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REVIEW ARTICLE

Updated Renal Dosage Recommendations for Rivaroxaban in Patients Experiencing or at Risk of Thromboembolic Disease

Albert A. Volkl[1] · Kenneth Todd Moore[1] · Lloyd Haskell[2] · Elliot S. Barnathan[2]

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Abstract
Patients with chronic kidney disease are at an increased risk of venous thromboembolism (VTE). The factor Xa inhibitor rivaroxaban has been shown to provide similar efficacy and a lower risk of bleeding compared with vitamin K antagonists for the treatment and prevention of VTE. Rivaroxaban has been studied in patients with varying degrees of renal impairment, and this review summarizes current knowledge supporting its use in patients with severe renal impairment (creatinine clearance [CrCl] of 15 to < 30 mL/min) for the prevention, treatment, or prophylaxis of VTE. Clinical pharmacology studies have demonstrated an increase in rivaroxaban systemic exposure, factor Xa inhibition, and prothrombin time with decreasing renal function. These changes reach a plateau with comparable increases in exposure among individuals with moderate or severe renal impairment and end-stage renal disease. The clinical development program for the treatment and prevention of VTE as well as prophylaxis of deep vein thrombosis (DVT) following orthopedic surgery excluded patients with CrCl < 30 mL/min; however, a limited number of patients with severe renal impairment were enrolled. Efficacy outcomes in these patients with severe renal impairment were not meaningfully different from those of patients with higher levels of renal function. There was also no increase in the incidence of major bleeding with rivaroxaban in patients with CrCl < 30 mL/min. Taken together, these pharmacological and clinical data suggest that in patients with severe renal impairment, the approved dosages of rivaroxaban can be used in the treatment and prevention of VTE and for prophylaxis of DVT after hip or knee replacement surgery.

1 Introduction

1.1 Renal Disease Is a Risk Factor for Thromboembolism

Venous thromboembolism (VTE) is a common disorder that manifests as deep vein thrombosis (DVT) in the majority of patients, while pulmonary embolism (PE) occurs with or without concomitant DVT in 30 to 40% of those afflicted [1]. Patients with renal impairment have an increased risk of VTE relative to those with normal renal function [2–4]. The relative risk of VTE increases with decreasing renal function, from 1.28 for those with mildly

Key Points

There is an increased risk of venous thromboembolism (VTE) in patients with chronic kidney disease.

Rivaroxaban was approved in 2011 for prophylaxis of deep vein thrombosis after hip or knee replacement surgery and in 2012 for the treatment and prevention of VTE but, at that time, approval did not include treatment of patients with chronic kidney disease.

Pharmacological and clinical data suggest that the approved dosages of rivaroxaban can be used in patients with severe renal impairment; the rivaroxaban label has thus been updated to include recommendations for VTE treatment and/or prophylaxis in patients with creatinine clearance ≥ 15 mL/min.

✉ Albert A. Volkl
avolkl@its.jnj.com

[1] Janssen Pharmaceuticals, Inc, 1125 Trenton Harbourton Rd, Titusville, NJ 08560, USA

[2] Janssen Research & Development, LLC, Raritan, NJ, USA

decreased renal function (estimated glomerular filtration rate [eGFR] between 60 and 89 mL/min) to 2.09 for those with eGFR between 15 and 59 mL/min [5]. Patients with end-stage renal disease (ESRD) receiving hemodialysis have a 2.3- to > 13-fold increased risk of VTE [2, 6]. Bleeding may also be increased in patients with renal disease, and those with ESRD undergoing hemodialysis are at risk of bleeding as a result of routine use of heparin to prevent clot formation in the extracorporeal circuit; the need for large blood vessel access; and perturbations in platelet motility, secretory function, and interactions with vessel walls [3, 7, 8].

An estimated 1 million people (approximately 1–2 per 1000) yearly are affected by VTE in the United States [9–11]. The 30-day mortality rate for VTE ranges from 3 to 5%, and the 1-year mortality rate is approximately 20% [10, 11]. Sudden death is the first symptom in about 25% of people who have a PE [9]. Among people who have had a DVT, up to one-third will have recurrent VTE and 50% or more will develop long-term complications of post-thrombotic syndrome that manifests as swelling, pain, discoloration, and scaling in the affected limb [9, 10]. Risk factors for developing a VTE include surgery, malignancies, pregnancy, and chronic medical conditions such as chronic kidney disease [9, 10, 12, 13]. The strongest risk factors include transient conditions of surgery and its resulting immobility and persistent conditions of active cancer/chemotherapy, autoimmune disorders, chronic infections, and chronic immobility [9, 14].

1.2 Anticoagulation Therapy in VTE

Treatment of VTE is usually divided into three phases: initial or acute (5–21 days), treatment (up to 3 months), and extended (beyond the initial 3 months) [12]. During the initial or acute phase, the aims of pharmacotherapy are to reduce mortality, early recurrence, proximal extension of a DVT, and to relieve symptoms [15]. To achieve these goals, parenteral or high-dose oral anticoagulation therapy is often administered. The goal of extended treatment is to prevent recurrence [12]. Randomized clinical trials in patients with VTE have shown that direct oral anticoagulants (DOACs), such as the factor Xa inhibitor rivaroxaban, provide similar efficacy as vitamin K antagonists (VKAs), such as warfarin, with a lower risk of major bleeding [16]. Factor Xa is a key component in the clotting cascade as it catalyzes the conversion of prothrombin to thrombin (factor IIa) that then mediates activation of coagulation and platelets [17]. Factor Xa inhibitors bind to the S1 and S4 pockets of factor Xa, causing dose-dependent inhibition, and thus blocking thrombin generation [17]. The advantages of DOACs over traditional VKA therapy include rapid onset of action, predictable pharmacokinetics (PK), consistent pharmacodynamics (PD) with dose-proportional increases in anticoagulant response, simplified treatment regimens, limited drug interactions, no requirement for routine monitoring, and lack of strict dietary restrictions [18].

Careful assessment of benefits and risks of anticoagulant therapy is necessary for treating patients with renal impairment experiencing a VTE or at risk for a VTE. Many of the currently approved pharmacotherapies for VTE, including rivaroxaban, are at least partly cleared by renal excretion [19]. Approximately one-third of the administered rivaroxaban dose is excreted in urine as unchanged drug. Of this, active renal secretion accounts for 30% and glomerular filtration accounts for 6% [20]. Careful consideration of rivaroxaban dosage is therefore required in patients with impaired kidney function. The current labeling for rivaroxaban recommends 15 mg twice daily (30 mg/day) for 21 days followed by 20 mg once daily for VTE treatment and 10 mg once daily for VTE prevention for all patients with creatinine clearance (CrCl) ≥ 15 mL/min [19]. There are limited data regarding the use of rivaroxaban in patients with CrCl < 15 mL/min for the treatment or prevention of VTE, and it is therefore not recommended (Table 1). This targeted review summarizes the relevant clinical pharmacology, efficacy, and safety data supporting the expanded use and regulatory approval of rivaroxaban for VTE treatment or prophylaxis in patients with severe renal impairment (CrCl 15 to < 30 mL/min) that were obtained from clinical trials conducted during rivaroxaban drug development [19]. Data were compiled from internal resources and publications that support the approved indication of rivaroxaban for the treatment and prevention of thromboembolic disease, including DVT and PE. PubMed literature search terms included ‘rivaroxaban’, ‘renal disease’, and ‘thromboembolism’.

2 Renal Dosing in Phase I Clinical Pharmacology Studies

Four phase I clinical pharmacology studies have evaluated the PK, PD, and safety of rivaroxaban in individuals with varying degrees of renal impairment versus healthy controls [20–22]. The first of these phase I studies enrolled 32 participants who were stratified according to CrCl: healthy controls (≥ 80 mL/min) versus those with mild (50–79 mL/min), moderate (30–49 mL/min), and severe (< 30 mL/min) renal impairment, but not requiring dialysis in the 4 weeks before enrollment [20]. Measurement of CrCl was consistent with guidelines for industry from the US Food and Drug Administration using the Cockcroft–Gault equation [18], which includes serum creatinine, age, weight, and

Table 1 Recommended dosage regimen of rivaroxaban for the treatment and prevention of VTE [19]

Indication	Dosage regimen for all patients with CrCl ≥ 15 mL/min[a]
Treatment of DVT/PE	15 mg bid for the first 21 days, followed by 20 mg qd
Reduction in risk of recurrence of DVT/PE	10 mg qd after ≥ 6 months of standard anticoagulant treatment
DVT prophylaxis following hip replacement surgery	10 mg qd for 35 days starting 6–10 h after surgery once hemostasis is established
DVT prophylaxis following knee replacement surgery	10 mg qd for 12 days starting 6–10 h after surgery once hemostasis is established
Prophylaxis of VTE in acutely ill medical patients	10 mg qd in hospital and after discharge for 31–39 days

bid twice daily, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *qd* once daily, *VTE* venous thromboembolism

[a]Patients with CrCl < 30 mL/min were not studied, but administration of rivaroxaban is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to < 50 mL/min); rivaroxaban is not recommended for patients with CrCl < 15 mL/min.

sex. PD parameters were assessed by evaluating the inhibition of factor Xa activity and prolongation of prothrombin time (PT) [20]. Both pre- and post-dose PK and PD samples were taken. Renal clearance of rivaroxaban decreased with increasing renal impairment, which led to a corresponding increase in systemic exposure [20]. Following a single 10 mg dose, mean area under the plasma concentration-time curve (AUC) values for rivaroxaban were increased by approximately 44% (mild impairment), 52% (moderate impairment), and 64% (severe impairment) relative to healthy controls [20]. The PD effects of rivaroxaban were also increased with decreasing renal function [20]. The mean AUC for factor Xa inhibition was increased in those with mild impairment by approximately 50%, moderate by 86%, and severe by 100% compared with healthy controls [20]. Similarly, AUC values for prolongation of PT were higher in participants with renal impairment versus healthy controls by approximately 33% (mild), 116% (moderate), and 144% (severe) [20].

The second study compared the PK and PD properties of rivaroxaban administered both before and after a 4-h hemodialysis session in patients with ESRD versus healthy volunteers (CrCl ≥ 80 mL/min) [21]. Eight patients with ESRD requiring maintenance hemodialysis thrice weekly for ≥ 3 months received rivaroxaban 15 mg approximately 2 h before initiating a 4-h hemodialysis session, and then 7 to 14 days later received rivaroxaban 15 mg 3 h after the completion of a 4-h hemodialysis session [21]. The 7- to 14-day washout period between dosing was selected to allow for complete elimination of rivaroxaban (five times the half-life) between dosing periods. The healthy control group ($n = 8$) received a single dose of rivaroxaban 15 mg [21]. Both pre- and post-dose PK and PD samples were taken during all dosing periods for both the active and control groups. In patients with ESRD, hemodialysis did not significantly affect rivaroxaban systemic exposure. Rivaroxaban administration prior to a 4-h hemodialysis session resulted in only a 5% lowering of plasma AUC as compared with the AUC with post-dialysis dosing. In comparison, rivaroxaban AUC increased by 56% when administered post-hemodialysis, representing a 35% decrease in the overall clearance of rivaroxaban. The increase in rivaroxaban AUC observed in ESRD patients after completing a 4-h hemodialysis session was comparable with the increases in exposure observed in participants with moderate (approximately 52%) or severe (approximately 64%) renal impairment observed in the initial study reported by Kubitza et al [20, 21]. Additionally, the effects on factor Xa inhibition and PT were generally consistent with the PK changes observed [21].

A third study assessed a single 5 mg and 15 mg oral dose of rivaroxaban in six patients with ESRD undergoing hemodialysis (data on file). A control group consisting of six age-, weight- and gender-matched healthy volunteers were included. A main difference between this study and the initial hemodialysis study reported by Dias et al was the assessment of rivaroxaban parameters when administered with and without unfractionated heparin during dialysis to prevent clotting of the dialysis machine. Both pre- and post-dose PK and PD samples were taken during all dosing periods for both the active and control groups. Participants with ESRD administered a 15 mg dose of rivaroxaban just prior to the start of the hemodialysis period and again during the hemodialysis-free period displayed comparable AUC values, which were in line with the previous hemodialysis study reported by Dias et al [21]. These findings support that hemodialysis has a very limited impact on the overall systemic exposure of rivaroxaban. When comparing PK parameters between ESRD subjects during a hemodialysis-free period with healthy matched controls, an increase in AUC (approximately 50%) was observed with the 15 mg dose. Once again, this is consistent with the systemic exposure changes observed in the other studies. However, a similar assessment comparing the PK parameters between ESRD subjects during a hemodialysis-free period with healthy controls reported an increase of 23% in AUC with the 5 mg rivaroxaban dose.

The results from these studies demonstrated that decreasing renal function increased rivaroxaban systemic exposure (as measured by AUC) while also increasing factor Xa

inhibition and further prolonging the PT interval (Table 2). Similar increases in systemic exposure were observed among patients with moderate or severe renal impairment and those with ESRD receiving hemodialysis, relative to healthy controls, across all three trials [20, 21]. This suggests a plateau is reached with regard to the changes in the PK profile when moderate to severe renal impairment occurs. Because active secretion is the dominant mechanism during renal elimination of rivaroxaban, the observed plateau effect suggests that the active transport function reaches a maximum before there is complete loss of passive filtration [21]. Therefore, once the renal P-glycoprotein transporters become saturated and no further drug is actively secreted, the passive filtration function likely takes over for any further elimination of rivaroxaban.

In a separate independent study conducted by De Vriese and colleagues, rivaroxaban PK and PD parameters were assessed in ESRD patients without residual renal function and who were undergoing maintenance hemodialysis [22]. Rivaroxaban 10 mg was administered during three different dosing periods: (1) as a single oral dose administered immediately after each of three consecutive hemodialysis sessions on Days 2, 4, and 6 ($n = 12$); (2) as a single oral dose administered either in the morning (prior to hemodialysis scheduled in the afternoon) or the previous evening (prior to hemodialysis scheduled in the morning; $n = 12$); or (3) as a single oral dose of 10 mg administered once daily (in the morning) for 7 days ($n = 6$), with dialysis occurring on Days 2, 4, and 6 [22]. The results from dosing period 1 confirmed that the systemic exposure of a single 10 mg dose of rivaroxaban immediately following hemodialysis was consistent with those reported by Kubitza et al in patients with moderate or severe renal impairment [20, 22]. Results from dosing period 2 confirmed that hemodialysis had no significant impact on plasma concentrations of rivaroxaban or PT duration, consistent with the results reported by Dias et al [22]. The results from dosing period 3 showed that significant drug accumulation did not occur, and maintenance hemodialysis did not affect steady-state drug concentrations [22]. Overall, the results of this study were consistent with the three phase I studies described above and suggest that in patients with severe renal impairment or ESRD, rivaroxaban administration results in serum concentrations similar to those reported in patients with moderate or severe renal impairment, irrespective of hemodialysis [22].

3 Efficacy and Safety by Renal Function Status in Pivotal Phase III Clinical Studies

Individuals with severe renal impairment (CrCl 15 to < 30 mL/min) were excluded from the phase III studies that assessed the use of rivaroxaban for both the treatment (EINSTEIN studies [23–25]) and prophylaxis (RECORD [26–28], MAGELLAN [29], and MARINER [30] studies) of VTE. The lack of data in these renally impaired patients was reflected in the original product labeling, thus limiting the use of rivaroxaban [19]. However, a limited number of patients with severe renal impairment (baseline CrCl ≥ 15 to < 30 mL/min) had been enrolled in error, considered protocol deviations, and received the standard dose of rivaroxaban as per each study design. When a post hoc subanalysis by renal function was conducted for each of these phase III trials, it was observed that the efficacy and safety data from these patients with severe renal impairment were consistent with those who had higher levels of renal function (i.e., normal function, mild, or moderate impairment) [Table 3]. These efficacy and safety data, combined with the pharmacological data previously described, suggest that patients with severe renal impairment could safely receive the standard approved dosage of rivaroxaban for both the VTE treatment and VTE prevention indications [19].

3.1 Prophylaxis of DVT Following Hip or Knee Replacement Surgery

RECORD 1, 2, and 3 were phase III studies that evaluated rivaroxaban for the prophylaxis of VTE in patients

Table 2 Percentage increase in rivaroxaban PK and PD measures in participants with renal impairment relative to healthy participants (CrCl ≥80 mL/min) from clinical pharmacology studies [20, 21]

Measure	Parameter	CrCl (mL/min)				
		50–79	30–49	15–29	ESRD (on dialysis)	ESRD (post-dialysis)
Exposure	AUC	44	52	64	47	56
Factor Xa inhibition	AUEC	50	86	100	49	33
PT prolongation	AUEC	33	116	144	112	158

AUC area under the plasma concentration-time curve, *AUEC* area under the effect-time curve, *CrCl* creatinine clearance, *ESRD* end-stage renal disease, *PD* pharmacodynamic, *PK* pharmacokinetic, *PT* prothrombin time

undergoing total knee or hip replacement surgery [26–28]. These studies compared rivaroxaban 10 mg once daily administered at least 6–8 h after wound closure with enoxaparin 40 mg once daily administered 12 h preoperatively. In a pooled analysis of these three studies, the incidence of the primary efficacy outcome of VTE was 50/1912 (2.6%) with rivaroxaban versus 161/1921 (8.4%) with enoxaparin in participants with normal renal function (CrCl ≥ 80 mL/min), 56/1140 (4.9%) versus 112/1153 (9.7%) in mild renal impairment (50 to < 80 mL/min), 8/198 (4.0%) versus 27/197 (13.7%) in moderate renal impairment (30 to < 50 mL/min), and 0/12 (0%) versus 2/12 (16.7%) in severe renal impairment (15 to < 30 mL/min; data on file). The incidence of major bleeding with rivaroxaban 10 mg once daily was 11/2645 (0.4%) in patients with normal renal function versus 3/2672 (0.1%) with enoxaparin, 3/1645 (0.2%) versus 4/1639 (0.2%) in mild renal impairment, 0/298 (0%) versus 1/324 (0.3%) in moderate renal impairment, and 0/25 (0%) versus 1/22 (4.5%) in severe renal impairment (data on file).

3.2 Treatment of DVT/PE

The phase III EINSTEIN DVT and EINSTEIN PE studies demonstrated noninferiority of rivaroxaban compared with enoxaparin and VKA therapy in preventing VTE recurrence, with similar principal safety outcomes (major or clinically relevant nonmajor bleeding) observed [23, 24]. Participants received an initial dose of rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily or standard therapy, which consisted of

Table 3 Efficacy and safety outcomes based on renal function from the VTE clinical development program

Clinical study and indication	Primary efficacy outcome		Safety[a]	
RF subgroup (by CrCl, in mL/min[b])	Rivaroxaban [*n/N* (%)]	Comparator [*n/N* (%)]	Rivaroxaban [*n/N* (%)]	Comparator [*n/N* (%)]
RECORD 1–3, prophylaxis of DVT after hip/knee replacement surgery [26–28]	10 mg qd	Enoxaparin	10 mg qd	Enoxaparin
Normal RF (≥ 80)	50/1912 (2.6)	161/1921 (8.4)	11/2645 (0.4)	3/2672 (0.1)
Mild RI (50 to < 80)	56/1140 (4.9)	112/1153 (9.7)	3/1645 (0.2)	4/1639 (0.2)
Moderate RI (30 to < 50)	8/198 (4.0)	27/197 (13.7)	0/298 (0)	1/324 (0.3)
Severe RI (< 30)	0/12 (0)	2/12 (16.7)	0/25 (0)	1/22 (4.5)
EINSTEIN, DVT/PE treatment [31]	15 mg bid, 20 mg qd	Enoxaparin/VKA	15 mg bid, 20 mg qd	Enoxaparin/VKA
Normal RF (≥ 80)	50/2772 (1.8)	52/2797 (1.9)	239/2763 (8.7)	245/2786 (8.8)
Mild RI (50 to < 80)	25/1036 (2.4)	31/1001 (3.1)	110/1030 (10.7)	123/1002 (12.3)
Moderate RI (30 to < 50)	11/323 (3.4)	10/313 (3.2)	37/320 (11.6)	43/310 (13.9)
Severe RI (< 30)	0/10 (0)	1/11 (9.1)	2/9 (22.2)	1/11 (9.1)
EINSTEIN CHOICE, long-term prevention of recurrent VTE [25]	10 mg qd	Aspirin 100 mg	10 mg qd	Aspirin 100 mg
Normal RF (≥ 80)	9/774 (1.2)	37/790 (4.7)	21/774 (2.7)	13/790 (1.6)
Mild RI (50 to < 80)	4/302 (1.3)	10/277 (3.6)	6/302 (2.0)	6/277 (2.2)
Moderate RI (30 to < 50)	0/51 (0)	3/64 (4.7)	0/51 (0)	4/64 (6.3)
Severe RI (< 30)	0/2 (0)	0/1 (0)	0/2 (0)	0/1 (0)
MAGELLAN, prevention of VTE in acutely ill [29]	10 mg qd	Enoxaparin	10 mg qd	Enoxaparin
Normal RF (≥ 80)	43/1222 (3.5)	44/1231 (3.6)	11/1608 (0.7)	5/1571 (0.3)
Mild RI (50 to < 80)	44/1110 (4.0)	66/1139 (5.8)	19/1450 (1.3)	7/1487 (0.5)
Moderate RI (30 to < 50)	39/543 (7.2)	56/591 (9.5)	12/780 (1.5)	3/804 (0.4)
Severe RI (< 30)	2/46 (4.3)	1/45 (2.2)	1/81 (1.2)	0/64 (0)
MARINER, prevention of VTE in acutely ill [30]	7.5 or 10 mg qd	Placebo	7.5 or 10 mg qd	Placebo
CrCl ≥ 50	10 mg: 32/4909 (0.65)	48/4913 (0.98)	10 mg: 13/4890 (0.27)	9/4890 (0.18)
Moderate RI (30 to < 50)	7.5 mg: 18/1098 (1.6)	18/1099 (1.6)	7.5 mg: 4/1092 (0.37)	0/1090 (0)

bid twice daily, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *RF* renal function, *RI* renal impairment, *qd* once daily, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

[a]Major and clinically relevant bleeding except for MAGELLAN, which only reports major bleeding

[b]Determined using the Cockcroft–Gault equation [18] based on guidelines for industry from the US Food and Drug Administration

enoxaparin 1 mg/kg twice daily for at least 5 days, until the international normalized ratio (INR) was ≥ 2.0 for 2 consecutive days plus VKA therapy initiated within 48 h after randomization and dose-adjusted to maintain an INR of 2.0 to 3.0. The duration of treatment (3, 6, or 12 months) was determined by the investigator before randomization [23, 24]. A total of 21 participants with severe renal impairment (CrCl 15 to < 30 mL/min; $n = 10$ in the rivaroxaban arm and $n = 11$ in the enoxaparin/VKA arm) were enrolled across these studies, despite being protocol deviations [31]. In a prespecified renal function subgroup analysis, a significantly increased rate of VTE recurrence was observed for both treatment groups combined as renal function decreased ($P_{trend} = 0.0001$), with rates of 1.8%, 2.8%, 3.3%, and 4.8% reported for patients with normal renal function and mild, moderate, and severe renal impairment, respectively [31]. Incidences of VTE recurrence were similar for the rivaroxaban and enoxaparin/VKA treatment arms across the renal function categories (Table 3) [31]. Within the severe renal impairment subgroup ($n = 21$), one recurrent VTE was observed with enoxaparin/VKA and no events occurred with rivaroxaban [31]. In both treatment arms, major and clinically relevant nonmajor bleeding increased with decreasing renal function, with bleeding rates of 8.7%, 10.7%, 11.6%, and 22.2% for rivaroxaban ($P_{trend} = 0.013$) and 8.8%, 12.3%, 13.9%, and 9.1% for enoxaparin/VKA ($P_{trend} < 0.001$) in patients with normal renal function and mild, moderate, and severe renal impairment, respectively [31]. Notably, major bleeding increased with decreasing renal function in participants treated with enoxaparin/VKA, but not with rivaroxaban [31]. In the rivaroxaban arm, major bleeding was reported in 0.8% of patients with normal renal function, 1.4% with mild renal impairment, 0.9% with moderate renal impairment, and none with severe renal impairment ($P_{trend} = 0.50$) compared with 1.0%, 3.0%, 3.9%, and 9.1%, respectively, in those treated with enoxaparin/VKA ($P_{trend} < 0.001$).

3.3 Reduction in Risk of Recurrence of DVT/PE

The phase III EINSTEIN CHOICE study was a randomized, double-blind study comparing the efficacy and safety of rivaroxaban 10 and 20 mg with aspirin 100 mg for the long-term prevention of recurrent symptomatic VTE [25]. Both doses of rivaroxaban were superior to aspirin in preventing recurrent VTE and were not associated with increased bleeding [25]. A prespecified subgroup analysis assessed efficacy and safety outcomes in patients based on renal function, as defined by CrCl rate (normal ≥ 80 mL/min; mild renal impairment 50 to < 80 mL/min; moderate to severe renal impairment < 50 mL/min) [25]. Included within the moderate to severe subgroup were four participants with severe renal impairment (CrCl 15 to < 30 mL/min) despite being protocol deviations; of these, two received rivaroxaban 10 mg, one received rivaroxaban 20 mg, and one received aspirin 100 mg [25]. In the subgroup analysis, the incidence of symptomatic recurrent fatal or nonfatal VTE was 9/774 (1.2%) with rivaroxaban 10 mg and 15/787 (1.9%) with rivaroxaban 20 mg versus 37/790 (4.7%) with aspirin in participants with normal renal function, 4/302 (1.3%) and 2/279 (0.7%) versus 10/277 (3.6%) in those with mild renal impairment, and 0/51 (0%) and 0/41 (0%) versus 3/64 (4.7%) in those with moderate to severe renal impairment [25]. The incidence of composite major and clinically relevant nonmajor bleeding was 21/774 (2.7%) with rivaroxaban 10 mg and 27/787 (3.4%) with rivaroxaban 20 mg versus 13/790 (1.6%) with aspirin in participants with normal renal function, 6/302 (2.0%) and 8/279 (2.9%) versus 6/277 (2.2%) in participants with mild renal impairment, and 0/51 (0%) and 1/41 (2.4%) versus 4/64 (6.3%) in participants with moderate to severe renal impairment [25]. Results by renal function were consistent with those of the overall study population [25]; however, the low number of participants with severe renal impairment precluded direct comparisons of rivaroxaban versus aspirin in this population.

3.4 Analyses in Acutely Ill Medical Patients Related to VTE

The phase III MAGELLAN study demonstrated the efficacy of rivaroxaban in reducing the risk for VTE and VTE-related death in approximately 8000 hospitalized, acutely ill medical patients, but with an elevated bleeding rate relative to control (enoxaparin) [29]. As a result, a retrospective analysis of MAGELLAN identified five key risk factors for bleeding, which were present in approximately 20% of the patients [32]. After exclusion of these patients with high risk of bleeding, analyses were conducted in the lower-bleeding risk subgroup of MAGELLAN, and the design of the subsequent MARINER study (described below) was refined to apply these risk factors to the selection criteria for patients.

In MAGELLAN, the incidence of the primary efficacy outcome of VTE at Day 35 was 43/1222 (3.5%) with rivaroxaban versus 44/1231 (3.6%) with enoxaparin in patients with normal renal function (CrCl ≥ 80 mL/min), 44/1110 (4.0%) versus 66/1139 (5.8%) in those with mild renal impairment (50 to < 80 mL/min), 39/543 (7.2%) versus 56/591 (9.5%) in those with moderate renal impairment (30 to < 50 mL/min), and 2/46 (4.3%) versus 1/45 (2.2%) in those with severe renal impairment (< 30 mL/min). The incidence of major bleeding at Day 35 with rivaroxaban 10 mg once daily was 11/1608 (0.7%) in patients with normal renal function versus 5/1571 (0.3%) with enoxaparin, 19/1450 (1.3%) versus 7/1487 (0.5%) in mild renal impairment, 12/780 (1.5%) versus 3/804

(0.4%) in moderate renal impairment, and 1/81 (1.2%) versus 0/64 (0%) in severe renal impairment [29]. Among the 'MARINER-like subpopulation of MAGELLAN', total VTE and VTE-related deaths occurred in 6.3% of patients receiving rivaroxaban 10 mg compared with 9.5% receiving enoxaparin [32]. Benefit was also observed in those with mild renal impairment (3.3% vs. 4.7%) [32].

MARINER was a phase III, multicenter, randomized, double-blind, placebo-controlled, event-driven trial comparing rivaroxaban 10 mg once daily (approximately 10,000 patients with CrCl ≥ 50 mL/min) and 7.5 mg once daily (approximately 2000 patients with CrCl 30 to < 50 mL/min) with placebo in acutely ill medical patients for 45 days post-hospital discharge [30]. Among patients treated with rivaroxaban 10 mg, all had CrCl ≥ 50 mL/min except for two patients in each treatment group, and the primary efficacy outcome of VTE occurred in 32/4909 (0.65%) compared with 48/4913 (0.98%) patients receiving placebo [30]. For those with CrCl of 30 to < 50 mL/min, there was no difference in the primary outcome: 18/1098 (1.64%) for rivaroxaban 7.5 mg and 18/1099 (1.64%) for placebo [30]. When the patients were grouped by CrCl of 50 to < 80 mL/min and ≥ 80 mL/min, the incidence of the primary efficacy outcome of VTE was 19/2354 (0.8%) and 13/2555 (0.5%) with rivaroxaban 10 mg once daily versus 28/2356 (1.2%) and 20/2556 (0.8%) with placebo, respectively. There were no patients with severe renal impairment (CrCl < 30 mL/min). The incidence of the primary safety outcome of major bleeding was 6/2543 (0.2%) with rivaroxaban 10 mg once daily versus 5/2543 (0.2%) with placebo in patients with normal renal function (CrCl ≥ 80 mL/min), and 7/2347 (0.3%) versus 4/2346 (0.2%) in those with mild renal impairment (CrCl 50 to < 80 mL/min). Major bleeding occurred in 4/1092 (0.4%) patients receiving rivaroxaban 7.5 mg versus none of the patients receiving placebo with moderate renal impairment (CrCl 30 to < 50 mL/min) [30].

3.5 Summary of Data From Participants With Severe Renal Impairment Across All Phase III Studies

Although relatively limited, these data from the phase III studies were still sufficient to suggest that in patients with CrCl of 15 to < 30 mL/min, despite receiving the same dose as other study participants, the point estimates of treatment effect were similar to those in patients with higher levels of renal function. The point estimates for the primary efficacy outcome of VTE in these patients were 2/70 (2.9%) for rivaroxaban and 4/69 (5.8%) for the comparator. Similarly, for major bleeding, the point estimates were 1/117 (0.9%) for rivaroxaban and 2/98 (2.0%) for the comparator. The current rivaroxaban product labeling reflects these findings, indicating that patients with CrCl of 15 to < 30 mL/min can be treated with the same dosage of rivaroxaban as recommended for patients with CrCl > 30 mL/min [19].

4 Clinical Implications and Dosing Recommendations

This review details the findings from key clinical pharmacology and treatment studies across VTE treatment and prevention to support the recommended dosage regimen for rivaroxaban currently allowed in the label (Table 1) [19]. No dose reduction is required for patients with renal impairment (CrCl ≥ 15 mL/min) for VTE treatment or prevention. Rivaroxaban dosing for VTE treatment includes a loading dose of 15 mg twice daily (30 mg/day) for 21 days followed by 20 mg once daily. To prevent VTE and VTE recurrence, the recommended dose of rivaroxaban is 10 mg once daily. These recommendations are based on the clinical studies for these indications, which included patients with normal renal function as well as those with mild and moderate renal impairment and a small population of patients with severe renal impairment. The results of these clinical trials showed similar efficacy and safety outcomes, with no excess bleeding, for these subgroups of patients.

Clinical pharmacology studies of rivaroxaban showed that a decrease in renal function leads to an increase in rivaroxaban exposure and an increase in PD effects on factor Xa inhibition and PT. These effects reach a plateau for patients with moderate/severe renal impairment and those with ESRD. However, patients with CrCl <15 mL/min were not included in the clinical studies for VTE treatment or prevention, and the use of rivaroxaban is not recommended for these patients.

The current labeling for rivaroxaban provides different recommendations for dosing based on indication and patient population [19]. In contrast to VTE treatment and prevention, dose reductions are recommended in patients with nonvalvular atrial fibrillation who have CrCl ≤ 50 mL/min. These differences are the result of several considerations made during the design of the clinical trials for each indication. For example, in the EINSTEIN studies, a dose adjustment was not warranted because VTE patients are typically younger with fewer comorbid conditions and have lower serum creatinine values compared with patients who have nonvalvular atrial fibrillation. Inadequate treatment of an initial blood clot (DVT or PE) is associated with an increased risk of recurrent VTE. The risk of VTE recurrence is high in the first month after a VTE event in patients receiving anticoagulant therapy, suggesting that dose modification may not be desirable [33]. In addition, patients with renal impairment have an increased risk of VTE as a result of various pathologies, including

changes in hemostasis and coagulation components, as well as environmental factors and comorbid conditions [2]. Given these risks for greater thrombosis, anticoagulant dose reduction, particularly for patients being treated for active VTE, was unwarranted. In addition, data from the MARINER study found that the lower dose of rivaroxaban (7.5 mg once daily) was not effective for VTE prophylaxis in the renally impaired, medically ill population [30].

Clinical data from the RECORD, EINSTEIN, MAGELLAN, and MARINER studies are limited by the number of patients with CrCl of 15 to <30 mL/min but generally show no meaningful differences in efficacy and safety outcomes from those observed for patients with high levels of renal function. These data combined with the exposure data suggest that in patients with severe renal impairment, the approved dosages of rivaroxaban can be used in the treatment and prevention of VTE and for prophylaxis of DVT in hip and knee replacement surgery.

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Data availability The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access [YODA] Project site at http://yoda.yale.edu.

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