	_____	
Skin ☐ Yes , ☐ No	_____	_____	
Neck ☐ Yes , ☐ No	_____	_____	
Heart ☐ Yes , ☐ No	_____	_____	
Lungs ☐ Yes , ☐ No	_____	_____	
Abdomen ☐ Yes , ☐ No	_____	_____	
Extremities ☐ Yes , ☐ No	_____	_____	
Neurology ☐ Yes , ☐ No	_____	_____	

Comments: _____

_____

Study Code: RESH-012　　　　　　　　　**Study Random No.:** ☐

7.2. ECG Examination

☐ Clinically normal　　　　☐ clinically abnormal　　　　☐ N/A

Comments (If any)

_____

_____

7.3 Clinical Chemistry and Hematology

The clinical laboratory results are;

☐ Accepted　　　　☐ Not Accepted　　　　☐ N/A

　*All Original laboratory tests are attached.

Comments (If Any)

_____

_____

Principal Investigator/Co-Investigator: _____ Date: ___/___/__

8. Clinical Assessments and Comments

Comments (if any):

_____

_____

"Hereby I confirm that the study participant duly completed this clinical trial. In my opinion, the participant can be closed-out from the study."		
Principal Investigator/ Co-Investigator: _____	Signature: _____	Date: ___/___/___

Appendix 5: Collection of Urine Samples

	Title
ICBR	**Collection of Urine samples**

Form	**Code: : FORM01/ SOP:BEC-029**	**Version:01**	**Status**
Supersedes: N/A	*Page 1 of 1*	**Effective Date: 06/07/2022**	

Study Code: **Date** ----------------------   **Time Interval from:** ----------   **To** ---------------

Study Random Number	Actual Time 1	Actual Time 2	Actual Time 3	Volume (ml) 1	Volume (ml) 2	Volume (ml) 3	Total Volume (ml)	Volunteer Signature	Checked by

Comment :--

Confidential

The following table shows the reference standards information for plasma and urine analysis:

Reference material	Purpose	Purity	Lot/batch number
Rivaroxaban USP	Analyte	99.7%	USP Lot number: F10350
Rivaroxaban-d4	Internal standard	98.84%	Batch number: CRC-1125-S-38

Before starting the measurement of rivaroxaban concentrations in plasma and urine samples, a full validation of the analytical method in both matrices (plasma and urine) was performed following the accepted international parameters for chromatographic methodologies. This included the evaluation of selectivity, absolute rivaroxaban recovery, linearity, precision and accuracy, limit of detection and limit of quantification, and sample stability.

Stock solution, dilute stock solution, calibrators, Quality control samples:

   A. Plasma:

Stock and diluted stock solutions of the reference standards (rivaroxaban USP and rivaroxaban-d4) in acetonitrile were prepared with the following concentrations: 500 µg/ml and 100 µg/ml for rivaroxaban stock and diluted stock respectively; 96.0 µg/ml and 0.096 µg/mL for rivaroxaban-d4 stock and diluted stock respectively. The linearity was assessed by plotting calibration curve for rivaroxaban; The plasma-based calibration ranged between 2.50 ng/ml – 1000.00 ng/ml rivaroxaban using 8 different concentrations (2.50, 5.0, 25.0, 100.0, 250.0, 500.0, 800.0, 1000.0 ng/ml). Quality

control samples (QC-low, QC-medium 1, QC-medium 2, QC-high) were prepare with the following concentrations: 7.50, 75.0, 300.0, 750.0 ng/ml, respectively.

B. Urine:

Stock and diluted stock solutions of the reference standards (rivaroxaban USP and rivaroxaban-d4) in acetonitrile were prepared with the following concentrations: 2000 µg/ml and 200 µg/ml for rivaroxaban stock and diluted stock respectively; 96.0 µg/ml and 0.096 µg/mL for rivaroxaban-d4 stock and diluted stock respectively. The linearity was assessed by plotting calibration curve for rivaroxaban; The plasma-based calibration ranged between (10.00– 30000.00) ng/mL rivaroxaban using 8 different concentrations (10.0, 20.0, 100.0, 500.0, 2000.0, 10000.0, 20000.0, 30000.0 ng/ml). Quality control samples (QC-low, QC-medium 1, QC-medium 2, QC-high) were prepare with the following concentrations: 30.00, 300.0, 9000.0, 22500.0 ng/ml, respectively.

Selectivity

Six different sources of both blank plasma and blank urine samples were collected (to simulate the plasma and urine matrix harvested from participants) under controlled conditions to simulate the plasma and urine matrix from participants. Samples were extracted, analysed, and compared with rivaroxaban-containing samples. There were no interferences from the extracted components in the signals of both rivaroxaban and the rivaroxaban-d4 in plasma and urine samples; and thus the method is selective for rivaroxaban and rivaroxaban-d4.

Carry-over

In the validation process, carry-over was assessed by injecting blank samples (plasma

and urine) after a high concentration sample at the upper limit of quantification (ULOQ were 1000.00 and 30000.00 ng/ml for plasma and urine, respectively). Carry-over in the blank plasma and urine samples following the high concentrations did not exceed 20% of the lower limit of quantification (LLOQ of rivaroxaban were 2.5 and 10.0 ng/ml for plasma and urine analysis, respectively) of rivaroxaban and did not exceed 20% of the internal standard.

Matrix effect

Matrix effect was studied in six different sources of plasma and urine for rivaroxaban spiked with QC-L (7.5 and 30.0 ng/ml respectively for plasma and urine) and QC-H (750.0 and 22500.0 ng/ml respectively for plasma and urine). Area ratios for the six sources were calculated and normalized to IS. The coefficient of variation (CV%) was 4.0 and 3.25 for QC-L and QC-H respectively for plasma samples, and 1.90 and 0.71 for QC-L and QC-H respectively for urine samples (in both matrices, normalized matrix factor did not exceed 15% as a CV% for QC-L and QC-H in six different sources.).

Accuracy and precision

    A. Plasma:

Six individually extracted plasma-based samples in LLOQ, QC-L, QC-M1, QC-M2 and QC-H concentrations were injected to evaluate within-run accuracy and precision. Within-run accuracy percentages for the indicated samples were 101.2, 89.56, 101.67, 99.92, 103.82 respectively (did not exceed ± 15% from their reference value). To assess within-run precision, coefficient of variation (CV%) for the six samples (in LLOQ, QC-L, QC-M1, QC-M2 and QC-H concentrations) were 4.64, 4.36, 1.08, 2.49, 1.20 respectively (did not exceed 15% as CV%).

In addition, between-run precision and accuracy were evaluated by analyzing plasma samples containing rivaroxaban at five different concentration levels including: LLOQ, QC-L, QC-M1, QC-M2 and QC-H. Six plasma samples were prepared daily (day 1, day 2, day 3) at each concentration level. Between-run accuracy percentages were 95.44, 96.53, 98.58, 97.84, 101.8 respectively for the indicated concentrations (did not exceed ± 15% from their reference value). Between-run precision CV% were 6.43, 8.61, 3.52, 1.86, 1.68 (did not exceed 15% as CV%).

B. Urine:

Six individually extracted urine-based samples in LLOQ, QC-L, QC-M1, QC-M2 and QC-H concentrations were injected to evaluate within-run accuracy and precision. Within-run accuracy percentages for the indicated samples were 102.52, 98.57, 97.36, 100.72, 95.96 respectively (did not exceed ± 15% from their reference value). To assess within-run precision, coefficient of variation (CV%) for the six samples (in LLOQ, QC-L, QC-M1, QC-M2 and QC-H concentrations) were 2.09, 2.85, 1.23, 0.66, 0.70 respectively (did not exceed 15% as CV%).

In addition, between-run precision and accuracy were evaluated by analyzing urine samples containing rivaroxaban at five different concentration levels including: LLOQ, QC-L, QC-M1, QC-M2 and QC-H. Six plasma samples were prepared daily (day 1, day 2, day 3) at each concentration level. Three days' average between-run accuracy percentages were 98.91, 96.17, 96.90, 100.94, 96.02 respectively for the indicated concentrations (did not exceed ± 15% from their reference value). Between-run precision CV% were 3.22, 2.53, 0.56, 0.39, 0.28 (did not exceed 15% as CV%).

Absolute and relative recovery

A. Plasma:

For absolute recovery, three different concentration rivaroxaban levels (comprising: QC-L, QC-M2 and QC-H) and the internal standard where spiked into plasma and equally into the mobile phase. Plasma samples were extracted and chromatographed. Matrix free QC samples were directly chromatographed as well. The absolute recoveries were 103.66% and 103.01% respectively for rivaroxaban and rivaroxaban-d4.

For the relative recovery, three different concentration levels (comprising QCL, QCM2 and QCH) of rivaroxaban were spiked into plasma and analysed. The relative recovery (for three measurements of each concentration) was 101.28%.

B. Urine:

For absolute recovery, three different concentration rivaroxaban levels (comprising: QC-L, QC-M2 and QC-H) and the internal standard where spiked into plasma and equally into the mobile phase. Plasma samples were extracted and chromatographed. Matrix free QC samples were directly chromatographed as well. The absolute recoveries were 86.91% and 85.55% respectively for rivaroxaban and rivaroxaban-d4.

For the relative recovery, three different concentration levels (comprising QCL, QCM2 and QCH) of rivaroxaban were spiked into plasma and analyzed. The relative recovery (for three measurements of each concentration) was 97.19%.

Linearity

Eight plasma samples were spiked with rivaroxaban in a manner to achieve the calibration growth curve (calibration standard concentrations were 2.50, 5.00, 25.00, 100.00, 250.00, 500.00, 800.00, 1000.00 ng/ml), covering the entire linear range (2.5 –

1000) ng /mL of rivaroxaban. These samples were extracted and assayed, and each calibration (curve1, curve2, curve3, curve4, curve5, and curve6) was demonstrated by plotting the area ratio (rivaroxaban/IS) versus calibrator's nominal values. Linear least squares regression (R^2) were 0.998, 0.998, 0.996, 0.997, 0.999, 0.997, and thus all R^2 values were ≥ 0.98 for calibration curves. The CV% for the 8 calibration standards were 5.37, 5.42, 1.82, 2.57, 3.51, 2.41, 1.25, 2.11 respectively (did not exceed 15% as CV%). In addition, rivaroxaban normalized concentrations were back calculated and CV% for the 8 back calculated rivaroxaban concentrations were 2.24, 4.31, 2.20, 2.29, 2.98, 1.99, 1.56, 2.50 (within ±15% of the calibration standards concentrations values).

Eight urine samples were spiked with rivaroxaban in a manner to achieve the calibration growth curve (calibration standard concentrations were 10.0, 20.0, 100.0, 500.0, 2000.0, 10000.0, 20000.0, 30000.0 ng/ml), covering the entire linear range (10.0 – 30000.0) ng /mL of rivaroxaban. These samples were extracted and assayed, and each calibration (curve1, curve2, curve3, curve4, curve5, and curve6) was demonstrated by plotting the area ratio (rivaroxaban/IS) versus calibrator's nominal values. Linear least squares regression (R^2) were 0.999, 0.999, 0.999, 0.999, 0.998, 0.999, and thus all R^2 values were ≥ 0.98 for calibration curves. The CV% for the 8 calibration standards were 5.13, 2.56, 0.98, 0.97, 0.64, 0.33, 1.21, 0.68 respectively (did not exceed 15% as CV%). In addition, rivaroxaban normalized concentrations were back calculated and CV% for the 8 back calculated rivaroxaban concentrations were 2.24, 4.31, 2.20, 2.29, 2.98, 1.99, 1.56, 2.50 (within ±15% of the calibration standards concentrations values).

Linearity range (limits of quantification and upper limit)

For the assay of rivaroxaban, the lower limit of quantification (LLOQ) was 2.500 ng/mL, whereas the upper limit of quantification (ULOQ) was 1000.000 ng/mL.

Stability

A. Short term stock solution stability: area for rivaroxaban spiked at the QC-L and QC-H concentration levels. Peak areas were measured from freshly prepared solutions with those obtained from solutions kept at room temperature for 23 hrs. The results demonstrate that rivaroxaban was stable in the mobile phase at room temperature for a period of 23 hrs. Stability percentages for 23 hrs samples compared to average of freshly prepared were 94.03 and 102.15 for QC-L and QC-H respectively.

B. Long term stock solution stability: areas were measured for rivaroxaban and the internal standard in solutions spiked with the QC-L and QC-H concentration levels. Peak areas were measured for freshly prepared samples and for those kept stored at -80 °C under prolonged storage conditions for 85 days for rivaroxaban. The measured responses were then compared with those obtained from freshly prepared solutions. Stability percentages for samples compared to average of freshly prepared were 100.22 and 96.41 for QC-L and QC-H respectively for 38 days; and were 101.52 and 101.45 for QC-L and QC-H respectively for 85 days.

C. Post preparative stability: the stability of plasma extracts for two concentration levels including QC-L and QC-H was investigated after processing by extraction. The stability was assessed over 41 hrs. Stability percentages for samples compared to average of freshly extracted samples were 97.45 and 101.45 for QC-L and QC-H respectively for 21 days; and were 94.75 and 101.53 for QC-L and QC-H respectively for 41 days.

D. Freeze and thaw stability: analyte stability was determined for four freeze and thaw cycles for each of QC-L, and QC-H concentration levels. Samples were

stored at –80°C for at least 12 hours and thawed unassisted at room temperature. When completely thawed, the samples were refrozen again for at least 12 hours under the same conditions; stability was investigated for four cycles. The stability percentages were 107.07, 105.39, 107.17, 112.09 for QC-L samples, and 96.23, 98.75, 100.03, 97. 65 for the QC-H samples.

E. Matrix-based short-term stability: matrix-based samples including QC-L and QC-H were kept unextracted at room temperature for 21 hours prior to extraction and analyses. The analytical concentration measured for rivaroxaban were compared with those measured from freshly extracted QC samples. The 21-hrs stability percentage were 99.90 and 97.31 for QC-L and QC-H, compared to freshly extracted and analysed samples.
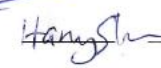
F. Matrix-based long-term stability: Matrix based long term stability of rivaroxaban was measured under prolonged storage conditions (-80 °C) for a period spanned over the time required to complete the analyses of samples collected from all the volunteers. Stability results indicated that rivaroxaban was stable in the matrix under conditions of sample collection, preparation, freezing and analyses. Stability percentages for samples compared to fresh samples were 103.67 and 96.07 for QC-L and QC-H respectively for 25 days; and were 106.07 and 97.31 for QC-L and QC-H respectively for 38 days.

Appendix 7: The Institution Review Board/Independent Ethics Committee Approval - The International Centre for Bioavailability, Pharmaceutical, and Clinical Research

	Title IRB Minutes of Meeting "IRB Favorable Opinion Letter"		
Form	Code:FORM04/SOP:QA-034	Version: 04	Status CHECKED
Supersedes: 03	*Page 1 of 1*	Effective Date: 18/07/2019	

The Institutional Review Board/Independent Ethics Committee (IRB/IEC) at International Center for Bioavailability, Pharmaceutical and Clinical Research. (ICBR). has reviewed the following related documents for **Rivaroxaban (20 mg Film Coated Tablet)** Pharmacokinetic and Pharmacodynamics Study.

1- The Final version of the study protocol outlining: the objective, design, conduct and analysis for the proposed study:
   Protocol Code :RESH-012
   Protocol Title:
2- Pharmacokinetic and Pharmacodynamics Study of a single dose of **Rivaroxaban (Xarelto® 20 mg Film Coated Tablets, (Bayer))** Under Fed Condition in Healthy Obese Participants
3- The study's "Team of investigators".
4- The informed consent form (ICF) and considered its suitablity and procedure.
5- The case report form(CRF).
6- The means of recruitment.
7- The provision for compensation to the participants.
8- Insurance Certificate.

Serial	Names	Signature	Date	Approved	Disapproved
1.	**Prof. Dr/Fathy Tash** Chairperson/Medical Person	*Fth.Tw*	29\06\2022	☑	❏
2.	**Prof.Dr /Azza Saleh** Scientific Representative	—	—	❏	❏
3.	**Prof.Dr/ Nabil Helmy** Legal Person	—	—	❏	❏
4.	**Dr/ Ahmed Ismail** Member	*signature*	29\06\2022	☑	❏
5.	**Prof.Dr/Saleh Hashem** Member	*Saleh*	29\06\2022	☑	❏
6.	**Dr/Hany Selim** Member	*HanySlm*	29\06\2022	☑	❏
7.	**Prof.Dr/ Fathy Ibrahem** Member	—	—	❏	❏

IRB VOTING:

IRB DECISION:

The IRB chairperson (president) hereby declared that the study is
   ☑ Approved
   ❏ Deferred (See notes and recommendation above)
   ❏ Disapproved

Confidential

IRB (RESH-012)

180

Appendix 8: Egypt Drug Authority Approval (Anonymous)

السيد الدكتور / مدير مركز International Center For Bioavailability, Pharmaceutical and Clinical Research (ICBR)

تحيـة طيبة وبعـد،،،

نحيط سيادتكم علماً بأنه قد تم إحاطتنا بالخطاب المرسل إلينا من قبل سيادتكم بتاريخ 2022/7/25 و الخاص بمستحضر :

- **Product Name: Xarelto 20mg FCT**
- **Dosage Form: FCT**
- **Active Ingredient(s): Rivaroxaban 20mg**

نحيط سيادتكم بأن الطلب المقدم من قبل سيادتكم لا يعتبر bioavilaibility or bioequivalence study، ولكن يعتبر clinical trial،

، و بالتالى فأسماء المتطوعين التاليين لم يتم إشتراكهم فى دراسات أخرى:

الرقم القومي	اسم المتطوع	م

-		

وذلك للإحاطة وإتخاذ اللازم.

وتفضلوا بقبول وافر الاحترام ،،،

Appendix 9: The Institution Review Board – Qatar University

Qatar University Institutional Review Board **QU-IRB**
QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

DATE: August 17, 2022

TO: Ahmed Awaisu
FROM: Qatar University Institutional Review Board (QU-IRB)

PROJECT TITLE: 1945114-1Pharmacokinetic and Pharmacodynamics Study of a Single Dose of Rivaroxaban (20 mg Film Coated Tablet) Under Fed Condition in Healthy Obese Participants
QU-IRB REFERENCE #: QU-IRB 1741-E/22
SUBMISSION TYPE: New Project

ACTION: DETERMINATION OF EXEMPT STATUS
DECISION DATE: August 17, 2022
REVIEW CATEGORY: Exemption category # 3

Thank you for your submission of New Project materials for this project. The Qatar University Institutional Review Board (QU-IRB) has determined this project is EXEMPT FROM IRB REVIEW according to Qatar Ministry of Public Health regulations. Please note that exempted proposals do not require renewals however, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

We will retain a copy of this correspondence within our records.

Documents Reviewed:

- Application Form - 1-QU-IRB Brief Application Form_v5_Rivaroxaban PK in Healthy Volunteers_Prof. Awaisu_v2.pdf (UPLOADED: 08/3/2022)
- Consent Form - 6-Consent form_Rivaroxaban PK in healthy volunteers.pdf (UPLOADED: 08/3/2022)
- Data Collection - 5-Case Report Form_FORM02 SOP BEC-025(VOLN).pdf (UPLOADED: 08/3/2022)
- Letter - 4-Egyptian Drug Authority_EDA approval (002).pdf (UPLOADED: 08/3/2022)
- Letter - 3-ICBR Egypt_IRB Approval.pdf (UPLOADED: 08/3/2022)
- Other - 7-QU-IRB Check List (6)_Rivaroxaban PK in Healthy Obese Subjects.pdf (UPLOADED: 08/3/2022)
- Protocol - 2-StudyProtocol_QU IRB_The impact of obesity on rivaroxaban pharmacokinetics_20220801.pdf (UPLOADED: 08/3/2022)
- Training/Certification - CITI completion certificate_Hazem Elewa.pdf (UPLOADED: 08/3/2022)
- Training/Certification - CITI completion certificates_Ibtihal Abdullah.pdf (UPLOADED: 08/3/2022)
- Training/Certification - CITI Completion Certificate_Majdoleen Alalawneh_2022.pdf (UPLOADED: 08/3/2022)
- Training/Certification - CITI Completion Certificate_Dr. Ousama Rachid_2022.pdf (UPLOADED: 08/3/2022)
- Training/Certification - CITI Completion Report and Certificate_Prof. Ahmed Awaisu_May 2022.pdf (UPLOADED: 08/3/2022)

- 1 -

If you have any questions, please contact QU-IRB at 4403 5307 or qu-irb@qu.edu.qa. Please include your project title and reference number in all correspondence with this committee.

Best wishes,

Dr. Mohamed Emara
Chairperson, QU-IRB

**Institutional Review Board
(IRB)
Office Of Academic Research**

This letter has been issued in accordance with all applicable regulations, and a copy is retained within Qatar University's records.

Generated on IRBNet

Appendix 10: Plasma Concentrations of Rivaroxaban vs. Time Curves

Following a Dose of Rivaroxaban 20 mg for Study Participants

Subject 1: non-obese

Subject 2: non-obese

Subject 3: non-obese

Subject 4: non-obese

Subject 9: non-obese

Subject 10: non-obese

Subject 11: non-obese

Subject 15: non-obese

187

Subject 16: non-obese

Subject 18: non-obese

Subject 19: non-obese

188

Subject 20: non-obese

Subject 21: non-obese

Subject 23: non-obese

189

Subject 27: non-obese

Subject 31: non-obese

Subject 33: non-obese

Subject 34: non-obese

Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Non-obese Subjects (n=18)

Log Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Non-obese Subjects (n=18)

192

Subject 5: obese

Subject 6: obese

Subject 7: obese

Subject 8: obese

Subject 12: obese

Subject 13: obese

Subject 14: obese

Subject 17: obese

Subject 22: obese

Subject 24: obese

Subject 25: obese

Subject 26: obese

Subject 28: obese

Subject 29: obese

Subject 30: obese

Subject 32: obese

Subject 35: obese

Subject 36: obese

Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Obese Subjects (n=18)

Log Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Obese Subjects (n=18)

Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Extremly Obese Subjects (n=6)

Log Plasma Concentrations vs. Time Curves Following a Dose of Rivaroxaban 20 mg for Extremly Obese Subjects (n=6)

200

Appendix 11: Plasma Concentrations and Prothrombin Time vs. Time Curves

Following a Dose of Rivaroxaban 20 mg for Study Participants

Non-obese subjects curves (1, 2, 3, 4, 9, 10, 11, 15, 16, 18, 19, 20, 21, 23, 27, 31, 33, 34)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 1)

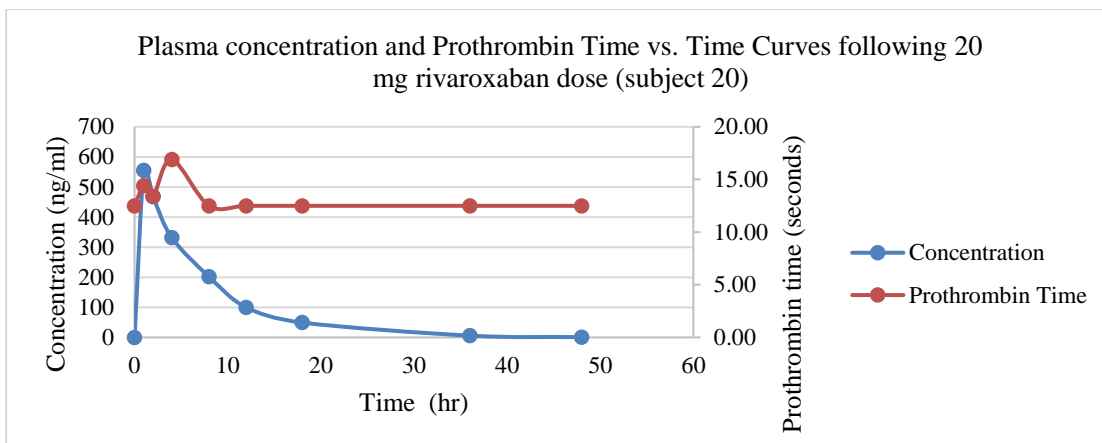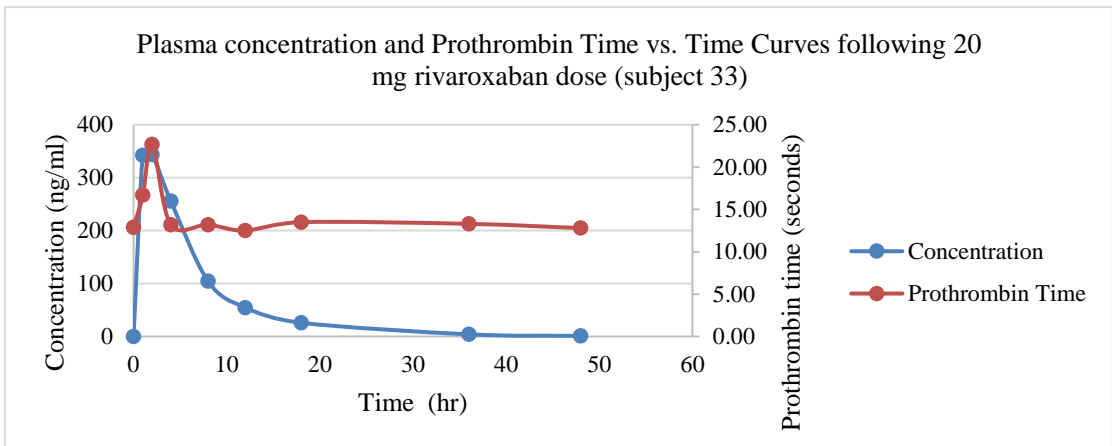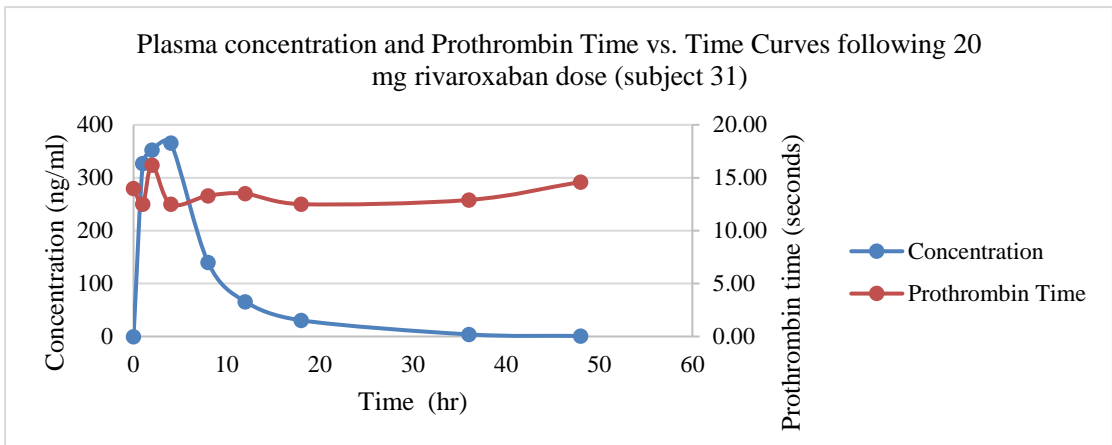Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 2)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 3)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 4)

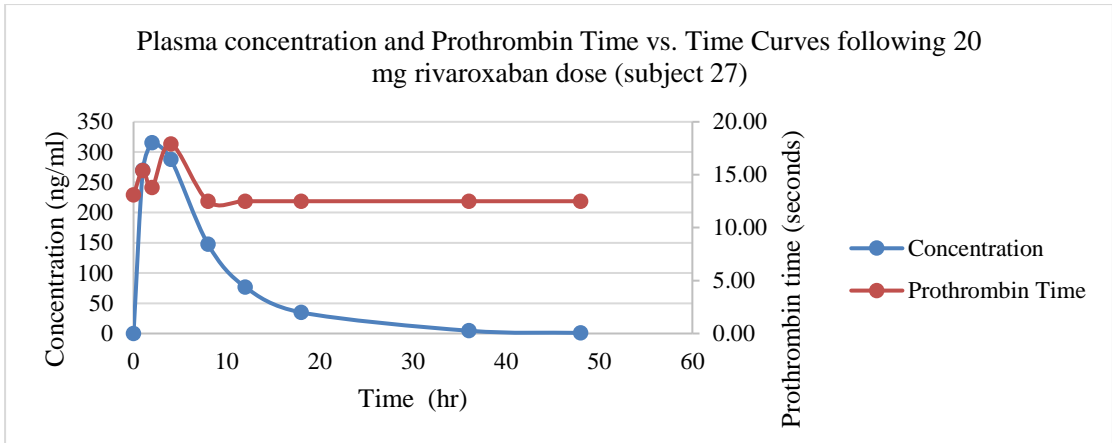Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 9)

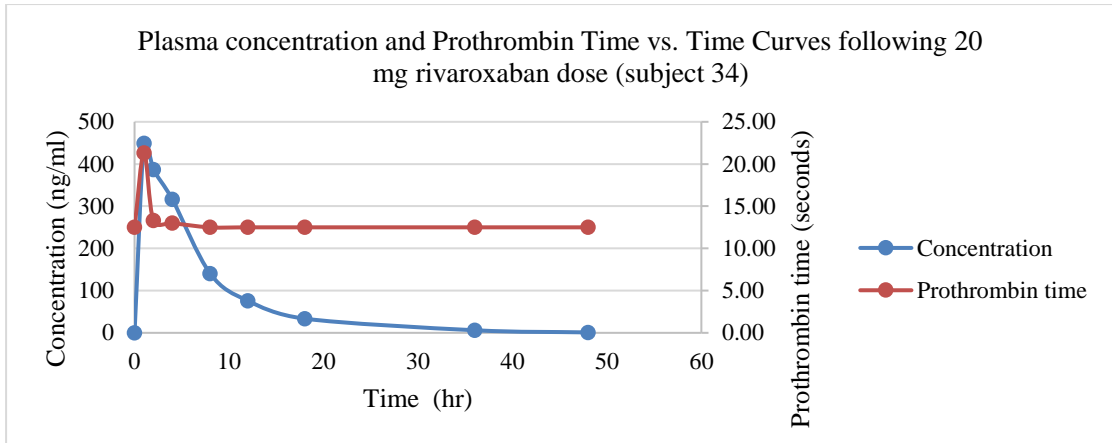Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 10)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 11)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 15)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 16)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 18)

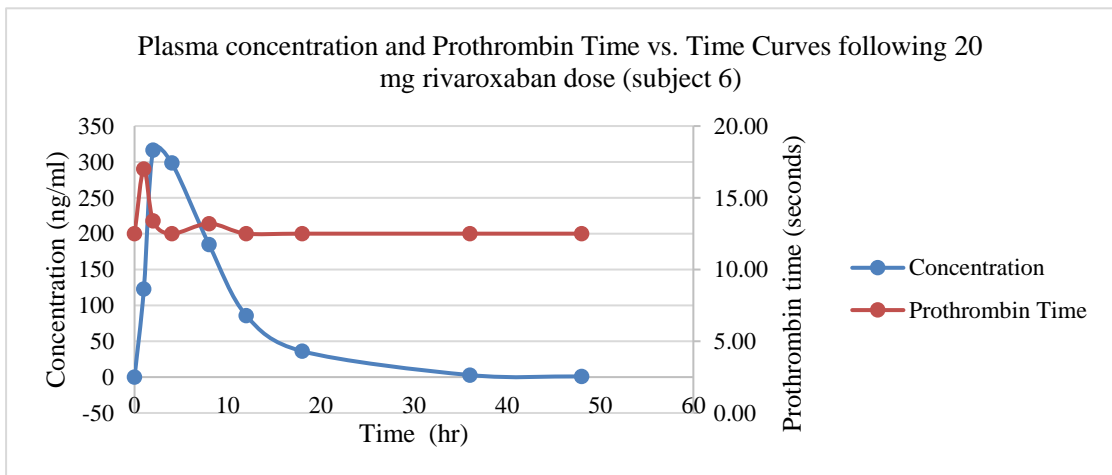Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 19)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 20)

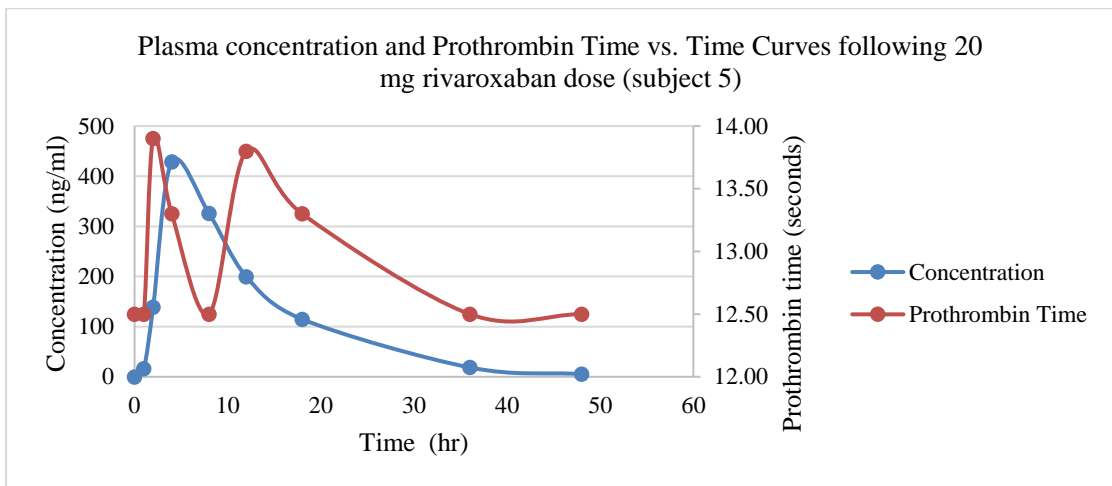Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 21)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 23)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 27)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 31)
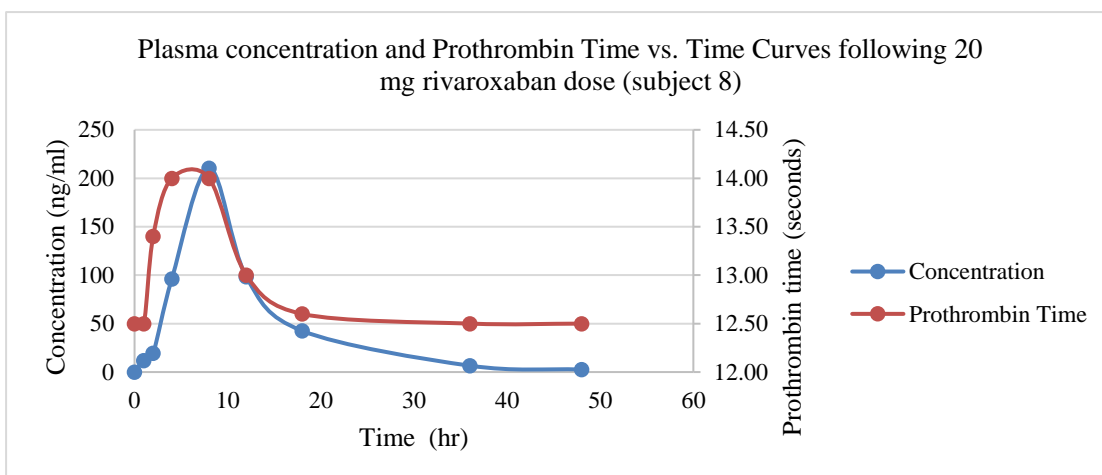

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 33)

206

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 34)

Obese subjects curves (5, 6, 7, 8, 12, 13, 14, 17, 22, 24, 25, 26, 28, 29, 30, 32, 35, 36)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 5)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 6)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 7)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 8)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 12)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 13)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 14)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 17)

209

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 22)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 24)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 25)

210

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 26)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 28)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 29)

211

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 30)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 32)

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 35)

212

Plasma concentration and Prothrombin Time vs. Time Curves following 20 mg rivaroxaban dose (subject 36)
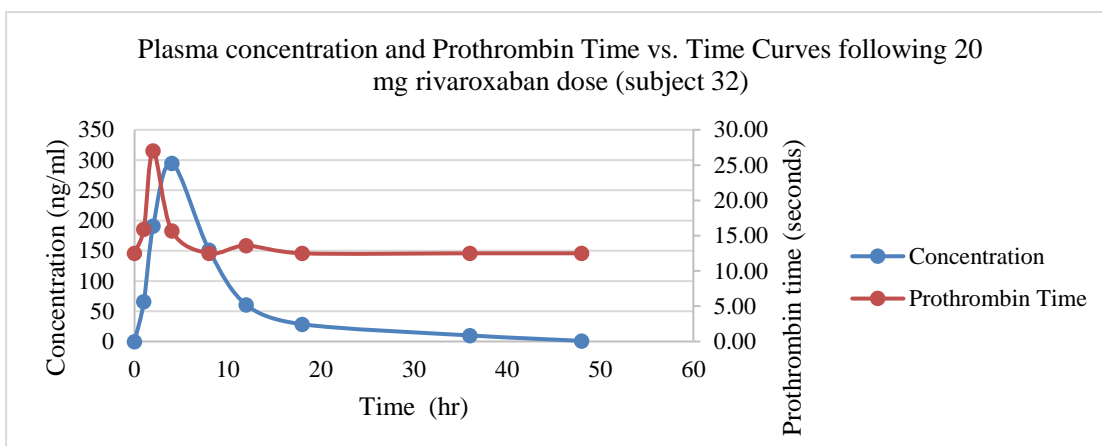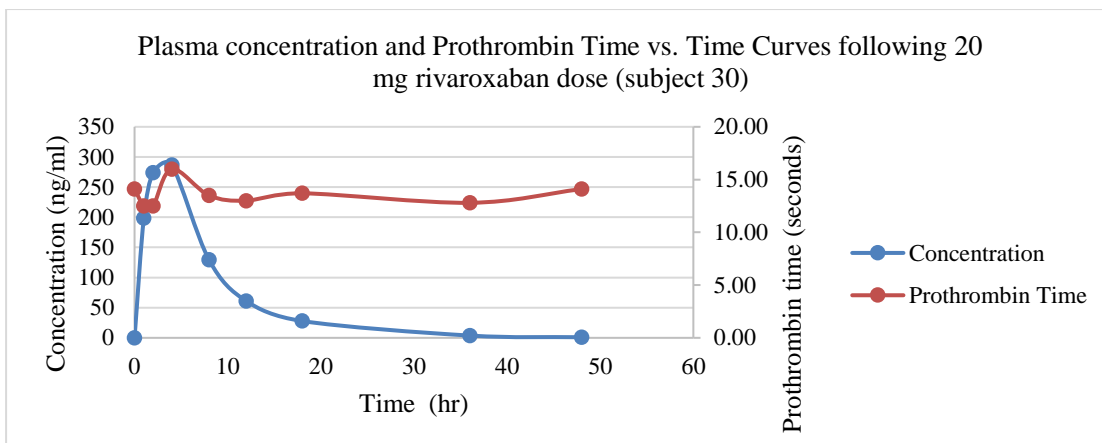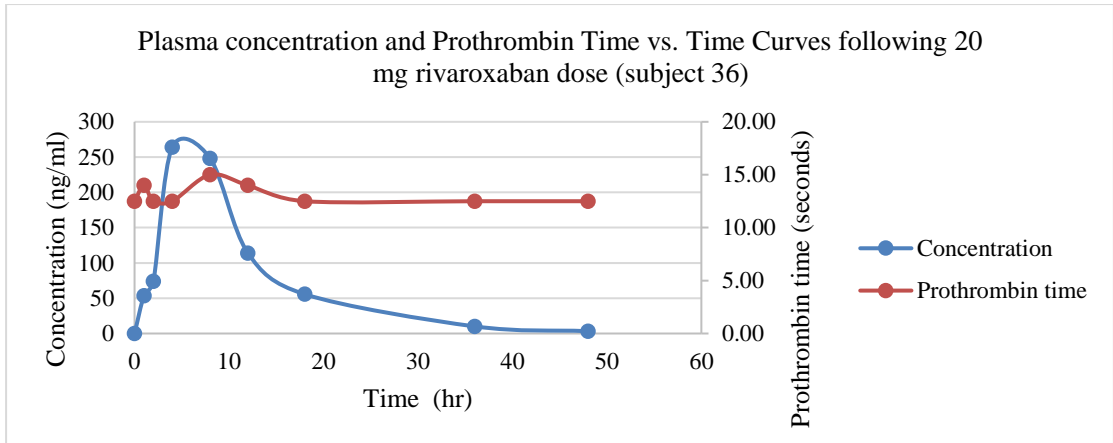
Appendix 12: Research Productivity and Output

List of conference abstracts and proceedings

1. Alalawneh M, Awaisu A, Rachid O. The Effect of Obesity on Pharmacokinetic and Pharmacodynamic Profile of Rivaroxaban. American Association for Pharmaceutical Sciences Conference at USA, Oct. 26 – Nov. 5, 2020 (Poster). Poster reference 894245, AAPS Poster Library. Alalawneh M. 10/25/20; 304892; 894245

2. Alalawneh M, Awaisu A, Rachid O, Elewa H, Abdallah I. Pharmacokinetics of a Rivaroxaban Single Oral Dose under Fed State in Obese vs. Non-Obese Healthy Subjects: Open-Label Controlled Clinical Trial. 2023 ACCP Virtual Poster Symposium May 23rd and 24th; 2023: American College of Clinical Pharmacy; 2023.

3. Alalawneh M, Rachid O, Abdallah I, Mahfouz A, Elewa H, Danjuma M, Mohamed A, Awaisu A. Trends in Prescribing and Outcomes in Obese versus Non-obese Patients Receiving Rivaroxaban Therapy: A Retrospective Observational Study Using Real-world Data. Sixth Qatar International Pharmacy Conference, November 3rd and 4th; 2023: ID# QIPC-85

4. Alalawneh M, Abdallah I, Elewa H, Awaisu A, Rachid O. Pharmacokinetics and Pharmacodynamics of Rivaroxaban after a Single Dose under Fed State in Obese vs. Non-Obese Subjects: Open-Label Controlled Clinical Trial. Sixth Qatar International Pharmacy Conference, November 3rd and 4th; 2023: ID# QIPC-79

List of journal publications

1. Alalawneh M, Awaisu A, Rachid O. Rivaroxaban Pharmacokinetics in Obese Subjects: A Systematic Review. Clinical Pharmacokinetics. 2022;61(12):1677-95. (Published)

2. Alalawneh M, Rachid O, Abdallah I, Mahfouz A, Elewa H, Danjuma MI, et al. Trends in Prescribing and Outcomes in Obese versus Non-obese Patients Receiving Rivaroxaban Therapy: An Observational Study Using Real-world Data. European Journal of Clinical Pharmacology. 2023;79(12):1675-85. (Published)

3. Alalawneh M, Awaisu A, Abdallah I, Elewa H, et al. Pharmacokinetics of Single Dose Rivaroxaban under Fed State in Obese vs. Non-Obese Subjects: An Open-Label Controlled Clinical Trial (RIVOBESE-PK). Clinical and Translational Science. (Accepted for publication)

List of awards

1. Distinguished Research Award (2024)

2. 3MT Thesis Presentation – 2nd place QU Health (2023)