Reducing the risk of stroke in elderly patients with non-valvular atrial fibrillation: a practical guide for clinicians

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Abstract: Non-valvular atrial fibrillation (NVAF) significantly contributes to the burden of stroke, particularly in elderly patients. The challenge of optimizing anticoagulation therapy is balancing efficacy and bleeding risk, especially as the same patients at high risk of stroke also tend to be at high risk of bleeding. Treating the elderly patient with NVAF presents special challenges because of their heightened risk for both stroke and bleeding. Despite clinical trial data and evidence-based guidelines, surveys indicate that physicians underuse anticoagulation in older patients for reasons that include overemphasis of bleeding risk, particularly with the increased risk of falling, at the cost of thromboembolic risk. Clinical trial data are now available, and real-world data are emerging, to illustrate the relative merits of the non-vitamin K antagonist oral anticoagulants compared with conventional anticoagulation in the treatment of elderly patients with this condition, and to suggest some subgroups of older patients who may be more suitable candidates for particular agents. Care of elderly patients with NVAF is often complicated by factors including risk of falling, adherence, health literacy, cognitive function, adverse effects, and involvement of caregivers, as well as other factors including the patient–provider relationship and logistical barriers to obtaining medication. Thus, conversations between clinicians and patients, as well as shared decision making, are important. In addition, elderly patients often suffer from comorbidities including hypertension, coronary heart disease, diabetes mellitus, COPD, and/or heart failure, which necessitate the use of multiple concomitant medications, increasing the risk of drug/drug interactions. This review provides an overview of clinical trial data on the use of non-vitamin K anticoagulant agents in elderly populations, and serves as a practical resource for the management of NVAF in the elderly patient.

Keywords: aged, non-vitamin K antagonist oral anticoagulants, stroke, warfarin, bleeding

Introduction

The prevalence of atrial fibrillation (AF) in the US population (estimated at 5.2 million in 2010) is projected to increase to 12.1 million by 2030. While age-adjusted incidence of clinically recognized AF has risen in recent decades, a 1993–2007 Medicare sample found a steady incidence, indicative of the association of AF with an aging population. AF, the most common cardiac arrhythmia, is a significant risk factor for stroke, increasing the risk fivefold.

In analysis of trial data from ~9,000 patients with AF, increasing age was found to be associated with elevated stroke risk (hazard ratio [HR] per decade increase, 1.45; 95% confidence interval [CI] 1.26–1.66). Elderly patients with AF also often suffer from impactful comorbidities, including hypertension, coronary heart disease, diabetes...
Reduced platelet count

HAS-BLED

Age

Prior bleed (2 points)

ATRIA

2

Hypertension (1 point)

Stroke, transient ischemic attack, Vascular disease, Age 65–74 years, Sex category)

CHA

Hypertension (1 point)

Anemia (3 points)

Table 1 Risk scales for predicting stroke and risk of bleeding

<table>
<thead>
<tr>
<th>Stroke risk</th>
<th>Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CHA&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;2&lt;/sub&gt;-VASc&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age ≥75 years (1 point)</td>
<td>Age ≥75 years (2 points), age 65–74 years (1 point)</td>
</tr>
<tr>
<td>History of stroke or TIA (2 points)</td>
<td>Previous stroke/TIA/thromboembolism (2 points)</td>
</tr>
<tr>
<td>Hypertension (1 point)</td>
<td>Hypertension (1 point)</td>
</tr>
<tr>
<td>CHF (1 point)</td>
<td>CHF/left ventricular dysfunction (1 point)</td>
</tr>
<tr>
<td>Diabetes mellitus (1 point)</td>
<td>Diabetes mellitus (1 point)</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) (1 point)</td>
<td>Reduced platelet count or function (1 point)</td>
</tr>
<tr>
<td>Female sex (1 point)</td>
<td>Ethanol abuse (1 point)</td>
</tr>
</tbody>
</table>

Notes: Reprinted from Chest, 137(2), Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. 263–272. Copyright 2010 with permission from Elsevier. Reprinted from Chest, 138(5), Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns H, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. 1093–1100. Copyright 2010, with permission from Elsevier. Abbreviations: ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CHA<sub>2</sub>D<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, transient ischemic attack, Vascular disease, Age 65–74 years, Sex category; CHADS<sub>2</sub>, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke, TIA, or non-central nervous system thromboembolism doubled; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio, Elderly, Drugs/alcohol; HEMORR_HAGES, Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Re-bleeding, Hypertension, Anemia, Genetic factors, Excessive fall risk, and Stroke; INR, international normalized ratio; TIA, transient ischemic attack.
(NOACs) – the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, edoxaban, and apixaban – have been approved by the US Food and Drug Administration (FDA) for reducing the risk of stroke and systemic embolism (SE) in patients with non-valvular AF (NVAF). The aims of this review are to examine current and emerging data regarding the risks of stroke and bleeding in elderly patients with NVAF, to discuss the risk–benefit balance of various treatment options for NVAF in elderly patients, and to review the unique clinical challenges of managing NVAF in patients of advanced age.

Conventional therapy for elderly patients with NVAF

Numerous trials have shown the benefits of warfarin treatment over placebo in patients with NVAF. Antiplatelet therapy has also been shown to reduce the risk of stroke in NVAF patients, albeit less effectively than anticoagulation and with less consistency among studies. Aspirin use continues to be prevalent in patients with AF, including older patients, as aspirin may be associated with lower bleeding risk vs warfarin. Physician surveys identify fear of bleeding risk as the most commonly reported reason for not using anticoagulation in elderly patients.

Despite physicians’ concerns, evidence suggests a generally positive balance of stroke risk and bleeding risk for warfarin in older patients. In 13,559 patients with NVAF (median age 73 years), patients aged ≥85 years were found to obtain particular benefit from VKA therapy, according to an analysis that accounted for both the rate of VKA-associated intracranial hemorrhage (ICH) and the rate of prevented ischemic strokes and systemic embolism. In patients aged ≥85 years receiving a VKA, the adjusted annual rate of thromboembolism was 2.86 events per 100 patients lower and the adjusted annual rate of ICH was 0.35 events per 100 patients higher than those not receiving a VKA; corresponding rates for the entire cohort showed a reduction of 1.04% in thromboembolism and a 0.24% increase in ICH.

Clinical trial data: NOACs in patients with NVAF

In four Phase III trials, patients with NVAF at moderate (CHADS$_2$ score ≥1) to high risk (CHADS$_2$ score ≥2) of stroke were randomly assigned to receive NOAC or VKA treatment. Primary findings from each of the trials are summarized in Table 2. As there are no trials directly comparing the NOACs, and each trial enrolled different baseline populations and used different methodologies, care must be taken when making comparisons between agents.

A total of 18,113 patients (mean CHADS$_2$ score 2.1; mean age 71 years) were randomized to dabigatran 110 or 150 mg or adjusted-dose warfarin in the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran (RE-LY) trial. In revised results from the intent-to-treat analysis, annual rates of stroke or SE in the dabigatran 150 mg group were superior vs warfarin (1.12% vs 1.72%; $P<0.001$), while rates in the dabigatran 110 mg group were comparable to warfarin (1.54% vs 1.72%). In the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), 14,264 patients (mean CHADS$_2$ score 3.5; mean age 73 years) were randomized to rivaroxaban 20 mg once daily (15 mg if creatinine clearance [CrCl] was 30–49 mL/min) or warfarin. Rivaroxaban was noninferior to warfarin in the intent-to-treat analysis (annual rates of stroke/SE of 2.1% vs 2.4%; $P<0.001$ for noninferiority) and superior to warfarin in prespecified analyses of events during treatment (annual rates of 1.7% vs 2.2%; $P=0.02$). The Evaluation of Efficacy and Safety of Edoxaban versus Warfarin in Subjects with Atrial Fibrillation – Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF-TIMI 48) trial randomized 21,105 patients with NVAF (mean CHADS$_2$ score 2.8; median age 72 years) to once-daily edoxaban 60 or 30 mg (in either group, the dose was halved if any of the following applied: estimated CrCl 30–49 mL/min; body weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone) or VKA. Both edoxaban doses demonstrated noninferiority to VKA in reducing the risk of stroke or SE in the primary analysis, including patients in the intent-to-treat population who received study drug during the treatment period (annual rates of 1.61%, 1.18%, and 1.50% for low-dose edoxaban, high-dose edoxaban, and warfarin, respectively); high-dose edoxaban showed a trend toward better efficacy vs warfarin in a prespecified superiority analysis of the intent-to-treat population during the entire study period (1.57% vs 1.80%; $P=0.08$). In Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), 18,201 patients (mean CHADS$_2$ score 2.1; median age 70 years) were randomized to apixaban 5 mg twice daily (2.5 mg doses were used in patients with two or more of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL) or warfarin. Apixaban
Table 2 Results of trials of NOACs for stroke prevention in NVAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RE-LY Dabigatran 110 mg&lt;sup&gt;28,30,31&lt;/sup&gt;</th>
<th>RE-LY Dabigatran 150 mg&lt;sup&gt;28,30,31&lt;/sup&gt;</th>
<th>ROCKET AF Rivaroxaban 20 mg&lt;sup&gt;28&lt;/sup&gt;</th>
<th>ENGAGE AF-TIMI 48 Edoxaban 30 mg&lt;sup&gt;28&lt;/sup&gt;</th>
<th>ENGAGE AF-TIMI 48 Edoxaban 60 mg&lt;sup&gt;28&lt;/sup&gt;</th>
<th>ARISTOTLE Apixaban 5 mg&lt;sup&gt;27&lt;/sup&gt;</th>
<th>AVERROES Apixaban 5 mg&lt;sup&gt;21,24&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
<td>Warfarin, target INR 2.0–3.0</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; (mean)</td>
<td>2.1</td>
<td>2.2</td>
<td>3.5</td>
<td>2.8</td>
<td>2.8</td>
<td>2.1</td>
<td>2.0/2.1</td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>71</td>
<td>72</td>
<td>73</td>
<td>72 (median)</td>
<td>72 (median)</td>
<td>70 (median)</td>
<td>70</td>
</tr>
<tr>
<td>Female</td>
<td>36%</td>
<td>37%</td>
<td>40%</td>
<td>39%</td>
<td>38%</td>
<td>36%</td>
<td>41%</td>
</tr>
<tr>
<td>Prior stroke/TIA Efficacy</td>
<td>20%</td>
<td>20%</td>
<td>55% (includes SE)</td>
<td>28%</td>
<td>28%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Stroke or SE (noninferiority analysis)</td>
<td>1.54 vs 1.71; RR: 0.90 (0.74–1.10); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.11 vs 1.71; RR: 0.65 (0.52–0.81); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PP: 1.7 vs 2.2; HR: 0.79 (0.66–0.96); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mITT: 1.61 vs 1.50; HR: 1.07 (0.87–1.31); P=0.005</td>
<td>mITT: 1.18 vs 1.50; HR: 0.79 (0.63–0.99); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.27 vs 1.60; HR: 0.79 (0.66–0.95); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.6 vs 3.7; HR: 0.45 (0.32–0.62); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke or SE (superiority analysis)</td>
<td>1.54 vs 1.72; RR: 0.89 (0.73–1.09); P=0.27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.12 vs 1.72; RR: 0.65 (0.52–0.81); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.1 vs 2.4; HR: 0.88 (0.75–1.03); P=0.12</td>
<td>2.04 vs 1.80; HR: 1.13 (0.96–1.34); P=0.10</td>
<td>1.57 vs 1.80; HR: 0.87 (0.73–1.04); P=0.08</td>
<td>1.27 vs 1.60; HR: 0.79 (0.66–0.95); P=0.01</td>
<td>1.6 vs 3.7; HR: 0.45 (0.32–0.62); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.12 vs 0.38; RR: 0.31 (0.17–0.56); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10 vs 0.38; RR: 0.26 (0.14–0.49); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.16 vs 0.47; HR: 0.33 (0.22–0.50); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.26 vs 0.47; HR: 0.54 (0.38–0.77); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.24 vs 0.47; HR: 0.51 (0.35–0.75); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.2 vs 0.3; HR: 0.67 (0.24–1.88); P=0.45</td>
<td>0.2 vs 0.3; HR: 0.67 (0.24–1.88); P=0.45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Ischemic or nonspecified: 1.34 vs 1.22; RR: 1.10 (0.88–1.37); P=0.42</td>
<td>Ischemic or nonspecified: 0.93 vs 1.22; RR: 0.76 (0.59–0.97); P=0.03</td>
<td>1.77 vs 1.25; HR: 0.81 (1.19–1.67); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.25 vs 1.25; HR: 1.00 (0.83–1.19); P=0.97</td>
<td>Ischemic or nonspecified: 0.97 vs 1.05; RR: 0.92 (0.74–1.13); P=0.12</td>
<td>1.1 vs 3.0; HR: 0.37 (0.25–0.55); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1 vs 3.0; HR: 0.37 (0.25–0.55); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.82 vs 0.64; RR: 1.29 (0.96–1.75); P=0.09</td>
<td>0.81 vs 0.64; RR: 1.27 (0.94–1.71); P=0.12</td>
<td>0.89 vs 0.75; HR: 1.19 (0.95–1.49); P=0.13</td>
<td>0.70 vs 0.75; HR: 0.94 (0.74–1.19); P=0.60</td>
<td>0.53 vs 0.61; HR: 0.88 (0.66–1.17); P=0.37</td>
<td>0.8 vs 0.9; HR: 0.86 (0.50–1.48); P=0.59</td>
<td>0.8 vs 0.9; HR: 0.86 (0.50–1.48); P=0.59</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.75 vs 4.13; RR: 0.91 (0.80–1.03); P=0.13</td>
<td>3.64 vs 4.13; RR: 0.88 (0.77–1.00); P=0.051</td>
<td>3.80 vs 4.35; HR: 0.87 (0.79–0.96); P=0.006</td>
<td>3.99 vs 4.35; HR: 0.92 (0.83–1.01); P=0.08</td>
<td>3.52 vs 3.94; HR: 0.89 (0.80–0.98); P=0.047</td>
<td>3.5 vs 4.4; HR: 0.79 (0.62–1.02); P=0.07</td>
<td>3.5 vs 4.4; HR: 0.79 (0.62–1.02); P=0.07</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2.43 vs 2.69; RR: 0.90 (0.77–1.06); P=0.21</td>
<td>2.28 vs 2.69; RR: 0.85 (0.72–0.99); P=0.04</td>
<td>CV death: 2.71 vs 3.17; HR: 0.85 (0.76–0.96); P=0.008</td>
<td>CV death: 2.74 vs 3.17; HR: 0.86 (0.77–0.97); P=0.013</td>
<td>CV death: 1.80 vs 2.02; HR: 0.89 (0.76–1.04); P=NS</td>
<td>2.7 vs 3.1; HR: 0.87 (0.65–1.17); P=0.37</td>
<td>2.7 vs 3.1; HR: 0.87 (0.65–1.17); P=0.37</td>
</tr>
<tr>
<td>Safety</td>
<td>Major bleeding 2.92 vs 3.61; RR: 0.80 (0.70–0.93); P=0.003</td>
<td>3.40 vs 3.61; RR: 0.94 (0.82–1.08); P=0.41</td>
<td>SOT: 1.61 vs 3.43; HR: 0.47 (0.41–0.55); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SOT: 2.75 vs 3.43; HR: 0.80 (0.71–0.91); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SOT: 2.13 vs 3.09; HR: 0.69 (0.60–0.80); P&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 vs 1.2; HR: 1.13 (0.74–1.75); P=0.57</td>
<td>1.4 vs 1.2; HR: 1.13 (0.74–1.75); P=0.57</td>
</tr>
</tbody>
</table>
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ALL columns show NOAC vs warfarin except AVERROES, which compared apixaban vs aspirin. All data are presented as annual rates per 100 patients and RRs/HRs with 95% confidence intervals. All analyses were performed in intent-to-treat populations unless otherwise specified.

Fifteen milligrams daily for those with moderately impaired renal function (CrCl 30–49 mL/min). The 2,950 (20.7%) patients with CrCl 30–49 mL/min had a mean age of 79 years.

Dose of edoxaban 30 or 60 mg daily or placebo was halved if any of the following characteristics were present at the time of randomization or during the study: estimated CrCl 30–50 mL/min; body weight <60 kg; or serum creatinine ≥1.5 mg/dL (133 μmol/L). A total of 6% of the patients in the apixaban group and 7% in the aspirin group received 2.5 mg twice a day according to protocol. A daily dose of 81 mg of aspirin or aspirin placebo was used in 65% of patients in the apixaban group and 64% in the aspirin group. Based on the full-analysis-set an additional 2.5 mg daily of apixaban was administered to patients with two or more of the following: age ≥75 years; diabetes mellitus; prior stroke, TIA, or non-central nervous system thromboembolism; age $≥$80 years; body weight $<60$ kg; or serum creatinine $≥1.5$ mg/dL (133 μmol/L).

In subgroups aged 75 years, the annualized rate of major bleeding for dabigatran 110 mg was 1.15% (95% CI 0.93–1.22) for dabigatran 150 mg vs warfarin; in patients aged 75 years or older subgroup, both doses of dabigatran were associated with lower risks of major bleeding compared with warfarin in those aged $<75$ years (RR, 0.62 [95% CI 0.50–0.77] and 0.70 [95% CI 0.57–0.86] for dabigatran 110 and 150 mg, respectively, vs warfarin). However, in the older subgroup, both doses of dabigatran were associated with more was superior to warfarin in the primary intent-to-treat analysis of the primary end point of stroke or SE (1.27% vs 1.60% annually; $P=0.01$).

In RE-LY, dabigatran 110 mg reduced the risk of major bleeding vs VKA (2.92% vs 3.61% annually; $P=0.003$), while dabigatran 150 mg was associated with a similar rate of major bleeding vs VKA (3.40% vs 3.61%; $P=0.41$).

Whereas major bleeding was the primary end point in other Phase III studies of NOACs in patients with NVAF, the principal safety end point in ROCKET AF was a composite of major and clinically relevant nonmajor bleeding; annual rates were 14.9% for rivaroxaban 20 mg and 14.5% for warfarin ($P=0.44$).

Annualized rates of major bleeding specifically were 1.61%, 2.75%, and 3.43% for low-dose edoxaban, high-dose edoxaban, and warfarin, respectively ($P<0.001$ for superiority for both edoxaban doses vs warfarin) in ENGAGE AF-TIMI 48. In ARISTOTLE, apixaban 5 mg was associated with reduced major bleeding vs warfarin (2.13% vs 3.09% annually; $P<0.001$).

In an additional study, 5,599 patients with NVAF (mean CHADS$_2$ score 2.1; mean age 70 years) who were unsuitable for VKA therapy were randomized to apixaban or aspirin. Apixaban was superior in reducing the risk of the primary outcome of stroke or SE (annual rates were 1.6% and 3.7% for apixaban and aspirin, respectively; $P<0.001$). The risk of major bleeding was similar between apixaban and aspirin (1.4% and 1.2% per year in the apixaban and aspirin groups, respectively).
Figure 1: Rates of stroke or systemic embolism by age subgroup in Phase III trials of NOACs in patients with NVAF.

Notes: Values represent rates per 100 patient-years. Data from the following studies.27,29,31–33

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CHADS2, Congestive heart failure, Hypertension, Age \( \geq 75 \) years, Diabetes mellitus, prior Stroke, TIA, or non-central nervous system thromboembolism doubled; ENGAGE AF-TIMI 48, Evaluation of Efficacy and Safety of Edoxaban versus Warfarin in Subjects with Atrial Fibrillation – Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE, systemic embolism; TIA, transient ischemic attack.

Figure 2: Rates of major bleeding by age subgroup in Phase III trials of NOACs in patients with NVAF.

Notes: \( p < 0.05 \) for interaction between age and treatment. Values represent rates per 100 patient-years. Data from the following studies.27,29,31–33

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CHADS2, Congestive heart failure, Hypertension, Age \( \geq 75 \) years, Diabetes mellitus, prior Stroke, TIA, or non-central nervous system thromboembolism doubled; ENGAGE AF-TIMI 48, Evaluation of Efficacy and Safety of Edoxaban versus Warfarin in Subjects with Atrial Fibrillation – Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE, systemic embolism; TIA, transient ischemic attack.
Table 3  Efficacy and safety results (patients aged ≥75 years) in trials of NOACs for reduction in the risk of stroke in NVAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RE-LY</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ENGAGE AF-TIMI 48</th>
<th>ENGAGE AF-TIMI 48</th>
<th>ARISTOTLE</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran 110 mg</td>
<td>Dabigatran 150 mg</td>
<td>Rivaroxaban 20 mg</td>
<td>Edoxaban 30 mg</td>
<td>Edoxaban 60 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (aged ≥75 years)</td>
<td>7,258</td>
<td>6,229</td>
<td>8,474</td>
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<td>Comparator</td>
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<td>INR 2.0–3.0</td>
<td>INR 2.0–3.0</td>
<td>INR 2.0–3.0</td>
<td>INR 2.0–3.0</td>
<td>INR 2.0–3.0</td>
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<td>Efficacy</td>
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<td>Stroke or SE</td>
<td>1.89 vs 2.14; RR:</td>
<td>1.43 vs 2.14; RR:</td>
<td>2.29 vs 2.85; HR:</td>
<td>2.55 vs 2.31</td>
<td>1.91 vs 2.31</td>
<td>1.56 vs 2.19; HR:</td>
<td>0.71 (0.53–0.95)</td>
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<tr>
<td></td>
<td>0.88 (0.66–1.17)</td>
<td>0.67 (0.49–0.90)</td>
<td>0.80 (0.63–1.02)</td>
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<td>2.0 vs 6.1; HR:</td>
<td>0.33 (0.20–0.54)</td>
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<td>Stroke, SE, vascular death</td>
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<td>5.27 vs 5.74; HR:</td>
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<td></td>
<td>0.92 (0.78–1.087)</td>
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<tr>
<td>Stroke, SE, MI, vascular death</td>
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<td></td>
<td>6.07 vs 6.68; HR:</td>
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<td></td>
<td></td>
<td></td>
<td>0.91 (0.78–1.06)</td>
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<tr>
<td>Hemorrhagic stroke</td>
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<td>0.34 vs 0.49; HR:</td>
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<td>0.70 (0.39–1.25)</td>
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<td>Ischemic stroke</td>
<td>1.71 vs 1.95; HR:</td>
<td>0.88 (0.67–1.16)</td>
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<td>1.6 vs 5.0; HR:</td>
<td>0.33 (0.18–0.56)</td>
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<tr>
<td>Stroke (undetermined)</td>
<td>0.09 vs 0.16; HR:</td>
<td>0.55 (0.19–1.65)</td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>5.42 vs 5.97; HR:</td>
<td>0.91 (0.77–1.07)</td>
<td>0.71 (0.50–0.99)</td>
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<tr>
<td>Safety</td>
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<tr>
<td>Major bleeding</td>
<td>4.43 vs 4.37; RR:</td>
<td>5.10 vs 4.37; RR:</td>
<td>4.86 vs 4.40; HR:</td>
<td>2.26 vs 4.83</td>
<td>4.01 vs 4.83</td>
<td>3.33 vs 5.19; HR:</td>
<td>2.6 vs 2.2; HR:</td>
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<tr>
<td></td>
<td>1.01 (0.83–1.23)</td>
<td>1.18 (0.98–1.42)</td>
<td>1.11 (0.92–1.34)</td>
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<td>0.64 (0.52–0.79)</td>
<td>1.21 (0.69–2.12)</td>
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<td>Hb drop</td>
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<td>3.85 vs 2.98; HR:</td>
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<td></td>
<td></td>
<td></td>
<td>1.29 (1.03–1.61)</td>
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<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td>2.28 vs 1.86; HR:</td>
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<td></td>
<td></td>
<td></td>
<td>1.23 (0.93–1.64)</td>
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<td>Clinical organ</td>
<td></td>
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<td>1.07 vs 1.42; HR:</td>
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<td>0.75 (0.52–1.08)</td>
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<td>Fatal bleeding</td>
<td></td>
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<td>0.28 vs 0.61; HR:</td>
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<td>0.45 (0.23–0.87)</td>
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<tr>
<td>Intracranial hemorrhage</td>
<td>0.37 vs 1.00; RR:</td>
<td>0.41 vs 1.00; RR:</td>
<td>0.66 vs 0.83; HR:</td>
<td></td>
<td></td>
<td>0.43 vs 1.29; HR:</td>
<td>0.6 vs 0.7; HR:</td>
</tr>
<tr>
<td></td>
<td>0.37 (0.21–0.64)</td>
<td>0.42 (0.25–0.70)</td>
<td>0.80 (0.50–1.28)</td>
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<td>0.34 (0.20–0.57)</td>
<td>0.84 (0.28–2.41)</td>
</tr>
<tr>
<td>Major or CRNM bleeding</td>
<td>19.83 vs 17.55; HR:</td>
<td>1.13 (1.02–1.25)</td>
<td></td>
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<td>6.7 vs 5.3; HR:</td>
<td>1.26 (0.88–1.80)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>2.19 vs 1.59; RR:</td>
<td>2.80 vs 1.59; RR:</td>
<td>1.39 (1.03–1.98)</td>
<td>1.79 (1.35–2.37)</td>
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<tr>
<td></td>
<td>1.39 (1.03–1.98)</td>
<td>1.79 (1.35–2.37)</td>
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<tr>
<td>Extracranial hemorrhage</td>
<td>4.10 vs 3.44; RR:</td>
<td>4.68 vs 3.44; RR:</td>
<td>1.20 (0.97–1.48)</td>
<td>1.39 (1.13–1.70)</td>
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<tr>
<td></td>
<td>1.20 (0.97–1.48)</td>
<td>1.39 (1.13–1.70)</td>
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</table>

(Continued)
Table 3 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RE-LY</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ENGAGE AF-TIMI 48</th>
<th>ENGAGE AF-TIMI 48</th>
<th>ARISTOTLE</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran 110 mg</td>
<td>Dabigatran 150 mg</td>
<td>Rivaroxaban 20 mg</td>
<td>Edoxaban 30 mg</td>
<td>Edoxaban 60 mg</td>
<td>Apixaban 5 mg</td>
<td>Apixaban 5 mg</td>
</tr>
<tr>
<td>Non-GI extracranial hemorrhage</td>
<td>2.00 vs 1.95; RR: 1.02 (0.76–1.36)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
<td>2.26 vs 1.95; RR: 1.16 (0.88–1.53)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
<td>23.5 vs 33.7; HR: 0.71 (0.56–0.89)</td>
</tr>
<tr>
<td>Net clinical events</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
<td>8.91 vs 10.9; HR: 0.82 (0.72–0.93)</td>
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</tbody>
</table>

Notes: All columns show NOAC vs warfarin except AVERROES, which compared apixaban vs aspirin. All data are presented as annual rates per 100 patients and RRs/HRs with 95% confidence intervals. Population numbers represent subjects in the total randomized population who were aged ≥75 years at baseline. Nineteen milligrams daily for those with moderately impaired renal function (CrCl 30–49 mL/min). The 2,950 (20.7%) patients with CrCl 30–49 mL/min had a mean age of 79 years. For patients in either group, dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated CrCl 30–50 mL/min; body weight ≤60 kg; or the concomitant use of verapamil, quinidine, or drotaridone. A reduced dose of apixaban 2.5 mg twice daily or placebo was administered in 790 patients ≥75 years of age (13.9% of patients ≥75 years). A reduced dose of apixaban (2.5 mg twice daily) was used throughout the study for patients who met two of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L). A total of 6% of the patients in the apixaban group and 7% in the aspirin group received 2.5 mg twice a day according to protocol. A daily dose of 81 mg of aspirin or aspirin placebo was used in 65% of patients in the apixaban group and 64% in the aspirin group. No significant interaction was seen between treatment effect and age, body weight, or renal function. A reduced dose of apixaban was used in patients aged ≥75 years (HR 0.71 [95% CI 0.56–0.89]) compared with patients aged <75 years (HR 0.95 [95% CI 0.76–1.20]). The US prescribing information for dabigatran (150/75 mg tablets) notes the efficacy end point of stroke or SE (apixaban vs warfarin) was 1.16 (95% CI 0.77–1.73) in patients aged ≥75 years. In an analysis from Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), apixaban was more efficacious than aspirin for reducing stroke risk in patients aged ≥75 years (HR 0.71 [95% CI 0.56–0.89]). In patients aged ≥75 years, the respective HRs in these subgroups defined according to age (<75 or ≥75 years) were: 1.11 (95% CI 0.92–1.30) in the ≤75 years and 1.11 (95% CI 0.92–1.30) in the ≥75 years age group. The HR for stroke/SE was 0.80 (95% CI 0.53–0.97) in patients aged ≥75 years (HR 0.95 [95% CI 0.76–1.20]) vs patients aged <75 years (HR 0.95 [95% CI 0.76–1.20]). The HR for stroke/SE was 0.35 (95% CI 0.21–0.59) in patients aged ≥75 years (HR 0.35 [95% CI 0.21–0.59]) vs patients aged <75 years (HR 0.35 [95% CI 0.21–0.59]).
Special clinical considerations in anticoagulation for the elderly patients with NVAF

Comorbidities

Additional factors complicating anticoagulation of elderly patients with NVAF include the frequent presence of multiple comorbidities. In a sample of almost 4 million patients hospitalized for AF (70% >65 years of age; 53% female), the most frequent comorbidities were hypertension (60%), diabetes mellitus (22%), and COPD (20%). Over the time observed (2000–2010), the comorbidity that most increased in prevalence was renal failure, which reached 12% by 2010. Among patients with AF, the prevalence of chronic kidney disease (CKD) increases with age, and the addition of CKD as a comorbidity is associated with increased risk of stroke or SE and of bleeding. Patients with NVAF and renal disease have been found to be more likely to experience bleeding when treated with either warfarin or aspirin compared with those with NVAF only.42

NOAC metabolism is altered to varying degrees in patients with renal impairment, while renal clearance is considered to be a minor determinant of anticoagulant response to warfarin, and no warfarin dosage adjustment is necessary for patients with renal impairment.16 Patient characteristics related to renal and hepatic function and age may influence the choice of NOAC or warfarin use; the potential impact of these characteristics is outlined in Table 4.43–46 Elderly patients in general are subject to changes in kidney function, which leave them vulnerable to acute renal failure provoked by causes including dehydration, surgery, sepsis, and radiocontrast procedures.43 It should be noted that NVAF is associated not only with the impairment in renal function normally seen in aging patients but also with greater progression of kidney disease. In a cohort of 206,229 adults with CKD (mean age 70.7 [standard deviation 11.0] years), incident AF was associated with a 67% higher relative rate of subsequent end-stage renal disease after adjustment for potential confounders.45

Interactions

The frequent presence of multiple comorbidities in elderly patients often necessitates multiple concomitant medications. In general, drug/drug interactions with NOACs are few compared with potential interactions with warfarin;46 however, clinicians must be aware of a number of conflicts to avoid. Potential drug interactions of concern for patients taking dabigatran and edoxaban include other agents that affect the P-gp transport system.49,50 For apixaban and rivaroxaban, strong dual CYP3A4/P-gp inhibitors or inducers may have relevant potential for interaction.17,18
Risk of falling

Significant predictors of not receiving warfarin in hospitalized patients aged ≥65 years with AF include increased age, cognitive impairment, history of hemorrhage, advanced malignancy, and history of falling. For patients ≥80 years of age, physicians cited risk of falling as the primary factor discouraging them from warfarin use.\(^4\) Retrospective analysis of records from elderly patients with AF or atrial flutter who fell (42,913 on oral anticoagulation vs 334,960 controls) indicated a significantly higher mortality risk in those receiving anticoagulation (6% vs 3.1%; \(P<0.001\)). The increase in risk corresponded to a higher CHA\(_2\)DS\(_2\)-VAsC score; patients with a score of 0–1 showed no additional mortality risk with anticoagulation, while patients with higher scores did show elevated risk.\(^6\) As age ≥75 years by itself receives 2 points in calculating CHA\(_2\)DS\(_2\)-VAsC score,\(^9\) these results suggest that older patients with NVAF receiving anticoagulation may be at elevated mortality risk from falls. Indeed, preinjury warfarin use was seen to increase the odds of ICH by 40% and double 30-day mortality among Medicare beneficiaries with head trauma.\(^44\) Conversations between clinicians and patients and shared decision making are important in light of these data, which provide another factor to include in the difficult balance of risk and benefit in patients at the lower end of the stroke risk continuum.

Caregivers and coordination of care

Caregivers frequently play an essential participatory role in the care of elderly patients; >65 million people in the US provide this service, which for an elderly patient with NVAF may include confirming dosages, transporting to the primary care physician or anticoagulation clinic, and monitoring for signs of bleeding.\(^28\) Caregivers may play essential roles in the coordination of care, as elderly patients with NVAF (who frequently have multiple comorbidities) are treated by an interdisciplinary team. A caregiver may also be important in transitioning between providers, as when an elderly patient with NVAF must move from hospitalization to

### Table 4 Effect of non-modifiable patient characteristics on oral anticoagulant use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran(^1)</th>
<th>Rivaroxaban(^1)</th>
<th>Edoxaban(^2)</th>
<th>Apixaban(^3)</th>
<th>Warfarin(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Dosing recommend</td>
<td>Use reduced dose</td>
<td>Reduce dose to</td>
<td>Not recommended</td>
<td>Reduce dose to</td>
</tr>
<tr>
<td></td>
<td>cannot be provided for those with CrCl &lt;15 mL/min or on dialysis</td>
<td>(15 mg qd) in patients with CrCl 15–50 mL/min</td>
<td>30 mg qd if CrCl 15–50 mL/min</td>
<td>if CrCl &lt;15 mL/min</td>
<td>2.5 mg bid if two or more of the following adjustment were met: age ≥80 years, body weight ≥60 kg, serum creatinine ≥1.5 mg/dL</td>
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<tr>
<td>Hepatic impairment</td>
<td>Administration in patients with moderate hepatic impairment showed large inter-subject variability but no evidence of consistent change in exposure</td>
<td>Avoid use in patients with Child–Pugh B and C hepatic impairment or any degree of hepatic disease associated with coagulopathy</td>
<td>Not recommended in patients with moderate or severe hepatic impairment</td>
<td>Not recommended in patients with severe hepatic impairment</td>
<td>Caution needed in patients with moderate-to-severe hepatic impairment</td>
</tr>
<tr>
<td>Age</td>
<td>Risk of stroke and bleeding increases with age, but risk–benefit profile is favorable in all age groups</td>
<td>Risk of stroke and bleeding increases with age, but risk–benefit profile is favorable in all age groups</td>
<td>Efficacy and safety are similar in elderly and younger patients</td>
<td>Reduce dose to 2.5 mg bid if two or more of the following were met: age ≥80 years, body weight ≥60 kg, serum creatinine ≥1.5 mg/dL</td>
<td>Consider lower initiation and maintenance doses of warfarin in patients ≥60 years</td>
</tr>
</tbody>
</table>

**Abbreviations:** bid, twice daily; CrCl, creatinine clearance; qd, once daily.

Factors such as disease-related knowledge, health literacy, and cognitive function; drug-related factors such as adverse effects and polypharmacy; and other factors including the patient–provider relationship and various logistical barriers to obtaining medications.\(^49\) Warfarin is associated with the need for regular monitoring and dose adjustment to maintain treatment within the therapeutic range (INR 2.0–3.0),\(^16\) and the INR testing at regular visits is used partially as a proxy for adherence to treatment. Although NOACs do not require monitoring,\(^17\)–\(^20\) regular administration is particularly important because of the quick onset/offset of action, making assessment of adherence an important component of follow-up visits. For patients with NVAF, the NOACs apixaban and dabigatran are to be taken twice daily, while rivaroxaban is administered once daily with the evening meal and edoxaban is taken once daily.\(^17\)–\(^20\)

### Monitoring and adherence

Potential barriers to anticoagulation therapy adherence in elderly patients include the following: patient-related
long-term care, requiring an accurate and complete exchange of information.\(^\text{51}\)

**Shared decision making**

In addition to balancing stroke/SE and bleeding risks and taking into account special considerations for the elderly (including risk of falls), the recent introduction of NOACs allows individual preferences regarding convenience to be considered in selecting an anticoagulant regimen for each patient. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend that antithrombotic therapy should be individualized for patients with NVAF based on shared decision making after discussion about the absolute risks and RRs of stroke and bleeding and the patient’s values and preferences.\(^\text{52}\)

**Emergent reversal**

Abundant data testify to the association of advanced age with bleeding risk, which indicates the potential importance of reversal of anticoagulant effect in elderly patients. Although the short half-life of NOACs may decrease the need for immediate reversal, in cases of urgent bleeding or overdose of factor Xa inhibitor, no antidote is readily available, whereas idarucizumab has recently been approved for the reversal of dabigatran,\(^\text{53–55}\) and the activity of warfarin can be reversed by administration of vitamin K.\(^\text{16–20}\) Idarucizumab is a humanized monoclonal antibody fragment indicated in dabigatan-treated patients when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery or urgent procedures and for life-threatening or uncontrolled bleeding.\(^\text{55}\) Idarucizumab received accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. However, continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.\(^\text{55}\) A recombinant protein for the reversal of factor Xa inhibitors\(^\text{56}\) and a small synthetic molecule for the reversal of all the NOACs are currently in development; idarucizumab is the only antidote that has yet received FDA approval.\(^\text{57,58}\) Procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated PCC, and recombinant factor VIIa, although not evaluated in clinical trials, may be considered for reversal of apixaban; activated PCC, recombinant factor VIIa, and/or concentrates of coagulation factors II, IX, or X may be considered for reversal of dabigatran but have not been evaluated in clinical trials; and PCC has partially reversed rivaroxaban-induced prothrombin time prolongation in healthy volunteers.\(^\text{15–19}\) Additionally, activated charcoal reduces absorption of apixaban, and dabigatran may be removed by hemodialysis, although there is no clinical evidence supporting these strategies in response to emergent bleeding.\(^\text{18,19}\)

**Conclusion**

Treating the elderly patients with NVAF presents special challenges for many reasons, including, at the most fundamental level, their heightened risk for both stroke and bleeding. Despite clinical trial data and evidence-based guidelines, surveys indicate that many clinicians continue to underuse anticoagulation in those elderly patients who could receive benefit from it. Although clinical experience with the NOACs is relatively limited vs the familiar characteristics of warfarin, subgroup analyses are now available to illustrate the relative merits of the new agents compared with standard anticoagulation in the treatment of elderly patients with NVAF.

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**Disclosure**

Joanne M Foody, MD, is an employee of Merck & Co. This work was completed when she was a faculty member at Harvard Medical School. At the time of the writing of this article, she was a consultant to Pfizer, Sanofi, Merck, and Janssen. The author reports no other conflicts of interest in this work.

**References**


