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Long-Term Anticoagulation in the Extreme Elderly with the Newer Antithrombotics: Safe or Sorry?

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Background and Objectives: The prevalence of atrial fibrillation (AF) doubles in the extreme elderly and is higher than in the rest of the population. Warfarin therapy to prevent thromboembolic events secondary to AF is often underutilized and under-prescribed in this subgroup, due to the fear of bleeding and other complications. Newer oral anticoagulants such as rivaroxaban and dabigatran offer alternative therapeutic options for the extreme elderly. We review the clinical trial data of these newer agents in the extreme elderly population.

Subjects and Methods: The primary literature was identified through PubMed, using the following search terms: anticoagulation, rivaroxaban, dabigatran, warfarin, elderly, AF, bleeding, stroke, and aging. Additional references were identified through the review of references from the articles obtained. We included clinical studies evaluating anticoagulation therapies in AF. Selection emphasis was placed on those evaluating anticoagulation in the elderly population.

Results: Dabigatran and rivaroxaban have predictable, dose-proportional pharmacokinetic and pharmacodynamic properties, which make them favorable options for the elderly. Fewer monitoring parameters and drug interactions allow for the greater ease of use. A landmark trial shows that the rate of intracranial hemorrhage with dabigatran is lower in this population compared to warfarin. However, the data is based on a small number of subjects enrolled in the clinical trials. As such, the real-world use of these agents may not replicate the published rates of bleeding and thrombosis in the study populations.

Conclusion: More research is needed in this area, specifically in this population, before newer agents such as rivaroxaban and dabigatran are widely recommended for use in the extreme elderly patients. **(Korean Circ J 2013;43:287-292)**

KEY WORDS: Anticoagulants; Aging; Atrial fibrillation; Stroke; Aged.

Background

The extreme elderly population, defined as patients greater than 75 years of age, is the fastest growing segment of the population. Along with the aging population comes a concomitant sharp rise in the incidence of atrial fibrillation (AF).[1] Long-term oral anticoagulation therapy is critical in the management of thromboembolic disorders such as AF, due to stroke rates that are particularly increased in the elderly. However, anticoagulants are also associated with an increased risk of bleeding, which may be a consideration in deciding the prescription of anticoagulants in the elderly patient.

As the incidence of AF grows with the aging population, extreme elderly patients are being treated with anticoagulant therapy with increasing frequency. The incidence of AF increases with age, with a prevalence of about 0.1% in people younger than 55 years and 9% in those over 80 years.[2] By year 2050, there will be an estimated 5.6 million people in the United States with AF. Of these, 50% will be over the age of 80. In the Asia-Pacific region, the prevalence of AF ranges from 770 per 100000 persons in China to 1634 per 100000 persons in Japan.[3] In South Korea, the prevalence of AF in one community-based cohort was reported to be 1.9% in patients aged 75-79 years old, and 4% in patients greater than 80 years old.[4]

Stroke Risk

Nonvalvular AF increases the risk of ischemic stroke by approximately five-fold and causes an estimated 15% of all strokes in the

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United States. In people aged 80 to 89 years, this proportion is even higher at approximately 24%.[5] In the Framingham cohort, the proportion of AF-associated strokes increased progressively with age, from 6.7% for ages 50 to 59 years to 36.2% for ages 80 to 89 years.[6] Strokes occurring from AF result in higher mortality and disability, making the prevention of AF-related stroke an important public health concern.

Multiple trials have established that antithrombotic therapy decreases the stroke risk. Aspirin therapy reduces the relative risk (RR) by 21% and the adjusted-dose warfarin {international normalized ratio (INR) 2.0-3.0} is associated with a RR reduction of about 68%. Warfarin is more effective than aspirin but is used less often than indicated, because of the hemorrhagic risk and the inconvenience of anticoagulation monitoring. Newer oral agents, such as the direct thrombin inhibitors dabigatran and ximelagatran, have been investigated for stroke prevention in AF patients in large clinical trials such as RE-LY and SPORTIF III and V.[7-9] The results suggest efficacy in fixed doses compared to well-controlled warfarin. Although anticoagulation intensity was not monitored or regulated during the treatment with dabigatran, it was associated with less bleeding than warfarin. Rivaroxaban, a factor Xa inhibitor, is also newly approved for stroke prevention in AF. Other antithrombotic agents, such as apixaban, are under development or approved as alternatives to warfarin, but sufficient data are not yet available to justify their clinical use in patients with AF.

Bleeding Concern with Warfarin

More than 1% of people aged 80 years and older are hospitalized each year from gastrointestinal (GI) bleeding. The incidence and outcome of GI bleeding in the elderly can also be influenced by the use of aspirin, NSAIDS, and antithrombotic agents. GI bleeding in the elderly can originate from lesions common to all age-groups or from lesions associated specifically with aging. In the elderly people, morbidity and mortality from GI bleeding is determined by both the nature of the bleeding lesion and the presence of comorbid medical conditions.

Anticoagulant response to warfarin increases with age and a number of studies considered the relationship of patient age to the risk of bleeding complications associated with long-term oral anticoagulation. A study showed that the incidence of major hemorrhage was 13.1 per 100 patient-years in patients 80 years or older, compared to 4.7 per 100 patient-years in patients less than 80 years (p=0.009).[10] A warfarin study with 4202 patients from the Netherlands corroborated that the incidence rate of all major bleeding events rises with increasing age. In those younger than 60 years, the bleeding rate was 1.5 {95% confidence interval (CI): 1.0-2.2} per 100 patient-years, compared to 4.2 (95% CI: 3.1-5.5) per 100 patient-years in those older than 80 years. The hazard ratio for major hemorrhage was 1.3 (95% CI: 0.8-2.0) for patients aged between 60-70 years, and increased to 2.7 (95% CI: 1.7-4.4) in patients older than 80 years.[11]

Table 1. Comparison of oral anticoagulants

Agent	Warfarin*	Dabigatran†	Rivaroxaban†
Mechanism of action	Inhibits synthesis of vitamin K-dependent clotting factors	Competitive inhibition of thrombin	Selectively blocks active site of Factor Xa
Dose in AF healthy patients	Individualized dosing	150 mg PO BID	20 mg PO QPM with food
Dose in AF patients with renal impairment	Dose adjustment not necessary	75 mg PO BID (for Clcr 15-30 mL/min)	10 mg PO QPM with food (for Clcr 15-50 mL/min)
Special pharmacodynamic considerations in elderly	Higher than expected INR response. Consider lower initial and maintenance doses	N/A	Higher plasma levels due to reduced total body and renal clearance
Metabolism	CYP 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4	P-glycoprotein	CYP 3A4 and P-glycoprotein
Pharmacokinetics with renal impairment	Not effected by renal impairment	Prolonged half-life, higher plasma levels	Higher plasma levels
Adverse effects (other than bleeding)	Skin necrosis, cholesterol microembolism	Dyspepsia and gastritis-like events	Extremity pain, pruritis
Laboratory monitoring	INR, PT	aPTT, ecarin clotting time	None
Monitoring frequency	Weekly to monthly, variable	None	None
Reversal of over-anticoagulation	Vitamin K	None	None

*Coumadin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company;2011, †Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc;2012, ‡Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc;2011. PO: with food, BID: twice daily, QPM: every night, INR: International Normalized Ratio, PT: Prothrombin Time, aPTT: Activated Partial Thromboplastin Time

Of all the types of bleeding, intracranial hemorrhage (ICH) is of the greatest concern in the older population. Fatal hemorrhage, which consists mostly of ICH, occurs in 0.3 per 100 patient-years in the general population, and with a lower rate of 0.1 per 100 patient-years for patients younger than 60 years.[11] ICH was strongly associated with 30-day mortality, even after adjusting for age, sex, anticoagulation intensity on admission, and other coexisting illnesses. ICH accounted for almost 90% of deaths from warfarin-associated bleeding and the majority of disability in survivors.[12] In another study, the odds ratio (OR) of ICH is increased at 85 years of age or older with age {adjusted OR 2.5 (95% CI: 1.3-4.7)}.[13]

Even though bleeding may be relatively higher in the elderly compared to the younger population, two Italian studies in the very old suggest that the actual bleeding rates are still low enough to justify the use of anticoagulation in this cohort. In a study with 4093 AF patients 80 years or older, there were 132 bleeding events (1.73 per 100 patient-years).[14] An increased bleeding risk was recorded with increasing age, with a significantly higher rate among patients greater than 85 years of age compared with those less than 85 years of age. Only the history of bleeding, active cancer, and history of falls were confirmed to be independently and strongly associated with the bleeding, suggesting that age in itself should not be considered a contraindication to treatment. This finding was also duplicated in another prospective cohort study in AF patients greater than 90 years old.[15]

Due to perceived lower risk of bleeding with aspirin, some providers may choose aspirin over warfarin for the older AF patients. However, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study which enrolled 973 patients aged 75 years or older (mean of 81.5 years) showed there was no difference in the major bleeding rates between warfarin and aspirin {1.9% vs. 2.0% risks per year; 0.97 RR (95% CI: 0.53-1.75)}. Additionally, patients on warfarin had significantly lower rates of the primary endpoint (composite of stroke, ICH, or arterial embolism), compared to those on aspirin {RR 0.48 (95% CI: 0.28-0.80) p=0.003}.[16] Therefore, the BAFTA study showed that aspirin is not an ideal substitute for warfarin in elderly patients who require anticoagulation in AF.

Underutilization of Anticoagulation Therapy in the Elderly/High Risk Patients

Clinicians lack the good tool to help predict a patient's risk for bleeding on warfarin in the real world, as patients enrolled in prospective studies are often ambulatory with good functional status. In an evaluation comparing the predictive values of the contemporary bleeding risk stratification schemas, all schemas provided only moderate predictive ability.[17] The HAS-BLED score appeared to be the best predictor of bleeding in patients taking warfarin {C statistic, 0.66 (95% CI: 0.61-0.71)}. The HAS-BLED is a scoring system used to evaluate the risk of bleeding that includes old age, increased systolic blood pressure, and a history of stroke. A study by Chen et al.[18] reviewed the association between $CHADS_2$ covariates and the risk of bleeding in patients receiving warfarin. This systematic review found that the strength of evidence supporting the association between $CHADS_2$ covariates and bleeding risk is low to very low, with the exception of advanced age, for which the strength of evidence is moderate. The authors suggest that given the known association of the $CHADS_2$ score and stroke risk, the decision to prescribe warfarin should be driven more by patients' risk of stroke rather than by the risk of bleeding.

Many risk factors for bleeding and relative contraindications to warfarin use are common in elderly patients, such as multiple comorbidities, multiple concurrent drugs, hypertension, renal failure, and reduced functional status with increased risk for falls. Indeed, the current guidelines report age as a risk factor for both hemorrhage and stroke, creating uncertainty about the optimum treatment of the elderly. These uncertainties are present in clinical practice and concur with the current under-treatment of the elderly patients. Several studies indicate that fewer than half of elderly patients who would benefit from anticoagulation actually receive warfarin. In one study, warfarin was initiated in only 42.1% of 31492 AF patients with high risk of stroke as defined by $CHADS_2$ scores between 3 and 6. The mean age of patients in this high-risk group ranged from 79.8 years, in those with $CHADS_2$ score of 3, to 82.3 years, in those with $CHADS_2$ score of 6.[19] The barriers to prescribing warfarin include the need for repeated blood monitoring, difficulty achieving optimal INR, complicated dosage regimens, compliance, and drug or dietary interactions.[20] Physician-cited reasons for the under-use of vitamin K antagonists in the elderly are: hemorrhage (33%), falls (32%), patient refused or history of non-adherence (14%), cognitive impairment (3%), advanced illness (8%), and alcohol abuse (2%).[21] Unfortunately, these barriers prevent the elderly from receiving anticoagulation therapy although they would benefit the most from the treatment.[22]

Utility of the Newer Oral Anticoagulation Agents in the Elderly

With rivaroxaban and dabigatran now on the market, the elderly population has several new therapeutic options for the long-term stroke prevention. Due to more predictable pharmacokinetics and pharmacodynamics, these agents have many properties that make them attractive alternatives. Unlike warfarin, they have set dosing schedules which are easier for the older patients to remember and

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therefore may improve the patient adherence. They do not need laboratory monitoring to ensure optimal anticoagulation levels, which has been a major barrier to the warfarin therapy. Frequent anticoagulation monitoring, which is usually required during the warfarin therapy, may be especially difficult in the elderly, due to possible lack of transportation to physician's offices or laboratories, high cost of portable monitors, and decreased fine motor skills necessary for self-monitoring.

These newer agents also have fewer interactions to other drugs, herbs, and foods. Compared to warfarin which is a substrate of cytochrome P450 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4, dabigatran does not have any CYP450 interactions.[23] Instead, it is a substrate of P-glycoprotein (P-gp) and therefore has drug interactions with P-gp inhibitors and inducers, such as rifampin, dronedarone, and ketoconazole.[24] Rivaroxaban has drug-drug interactions with agents that are combined CYP450 3A4 and P-gp inhibitors, such as ketoconazole, ritonavir, clarithromycin, and erythromycin.[25] In addition, rivaroxaban and dabigatran do not have drug-food interactions with vitamin K-containing foods or known genetic polymorphisms that alter drug metabolism such as CYP 2C9 polymorphism and VKORC1 polymorphism. The VKORC1 polymorphism is an important determinant of treatment response to warfarin in Chinese and potential other Asian populations.[26] The lack of known drug-herb interactions with rivaroxaban and dabigatran may make these agents particularly attractive in populations that frequently use herbal medications.

Bleeding Rates with the Newer Oral Anticoagulation Agents

The safety and efficacy of dabigatran was shown in the landmark trial RE-LY.[7] When the results of this trial were examined by the prespecified age ranges (<65, 65-74, ≥75 years of age), dabigatran 110 mg twice daily (BID) compared to warfarin was associated with a similar risk of major bleeding in those aged 75 years or older {4.43% vs. 4.37%; RR=1.01 (95% CI: 0.83-1.23); p=0.89; p for interaction < 0.001}.[27] When dabigatran 150 mg BID was compared with warfarin, it had a trend toward higher risk of major bleeding in those aged 75 years or older {5.10% vs. 4.37%; RR=1.18 (95% CI: 0.98-1.42); p=0.07; p for interaction <0.001}. However, the rates of ICH in the dabigatran groups were significantly lower (0.31% and 0.23% with dabigatran 150 mg and 110 mg, respectively) than in the warfarin group (0.71%) (p<0.001). Warfarin was an independent predictor of ICH (RR 2.9, p<0.001) in the RE-LY study.[28] It seems that dabigatran at the 110 mg BID dosing may be a favorable option compared to warfarin for the elderly population due to the lower risk of ICH.[29]

Renal Function in the Elderly and the Newer Antithrombotics

Prescribing for the older patient presents some challenges, due to the multiple comorbid illnesses and age-associated decline in renal function. The clearance of renally excreted drugs and their metabolites is reduced by renal insufficiency, thus increasing the risk of adverse events. Appropriate studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of dabigatran in the elderly. However, elderly patients are more likely to have age-related kidney problems, which may require caution and dose adjustments for the patients receiving dabigatran. The U.S. product labeling recommends dabigatran 75 mg, BID, for patients with severe renal impairment (CrCl 15-30 mL/min). Dabigatran is eliminated unchanged, primarily by the kidneys. In severe renal impairment, area under the curve is increased 6.3x normal baseline, and the half-life increases to 27 hours from 13 hours in normal renal function.[24]

In the RE-LY trial, the risk of bleeding also increased with decreasing creatinine clearance and concomitant aspirin use, but there were no significant statistical interactions between creatinine clearance and randomized treatment.[27] However, the trial excluded patients with CrCl <30 mL/min and only 19% of the RE-LY population had creatinine clearance, between 30 and 50 mL/min.

Similarly, rivaroxaban is also affected by renal clearance. About one-third of the drug is excreted renally. In moderate impairment (30-49 mL/min) and severe impairment (<30 mL/min), the plasma level of rivaroxaban is increased significantly. The U.S. product labeling for rivaroxaban recommends a dose adjustment for renal function: 15 mg with food nightly for patients with CrCl 15-50 mL/min and avoiding the use of rivaroxiban in patients with CrCl <15 mL/min.[25]

Summary

Despite the many strong reasons to believe that warfarin therapy reduces stroke risk and improves net clinical benefit in elderly patients, it is often underutilized and under-prescribed in the eligible patients. The decision to withhold anticoagulation in the elderly with AF in the absence of formal contraindications is often multifactorial, the result of a combination of underestimating the thromboembolic risk, overestimating the bleeding risk including ICH, frailty, risk of falling, and the need for monitoring.[30]

With the introduction of new oral anticoagulants such as rivaroxaban and dabigatran, these options are equally efficacious to warfarin and possibly safer in terms of the ICH risk. With more favorable pharmacokinetic and pharmacodynamic profiles, these agents may

overcome some of the barriers that once prevented the extreme elderly patients from receiving anticoagulation therapy. Although current data for these agents seem favorable, it is unknown how it will translate to real world clinical practice.

Conclusion

There are several anticoagulation regimens available and newer studies include the extreme elderly age groups. Although there is evidence that they are safer than the older agents, it is still unreasonable to assume that all elderly patients should be started on the newer antithrombotics, as the research data do not always apply to the real world situations. The elderly research subjects tend to be more mobile and healthier, with fewer comorbid conditions. There is still little data available on the bleeding risks in the very old patients, who are usually under-represented in the clinical trials. The real risk of bleeding in these groups is still uncertain. As such, the determination of the benefit-to-risk ratio of anticoagulation in the very old subjects is complex.

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