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REVIEW

## Atrial Fibrillation in the Elderly

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### ABSTRACT

Atrial fibrillation is increasingly prevalent among older adults. It causes approximately 24% of strokes in patients aged 80 to 89 years. The management of atrial fibrillation is directed at preventing thromboembolism and controlling the heart rate and rhythm. Stroke prevention is most effectively accomplished through administering anticoagulants such as warfarin, although older patients have higher hemorrhagic risk. Cognitive dysfunction, functional impairments, and increased fall risk further complicate warfarin management in elderly patients. The use of risk stratification schemes can help guide the anticoagulation decision, although the benefits of warfarin generally outweigh the risks in most older patients with atrial fibrillation. Pharmacologic rate control has been shown to result in similar outcomes compared with pharmacologic restoration of sinus rhythm and should be the initial therapy for elderly patients. Anti-arrhythmic medications should be selected based on an individual patient's coexisting medical conditions. In symptomatic patients who fail pharmacologic therapy, invasive strategies such as AV nodal ablation may help improve quality of life and symptoms, although such strategies do not obviate the need for antithrombotic therapy. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Anti-arrhythmic; Anticoagulants; Atrial fibrillation; Elderly; Hemorrhage; Rate control; Rhythm control; Stroke

Atrial fibrillation is a signature disease of aging, with a prevalence of about 5% in people aged 65 years and older and affecting approximately 10% of those over the age of 80 years (Figure 1).<sup>1,2</sup> The prevalence of atrial fibrillation is increasing, in part because of the aging of the population.<sup>3</sup> By year 2050, there will be an estimated 5.6 million people in the United States with atrial fibrillation; of these, 50% will be over the age of 80 years.<sup>1</sup> The management of atrial fibrillation focuses on preventing thromboembolism and heart rate and rhythm control.

Nonvalvular atrial fibrillation increases the risk of ischemic stroke by approximately 5-fold and causes an estimated 15% of all strokes in the United States. In people

aged 80 to 89 years, this proportion is even higher, approximately 24%.<sup>3</sup> Strokes occurring from atrial fibrillation result in higher mortality and disability, making the prevention of atrial fibrillation-related stroke an important public health concern. Oral anticoagulants are highly effective in preventing atrial fibrillation-related stroke,<sup>4</sup> but because the oldest patients have both the highest risk for stroke off warfarin and the highest risk for hemorrhage on warfarin, prescribing anticoagulation is a central challenge in treating atrial fibrillation in the elderly. This review addresses the management of atrial fibrillation in older patients, focusing on the risks and benefits of anticoagulation, drug therapy for heart rate and rhythm control, and invasive strategies for controlling atrial fibrillation.

### STROKE PREVENTION IN ATRIAL FIBRILLATION

Multiple randomized trials have convincingly demonstrated the efficacy of oral vitamin K antagonists such as warfarin in reducing the risk of stroke in patients with atrial fibrillation.<sup>4,5</sup> Warfarin reduces stroke risk by about 68% and

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mortality by 33%, and it also appears to prevent the most severe types of strokes.<sup>6</sup>

Despite its efficacy, warfarin's narrow therapeutic window and associated hemorrhagic risks can make anticoagulation management difficult. Optimal anticoagulation intensity, as measured by the International Normalized Ratio (INR), appears to be between 2.0 and 3.0.<sup>7</sup> Low fixed-dose warfarin is ineffective in preventing strokes.<sup>8</sup> Although clinicians may target lower INRs in older patients, it is clear that INRs <2.0 significantly raise the risk for stroke while failing to protect against intracranial hemorrhage.<sup>7,9</sup>

If warfarin is contraindicated, therapy with aspirin provides some protection from stroke, albeit much less than warfarin.<sup>10</sup> Aspirin reduces stroke risk by about 21% and has fewer hemorrhagic complications than warfarin; still, gastrointestinal side effects and bleeding with aspirin remain concerns in older patients. A recent small randomized trial comparing warfarin with aspirin in patients between the ages of 80 and 90 years showed that more patients discontinued aspirin therapy compared with warfarin, mostly due to gastrointestinal side effects.<sup>11</sup>

Investigations into the efficacy of other antithrombotic drugs have thus far failed to identify alternative agents equivalent to warfarin in terms of efficacy and safety. The Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and V trials found that the direct thrombin inhibitor ximelagatran was not inferior to warfarin, but the drug was eventually withdrawn from

the market due to an unacceptably high rate of hepatic toxicity.<sup>12,13</sup> The warfarin arm of the recent Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study found warfarin superior to combined clopidogrel plus aspirin with similar rates of hemorrhagic complications.<sup>14</sup> Although investigations into other antithrombotic agents continue, for now warfarin remains the most effective drug to prevent stroke in atrial fibrillation.

**CLINICAL SIGNIFICANCE**

- Atrial fibrillation management is directed at stroke prevention and heart rate and rhythm control.
- Risk stratification schemes can help guide the anticoagulation decision, although warfarin's benefits generally outweigh its risks.
- Rate and rhythm control result in similar outcomes; rate control is usually the initial therapy for elderly patients.
- Invasive strategies to control atrial fibrillation can improve quality of life but do not obviate the need for antithrombotic therapy.

**BLEEDING COMPLICATIONS IN THE ELDERLY**

The risk for warfarin-associated hemorrhage increases with age,<sup>9,15,16</sup> and the annual rate of significant warfarin-associated hemorrhage ranges from 0.3% to nearly 10% in various patient populations.<sup>17,18</sup> In one large cohort of patients with atrial fibrillation, hospitalization rates for intracranial and extracranial hemorrhage were 0.47% and 0.64% per year, respectively (Figure 2).<sup>16</sup> High anticoagulation intensity and INR variability are risk factors for

hemorrhage, as is the period following warfarin initiation.<sup>18,19</sup> Numerous other risk factors for major hemorrhage have been identified, including prior stroke and gastrointestinal bleeding, hypertension, concomitant aspirin use, anemia, renal insufficiency, neuropsychiatric disease, and malignancy.<sup>9,18-20</sup> Polypharmacy and insufficient education about anticoagulation also have been linked to hemorrhage.<sup>21</sup>

Several risk schemes to predict hemorrhage are available,<sup>22-24</sup> although none thus far specifically predict intracranial hemorrhage, the most lethal complication of warfa-

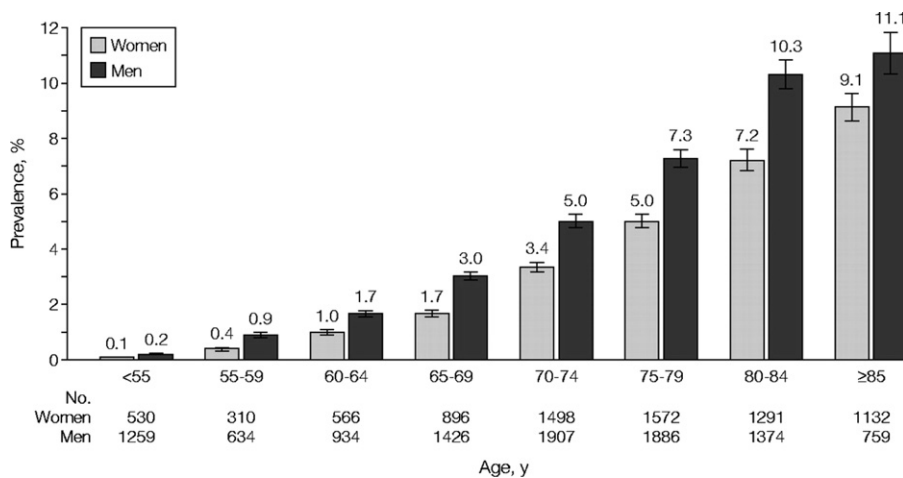
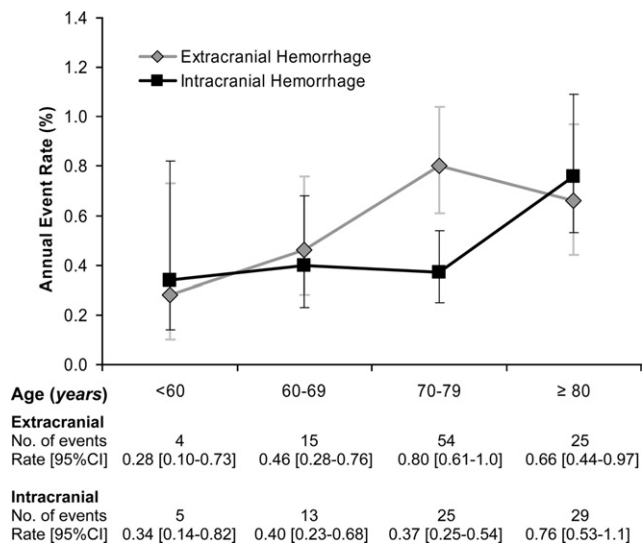


Figure 1 Prevalence of atrial fibrillation by age and sex in the ATRIA cohort. Data from Go et al.<sup>1</sup>



**Figure 2** Annualized rates of warfarin-associated extracranial and intracranial hemorrhage by age in the ATRIA cohort. Adapted from Fang et al.<sup>16</sup>

rin. One decision analysis examined the relative utilities of stroke versus gastrointestinal hemorrhage and concluded warfarin to be the preferred option for the majority of patients with atrial fibrillation unless the annual bleeding risk exceeded 10%.<sup>25</sup>

**PRESCRIBING BASED ON RISK STRATIFICATION**

Older patients are less likely than younger patients to receive anticoagulation and are more likely to be under-anticoagulated.<sup>26,27</sup> Although the use of warfarin in the elderly has been increasing, fewer than half of eligible patients take warfarin.<sup>28,29</sup> Surveys of physicians show that major deterrents to prescribing warfarin are high fall risk, history of bleeding, nonadherence, and dementia, factors that are prevalent among the elderly.<sup>30,31</sup> Physicians generally consider major hemorrhages worse outcomes than do patients<sup>32</sup> and may be disproportionately influenced by prior adverse experiences,<sup>33</sup> making guidelines and decision aids helpful in quantifying the risks and benefits of therapy.

A more sophisticated approach to assessing the risks and benefits of warfarin is through risk factor-guided decision-making. Clinical risk factors for stroke include prior stroke/transient ischemic attack (TIA), older age, female sex, hypertension, left ventricular systolic dysfunction, and diabetes mellitus.<sup>4,34,35</sup> Although imperfect, risk stratification schemes can help guide clinicians toward prescribing warfarin for patients with the highest risks for stroke.<sup>4,34,36,37</sup> One widely cited risk scheme is the CHADS<sub>2</sub> score, which assigns points according to the presence of 5 clinical risk factors: 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and 2 points for prior stroke/transient ischemic attack (Figure 3).<sup>36</sup> For patients with a CHADS<sub>2</sub> score of 0 (annual stroke risk <1%), the absolute benefit of warfarin is not substantially greater than that for aspirin; for patients with a CHADS<sub>2</sub> score of 2

or more (annual stroke risk ≥4%), warfarin is both cost-effective and associated with a net improvement in quality of life.<sup>38</sup> In patients with a CHADS<sub>2</sub> score of 1, it is particularly important to gauge an individual’s preferences for care. Because most patients over age 75 years with atrial fibrillation will have a CHADS<sub>2</sub> score of 2 or higher, it follows that the majority of patients in this age group are appropriate candidates for warfarin. For most older patients, taking warfarin does not appear to significantly reduce quality of life.<sup>39,40</sup>

The type of atrial fibrillation should not affect the anti-coagulation decision. Because paroxysmal atrial fibrillation and atrial flutter are associated with similar stroke rates as chronic atrial fibrillation, the anticoagulation decision in these situations should be guided by the same risk factor schemes.<sup>4,41</sup>

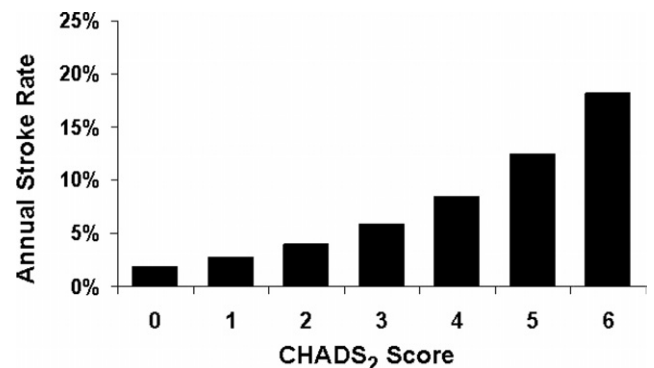
**SPECIAL CONSIDERATIONS REGARDING WARFARIN MANAGEMENT IN THE ELDERLY**

Aside from the known hemorrhagic complications, warfarin poses a number of other challenges in the elderly.

**Warfarin Initiation and Dosing**

Older patients require lower doses of warfarin, are more likely to have INR values outside the therapeutic range, and have delayed return to therapeutic range if supratherapeutic.<sup>42,43</sup> Although studies have not generally found older patients to have significantly worse INR control than younger patients, elderly patients are poorly represented in most studies of warfarin initiation and the most effective starting dose and monitoring schedule is not well delineated.<sup>44</sup> One study showed that the weekly maintenance warfarin dose was 0.4 mg lower for every additional year of age, and the average maintenance dose of warfarin for patients older than 70 was <5 mg.<sup>45</sup> It is thus appropriate to exercise greater caution in the initiation of warfarin in older patients (particularly in women, who require a lower dose of warfarin), by using a starting dose of <5 mg daily without a loading dose.

Studies also do not provide clear evidence regarding the optimal frequency of INR testing during initiation of war-



**Figure 3** Annual stroke risk by CHADS<sub>2</sub> score in 1733 patients with atrial fibrillation not taking warfarin. Data from Gage et al.<sup>36</sup>

farin in elders. The clinical practice guideline from the American Geriatrics Society recommends daily INR testing until stable, followed by INR testing 2 to 3 times a week for 1 to 2 weeks, weekly testing for 1 month, and monthly testing thereafter.<sup>46</sup> Such intensive monitoring may produce significant burden on individual patients, particularly those with mobility impairments or lack of transportation. In these patients, home INR monitoring could have a positive impact.

### Cognitive Impairment

Cognitive and functional impairments have been associated with supratherapeutic INR values and poorer INR control, and psychosocial risk factors for nonadherence have been associated with worse outcomes on warfarin.<sup>47-50</sup> Interestingly, in at least one study older patients were more compliant with warfarin therapy than younger patients.<sup>51</sup> At present, however, there are no guidelines addressing the use of warfarin in patients with cognitive dysfunction or severe functional limitations.

### Fall Risk

High fall risk is an important deterrent to warfarin use,<sup>52</sup> but few studies have quantified the absolute risk associated with falls. Data are limited in part because most studies of anticoagulation excluded patients at high fall risk. One decision analysis estimated that a patient would have to fall nearly 300 times per year for warfarin to no longer be the preferred therapy.<sup>53</sup> Another study of Medicare patients found that hospitalized patients with atrial fibrillation who had documented high fall risk had higher subsequent rates of intracranial hemorrhage.<sup>54</sup> This study concluded that for patients with high fall risk but low stroke risk, anticoagulation was not likely to be beneficial (Table). Conversely, patients with high fall risk at moderate or high risk for stroke still appeared to benefit from warfarin.

Finally, warfarin decreases bone mineral density in experimental studies. One retrospective analysis found that long-term warfarin use increased the risk of osteoporotic fractures by 25%.<sup>55</sup> In this study, high fall risk and neuropsychiatric disease also were risk factors for fractures, emphasizing the importance of close monitoring in cognitively and functionally impaired older adults taking warfarin.

**Table** Hazard Ratio of Warfarin for Composite Outcome (Out-of-Hospital Death or Hospitalization for Stroke, Myocardial Infarction, or Hemorrhage) in 1245 Patients at High Risk for Falls<sup>54</sup>

CHADS <sub>2</sub> score	Hazard ratio (95% CI)	P Value	Recommended Antithrombotic Therapy
0-1	0.98 (0.56-1.72)	.94	Aspirin or nil
2-6	0.75 (0.61-0.91)	.004	Anticoagulant

## NEW APPROACHES TO ANTICOAGULATION MANAGEMENT

Anticoagulation clinics have been shown to improve the proportion of time patients are in therapeutic INR range, although data are less compelling on stroke and hemorrhage outcomes.<sup>56</sup> Multidisciplinary approaches targeted at anticoagulation management also may improve anticoagulation control and outcomes.<sup>57</sup> For patients who have limited mobility or highly variable INR control, home INR testing may provide anticoagulation control that is at least as effective as conventional care.<sup>58,59</sup> At present, however, poor reimbursement for such services is a barrier to widespread dissemination.

### PHARMACOLOGIC RATE AND RHYTHM CONTROL

Randomized trials clearly demonstrate that pharmacologic rhythm control is not superior to rate control in the management of atrial fibrillation, nor do anti-arrhythmic medications prevent ischemic stroke or obviate the need for chronic anticoagulation.<sup>60,61</sup> Rhythm control, in fact, has been associated with higher mortality in older patients<sup>60</sup>; rate control, therefore, is a reasonable initial therapy for older patients to reduce symptoms and prevent tachycardia-induced cardiomyopathy. Beta-blockers, nondihydropyridine calcium channel blockers, and digoxin are the most frequently used medications for rate control in atrial fibrillation,<sup>29</sup> but all may induce excess bradycardia and heart block in elderly patients. Digoxin especially should be used with caution due to potential drug toxicity and is generally best suited for patients with impaired systolic function. The optimal target heart rate is unclear, but one prominent guideline suggests a target resting heart rate of 60 to 80 beats per minute and 90 to 115 beats per minute during moderate exercise.<sup>62</sup>

Anti-arrhythmic drugs to maintain sinus rhythm may be beneficial in patients who remain symptomatic despite effective rate control. However, older patients are at increased risk for proarrhythmia and drug interactions when using anti-arrhythmic drugs, in part due to reduced hepatic and renal clearance and increased likelihood of polypharmacy. Although some evidence supports amiodarone as the most effective agent to maintain sinus rhythm, the choice of drug should depend on patient safety and coexisting medical conditions. Drugs such as flecainide and propafenone increase mortality in patients with structural heart disease,<sup>63</sup> and sotalol and dofetilide should be avoided in patients with renal impairment. Amiodarone appears effective and safe in patients with heart failure, although careful monitoring of thyroid, liver, and pulmonary status is required. In addition, warfarin and digoxin dosages should be reduced when starting amiodarone due to its effect on drug plasma levels. Finally, invasive strategies should be considered in symptomatic patients if pharmacologic therapy fails.

## INVASIVE TREATMENT OF ATRIAL FIBRILLATION IN THE ELDERLY

Invasive strategies for rate and rhythm control of atrial fibrillation, including AV node ablation with pacemaker implantation, catheter-based ablation of atrial fibrillation, and the Cox-Maze procedure, may eventually prove more effective than pharmacologic agents. Currently, these strategies should be considered for patients who remain highly symptomatic despite medical management.

AV node ablation provides effective rate control for patients with rapid ventricular response rates refractory to medical management. The procedure involves transvenous ablation of the AV node with radiofrequency energy and placement of a permanent pacemaker for the resulting complete heart block. The procedure is associated with minimal mortality and morbidity. In a study of 350 patients with atrial fibrillation (mean age  $68 \pm 11$  years), AV node ablation with pacemaker implantation did not alter long-term survival when compared with patients who were treated medically.<sup>64</sup> Because it does not eliminate atrial fibrillation, chronic anticoagulation continues to be indicated.

Percutaneous radiofrequency catheter ablation of atrial fibrillation is based on the observation that focal sources of ectopic beats, usually arising from the pulmonary veins, often initiate atrial fibrillation.<sup>65</sup> The current technique involves circumferential anatomical and electrical isolation of the pulmonary veins from the left atrium.<sup>66</sup> Success rates approach 75% to 85%, with complication rates of 1% to 5% in experienced centers<sup>67</sup>; however, most data are in patients younger than 65 years without heart disease or comorbidities. In general, radiofrequency ablation for chronic atrial fibrillation is less successful than for paroxysmal atrial fibrillation<sup>68</sup> and associated with higher complication rates in older patients with structural heart disease.<sup>69</sup> It is not clear that warfarin can be safely discontinued after ablation therapy, especially in patients over 65 years of age.<sup>70</sup>

The most invasive treatment of atrial fibrillation is the Cox-Maze procedure, which is performed only by experienced cardiothoracic surgeons in selected centers and requires cardiopulmonary bypass. The procedure involves making a series of incisions in the atria, eliminating the electrophysiologic substrate necessary for the development and propagation of atrial fibrillation, followed by atrial reconstruction. Performed since 1988, the procedure has an established cure rate of >90% at 10 years, a perioperative mortality of 2% to 3%, and is associated with a decrease in stroke risk to <1%.<sup>71</sup> Sinus node dysfunction after surgery approaches 10% and often requires implantation of a permanent pacemaker. Because of the increase in complications that may result from prolonged cardiopulmonary bypass time, the procedure usually has not been considered a desirable option for elderly patients. However, a more recent technique (Cox Maze IV), using bipolar radiofrequency energy delivered between the jaws of 2 closely-spaced clamps, reduces the time and expertise required

relative to the original "cut and sew" technique; one study of 100 patients demonstrated 91% freedom from atrial fibrillation at 1 year.<sup>72</sup> Another study showed that, in patients undergoing concomitant cardiac surgery and Cox Maze IV, patients  $\geq 70$  years old had pump times and total operation times similar to younger patients.<sup>73</sup>

## CONCLUSION

Atrial fibrillation is a common medical problem affecting older adults that is associated with significant morbidity and adverse effects on quality of life. The management of atrial fibrillation is directed at preventing thromboembolism and controlling the heart rate and rhythm. Because treatment options for atrial fibrillation involve potential risks and inconveniences, a clear determination of the individual patient's goals of care and preferences should be elicited. Warfarin is highly effective in preventing strokes but cognitive dysfunction, functional impairments, and increased fall risk can complicate warfarin management in elderly patients. The use of risk stratification schemes can help guide the anticoagulation decision, although the net benefit outweighs the harm in most patients with atrial fibrillation. At present there are no risk stratification models that effectively predict warfarin-associated intracranial hemorrhage; such information is needed to help weigh the risks associated with warfarin.

Heart rate control, generally with beta-blockers or calcium channel blockers, is usually considered initial therapy along with stroke prevention. If using anti-arrhythmic drugs, side effects and coexisting medical conditions should be considered. AV node ablation with pacemaker implantation improves heart rate control and quality of life, albeit without altering long-term mortality. The safety and efficacy of catheter ablation of atrial fibrillation in the elderly is unproven and should be undertaken only in highly symptomatic patients with due consideration for potential complications. In patients who require cardiac surgery, a concomitant Cox-Maze procedure, particularly in experienced centers where radiofrequency techniques are available, can be considered.

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