Selecting a Direct Oral Anticoagulant for the Geriatric Patient with Nonvalvular Atrial Fibrillation

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ABSTRACT

- **Objective:** To provide a clinical summary of the available data evaluating the use of direct oral anticoagulants (DOACs) in geriatric patients with nonvalvular atrial fibrillation.
- **Methods:** MEDLINE, Web of Science, and Google Scholar were used to identify pertinent systematic reviews, randomized controlled trials, observational studies, and pharmacokinetic studies evaluating use of DOACs in the geriatric population.
- **Results:** A total of 8 systematic reviews, 5 randomized controlled trials, 2 observational trials, and 5 pharmacokinetic studies of relevance were identified for inclusion in this review. The landscape of anticoagulation has dramatically changed over the past 5 years beginning with the development and marketing of an oral direct thrombin inhibitor and followed by 3 oral direct factor Xa inhibitors. Despite significant advances in this oral anticoagulation arena, many questions remain as to the best therapeutic approach in the geriatric population as the literature is lacking. This population has a higher risk of stroke; however, due to the increased risk of bleeding clinicians may often defer anticoagulant therapy due to the fear of hemorrhagic complications. Clinicians must consider the risk-benefit ratio and the associated outcomes in geriatric patients compared to other patient populations.
- **Conclusions:** Interpreting the available literature and understanding the benefits and limitations of the DOACs is critical when selecting the most appropriate pharmacologic strategy in geriatric patients.

Anticoagulants are among the top 5 drug classes associated with patient harm in the US [1] and are commonly reported as contributing to hospitalizations [2]. In just one quarter in 2012 alone, warfarin, dabigatran, and rivaroxaban accounted for 1734 of 50,289 adverse events reported to the Food and Drug Administration (FDA), including 233 deaths [3]. Appropriate use of anticoagulant agents and consideration of individual patient risk factors are essential to mitigate the occurrence of adverse consequences, especially in the geriatric population. This population is more likely to have risk factors for adverse drug events, for example, polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics, and diminished organ function (ie, renal and hepatic) [4,5]. Another important consideration is the lack of consensus on the definition of a “geriatric” or “elderly” patient. Although many consider a chronological age of > 65 years as the defining variable for a geriatric individual, this definition does not account for overall health status [6,7]. Clinicians should consider this shortcoming when evaluating the quality of geriatric studies. For example, a study claiming to evaluate the pharmacokinetics of a drug in a geriatric population enrolling healthy subjects aged > 65 years may result in data that do not translate to clinical practice.

Compounding the concern for iatrogenic events is the frequency of anticoagulant use in the geriatric population, as several indications are found more commonly in this age-group. Stroke prevention in nonvalvular atrial fibrillation (AF), the most common arrhythmia in the elderly, is a common indication for long-term anticoagulation [8]. The prevalence of AF increases with age and is usually higher in men than in women [9,10]. AF is generally uncommon before 60 years of age, but the prevalence increases noticeably thereafter, affecting approximately 10% of the overall population by 80 years of age [11]. The median age of patients who have AF is 75 years with

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approximately 70% of patients between 65 and 85 years of age [8,12]. Currently in the United States, an estimated 2.3 million people are diagnosed with AF [8]. In 2020, the AF population is predicted to increase to 7.5 million individuals with an expected prevalence of 13.5% among individuals ≥ 75 years of age, and 18.2% for those ≥ 85 years of age [13]. These data underscore the importance of considering the influence of age on the balance between efficacy and safety of anticoagulant therapy.

Direct oral anticoagulants (DOACs) represent the first alternatives to warfarin in over 6 decades. Currently available products in US include apixaban, dabigatran, edoxaban, and rivaroxaban. DOACs possess many of the characteristics of an ideal anticoagulant, including predictable pharmacokinetics, a wider therapeutic window compared to warfarin, minimal drug interactions, a fixed dose, and no need for routine evaluation of coagulation parameters. The safety and efficacy of the DOACs for stroke prevention in nonvalvular AF have been substantiated in several landmark clinical trials [14–16]. Yet there are several important questions that need to be addressed, such as management of excessive anticoagulation, clinical outcome data with renally adjusted doses (an exclusion criterion in many landmark studies was a creatinine clearance of < 25–30 mL/min), whether monitoring of coagulation parameters could enhance efficacy and safety, and optimal dosing strategies in geriatric patients. This review provides clinicians a summary of data from landmark studies, post-marketing surveillance, and pharmacokinetic evaluations to support DOAC selection in the geriatric population.

Evaluating Bleeding Risk
Anticoagulation is highly effective for the prevention of thrombotic events, however, bleeding risk is always present. Tools have been developed for the assessment of bleeding risk during anticoagulation therapy, but they have limitations. Several instruments have been validated in patients with AF and are summarized in Table 1 [17–19].

These tools have been extensively evaluated with warfarin therapy, but their performance in predicting DOAC-related bleeding has not been definitively established. Nonetheless, until tools evaluated specifically for DOACs are developed, it is reasonable to use these for risk-prediction in combination with clinical judgment. As an example, the European Society of Cardiology guideline on the use of non–vitamin K antagonist (VKA) anticoagulants in patients with nonvalvular AF suggests that the HAS-BLED score may be used to identify risk factors for bleeding and correct those that are modifiable [20]. The HAS-BLED score is validated for VKA and non-VKA anticoagulants (early-generation oral direct thrombin inhibitor ximelagatran) [21] and is the only bleeding risk score predictive for intracranial hemorrhage [19]. In a 2013 “real world” comparison, HAS-BLED was easier to use and had better predictive accuracy that ATRIA [22].

One of the major challenges in geriatric patients is that those at highest risk for bleeding are those who would have the greatest benefit from anticoagulation [23]. The prediction scores can help clinicians balance the risk-benefit ratio for anticoagulation on a case by case basis. Although the scoring systems take into consideration several factors, including medical conditions that have been shown to significantly increase bleeding risk, including hypertension, cerebrovascular disease, ischemic stroke, serious heart disease, diabetes, renal insufficiency, alcoholism and liver disease, not all are included in every scoring scheme [23]. These conditions are more common among elderly patients, and this should be taken into account when estimating the risk-benefit ratio of oral anticoagulation [15]. Patients’ preferences should also be taken into account. It is essential for clinicians to clearly discuss treatment options with patients as data suggest that clinician and patient perceptions of anticoagulation are often mismatched [24–26].

Performance of TSOACs in Landmark Studies
Due to the lack of head-to-head studies comparing the DOACs, clinicians must cautiously rely on indirect comparisons of these agents. Important considerations include differences in landmark study design, population, and outcomes. Table 2 [14–16,27] highlights some of the study design differences.

Some specific differences in outcomes seen in landmark studies that may facilitate selection among the DOACs include the risk of major bleeding, risk of gastrointestinal bleeding, risk of acute coronary syndrome, exclusion of valvular heart disease, and noninferiority versus superiority as the primary endpoint when compared to warfarin.

Major Bleeding
Table 3 and Table 4 [28–31,56] provide a summary of major bleeding rates reported in landmark trials for the total and age-specific populations. Both apixaban
and edoxaban (60 mg and 30 mg) were associated with significantly fewer major bleeding events compared to warfarin (apixaban: 2.1%/year versus 3.1%/year, \(P < 0.001\); edoxaban: 60 mg 2.75%/year and 30 mg 1.61%/year versus 3.43%/year, \(P < 0.001\)) [16, 27]. Dabigatran and rivaroxaban had similar major bleeding rates compared to warfarin (3.1%/year versus 3.5%/year, \(P = 0.31\) and 5.6% versus 5.4%, \(P = 0.58\), respectively). A pooled analysis of the DOACs reported that major bleeding in patients \(\geq 75\) years was at least similar to warfarin (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.74–1.17) [32].

### Table 1. Summary of Bleeding Risk Scoring Systems [17–19]

<table>
<thead>
<tr>
<th>Bleeding Risk Assessment Scoring Tools</th>
<th>Factors in Scoring System</th>
<th>Scoring</th>
</tr>
</thead>
</table>
| **Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)** | 1 point for presence of each: | Low: 0–3  
| | – Bleeding history | Moderate: 4  
| | – Hypertension | High: 5–10  
| | 2 points for presence of: | Maximum of 10 points  
| | – Age \(\geq 75\) |  
| | 3 points for presence of each: |  
| | – Anemia |  
| | – Severe renal failure |  
| **HAS-BLED** | 1 point for presence of each: | Low: 0  
| | – Hypertension | Moderate: 1–2  
| | – Abnormal renal/liver function (2 pts for both) | High: \(\geq 3\)  
| | – Stroke | Maximum of 9 points  
| | – Bleeding history |  
| | – Predisposition |  
| | – Labile INRs |  
| | – Drug therapy/alcohol intake (2 pts for both) |  
| **HEMORRHAGES** | 1 point for each risk factor present: | Low: 0  
| | – Hepatic or renal disease | Moderate: 2–3  
| | – ETOH abuse (ethyl alcohol) | High: \(\geq 4\)  
| | – Malignancy | Maximum of 12 points  
| | – Age \(> 75\) years |  
| | – Reduced platelet count or function |  
| | – Rebleeding risk* |  
| | – Hypertension (uncontrolled) |  
| | – Anemia |  
| | – Genetic factors (CYP2C9) |  
| | – Excessive fall risk |  
| | – Stroke |  
| | *2 points for previous bleed |  
| **Outpatient Bleeding Risk Index (OBRI)** | 1 point for presence of each condition and 0 if absent: | Low: 0  
| | – Age \(\geq 65\) years | Moderate: 1–2  
| | – GI bleed in past 2 weeks | High: \(\geq 3\)  
| | – Previous stroke | Maximum of 4 points  
| | – Comorbidities (recent MI, Hct < 30%, diabetes, creatinine > 1.5 mg/dL) |  

Hct = hematocrit; MI = myocardial infarction.
Gastrointestinal Bleeding
Among all of the DOACs, gastrointestinal (GI) bleeding was significantly greater with dabigatran, edoxaban, and rivaroxaban when compared to warfarin (HR, 1.49; 95% CI, 1.21–1.84; HR, 1.23; 95% CI, 1.02–1.50; and HR, 1.61; 95% CI, 1.30–1.99, respectively; \( P < 0.05 \) for all) [14–16] in landmark studies. Based on these data, clinicians may consider the selection of apixaban in patients with a previous history of GI pathology. GI bleeding may be more common in elderly patients due to the potential for preexisting GI pathology and high local concentrations of drug [29]. Clemens and colleagues suggested an “anticoagulation GI stress test” may predict GI malignancy [33]. They found that patients on DOACs that presented with a GI bleed were more likely to present with a GI malignancy. As such, it is reasonable to screen patients with a fecal occult blood test within the first month after initiating TSOAC treatment and then annually.

Acute Coronary Syndrome
A higher rate of myocardial infarction was observed with dabigatran 150 mg versus warfarin (0.74% vs 0.53% per year; \( P = 0.048 \)) in the RE-LY study [16]. Whether the increase in myocardial infarction was due to dabigatran as a causative agent or warfarin's ability to reduce the risk of myocardial infarction to a larger extent compared with dabigatran is unknown. Nonetheless, it may be prudent to use an alternative therapy in patients with a history of acute coronary syndrome.

Valvular Heart Disease
The risk of stroke and systemic embolism is higher in patients with valvular heart disease [34]. Patients with moderate to severe mitral stenosis or mechanical prosthetic heart valves were excluded from the DOAC landmark studies. Dabigatran was evaluated for prevention of stroke and systemic embolism in patients with valvular heart disease in the RE-ALIGN study [35,36]. Patients were randomized to warfarin titrated to a target INR of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk or dabigatran 150 mg, 220 mg, or 300 mg twice daily adjusted to a targeted trough of \( \geq 50 \) ng/mL. The trial was terminated early due to a worse primary outcome (composite of stroke, systemic embolism, myocardial infarction, and death) with dabigatran versus warfarin (HR, 3.37, 95% CI, 0.76–14.95; \( P = 0.11 \)). In addition, bleeding rates (any bleeding) was significantly greater with dabigatran (27%) versus warfarin (12%) \( (P = 0.01) \). Based on these data and the lack of data with the other TSOACs, warfarin remains the standard of care for valvular heart disease [37]. In patients with a previous bioprosthetic valve with AF, patients with mitral insufficiency, or aortic stenosis, TSOACs may be considered [37].

Landmark Study Efficacy Endpoints
The primary endpoint in each of the landmark studies was a composite of stroke (ischemic or hemorrhagic) and systemic embolism. For the primary endpoint only

Table 2. Comparison of Landmark Study Characteristics [14–16,27]

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE (Apixaban)</th>
<th>RE-LY (Dabigatan)</th>
<th>ENGAGE-AF TIMI 48 (Edoxaban)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment, n</td>
<td>18,201</td>
<td>18,113</td>
<td>21,105</td>
<td>14,264</td>
</tr>
<tr>
<td>Renal exclusion criteria</td>
<td>CrCl &lt; 25 mL/min or sCr &gt; 2.5 mg/dL</td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Warfarin naïve, %</td>
<td>43</td>
<td>50</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Median age, years*</td>
<td>70</td>
<td>72</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Female, %</td>
<td>35</td>
<td>41.6</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Patients over age 75 years, %</td>
<td>31</td>
<td>40</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2.1</td>
<td>2.2</td>
<td>2.8</td>
<td>3.5</td>
</tr>
<tr>
<td>TTR</td>
<td>66</td>
<td>66</td>
<td>68</td>
<td>58</td>
</tr>
<tr>
<td>Median follow-up, years</td>
<td>1.8</td>
<td>2.0</td>
<td>2.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Value in the RE-LY study represents the mean age.

\( TTR = \text{time in therapeutic range.} \)
Direct oral anticoagulants were found to be superior to warfarin for the prevention of stroke or systemic embolism in nonvalvular AF (HR, 0.66; 95% CI, 0.53–0.82; P < 0.001 and HR, 0.66; 95% CI, 0.66–0.95; P = 0.01, respectively). Both edoxaban (60 mg and 30 mg daily) and rivaroxaban were noninferior to warfarin for the primary endpoint.

In terms of ischemic stroke, only dabigatran 150 mg twice daily was superior to warfarin for the reduction in ischemic stroke in patients with nonvalvular AF (HR, 0.76; 95% CI, 0.60–0.98; P = 0.03) [19]. All of the DOACs demonstrated a reduction in hemorrhagic stroke.

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**Table 3. Summary of Findings for Major Bleeding Events in Landmark Clinical Trials Evaluating DOACs for the Prevention of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation [14–16,27,86]**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Criteria for Major Bleeding Events</th>
<th>DOAC Dose</th>
<th>Comparator Dose</th>
<th>DOAC (%)</th>
<th>Comparator (%)</th>
<th>HR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY (Connolly et al)</td>
<td>Reduction in Hb ≥ 2.0 g/L Transfusion ≥ 2 units blood Symptomatic bleeding in a critical area or organ</td>
<td>110 mg twice daily</td>
<td>Warfarin (INR 2–3)</td>
<td>2.7/year</td>
<td>3.4/year</td>
<td>RR 0.80 (0.69–0.93) P = 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg twice daily (INR 2–3)</td>
<td>Warfarin (INR 2–3)</td>
<td>3.1/year</td>
<td>3.4/year</td>
<td>RR 0.93 (0.81–1.07) P = 0.031</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET AF (Patel et al)</td>
<td>ISTH major bleeding* and/or bleeding causing permanent disability</td>
<td>20 mg once daily</td>
<td>Warfarin (INR 2–3)</td>
<td>3.6/year</td>
<td>3.4/year</td>
<td>HR 1.04 (0.90–1.20) P = 0.58</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVERROES (Connolly et al)</td>
<td>ISTH major bleeding*</td>
<td>5 mg twice daily</td>
<td>Aspirin (81 to 324 mg daily)</td>
<td>1.4/year</td>
<td>1.2/year</td>
<td>HR 1.13 (0.74–1.75) P = 0.57</td>
</tr>
<tr>
<td>ARISTOTLE (Granger et al)</td>
<td>ISTH major bleeding*</td>
<td>5 mg twice daily</td>
<td>Warfarin (INR 2–3)</td>
<td>2.1/year</td>
<td>3.1/year</td>
<td>HR 0.69 (0.60–0.80) P &lt; 0.001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE-TIMI 48 (Giugliano et al)</td>
<td>ISTH major bleeding*</td>
<td>60 mg daily</td>
<td>Warfarin (INR 2–3)</td>
<td>2.75/year</td>
<td>3.43/year</td>
<td>HR 0.8 (0.71–0.91) P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg daily</td>
<td>Warfarin (INR 2–3)</td>
<td>1.6/year</td>
<td>3.43/year</td>
<td>HR 0.47 (0.41–0.55) P &lt; 0.001</td>
</tr>
</tbody>
</table>

Hb = hemoglobin; ISTH = International Society on Thrombosis and Haemostasis.

*ISTH major bleeding is defined as one of the following three: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intracranial, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

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**TSOAC Use in Elderly Patients**

**Pharmacokinetic Evaluations**

Several pharmacokinetic studies have evaluated the influence of age on DOAC disposition. In a study evaluating the influence of age on apixaban disposition, the area under the concentration-time curve to infinity was 32% higher in the elderly (aged 65 years or older) compared to the younger subjects (< age 40 years) [38]. These data provide the rationale for dosage adjustment in individuals aged 80 years or older with either low body mass (weight less than or equal to 60 kg) or renal impairment (serum creatinine 1.5 mg/dL or higher). In a pharmacokinetic study evaluating dabigatran in patients > 65
years of age, the time to steady state ranged from 2 to 3 days, correlating to a half-life of 12 to 14 hours, and peak concentrations (256 ng/mL females, 255 ng/mL males) were reached after a median of 3 hours (range, 2.0–4.0 hours) [39]. These data suggest a 1.7- to twofold increase in bioavailability. The area under the curve of rivaroxaban was significantly higher in subjects > 75 years versus subjects 18-45 years, while total and renal clearance were decreased [40]. However, the time to maximum factor Xa inhibition and C max were not influenced by age.

**Clinical Evaluations**

Although DOACs offer advantages over warfarin [41], there is still no assurance regarding the promise of reduced or similar risk of bleeding with DOACs compared with warfarin in the geriatric population. Generalizability of bleeding rates reported in landmark studies leads to underestimating the risk of bleeding in geriatric patients [42]. For example, in one case series 67% of the bleeding complications with dabigatran were in patients ≥ 80 years old [43]. Furthermore, although subgroup analyses were performed evaluating geriatric patients in the landmark studies, these analyses are inherently biased. First, they represent post-hoc analyses and are not adequately powered. Second, geriatric patients included in landmark studies may have lower CHADS2 scores compared to those seen in clinical practice. Third, patients with severe renal dysfunction (ie, CrCl < 25–30 mL/min) were excluded from many landmark studies. However, several large observational studies have found that the DOACs pose no disproportionate risk of bleeding the geriatric population versus warfarin [44–46]. A review of major bleeding complications reported from landmark clinical trials are summarized Table 3 [29–31,47–50]. Figure 1 depicts the hazard ratios for stroke and major hemorrhage reported in geriatric subgroup analyses in the landmark studies [29–31,44–46]. Below we describe geriatric subgroup data for each DOAC. Analyses of geriatric subgroups are yet to be published in full for edoxaban.

### Table 4. Age Subgroup Analysis of Major Bleeding in Phase 3 Clinical Trials Comparing DOACs with Warfarin in Patients with Atrial Fibrillation [28–31,56]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Age Group</th>
<th>n/N</th>
<th>%/yr</th>
<th>n/N</th>
<th>%/yr</th>
<th>HR (95% CI); P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>&lt; 75</td>
<td>138/3661</td>
<td>1.89</td>
<td>215/3592</td>
<td>3.04</td>
<td>0.62 (0.50–0.77); P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>204/2354</td>
<td>4.43</td>
<td>206/2430</td>
<td>4.37</td>
<td>1.01 (0.83–1.23); P interaction &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>&lt; 80</td>
<td>244/5041</td>
<td>2.43</td>
<td>331/5028</td>
<td>3.35</td>
<td>0.72 (0.61–0.85); P interaction = 0.0090</td>
</tr>
<tr>
<td></td>
<td>≥ 80</td>
<td>98/974</td>
<td>5.24</td>
<td>90/994</td>
<td>4.68</td>
<td>1.13 (0.85–1.50)</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>&lt; 75</td>
<td>153/3602</td>
<td>2.12</td>
<td>215/3592</td>
<td>3.04</td>
<td>0.70 (0.57–0.86); P interaction &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>246/2474</td>
<td>5.10</td>
<td>206/2430</td>
<td>4.37</td>
<td>1.18 (0.98–1.42)</td>
</tr>
<tr>
<td></td>
<td>&lt; 80</td>
<td>273/5017</td>
<td>2.73</td>
<td>331/5028</td>
<td>3.35</td>
<td>0.81 (0.69–0.96); P interaction = 0.0017</td>
</tr>
<tr>
<td></td>
<td>≥ 80</td>
<td>126/1059</td>
<td>6.23</td>
<td>90/994</td>
<td>4.68</td>
<td>1.35 (1.03–1.77)</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD*</td>
<td>&lt; 80</td>
<td>59/1646</td>
<td>2.21</td>
<td>59/1642</td>
<td>2.16</td>
<td>1.02 (0.71–1.46)</td>
</tr>
<tr>
<td></td>
<td>65–75</td>
<td>133/2777</td>
<td>3.04</td>
<td>148/2781</td>
<td>3.34</td>
<td>0.94 (0.73–1.21)</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>203/2688</td>
<td>5.16</td>
<td>179/2702</td>
<td>4.47</td>
<td>1.11 (0.91–1.34); P interaction = 0.33</td>
</tr>
<tr>
<td>Apixaban 5 mg BID†</td>
<td>&lt; 65</td>
<td>56/2723</td>
<td>1.17</td>
<td>72/2732</td>
<td>1.51</td>
<td>Not reported; P interaction = 0.64</td>
</tr>
<tr>
<td></td>
<td>65–75</td>
<td>120/3529</td>
<td>1.99</td>
<td>166/3501</td>
<td>2.82</td>
<td>Not reported; P interaction = 0.64</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>151/2836</td>
<td>3.33</td>
<td>224/2819</td>
<td>5.19</td>
<td>Not reported; P interaction = 0.64</td>
</tr>
<tr>
<td>Edoxaban 60/30 mg QD</td>
<td>&lt; 80</td>
<td>n = 5835Δ</td>
<td>1.10</td>
<td>n = 5817Δ</td>
<td>1.19</td>
<td>0.83 (0.71–0.96); P interaction = 0.83</td>
</tr>
<tr>
<td></td>
<td>≥ 80</td>
<td>n = 1177Δ</td>
<td>1.31</td>
<td>n = 1195Δ</td>
<td>2.02</td>
<td>0.75 (0.58–0.98); P interaction = 0.54</td>
</tr>
</tbody>
</table>

*Reduced dose of rivaroxaban (15 mg QD) was used for patients with an eGFR 30-50 mL/min.
†Reduced dose of apixaban 2.5 mg BID was used for patients with 2 of the following criteria: ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 133 µmol/L (1.5 mg/dL).
Δ Analysis did not report total number (N) of elderly patients (≥ 80 or < 80 years of age) that experienced a major bleeding event.
**Direct Oral Anticoagulants**

![Graph showing performance of direct oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation in patients aged 75 years or older. HR = hazard ratio.*P < 0.05; †Medicare data published in abstract form only; no confidence interval provided, no hazard ratio provided for hemorrhage.](image)

**Dabigatran**

In a post-hoc analysis of the RE-LY trial, Eikelboom and colleagues found that patients 75 years of age and older treated with dabigatran 150 mg twice daily had a greater incidence of GI bleeding irrespective of renal function compared with those on warfarin (1.85%/year vs. 1.25%/year; *P < 0.001*) [29]. A higher risk in major bleeding also was seen in dabigatran patients (5.10% versus 4.37%; *P = 0.07*). As a result, the 2012 Beer’s Criteria lists dabigatran as a potentially inappropriate medication. An analysis was conducted of 134,414 elderly Medicare patients (defined as age > 65 years) with 37,587 person-years of follow-up who were treated with dabigatran or warfarin [44]. Approximately 60% of patients included in the analysis were over age 75 years. Dabigatran was associated with a significant reduction in ischemic stroke: HR 0.80 (CI 0.67–0.96); intracranial hemorrhage: HR 0.34 (CI 0.26–0.46); and death: HR 0.86 (CI 0.77–0.96) when compared with warfarin. As in the Eikelboom study, major gastrointestinal bleeding was significantly increased with dabigatran (HR, 1.28 [95% CI, 1.14–1.44]).

**Rivaroxaban**

For rivaroxaban, a subgroup analysis of patients ≥ 75 years in the ROCKET-AF trial reported similar rates of major bleeding (HR, 1.11; 95% CI, 0.92–1.34) with rivaroxaban compared with warfarin [31]. Clinically relevant non-major bleeding was significantly higher for patients aged ≥ 75 years compared with patients aged < 75 years (*P = 0.01*).

**Apixaban**

Halvorsen and colleagues found that age did not influence the benefits of apixaban in terms of efficacy and safety [47]. In the cohort of patients aged 75 years or older, major bleeding was significantly reduced compared to warfarin (HR, 0.64; 95% CI, 0.52–0.79). The safety benefits persisted even in the setting of age greater than 75 years and renal impairment. A significant reduction in major bleeding (HR, 0.35; 95% CI, 0.14–0.86) was seen in elderly patients with a CrCl; ≤ 30 mL/min (*n = 221*) treated with apixaban versus warfarin. Similarly, in elderly patients with a CrCl 30 to 50 mL/min (*n = 1898*) a significant reduction in major bleeding was reported.
(HR, 0.53; 95% CI, 0.37–0.76). These data are consistent with a meta-regression analysis that found a linear relationship between the relative risk of major bleeding and the magnitude of renal excretion for the DOACs ($r^2=0.66$, $P = 0.03$) [48]. In this analysis, apixaban had the most favorable outcomes in terms of major bleeding compared to the other DOACs and also has the least dependence on renal function for clearance. In a pooled analysis of data from landmark trials, Ng and colleagues found that in elderly patients (defined as age > 75 years) with nonvalvular AF, only apixaban was associated with a significant reduction in both stroke and major hemorrhage (Figure 1) [49,50].

**Edoxaban**

Kato and colleagues performed a subgroup analysis of patients aged 75 years or older enrolled in the ENGAGE TIMI 48 study [50]. Currently the results are only published in abstract form. Regardless of treatment, the risk of major bleeding and stroke significantly increased with age ($P < 0.001$). An absolute risk reduction in major bleeding was reported with both 60 mg and 30 mg of edoxaban versus warfarin (4.0%/year and 2.2%/year versus 4.8%/year, respectively; no $P$ value provided).

**Therapeutic Drug Monitoring**

Collectively, the data on assessment of the anticoagulant activity of DOACs using coagulation assays is evolving. These tests include but are not limited to prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin clotting time (TT), dilute TT, activated clotting time (ACT), anti factor Xa, and ecarin clotting time (ECT) assays. Although routine monitoring is not desirable, the ability to assess degree of anticoagulation in select patient populations may prove beneficial. Future studies are essential to confirm whether assessing DOAC activity using coagulation assays in vulnerable populations such as the elderly improves clinical outcomes. Several reviews on this subject matter have been published [51–55]. The reader is encouraged to review these data as there are significant limitations to currently available assays and incorrect interpretation may lead to suboptimal treatment decisions.

**Renal and Hepatic Dysfunction**

Depending on the specific agents, DOACs renal clearance varies from 27% to 80% [56–59]. Clinical trials often use the Cockcroft-Gault formula (CG) based on actual body weight to estimate renal function. Landmark trials evaluating the DOACs differed in their strategy for estimation of renal function using CG. For example, RE-LY and ROCKET-AF used actual body weight for the estimation of renal function, while ARISTOTLE did not specify which body weight to use. Estimation of renal function or glomerular filtration rate (GFR) by CG is frequently in discordance with actual renal function in the elderly [60]. MDRD (modification of diet in renal disease) and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) are also common estimations that provide an estimate of GFR. In a cross-sectional study, comparing the CG, MDRD, and EPI formulas in a clinical setting, data from potential kidney donors and adult patients who underwent a GFR measurement revealed that MDRD has the smallest mean bias. The influence of age was the absolute bias for estimation of renal function for all formulas. CG is additionally influenced by body weight and body mass index. When compared to CG, MDRD actually reported more accurate predictor of GFR in adults < 70 years old [61]. However, package inserts recommend dose adjustments based on estimation of CrCl using CG formula. This poses a problem in adjusting DOAC doses in elderly patients who are subject to overestimation of renal function with this antiquated equation. Among elderly patients with renal impairment, discordance between estimated and actual renal function was higher for dabigatran and rivaroxaban than for apixaban dosages [61].

Only 27% of apixaban is renally cleared, and the manufacturer does not indicate dose adjustments for patients with renal insufficiency [57]. Therefore, apixaban is the favorable anticoagulant in the elderly population with renal disease. Prescribing information recommends reducing the dose from 5 mg twice daily to 2.5 mg twice daily for nonvalvular AF patients, if patients meet 2 of the following criteria: age ≥ 80 years of age, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL. (Table 5) [57]. In patients with end-stage renal disease (ESRD) maintained on hemodialysis, the recommended dose of apixaban is 5 mg twice daily, unless the patient is ≥ 80 years or has a body weight ≤ 60 kg, in which case the dose should be reduced to 2.5 mg twice daily. Clinicians should consider the source of the aforementioned dosing strategy as patients with a CrCl < 25 mL/min were excluded from the ARISTOTLE study. Dosing in hemodialysis is supported by a small study that showed an increase in AUC of 36% after a single dose. The extent
of drug accumulation is unknown and dialysis only clears a small portion of apixaban (~14%).

Renal excretion of unchanged dabigatran is the predominant pathway for elimination (~80%) [58]. The FDA-approved dosing strategy in the US for dabigatran is 150 mg twice daily in patients with a CrCl ≥ 30 mL/min, 75 mg twice daily in patients with severe renal impairment (CrCl 15–30 mL/min), and is contraindicated in patients with a CrCl < 15 mL/min [58]. By comparison, the Canadian and the European Medicines Agency have listed patients with a CrCl < 30 mL/min (severe renal impairment) as a contraindication for use. The US-approved dosage for severe renal impairment was derived during the approval phase of dabigatran using a simulation pharmacokinetic model [62,63]. The dosage was estimated by pharmacokinetic simulation to provide similar $C_{\text{max}}$ and $C_{\text{min}}$ concentrations compared to the 150 mg twice-daily dosage in moderate renal impairment. Compared to patients with CrCl ≥ 80 mL/min, there was a 1.29- and a 1.47-fold increase in dabigatran trough plasma concentration in the CrCl 50–80 mL/min patients and the CrCl 30–50 mL/min patients, respectively. There have been many postmarketing reports of hemorrhage with dabigatran [36,84,85]. Although reporting bias is likely due to the novelty of the agent, clinicians may take key clinical pearls away from these reports. Patients often had risk factors, including low body weight, renal impairment, and polypharmacy with interacting drugs (eg, amiodarone). These risk factors are also important with the other DOACs.

**Table 5. Summary of Dose Adjustment for Renal and Hepatic Insufficiency for DOACs in Nonvalvular AF [56–59]**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Renal Dosing</th>
<th>Hepatic Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.5 mg twice daily</td>
<td>Child-Pugh Class A: No dose adjustment is required in patients with mild hepatic impairment.</td>
</tr>
<tr>
<td></td>
<td>For patients with <strong>at least 2</strong> of the following:</td>
<td>Child-Pugh Class B: May have intrinsic coagulation abnormalities and limited experience, dosing recommendations cannot be provided.</td>
</tr>
<tr>
<td></td>
<td>• Age ≥ 80 years</td>
<td>Child-Pugh Class C: Not recommended</td>
</tr>
<tr>
<td></td>
<td>• Body weight ≤ 60 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum creatinine ≥ 1.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No dose adjustment of ESRD, except if one of the following patient characteristics (age ≥ 80 years or body weight ≤ 60 kg) is present</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt; 30 mL/min: 150 mg twice daily</td>
<td>No dose adjustment recommended.</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 to 30 mL/min: 75 mg twice daily</td>
<td>Note: Administration in patients with moderate hepatic impairment (Child-Pugh Class B) showed a large inter-subject variability.</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 15 mL/min: contraindicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors: consider reducing dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or ketoconazole. Dose adjustment is not necessary when coadministered with other P-gp inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt; 50 mL/min: 20 mg once daily with evening meal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 15-50 mL/min: 15 mg once daily with evening meal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 15 mL/min: Avoid use</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>CrCl &lt; 15 mL/min: Avoid use</td>
<td>Moderate or severe hepatic impairment (Child-Pugh B or C): Not recommended</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 to ≤ 50 mL/min: 30 mg once</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &gt; 50 to ≤ 95 mL/min: 60 mg once</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &gt; 95 mL/min: Avoid</td>
<td></td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; ESRD = end-stage renal disease; P-gp = P-glycoprotein.
A subgroup analysis of ROCKET-AF evaluating rivaroxaban 15 mg daily in patients with a CrCl of 30–49 mL/min did not identify any differences in endpoints with the exception of fatal bleeding, which occurred less often with rivaroxaban (0.28%/yr vs. 0.74%/yr; \( P = 0.047 \)) [64].

Monitoring of renal function is essential to mitigate the risk of drug accumulation. Clinicians should consider obtaining a baseline renal assessment with annual reassessments in patients with normal (CrCl \( \geq 80 \) mL/min) or mild (CrCl 50–79 mL/min) renal impairment, and 2 to 3 times per year in patients with moderate (CrCl 30–49 mL/min) renal impairment [65]. A summary of renal dose adjustments for DOAC therapy may be found in Table 5 [56–59].

In addition to renal function, hepatic impairment can also affect the metabolism of anticoagulants. Severe hepatic impairment can lead to prolonged PT. Therefore, patients who have liver dysfunction and are treated with anticoagulation have increased risk of hemorrhagic events. Large pivotal trials on the key indications of dabigatran, apixaban, and rivaroxaban excluded patients with significant signs of hepatic impairment. Table 5 provides dosing recommendations for the different DOACs in the setting of hepatic impairment [56–59].

**Polypharmacy and the Potential for Adverse Consequences**

Polypharmacy is defined as concomitantly using multiple medications. The likelihood of an adverse drug reaction increases exponentially with the number of drugs taken, independent of the class of medication [66]. Older adults use over the counter (46%) and herbal supplements (52%) while taking prescription medications and 50% of them are noted to have a drug interaction with anticoagulants. This leads to approximately 1 out of 25 older adults at risk for significant drug-drug interactions [67]. Some DOACs have recommendations for dosage reductions in the setting of advanced age (Table 6). Therefore, it is reasonable to assume that advanced age and drug interactions may place patients at greater risk of treatment failure. Further investigations are needed to understand polypharmacy and drug-drug interactions in geriatric patients [68]; however, clinicians should be aware of the potential pharmacokinetic interactions with DOACs (Table 7) [56–59]. Clinicians should review the patient’s entire medication profile and discontinue any unnecessary medications that may interact with one another if possible. There are several pharmacodynamic interactions that should also be considered. Concomitant use of antiplatelets and NSAIDs with DOACs may increase bleeding risk. In many cases NSAIDs may be discontinued. Patients on dual antiplatelet therapy and an anticoagulant are at an increased risk of bleeding. Clinicians should question the need for dual antiplatelet therapy with anticoagulation. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial suggested that triple therapy (eg, oral anticoagulant plus aspirin plus clopidogrel) is associated with greater risks than benefits in individuals with AF and coronary stents [69, 70].

### Table 6. Review of Dose Recommendations for the Elderly Patient [56–59,82]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Dose for Nonvalvular AF/VTE</th>
<th>Recommended Dose Reduction in Elderly Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>In AF, 110-mg BID should be considered for age 75–79 years [82] 110-mg BID for AF patients ( \geq 80 ) years Note: dabigatran 110 mg is only EMA-approved</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg QD (for VTE, 15 mg BID in first 21 days)</td>
<td>Elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being ~50% higher, mainly due to reduced (apparent) total body weight and renal clearance.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg BID</td>
<td>2.5-mg BID EMA/FDA-approved if 2 or more of: age ( \geq 80 ) years, body weight ( \leq 60 ) kg, sCr ( \geq 1.5 ) mg/dL</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg daily</td>
<td>No dose reductions recommended</td>
</tr>
</tbody>
</table>

EMA = European Medical Association; VTE = venous thromboembolism.
Direct oral anticoagulants

Costs and Cost-Effectiveness of DOACs

With the high burden of AF and the aging population, analysis of cost and value is an important consideration [76]. There are limited publications comparing the cost-effectiveness between the anticoagulation options. However, numerous cost-effectiveness studies have evaluated the individual DOACs [71–79]. Overall, the studies suggest that the DOACs are a cost-effective alternative to warfarin in the general and elderly populations. One analysis reported that dabigatran may not be cost-effective in patients with a low CHADS2 score (≤ 2) [71].

Harrington et al [80] compared the cost-effectiveness of dabigatran, rivaroxaban, and apixaban versus warfarin. This cost-effectiveness study used published clinical trial

Table 7. Clinically Relevant Pharmacokinetic Drug Interactions with DOACs [56–59]

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids, PPIs</strong></td>
<td>Decreased concentration</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
</tr>
<tr>
<td>Should be administered 2 hrs before antacids and PPI</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td></td>
</tr>
<tr>
<td><strong>P-gp inhibitors</strong></td>
<td>Increased concentration</td>
<td>Increased concentration</td>
<td>Increased concentration</td>
<td>Lower concentration</td>
</tr>
<tr>
<td>Reduce dabigatran dose with verapamil</td>
<td>Avoid administration with potent inhibitors</td>
<td>For patients receiving doses greater than 2.5 mg twice daily with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) reduce by 50%. Avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp if patient already taking 2.5 mg twice daily.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid administration with dronedarone</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose adjustment with amiodarone and digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-gp inducers</strong></td>
<td>Increased concentration</td>
<td>Decreased concentration</td>
<td>Decrease concentration</td>
<td>Increased concentration</td>
</tr>
<tr>
<td>Avoid administration with rifampin</td>
<td>Avoid administration with rifampin</td>
<td>Avoid administration with rifampin</td>
<td>Avoid administration with rifampin</td>
<td></td>
</tr>
<tr>
<td>Caution with ketoconazole, clarithromycin, chloramphenicol</td>
<td>Caution with phenytoin, carbamazepine</td>
<td>Caution with phenytoin, carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4 inhibitors</strong></td>
<td>Increased concentration</td>
<td>Increased concentration</td>
<td>Increased concentration</td>
<td>No interaction</td>
</tr>
<tr>
<td>Caution with strong inhibitors</td>
<td>Caution with strong inhibitors</td>
<td>Avoid administration with ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4 inducers</strong></td>
<td>Decreased concentration</td>
<td>Decreased concentration</td>
<td>Decreased concentration</td>
<td>No interaction</td>
</tr>
<tr>
<td>Avoid administration with rifampin</td>
<td>Avoid administration with rifampin</td>
<td>Avoid administration with rifampin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPI = proton pump inhibitors; P-gp = P-glycoprotein; CYP = cytochrome P-450 enzyme.

*P-gp inhibitors: verapamil, amiodarone, dronedarone, digoxin.
†P-gp inducers: rifampin, ketoconazole, chloramphenicol, clarithromycin, phenytoin, carbamazepine.
‡CYP3A4 inhibitors: ketoconazole, clarithromycin, ritonavir.
§CYP3A4 inducers: rifampin.
data to build a decision model, and results indicated that for patients \( \geq 70 \) years of age with an increased risk for stroke, normal renal function, and no previous contraindications to anticoagulant therapy, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were cost-effective substitutes for warfarin for the prevention of stroke in nonvalvular AF [80]. Apixaban was the preferred anticoagulant for their hypothetical cohort of 70-year-old patients with nonvalvular AF, as it was most likely to be the cost-effective treatment option at all willing-to-pay thresholds > $40,000 per quality-adjusted life-year gained [76,81].

Prescription costs may vary depending on payor and level of insurance. If a patient does not have prescription insurance, the annual price of generic warfarin is roughly $200 to $360, depending on dosage. Approximate annual costs for the DOACs are greater than 20 times the cost of warfarin (apixaban $4500, dabigatran $4500, and rivaroxaban $4800) [82]. However, most patients on these medications are over 65 years old and have prescription coverage through Medicare Part D. Of note, patients may have more of a burden if or when they reach the “donut hole” coverage gap. Currently, once patients spend $2960 (for 2015) and $3310 (for 2016) on covered drugs they will fall into the donut hole unless they qualify for additional assistance. At this point Medicare Part D will reimburse 45% of the cost of the newer anticoagulants since generics are currently unavailable.

Figure 2. DOAC selection algorithm for geriatric patients. NVAF = nonvalvular atrial fibrillation; CrCl = creatinine clearance; GI = gastrointestinal; MI = myocardial infarction; ESRD = end-stage renal disease. Refer to Table 5 and Table 6 for dosage recommendations.
As a result, individual affordability may become an issue. Further complicating the scenario is the inability to apply coupon and rebate cards in the setting of government-funded prescription coverage. Clinicians should discuss these issues with their patients to help select the most valuable therapy.

Conclusions and Recommendations
With life expectancy among the elderly continuing to improve, the number of patients requiring chronic anticoagulation will continue to rise. Understanding the strengths and limitations of oral anticoagulants and the literature to support their use is essential to select the most appropriate agent in the geriatric patient. When selecting an anticoagulant strategy, clinicians should consider clinical data, patient factors, and patient preferences. Figure 2 provides a suggested anticoagulant selection pathway to complement the clinical decision process [83,84].

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