The likelihood of decreasing strokes in atrial fibrillation patients by strict application of guidelines

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Aims

Despite the known increased stroke risk associated with AF and the benefit of oral anticoagulation (OAC) in high-risk patients, still ~20% of all ischaemic strokes are atrial fibrillation (AF) related. We aimed to evaluate the frequency of inappropriate anticoagulation in all patients admitted with AF associated ischaemic stroke and calculate the theoretical number of preventable strokes in case of proper guideline adherence and assess secondary stroke prevention at discharge.

Methods and results

In this cross-sectional study, all patients with ischaemic strokes admitted to our hospital during May 2003–August 2006 in whom the diagnosis AF was either known or established during hospital stay were identified. We studied if their admission and discharge antithrombotic therapy was in accordance with the published guidelines. Subsequently, we calculated the number of preventable strokes in case AF patients would have received adequate antithrombotic treatment on admission. On admission, in 51% of the OAC eligible known AF patients the drug was withheld. Improved antithrombotic guideline adherence potentially would have prevented 20 out of the 89 (22%) ischaemic strokes. At discharge at least 10% of the patients were still insufficiently protected against recurrent stroke.

Conclusion

Many known AF patients admitted with ischaemic stroke lack adequate antithrombotic treatment on admission. Antithrombotic guideline adherence in these patients has the potential to prevent a substantial number strokes. Secondary stroke prevention at discharge is also suboptimal.

Keywords

Atrial fibrillation • Ischaemic stroke • Oral anticoagulation

Introduction

Atrial fibrillation (AF) is associated with an increased risk of ischaemic stroke and accounts for almost 20% of all ischaemic strokes.1 Stroke due to AF is often more severe and has a worse prognosis.2

The risk of AF related stroke can be lowered with adequate antithrombotic therapy (ATT). Stroke prevention with aspirin in AF patients with a low thrombo-embolic risk seems justified,3 whereas in high-risk AF patients treatment with vitamin K antagonists is superior to placebo and aspirin.4,5 Despite overwhelming evidence antithrombotic guideline adherence in AF patients is suboptimal6,7 and treatment is not at all tailored to risk score8,9 resulting in undertreatment in primary and secondary stroke prevention, both quantitatively and qualitatively.10

However, mostly underuse of only oral anticoagulation (OAC) is considered in a numerical way without any indication of the associated clinical toll. Therefore, the aim of the present hospital based study among all admissions for AF related ischaemic strokes, is to

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assess primary and secondary quantitative antithrombotic undertreatment as a and estimate the possible decrease in numbers of strokes if antithrombotic guidelines are strictly applied.

Methods

Patients
In this retrospective cross-sectional study, we included all consecutive patients admitted with a (first) CT or MRI proven ischaemic stroke to our hospital during the period May 2003–August 2006 in whom the diagnosis AF was either known or newly detected during hospital stay. Patients were identified using the Maastricht Stroke Registry, a registry of all consecutive stroke admissions.

We defined AF according to the most recent guidelines as an episode of more than 30 s where consistent P waves are substituted by fibrillatory waves together with an irregular, often rapid ventricular response when atrioventricular conduction is intact.3 Patients without an AF history prior to admission but an ECG with AF during hospital stay were classified as ‘newly detected AF’. Patients with a history of AF were considered ‘known AF’ patients. All ECGs retrieved from the hospitals electronic ECG database, were reviewed by two of us (R.P. and H.C.) to verify the diagnosis.

Using hospital chart review we retrieved medical history, admission and discharge medication. On the basis of medical history prior to the index stroke, the CHADS2 score was calculated.12 We use the phrase ‘virtual CHADS2 score’ to refer to patients exhibiting associated diseases without the diagnosis AF (prior to the index stroke).

The study was approved by the institutional review board at the University Maastricht Medical Centre.

Admission guideline adherence assessment
As the period of observation stretched from 2003 to 2006 we used the ACC/AHA/ESC 2001 guidelines for the management of patients with AF to classify patients accordingly as high, medium, or low risk.11 Guideline adherent ATT consisted of OAC in patients with at least one high-risk factor or more than one intermediate risk factor and aspirin in low-risk patients. We defined undertreatment in case high-risk AF patients were not using OAC and whenever low-risk AF patients did not use aspirin.

We considered a documented history of malignancy or bleeding (gastro-intestinal bleeding or intracranial haemorrhage (ICH)), severe kidney or liver dysfunction (glomerular filtration rate <30 mL/min, aspartate transaminase and alanine transaminase more than three times the upper limit, respectively), alcohol abuse or non-compliance (e.g. unwilling or dementia) to be contraindications for OAC. In these cases any regimen (OAC, aspirin or no antithrombotic medication) was considered guideline adherent irrespective of stroke risk.

Discharge guideline adherence assessment
Patients receiving OAC at discharge were considered to be treated according to the guidelines. In patients with either the above mentioned contraindications for the use of OAC, or a documented reason by the treating neurologist to withhold OAC (i.e. poor neurological outcome) any antithrombotic regimen was also considered guideline adherent. All other scenarios were classified as antithrombotic undertreatment.

Calculation of the number of potential preventable ischaemic strokes
Figure 1 displays the methods for calculating the theoretic number of preventable strokes with strict use of OAC. For example, assume that of 18 OAC eligible, AF related stroke patients six receive aspirin, four receive OAC, and eight receive no antithrombotic medication. In theory, OAC prescription in this population could have prevented 6 × 0.40 = 2.4 strokes (benefit OAC vs. aspirin) plus 8 × 0.60 = 4.8 strokes (benefit OAC vs. placebo), in total 7.2 strokes per year. On the basis of the deduced population we took the additional cases of OAC associated ICH (0.4%) into account, producing a net number of preventable strokes.

Statistical analysis
Data analysis was performed with SPSS statistical software (release 15.0, SPSS Inc., Chicago, IL, USA). Results in Table 1 are reported as mean ± standard deviation for age and CHADS2 score and as proportion within the column for the remaining variables. When testing continuous variables for differences between two groups we used the t-test, for detecting differences between categorical variables the χ² statistic was used. A P-value < 0.05 was considered statistically significant.

Results

Patient characteristics
Of the 1120 stroke admissions, 163 (15%) were associated with AF, of which 89 (55%) were known AF and 74 (45%) newly detected AF patients. In total, 138 patients (85%) were discharged alive and thus survived the index stroke. Baseline characteristics are shown in Table 1. The average CHADS2 score prior to the index stroke was 2.34 in the known AF patients and in the newly detected group 2.05. The CHADS2 score distribution is displayed in Figure 2. Twelve of the known AF patients had a (relative) contraindication for OAC being either a history of malignancy (n = 4, two patients with colorectal cancer, one patient with bladder cancer, and another with prostate cancer) or bleeding (n = 8).

Potentially preventable ischaemic strokes
Prior to admission, a total of 45 out of the 89 patients (51%) with known AF were insufficiently protected against ischaemic stroke (Figure 3). In 41 (58%) of the high-risk patients, OAC was unrightfully withheld, although 4 (67%) of the low-risk patients did not receive aspirin.

The remaining 44 (49%) patients did receive guideline adherent ATT (Figure 3). Taking into account the extra cases of ICH caused by the use of OAC, the total net number of potentially preventable strokes with guideline adherent ATT in the known AF patients was 20 out of 89 (22%).
Table 1 Baseline characteristics of known and the newly detected atrial fibrillation patients admitted with a stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Known AF (n = 89)</th>
<th>Newly detected AF (n = 74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>80 ± 8</td>
<td>80 ± 9</td>
<td>0.881</td>
</tr>
<tr>
<td>Female sex</td>
<td>48 (54)</td>
<td>48 (65)</td>
<td>0.158</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>2.3 ± 1.4</td>
<td>2.05 ± 1.27(^a)</td>
<td>0.221</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>13 (15)</td>
<td>6 (8)</td>
<td>0.209</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>42 (48)</td>
<td>40 (55)</td>
<td>0.372</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>19 (21)</td>
<td>11 (15)</td>
<td>0.306</td>
</tr>
<tr>
<td>History of ischaemic stroke</td>
<td>26 (29)</td>
<td>15 (21)</td>
<td>0.207</td>
</tr>
<tr>
<td>History of transient ischaemic attack</td>
<td>9 (10)</td>
<td>7 (10)</td>
<td>0.912</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Contra indications for oral anticoagulation</th>
<th>Known AF (n = 89)</th>
<th>Newly detected AF (n = 74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of bleeding</td>
<td>8 (9)</td>
<td>2 (3)</td>
<td>0.100</td>
</tr>
<tr>
<td>History of malignancy</td>
<td>4 (5)</td>
<td>9 (12)</td>
<td>0.072</td>
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<tr>
<th>Medication</th>
<th>Known AF (n = 89)</th>
<th>Newly detected AF (n = 74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation</td>
<td>24 (38)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>33 (37)</td>
<td>28 (38)</td>
<td>0.760</td>
</tr>
<tr>
<td>Bêta blocker</td>
<td>45 (51)</td>
<td>32 (43)</td>
<td>0.544</td>
</tr>
<tr>
<td>RAS inhibitor</td>
<td>38 (42)</td>
<td>21 (28)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, % of patients per group or absolute numbers of patients (n). Analysis was by t-test and \( \chi^2\) as appropriate.

AF, atrial fibrillation; CHADS2, congestive heart failure, hypertension, age >75, diabetes mellitus and previous stroke/transient ischaemic attack (doubled); RAS, renin–angiotensin aldosterone system.

\(^a\)This figure represents the virtual CHADS2 score: patients exhibiting associated diseases without the diagnosis AF.
Secondary stroke prevention

Of all patients, survival status at discharge was missing in one case. We found no significant difference in the number of patients alive at discharge between the known AF patients and the newly detected AF group (83 vs. 87%, $P = 0.664$), nor between the undertreated and guideline adherently treated known AF patients (82 vs. 84%, $P = 0.852$).

At discharge OAC was prescribed to 84 (61%) patients. Of all 53 (39%) patients not receiving OAC, 10 had a (relative) contraindication for OAC: being a history of bleeding ($n = 3$) or malignancy ($n = 5$), one case of alcohol abuse and one patient with severe dementia. In the 43 patients who did not have any OAC contraindication, the decision was motivated in 28 (65%) of the 43 patients. Poor neurological outcome was the main reason ($n = 12$), followed by excessive fall risk ($n = 5$), temporary aspirin use to prevent hemorrhagic transformation ($n = 3$), recent bleeding ($n = 3$; haematuria, rectal blood loss, unspecified bleeding condition), and high age ($n = 2$). High blood pressure, presence of retinopathy, and type A aortic dissection were reasons to withhold OAC in the remaining three patients. Taking all this into account, at discharge at least 15 (10%) patients were insufficiently protected against recurrent stroke.

Discussion

We found more than 50% of the known AF patients admitted because of ischaemic stroke to have insufficient antithrombotic protection, with only 30 (42%) of the eligible high-risk AF patients receiving OAC. Theoretically, one-fifth of these strokes could have been prevented just by prescribing guideline adherent antithrombotic medication. Secondary stroke prevention is also suboptimal since at least 10% of the AF patients admitted with an ischaemic stroke leave the hospital insufficiently protected against recurrent stroke.

The use of OAC as primary stroke prevention in our population of high-risk AF patients is in line with the recent report by Gladstone et al. Both are rather disappointingly low compared with the 68% of AF patients receiving OAC in clinical practice reported by Nieuwlaat et al. and considering the trend of increased OAC prescription. The high undertreatment is likely attributable to the advanced age of our population, which tends to discourage physicians to prescribe OAC.

Potentially preventable strokes

Antithrombotic undertreatment resulted in the highest absolute number of potentially preventable ischaemic strokes in the CHADS$_2$ score 1 group (data not shown). This represents the prevention paradox: despite the lowest relative ischaemic stroke risk the majority of patients fall into the lower CHADS$_2$ categories resulting in the highest absolute ischaemic stroke numbers. The latest, 2006, guidelines on the antithrombotic management of AF patients let patient and physician preference determine the use of either OAC or aspirin in the CHADS$_2$ score 1 group whereas the 2001 version recommend OAC in these patients. Our findings question the switch to a less vigorous OAC regimen because seemingly low-risk patients actually appear to have such a high ischaemic stroke risk that aspirin does not provide sufficient protection. This could in part be explained by the presence of other, currently infrequently used stroke risk increasing characteristics. The recent fine-tuning of the CHADS$_2$ score by Lip et al. embodies this hypothesis. Beside re-evaluating age as a risk factor Lip et al. added female gender (Sc) and vascular disease (V) to the score, producing the acronym CHA$_2$DS$_2$-VASc. Compared with conventional stroke risk schema the CHA$_2$, DS$_2$-VASc score proved to be superior in correctly identifying AF
patients with a truly low stroke risk. Together with recent evidence that treatment of patients with a CHADS2 score of 1 with OAC relates to a significantly better prognosis (combined endpoint of stroke and all-cause mortality) compared with patients treated with only an antiplatelet agent and that the significant benefit of OAC in these individuals is offset by a limited increase in risk of bleeding, advocates use of OAC in this ‘grey area’. Finally, another opportunity to increase the potentially preventable strokes is hinted by the large number of stroke patients with here-tofore undetected: AF screening programs. Particularly in individuals with a high ‘virtual’ CHA2DS2-VASc score, i.e. patients in whom the presence of AF necessitates use of OAC, this might proof to be cost-effective on the long run.

Antithrombotic guideline adherence at discharge
Considering ischaemic stroke is a strong independent risk factor for recurrent ischaemic stroke it is disappointing to find at least 10% of patients insufficiently protected against recurrent stroke at discharge. This percentage might even be higher because of the 90% guideline-treated patients only 59% actually received OAC (data not shown). In the remaining cases written documentation was provided why OAC was withheld. The validity of these reasons—as reported by the neurologists—could not be checked because of the retrospective nature of the study. However, based on evidence regarding risk of (intracerebral) bleeding in elderly AF patients on OAC and in patients with an excessive fall risk, at least 6 (21%) of the motivations not to prescribe OAC can be considered invalid.

Limitations
First, we did not dispose of admission international normalized ratio (INR) values of the patients on OAC. This is a missed opportunity to study the importance of qualitative guideline deviance. In a similar setting Gladstone et al. recently revealed that 75% of the AF patients using OAC as primary stroke prevention had subtherapeutic INR values at the time of the stroke, making (widespread) qualitative undertreatment among our population very likely. Another indication of subtherapeutic INR values on admission lies in the observed lack in survival difference of the index stroke...

Figure 3 Admission antithrombotic medication in the known atrial fibrillation patients. Values are expressed as number of patients (n) or % of patients. OAC, oral anticoagulation.
between guideline adherent and undertreated patients, despite the known detrimental outcome of low INR values in this matter.24 However, our goal was to assess quantitative underuse of OAC. The probable presence of qualitative undertreatment only increases the percentage of undertreated patients and the number of potentially preventable strokes, underlining the message that still a lot of gain in stroke prevention lies in correct use of available drugs.

Secondly, the single, AF specialized university centre nature makes extrapolation of our results both within and beyond the Netherlands difficult. However, our findings are in line with the multi-centre study of Gladstone et al.10 and the EXAMINE-AF study found similar antithrombotic prescription in AF patients among Dutch general practitioners, internists, and cardiologists.6

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