Stroke prevention with oral anticoagulant (OAC) treatment is an essential part of the management of atrial fibrillation (AF), with a resultant reduction in all strokes (by 64%), ischaemic stroke (by 67%) and all-cause-mortality (by 26%) with the vitamin K antagonists (VKA, e.g. warfarin) when compared to control/placebo (1). Thus, VKAs not only prevent strokes but saves lives, and given the likely advantage of the non-VKA oral anticoagulants (NOACs) over VKAs, the benefits are probably even better (2).

As the risk of stroke in AF is not homogeneous, different stroke risk stratification schemes (or risk scores) have emerged and have been subsequently refined, to help clinicians identify ‘high risk’ patients to be targeted for an ‘inconvenient’ drug, warfarin. The scores provide stratification according to the risk of stroke based on various risk factors. Differences between the developed schemes have led to different guideline recommendations, and to discussion among experts which score is better. It is, however, important to keep in mind that these schemes aim to aid everyday clinical practice; the main purpose is to design the study. Yet, one may expect that patient data from RCTs truly did not receive OAC treatment (due to the nature of the controlled environment), but the population can be (highly) selected, reflecting the inclusion/exclusion criteria for the particular RCT. In observational data, e.g. Swedish, Taiwan or Danish nationwide cohorts, the baseline assumption of no OAC treatment may be violated during follow-up as indications (not known) for the treatment may shift. One may be tempted to exclude patients at baseline if a prescription claim is observed during follow-up; however, this could lead to deflated event rates and may well introduce a potential bias (6, 7). For convenience, a more appropriate methodological approach (i.e. no conditioning on the future) would be to censor person-time at the time of a prescription claim (8). On the other hand, formal methodological assessment of the time on-treatment (continuously) has only limited impact on stroke event rates (9).

A recent paper by Friberg et al. also made some effort into clarifying why quarantine periods are important (6). The main objective is to obtain a ‘stable study population’ when observation time is started. However, arbitrary choices of quarantine periods relative to time of AF diagnosis could possibly fail in achieving the main objective. Applying a more generic approach by defining index date relative to the day of hospital discharge may reassure more stable study population (discharged from hospital). Indeed, different reported event rates may reflect different study settings, populations (hospitalised vs community), and healthcare plan (or not). Another example is the ATRIA cohort that potentially may have been affected by biases as only 52% of the available population was included (selection bias), and

**Different event rates from different populations**

The devil is perhaps in the details of the methodology. It is essential to ensure similar populations and settings when attempting to compare the performance of different stroke risk stratification schemes. While some research is based on data from randomised controlled trials (RCT) investigating AF patients without OAC treatment, others are based on large cohorts of AF patients deemed not on OAC treatment. Both types of data should be regarded as observational data when designing the study. Yet, one may expect
Additionally only included patients who had more than one AF diagnosis during follow-up (conditioning on the future) if no electrocardiogram with AF was available, as well as an existing healthcare plan (10).

With AF patients, we are not dealing with a 'static' healthcare state, as patient risk factors change over time, and hospitalisations are common in AF patients (11), leading to greater mortality (12). Hence, different follow-up times may reflect the different event rates published for the same study population. Perhaps a feasible explanation to this is that during the first year of follow-up more accurate stroke rate estimations for different risk factors can be obtained. But as age is a powerful driver of stroke risk, the estimates may become less accurate for longer follow-up times. This should argue for using shorter (e.g. 1 year) than those proposed by ESC/NICE guidelines recommendations.

Table 1: Overview of event rates from various studies investigating patients off oral anticoagulant treatment and stratified according to ESC/NICE guidelines recommendations.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Study period</th>
<th>Data source</th>
<th>Number of patients</th>
<th>Outcome of interest</th>
<th>Event rate in CHA2DS2-VASc score of 0</th>
<th>Event rate in CHA2DS2-VASc score 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friberg et al.</td>
<td>2012</td>
<td>2005 to 2008</td>
<td>Nationwide cohort</td>
<td>90,706</td>
<td>Ischaemic stroke</td>
<td>0.2%/year (n=15)</td>
<td>0.6%/year (n=63)</td>
</tr>
<tr>
<td>Olesen et al.</td>
<td>2012</td>
<td>1997–2006</td>
<td>Nationwide cohort</td>
<td>73,538</td>
<td>Ischaemic stroke/SE/PE</td>
<td>0.78%/year</td>
<td>2.01%/year</td>
</tr>
<tr>
<td>Singer et al.</td>
<td>2013</td>
<td>1996 to 1997</td>
<td>Ambulatory based cohort</td>
<td>10,927</td>
<td>Ischaemic stroke/thromboembolic events</td>
<td>0.04%/year</td>
<td>0.55%/year</td>
</tr>
<tr>
<td>Taillandier et al.</td>
<td>2013</td>
<td>2000 to 2010</td>
<td>Community based cohort</td>
<td>8,962</td>
<td>Ischaemic stroke/thromboembolism</td>
<td>0.69%/year</td>
<td>NR</td>
</tr>
<tr>
<td>Lip et al.</td>
<td>2014</td>
<td>1999–2012</td>
<td>Nationwide cohort</td>
<td>47,090</td>
<td>Ischaemic stroke/SE/TIA</td>
<td>1.13%/year</td>
<td>2.94%/year</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2014</td>
<td>1997 to 2011</td>
<td>Hospital based cohort</td>
<td>548</td>
<td>Ischaemic stroke</td>
<td>2.4%/year</td>
<td>6.6%/year</td>
</tr>
<tr>
<td>Chao et al.</td>
<td>2014</td>
<td>1996–2011</td>
<td>National Health Insurance Database</td>
<td>9,416</td>
<td>Ischaemic stroke</td>
<td>1.15%/year</td>
<td>NR</td>
</tr>
<tr>
<td>Chao et al.</td>
<td>2015</td>
<td>1996 to 2011</td>
<td>National Health Insurance Database</td>
<td>12,935</td>
<td>Ischaemic stroke</td>
<td>NR</td>
<td>2.75%/year</td>
</tr>
<tr>
<td>Lip et al.</td>
<td>2015</td>
<td>1998–2012</td>
<td>Nationwide cohort</td>
<td>39,400</td>
<td>Ischaemic stroke</td>
<td>0.49%/year</td>
<td>1.50%/year</td>
</tr>
<tr>
<td>Lip et al.</td>
<td>2015</td>
<td>1999–2012</td>
<td>Nationwide cohort</td>
<td>22,582</td>
<td>Ischaemic stroke/SE/TIA</td>
<td>1.13%/year</td>
<td>4.32%/year</td>
</tr>
</tbody>
</table>


next step is to assure proper communication of the obtained results. Rothman et al. are quite clear on the matter of reporting risk or rates: “Apart from insensitivity to important distinctions, incidence rates have interpretational difficulties insofar as they are often confused with risks (probabilities)” (13). Observational studies investigating performances of CHADS$_2$ or CHA$_2$DS$_2$-VASc scores are almost inevitably ‘disturbed’ by competing risk of death (if not handled properly). This causes researchers to report event rates, which cannot be regarded as absolute risks; and this has interpretational differences. Heuristically, the rate provides the ‘instantaneous risk’ relative to the current risk set while the absolute risk is the risk relative to the original risk set (population at baseline). The latter is the scale of interest for risk stratification because it reflects the clinical question in mind: “What is the probability that my patient will have a stroke during the next X years?” Instead of the somewhat ambiguous rate statement: „On average, if my patient is still alive at some unspecified time point during the next X years, what would the risk be of having a stroke the next day?” When the current risk set changes substantially during follow-up because of competing risks, conclusions based on comparison of rates may be qualitatively different from those obtained from considering absolute risks (14, 15). Also, this should not be overlooked when interpreting reported results (especially related to performances of risk stratification schemes). The interpretational difficulty from risks and event rates persists to hazard ratios (HR), e.g. contrasting outcomes stratified according to certain risk factors. Hence, HRs should preferably not be discouraged, but the reader should keep in mind that these HRs also exist on a rate scale and not a risk scale. HRs or rate ratios have been and most likely will continue to be extensively used – perhaps because they are computationally convenient. Indeed, computational convenience and simplicity/practicality seems to have played a key role in the stroke risk literature, and additionally, may be a reason why ‘additive risk scores’ are preferred.

Communicating the message

Under the assumption that the selected methods and designs are applicable, the...
Using the risk stratification schemes

The risk of stroke is not homogeneous. Stroke risk in AF patients is a continuum, and patients have previously been divided into artificial categories of low-, moderate-, and high-risk strata. As stroke rates have decreased over the last decades (16), the focus has shifted into identifying the ‘truly low-risk’ AF patients who will benefit from OAC treatment (17).

Several studies have reported stroke rates for patients with and without indication for OAC treatment using the CHA2DS2-VASc score - the risk score endorsed by the European Society of Cardiology (ESC), National Institute of Clinical Excellence (NICE), and lately by the American College of Cardiology/American Heart Association/Heart Rhythm Society (AHA/ACC/HRS). The CHA2DS2-VASc score has been proposed as being best at identifying ‘truly low risk’ patients (18), even being able to predict the absence of stroke amongst lone AF patients over a 12-year follow-up period (19).

As ►Table 1 shows, the stroke event rates for patients with a CHA2DS2-VASc score of 0 varied between 0.04%/year to 2.4%/year, while for patients with a CHA2DS2-VASc score of 1 the event rate ranged 0.55%/year to 6.6%/year. An important element is to identify patients with 1 point (if male sex, or 2 points if female sex) as this additional stroke risk factor will trigger a recommendation for effective stroke prevention, which essentially means OAC treatment. Improper distinct of the sex category may lead to inadequacy of reported results (6). Whilst for scientific purposes, classifying patient’s stroke risks (or not) according to the current risk profile. This may also mitigate the discussion on whether or not an additive approach (which assumes equal weight of each risk factor) is appropriate (20). Indeed, untreated patients with CHA2DS2-VASc = 1 (males) and 2 (females) displayed a high stroke and mortality event rate depending on the length of follow-up and included stroke diagnoses.

The net clinical benefit, balancing ischaemic stroke reduction against serious bleeding is positive, for patients with ≥1 additional stroke risk factor, especially in the era of NOACs (21, 22). Thus, treating clinicians really need to ask whether it is really worth taking the risk by not anticoagulating those AF patients with ≥1 additional stroke risk factor, that is, a CHA2DS2-VASc score of 1 (males) and 2 (females)? Particularly since AF patients are also desperate to prevent strokes (for some, viewed as a fate worse than death), and simply to prevent one stroke, patients are even prepared to sustain four major bleeds (23, 24).

In summary, we need to do better for our patients, and even one stroke risk factor confers real risks of fatal and disabling strokes, and OAC offers a positive net clinical benefit for our patients.

Acknowledgement

Anders Gorst-Rasmussen and Flemming Skjøth are thanked for their highly valuable inputs.

Conflicts of interest

None declared.

This Viewpoint Article reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

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Thrombosis and Haemostasis 113.6/2015

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