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REVIEW

Influence of Renal Function on the Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of Non–Vitamin K Antagonist Oral Anticoagulants

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Abstract

With the growing integration of non–vitamin K antagonist oral anticoagulants (NOACs) into clinical practice, questions have arisen regarding their use in special populations, including groups that may have been underrepresented in clinical trials. Patients with renal impairment, particularly in the lower echelons of renal function, are one such group. In an effort to elucidate the current evidence regarding the use of NOACs in patients with renal impairment, a systematic assessment of the literature was performed. The MEDLINE database was interrogated for studies and analyses evaluating the influence of renal function on the pharmacokinetics, pharmacodynamics, efficacy, and safety of NOACs published from January 1, 2000, through August 2, 2017. The 82 relevant publications retrieved highlight the diversity in the NOAC class regarding the impact of renal function on drug clearance, drug exposures, and clinical trial outcomes. In several large clinical trials, subgroup analyses revealed no significant differences when patients were stratified by creatinine clearance as a measure of renal function. Efficacy findings, in particular, were largely aligned with the overall population in the included studies. However, relative risks of bleeding were shown to vary, sometimes driven by changes in bleeding event rates in the comparator arm (eg, warfarin, enoxaparin). With few exceptions, minimal influence of mild renal impairment was observed on the relative efficacy and safety of NOACs. Taken together, the evidence suggests that the presence of renal impairment merits careful consideration of anticoagulant choice but should not deter physicians from appropriate use of NOACs.

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Non–vitamin K antagonist oral anticoagulants (NOACs) have become a standard option for the management of thromboembolic disease and thromboprophylaxis across a variety of clinical indications. Commensurate with the integration of NOACs into routine care and the epidemiologic overlap among at-risk groups, the likelihood of encountering patients with renal impairment who may be candidates for treatment with a NOAC is high,[1,2] yet there remains uncertainty regarding the utility, selection, and dosing of NOACs in this population.[3] Indeed, inappropriate use or dosing of NOACs based on renal function is not uncommon[3,4] and can have potentially serious ramifications.[5] Given the clinical uncertainty, some studies have advocated use of vitamin K antagonists (VKAs) rather than NOACs in patients with impaired renal function.[6] This may be an oversimplification because differences in the effect of renal function on individual NOACs are anticipated based on the unique pharmacological properties of the various drugs.

The purpose of this review was to examine the current body of literature to (1) determine the effects of renal function on the clinical pharmacology (pharmacokinetics [PK] and pharmacodynamics [PD]), efficacy, and safety of individual NOACs and (2) ascertain how these findings might influence clinical practice.

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ARTICLE HIGHLIGHTS

- The influence of renal impairment on the pharmacokinetic, pharmacodynamic, efficacy, and safety profiles of non–vitamin K antagonist oral anticoagulants (NOACs) varies among individual members of the drug class.
- Except for severe renal impairment (creatinine clearance <30 mL/min per 1.73m^2 for dabigatran and <15 mL/min per 1.73m^2 for factor Xa inhibitors), NOAC use is not restricted in patients with renal dysfunction.
- Renal function should be assessed before initiating and during treatment with oral anticoagulants (whether NOACs or other agents), and the presence and degree of renal impairment should guide an appropriate therapeutic regimen and dosing.

IDENTIFICATION OF RELEVANT PUBLICATIONS

Two search methods were used to identify publications that explored the influence of renal function on the clinical pharmacology, efficacy, and safety of established, guideline-recommended NOAC agents (apixaban, dabigatran, edoxaban, and rivaroxaban). Both searches involved interrogation of the MEDLINE database for articles reporting results from prospective clinical trials, subgroup analyses, or PK studies published in English from January 1, 2000, through August 2, 2017. The first search focused on publications with a clear inclusion of renal function analyses. To prevent missing relevant studies in which renal function was not described in the abstract or key words, a second search was performed with the renal terms removed and the type of study limited to phase 2 or 3 clinical trials.

Results from the 2 searches were combined and duplicate publications removed. Retrospective studies, articles that evaluated NOACs as a group (rather than individual agents), studies of unapproved indications, and publications unrelated to the clinical pharmacology, efficacy, or safety of NOACs as they relate to renal function were excluded from the review. Primary publications from secondary or subgroup analyses were included if they were used to source study information and were found to contain relevant renal function analyses. Search terms and a schematic of the publication selection process are presented in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org).

APIXABAN

Influence of Renal Function on Apixaban PK/PD

Elimination of apixaban, a direct factor Xa inhibitor, occurs via renal and nonrenal pathways, with 27% of total drug clearance accounted for by renal excretion.[7] Chang et al[8] evaluated the clinical pharmacology after administration of a single apixaban 10-mg dose in patients with mild, moderate, or severe renal impairment compared with healthy volunteers. Decreases in renal function were shown to modestly increase apixaban systemic exposure (area under the plasma concentration-time curve), with predicted increases of 16%, 29%, and 38% corresponding to 24-hour creatinine clearance (CrCL) values of 65, 40, and 25 mL/min, respectively, compared with a reference CrCL of 100 mL/min.

Similar results were reported in a single-dose study of apixaban 5 mg administered to patients with end-stage renal disease (ESRD) and healthy volunteers.[9] Apixaban exposure increased by 36% in patients with ESRD compared with healthy volunteers. This is consistent with values estimated by Chang et al[8] at a CrCL of 25 mL/min (ie, severe renal impairment). Hemodialysis in patients with ESRD had minimal effect on apixaban exposure (14% decrease),[9] which is likely owing to the relatively high protein binding of apixaban.

Steady-state PK was explored by Mavrakanas et al[10] in a multiple-dose study of apixaban (2.5 and 5.0 mg twice daily [BID] administered during separate study periods) in 7 patients with nonvalvular atrial fibrillation (AF) and ESRD undergoing hemodialysis. Significant increases in apixaban exposure were observed from day 1 to day 8 of treatment with both doses ($P \leq .03$) and can be attributed to significant accumulation in this population. The increase in exposure with the 5.0-mg dose was considered supratherapeutic, and that of the 2.5-mg dose was comparable with standard dosing in patients with AF and normal renal function (5.0 mg BID). Hemodialysis removed only 4% of the drug

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TABLE. Characteristics of and Renal Dysfunction Representation in Randomized Controlled Efficacy and Safety Studies[a]

Study and conditions	Treatment groups	Patients (No. [%]) Normal function (CrCL >80 mL/min)	Mild dysfunction (CrCL >50-80 mL/min)	Moderate dysfunction (CrCL >30-50 mL/min)	Severe dysfunction (CrCL ≤30 mL/min)
Apixaban					
ARISTOTLE[12-15]	Apixaban 5 mg BID[b] (n=9120)	3761 (41.2)	3817 (41.9)	1365 (15.0)	137 (1.5)
AF and ≥1 stroke risk factor	Warfarin (n=9081)	3757 (41.4)	3770 (41.5)	1382 (15.2)	133 (1.5)
AVERROES[16-19]	Apixaban 5 mg BID[b] (n=2808)	2021 (36.1)	2374 (42.4)	1198 (21.4)	
AF and ≥1 stroke risk factor	Aspirin (n=2791)				
ADVANCE-2 and -3[20]	Apixaban 2.5 mg BID (n=4236)	2646 (62.5)	1303 (30.8)	217 (5.1)	
Elective TKA or THA	Enoxaparin (n=4228)	2609 (61.7)	1347 (31.9)	220 (5.2)	
AMPLIFY-J[21]	Apixaban 10/5 mg BID (n=40)	20 (50.0)	18 (45.0)	1 (2.5)	1 (2.5)
Symptomatic DVT or PE (with or without DVT)	UFH/warfarin (n=40)	14 (35.0)	17 (42.5)	5 (12.5)	3 (7.5)
AMPLIFY-EXT[22,23]	Apixaban 2.5 mg BID (n=840)[c]	595 (70.8)	174 (20.7)	47 (5.6)	1 (0.1)
Symptomatic DVT or PE (with or without DVT)	Apixaban 5 mg BID (n=813)	580 (71.3)	168 (20.7)	41 (5.0)	3 (0.4)
	Placebo (n=829)	564 (68.0)	194 (23.4)	44 (5.3)	2 (0.2)
Dabigatran					
RE-LY[24-27]	Dabigatran 110 mg BID (n=6015)	5826 (32.2)[d]	8766 (48.4)[d]	3505 (19.4)[d]	—
AF and ≥1 stroke risk factor	Dabigatran 150 mg BID (n=6076)	3880 (21.4)[e]	10697 (59.1)[e]	3374 (18.6)[e]	
	Warfarin (n=6022)				
RE-NOVATE, RE-NOVATE II[28]	Dabigatran 220 mg OD (n=2156)	1056 (64.5)[f]	495 (30.2)[f]	82 (5.0)[f]	5 (0.3)[f]
Elective THA	Enoxaparin 40 mg (n=2157)	1061 (64.5)[f]	508 (30.9)[f]	72 (4.4)[f]	4 (0.3)[f]
RE-COVER, RE-COVER II[29]	Dabigatran 150 mg BID (n=2553)	1861 (72.9)	538 (21.1)	114 (4.5)	12 (0.5)
Symptomatic DVT or PE	Warfarin (n=2554)	1837 (71.9)	562 (22.0)	123 (4.8)	11 (0.4)
Edoxaban					
ENGAGE AF-TIMI 48[30-32]	Edoxaban 60 mg[g] (n=7035)	5656 (80.4)		1379 (19.6)	—
AF and $CHADS_2$ ≥2	Edoxaban 30 mg[g] (n=7034)	5700 (81.0)		1334 (19.0)	
	Warfarin (n=7036)	5675 (80.7)		1361 (19.3)	
ENSURE-AF[33]	Edoxaban 60 mg[g] (n=1095)	643 (58.7)	304 (27.8)	83 (7.6)	
AF undergoing electrical cardioversion	Enoxaparin-warfarin (n=1104)	636 (57.6)	315 (28.5)	76 (6.9)	
Hokusai-VTE[34]	Edoxaban 60 mg[g] (n=4118)	3850 (93.5)		268 (6.5)	—
Symptomatic DVT or PE (with or without DVT)	Warfarin (n=4122)	3849 (93.4)		273 (6.6)	
Rivaroxaban					
ROCKET AF[35-40]	Rivaroxaban 20 mg OD[h] (n=7131)	2285 (32.3)[f]	3298 (46.6)[f]	1490 (21.1)[f]	—
AF and $CHADS_2$ ≥2	Warfarin (n=7133)	2222 (31.4)[f]	3400 (48.0)[f]	1459 (20.6)[f]	
J-ROCKET AF[41-44]	Rivaroxaban 15 mg OD[i] (n=639)	170 (26.6)	328 (51.3)	141 (22.1)	—
AF and $CHADS_2$ ≥2	Warfarin (n=639)	168 (26.3)	328 (51.3)	143 (22.4)	
RECORD1, 2, 3, 4[45]	Rivaroxaban 10 mg OD (n=6356)	3617 (59.1)[f]	2093 (34.2)[f]	409 (6.7)[f]	—
Elective TKA or THA	Enoxaparin (n=6373)	3598 (58.5)[f]	2114 (34.4)[f]	437 (7.1)[f]	
EINSTEIN DVT[46]	Rivaroxaban 15//20 mg (n=1731)	1193 (68.9)	393 (22.7)	115 (6.6)	6 (0.3)

Continued on next page

TABLE. Continued

Study and conditions	Treatment groups	Patients (No. [%]) Normal function (CrCL >80 mL/min)	Mild dysfunction (CrCL >50-80 mL/min)	Moderate dysfunction (CrCL >30-50 mL/min)	Severe dysfunction (CrCL ≤30 mL/min)
Rivaroxaban, continued					
Symptomatic proximal DVT without symptomatic PE	Enoxaparin/warfarin (n=1718)	1170 (68.1)	399 (23.2)	120 (7.0)	9 (0.5)
EINSTEIN PE[47]	Rivaroxaban 15/20 mg (n=2419)	1555 (64.3)	637 (26.3)	207 (8.6)	4 (0.2)
Symptomatic PE with or without DVT	Enoxaparin/warfarin (n=2413)	1617 (67.0)	593 (24.6)	191 (7.9)	2 (<0.1)
EINSTEIN DVT, EINSTEIN PE[48,49]	Rivaroxaban 15/20 mg (n=4150)	2772 (66.8)	1036 (25.0)	323 (7.8)	10 (0.2)
Symptomatic DVT or PE	Enoxaparin/warfarin (n=4131)	2797 (67.7)	1001 (24.2)	313 (7.6)	11 (0.3)
EINSTEIN CHOICE[50]	Rivaroxaban 20 mg OD (n=1107)	787 (71.1)	279 (25.2)	40 (3.6)	1 (0.1)
Symptomatic proximal DVT or PE and 6-12 mo of anticoagulation	Rivaroxaban 10 mg OD (n=1127)	774 (68.7)	302 (26.8)	49 (4.3)	2 (0.2)
	Aspirin 100 mg (n=1131)	790 (69.8)	277 (24.5)	63 (5.6)	1 (0.1)

[a]AF = atrial fibrillation; BID = twice daily; CrCL = creatinine clearance; DVT = deep vein thrombosis; OD = once daily; PE = pulmonary embolism; THA = total hip arthroplasty; TKA = total knee arthroplasty; UFH = unfractionated heparin; VTE = venous thromboembolism.

[b]Apixaban dose reduced to 2.5 mg BID for patients with 2 or more of the following criteria: age 80 years or older, weight of 60 kg or less, or serum creatinine concentration of at least 1.5 mg/dL (to convert to μmol/L, multiply by 88.4). Overall, 428 patients (5%) in ARISTOTLE and 179 (6%) in AVERROES received the 2.5-mg dose.

[c]Patients with estimated CrCL less than 40 mL/min were randomly assigned to receive apixaban 2.5 mg BID or placebo.

[d]Based on the Cockcroft-Gault equation.

[e]Based on the Chronic Kidney Disease Epidemiology Collaboration equation.

[f]Numbers (percentages) of patients based on those assessed in subgroup analyses; values for the overall population are not presented.

[g]Edoxaban dose reduced by half in patients with estimated CrCL of 30 to 50 mL/min, a body weight of 60 kg or less, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).

[h]Rivaroxaban dose reduced to 15 mg daily in patients with CrCL of 30 to 49 mL/min at baseline (n=1474; 21%).

[i]Rivaroxaban dose reduced to 10 mg daily in patients with CrCL of 30 to 49 mL/min at baseline (n=141; 22%).

(on par with the 7% reported in the single-dose study[9]).

A population PK analysis showed a correlation between apparent total clearance after oral administration (CL/F) of apixaban and CrCL, but the effect was generally modest.[11] Severe renal impairment (CrCL of 15 to <30 mL/min) was predicted to decrease CL/F by 36% and increase exposure by 56%, whereas in mild (CrCL of 50-80 mL/min) or moderate (CrCL of 30 to <50 mL/min) renal impairment, the commensurate increases in exposure were 17% and 34%, respectively.

Influence of Renal Function on Apixaban Efficacy and Safety

The largest of the efficacy and safety studies identified for apixaban was ARISTOTLE, which randomized more than 18,000 patients with AF and at least 1 additional stroke risk factor to treatment with apixaban 5 mg BID or warfarin[12] (Table).[12-50] Patients with severe renal impairment—defined in this study by a serum creatinine concentration greater than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4) or CrCL less than 25 mL/min—were excluded. A reduced dose (2.5 mg BID) was applied in patients who fulfilled 2 or more of the following criteria: serum creatinine level greater than 1.5 mg/dL, age 80 years or older, or body weight of 60 kg or less. Thus, patients with renal impairment alone received the normal 5-mg apixaban dose. In the overall population, apixaban demonstrated superiority to warfarin in preventing stroke or systemic embolism and was associated with lower rates of bleeding and mortality. Results for the primary outcome (stroke or systemic embolism) were consistent across renal function subgroups (Figure 1A)[12,15-17,19]; however, patients with impaired renal function (CrCL ≤50 mL/min) seemed to have experienced the greatest reduction in major bleeding (Figure 1B).[12,14-17,19] Subsequent analysis of

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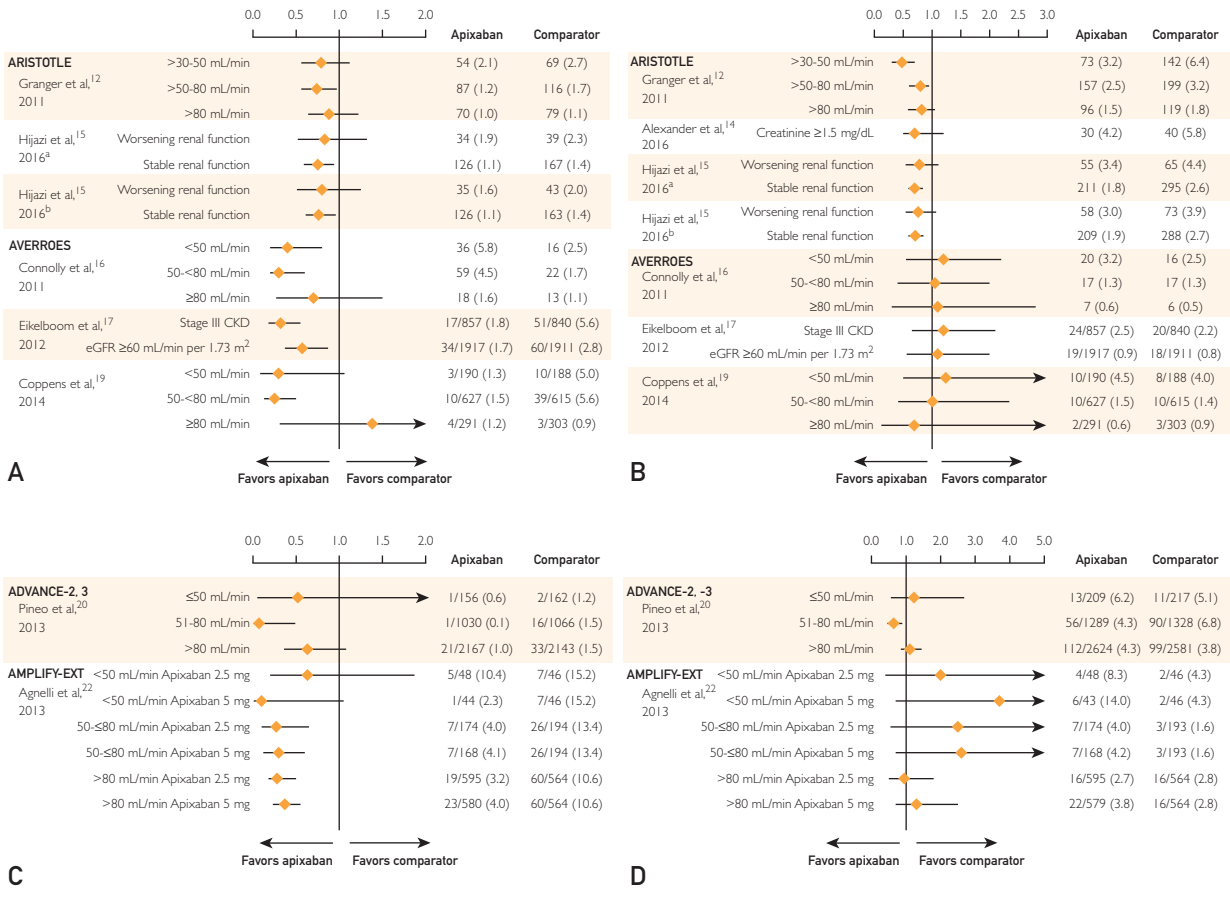

FIGURE 1. Relative efficacy and safety of apixaban in renal function subgroups.[12,14-17,19,20,22] Forest plots of hazard ratios and 95% CIs for (A) stroke and systemic embolism in atrial fibrillation (AF) clinical trials,[12,15-17,19] (B) major bleeding in AF clinical trials,[12,14-17,19] (C) major venous thromboembolism (VTE)[20] or recurrent VTE and all-cause death[22] in deep vein thrombosis (DVT) prophylaxis or VTE treatment clinical trials, and (D) major bleeding[20] or major and clinically relevant nonmajor bleeding[22] in DVT prophylaxis or VTE treatment clinical trials. Relative risk values for the ADVANCE-2, -3 safety analysis were calculated from event rates provided by Pineo et al.[20] [a]Creatinine clearance as determined by the Cockcroft-Gault equation. [b]Estimated glomerular filtration rate (eGFR) as determined by the Chronic Kidney Disease Epidemiology Collaboration equation. All definitions and renal function categories are maintained as used in the original studies. CKD = chronic kidney disease. To convert creatinine values to μmol/L, multiply by 88.4.

major bleeding confirmed a greater reduction in risk with apixaban vs warfarin in patients with renal dysfunction.[13] Patients with serum creatinine levels greater than 1.5 mg/dL but no other criteria for dose reduction were also found to derive similar benefit from apixaban 5 mg compared with that of the overall population[14] (Figure 1B).[12,14-17,19]

During 12 months of follow-up in the ARISTOTLE trial, 13.6% of patients experienced worsening renal function, defined as a decline in estimated glomerular filtration rate (eGFR) of at least 20%.[15] Treatment assignment did not seem to influence observed renal function changes. In patients with worsening renal function, greater relative reductions in risk of stroke or systemic embolism and in major bleeding rates were maintained with apixaban vs warfarin (Figure 1A and B).[12,14-17,19]

In AVERROES, patients with AF at increased risk for stroke who were not candidates for VKA therapy were randomized to treatment with apixaban 5 mg BID or low-dose aspirin.[16] Renal impairment exclusion and dose reduction criteria followed those of ARISTOTLE. Overall, apixaban was found to decrease risk of stroke or systemic embolism without significantly increasing rates of major

bleeding or intracranial hemorrhage compared with aspirin. Primary efficacy and safety outcomes were comparable across renal function subgroups (Figure 1A and B).[12,14-17,19] Subsequent analyses reported similar findings in patients with stage III chronic kidney disease (CKD) (eGFR of 30-59 mL/min per 1.73 m^2) compared with patients with preserved renal function (eGFR of ≥60 mL/min per 1.73 m^2)[17] and among renal function strata in patients who had previously tried and failed VKA therapy[19] (Figure 1A and B).[12,14-17,19] In addition, an analysis by Lip and colleagues[18] found that risk of stroke was increased in patients with renal dysfunction (eGFR <60 mL/min per 1.73 m^2) who received aspirin, whereas no such increase was observed in the apixaban treatment group.

The ADVANCE-2 and ADVANCE-3 clinical trials examined venous thromboembolism (VTE) prophylaxis with apixaban 2.5 mg BID vs enoxaparin 40 mg once daily (OD) in patients undergoing elective total knee arthroplasty (TKA) or total hip arthroplasty (THA).[20] Notably, CrCL less than 30 mL/min was an exclusion criterion in both studies. No significant differences in VTE or major bleeding rates were observed among renal function subgroups (Figure 1C[20,22] and data not shown). However, there did seem to be a reduced risk of major and clinically relevant nonmajor bleeding with apixaban vs enoxaparin in patients with CrCL of 51 to 80 mL/min, which was not observed in other renal function subgroups (Figure 1D).[20,22]

Two studies of apixaban for the treatment of VTE were identified: AMPLIFY-J[21] and AMPLIFY-EXT.[22] Both studies excluded patients with severe renal impairment (CrCL <25 mL/min). The AMPLIFY-J study randomized 80 Japanese patients with symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) (with or without DVT) to receive treatment with apixaban (10 mg BID for 7 days, followed by 5 mg BID for 23 weeks) or unfractionated heparin/warfarin.[21] In this small cohort, no difference was observed in recurrent VTE rates between treatment groups, although the major and clinically relevant nonmajor bleeding rate was lower with apixaban. Results were consistent in the predefined renal subgroup analyses. In AMPLIFY-EXT, patients with symptomatic DVT or PE (with or without DVT) who had completed 6 to 12 months of anticoagulation therapy received apixaban 2.5 or 5.0 mg BID or placebo for 12 months.[22] The risk of the composite efficacy end point of symptomatic recurrent VTE and all-cause mortality was consistent in renal function subgroups with that of the overall population (Figure 1C).[20,22] Lower rates of hospitalization were also observed with apixaban vs placebo regardless of renal function.[23] Bleeding outcomes were comparable among renal function subgroups, although the small numbers of patients with moderate renal impairment and the low event rates suggest caution in interpretation of these data[22] (Figure 1D).[20,22]

DABIGATRAN

Influence of Renal Function on Dabigatran PK/PD

Elimination of dabigatran, a direct thrombin inhibitor, occurs predominantly via renal excretion (80%).[51] Of all the NOACs, the PK of dabigatran depends most critically on renal function. In the pivotal dabigatran PK study, drug exposure was 1.5, 3.2, and 6.3 times greater in patients with mild, moderate, or severe renal impairment, respectively, compared with healthy individuals.[52] The mean half-life of dabigatran increased with decreasing renal function, resulting in an approximately 2 times longer half-life in patients with severe renal impairment (CrCL <30 mL/min) compared with those without renal insufficiency.

An early population PK analysis by Trocóniz et al[53] reported overlapping simulation-predicted dabigatran drug concentration-vs-time profiles for patients with normal renal function and those with mild, moderate, or severe renal impairment. In addition, using data from a phase 3 study (RE-LY), simulations by Liesenfeld et al[54] predicted similar exposures with 75 mg BID in patients with severe renal impairment to those of 150 mg BID in patients with normal renal function. The RE-LY study compared 2 doses of dabigatran (110 and 150 mg BID) with warfarin for the prevention of stroke and systemic embolism in patients with AF and at least 1 additional stroke risk factor[27] (Table).[12-50] Patients with CrCL less than 30 mL/min were excluded from the study. Use of the 75-mg dose in patients with severe renal impairment was further

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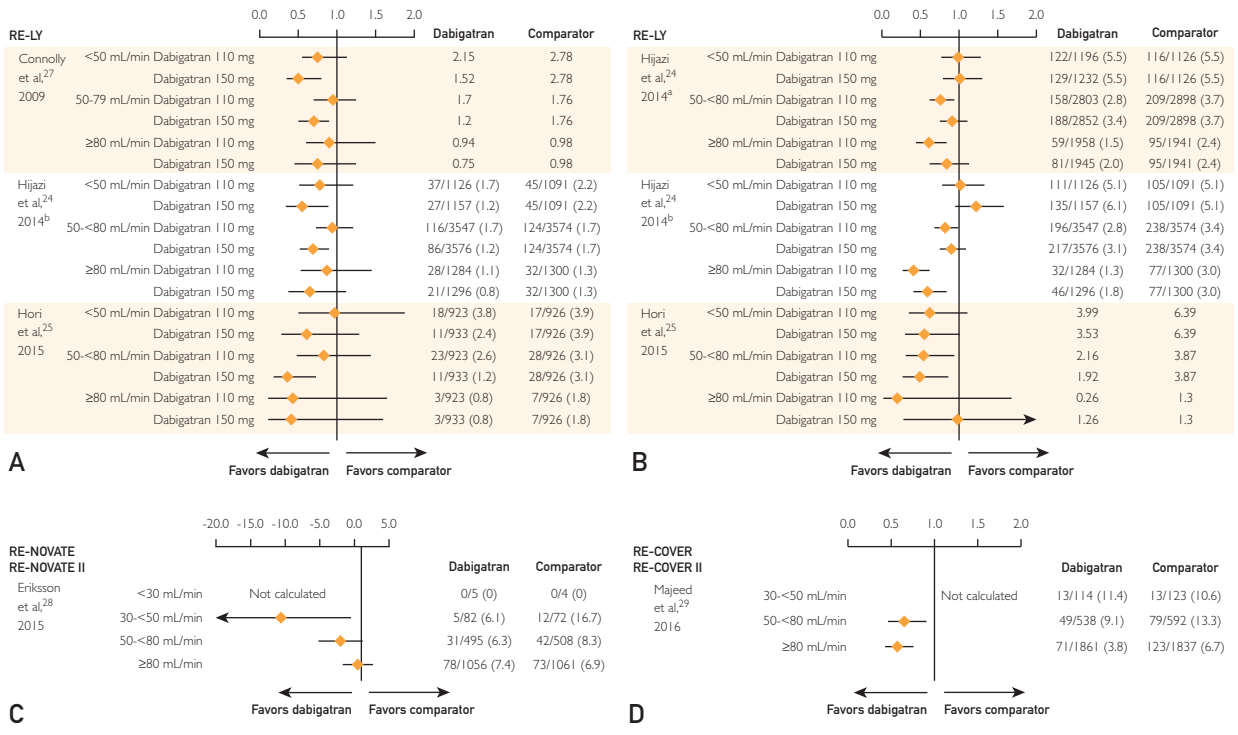

FIGURE 2. Relative efficacy and safety of dabigatran in renal function subgroups.[24,25,27-29] Forest plots of hazard ratios and 95% CIs for (A) stroke and systemic embolism in atrial fibrillation (AF) clinical trials,[24,25,27] (B) major bleeding in AF clinical trials,[24,25] (C) total venous thromboembolism (VTE) and all-cause mortality in deep vein thrombosis (DVT) prophylaxis clinical trials,[28] and (D) major and clinically relevant nonmajor bleeding in VTE treatment clinical trials.[29] Data for Eriksson et al[28] are absolute risk differences (the difference in the proportion of patients with an event) rather than hazard ratios.[28] [a]Creatinine clearance as determined by the Cockcroft-Gault equation. [b]Estimated glomerular filtration rate as determined by the Chronic Kidney Disease Epidemiology Collaboration equation. All definitions and renal function categories are maintained as used in the original studies.

supported by simulations performed by Hariharan and Madabushi[55] and Lehr et al.[56] Use of a 75-mg BID regimen (as well as 110- and 150-mg BID regimens) was also tested in simulations of patients undergoing maintenance hemodialysis.[57] All of the BID dosing regimens resulted in higher exposures than predicted for the typical RE-LY patient. In contrast, simulated exposures with dabigatran 75 and 110 mg OD were more aligned with the prototypical RE-LY patient.

Only recently, the PK of lower-dose dabigatran (75 mg BID) was directly measured in an open-label, single-center study that enrolled 16 patients with severe renal impairment (CrCL of 15-30 mL/min).[58] During the 7.5-day treatment period, mean steady-state drug exposures were comparable with model-predicted values. The study also demonstrated that dabigatran 75 mg BID in patients with severe renal impairment is not associated with drug accumulation beyond 5 days of treatment.

A single-arm, open-label study assessed dabigatran 150 mg OD in patients undergoing elective TKA or THA who had moderate renal impairment.[59] Trough dabigatran concentrations in this population were similar to previous reports in patients with mild renal impairment.

Dabigatran has been studied in patients with ESRD receiving hemodialysis but with an eye toward removing circulating drug levels in those with a bleeding emergency rather than assessing clinical utility. Hemodialysis has proved to be an effective means to remove dabigatran from the circulation.[52,60,61]

Multiple studies and population PK models have reported a strong correlation between CrCL and dabigatran CL/F, as well as an increase in dabigatran exposure in patients with

renal impairment.[52-55,62-67] Commensurate effects on efficacy and safety are possible because anticoagulant activity is linearly related to plasma dabigatran concentration.[60,65,67]

Influence of Renal Function on Dabigatran Efficacy and Safety

In the RE-LY study, dabigatran 110 mg produced similar reductions in stroke and systemic embolism to those of warfarin, with a lower rate of major bleeding.[27] Dabigatran 150 mg decreased the risk of stroke or systemic embolism more than warfarin but had a comparable rate of major bleeding. In the original assessment, wherein CrCL was estimated using the Cockcroft-Gault equation, the results for the primary efficacy and safety end points were consistent across renal function subgroups (Figure 2A and B).[24,25,27] However, a subsequent assessment, in which renal function was estimated using the Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease Study Group equations, detected a significant interaction ($P<.05$) between treatment and renal function such that a notable reduction in major bleeding was observed with either dose of dabigatran compared with warfarin in patients with an eGFR of at least 80 mL/min per 1.73 m^2 but not in patients with renal impairment (Figure 2B[24,25,27] and data not shown). No interaction was found between treatment effects (either efficacy or safety) and renal function in a subsequent Asian subgroup analysis; however, CrCL was calculated using the Cockcroft-Gault equation in this analysis.[25]

Böhm et al[26] conducted an analysis of changes in renal function during RE-LY. Over a 30-month observation period, significantly greater mean ± SE declines in renal function were observed in patients who received warfarin (GFR, −3.68±0.24 mL/min) compared with either dabigatran 110 mg (GFR, −2.57±0.24 mL/min; $P=.0009$ vs warfarin) or dabigatran 150 mg (GFR, −2.46±0.23 mL/min; $P=.0002$ vs warfarin).[26]

The effect of renal function on efficacy and safety measures was also evaluated in a pooled analysis from RE-NOVATE and RE-NOVATE II.[28] Patients in both studies received dabigatran (150 or 220 mg) or enoxaparin 40 mg OD for DVT prevention after elective THA. Because RE-NOVATE II did not include the 150-mg dose, only the 220-mg dose was evaluated in the pooled analysis. Reductions in VTE and all-cause mortality (the primary efficacy outcome) were consistent across renal function strata (Figure 2C).[28]

An observational study of dabigatran 150 mg OD was recently conducted in patients with moderate renal impairment undergoing elective TKA or THA.[68] In this study, the rates of major bleeding (2.1%) and symptomatic VTE or death (0.7%) were low, suggesting that the lower dosing regimen may be appropriate for patients with moderate renal impairment.

The effects of renal function on bleeding risk were described in 2 pooled analyses. Using data from the RE-LY, RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, Majeed et al[69] reported that patients who experienced major bleeding while receiving dabigatran had lower mean CrCL values compared with those who experienced major bleeding while taking warfarin. No significant interaction was found between treatment and renal function subgroup with respect to bleeding events in a separate pooled analysis from the RE-COVER and RE-COVER II trials, which compared dabigatran and warfarin for the treatment of symptomatic proximal DVT or PE (Figure 2D).[29]

EDOXABAN

Influence of Renal Function on Edoxaban PK/PD

The direct factor Xa inhibitor edoxaban is eliminated via renal and nonrenal pathways, with approximately 50% of total clearance accounted for by renal clearance.[70] Edoxaban area under the plasma concentration-time curve increases with decreasing renal function, with 32%, 74%, and 72% higher levels of exposure reported in patients with mild, moderate, and severe renal impairment, respectively, compared with healthy individuals.[71] To offset the increased exposure, a 50% dose reduction in patients with moderate or severe renal impairment was suggested by Salazar et al[72] and Yin et al[73] based on PK model predictions. However, using data from clinical trials in which the dose reduction was applied in patients with moderate renal

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impairment, 2 subsequent population PK analyses determined that the resulting exposures from this dose reduction were lower than those of patients receiving a standard edoxaban dose.[74,75] In patients with moderate renal impairment who were given a dose reduction (30 mg OD) in the Hokusai-VTE study, clinically relevant bleeding was lower than in the 60-mg OD dose group (7.91% and 8.60%, respectively), although recurrent VTE occurred more frequently (1.77% and 1.57%, respectively).[76] A third modeling analysis determined that in patients with severe renal impairment, a dose reduction to 30 mg OD resulted in similar predicted exposure levels to those of patients with normal or mild renal impairment receiving the standard 60-mg OD dose.[77] Clinical data supporting dose reduction come from a 12-week open-label study in which Japanese patients with nonvalvular AF and severe renal impairment received edoxaban 15 mg OD and patients with normal renal function or mild renal impairment were randomized to receive edoxaban 30 or 60 mg OD.[78] Plasma concentrations, bleeding rates, and biomarker profiles were comparable among the treatment groups.

Use of edoxaban in patients with ESRD on hemodialysis was investigated in an open-label study in which patients received a single dose of edoxaban 15 mg either 2 hours before dialysis or on off-dialysis days.[79] Hemodialysis resulted in a slight decrease in edoxaban exposure compared with observations in the off-dialysis population, but not enough to justify a change in dose.

Multiple population PK analyses detected a significant correlation between CrCL and edoxaban CL/F.[72,73,75,80] Correlations were also observed between model-predicted increases in edoxaban exposure and degree of renal impairment, with the greatest elevations in the lowest tier of CrCL.[72,81]

Influence of Renal Function on Edoxaban Efficacy and Safety

Three edoxaban clinical trials assessed efficacy and safety based on renal function: ENGAGE AF-TIMI 48, ENSURE-AF, and Hokusai-VTE (Table).[12-50] ENGAGE AF-TIMI 48 randomized patients with AF and $CHADS_2$ of 2 or greater to receive edoxaban 60 mg OD, edoxaban 30 mg OD, or warfarin.[30] Patients with CrCL less than 30 mL/min were excluded from the study, and the edoxaban dose was reduced by 50% in patients with CrCL of 30 to 50 mL/min in both dosing groups. In the overall population, treatment with either dose of edoxaban reduced the risk of stroke or systemic embolism and was associated with lower rates of bleeding and mortality compared with warfarin. Those in the higher edoxaban dose group who received a reduction due to renal impairment, the decline in bleeding observed with edoxaban was further augmented.[31] When parsed into groups with CrCL of 30 to 50 mL/min vs greater than 50 mL/min, the relative efficacy was equivalent (Figure 3A).[31,32] Yet, exploratory analyses suggest some decline in benefit at higher CrCL levels (hazard ratio [HR], 0.78; 95% CI, 0.64-0.96 for CrCL >50-95 mL/min; HR, 1.36; 95% CI, 0.88-2.10 for CrCL >95 mL/min) in the comparison between edoxaban and warfarin.[32] The Food and Drug Administration has limited approval of high-dose edoxaban to patients with a CrCL of 95 mL/min or lower based on the increased risk of ischemic stroke in patients with CrCL greater than 95 mL/min in this trial.

ENSURE-AF compared edoxaban 60 mg OD with enoxaparin/warfarin in patients with nonvalvular AF undergoing cardioversion.[33] The edoxaban dose was reduced to 30 mg OD in patients with CrCL of 15 to 50 mL/min. In the overall cohort, rates of thromboembolism and major bleeding were similar with edoxaban and enoxaparin/warfarin. No difference in the primary efficacy end point (composite of stroke, systemic embolism, myocardial infarction, and cardiovascular mortality), major bleeding, or net clinical benefit was observed across CrCL strata (Figure 3A and B[32,33] and data not shown).

Hokusai-VTE examined treatment with heparin followed by edoxaban 60 mg OD or warfarin in patients with symptomatic DVT or PE (with or without DVT).[34] Edoxaban dose was reduced to 30 mg OD in patients with CrCL of 30 to 50 mL/min. Edoxaban was noninferior to warfarin in terms of the primary end point (recurrent symptomatic VTE; $P<.001$ for noninferiority) and was associated with significantly less major or clinically relevant nonmajor bleeding compared with warfarin ($P=.004$ for superiority). The relative

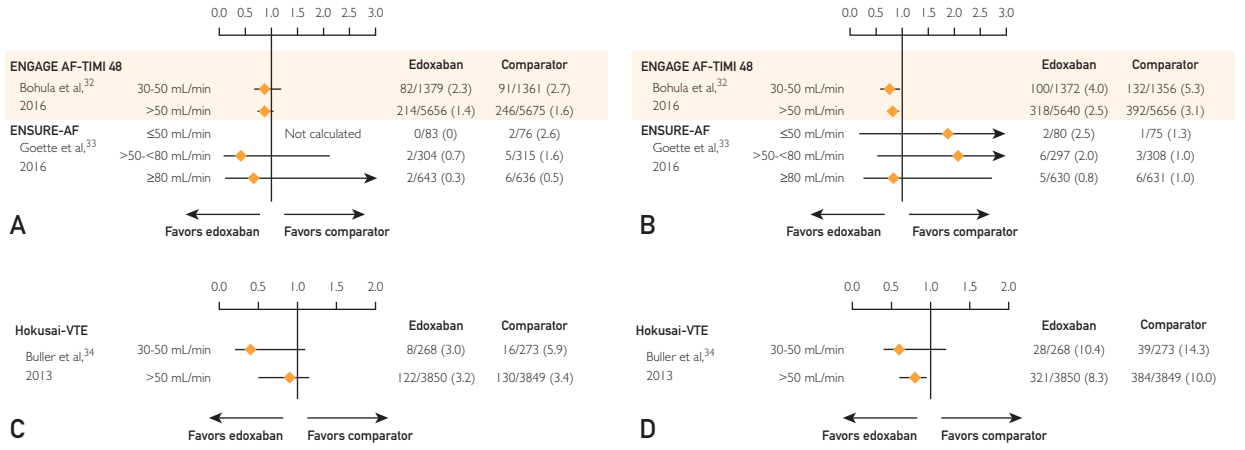

FIGURE 3. Relative efficacy and safety of edoxaban in renal function subgroups.[32-34] Forest plots of hazard ratios and 95% CIs for (A) stroke and systemic embolism in atrial fibrillation (AF) clinical trials,[32,33] (B) major bleeding[32] or major and clinically relevant nonmajor bleeding[33] in AF clinical trials, (C) recurrent venous thromboembolism (VTE) in VTE treatment clinical trials,[34] and (D) major and clinically relevant nonmajor bleeding in VTE treatment clinical trials.[34] Relative risk values for the ENSURE-AF efficacy and safety analyses were calculated from event rates provided by Goette et al.[33] All definitions and renal function categories are maintained as used in the original studies.

efficacy of edoxaban vs warfarin was maintained across renal function subgroups (Figure 3C and D).[34]

RIVAROXABAN

Influence of Renal Function on Rivaroxaban PK/PD

Rivaroxaban, a direct factor Xa inhibitor, is eliminated through renal excretion (approximately one-third of active drug) as well as by fecal/biliary routes.[82] The effect of renal function on rivaroxaban clearance was found to be moderate, even in the context of severe renal impairment.[83] Among patients with mild, moderate, or severe renal impairment enrolled in a dedicated PK study, rivaroxaban exposure after a single 10-mg dose was 44%, 52%, and 64% higher, respectively, compared with healthy individuals.[83]

Two studies explored rivaroxaban dosing in patients with ESRD undergoing maintenance hemodialysis.[84,85] The first study reported that administration of a single dose of rivaroxaban 10 mg in patients receiving hemodialysis resulted in comparable drug exposure levels (by indirect comparison) to that of rivaroxaban 10 mg in patients with moderate or severe renal impairment in a previous study.[84] In addition, the study demonstrated that there was no accumulation of rivaroxaban after dosing for 1 week. In the second study, a single dose of rivaroxaban 15 mg was administered to patients receiving hemodialysis and matched healthy volunteers.[85] A direct comparison indicated an increase in exposure by 56% in patients undergoing hemodialysis,[85] which is consistent with known effects in patients with moderate-to-severe renal impairment who were not undergoing dialysis.[83] In both studies, hemodialysis did not appreciably reduce plasma rivaroxaban concentrations, likely owing to high protein binding.[84,85]

In population PK studies, renal function was shown to influence rivaroxaban clearance; however, the magnitude of effect was within the range of interindividual variability.[86-88] The decrease in clearance produces a predicted moderate increase in drug exposure consistent with previous observations.[86-91] Population PK model-derived simulations conducted in support of the ROCKET AF trial (described later herein) demonstrated that a dose reduction of rivaroxaban (15 mg OD) in patients with moderate renal impairment would result in a PK profile comparable with that of a standard dose (20 mg OD) in patients with mild or no renal impairment.[88,90]

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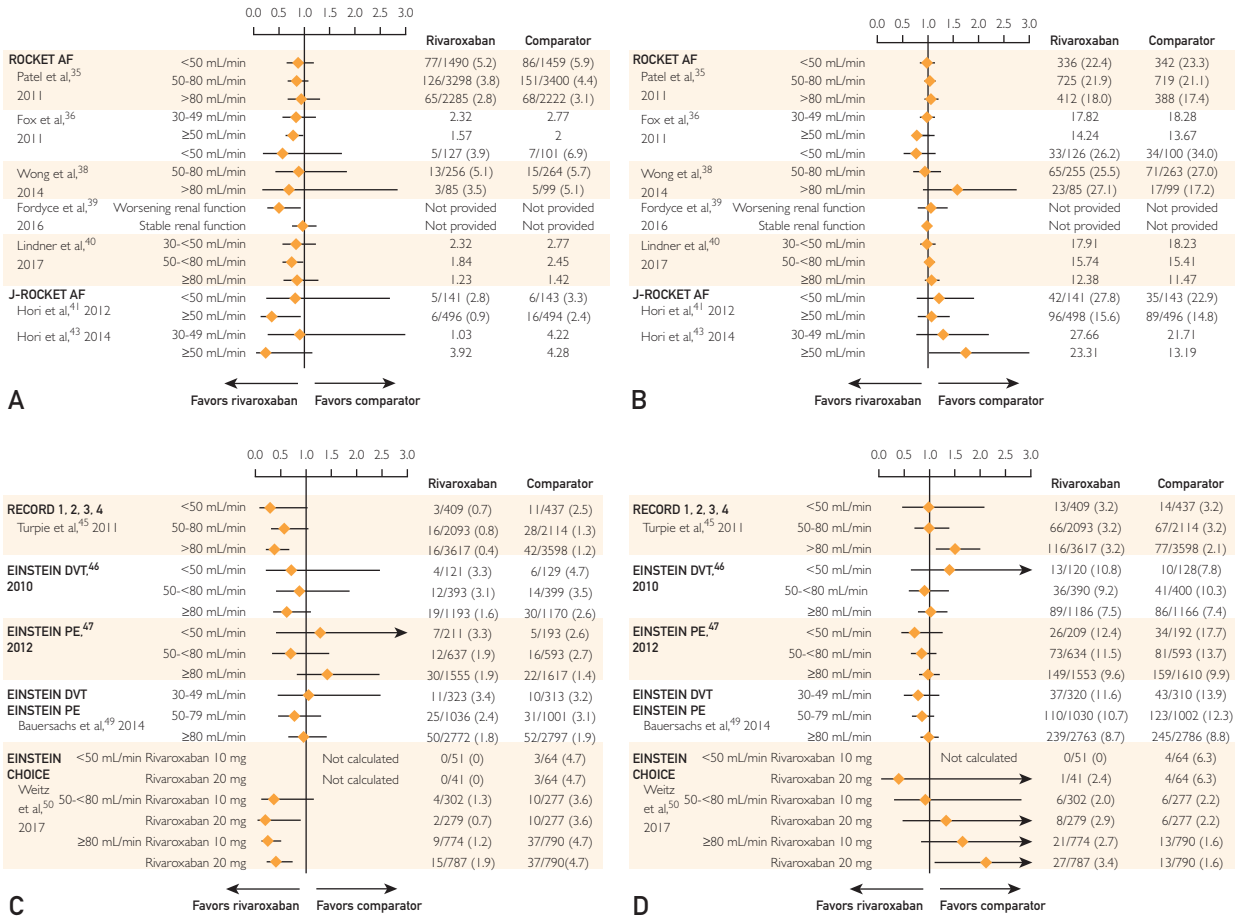

FIGURE 4. Relative efficacy and safety of rivaroxaban in renal function subgroups.[35,36,38-41,43,45-47,49,50] Forest plots of hazard ratios and 95% CIs for (A) stroke and systemic embolism in atrial fibrillation (AF) clinical trials,[35,36,38-41,43] (B) major and clinically relevant nonmajor bleeding in AF clinical trials,[35,36,38-41,43] (C) symptomatic venous thromboembolism (VTE) plus all-cause mortality,[45] symptomatic recurrent VTE or symptomatic VTE,[46,47,49] and unexplained death[50] in deep vein thrombosis (DVT) prophylaxis or VTE treatment clinical trials, and (D) major and clinically relevant nonmajor bleeding in DVT prophylaxis or VTE treatment clinical trials.[45-47,49,50] All definitions and renal function categories are maintained as used in the original studies.

The PK of all NOACs, including rivaroxaban, is affected by P-glycoprotein or cytochrome P450 3A4 (CYP3A4) activity.[92] However, many NOACs did not assess the potential for combined drug-drug-disease interactions, which, in theory, could lead to additive or synergistic increases.[93] In this regard, an important study evaluated the combined effect of moderate renal impairment and the concomitant use of a combined P-glycoprotein and moderate CYP3A4 inhibitor (erythromycin) on the PK of rivaroxaban. This analysis observed increases in rivaroxaban exposure that were slightly more than additive and suggests that rivaroxaban should not be used in patients with renal impairment receiving concomitant treatment with a combined P-glycoprotein and moderate CYP3A4 inhibitor, unless the potential benefit justifies the potential risk.[93]

Influence of Renal Function on Rivaroxaban Efficacy and Safety

Two clinical trials of rivaroxaban for the prevention of stroke and systemic embolism in patients with AF were identified in the current search: ROCKET AF and J-ROCKET AF (Table).[12-50] In ROCKET AF, patients with AF and a $CHADS_2$ score of at least 2 were randomly assigned to treatment with

rivaroxaban 20 mg OD or dose-adjusted warfarin.[35] Based on the modeling and simulations mentioned previously, the rivaroxaban dose was reduced to 15 mg OD in patients with moderate renal impairment, and patients with CrCL less than 30 mL/min were excluded from the study. The overall analysis demonstrated noninferiority of rivaroxaban for the primary efficacy end point and no significant difference in rates of major and clinically relevant nonmajor bleeding between groups, although fewer patients in the rivaroxaban treatment group experienced intracranial or fatal bleeding. The relative efficacy and safety in ROCKET AF were maintained across renal impairment subgroups[35-38,40] (Figure 4A and B[35,36,38-41,43] and data not shown). However, when risk of major bleeding was examined with CrCL as a continuous variable, a significant interaction was found due to a lower bleeding rate in warfarin-treated patients with normal renal function in post hoc analysis.[40] In this study, there was also a minor trend toward higher relative rates of stroke and systemic embolism with rivaroxaban in the group of patients with CrCL greater than 95 mL/min (HR, 1.47; 95% CI, 0.81-2.68).[40] However, this trend had no effect on the Food and Drug Administration label for rivaroxaban.

Fordyce et al[39] evaluated the effect of worsening renal function on ROCKET AF outcomes. Of patients with evaluable follow-up data for this analysis, 26.3% experienced worsening renal function during the study, defined as a reduction in CrCL of 20% or more.[39] Patients with worsening renal function who received rivaroxaban had a lower stroke and systemic embolism event rate compared with warfarin-treated patients, whereas patients with stable renal function experienced comparable rates in both treatment groups (Figure 4A).[35,36,38-41,43] Rates of major and clinically relevant nonmajor bleeding were similar in those with worsening or stable renal function (Figure 4B).[35,36,38-41,43]

J-ROCKET AF, conducted in Japan, applied a similar study design to that of ROCKET AF but with a lower 15-mg OD standard dose of rivaroxaban and a 10-mg reduced dose in patients with moderate renal impairment; in addition, a different international normalized ratio target for patients receiving warfarin was applied[41] (Table).[12-50] In the overall population, rivaroxaban was noninferior to warfarin for the primary safety end point and demonstrated lower rates of intracranial hemorrhage and stroke or systemic embolism. The presence of moderate renal impairment, and thus the use of the lower rivaroxaban dose, did not influence the relative safety or efficacy of rivaroxaban vs warfarin, even in elderly patients[41,42] (Figure 4A and B).[35,36,38-41,43] In addition, an analysis of net clinical benefit from J-ROCKET AF found no significant differences among renal function strata.[44]

Data on rivaroxaban use in real-world patients with AF and renal impairment are available from the prospective, noninterventional XANTUS study.[94] Of 6784 patients with nonvalvular AF who had just begun a rivaroxaban regimen, 9.4% had documented moderate or severe renal impairment. These patients experienced higher rates of major bleeding compared with patients with CrCL of 50 mL/min or greater. Notably, 36% of patients with moderate or severe renal impairment received the 20-mg dose rather than the label-recommended 15-mg dose, and for 34% of patients, information on renal function was missing.

Turpie et al[45] performed a subgroup analysis by renal function category using pooled data from the RECORD1, RECORD2, RECORD3, and RECORD4 studies (Table).[12-50] Patients in the RECORD studies received rivaroxaban (10 mg OD) or enoxaparin (40 mg OD or 30 mg BID) for the prevention of VTE after THA or TKA. The studies excluded patients with severe renal impairment (CrCL <30 mL/min). In each of the studies, rivaroxaban was superior to enoxaparin for the primary efficacy end point (composite of symptomatic and asymptomatic DVT, nonfatal PE, and all-cause mortality). Reductions in the primary end point in the pooled analysis were consistent among renal function subgroups (Figure 4C).[45-47,49,50] Major and clinically relevant nonmajor bleeding rates with rivaroxaban were identical across the CrCL strata.

The EINSTEIN DVT and EINSTEIN PE studies compared rivaroxaban (15 mg BID for 3 weeks, then 20 mg OD) or enoxaparin followed by a VKA in patients with DVT or PE.[46,47] Patients with CrCL less than

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30 mL/min were excluded from the studies. In both studies, rivaroxaban was noninferior to enoxaparin/VKA in terms of efficacy, with comparable rates of clinically relevant bleeding between treatment groups. Efficacy and safety results were comparable in renal function subgroups (Figure 4C and D).[45-47,49,50] A prespecified subgroup analysis in patients with renal impairment was conducted using pooled data from the EINSTEIN DVT and EINSTEIN PE studies.[49] No difference was observed between renal function subgroups in relative rates of recurrent VTE (Figure 4C)[45-47,49,50]; however, an increase in clinically relevant bleeding risk was observed in patients with renal impairment.[45-47,49,50] The risk of major bleeding increased with declining renal function in patients who received enoxaparin/VKA ($P_{trend}<.001$) but not in patients who received rivaroxaban ($P_{trend}=.50$). Similar results were observed for clinically relevant bleeding in a renal function analysis of Chinese patients enrolled in the EINSTEIN DVT and EINSTEIN PE studies.[48]

The EINSTEIN CHOICE study compared rivaroxaban (10 or 20 mg OD) with aspirin in patients with symptomatic proximal DVT or PE who had completed 6 to 12 months of anticoagulant therapy.[50] Both doses of rivaroxaban significantly reduced the risk of symptomatic recurrent fatal or nonfatal VTE compared with aspirin ($P<.001$). This effect was maintained when patients were stratified by CrCL. In the overall population, bleeding rates were not appreciably increased with rivaroxaban relative to aspirin; however, there did seem to be a lower rate of clinically relevant bleeding in patients with normal renal function in the aspirin treatment group, whereas bleeding rates were consistent with rivaroxaban in renal function subgroups.

Clinical trial results in the VTE setting for rivaroxaban are also supported by the prospective, noninterventional XALIA study, which compared rivaroxaban with standard anticoagulation therapy in 5142 patients with DVT with or without PE.[95] Renal impairment was documented for 24% of patients. In these real-world patients, the relative safety (major bleeding) and efficacy (recurrent VTE) of rivaroxaban vs standard anticoagulation were comparable regardless of renal function category (Figure 4C and D).[45-47,49,50]

CLINICAL IMPLICATIONS

The existing body of literature supports diversity in the NOAC class in terms of the impact of renal impairment on the PK, PD, efficacy, and safety profiles, and also highlights that NOACs can be used safely in individuals with various degrees of renal impairment. Although there are regional variations in dosing recommendations (Supplemental Table, available online at http://www.mayoclinicproceedings.org), except for severe renal impairment (CrCL of 15-29 mL/min and ESRD (CrCL <15 mL/min), NOAC use is not restricted in those with renal dysfunction. Note that guidance on the use of factor Xa inhibitors in patients with severe renal impairment (CrCL of 15-29 mL/min) or ESRD (CrCL <15 mL/min) undergoing hemodialysis is solely based on PK data, many times indicating that the change in exposure observed led to concentrations that were similar in patients with moderate renal impairment studied in their respective phase 3 trials. However, note that patients with CrCL less than 25 to 30 mL/min were generally excluded from these pivotal phase 3 clinical trials; therefore, adequate safety and efficacy data are lacking.

Differences in outcomes based on renal function reinforce the importance of quantifying renal function before determining treatment (with either NOACs or alternatives, as the data have shown renal dependence of efficacy or safety occurring in both groups), dosing NOACs appropriately, and monitoring changes in renal function over time. Renal function measurement before treatment is particularly important in AF because dosing of all NOACs in this setting is affected by renal function. The importance of assessing changes in renal function should be emphasized, as evidence suggests that routine monitoring is not being adequately performed in clinical practice.[94-96]

The present assessment of the available evidence also reveals a disconnect between clinical data and real-world practice patterns. In a recent survey of electrophysiology center practices conducted by the European Heart Rhythm Association, a preference was observed for any NOAC over VKA therapy for patients with AF and mild CKD,[97] which is consistent with clinical trial evidence.

However, apixaban was identified as the preferred treatment option for patients with moderate CKD. Based on the clinical trial evidence presented herein, patients with moderate renal impairment who receive appropriate doses of dabigatran, edoxaban, or rivaroxaban experienced comparable clinical benefit to that of patients with normal renal function, so there seems to be an obvious disconnect. Moreover, data from ROCKET AF demonstrated that patients who experienced worsening renal function (as is more likely in those with established kidney disease) derived greater relative thromboembolic risk reduction with rivaroxaban.[39] Notably, prospective, noninterventional study data for patients with renal impairment are currently available only for rivaroxaban (XANTUS and XALIA).

Part of the challenge in determining an appropriate course of therapy is variability in recommendations across indications and throughout the world. For example, dabigatran is contraindicated in patients with severe renal impairment in Europe and Canada but not in the United States (Supplemental Table). Comparisons among study populations are also complicated by different definitions and measures used to quantify renal function, as reflected in the subgroup thresholds shown in Figures 1 to 4. Subpopulations for which there are limited data, such as patients with ESRD receiving hemodialysis, represent another quandary. The available PK evidence suggests that apixaban, edoxaban, and rivaroxaban are not appreciably eliminated via hemodialysis, but clinical trials evaluating their efficacy and safety in patients with ESRD are, again, lacking.

CONCLUSION

The studies included herein were identified using the prespecified literature search method. Although other search methods could be used, we believe that most of the relevant data have been included, with the understanding that additional studies that performed renal function subgroup analyses may not have been captured, as well as information on the studies currently being performed. This analysis is also limited by the data available. In particular, data regarding drug-drug-disease interactions are scarce. Only 1 such study, which evaluated concomitant use of rivaroxaban with a combined P-glycoprotein and moderate CYP3A4 inhibitor in the context of renal impairment, was identified. The potential for synergistic or additive effects with this potential interaction warrants further evaluation with the other NOACs.

As with all forms of anticoagulation, treatment choices, whether warfarin or one of the NOACs, need to be carefully individualized. The influence of medical comorbidity, concomitant medications, convenience, patient preference, and, most importantly, therapeutic index needs to be considered, especially in patients with CKD, whether receiving dialysis or not.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **BID** = twice daily; **CKD** = chronic kidney disease; **CL/F** = apparent total clearance after oral administration; **CrCL** = creatinine clearance; **CYP3A4** = cytochrome P450 3A4; **DVT** = deep vein thrombosis; **eGFR** = estimated glomerular filtration rate; **ESRD** = end-stage renal disease; **HR** = hazard ratio; **NOAC** = non–vitamin K antagonist oral anticoagulant; **OD** = once daily; **PE** = pulmonary embolism; **PK** = pharmacokinetics; **PD** = pharmacodynamics; **THA** = total hip arthroplasty; **TKA** = total knee arthroplasty; **UFH** = unfractionated heparin; **VKA** = vitamin K antagonist; **VTE** = venous thromboembolism

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