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

Running title: Siu et al.; Net Benefit of Warfarin in Atrial Fibrillation Elderly

Chung-Wah Siu, MD and Hung-Fat Tse, MD, PhD

Cardiology Division, Department of Medicine, Queen Mary Hospital,
University of Hong Kong, Hong Kong

Correspondence:
Chung-Wah SIU, MD
Cardiology Division, Department of Medicine,
The University of Hong Kong
Queen Mary Hospital
Hong Kong
China
Tel.: (852) 2255-4694
Fax: (852) 2818-6304
E-mail: cwdsiu@hku.hk

Abstract:

**Background** - Little is known about the net clinical benefit of warfarin therapy in very elderly patients with atrial fibrillation (AF).

**Methods and Results** - We studied 2,339 Chinese patients with non-valvular AF aged ≥80 years: 1,805 with no antithrombotic therapy and 534 on warfarin therapy. Patients were stratified according to their CHA2DS2-VASc and HAS-BLED score. The primary endpoint was a composite of hospital admission with ischemic stroke, or death. After 2.2-year follow-up (5,199 patient-years), a primary endpoint had occurred for 1,861 patients (79.6%): 66.9% in patients on warfarin (66.9%) compared with 80.8% in patients with no antithrombotic therapy (80.8%) (HR: 0.53, 95% CI:0.48-0.58, p<0.001). This was related to substantially better mortality rate (HR: 0.40, 95%CI: 0.37-0.45, p<0.0001) and ischemic stroke rate (HR: 0.64, 95%CI: 0.54-0.77, p<0.0001) amongst patients on warfarin. For the net clinical benefit, 510 ischemic strokes and 42 ICH were recorded. The annual incidence of ischemic stroke and ICH was 11.3%/year and 0.6%/year respectively in patients prescribed no antithrombotic therapy, and 7.1%/year and 1.1%/year 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 ICH 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 very elderly patients with AF, warfarin therapy is associated with lower death and ischemic stroke, and an overall net-clinical benefit.

**Key words:** atrial fibrillation, elderly, warfarin
Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.\textsuperscript{1,2} Its prevalence increases with age from 0.5\% in patients aged <40 years to up to 15\% in those aged >80 years.\textsuperscript{3-5} With the progressively aging population, the global prevalence of AF is projected to more than double over the next two decades.\textsuperscript{4,6,7} 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 increased from 1.5\% at 50-59 years to 23.5\% at 80-89 years.\textsuperscript{8} Randomized controlled trials have demonstrated the beneficial effect of long-term warfarin therapy over placebo in reducing AF-related ischemic stroke.\textsuperscript{9} Amongst these, only one trial, the BAFTA study, targets specifically older AF population (age: 75 years or over) and shows that warfarin is more effective than aspirin in stroke prevention in this population.\textsuperscript{10} Nonetheless warfarin therapy remains widely underutilized in clinical practice: only 15 to 50\% of eligible patients are prescribed therapy.\textsuperscript{11-15} 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.\textsuperscript{16,17}

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 Caucasian population, ICH accounts only for 10-15\% of all types of strokes. In stark contrast, one-third of all strokes in Chinese patients result from ICH, a three-fold higher incidence.\textsuperscript{18-20} This difference makes the clinical decision to initiate anticoagulation therapy more challenging.\textsuperscript{21} Overestimation of the benefits of ischemic stroke
prevention and/or 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 or above) 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 younger than 80 years, had significant valvular heart disease and/or previous valvular replacement, or had incomplete clinical and/or follow-up data. The final analysis included 1,805 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 co-morbidities is provided in the supplemental data.

**Outcomes**

The primary endpoint was a composite of hospital admission with ischemic stroke, or death
during the follow-up period. The secondary endpoint 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 following intracranial hemorrhage (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.22

**Statistical Analysis**

Continuous and discrete variables are expressed as mean ± standard derivation and percentages, respectively. Statistical comparisons of the baseline clinical characteristics were performed using Student’s t test, one-way ANOVA or Fisher’s exact test as appropriate. Kaplan-Meier survival analyses with the log-rank test were carried out and the Cox proportional hazards regression model was used to calculate the hazard ratio (HR) of some predictive factors and their 95% confidence interval (CIs) 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 intracranial hemorrhage was calculated according to the HAS-BLED score. Calculations were performed using SPSS software (version 12.0). All tests are two-sided, and p-values were considered significant if < 0.05.
Results

A total of 2,339 patients with non-valvular AF and age older than 80 years was included in this analysis. Table 1 summarizes the clinical characteristics of the study population. The mean age was 86.7 ± 4.9 years old 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, 1,805 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 female, but less likely to have hypertension, diabetes, 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 5,199 patient-years), a primary endpoint had occurred for 1,861 patients (79.6%). The overall high incidence of primary composite endpoint indicated a very high-risk population. The primary endpoint had been reached by 357 patients on warfarin therapy (66.9%) compared with 1,504 patients with no antithrombotic therapy (80.8%) (HR: 0.53, 95% CI: 0.48-0.58, p=0.001) (Figure 1A). The disparity of primary endpoint was associated with a substantially better mortality rate (HR: 0.40, 95% CI: 0.37-0.45, p<0.0001) and ischemic stroke rate (HR: 0.64, 95% CI: 0.54-0.77, p<0.0001) amongst patients on warfarin therapy (Figure 1B and IC).

Net Clinical Benefit

There were altogether 510 ischemic strokes. Of these, 380 occurred in 1,805 elderly AF patients with no antithrombotic therapy (21.1%). The overall annual incidence of ischemic stroke was 11.3% per year. 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 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-E).

On the other hand, there were 42 ICH during the follow-up period: 21 in patients on no
antithrombotic therapy (0.6% per years) and 21 in patients on warfarin therapy (1.1% per year).
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 from
warfarin therapy was in those with high stroke and ICH risk. In these high-risk patients, warfarin
therapy was associated with 7.2 to 8.0 fewer events per 100 patient-years compared with patients
who received no antithrombotic therapy.
Discussion

To the best of our knowledge, this is the largest, real world registry of elderly Chinese patients with AF (age ≥ 80 years), in which we have demonstrated a high risk of death and ischemic 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 this, 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 or younger. 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 amongst the AF population, and the magnitude of such risk appears to increase continuously after 60 years of age without a clear cutoff.\(^8\) CHA\(_2\)DS\(_2\)-VASC score, the modified version of previous CHADS\(_2\) 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.\(^{25}\) In the present study, the overall annual incidence of ischemic stroke amongst elderly AF patients aged ≥ 80 years was as high as 11.3% per year. Even amongst those without any additional risk factors other than advanced age, i.e., CHA\(_2\)DS\(_2\)-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, while 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 (INR) in elderly AF patients because of the concern about bleeding complications. In Asia, there are guidelines recommending a lower target INR (1.6 to 2.6) for those ≥ 70 years. Nonetheless this sub-therapeutic INR has also been demonstrated to be associated with the higher risk of ischemic stroke. Unfortunately, we lacked access to INR 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. It is commonly believed that the baseline risk of ICH is higher amongst the elderly. Nonetheless in the present study, the annual incidence of ICH in 1,805 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. Amongst 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 amongst elderly patients with AF, the decision to prescribe warfarin must be based on careful consideration of these two factors. In concordance with previous studies of general AF populations, 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 CHA2DS2VASc 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 appears that
warfarin therapy should be the rule for all elderly AF patients aged 80 years or above. There may
nonetheless be an important exception to warfarin therapy in addition to patient preference
and/or 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, amongst various individual
components constituting the score, predicted subsequent development of ICH. Contrary to this
prior intracranial hemorrhage, but not history of other major bleeding, conferred the highest risk
amongst all risk factors for subsequent ICH. This is in agreement with previous registries,22 in
which prior intracranial hemorrhage conferred a 2-3 times higher risk for subsequent ICH than
any other form of severe bleeding (hazard ratio: 10.2 vs. 3.5). The HAS-BLED score may thus
have underestimated the contributory effects of prior intracranial hemorrhage 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=4.21 Such excess risk of ICH
amongst those with previous ICH could offset the clinical benefits of warfarin therapy implied
by a reduction in ischemic stroke. This is in part 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 non-valvular AF patients,
especially those at high risk of recurrence.30 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 ethnically possible to perform, given the well-documented benefit of anticoagulation. Thus a large ‘real world’ registry offers a good alternative. Nonetheless, due to the nature of the registry design, the selection of antithrombotic strategies could not be in a randomized control fashion. As a result, patients whom were prescribed warfarin were in some ways different from their counterparts whom were not treated with warfarin as judged by their attending physicians, thus imposing a selection bias in our cohort. In addition, while we carefully ascertained all strokes and ICH by careful examination of hospitalization records, laboratory and imaging results, patients with a milder form of stroke and/or ICH who were not hospitalized were not included. In addition, subjects in the present study were exclusively Chinese living in Hong Kong thereby potentially limiting the generalizability our results to other ethnic groups, given the possible variations in disease processes such as bleeding risk. Likewise, there are factors such as socio-economic factors that may influence or associate with the use of warfarin, which by themselves may beneficially (or adversely) affect the patients’ outcomes that have not been included in this study. However, given the nature of the study, we lack the ability and access to have all these factors described, quantified and compared. Furthermore, while in the present study we primarily focused on the two key outcomes: ischemic stroke and ICH, other clinical events such as gastrointestinal bleeding, albeit of much lesser weight, remain contributory to the overall “net” clinical benefit or risk, thus not to be overlooked in the decision of antithrombotic therapy.

Conclusions

This study demonstrates that elderly patients with AF are at high risk of ischemic stroke.
Warfarin therapy reduces the ischemic stroke risk but with an increased risk of ICH. Nonetheless, net clinical benefit favors warfarin therapy in elderly patients with AF in all combinations of stroke and ICH risk.

**Conflict of Interest Disclosures:** None.

**Reference:**


Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n=2,339)</th>
<th>No antithrombotic therapy (n=1,805)</th>
<th>Warfarin (n=534)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, (years)</td>
<td>86.7 ± 4.9</td>
<td>87.3 ± 5.2</td>
<td>85.1 ± 4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2,627 (61.6)</td>
<td>1,135 (62.9)</td>
<td>314 (58.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1,279 (54.7)</td>
<td>948 (52.2)</td>
<td>336 (62.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>444 (19.0)</td>
<td>307 (17.0)</td>
<td>137 (25.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperthyroidism, n (%)</td>
<td>99 (4.2)</td>
<td>76 (4.2)</td>
<td>23 (4.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2,627 (61.6)</td>
<td>1,135 (62.9)</td>
<td>314 (58.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Renal failure on dialysis, n (%)</td>
<td>19 (0.8)</td>
<td>13 (0.7)</td>
<td>6 (1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>652 (27.9)</td>
<td>459 (25.4)</td>
<td>193 (36.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>337 (14.4)</td>
<td>176 (9.8)</td>
<td>161 (30.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral arterial disease, n (%)</td>
<td>86 (3.7)</td>
<td>28 (1.6)</td>
<td>58 (10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior ischemic stroke/TIA, n (%)</td>
<td>549 (23.5)</td>
<td>369 (20.4)</td>
<td>180 (33.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior Intracranial hemorrhage, n (%)</td>
<td>93 (4.0)</td>
<td>75 (4.2)</td>
<td>18 (3.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc score</td>
<td>4.5 ± 1.5</td>
<td>4.1 ± 1.4</td>
<td>4.9 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHA2DS2-VASc: 2, n (%)</td>
<td>239 (10.2)</td>
<td>214 (11.9)</td>
<td>25 (4.7)</td>
<td></td>
</tr>
<tr>
<td>3, n (%)</td>
<td>548 (23.4)</td>
<td>457 (25.3)</td>
<td>91 (17.0)</td>
<td></td>
</tr>
<tr>
<td>4, n (%)</td>
<td>616 (26.3)</td>
<td>499 (27.6)</td>
<td>117 (21.9)</td>
<td></td>
</tr>
<tr>
<td>5, n (%)</td>
<td>474 (20.3)</td>
<td>350 (19.4)</td>
<td>124 (23.4)</td>
<td></td>
</tr>
<tr>
<td>6, n (%)</td>
<td>271 (11.6)</td>
<td>181 (10.0)</td>
<td>90 (16.9)</td>
<td></td>
</tr>
<tr>
<td>7, n (%)</td>
<td>125 (5.3)</td>
<td>73 (4.0)</td>
<td>52 (9.7)</td>
<td></td>
</tr>
<tr>
<td>8, n (%)</td>
<td>55 (5.3)</td>
<td>28 (1.6)</td>
<td>27 (5.1)</td>
<td></td>
</tr>
<tr>
<td>9, n (%)</td>
<td>3 (0.2)</td>
<td>8 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HAS-BLED score</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.9</td>
<td>2.4 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAS-BLED: 1, n (%)</td>
<td>465 (19.9)</td>
<td>399 (22.1)</td>
<td>66 (12.4)</td>
<td></td>
</tr>
<tr>
<td>2, n (%)</td>
<td>1091 (46.6)</td>
<td>845 (46.8)</td>
<td>246 (46.1)</td>
<td></td>
</tr>
<tr>
<td>3, n (%)</td>
<td>616 (26.3)</td>
<td>445 (24.7)</td>
<td>171 (32.0)</td>
<td></td>
</tr>
<tr>
<td>4, n (%)</td>
<td>154 (6.6)</td>
<td>106 (5.9)</td>
<td>48 (9.0)</td>
<td></td>
</tr>
<tr>
<td>5, n (%)</td>
<td>12 (0.5)</td>
<td>9 (0.5)</td>
<td>6 (0.6)</td>
<td></td>
</tr>
<tr>
<td>6, n (%)</td>
<td>1 (0.0)</td>
<td>0 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Associations between baseline factors and ischemic stroke in elderly AF patients without antithrombotic therapy

<table>
<thead>
<tr>
<th></th>
<th>Number of ischemic stroke</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>299</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>81</td>
<td>1.01 (0.79-1.29)</td>
<td>0.97</td>
</tr>
<tr>
<td>Female</td>
<td>260</td>
<td>1.12 (0.9-1.39)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>203</td>
<td>1.24 (1.02-1.52)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>68</td>
<td>1.48 (1.14-1.92)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>22</td>
<td>0.80 (0.69-1.63)</td>
<td>0.80</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>4</td>
<td>1.70 (0.63-4.55)</td>
<td>0.29</td>
</tr>
<tr>
<td>Heart failure</td>
<td>79</td>
<td>0.95 (0.74-1.22)</td>
<td>0.71</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>46</td>
<td>1.12 (0.83-1.53)</td>
<td>0.46</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>8</td>
<td>2.63 (1.30-5.32)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Prior ischemic stroke/TIA</td>
<td>72</td>
<td>1.37 (1.06-1.78)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Prior Intracranial hemorrhage</td>
<td>12</td>
<td>0.79 (0.45-1.41)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Table 3. Associations between baseline factors and intracranial hemorrhage in Chinese AF patients without anti-platelet agent and anticoagulation (n=1,805)

<table>
<thead>
<tr>
<th></th>
<th>Number of intracranial hemorrhage</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>15</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>6</td>
<td>1.59 (0.60-4.17)</td>
<td>0.35</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>0.81 (0.33-1.96)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>1.48 (0.62-3.52)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>1.12 (0.33-3.77)</td>
<td>0.87</td>
</tr>
<tr>
<td>Liver disease</td>
<td>5</td>
<td>1.50 (0.55-4.12)</td>
<td>0.43</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>0</td>
<td>0.49(0.0-4131857578)</td>
<td>0.81</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
<td>0.60 (0.18-2.05)</td>
<td>0.42</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
<td>0.40 (0.05-2.94)</td>
<td>0.36</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0</td>
<td>0.49 (0.00-10^8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Prior ischemic stroke/TIA</td>
<td>7</td>
<td>3.13 (1.25-7.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior Intracranial hemorrhage, n (%)</td>
<td>4</td>
<td>5.36 (1.80-16.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior major bleeding except intracranial hemorrhage</td>
<td>0</td>
<td>0.05 (0.00-38557)</td>
<td>0.61</td>
</tr>
<tr>
<td>Medication predisposing to bleeding</td>
<td>0</td>
<td>0.05 (0.00-4843)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Table 4. Net benefit of warfarin therapy (avoided ischemic strokes with warfarin per year minus excess intracranial hemorrhage with warfarin per year with a weight of 1.5)

<table>
<thead>
<tr>
<th>CHA_{2}DS_{2}-VASc:</th>
<th>HAS-BLED</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3-6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>--</td>
<td>6.82</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>7.49</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>--</td>
<td>5.01</td>
<td>7.16</td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>--</td>
<td>--</td>
<td>7.99</td>
<td></td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Kaplan-Meier estimates of (A) primary composite endpoint free survival, (B) Mortality, and (C) Ischemic stroke-free survival in elderly AF patients with no antithrombotic therapy versus warfarin therapy.

Figure 2. (A) Relation between CHA_{2}DS_{2}-VASc score and the annual risk of ischemic stroke in elderly AF patients with no antithrombotic therapy and warfarin. (B-E) Kaplan-Meier estimates of ischemic stroke-free survival in elderly AF patients with no antithrombotic therapy versus warfarin therapy stratified according to CHA_{2}DS_{2}-VASc score. (F) Relation between HAS-BLED score and the annual risk of intracranial hemorrhage in elderly AF patients with no antithrombotic therapy and warfarin.
Percentage of patients with primary composite endpoint-free survival (%)

Log-rank: 164.1, $p<0.0001$

HR: 0.53, 95%CI: 0.48-0.58

Warfarin therapy

No therapy
Percentage of patients survived (%)

- Warfarin therapy: HR: 0.40, 95 CI: 0.37-0.45
- No therapy

Log-rank: 316.4, $p<0.0001$
Percentage of patients with ischemic stroke-free survival (%)

Log-rank: 22.1, \( p < 0.0001 \)

HR: 0.64, 95% CI: 0.54-0.77

No therapy
Warfarin therapy
Annual risk of ischemic stroke (%) by CHA$_2$DS$_2$-VASC score

- No therapy
- Warfarin
Percentage of patients with ischemic stroke-free survival (%)

CHA$_2$DS$_2$-VASc: 2-3

HR: 0.60, 95%CI: 0.42-0.85
Log-rank: 8.05, $p$=0.005
Percentage of patients with ischemic stroke-free survival (%) at different CHA\textsubscript{2}DS\textsubscript{2}-VASc scores.

- **CHA\textsubscript{2}DS\textsubscript{2}-VASc: 4**
  - **No therapy**
  - **Warfarin therapy**

- **HR: 0.64, 95\%CI: 0.45-0.91**
- **Log-rank: 6.2, p=0.01**
Percentage of patients with ischemic stroke-free survival (%)

CHA$_2$DS$_2$-VASc: 5

HR: 0.58, 95%CI: 0.39-0.87
Log-rank: 6.9, $p=0.008$

No therapy
Warfarin therapy
Percentage of patients with ischemic stroke-free survival (%)

CHA$_2$DS$_2$-VASc: 6

HR: 0.57, 95%CI: 0.38-0.86

Log-rank: 7.25, p=0.0071
Annual risk of intracranial hemorrhage (%) by HAS-BLED score.

- No therapy:
  - HAS-BLED score 1: 0.5%
  - HAS-BLED score 2: 0.4%
  - HAS-BLED score 3: 1.1%

- Warfarin:
  - HAS-BLED score 1: 0.9%
  - HAS-BLED score 2: 1.0%
  - HAS-BLED score 3: 1.3%
Net Clinical Benefit of Warfarin Therapy in Very Elderly Chinese Patients with Atrial Fibrillation
Chung-Wah Siu and Hung-Fat Tse

Circ Arrhythm Electrophysiol. published online March 7, 2014;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/early/2014/03/07/CIRCEP.113.000858

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2014/03/07/CIRCEP.113.000858.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/
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 \( \geq 7.0 \text{mmol/l} \) 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).\(^1,2\) 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.\(^3-5\)

Supplemental References:


