Stroke risk in atrial fibrillation: Do we anticoagulate CHADS\(_2\) or CHA\(_2\)DS\(_2\)-VASc \(\geq 1\), or higher?

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Introduction

For every patient with atrial fibrillation (AF) one of the first decisions to be made is whether to recommend anticoagulation. For this decision the physician needs to weigh the benefit of reducing the risk of thromboembolism against the risk of causing serious bleeding by treatment. Randomised controlled trials provide the strongest evidence and have in AF patients demonstrated that vitamin K antagonists (VKA) reduce the risk of (all) stroke/systemic embolism and all-cause mortality, when compared to placebo (1). These studies were conducted in patients with a placebo stroke rate of around 4.5 strokes per 100 years (1). In more recent studies comparing warfarin with the non-VKA oral anticoagulants (NOACs), the warfarin event rate of stroke or systemic embolism varied between 1.5 and 2.4 per 100 years, and yet a significant reduction of stroke/systemic embolism was still obtained with dabigatran and apixaban compared with warfarin (2).

What perhaps really matters is whether a meaningful risk reduction can be obtained rather than the risk without treatment, and it is noteworthy that even the small risk of stroke or systemic embolism observed on warfarin in recent trials could be further reduced with the new agents.

However, what the clinical trials do not tell us is where the threshold for starting anticoagulation is. To aid this decision, stroke risk stratification scores have been developed to guide the clinician in decision-making.

The CHADS\(_2\) (Congestive heart failure, Hypertension, Age \(\geq 75\) years, Diabetes, previous Stroke) score is used in the American College of Chest Physicians (ACCP) (3) and Canadian guidelines (4) and the CHA\(_2\)DS\(_2\)-VASc (Congestive heart failure, Hypertension, Age \(\geq 75\) years, Diabetes, previous Stroke, Vascular disease, Age \(\geq 65\) years, Sex category [female]) used in European and National Institute of Clinical Excellence (NICE) guidelines (5). Both scores are easy to learn with one arguably being a bit more complex than the other with more risk factors. The use of two risk scores naturally generates a discussion as to which is better. Indeed, the randomised trials testing the NOACs against warfarin did not include many patients with a CHA\(_2\)DS\(_2\)-VASc score of 1, and hence these drugs have not been tested in all the patients currently recommended for anticoagulation by the European Society of Cardiology (ESC) and NICE guidelines.

In this Viewpoint article, we will address this discussion by focusing on three principal questions: a) What is the stroke rate at various points of the risk scores in various populations; b) How should the scores be used and when to anticoagulate; and c) How best to move forward.

What is the risk at different points of the CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores

With one additional stroke risk factor (i.e. omitting female as the only risk factor with CHA\(_2\)DS\(_2\)-VASc, that is CHA\(_2\)DS\(_2\)-VASc score of 1 for males, 2 for females) is currently sufficient to generally recommend treatment with oral anticoagulation, especially with the NOACs and well managed VKA. With the latter, stroke and bleeding risks are low with good quality anticoagulation control, as reflected by a high time in therapeutic range (TTR), i.e. above 70\% (6, 7). To strengthen a discussion we have shown the event rate of thromboembolism in relation to different points on the two scoring systems in \(\uparrow\) Figure 1 and \(\uparrow\) Figure 2. It is clear that there are differences even though all studies only investigated patients not treated with anticoagulation. Differences are likely driven by selection bias, a type of bias that the nationwide registries are less prone to.

The CHADS\(_2\) score

Focusing on CHADS\(_2\) it is clear that in the two Japanese cohorts (8, 9) as well as in the ATRIA cohort (10) the event rates with CHADS\(_2\) scores of 0 and 1 are very low (\(\uparrow\) Figure 1). Notably, the overall stroke rate off-anticoagulation in these cohorts were even lower than on-warfarin in some of the trials (11), and much lower than the stroke rate observed in the placebo arms of the original warfarin studies (12, 13). Suzuki et al. found a stroke rate of 1.3 per 100 years, Okumura et al. a stroke rate of 1.5 per 100 years, and the ATRIA cohort found a stroke rate of 2.1 per 100 years. Nonetheless, when screening stable outpatients not selected for anticoagulation, for example, in the ATRIA cohort, the stroke rate will be markedly lower than in average patients with AF. Another possibility for the very low event rates found in the ATRIA cohort may be due to the methodological approach, e.g. conditioning on the future when including patients at the time of the first diagnosis with AF while presupposing that the patients will live until two diagnoses with AF (10). Also, ATRIA even excluded patients with no health plan membership after diagnosis of AF and those...
with no outpatient care during the 12 months after index date (14).

Data from Framingham only demonstrated the stroke rate associated with a CHADS\textsubscript{2} score of 0 (15). Much higher stroke rates were observed in the US National Registry of Atrial Fibrillation (NRAF) study that relied on hospitalised cases (16). However, in this study Medicare beneficiaries who had acute AF and those age 65 were excluded, which may explain the reduced risk compared to the Danish and Swedish nationwide cohorts. Hospitalised AF patients also dominated the one- and 10-year risk of the Danish cohort (17) as well as the Swedish cohort (18).

In the Danish cohort the stroke rates (including ischaemic stroke, transient ischaemic attack (TIA), and systemic thromboembolism) were 3.7 for men and 5.4 per 100 years for women (19), and in the Swedish cohort, the event rate was 4.5 per 100 years (18). Hence, in these unselected patient populations the event rates off-anticoagulation more closely resemble the true ‘real world’ stroke rate for patients with AF.

Examine these results combined makes it clear that in studies a CHADS\textsubscript{2} score of 0 confers an event rate as high as that observed in the warfarin group of recent trials and in other studies a score of 1 hardly justifies anticoagulation.

The CHA\textsubscript{2}DS\textsubscript{2}-VASc score

Figure 2 shows similar data for CHA\textsubscript{2}DS\textsubscript{2}-VASc classification. The score was developed from the European Heart Survey (20) which included mainly outpatients. This study, as well as those by Suzuki (8) and Singer (10), display very low event rates at scores of 0 and 1. As expected from above, the Danish (17) and Swedish cohorts (18) demonstrate much higher risks, clearly indicating a possibility for benefit of anticoagulation with one additional stroke risk factor, that is, men with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1, or females with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 2. However, the limitations with these registries are the lack of some clinical data and information on why the specific subject was not anticoagulated.

Currently, the tipping point for when to recommend anticoagulation is set at 0.9 ischaemic strokes/systemic embolisms per 100 years (21). Even at a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1, the net clinical benefit for anticoagulation is positive (22).

Thromboembolic events

A recent study by Friberg et al. elegantly displays the impact of changing the definition of the outcome event, i.e. using ischaemic stroke only or using a combination of ischaemic stroke, unspecified stroke, TIA, and pulmonary embolism (23). Unsurprisingly, narrowing the definition of the outcome reduced the ‘headline’ event rate and with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1 the event rate ranged between 0.5 and 0.9 per 100 years, depending on the definition. The corresponding figures were not displayed for men and women separately which would have been valuable since women with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1 are not recommended anticoagulation.

Unfortunately, it seems like the authors ex-
cluded all patients at baseline if they initiated anticoagulation during follow-up, i.e. conditioning on the future, and this will lead to the exclusion of a number of subjects with an event. Indeed, AF patients are likely to initiate anticoagulation subsequent an ischaemic event. Also, a TIA should not be easily dismissed as such patients are at very high risk of a full-blown stroke, and in validated registries, administrative ICD-9 codes 434.XX, 433.X1, and V12.54 can have consistently high positive predictive values in identifying such patients with a confirmed cerebral event (24). Systemic embolism remains a highly relevant clinical endpoint in AF, reflecting which arterial tree the clot has ended up, and is significantly reduced by oral anticoagulation (25).

How to use CHADS$_2$ and CHA$_2$DS$_2$-VASc

It is clear from above that a score of 1 on either scale may represent patients that benefit or do not benefit from anticoagulation dependent on the population from where patients were selected. Different studies, from different time points or settings all contribute to the variation, but AF patients are far from 'static' and the risk profile should be regarded as dynamic. AF patients have high rates of hospitalisation and additional stroke risk factors emerge along the way, which translate to a greater risk of adverse cardiovascular outcomes (26, 27). For many patients the decision for the clinician is easy regardless of which score is used, i.e. patients at increased risk profits from anticoagulation, and the effort should be placed on the minority where the benefit is marginal compared to the risk. Hence, the focus should be drawn the patients categorised as low risk of thromboembolism.

Several studies (17, 18) have highlighted that the risk of thrombosis is highest immediately after diagnosis but Singer (28) suggests that the immediate risk category should not be part of decision. We disagree. The decision to anticoagulate takes into account also the near future and therefore the immediate risk is highly relevant. The question essentially raised is whether certain subpopulation should only receive temporary anticoagulation, a whole new question.

Much discussion about stroke risk uses hazard ratios (HR), and we suggest this should be strongly discouraged in the evaluation of scores such as these where there is competing risk. The HR describes the immediate risk at any time and because of competing risk the same HR is much more important for a young than for an older individual where the risk of dying from unrelated causes is much greater.

Nonetheless, an addition to just calculating a score the careful clinician will also take other data into account including the setting (29, 30). Consider an 80-year-old patient with known atherosclerosis admitted to hospital with AF, then this patient is naturally at higher risk compared to an otherwise healthy 80-year-old man where perhaps longstanding asymptomatic AF results in referral to the outpatient clinic.
Even though their stroke risk score may be identical.

Even more important is the risk factors that make up a stroke risk score of 1 – or 2. In Figure 3 and Figure 4 we have shown the event rate of thromboembolism is dependent on which component makes up a score of 0, 1, or 2 by CHADS₂ or CHA₂DS₂-VASc. Due to small numbers in several of the groups the estimates are associated with wide confidence limits, however, it would also be simplistic to suggest that all risk factors carry equal weight, and numerous studies have shown that this is not the case (29, 30). As not all risk factors are equal, by using a simple additive score, practicality and simplicity is gained at the cost of accuracy (17).

For patients at low or intermediate risk of thromboembolism it is not wise to use any score rigidly, but the actual components providing the score, the clinical setting, the duration of AF – and other factors, including patient values and preferences should be taken into account before making a decision (31). A recent study has shown that AF patients are desperate to avoid a stroke, and simply to avoid one stroke they are even prepared to sustain four major bleeds (32).

How best to move forward

Available studies of the relation between risk and actual use of anticoagulation (33) indicate a rather haphazard relation between use of anticoagulation and stroke risk, i.e. patients at higher risk of stroke do not have an increased usage of anticoagulation compared to patients at lower stroke risk (34). The main focus should therefore be on having physicians actually evaluate risk as part of the decision process rather than refining scores for the experts. Indeed, the European Society of Cardiology (ESC) guidelines de-emphasised the artificial categorisation into low, moderate and high risk strata, since stroke risk in AF is a continuum – and a risk factor-based approach is recommended instead. More importantly, rather than a didactic use of scores to artificially categorise into treatment groups, the 2012 ESC guidelines and NICE guidelines recommended that the first step is to use identify the ‘truly low risk’ patients (that is, CHA₂DS₂-VASc score 0 for males, 1 for females) who do not need any antithrombotic therapy. Subsequent to this step is to offer effective stroke prevention to AF patients with ≥1 additional stroke risk factors, and this means oral anticoagulation, whether this is well controlled VKA or treatment with a NOAC (5).

For the future, we may perhaps need better risk scores. However, derivation of any new risk scores should rely on extremely large studies of patients with AF not treated with anticoagulation, which would be difficult to find these days. A new score(s) should use absolute risk over a clinically relevant length of time such as
three or five years. All stroke risk factors do not necessarily carry equal risk, and it would be simplistic to assume otherwise.

Conflicts of interest
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