Dosing of Target-Specific Oral Anticoagulants in Special Populations

Amanda M. Morrill, PharmD, BCPS¹, Dan Ge¹, and Kristine C. Willett, PharmD, FASHP¹

Abstract

Objective: To review current literature for target-specific oral anticoagulants (TSOACs) and provide critical analysis for dosing recommendations in special population groups. Data Sources: A literature search was conducted in Medline (1996 to April week 2 2015) and Embase (1980 to 2015 week 16) using key terms dabigatran, rivaroxaban, apixaban, edoxaban, kidney diseases, liver diseases, elderly, obesity, and special populations. Study Selection and Data Extraction: Randomized controlled trials in English assessing efficacy and safety of TSOACs in healthy adults and special populations were selected for analysis. Data Synthesis: Phase 3 trials for TSOACs predominately excluded patients with severe renal impairment or active liver disease. There were no exclusion criteria based on age, body weight or body mass index. Additional conclusions were made in special populations, including those with renal or liver impairment and obese and elderly patients, based on secondary analyses, pharmacokinetic, and pharmacodynamic studies. Conclusions: Pharmacokinetic and pharmacodynamic changes associated special populations may alter clinical decision with regard to drug selection and dosing. It is valuable to understand the rationale for labeled dosing recommendations in nonvalvular atrial fibrillation and venous thromboembolism treatment and prevention, particularly in patients that fall into special population groups. Furthermore, the use of TSOACs is likely to increase as clinicians gain experience with these agents and additional TSOACs and indications are approved.

Keywords
anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban geriatrics, clinical practice, obesity, hepatic, renal failure, literature evaluation

Background

Prior to 2010, vitamin K antagonists (VKAs) were the sole oral anticoagulant available in the United States for the treatment and prevention of venous thromboembolism (VTE) and prevention of stroke in patients with atrial fibrillation (AF). VKAs are associated with numerous challenges, including wide interpatient variability, a prolonged onset of action, and numerous drug-drug and drug-food interactions, requiring regular monitoring of therapeutic response using the international normalized ratio (INR).¹ Maintaining a therapeutic INR can be challenging; it is estimated that mean time in therapeutic range is 58% for outpatient warfarin therapy.² In 2010 dabigatran was approved by the Food and Drug Administration (FDA), promising change in the landscape of long-term anticoagulation management for nonvalvular AF (NVAF) and VTE. This was followed by a wave of several other oral anticoagulants approvals. Often referred to as target-specific oral anticoagulants (TSOACs), these agents include the aforementioned direct thrombin inhibitor, dabigatran (Pradaxa), in addition to 3 factor Xa (FXa) inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa).³⁴ In contrast to VKAs, TSOACs have a shorter onset of action, fewer monitoring requirements, and fewer drug interactions.⁷

Despite the decreased monitoring and need for dose individualization, the pharmacokinetic and pharmacodynamic properties necessitate dose adjustments in a variety of special populations. Because of the diversity of patients treated with anticoagulation, it is important to understand the limitations of TSOACs in patients with renal impairment, hepatic impairment, obesity and advanced age. The 2012 census approximated that there are 43 million US adults age 65 years or older, comprising 13.7% of the population.⁶ This number is expected to continue to increase to 20% by 2050. With increasing age, a number of comorbidities arise, accompanied by pharmacokinetic changes that must be considered when treating this population. Chronic kidney disease (CKD) is present in 26 million patients in the United

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States. Interestingly, renal impairment independently confers an increased risk of bleeding, regardless of anticoagulant utilized. Furthermore, 1 in 10 patients in the United States is affected by liver impairment, which includes a spectrum of diseases from mild hepatitis to cirrhosis. Finally, the prevalence of obesity is estimated to affect one-third or 78.6 million US adults.

The large proportion of individuals with body mass index (BMI) greater than 30 kg/m² necessitates understanding of the implications of obesity in dosage considerations. A complete summary of TSOAC-approved indications and dosing recommendations can be found in Table 1.

Because of the recent approval of TSOACs, their use in special populations has not been well defined and may pose challenges to providers as they gain familiarity with these agents. This review seeks to identify studies on dosing in special populations, including patients with renal or hepatic impairment and obese or elderly patients to provide a summary of recommendations.

Data Sources
A literature search was conducted in Medline (1996 to April week 2 2015) and Embase (1980 to 2015 week 16) using keywords dabigatran, rivaroxaban, apixaban, edoxaban, kidney diseases, liver diseases, elderly, obesity, and special populations. Randomized controlled trials, written in the English language establishing the safety and efficacy of TSOACs at a variety of doses in adult healthy and special populations were selected for inclusion in this review. Additional literature was obtained by bibliographic review of published trials.

Results
Studies for TSOAC drug approvals were done in the general population. A thorough analysis of published studies is necessary to optimize clinical management of patients needing oral anticoagulants for NVAF or VTE treatment and prevention. The prevalence of special populations requires an understanding of pharmacokinetic, efficacy, and safety differences in these patients. A complete list of TSOAC pharmacokinetic and clinical studies can be found in Table 2.

Special Populations: Renal Impairment
Results from a large database published in 2009 found that the incidence of ischemic stroke or VTE is greater in patients with impaired renal function. Thus, the judicious selection of an oral anticoagulant requires a thorough understanding of the limits of each TSOAC and its potential role in patients with renal impairment. In some TSOAC trials, patients with severe renal impairment, defined as a creatinine clearance (CrCl) less than 30 mL/min, were excluded, and the doses recommended and approved by the FDA were extrapolated from early trials or smaller subgroup analyses.

Glomerular filtration rate (GFR) is utilized as a marker of kidney function, but cannot be directly measured. Therefore, GFR is estimated using validated equations, such as the Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. These equations utilize serum creatinine (SCr) and other patient variables (eg, age, sex, weight, and race) to estimate renal function, which may result in incongruent estimations among patients. Studies that lead to the approval of dabigatran, rivaroxaban, and apixaban estimated renal function using the CG equation. Notably, dabigatran and rivaroxaban studies specified that CrCl was calculated using actual body weight. Dabigatran, the active metabolite of dabigatran etexilate, has greater than 80% renal elimination through glomerular filtration. Studies found that patients with moderate (CrCl = 30-50 mL/min) and severe (CrCl = 15-30 mL/min) renal impairment had a substantial increase in area under the curve (AUC) compared with patients with normal renal function. There was a similar, but less significant, increase in Cmax. Dabigatran’s half-life increased to 27 hours in patients with severe renal impairment compared with 13 hours in patients with normal renal function. An inverse relationship between several anticoagulation parameters, such as activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), INR, and thrombin time (TT), and renal function was also found and attributed to increased drug exposure. However, the increase in aPTT was clinically insignificant. The relationship between the pharmacokinetic and pharmacodynamic parameters was not significantly different among healthy patients compared with those with renal impairment. Although not tested in vivo in clinical studies, the pharmacokinetic profile was used to extrapolate the FDA approved dosing recommendations for dabigatran in patients with severe renal impairment.

Using pharmacokinetic data from phase 1, 2, and 3 studies, a computer model confirmed the approved dosing recommendations and nonlinear relationship between reduced renal function and dabigatran exposure. In a subgroup analysis of the RE-LY study, there was an inverse relationship between the primary outcome of stroke or systemic embolism rates and renal function. Furthermore, annual major bleeding rates increased as with decreasing renal function. Likewise, there was a concurrent increase in intracranial bleeds.

Interestingly, the estimation of CrCl using the MDRD, CG, and CKD-EPI equations were compared, and the CKD-EPI provided the most accurate assessment of renal function. According the National Kidney Foundation, MDRD or CG can be used in drug dosing in adults. Although it is the most commonly used equation in practice
<table>
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<tr>
<th>Drug (Brand)</th>
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</table>
| Dabigatran etexilate\(^3\) (Pradaxa) | Direct thrombin inhibitor | Reduction of stroke and systemic embolism in NVAF | 150 mg BID | Renal: If CrCl 15-30 mL/min, reduce dose to 75 mg BID; avoid if CrCl <15 mL/min  
Renal: Avoid if CrCl <50 mL/min |
| | | Treatment of VTE | 150 mg daily for 5-10 days, then 150 mg BID |  |
| | | Prevention of VTE in patients undergoing THR or TKR | 150 mg BID |  |
| Rivaroxaban\(^4\) (Xarelto) | Factor Xa inhibitor | Reduction of stroke and systemic embolism in NVAF | 20 mg daily with evening meal | Renal: If CrCl 15-50 mL/min, reduce dose to 15 mg daily; avoid if CrCl <15 mL/min  
Hepatic: Avoid use with moderate to severe impairment (Child-Pugh class B and C)  
Renal: Avoid if CrCl <50 mL/min |
| | | Treatment of VTE | 15 mg BID for 21 days, then 20 mg daily |  |
| | | Prevention of VTE | 20 mg daily |  |
| | | Prevention of VTE in patients undergoing THR or TKR | 10 mg daily |  |
| Apixaban\(^5\) (Eliquis) | Factor Xa inhibitor | Reduction of stroke and systemic embolism in NVAF | 5 mg BID | Dose reduction to 2.5 mg BID with two of the following risk factors: Scr $\geq$ 1.5 mg/dL, weight $\leq$ 60 kg, age $\geq$ 80 years  
Hepatic: Avoid use with severe impairment (Child-Pugh class C)  
Hepatic: Avoid use with severe impairment (Child-Pugh class C)  
Weight: If $\leq$ 60 kg, reduce dose to 2.5 mg BID |
| | | Treatment of VTE | 10 mg BID for 7 days, then 5 mg BID |  |
| | | Prevention of VTE | 2.5 mg BID |  |
| | | Prevention of VTE in patients undergoing THR or TKR | 2.5 mg BID |  |
| Edoxaban\(^6\) (Savaysa) | Factor Xa inhibitor | Reduction of stroke and systemic embolism in NVAF | 60 mg daily | Renal: Avoid if CrCl >95 mL/min or $<15$ mL/min;  
If CrCl 15-50 mL/min, reduce dose to 30 mg daily  
Hepatic: Avoid use with moderate to severe impairment (Child-Pugh class B and C)  
Weight: If $\leq$ 60 kg, reduce dose to 30 mg daily  
Renal: If CrCl 15-50 mL/min, reduce dose to 30 mg daily; avoid if CrCl <15 mL/min;  
Hepatic: Avoid use with moderate to severe impairment (Child-Pugh class B and C)  
Weight: If $\leq$ 60 kg, reduce dose to 30 mg daily |
| | | Treatment of VTE | 60 mg daily |  |

Abbreviations: BID, twice daily; CrCl, creatinine clearance; NVAF, nonvalvular atrial fibrillation; Scr, serum creatinine; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.
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<tr>
<td>Stangier et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Dabigatran 150 mg once or dabigatran 50 mg (for ESRD on HD)</td>
<td>None</td>
<td>Single center, open label, parallel group study assessing the effect of mild to severe renal impairment on the pharmacokinetics and pharmacodynamics of one dose of dabigatran</td>
<td>Renal: Moderate and severe renal impairment was associated with a respective 3.2- and 6.3-fold increase in AUC, and a 1.7- and 2.1-fold increase in Cmax. The half-life was prolonged by 4.9 and 13.7 hours in moderate and severe renal impairment, respectively. Hemodialysis may be used to remove drug. Pharmacodynamic parameters changed proportionally to increased serum concentration.</td>
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<tr>
<td>Stangier et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Dabigatran 150 mg once</td>
<td>None</td>
<td>Single center, single dose, open label, parallel trial comparing the pharmacokinetics and pharmacodynamics of one dose of dabigatran in patients with moderate hepatic impairment to healthy controls</td>
<td>Hepatic: Moderate hepatic impairment resulted in a clinically insignificant reduction in Cmax. No changes in AUC, half-life or clearance or pharmacodynamic (aPTT, ECT, or TT) parameters in moderate hepatic impairment compared with control group.</td>
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<td>Connolly et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Dabigatran 110 mg or 150 mg twice daily</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Multicenter, open label, outcome blinded, randomized, noninferiority trial comparing the safety and efficacy of 2 fixed doses of dabigatran to warfarin for the prevention of stroke and systemic embolism in NVAF</td>
<td>Dabigatran 150 mg was superior to warfarin for the prevention of stroke and systemic embolism (P &lt; 0.001). There was no difference in the rate of major bleeding or mortality, but significantly less hemorrhagic stroke was seen in the dabigatran 150 mg group compared with warfarin (P &lt; 0.001). Renal: Excluded patients with a CrCl less than 30 mL/min. Hepatic: Excluded patients with active hepatic impairment.</td>
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<td>Schulman et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Dabigatran 150 mg twice daily</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Multicenter, double-blind, randomized double dummy, noninferiority trial comparing dabigatran to warfarin to assess the safety and efficacy for the treatment of DVT or PE for 6 months</td>
<td>Dabigatran was noninferior to warfarin with regard to the primary outcome (P &lt; 0.001). Major of clinically relevant nonmajor bleeding occurred in less patients in the dabigatran group compared with controls (P = 0.002). Renal: Excluded patients with a CrCl less than 30 mL/min. Hepatic: Excluded patients with serum transaminases greater than 2 times the upper limit of normal.</td>
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| Schulman et al\(^{16}\) | Dabigatran 150 mg twice daily | Warfarin (adjusted to INR of 2-3) | Multicenter, double-blind, randomized double dummy, noninferiority trial comparing dabigatran to warfarin to assess the safety and efficacy for the treatment of DVT or PE for 6 months pooled with data from RECOVER 1 | Dabigatran was noninferior to warfarin with regard to the primary outcome (\(P < 0.001\))  
Renal: Excluded patients with a CrCl less than 30 mL/min  
Hepatic: Excluded patients with serum transaminases greater than 3 times the upper limit of normal  
Obesity: No significant relationship between body mass index and efficacy identified in pooled subgroup analysis  
Elderly: No significant relationship between age and efficacy identified in pooled subgroup analysis |
| Hijazi et al\(^{17}\)   | Dabigatran 110 or 150 mg twice daily | Warfarin (adjusted to INR of 2-3) | Prespecified subgroup analysis of a multicenter, open label, outcome blinded, randomized noninferiority trial comparing the safety and efficacy of 2 fixed doses of dabigatran to warfarin for the prevention of stroke and systemic embolism in NVAF assessing the outcomes in relation to renal function using 3 equations: CG, CKD-EPI, and MDRD | Renal: No significant change in efficacy or safety outcomes associated with the use of the following equations for renal function estimation: MDRD, CG, or CKD-EPI. Incidence of stroke and systemic embolism increased with decreasing renal function. Annual major bleeding rates increased as renal function decreased, ranging from 1.98% in patients with a CrCl greater than 80 mL/min to 5.48% in those with a CrCl less than 50 mL/min, but did not significantly differ from rates of bleeding in patients taking warfarin |
| Weinz et al\(^{18}\)    | Rivaroxaban 10 mg once | None                        | Single center, open label, nonrandomized, non–placebo controlled trial to assess the in vivo metabolism and excretion of a single dose of rivaroxaban | Renal: Rivaroxaban had no major circulating active metabolites. Renal excretion is the primary route of elimination with 36% of drug unchanged |
| Kubitz et al\(^{19}\)   | Rivaroxaban 10 mg once | None                        | Single center, randomized, single blind, placebo controlled, parallel group trial assessing the effect of extremes of body weight on rivaroxaban pharmacokinetics and pharmacodynamics in healthy adults | Obesity: No difference in Cmax, AUC, or Tmax in obese patients compared with normal weight or in males compared with females. Cmax increased 24% in the less than 50-kg group compared with normal weight (\(P = 0.04\)) |

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Kubitza et al. Rivaroxaban 10 mg once. Single center, nonrandomized, parallel group trial assessing the effect of mild and moderate hepatic impairment on rivaroxaban pharmacokinetics and pharmacodynamics.

- Hepatic: AUC increased significantly in patients with moderate hepatic impairment to 2.27 times that of healthy patients ($P < 0.0004$). Duration of PT prolongation, Cmax, and half-life also increased in the study group. Moderate impairment (but not mild impairment) is associated with decreased rivaroxaban clearance.

Kubitza et al. Rivaroxaban 10 mg once. Single blind, randomized, placebo controlled parallel group study comparing the pharmacokinetics and pharmacodynamics of rivaroxaban in males to females and adults aged 18-45 years to adults older than 75 years.

- Gender had no significant influence on pharmacokinetics or pharmacodynamics.

- Elderly: There was a 41% increase in AUC of rivaroxaban between the younger group and the elderly group ($P = 0.0013$). Age did not affect Cmax or efficacy as measured by PT and FXa activity.

Kubitza et al. Rivaroxaban 10 mg once. Two-center, open label, nonrandomized cohort trial assessing the effects of mild, moderate, and severe renal impairment on rivaroxaban pharmacokinetics and pharmacodynamics compared with normal renal function.

- Renal: Reduction in CrCl directly correlated with decreased rivaroxaban clearance ($P = 0.006$) and an increase in AUC ($P < 0.03$). In patients with severe renal impairment, there was a small increase in half-life compared with normal renal function (8.3-9.5 hours). The AUC for FXa inhibition significantly increased ($P = 0.0067$), but the Emax for FXa inhibition did not ($P = 0.44$) as renal function decreased. Fraction unbound did not change with renal impairment.

The EINSTEIN Investigators Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily for 3, 6, or 12 months. Enoxaparin 1 mg/kg subcutaneously daily for at least 5 doses and therapeutic INR and VKA started within 48 hours.

- Renal: Excluded patients with a CrCl less than 30 mL/min.

- Hepatic: Excluded patients with significant hepatic impairment.

Rivaroxaban was noninferior compared with enoxaparin in prevention of recurrent symptomatic VTE ($P < 0.001$). There was no difference in safety outcomes.

- Renal: Excluded patients with a CrCl less than 30 mL/min.

- Hepatic: Excluded patients with significant hepatic impairment.
### Table 2. (continued)

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<td><strong>The EINSTEIN-PE Investigators</strong> 24</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily for 3, 6, or 12 months</td>
<td>Enoxaparin 1 mg/kg subcutaneously daily for at least 5 doses and therapeutic INR and VKA started within 48 hours</td>
<td>Open label, randomized event driven, noninferiority trial comparing the safety and efficacy of rivaroxaban with enoxaparin and VKA for acute symptomatic PE</td>
<td>Rivaroxaban was noninferior to enoxaparin in the prevention of symptomatic recurrent VTE ($P = 0.003$). There was no difference in major or clinically relevant nonmajor bleeding, but there was more major bleeding in the treatment group ($P = 0.003$).&lt;br&gt;<strong>Renal:</strong> Excluded patients with a CrCl less than 30 mL/min&lt;br&gt;<strong>Hepatic:</strong> Excluded patients with significant hepatic impairment</td>
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<td><strong>Patel et al</strong> 25</td>
<td>Rivaroxaban 20 mg daily or 15 mg daily (for CrCl 30-49 mL/min)</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Multicenter, double-blind, randomized double dummy event driven, noninferiority trial comparing rivaroxaban to warfarin for the prevention of stroke and systemic embolism due to NVAF</td>
<td>Rivaroxaban is noninferior to warfarin for the prevention of stroke or VTE ($P &lt; 0.001$). There was no difference in major or clinically relevant nonmajor bleeding. However, there was significantly more gastrointestinal bleeding ($P &lt; 0.001$) in the treatment group and significantly less intracranial bleeding ($P = 0.02$).&lt;br&gt;<strong>Renal:</strong> Excluded patients with a CrCl less than 30 mL/min&lt;br&gt;<strong>Hepatic:</strong> Excluded patients with significant hepatic impairment</td>
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<tr>
<td><strong>Mueck et al</strong> 26</td>
<td>Rivaroxaban 2.5, 5, 10, 20, or 30 mg twice daily</td>
<td>THR: Enoxaparin 40 mg subcutaneously daily; TKR: Enoxaparin 30 mg subcutaneously daily</td>
<td>Population blood sample analysis of 2 multicenter, double blind, double dummy, randomized controlled active comparator studies of twice daily rivaroxaban for the prevention of VTE after THR or TKR surgery to model population pharmacokinetic and pharmacodynamic characteristics of rivaroxaban</td>
<td>Plasma concentrations increased directly with the dose. No correlation between absorption and gender, food, or medications was identified. &lt;br&gt;<strong>Renal:</strong> In TKR patients, CrCl decreased by 1 mL/min from 103 mL/min resulted in a 0.2% decrease in clearance. In the THR patients, there was a decrease in clearance of 2.1% for every 0.1 mg/dL increase in Scr over 0.78 mg/dL. &lt;br&gt;<strong>Obesity:</strong> No relationship between weight and pharmacokinetic or pharmacodynamic parameters &lt;br&gt;<strong>Elderly:</strong> In the THR study only, rivaroxaban clearance 1.5% annually after age 65 years</td>
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<td>Halperin et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Rivaroxaban 20 mg daily or 15 mg daily (for CrCl 30-49 mL/min)</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Subgroup analysis comparing the outcomes of a multicenter, double blind, blinded randomized double dummy event driven, noninferiority trial comparing rivaroxaban with warfarin for the prevention of stroke and systemic embolism due to NVAF in adults greater than and less than 75 years old</td>
<td>Elderly: No difference in the primary outcome was identified between patients aged greater than 75 years to those aged less than 75 years. Major bleeding event rates were higher in patients greater than 75 years old compared with younger patients ($P &lt; 0.0001$), but there was no difference when comparing rivaroxaban to warfarin</td>
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<tr>
<td>Granger et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Apixaban 5 mg twice daily or 2.5 mg twice daily with presence of 2 risk factors: SCr ≥ 1.5 mg/dL, age &gt;80 years, weight ≤ 60 kg</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Randomized, double blind, double dummy, noninferiority trial comparing the safety and efficacy of apixaban and warfarin in preventing rate of stroke or systemic thromboembolism due to NVAF</td>
<td>Apixaban was superior to warfarin in prevention of stroke or systemic embolism ($P = 0.01$). The rate of death from any cause was lower in the apixaban group ($P = 0.047$). Major bleeding occurred significantly more in the warfarin group ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Hohnloser et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Apixaban 5 mg twice daily or 2.5 mg twice daily with presence of 2 risk factors: SCr ≥ 1.5 mg/dL, age &gt;80 years, weight ≤ 60 kg</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Prespecified secondary analysis of a randomized, double blind, double dummy, noninferiority trial comparing the safety and efficacy of apixaban and warfarin in preventing rate of stroke or systemic thromboembolism in patients with NVAF in relation to renal function as assessed by the CG and CKD-EPI equations and cystatin C</td>
<td>Renal: Excluded patients with severe renal impairment (CrCl &lt;25 mL/min, SCr &gt;2.5 mg/dL)</td>
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<td>Hepatic: Excluded patients with active liver impairment</td>
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<td>Renal: Rate of annual ischemic stroke in patients with CrCl &lt;50 mL/min was 1.70% compared with 0.76% in patients with normal renal function (CrCl &gt;80 mL/min). Risk of all-cause mortality was 7.71% in patients with CrCl &lt;50 mL/min compared with 2.52% in normal renal function. Risk of major bleeding was highest in severe renal impairment. Equation used to calculate renal function did not affect the outcome</td>
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<tr>
<td>Connolly et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Apixaban 5 mg twice daily or 2.5 mg twice daily with presence of 2 risk factors: SCr $\geq 1.5$ mg/dL, age $&gt;80$ years, weight $\leq 60$ kg</td>
<td>ASA 81-325 mg once daily</td>
<td>Multicenter, randomized, double blind superiority trial assessing the safety and efficacy of apixaban compared with aspirin in preventing stroke of systemic embolism due to NVAF in patients unable to receive warfarin</td>
<td>Apixaban was found to be superior to aspirin in the prevention of stroke or systemic embolism ($P &lt; 0.001$). There was no difference in major bleeding or death between the 2 groups. Renal: Excluded patients with severe renal failure (CrCl $&lt;25$ mL/min, SCr $&gt;2.5$ mg/dL). Hepatic: Excluded patients with serum transaminases 2 times the upper limit of normal or total bilirubin 1.5 times the upper limit of normal.</td>
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<tr>
<td>Lassen et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg twice daily 12-24 hours after TKR</td>
<td>Enoxaparin 30 mg subcutaneously every 12 hours</td>
<td>Randomized, double blind, double dummy, noninferiority trial comparing apixaban and enoxaparin treatment for 10-14 days for the prevention of a composite of DVT, nonfatal PE, and all-cause mortality for 60 days after treatment discontinuation</td>
<td>Apixaban did not meet criteria for noninferiority compared with enoxaparin for the prevention of the primary endpoint. There was no significant difference in major bleeding, but apixaban was associated with significantly less clinically relevant major and nonmajor bleeding ($P = 0.03$). Renal: Excluded patients with significant renal impairment. Hepatic: Excluded patients with active hepatic impairment.</td>
</tr>
<tr>
<td>Lassen et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg twice daily 12-24 hours after TKR</td>
<td>Enoxaparin 40 mg subcutaneously daily started 12 hours before TKR</td>
<td>Multicenter, randomized, double blind, noninferiority trial comparing apixaban and enoxaparin treatment for 10-14 days for the prevention of a composite of DVT, nonfatal PE, and all-cause mortality for 60 days after treatment discontinuation</td>
<td>Apixaban was superior to enoxaparin for prevention of primary outcome ($P &lt; 0.0001$). No difference in bleeding outcomes was identified. Renal: Excluded patients with significant renal impairment. Hepatic: Excluded patients with active hepatic impairment.</td>
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<tr>
<td>Lassen et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg twice daily 12-24 hours after THR</td>
<td>Enoxaparin 40 mg subcutaneously daily started 12 hours before THR</td>
<td>Multicenter, randomized, double blind, noninferiority trial comparing apixaban and enoxaparin treatment for 35 days for the prevention of a composite of DVT, nonfatal PE, and all-cause mortality for 60 days after treatment discontinuation</td>
<td>Apixaban was superior to enoxaparin for the prevention of the primary endpoint ($P &lt; 0.001$). No significant difference in major or minor bleeding was identified. Renal: Excluded patients with a CrCl $&lt;30$ mL/min as calculated by CG. Hepatic: Excluded patients with active hepatic impairment.</td>
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<td>Study</td>
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<td>Study Results and Implications in Special Populations</td>
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<td>The Hokusai-VTE Investigators (^{34})</td>
<td>Edoxaban 60 mg daily or 30 mg daily (for CrCl = 30-50 mL/min, weight &lt;60 kg, or concomitant use of verapamil or quinidine)</td>
<td>Warfarin (adjusted to INR of 2-3)</td>
<td>Double blind, randomized, noninferiority trial comparing the safety and efficacy of edoxaban to warfarin for the treatment of symptomatic VTE</td>
<td>Edoxaban was noninferior to warfarin in the prevention of recurrent VTE primary endpoint ((P &lt; 0.001)). Edoxaban patients had less clinically relevant major and nonmajor bleeding ((P = 0.004)). Patients in the reduced dose group experienced less bleeding than the comparator group without reduced efficacy. (\text{Renal: Excluded patients with a } \text{CrCl } &lt;30 \text{ mL/min. No relationship between } \text{CrCl and primary safety or efficacy outcomes identified in prespecified subgroup analysis.} \text{Hepatic: Excluded patients with active liver disease.} \text{Obesity: No difference in primary efficacy or safety outcomes in patients greater than or less than 60 or 100 kg in prespecified subgroup analysis.} \text{Giugliano et al}^{35} )</td>
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| Giugliano et al \(^{35}\) | Edoxaban 60 mg daily or 30 mg daily (for CrCl = 30-50 mL/min, weight <60 kg, or concomitant use of verapamil or quinidine) | Warfarin (adjusted to INR of 2-3) | Double blind, randomized, double dummy comparing the safety and efficacy of 2 doses of edoxaban to warfarin for the prevention of stroke or systemic embolism in NVAF | Edoxaban was superiority to warfarin for the prevention of stroke or systemic embolism \((P = 0.02)\). In patients receiving the low dose, edoxaban was noninferiority for stroke and systemic embolism prevention compared with warfarin \((P = 0.005)\). Major bleeding was significantly lower in both the 60- and 30-mg edoxaban groups compared with warfarin \((P < 0.001 \text{ for both})\) \(\text{Renal: Patients with a } \text{CrCl }>95 \text{ mL/min had increased rate of thrombotic events} \text{Hepatic: Excluded patient with active liver impairment.} \text{Abbreviations: aPTT, activated partial thromboplastin time; AUC, area under the curve; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; DVT, deep vein thrombosis; ECT, ecarin clotting time; ESRD, end-stage renal disease; FXa, factor Xa; HD, hemodialysis; INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation; MDRD, Modification of Diet in Renal Disease; PE, pulmonary embolism; PT, prothrombin time; SCR, serum creatinine; TT, thrombin time; THR, total hip replacement; TKR, total knee replacement; VKA, vitamin K antagonist; VTE, venous thromboembolism.} \)
and clinical trials, the CG equation overestimates renal function. Half of patients with a CrCl greater than or equal to 80 mL/min, as calculated by CG, had a CrCl less than 80 mL/min when using CKD-EPI.17 Regardless of the equation used, the efficacy of dabigatran was consistent across varying levels of renal function compared with warfarin.

In contrast to dabigatran, only one-third of rivaroxaban is renally excreted unchanged.4,18 However, as seen with trials involving dabigatran, patients with a CrCl less than 30 mL/min were excluded from rivaroxaban studies.23,25 More than 60% of patients included in VTE trials had a CrCl greater than 80 mL/min.23,24 Additionally, ROCKET-AF investigators reported an average CrCl of 64 mL/min. Patients with a CrCl less than 50 mL/min were administered a lower dose of rivaroxaban, and there was no difference in bleeding found in either the rivaroxaban or warfarin groups regardless of the renal function.25 In an assessment of the pharmacokinetics and pharmacodynamics of a single rivaroxaban dose in patients with varying degrees of renal impairment, decreasing renal function significantly correlated with decreasing rivaroxaban clearance (P < 0.001) and increasing AUC (P < 0.03).4,22 In severe renal impairment, AUC increase correlated with a mildly prolonged half-life. Of note, the severe renal impairment group had an average CrCl greater than 15 mL/min. While mild adverse drug reactions were reported, none were related to bleeding. Despite increased total unbound concentrations, there was no change in the fraction unbound and no significant increase in the Emax for FXa inhibition. These changes in pharmacokinetic and pharmacodynamic parameters were not considered clinically significant in mild and moderate renal impairment. Further evaluations of the relationship between rivaroxaban pharmacokinetics and renal function were done in orthopedic patients and indicated a reduction in drug clearance associated with increasing serum creatinine in hip surgery patients.26 Similarly, patients undergoing knee surgery experienced a decrease in drug clearance with decreasing CrCl. Patients with a CrCl less than 30 mL/min and Scr less than 1.5 mg/dL were excluded, but the authors utilized a model to estimate the exposure to rivaroxaban would be increased 15% to 35% in these patients.

Similar to rivaroxaban, one-third of apixaban is excreted renally unchanged.3 Studies evaluating apixaban in patients with NVAF for prevention of stroke excluded patients with severe renal disease, which investigators defined as a CrCl less than 25 mL/min or a Scr greater than 2.5 mg/dL.14,28,29 Interestingly, patients enrolled with moderate renal disease (Scr greater than 1.5 mg/dL) and at least one of the following risk factors: age greater than 80 years or weight less than 60 kg, received reduced doses of 2.5 mg twice daily. Study investigators concluded that apixaban decreases the risk of stroke or VTE in patients without increasing major bleeding risk. Subsequently, Hohnloser et al20 conducted a subgroup analysis to further evaluate these findings relative to renal function. Results of this investigation found increased risk of events in patients with impaired renal function. Study subjects were stratified into 1 of 3 groups using CrCl, as calculated by CG: CrCl greater than 80 mL/min (42%), 50 to 80 mL/min (42%), and less than 50 mL/min (15%). Patients with a CrCl less than 50 mL/min had twice the rate of annual ischemic stroke rate and higher all-cause mortality compared with patients with without renal impairment. Finally, risk of major bleeding was greatest in severe renal impairment group. These findings remained consistent when evaluated using both the MDRD and CKD-EPI equations. Conversely, in a meta-analysis of 6 studies comparing the bleeding risk in patients with mild and severe renal impairment, apixaban was found to have similar risks to conventional anticoagulants.38 These conflicting results highlight the importance of careful consideration before recommending apixaban in patients with renal disease.

Half of edoxaban’s clearance occurs renally, and similar to the other TSOACs, requires adjustment in renal impairment.6 Unlike the other agents, however, a CrCl greater than 95 mL/min is a contraindication to edoxaban for NVAF because of increased risk of thromboembolic events. Also, unlike other agents, the manufacturer explicitly recommends using CG to calculate renal function, but does not specify what weight should be used in the equation. The Hokusai-VTE Investigators excluded patients with a CrCl less than 30 mL/min and reduced the dose by 50% in patients with a CrCl of 30-50 mL/min.34 Despite using lower doses, there was no difference in the rate of VTE, but a 2.1% increase in bleeding was identified.35 The investigators used the same dosing regimen and exclusion criteria in patients with NVAF. Notably, this study found no increase in bleeding in patients on edoxaban with renal impairment compared with those with normal renal function. However, when compared with warfarin, renally impaired patients on edoxaban had less bleeding but no change in efficacy.

Special Populations: Hepatic Impairment

Target-specific oral anticoagulants undergo hepatic metabolism through either glucuronidation or the cytochrome P450 system.39 With apixaban and rivaroxaban, this is further complicated by extensive plasma protein binding. Alterations in hepatic function may affect metabolism, protein binding, as well as synthesis of clotting factors.39 Typically, liver disease is either staged using the Child-Pugh (C-P) or the Model for End-Stage Liver Disease (MELD) scoring systems.40 Most TSOAC studies used C-P to determine level of hepatic impairment in trial subjects. C-P scores utilize INR, level of ascites, grading of encephalopathy, albumin levels, and bilirubin levels to determine severity of disease: mild (class A), moderate (class B), or severe (class C).41,42
Dabigatran undergoes limited hepatic metabolism. Patients with active liver disease (eg, hepatitis, cirrhosis, or elevated serum transaminases) were excluded from the trials leading to dabigatran approval.14,15 Stangier et al13 found that patients with moderate hepatic impairment had a lower Cmax after oral administration of the medication, but the bioavailability of the medication remained comparable. There was also no difference found pharmacodynamic parameters in dabigatran patients with moderate hepatic impairment. Based on these findings, in patients with mild to moderate hepatic impairment, dosage adjustment is not warranted.

Similarly, phase 3 trials for rivaroxaban excluded participants that had active liver disease.23,25 In contrast to dabigatran, a pharmacokinetic study of a single dose of rivaroxaban in hepatically impaired patients, identified a significant increase in rivaroxaban exposure compared with healthy patients (P < 0.0004).20 Furthermore, hepatic impairment was associated with a prolonged prothrombin time (PT). While safe to use in mild hepatic impairment, in patients with moderate impairment an alternative anticoagulant should be considered.

Consistent with the aforementioned agents, phase 3 trials for apixaban also excluded patients with active liver disease.28,30,32,33 Patients with mild to moderate hepatic impairment who received a single dose of apixaban showed no significant difference in AUC, Cmax, protein binding, or changes in INR when compared with healthy subjects.22

Edoxaban’s phase 3 trials also excluded patients with active liver disease.34,35 A phase 1 study evaluating the pharmacokinetics of edoxaban in patients with hepatic impairment found a decreased AUC and Cmax and increased half-life.43 Based on pharmacokinetic findings, these patients were excluded from approval studies. Thus, edoxaban should be avoided in patients with moderate to severe hepatic impairment.

Special Populations: Obesity

Obesity is an independent risk factor for both AF and VTE.44,45 The large proportion of individuals with BMI greater than 30 kg/m² in the United States dictates the need to understand how obesity may affect efficacy and safety of TSOCs.

In the RE-LY and RECOVER trials, participants had an average body weight of 83 and 85 kg, respectively, with no exclusion criteria for body weight or BMI.14,15 Interestingly, further analyses of the relationship between weight and thromboembolic events were contradictory. RE-LY found a trend toward increased risk of stroke or VTE in patients weighing less than 50 kg compared with patients weighing greater than 100 kg, whereas RECOVER found a higher incidence of stroke or VTE in patients with weight greater than 100 kg. These findings highlight the need for further studies evaluating dabigatran dosing in this population.

The EINSTEIN and ROCKET AF trials, which evaluated rivaroxaban, did not account for body weight or BMI in the exclusion criteria.23,24 In EINSTEIN, 14% of the participants weighed greater than 100 kg, while ROCKET AF participants had an average BMI of 28 kg/m². Neither trial found a relationship between body weight or BMI and clinical safety or efficacy endpoints. Furthermore, pharmacokinetic and pharmacodynamic studies support these findings, as AUC, Cmax, Tmax, half-life, and FXa inhibition were not significantly different in varying weight groups.19

As with dabigatran and rivaroxaban studies, phase 3 trials evaluating apixaban did not exclude participants based on either body weight or BMI.28,30,46 However, dosage reduction occurred in patients weighing less than 60 kg when another risk factor was present (SCr ≥ 1.5 mg/dL or age ≥ 80 years). This is likely due to a phase I study, which identified a linear relationship between apixaban exposure and body weight.47 In otherwise healthy patients, this was deemed clinically insignificant; however, investigators postulated that the presence of additional risk factors, such as renal impairment or advanced age, may necessitate dose adjustment. Although ARISTOTLE and AVERROES evaluated efficacy of apixaban for systemic embolism in patients with NVAF, only ARISTOTLE further analyzed results based on patient weight.28,30 No difference was found between patients weighing less than or greater than 60 kg.28 Similarly, an analysis of the ADVANCE trials identified no significant relationship between the incidence of VTE and increasing BMI or weight in orthopedic patients.36

Consistent with apixaban, edoxaban dosing was decreased in both phase 3 studies in participants weighing less than 60 kg because of concerns about bleeding risk.34,35 Using the lower doses of edoxaban, there was no relationship found between body weight and incidence of VTE or major bleeding in patients.34

Special Populations: Elderly

The incidence of NVAF in patients older than 65 years is 5% and doubles to 10% in patients 80 years or older.48 This is further compounded by increasing risks of renal and hepatic impairment and greater susceptibility to bleeding with anticoagulants in elderly patients. These factors are important when considering the optimal oral anticoagulant for patients older than 65 years and is underscored by the increasing incidence of VTE with advanced age.49

Evaluation of dabigatran efficacy based on age related differences was done in VTE patients, but not NVAF patients.14,16 No difference in dabigatran efficacy was found in the elderly population.15,16 However, safety analysis revealed age-related differences in risk reduction compared with warfarin in patients older than 85 years. That is, using age as a continuous variable, patients aged 85 years and older on dabigatran had a decreased risk of bleeding compared with those patients taking warfarin.
Similar findings were observed in rivaroxaban studies. A secondary analysis from ROCKET AF evaluating the relationship between age and efficacy found no difference compared with all study subjects. The rates of major bleeding were significantly higher in patients greater than or equal to 75 years compared with younger patients (P < 0.0001); however, there was no difference between major bleeding events in the rivaroxaban and warfarin groups. Significant differences in rates of extracranial bleeding occurred in elderly patients randomized to rivaroxaban (P = 0.009), which investigators attributed to gastrointestinal bleeding. Notably, this age-related evaluation did not have adequate power to detect differences in safety outcomes, as the incidence of event rates was too small. An evaluation of pharmacokinetic differences found a significant increase in AUC in patients older than 75 years, which was attributed to reduced renal clearance of rivaroxaban (P = 0.0013). The increase in AUC was not clinically significant, as the maximum plasma concentration of the drug and efficacy did not change concomitantly.

Compared with age-related safety concerns with dabigatran and rivaroxaban, analysis from apixaban studies arrived at different conclusions. Studies evaluating efficacy and safety in NVAF patients and VTE prophylaxis in orthopedic patients aged 80 years or older used dose adjusted apixaban if other risk factors were present (Scr ≥ 1.5 mg/dL or weight <60 kg). A subgroup analysis from ADVANCE 2 and ADVANCE 3 found statistical differences favoring the use of apixaban over enoxaparin for prevention of VTE; however, a significant increase in bleeding was also found. Thus, results indicate that advanced age is independent of risk benefit analysis of safety versus efficacy.

There is limited data describing the use of edoxaban in elderly patients.

**Conclusions**

While the pharmacokinetics and pharmacodynamics of TSOACs confer the advantage of minimal testing compared with warfarin, it is also these parameters that necessitate additional consideration for use in special populations. However, it cannot be assumed that pharmacokinetic changes significantly alter clinical outcomes. It is valuable to understand where labeled dosing recommendations originated, as it may affect clinical decisions, particularly as more TSOACs become available.

Available evidence suggests that patients with renal impairment will be best treated with rivaroxaban at recommended doses. Despite changes in pharmacokinetic parameters, there were no clinically significant changes in the safety and efficacy of rivaroxaban. In patients with NVAF and impaired renal function, edoxaban may also be considered. While all available TSOACs may be used in patients with mild hepatic impairment, moderate impairment limits use to dabigatran and apixaban. TSOACs are not recommended for patients with severe hepatic impairment because of bleeding concerns. Trials included participants’ with a wide range of body weights and BMI. For NVAF and VTE studies of rivaroxaban and VTE studies of apixaban, there was no difference in efficacy or safety identified in obese patients, thus making either a logical option. Despite this and the pharmacokinetic and pharmacodynamic changes in obese patients, fixed doses of TSOACs are still recommended in this population. Of note, patients with low body weight require dose adjustment for apixaban and edoxaban because of bleeding concerns. Finally, efficacy outcomes do not appear to be affected by age. When compared with warfarin, dabigatran, and rivaroxaban are associated with decreased bleeding risk as patients’ age. However, regardless of anticoagulant, patients were more likely to experience a bleeding event as age increased. When compared with enoxaparin for thromboprophylaxis, improved efficacy in elderly patients on apixaban was accompanied by an increased bleeding risk as well. Recommendations for edoxaban use are limited by the lack of published data. The use of TSOACs is likely to increase as clinicians gain experience with these agents and additional TSOACs and indications are approved. Further studies are needed to assess comparative efficacy and safety in special populations.

**Declaration of Conflicting Interests**

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Corrigendum


In Table 1 on page 1033 of the above article, in the dosing recommendation section for dabigatran (4th and 5th column), there is a sentence which reads: Treatment of VTE “150 mg daily for 5-10 days, then 150 mg BID” and “Renal: Avoid if CrCl <50 mL/min”

This sentence should have read: “150 mg BID” and “Renal: Avoid if CrCl <30 mL/min” respectively.