Net Clinical Benefit of Warfarin Therapy in Elderly Chinese Patients With Atrial Fibrillation

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Background—Little is known about the net clinical benefit of warfarin therapy in elderly patients with atrial fibrillation.

Methods and Results—We studied 2339 Chinese patients with nonvalvular atrial fibrillation aged ≥80 years: 1805 with no antithrombotic therapy and 534 on warfarin therapy. Patients were stratified according to their CHA2DS2-VASc and HAS-BLED score. The primary end point was a composite of hospital admission with ischemic stroke or death. After 2.2-year follow-up (5199 patient-years), a primary end point had occurred for 1861 patients (79.6%): 66.9% in patients on warfarin (66.9%) compared with 80.8% in patients with no antithrombotic therapy (80.8%; hazard ratio, 0.53; 95% confidence interval, 0.48–0.58; \( P<0.001 \)). This was related to substantially better mortality rate (hazard ratio, 0.40; 95% confidence interval, 0.37–0.45; \( P<0.0001 \)) and ischemic stroke rate (hazard ratio, 0.64; 95% confidence interval, 0.54–0.77; \( P<0.0001 \)) among patients on warfarin. For the net clinical benefit, 510 ischemic strokes and 42 intracranial hemorrhage were recorded. The annual incidence of ischemic stroke and intracranial hemorrhage was 11.3%/y and 0.6%/y, respectively, in patients prescribed no antithrombotic therapy and 7.1%/y and 1.1%/y, respectively, in those prescribed warfarin. The adjusted net clinical benefit favored warfarin for all elderly patients, and the best net benefit from warfarin was in those with high stroke and intracranial hemorrhage risk. In these high-risk patients, warfarin therapy was associated with 7.2 to 8.0 fewer events per 100 patient-years compared with no antithrombotic therapy.

Conclusions—In elderly patients with atrial fibrillation, warfarin therapy is associated with lower death and ischemic stroke and an overall net clinical benefit.

Key Words: aged • atrial fibrillation • warfarin

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. Its prevalence increases with age from 0.5% in patients aged <40 years to ≥15% in those aged ≥80 years. With the progressively aging population, the global prevalence of AF is projected to more than double during the next 2 decades. The management of AF in elderly patients is of paramount importance, not merely because aging increases its prevalence, but because increasing age is clearly an important, independent risk factor for ischemic stroke and intracranial hemorrhage (ICH): the attributable risk of stroke in AF increases from 1.5% at 50 to 59 years to 23.5% at 80 to 89 years. Randomized controlled trials have demonstrated the beneficial effect of long-term warfarin therapy over placebo in reducing AF-related ischemic stroke. Among these, only 1 trial, the Birmingham Atrial Fibrillation Treatment of the Aged Study, targets specifically older AF population (age, ≥75 years) and shows that warfarin is more effective than aspirin in stroke prevention in this population. Nonetheless, warfarin therapy remains widely underused in clinical practice: only 15% to 50% of eligible patients are prescribed therapy. The situation is compounded by the fact that elderly patients with AF are less likely to be prescribed warfarin than their younger counterparts and if treatment is prescribed, they are often under-anticoagulated.

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The debate about prescription of warfarin therapy in a patient with AF involves balancing the risk of ischemic stroke in the absence of therapy against the risk of major bleeding, particularly ICH, with therapy. In the white population, ICH accounts only for 10% to 15% of all types of strokes. In stark contrast, one third of all strokes in Chinese patients result from ICH, a 3-fold higher incidence. This difference makes the clinical decision to initiate anticoagulation therapy more challenging. Overestimation of the benefits of ischemic stroke prevention and underestimation of the risk of ICH can tilt the scales in the wrong direction. Unfortunately, to date, clinical trials have not specifically targeted elderly patients and study subjects have not been representative of the elderly. As such results cannot be extrapolated to elderly patients with AF. The objective of this study was to determine the net clinical benefit of warfarin therapy in elderly patients (age, ≥80 years) with regard to the risk of ischemic stroke and ICH.
Methods

Patients
Between July 1997 and December 2011, 10,195 Chinese patients with a diagnosis of AF at Queen Mary Hospital, Hong Kong, were identified through the computer-based clinical management system. Patients were excluded if they were <80 years, had significant valvular heart disease and previous valvular replacement, or had incomplete clinical and follow-up data. The final analysis included 1805 AF patients prescribed no antithrombotic therapy and 534 patients on warfarin.

Study Design
The study was approved by an institutional review committee. All hospital admissions, outpatient clinic visits, laboratory results, and radiological images have been recorded in the computer-based clinical management system since 1996. Demographic data, cardiovascular risk factors, and medications were recorded at baseline. The definition of comorbidities is provided in the Data Supplement.

Outcomes
The primary end point was a composite of hospital admission with ischemic stroke or death during the follow-up period. The secondary end point was net benefit defined as number of ischemic strokes prevented with warfarin therapy minus the number of excess intracranial bleedings with a weight of 1.5 to compensate for the generally more severe outcome after ICH. The data were retrieved from the medical records and discharge summaries from the territory-wide information network of all public hospitals in Hong Kong. The index date was defined as the date of the first occurrence of AF. For the registration of outcome during follow-up, a blanking period of 14 days after the index date was applied as the occurrence of an ischemic stroke or ICH within the first few days of the diagnosis of AF was most likely related to initial presentation of AF rather than a new event.

Statistical Analysis
Continuous and discrete variables are expressed as mean±SD and percentages, respectively. Statistical comparisons of the baseline clinical characteristics were performed using Student t test, 1-way ANOVA, or Fisher exact test as appropriate. Kaplan–Meier survival analyses with the log-rank test were performed and the Cox proportional hazards regression model was used to calculate the hazard ratio of some predictive factors and their 95% confidence interval for the incidence of ischemic stroke. For descriptive purposes, patients were classified into strata according to CHA2DS2-VASc scores. The annual risk of
ischemic stroke was calculated for each stratum of CHA₂DS₂-VASc score. Likewise, the incidence of ICH was calculated according to the HAS-BLED score. Calculations were performed using SPSS software (version 12.0). All tests are 2-sided, and P values were considered significant if <0.05.

Results
A total of 2339 patients with nonvalvular AF and age >80 years were included in this analysis. Table 1 summarizes the clinical characteristics of the study population. The mean age was 86.7±4.9 years with a female predominance (61.6%). The mean CHA₂DS₂-VASc and HAS-BLED score was 4.5±1.5 and 2.2±0.9, respectively. Of this population, 1805 elderly patients (77.2%) were prescribed no antithrombotic agent therapy, 534 (22.8%) were on warfarin therapy, and none of them on novel anticoagulants. Elderly patients not on antithrombotic therapy were older and more likely to be women, but less likely to have hypertension, diabetes mellitus, heart failure, previous ischemic stroke, coronary artery disease, or peripheral artery disease, thus having a lower mean CHA₂DS₂-VASc and HAS-BLED score (Table 1).

Clinical Outcomes
After a mean follow-up of 2.2 years (a total 5199 patient-years), a primary end point had occurred for 1861 patients (79.6%). The overall high incidence of primary composite end point indicated a high-risk population. The primary end point had been reached by 357 patients on warfarin therapy (66.9%) compared with 1504 patients with no antithrombotic therapy (80.8%; hazard ratio, 0.53; 95% confidence interval, 0.48–0.58; P<0.001; Figure 1A). The disparity of primary end point was associated with a substantially better mortality rate (hazard ratio, 0.40; 95% confidence interval, 0.37–0.45; P<0.0001) and ischemic stroke rate (hazard ratio, 0.64; 95% confidence interval, 0.54–0.77; P<0.0001) among patients on warfarin therapy (Figure 1B and 1C).

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There were altogether 510 ischemic strokes. Of these, 380 occurred in 1805 elderly AF patients with no antithrombotic therapy (21.1%). The overall annual incidence of ischemic stroke was 11.3% per year. Table 2 summarizes the association between individual baseline factors and ischemic stroke in patients without antithrombotic therapy. There was a progressive increase in annual risk of ischemic stroke with increasing CHA₂DS₂-VASc score (Figure 2). The annual stroke risk for patients with CHA₂DS₂-VASc=2 was 8.2%, increasing to 13.7% for those with CHA₂DS₂-VASc ≥6. By comparison, the annual incidence of ischemic stroke in elderly AF patients on warfarin therapy was 7.1%. Similar to patients prescribed no antithrombotic therapy, an increase in CHA₂DS₂-VASc score was associated with increased risk of ischemic stroke (Figure 2A). Across all CHA₂DS₂-VASc strata, the incidence of ischemic stroke in patients receiving warfarin therapy was lower than that of patients with no antithrombotic therapy, with

![Figure 1](http://circ.epub.ahajournals.org/) Kaplan–Meier estimates of (A) primary composite end point–free survival, (B) mortality, and (C) ischemic stroke–free survival in elderly atrial fibrillation patients with no antithrombotic therapy vs warfarin therapy. CI indicates confidence interval; and HR, hazard ratio.
an average 37.7% reduction. Kaplan–Meier analyses revealed that at each stratum of CHA2DS2-VASc, there was a significantly lower incidence of stroke in patients on warfarin therapy with increased CHA2DS2-VASc score (Figure 2B–2E).

However, there were 42 ICH during the follow-up period: 21 in patients on no antithrombotic therapy (0.6% per year) and 21 in patients on warfarin therapy (1.1% per year). Table 3 summarizes the association between individual baseline factors and ICH in patients without antithrombotic therapy. The risk of ICH increased with increasing HAS-BLED score in patients with and without warfarin therapy (Figure 2F). The risk of ICH in patients on warfarin therapy was higher than in those with no antithrombotic therapy for a corresponding HAS-BLED score (Figure 2F). The adjusted net clinical benefit of warfarin therapy for the main end point in relation to CHA2DS2-VASc and HAS-BLED score is summarized in Table 4. The net result favored warfarin therapy for all elderly AF patients with CHA2DS2-VASc >2. The best net benefit
stroke in elderly patients with AF. Similar to the AF population in general, warfarin therapy was associated with lower risk of death and ischemic stroke. Nonetheless, elderly patients with AF prescribed warfarin had a higher risk of ICH than those not on any antithrombotic therapy. Despite, the net clinical benefit analysis revealed that the stroke risk in elderly AF patients without antithrombotic therapy exceeded the ICH risk with warfarin therapy in all combinations of stroke and ICH risks. The net clinical benefit of warfarin therapy was highest among those at high risk of both ischemic stroke and ICH.

The decision to prescribe long-term oral anticoagulation therapy in elderly AF patients remains challenging because of the lack of clinical data concerning the risk of both ischemic stroke and ICH specifically for the elderly age group. Evidence used to justify the benefit of warfarin therapy in AF patients is mainly derived from randomized controlled trials with participants typically aged around 70 years. Thus, direct extrapolation of these results to a much older population may be inappropriate. It is clear that age is an independent risk factor for ischemic stroke among the AF population, and the magnitude of such risk seems to increase continuously after 60 years of age without a clear cutoff. CHA2DS2-VASc score, the modified version of previous CHADS2 score, has taken the incremental impact of increasing age on ischemic stroke risk in AF into account by adding an additional point to patients aged ≥75 years. In the present study, the overall annual incidence of ischemic stroke among elderly AF patients aged ≥80 years was as high as 11.3% per year. Even among those without any additional risk factors other than advanced age, that is, CHA2DS2-VASc=2, the annual incidence of ischemic stroke was 8.2%, higher than the reported incidence in patients with the score, indicating the urgent need for thromboprophylaxis. In the present study, although qualitatively consistent with previous randomized control trials, warfarin therapy significantly reduced ischemic stroke risk in our cohort of elderly AF patients but with important quantitative differences. In our cohort, the average ischemic stroke risk reduction was only 37.7%, much lower than the reported reduction of 64%. A plausible explanation may be related to a lower target international normalized ratio in elderly AF patients because of the concern about bleeding complications. In Asia, there are guidelines recommending a lower target international normalized ratio (1.6–2.6) for those aged ≥70 years. Nonetheless,
this subtherapeutic international normalized ratio has also been demonstrated to be associated with the higher risk of ischemic stroke.\(^2^8\) Unfortunately, we lacked access to international normalized ratio data, thus precluding further analysis.

The risk of ICH treated with warfarin therapy must also be considered and is the major deterrent to such therapy in elderly patients with AF.\(^2^9\) It is commonly thought that the baseline risk of ICH is higher among the elderly. Nonetheless in the present study, the annual incidence of ICH in 1805 elderly patients with AF with no antithrombotic therapy was 0.6% per year, no higher than the reported rates of ICH in a general AF population.\(^2^6\) Among those on warfarin therapy, there was a 2-fold increase in the incidence of ICH. This suggests an increased susceptibility to ICH with warfarin in elderly AF patients.

Notwithstanding the higher risk of both ischemic stroke risk and ICH among elderly patients with AF, the decision to prescribe warfarin must be based on careful consideration of these 2 factors. In concordance with previous studies of general AF populations,\(^2^3\) the risk of ischemic stroke in elderly patients with AF not on warfarin therapy exceeds the risk of ICH with warfarin at all combinations of CHA\(_2\)DS\(_2\)-VASc and HAS-BLED scores. Net clinical benefit analysis clearly favors warfarin therapy over no antithrombotic therapy in all elderly patients with AF, primarily driven by the substantial ischemic stroke risk reduction. It thus seems that warfarin therapy should be the rule for all elderly AF patients aged ≥80 years. There may nonetheless be an important exception to warfarin therapy in addition to patient preference and other logistic issues. In our cohort of elderly patients with AF, while the risk of ICH increased with HAS-BLED score, only prior ischemic stroke, among various individual components constituting the score, predicted subsequent development of ICH. In contrary to this prior ICH, but not history of other major bleeding, conferred the highest risk among all risk factors for subsequent ICH. This is in agreement with previous registries,\(^2^3\) in which prior ICH conferred a 2 to 3× higher risk for subsequent ICH than any other form of severe bleeding (hazard ratio, 10.2 versus 3.5). The HAS-BLED score may thus have underestimated the contributory effects of prior ICH on subsequent ICH. In a recent report stratifying the risk of recurrence of ICH using HAS-BLED score in a cohort of 434 ICH survivors, the overall annual recurrence rate was 2.25% per year ranging from 1.37% in those with HAS-BLED=1 to 2.90% in HAS-BLED=4.\(^2^1\) Such excess risk of ICH among those with previous ICH could offset the clinical benefits of warfarin therapy implied by a reduction in ischemic stroke. This is in part in agreement with guidelines for the management of spontaneous intracerebral hemorrhage from the American Heart Association/American Stroke Association for the avoidance of long-term anticoagulation for nonvalvular AF patients, especially those at high risk of recurrence.\(^3^8\) It may not be applicable to the few novel oral anticoagulants, whose risk of ICH is much lower than warfarin therapy.

Limitations
This study was limited by its single-centered observational design. The gold standard to demonstrate treatment effects is a well-conducted randomized placebo-control trial; this would not be ethically possible to perform, given the well-documented benefit of anticoagulation. Thus, a large real-world registry offers a good alternative. Nonetheless, because of the nature of the registry design, the selection of antithrombotic strategies could not be made in a randomized control fashion. As a result, patients who were prescribed warfarin were in some ways different than their counterparts who were not treated with warfarin as judged by their attending physicians, thus imposing a selection bias in our cohort. In addition, although we carefully ascertainment all strokes and ICH by careful examination of the Framingham Heart Study. JAMA. 1994;271:840–844.


Atrial fibrillation is highly prevalent in the elderly population, and ≈1 in 4 elderly patients aged >80 years has the arrhythmia. It is known that the risk of atrial fibrillation–related ischemic stroke increases substantially with age, and that it can be greatly reduced by long-term oral anticoagulation therapy. However, such therapy is grossly underused in the elderly population, probably related to the age-related increase in risk of intracranial hemorrhage. Furthermore, elderly patients have been under-represented in most clinical trials for stroke prevention in atrial fibrillation, probably related to attitudes about anticoagulation for nonvalvular atrial fibrillation in the elderly. Consequently, elderly patients with atrial fibrillation are unsuitable for many of the randomized clinical trials on stroke prevention.

### Clinical Perspective

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### Clinical Benefit


### Anticoagulation and Risk Factors


### Meta-analysis


### Randomized Trials


### Risk Stratification


### Meta-analysis


### Randomized Trials


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SUPPLEMENTAL MATERIALS

Definitions

Hypertension was defined as resting systolic or diastolic blood pressure $\geq 140/90$ mmHg on two occasions or prescription of anti-hypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose $\geq 7.0$ mmol/l or prescription of anti-diabetic medication. Significant valvular heart diseases include mitral stenosis, any valvular lesions requiring surgery, and previous valvular repair or replacement. Heart failure was defined according to the Framingham Heart Study. Smoking status was recorded as smoker (past and current) or non-smoker. Stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 hours, and corresponded to a vascular territory in the absence of primary hemorrhage, and that could not be explained by other causes (trauma, infection, vasculitis).\textsuperscript{1,2} Both stroke and ICH were as confirmed by computerized axial tomography or magnetic resonance imaging of the brain. ICH was further classified as intra-cerebral hemorrhage, subarachnoid hemorrhage or subdural hemorrhage.\textsuperscript{3-5}

Supplemental References:


