REVIEW

THE AMERICAN JOURNAL of MEDICINE®

New Oral Anticoagulants in Elderly Patients with Atrial Fibrillation

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ABSTRACT

The prevalence of atrial fibrillation increases with age, augmenting the risk of embolic stroke in elderly individuals. Clinical practice guidelines recommend the long-term use of oral anticoagulation in elderly patients with atrial fibrillation to reduce risk of stroke. Until recently, vitamin K antagonists (eg, warfarin) were the only oral anticoagulants available, but using warfarin in elderly patients can be challenging. Newer oral anticoagulants may offer specific benefits and increased convenience for elderly patients, because they have predictable pharmacologic profiles, a rapid onset of action, a wide therapeutic window, no requirement for routine coagulation monitoring, and fewer and better-defined food and drug interactions compared with warfarin. This review highlights the benefits and challenges of warfarin use in elderly patients with atrial fibrillation and discusses potential efficacy and safety benefits for newer oral agents in these patients. The potential for increased rates of major bleeding in the elderly, particularly those with numerous concomitant medications or renal impairment, also is discussed. Practical considerations for the use of long-term anticoagulation in elderly patients also are discussed.

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KEYWORDS: Apixaban; Atrial fibrillation; Dabigatran; Elderly; Oral anticoagulants; Rivaroxaban; Warfarin

More than 75% of strokes occur in individuals aged >65 years, and the risk of stroke more than doubles with each decade of life after 55 years. Morbidity and mortality rates following stroke also are particularly high in older patients.[1]

The prevalence of atrial fibrillation, a common cardiac arrhythmia that significantly increases the risk of embolic stroke, increases with age, from approximately 0.1% in individuals aged <55 years to 9.0% in those aged ≥80 years.[2] As the population ages, the number of individuals with atrial fibrillation in the US is expected to increase from 2.3 million currently to double this number by 2050.[2,3] Compared with persons without atrial fibrillation, those with it have a fivefold increased risk of ischemic stroke.[4] Among the approximately 795,000 Americans who experience a new or recurrent ischemic stroke each year, atrial fibrillation is believed to have a causative role in approximately 20% of cases.[5,6] Atrial fibrillation-related strokes are more severe, are more likely to cause disability or to recur, and carry a higher mortality risk than strokes in patients without atrial fibrillation.[7-9]

The contribution of age to stroke risk in patients with atrial fibrillation is reflected in contemporary risk-stratification schemes. In the $CHADS_2$ (cardiac failure, hypertension, age, diabetes stroke) scheme, age >75 years contributes 1 point toward a maximum risk score of 6.[10] In the more recent CHA_2DS_2-VASc (vascular disease, age 65-74 years, sex category) scheme, ages 65-75 or >75 years contribute 1 or 2 points, respectively, toward a maximum score of 9.[11,12] This reflects the designation of age >75 years as a "major" risk factor, alongside prior stroke or transient ischemic attack, in CHA_2DS_2-VASc.[12] Other risk factors (eg, heart failure, hypertension, diabetes mellitus, and vascular disease) also are more common in older individuals.[13-15]

Clinical practice guidelines developed by the American College of Cardiology, American Heart Association, European Society of Cardiology, and American College of Chest

Funding: The author acknowledges Richard Dobson, PhD, who provided editorial support with funding from Janssen Scientific Affairs, LLC.

Conflict of Interest: The author has no conflicts to report.

Authorship: The author is entirely responsible for the content of the article.

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0002-9343/$ -see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjmed.2012.10.012

Physicians recommend that all patients with atrial fibrillation and a $CHADS_2$ or CHA_2DS_2-VASc score ≥2 should receive long-term oral anticoagulation.[12,16,17] In the American College of Chest Physicians and European Society of Cardiology guidelines, oral anticoagulation also is recommended in patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 1.[12,17] Until recently, vitamin K antagonists (eg, warfarin) were the only oral anticoagulants available. However, recently updated guidelines discuss the newer oral anticoagulants as potential alternatives to vitamin K antagonists for stroke prevention.[12,17,18]

This review highlights warfarin's benefits and challenges in elderly patients with atrial fibrillation and discusses the potential of newer oral agents to address unmet medical needs in this group.

CLINICAL SIGNIFICANCE

- Using warfarin to reduce the risk of stroke in elderly patients with atrial fibrillation is limited by practical considerations that affect uptake and compliance.
- Newer anticoagulants offer elderly patients simplified dosing, reduced drug-drug interactions, and reduced monitoring requirements.
- Phase III trial data suggest that newer anticoagulants offer an effective alternative to warfarin, with efficacy and safety in elderly patients similar to in the overall trial populations.

ORAL ANTICOAGULATION WITH WARFARIN

Benefits

Long-term anticoagulation reduces the incidence of stroke in patients with atrial fibrillation. In a meta-analysis, adjusted-dose warfarin reduced the risk of stroke by 64% versus placebo and by approximately 40% versus antiplatelet therapy.[19] In a US analysis of 39,000-67,000 Medicare patients with atrial fibrillation aged ≥65 years sampled annually from 1992 to 2002, warfarin use significantly reduced hazard ratio for stroke, driven by reductions in ischemic stroke.[20] In the randomized Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial of patients aged ≥75 years with atrial fibrillation (n = 973), warfarin significantly reduced the incidence of primary events (stroke, systemic embolism, or intracranial hemorrhage) versus aspirin (relative risk 0.48; $P = .003$), without increasing the incidence of major bleeding events.[21] In the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study cohort of patients with nonvalvular atrial fibrillation (n = 13,559; median age 73 years), net clinical benefit for warfarin increased with age.[22]

Underuse

Despite its benefits, several studies have shown that warfarin is under-prescribed for older patients.[23-26] In ATRIA, among elderly individuals with nonvalvular atrial fibrillation and no contraindications, warfarin was used in approximately 60% of patients aged 65-84 years and only 35% of those aged ≥85 years.[27] Among hospitalized patients with atrial fibrillation from a single US institution, warfarin was prescribed at discharge to 75% of those aged 65-69 years, 59% of those aged 70-79 years, 45% of those aged 80-89 years, and 24% of those aged ≥90 years.[24] A study of >50,000 US elderly long-term-care residents with prior stroke found that fewer than one third were receiving antithrombotic drug therapy.[26]

Practical Issues

To achieve optimal benefits from warfarin while minimizing the risk of bleeding, guidelines recommend that patients should be maintained within an international normalized ratio (INR) range of 2.0-3.0.[12,16] However, maintaining appropriate anticoagulation levels with warfarin is often difficult because of variable dose responses, multiple drug-drug and drug-food interactions, a slow onset and offset of action, and effects of genotypic variations. Warfarin-treated patients require routine coagulation monitoring, dose adjustments, and dietary precautions to ensure a balance between therapeutic anticoagulation and bleeding risk.[28-30] These limitations may be problematic for elderly patients and may negatively influence prescribing. Elderly patients often have cognitive and physical impairments,[31-34] limiting their ability to comply with complex treatment and monitoring requirements. Their increased intrinsic sensitivity to warfarin[35] means that it takes them longer to achieve a therapeutic INR after dosing.[36] They often require multiple medications for comorbid conditions, increasing the potential for drug-drug interactions with vitamin K antagonists.[37] In a pan-European survey of 711 patients with atrial fibrillation (mean age 68 years), many patients were unaware of the risks associated with over-anticoagulation and under-anticoagulation, and most considered the management requirements of warfarin burdensome.[38]

Advanced age is a risk factor in several bleeding-risk scoring schemes.[39-41] Increased risk of falls and bleeding in the elderly is a commonly cited reason for not prescribing warfarin.[24,33,42] However, a systematic literature review of anticoagulant-related bleeding in older patients concluded that physicians' fears of the risk of bleeding may be unfounded, and that anticoagulant use should be based on stroke-risk stratification.[43]

NEWER ORAL ANTICOAGULANTS

Newer oral anticoagulants lack the limitations associated with vitamin K antagonists and may offer benefits and increased convenience for elderly patients. Newer agents have predictable pharmacologic profiles, a rapid onset of action, a wide therapeutic window, no requirement for rou-

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