The Net Clinical Benefit of Warfarin: Extending the Reach of Antithrombotic Therapy for Atrial Fibrillation

Running title: Fuster et al.; Net benefit of antithrombotic therapy

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The decision to use antithrombotics for stroke prevention in atrial fibrillation (AF) requires assessment of an individual patient’s risk of stroke balanced with their likelihood of bleeding on treatment. United States (U.S.) practice guidelines have recommended the use of the CHADS2 score (graded from 0 to 6 according to presence of major risk factors, see Table 1) for assessment of stroke risk in patients with AF. However, this score cannot precisely categorize all patients at different risks of thromboembolism. The CHADS2 model does not account for certain previously underappreciated risk factors, including the increase in stroke risk with age in patients less than 75 years old and in those with vascular disease, and thus allocates many patients to the low and intermediate risk categories who might actually be relatively stroke-prone. The 2010 European Society of Cardiology (ESC) guidelines for the management of AF recommend use of the more inclusive CHA2DS2-VASc score (graded 0 to 9, see Table 1), which incorporates additional risk factors including age 65-74 years and vascular disease. Validation studies have shown that the CHA2DS2-VASc score performs better than CHADS2 in distinguishing patients at low or intermediate thromboembolic risk. In a large Danish registry, thromboembolism rates at 1 year for patients at low risk (score = 0) were 0.78%/year with CHA2DS2-VASc and 1.67%/year with CHADS2.

Risk models have also been developed to stratify bleeding risk in anticoagulated patients. The ESC guidelines recommend the use of the HAS-BLED score (graded from 0 to 9 based on presence of risk factors for hemorrhage, see Table 1), which was derived from multivariate analysis of predictors of bleeding in several cohorts of patients with AF treated with antithrombotics. Increasing HAS-BLED scores correlate well with progressive bleeding risk. However, this model and others similar to it include many of the same risk factors that also impose greater risk of thromboembolism (e.g. increasing age, prior stroke and hypertension),
making clinical decisions difficult when faced with a patient considered to be at high risk of both stroke and bleeding.

In this issue of the Journal, Friberg et. al. present a retrospective analysis of the Swedish nationwide Hospital Discharge Register evaluating the overall net benefit of warfarin anticoagulation amongst patients with AF at various strata of stroke and bleeding risk. The authors evaluated one of the largest cohorts of patients ever studied (n=170,292) and followed them for an average of 1.5 years. Net benefit was defined as the rate of stroke without warfarin minus the rate of intracranial hemorrhage on warfarin, and an adjusted net benefit was calculated as the rate of stroke prevented by warfarin relative to the rate of intracranial hemorrhage attributable to warfarin, with the latter multiplied by a weighting factor of 1.5 to account for the more severe outcomes associated with intracranial hemorrhage. The presence of risk factors in study patients and definitions of diagnoses and outcomes were based, respectively, on appropriate ICD-codes established during hospital contacts. Information regarding patient medication use was derived from the Swedish national Prescribed Drug registry when available, and alcohol intake was also assessed from diagnostic codes when applicable.

The two major findings of this important study are: 1) In nearly all patients with AF, except those at lowest stroke risk, warfarin reduces the stroke risk to a greater extent than it augments risk of intracranial hemorrhage, resulting in a positive net benefit from treatment; this conclusion remains valid even in patients considered moderate-to-high risk for bleeding as assessed by the HAS-BLED score. 2) The CHA2DS2-VASc score is more effective than the traditional CHADS2 risk model in identifying the group of patients at very low risk of stroke, in whom the risk balance of warfarin therapy versus no anticoagulation favors more conservative management.
In patients with high risk scores using either CHA2DS2-VASc or HAS-BLED, which are frequently both elevated in patients with advancing age, warfarin use was associated with the most substantial net benefit. Even when the frequently disastrous consequences of intracranial hemorrhage were weighted as 1.5 times the severity of ischemic stroke, the net benefit favored warfarin treatment in all patients except those at lowest stroke risk (CHA2DS2-VASc =0). Advancing age is a known major risk factor for both stroke and warfarin-associated hemorrhage. Though the risk of bleeding rises only modestly in comparison to the age-related risk of stroke in patients with AF, the fear of hemorrhage in the elderly is often cited as justification to withhold anticoagulation. Singer et. al. found the net clinical benefit of anticoagulation to rise steadily with age and was highest for those 85 years or older. Furthermore, the net benefit favoring anticoagulation in this study persisted even when intracranial hemorrhage was given a severity weighting factor up to double that of ischemic stroke, highlighting the importance of effective stroke prevention in the elderly despite elevated bleeding risk. Nevertheless, though such severity weighting is appropriate within this context, it is also arbitrary, as ischemic strokes related to AF are typically quite severe.

The findings by Friberg et. al. also reinforce the superior clinical utility of the CHA2DS2-VASc model relative to CHADS2 for stroke risk stratification. While warfarin appeared beneficial in patients across all CHADS2 scores in this study, a CHA2DS2-VASc score =0 identified a cohort of patients at very low stroke risk in whom anticoagulation was associated with no benefit or some degree of risk. The finding that the lowest-risk patients, as assessed by CHA2DS2-VASc but not CHADS2, may safely defer anticoagulation is supported by the analysis of the Danish registry which found rates of thromboembolism to be lowered with vitamin K antagonists in all risk categories except those with a CHA2DS2-VASc score =0. Together, such
observations suggest that a low-risk CHADS2 score may provide false reassurance, prompting clinicians to defer anticoagulation in patients who might actually benefit. The authors suggest that anticoagulation should be considered the rule in patients with AF, deferring only in cases of patients with no CHA2DS2-VASc risk factors or those at “very high” bleeding risk (i.e. those with prior episodes of major bleeding or malignant hypertension). This approach will make clinical decisions frequently less complex, and will undoubtedly result in many more patients with AF being offered antithrombotic therapy than are currently in the U.S. (Figure 1).

Appreciation of an elevated bleeding risk based on a HAS-BLED score ≥3 likely is most clinically useful in patients at intermediate stroke risk, when deferring anticoagulation may be prudently considered.

There are two relative limitations related to the design of this retrospective, non-blinded, non-randomized cohort study, as acknowledged by the authors. 1) The authors used a national registry to identify both patients with AF and cases of ischemic and hemorrhagic stroke during hospital contacts; the full validity and selection bias associated with such registries can be questioned. Furthermore, such registries preclude identification of other important risk factors such as labile INRs and concomitant use of illicit and over-the-counter agents, and may fail to account for malleable risk factors such as control of hypertension. 2) Warfarin’s effect on both ischemic stroke prevention and hemorrhagic risk is strongly correlated to the time spent within the target therapeutic range (TTR), information impossible to provide in such a retrospective registry analysis. Of interest, in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study, the TTR among warfarin-treated patients in Sweden was particularly high and substantially superior to that seen worldwide including in the U.S.,13 raising questions as to whether the balance of risk and benefit is different in centers with less successful
management of anticoagulation intensity.

This study by Friberg et. al.\textsuperscript{8} highlights three evolving directions in the field of antithrombotic therapy for stroke prevention in patients with AF. 1) Warfarin is associated with substantial clinical benefit in most patients with AF, thus the decision whether to implement anticoagulation should be based less on appreciation of high-risk patients, but instead on the careful identification of those at very low thromboembolic risk (achieved more effectively with the CHA\textsubscript{2}DS\textsubscript{2}-VASc model) in whom anticoagulation may be safely deferred. 2) As stroke and bleeding risk frequently track together in an individual patient, bleeding risk models such as HAS-BLED should not be used alone to dissuade the use of anticoagulation in patients at high stroke risk; rather, an elevated bleeding score should be considered in patients at intermediate risk of stroke in whom deferral of anticoagulation may be reasonable. Clinical practice will likely move towards the use of anticoagulants for all patients with AF, except in those at very low risk of stroke or very high risk of bleeding (i.e. those with malignant hypertension or prior episodes of major hemorrhage). 3) Looking forward, the emergence of new oral antithrombotic alternatives to warfarin may further lower the anticoagulation threshold. Dabigatran, rivaroxaban, and apixaban have each demonstrated at least similar efficacy for ischemic stroke prevention compared to warfarin with lower rates of intracranial hemorrhage.\textsuperscript{14-16} Future assessments of net benefit using novel agents may progressively favor treatment in patients at incrementally lower risk of stroke, so that even more patients with AF will be offered antithrombotic therapy.

\textbf{Conflict of Interest Disclosures:} None
References:


Table 1. CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED Risk Factors and Scoring Schema

<table>
<thead>
<tr>
<th>CHAD&lt;sub&gt;2&lt;/sub&gt;</th>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc</th>
<th>HAS-BLED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Congestive heart failure/Left ventricular dysfunction*</td>
<td>Hypertension†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Abnormal renal‡ or liver§ function (1 point each)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>Age ≥75 years (2 points)</td>
<td>Stroke</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Diabetes mellitus</td>
<td>Bleeding history or predisposition**</td>
</tr>
<tr>
<td>Stroke (2 points)</td>
<td>Stroke/TIA/thrombo-embolism (2 points)</td>
<td>Labile INR††</td>
</tr>
<tr>
<td>Vascular disease‡‡</td>
<td>Elderly (age ≥75 years)</td>
<td>Drugs or Alcohol§§</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td></td>
<td>(1 point each)</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maximum 6 points | Maximum 9 points | Maximum 9 points

INR indicates international normalized ratio; TIA, transient ischemic attack
* Left ventricular ejection fraction ≤40%
† Systolic blood pressure >160mmHg
‡ Chronic dialysis, renal transplant, or serum creatinine ≥200 μmol/L
§ Chronic hepatic disease (e.g. cirrhosis) or bilirubin >2x, and serum transaminases >3x, upper limit of normal
** Previous bleeding requiring hospitalization or causing a decrease in hemoglobin >2 g/L and/or requiring blood transfusion, or predisposition to bleeding such as bleeding diathesis or anemia.
†† Time spent within target therapeutic range <60%
‡‡ Prior myocardial infarction, peripheral artery disease, and/or aortic plaque
§§ Concomitant use of aspirin, non-steroidal anti-inflammatory drugs or alcohol >20 U/week

Figure Legend:

**Figure 1.** Recommendations for Prevention of Stroke in Patients with Atrial Fibrillation. The inner circle represents treatment recommendations based on the use of the CHADS<sub>2</sub> score, as in U.S. Guidelines. The outer circle represents recommendations based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc model, as outlined in the European guidelines, which advise anticoagulant therapy in a larger proportion of patients with atrial fibrillation. Bleeding risk assessment is recommended for patients at intermediate stroke risk (yellow-shaded area), with particular caution and regular patient review for those on warfarin therapy when the HAS-BLED score is ≥3. For patients at very high risk of bleeding (e.g. those with malignant hypertension or prior episodes of major bleeding), conservative monitoring without treatment should be considered. OAC indicates oral anticoagulation.
CHA\textsubscript{2}DS\textsubscript{2}VASc = 0
Prefer no treatment rather than aspirin

CHA\textsubscript{2}DS\textsubscript{2}VASc = 1
Prefer OAC rather than aspirin

CHADS\textsubscript{2} = 0
Aspirin

CHADS\textsubscript{2} = 1
Prefer aspirin rather than OAC

CHA\textsubscript{2}DS\textsubscript{2}VASc \geq 2
OAC
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