

The CHADS₂ score for stroke risk stratification in atrial fibrillation – friend or foe?

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The risk of stroke in patients with non-valvular atrial fibrillation (NVAF) varies widely depending on patient age and the presence of other risk factors such as hypertension, diabetes mellitus, congestive heart failure or prior stroke or transient ischaemic attack (TIA) (1, 2). Warfarin reduces the risk of stroke by about two-thirds when compared to placebo or no treatment, and by about two-fifths when compared to aspirin, but substantially increases major bleeding (2, 3). The most feared complication of warfarin is intracranial bleeding which occurs at the rate of 2–5 per 1,000 patients per year and often results in disability or death (3). Consequently, the decision to use warfarin must balance the benefits of warfarin for stroke prevention against the risk of major bleeding.

The goal of stroke prediction models is to help clinicians and patients select the most appropriate antithrombotic therapy for stroke prevention. Because the absolute benefit of warfarin for stroke prevention increases with increasing baseline stroke risk whereas the absolute risk of major bleeding is more constant (3, 4), the balance between benefits and risks of warfarin in individual patients is determined primarily by their baseline untreated stroke risk. In this paper we critically examine the value of the CHADS₂ (acronym for recent Congestive heart failure, history of Hypertension, Age ≥ 75 years, Diabetes mellitus, and past history of Stroke or TIA) risk index to estimate stroke risk in patients with NVAF.

Baseline risk of stroke and net benefit of warfarin therapy

The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines and the American College of Chest Physicians guidelines recommend oral anticoagulation for patients with NVAF who are at high risk of stroke (prior thromboembolism or more than one moderate risk factor for stroke i.e., congestive heart failure, hypertension, age > 75 years,

diabetes), either oral anticoagulation or aspirin for patients at intermediate risk of stroke (those with a single moderate risk factor) and aspirin alone for those at low risk of stroke (no risk factors). These recommendations assume that there is no net benefit of oral anticoagulation in patients at low risk of stroke because any reduction in cardio-embolic stroke is likely to be outweighed by the increase in major and intracranial bleeding. Consistent with this assumption, recent analyses by the ATRIA (AnTicoagulation and Risk Factors In Atrial Fibrillation) Study investigators involving 13,559 adults with 66,000 patient-years of follow-up demonstrated no net benefit of warfarin in patients with a CHADS₂ score of 0 or 1 and an increasing net benefit in patients with a CHADS₂ score of 2 or above (5) (► Fig. 1). These analyses weighted intracranial haemorrhage by a factor of 1.5 relative to ischaemic stroke, reflecting the greater clinical impact of haemorrhagic vs. ischaemic stroke on clinical outcome.

The ATRIA analyses suggest that a stroke prediction rule would be useful if it reliably discriminated patients at low risk of stroke (CHADS₂ < 2 or annual stroke risk ≤ 2.5/100 patient-years) from those at higher risk. Increases or decreases from this threshold may be observed depending upon the relative weights attributed to the different outcomes and the higher bleeding rates observed in the community compared to a clinical trial setting. While some patients may rank the disutility due to stroke at the same level as death (6, 7), others are more averse to the risks of bleeding and the inconvenience of warfarin therapy. Distinguishing patients at intermediate risk of stroke (3–5 per 100 patient-years) from those who are at high risk (> 5 per 100 per year), is of lesser importance because all intermediate and high risk patients are likely to benefit from warfarin therapy unless they are at increased risk of bleeding or have another contraindication for oral anticoagulation (8, 9).

The CHADS₂ risk-prediction index

Numerous schemes have been devised for predicting stroke risk. The most popular of these is the CHADS₂ index (10). The risk factors included in the index were chosen from among those that independently predicted the risk of stroke in the Atrial Fibrillation Investigators (AFI) and Stroke Prevention in Atrial Fibrillation (SPAF) trials (11, 12). Two points are assigned for a prior history of stroke or TIA, and one point for each of the other four risk factors, and the score is calculated as the sum of the assigned points.

The characteristics of a high-quality prediction rule are that the predictive variables are derived by a methodologically rigorous process, the rule is validated independently in populations representative of the target population, and its usefulness in clinical

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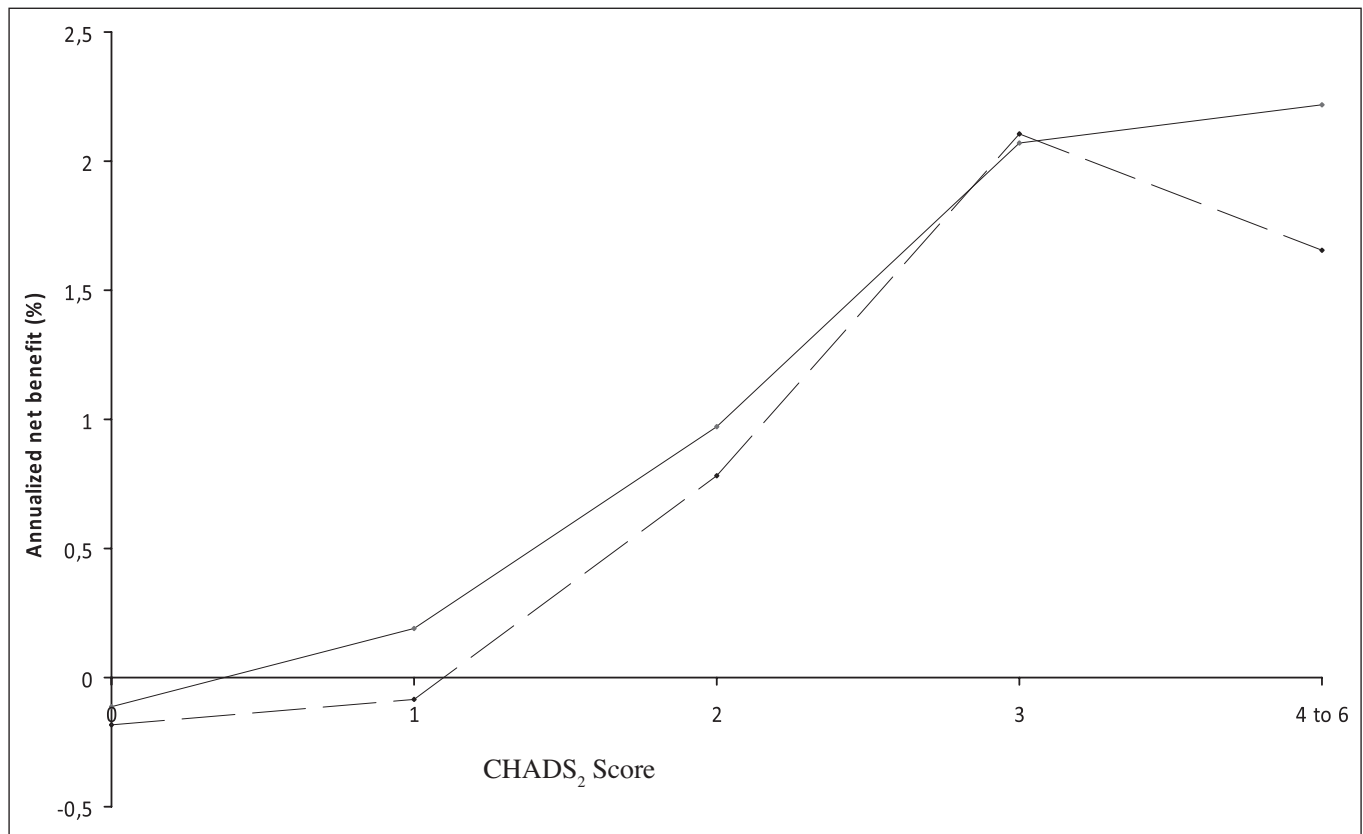


Figure 1: Net benefit of warfarin therapy in atrial fibrillation. Net benefit plotted as a function of CHADS₂ score at baseline. Indicates lack of net benefit when the CHADS₂ score is 0 (or even 1, when the weight attributed to ICH is greater). Bold line – ICH weight 1.5; dashed line – ICH weight 2.5. Data are from reference (5). Net benefit was calculated using the formula (thromboembolism rate_{off warfarin} – thromboembolism rate_{on warfarin}) – weight × (ICH rate_{on warfarin} – ICH rate_{off warfarin}). Singer et al. attributed a

weight of 1.5 to ICH (5). The weight of 2.5 is derived from previously published data from the ATRIA study which suggests that patients with ICH are 2.5 times as likely to die or have severe disability when compared to those with ischaemic stroke (23, 24). Baseline risk of stroke was 0.37, 1.19, 2.54, 3.89 and 6.34 per 100 patient-years in patients with CHADS₂ scores of 0, 1, 2, 3 and 4-6, respectively (5). ICH – intracranial haemorrhage.

practice has been established in a formal impact analysis. Although the choice of risk factors for inclusion in the CHADS₂ index was by expert consensus, its utility in categorising stroke risk has been extensively validated (10, 13–16). In the original validation study involving 1,733 patients in the US National Registry of Atrial Fibrillation, the stroke rate per 100 patient-years increased by a factor of 1.5 with each 1-point increase in score, such that patients with a CHADS₂ score of 0 had an adjusted stroke rate of 1.9/100 patient-years and patients with a score of 6 had a stroke rate of 18.2/100 patient-years (10). The *c* statistic, a measure of the accuracy of the model for predicting stroke, was 0.82. An ideal prediction rule has a *c* statistic of 1. More recent validation studies have yielded a lower *c* statistic, possibly because of changing risk factor profiles in contemporary patient populations with atrial fibrillation (due to greater awareness and better concurrent treatments in current practice) leading to lower risk of stroke. In most analyses, the predictive ability of the CHADS₂ index is at least as good as other risk stratification schemes (13–15). The CHADS₂ index has not undergone a formal impact analysis, but neither have the other risk prediction tools. Primarily because of its simplicity and broad appli-

cability, the CHADS₂ index has been widely adopted by physicians and guideline panels for stratifying stroke risk.

Does CHADS₂ reliably identify patients who do not require warfarin?

The CHADS₂ index has been collapsed into three strata to facilitate comparison with other clinical prediction rules, with a score of 0 constituting low risk, 1–2 intermediate risk, and 3–6 high risk of stroke (13–15, 17, 18). Most studies categorise about 10–25% of patients with NVAF as low risk (CHADS₂ score of 0) (13, 15, 17, 19), corresponding to stroke rates of 0.25 to 0.8/100 patient-years, with the upper limit of the 95% confidence intervals not exceeding 2/100 patient-years (13, 15–17, 19). In the most recent validation study using patients from the EuroHeart Survey, the CHADS₂ index categorised about 20% of patients into the low risk category with a risk of thromboembolic events of 1.4% (16). These data indicate that patients with a CHADS₂ score of 0 are at low risk of

stroke and can be safely treated with aspirin. The majority of patients (50–60%) have a CHADS₂ score of 1–3 and a risk of stroke in the range of 2.7–5.9/100 patient-years (10, 13, 14, 16). There are exceptions; in one series, patients with a CHADS₂ score of 1 constituted 32% of the total population and had stroke rates of 1.5 per 100 patient years (17). Nevertheless, the majority of patients with a CHADS₂ score of 1 are likely to benefit from warfarin therapy. Patients with a CHADS₂ score 4–6 have high stroke rates and should receive warfarin unless they have a contraindication.

Limitations of the CHADS₂ index

Although the CHADS₂ index appears to be at least as accurate as other risk prediction rules for stratifying patients with NVAf and for identifying those at low risk who do not require warfarin, some limitations exist (► Table 1). The CHADS₂ index categorises the majority of patients as being at intermediate risk for stroke but some patients with a score of 1 or 2 may have a stroke risk close to or even below the threshold of net benefit, potentially exposing them unnecessarily to the risks and burden of warfarin therapy (17, 18). Risk discrimination might be improved by including factors such as female sex (19), von Willebrand factor levels (14), and left ventricular function on echocardiography (20) in the index, but the latter laboratory tests are not universally available, are expensive and may compromise the simplicity of the CHADS₂ index and its applicability to practices across the world.

Risk prediction might also be improved by taking into account the stroke type (cardioembolic vs. other ischaemic stroke subtypes) in patients with a history of stroke, thereby providing further information to guide the choice between aspirin and warfarin (warfarin is better than aspirin for preventing cardioembolic stroke but not for preventing other stroke subtypes). But, brain imaging with magnetic resonance imaging would be required in order to obtain this information, again compromising the simplicity of the existing index. Finally, the CHADS₂ index may require re-evaluation for identification of patients suitable for prophylaxis with dabigatran and other emerging new anticoagulants.

Modifications of the CHADS₂ index

Lip et al. have proposed the CHA₂DS₂VASc index which combines the presence of vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age between 65 and 74 and female sex with the risk factors included in the original CHADS₂ index (16). Each of these three additional risk factors adds one point to the overall score and age ≥75 years adds two points (16). Patients with a CHA₂DS₂VASc score of 0, 1 and ≥2 are classified as being at low, intermediate and high risk for thromboembolic events, respectively. In the validation population, the index categorised about 9% of patients as being at low risk (0% per year), 15% as being at intermediate risk (0.6% per year) and 75% at high risk for stroke (3% per year; range

Table 1: Pros and Cons of the CHADS₂ index.

Pros
<ul style="list-style-type: none"> ● Simple ● Low cost ● Widely applicable ● Identifies low risk subjects who may not benefit from warfarin therapy (and may be safely treated with aspirin instead) ● Well validated
Cons
<ul style="list-style-type: none"> ● Classifies the majority of patients as being at intermediate risk (including some patients who may be at low risk) ● Does not include additional risk factors which may influence stroke-risk (e.g. female sex, von Willebrand factor levels, left ventricular ejection fraction) ● Does not distinguish between etiological subtypes of stroke ● Has not undergone formal impact analysis ● May not apply to new oral anticoagulants

1.6 to 11%) (16). While the risk of thromboembolic events in the low-risk patients was indeed low (i.e. 0%), this modification may not rectify the principal problem with the original CHADS₂ index, namely the miscategorisation of low risk patients as intermediate risk, thereby unnecessarily exposing them to the risks of warfarin therapy. Moreover, some patients classified as high risk with the modified index may have stroke risks below the threshold of net benefit with warfarin therapy (16). The *c* statistic for risk prediction with the CHA₂DS₂VASc index (0.602) was not different from that of the CHADS₂ score (0.586) (16).

Rietbrock et al. modified the CHADS₂ score by including female sex as a risk factor, extending the age categories (with increasing scores for age 40–64 through 85–115) and reweighing the scores assigned to stroke and TIA. The *c* statistic for this modified score (calculated as a continuous variable) was marginally better than that of the CHADS₂ score (0.72 vs. 0.68) (21). However, it is unclear whether using this modified score to categorise patients according to their risk of stroke improves the discrimination between low- and intermediate-risk patients.

Risk prediction in the era of new anticoagulants

By virtue of their efficacy, safety and improved convenience, one or more of the new oral anticoagulants is likely to replace warfarin for stroke prevention in NVAf. In the RE-LY trial, the new oral direct thrombin inhibitor, dabigatran 150 mg twice daily was superior to warfarin and dabigatran 110 mg twice daily was non-inferior to warfarin in preventing stroke or systemic embolism (22). Furthermore, the rates of haemorrhagic stroke and life threatening bleeding were significantly reduced with both doses of dabigatran (22). These data suggest that the threshold for net benefit with dabigatran treatment will be lower than that for warfarin therapy, and some patients classified as low risk by the CHADS₂ index may stand to benefit from anticoagulation with dabigatran. The

CHA₂DS₂VASc index may help to distinguish very-low-risk patients from the majority of patients who are likely to benefit from treatment with dabigatran.

Conclusion

The CHADS₂ index is a simple stroke risk prediction tool which in the majority of patients reliably discriminates those at low risk of stroke who are unlikely to benefit from warfarin therapy, from those at intermediate or high risk. Further improvements in risk discrimination can almost certainly be achieved by taking into account additional clinical and laboratory risk factors for stroke but this is likely to increase the cost and complexity of applying the index in clinical practice. As a result, the most important advantages of the CHADS₂ index – its simplicity and broad applicability – might be compromised, to the potential detriment of an already large and rapidly growing worldwide population of patients with NVAF.

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