Impact of advanced age on management and prognosis in atrial fibrillation: insights from a population-based study in general practice

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Abstract

Objectives: to examine the use of antithrombotic therapy and predictors of stroke and death in very elderly (≥85 years) atrial fibrillation (AF) patients in a general practice cohort from the UK.

Design: retrospective, observational cohort study; 12-month follow-up period.

Setting: eleven general practices serving the town of Darlington, England representing a population of 105,000 patients.

Patients: two thousand two hundred and fifty-nine patients with a history of AF, 561 (24.8%) aged ≥85 years.

Main outcome measures: use of antithrombotic therapy by age group and predictors of stroke and death.

Results: five hundred and sixty-one (24.8%) AF patients aged ≥85 years (mean (SD) age 89 (4) years; 66% female) identified with a mean CHA2DS2-VASc score of 4.6 (SD 1.4). Thirty-six per cent received oral anticoagulation (OAC) compared with 57% in the 75–84 years age group. Forty-nine per cent of the very elderly received antiplatelet (AP) monotherapy; recorded OAC contraindications and declines were greatest among those aged ≥85 years. Stroke risk was highest among the very elderly (5.2% per annum), despite anticoagulation (3.9%). Multivariate analyses demonstrated an increased risk of stroke with AP monotherapy (odds ratio (OR) 2.45, 95% confidence intervals (CIs) 1.05–5.70) and a significant reduction in all-cause mortality with OAC therapy (OR 0.59, 95% CI 0.36–0.99).

Conclusion: the majority of very elderly AF patients in general practice do not receive OAC despite their higher stroke risk; almost half received AP monotherapy. AP use independently increased the risk of stroke, signifying that effective stroke prevention requires OAC regardless of age, except where true contraindications exist.

Keywords: atrial fibrillation, antithrombotic therapy, age, stroke, general practice, older people

Introduction

Advancing age is a principal risk factor for stroke in atrial fibrillation (AF) [1–3]. Elderly patients benefit as much from anticoagulation therapy, and the net clinical benefit compared with aspirin therapy is even greater than in younger AF patients [4–6]. Despite this the literature suggests that elderly patients do not receive adequate stroke prevention in the form of oral anticoagulation [7–9] and many are treated with antiplatelet agents instead which is strongly discouraged by current guidelines [10–12]. Many barriers exist which may explain why elderly patients are less likely to receive oral anticoagulation. There is doubt among many physicians that stroke prevention evidence derived from highly selective AF populations translates into ‘real-world’ practice.

The present study compared AF patients aged ≥85 years from a general practice population in the UK with younger age groups in relation to the choice of antithrombotic therapy and to determine the predictors of stroke and death.

Methods

Study population

All patients living in Darlington and registered with a general practice were eligible (11 practices, 105,000 residents).
Patients were included if they had a diagnosis of AF or atrial flutter, at any point, entered in their electronic medical records and were alive in March 2012.

**Data collection**

Data were collected predominantly using the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) tool. This electronic record interrogation software collects demographics, details about the AF diagnosis, stroke risk factors, antithrombotic treatment and has been described previously [9]. Separate searches of the database were conducted to identify patients who experienced a stroke or died in the 12-month observation period as these data are not collected by GRASP-AF. This was facilitated by all practices using TPP’s SystemOne® electronic record system (Supplementary data, Table S1, are available in *Age and Ageing* online). All events were manually reviewed and adjudicated.

Data were analysed according to four age bands: ≥85, 75–84, 65–74 and ≤64 years. Refer to Supplementary data, available in *Age and Ageing* online, for details on methodology and statistical analysis.

**Results**

A total of 2,259 (2.15%) patients with AF were included in the present analysis. The majority were elderly (mean (standard deviation, SD) age 76 [12] years); 59% were aged ≥75 years, with one-quarter aged ≥85 years (Table 1).

There was a significant drop in utilisation of OAC in the very elderly (≥85 years) (mean (SD) age 89 [4] years) compared with the 75–84 years age group (36 versus 57%, respectively, \(P < 0.001\)); this reduction in OAC usage was partly attributable to the trends towards a higher rate of OAC decline by patients (8.0 versus 5.5%, respectively, \(P = 0.07\)) and a higher perceived risk of contraindication to OAC (16 versus 8.9%, respectively, \(P = 0.053\)) among the very elderly. In contrast, almost half of the patients aged ≥85 years were receiving antiplatelet monotherapy (Table 1).

The incidence of new stroke increased significantly with age, with a trend towards greater risk of stroke among the very elderly within the 1-year of follow-up compared with those aged 75–84 years (5.2 versus 3.3%; \(P = 0.097\)). As expected, there was a prominent increase in mortality in the oldest group (21%, \(P < 0.001\) versus all other age groups). Of note, very elderly patients had a relatively high risk of stroke despite OAC (3.9%). There were very few haemorrhagic strokes overall and no significant differences between the age groups (in the whole population and in those receiving OAC) (Table 1).

Univariate analysis revealed that history of diabetes, previous stroke and use of antiplatelet therapy (\(P = 0.036\)) were the strongest predictors of future stroke (Table 2). Multivariate analysis, after adjustment for stroke risk factors, revealed that utilisation of antiplatelet agents was a significant independent predictor of future stroke among AF patients in the UK general practice.

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**Table 1. Demographic and clinical characteristics of the cohort by age groups**

<table>
<thead>
<tr>
<th></th>
<th>&lt;65 years</th>
<th>65–74 years</th>
<th>75–84 years</th>
<th>≥85 years</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N) (%)</td>
<td>367 (16)</td>
<td>554 (25)</td>
<td>777 (34)</td>
<td>561 (25)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>55 ± 9</td>
<td>70 ± 3</td>
<td>80 ± 3</td>
<td>89 ± 4</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>110 (30)*</td>
<td>192 (35)*</td>
<td>369 (47)*</td>
<td>370 (66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (37)*</td>
<td>334 (60)*</td>
<td>528 (68)</td>
<td>406 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>54 (15)*</td>
<td>148 (27)*</td>
<td>175 (23)</td>
<td>113 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>55 (15)</td>
<td>108 (19)*</td>
<td>178 (23)*</td>
<td>173 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>28 (7.6)*</td>
<td>93 (17)</td>
<td>168 (22)</td>
<td>139 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous haemorrhagic stroke</td>
<td>0 (0.0)</td>
<td>6 (1.1)</td>
<td>4 (0.5)</td>
<td>7 (1.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>24 (6.5)*</td>
<td>95 (17)</td>
<td>152 (20)</td>
<td>118 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAC used</td>
<td>121 (33)*</td>
<td>297 (54)</td>
<td>445 (57)*</td>
<td>202 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAC + antiplatelet agents</td>
<td>12 (3)</td>
<td>34 (6)</td>
<td>41 (5)</td>
<td>22 (4)</td>
<td></td>
</tr>
<tr>
<td>OAC</td>
<td>109 (30)</td>
<td>263 (48)</td>
<td>404 (52)</td>
<td>180 (32)</td>
<td></td>
</tr>
<tr>
<td>Antiplatet agents</td>
<td>124 (34)</td>
<td>181 (33)</td>
<td>247 (32)</td>
<td>275 (49)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>122 (33)</td>
<td>76 (14)</td>
<td>85 (11)</td>
<td>84 (15)</td>
<td></td>
</tr>
<tr>
<td>OAC declined</td>
<td>7 (1.9)</td>
<td>18 (3.2)*</td>
<td>43 (5.5)(^a)</td>
<td>45 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAC contraindicated</td>
<td>8 (2.2)</td>
<td>23 (4.2)*</td>
<td>69 (8.9)*</td>
<td>87 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New stroke</td>
<td>3 (0.8)</td>
<td>9 (1.6)*</td>
<td>26 (3.3)(^a)</td>
<td>29 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New haemorrhagic stroke</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
<td>2 (0.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.5)*</td>
<td>24 (4.3)*</td>
<td>68 (8.8)*(^b)</td>
<td>120 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New stroke on OAC</td>
<td>1 (0.7)</td>
<td>8 (2.7)</td>
<td>13 (2.9)</td>
<td>8 (4.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>New haemorrhagic stroke on OAC</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Death on OAC</td>
<td>2 (1.5)</td>
<td>12 (4.0)</td>
<td>27 (6.1)</td>
<td>27 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVA as a cause of death on OAC</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0.79</td>
</tr>
</tbody>
</table>

CV A, cerebrovascular accident; OAC, oral anticoagulation.

*\(P < 0.05\) versus the next older age category.

\(^a\)\(P < 0.001\) versus the next older age category.

\(^b\)\(P < 0.053\) versus the next older age category.

\(^c\)\(P < 0.097\) versus the next older age category.
predictor of stroke (odds ratio (OR) 2.45, 95% confidence interval (CI) 1.05–5.70, P = 0.038), while treatment with OAC showed a non-significant reduction in stroke (OR 0.53, 95% CI 0.22–1.28, P = 0.16).

Univariate predictors of all-cause mortality were age, history of vascular disease and diabetes, with a trend towards increased risk of death associated with previous stroke and heart failure. Use of OAC was associated with a significant reduction in mortality risk, while antiplatelet agents had no significant impact on death (P = 0.35). After adjustment for stroke risk factors, treatment with OAC remained independently predictive of a lower risk of all-cause mortality (OR 0.59, 95% CI 0.36–0.99, P = 0.047), with a similar but non-significant trend seen for antiplatelet agents (Table 2).

**Discussion**

Previous primary care-based studies have demonstrated that nearly 20% of AF cohorts are aged ≥85 years [13, 14]. This study, compared with older studies, found that 25% of AF patients were ≥85 years, possibly reflecting that this is the fastest growing age group in developed countries [15]. This study confirmed that older age was a prohibiting factor for OAC use; the difference was considerable (57% in those aged 75–84 years versus 36% in ≥85 years) while Cowan and colleagues [9] found a smaller disparity in OAC prescription by age in a large UK primary care cohort (58% in 65–79 age group versus 46% in ≥80 age group). However, Scowcroft and colleagues [16] found a similar drop in the anticoagulation rate with increasing age from 55% in 70- to 79-year-old patients to 32% in patients aged ≥80 years in the UK General Practice Research Database.

There are many contributing factors to explain why frail elderly patients are less likely to receive OAC. Although logistic difficulties and perception issues with vitamin K antagonists (VKA) have been largely overcome by non-VKA oral anticoagulants (NOACs) [17–19], factors like concomitant disease, cognitive decline, reduced life expectancy and, in particular, fear of bleeding and falls persist. The bleeding risk associated with VKA increases with old age [4, 20, 21]. Thus, many elderly patients are treated with antiplatelet agents instead which was again confirmed by our study [9, 13, 14]. This is unfortunate as trial data from elderly cohorts like BAFTA [5] (mean age 81.5 years) confirmed superior efficacy with VKA compared with aspirin, also evident in younger cohorts, but with no difference in major bleeding. In addition, the WASPO trial of elderly patients (mean age 83.9 years) [22] showed better tolerability of VKA compared with aspirin. Furthermore, high risk of falling was not associated with significantly increased risk for major bleeding [23]. This study only collected data on intracranial haemorrhage, for which age ≥85 years is a risk significant factor [24]. Reassuringly, the intracranial haemorrhage rate was low across all age bands in this study including patients aged ≥85 years (0.4% per annum) [24].

There is concern that trial data do not translate well to ‘real-world practice’ due to the selectivity of study populations. For example, BAFTA [5] included only 21% of all identified AF patients. Hence, it is important that this entirely unselected primary care cohort showed that antiplatelet treatment was an independent predictor of stroke, increasing the risk >2-fold compared with OAC which in turn showed a non-significant reduction in stroke risk, but a significant reduction in all-cause mortality. It should be acknowledged that differences in the reasons for, and rate of, recorded contraindications and patient’s declining treatment with OAC and antiplatelet therapy within and between age groups are a potential source of bias.

The residual stroke risk despite anticoagulation remained significantly raised among the very elderly at 3.9% compared with other studies [4, 5], although the average age was considerably higher in this study (89.4 years). Given that the adjacent age band in our cohort (75–84 years, mean age 80)

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**Table 2. Predictors of stroke and death in patients at moderate–high risk of stroke**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Stroke OR (95% CI)</th>
<th>P value</th>
<th>Death OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of oral anticoagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of antiplatelet agents</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*Predictive value of antithrombotic agents after adjustment for stroke risk factors.
showed an identical residual stroke risk of 1.6% compared with BAFTA [5] (mean age 81.5 years) might indicate that anticoagulation at an even more advanced age is indeed associated with significantly higher stroke risk; this requires further evaluation.

**Key points**

- The majority of all AF patients managed in primary care are aged 75 years or older, with roughly a quarter aged ≥85 years.
- Most very old AF patients (aged ≥85 years) in UK general practice do not receive OAC, despite their higher stroke risk.
- Almost half of those aged ≥85 years receive antiplatelet monotherapy.
- Antiplatelet use independently increased the risk of stroke in the very old.
- Effective stroke prevention requires OAC regardless of age, except where true (and absolute) contraindications exist.

**Conflicts of interest**

Prof. G.L. has served as a consultant for Bayer, Astellas, Merck, Sanoﬁ, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Sanoﬁ Aventis. Dr D.L. has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare, BMS/Pfizer. In addition, Dr D.L. is on the Steering Committee of a Phase IV apixaban study (AEGEAN). Both Prof. G.L. and Dr D.L. have participated in various clinical trials of stroke prevention in atrial fibrillation. Dr A.W. has served as a clinical advisor to Boehringer Ingelheim, Pfizer, BMS, Sanoﬁ Aventis and Daiichi-Sankyo and also received educational grants and investigator payments. In addition, he served as speaker for Boehringer Ingelheim, Sanoﬁ and Pfizer. Dr E.S. has no conflicts of interest to declare.

**Supplementary data**

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**References**

Inflammatory and vascular markers and olfactory impairment in older adults

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Abstract

Background: the incidence of olfactory impairment increases sharply in the eighth and ninth decades of life but the aetiology of age-related olfactory decline is not well understood. Inflammation and atherosclerosis are associated with many age-related conditions and atherosclerosis has been associated with olfactory decline in middle-aged adults.

Objective: to determine if inflammatory markers and atherosclerosis are associated with the development of olfactory impairment in older adults.

Design: longitudinal, population-based study.

Setting/participants: a total of 1,611 participants, aged 53–97 years in the Epidemiology of Hearing Loss Study without olfactory impairment at the 1998–2000 examination and with follow-up at a subsequent examination 5 and/or 10 years later.

Methods: the San Diego Odor Identification Test was used to measure olfaction. High sensitivity C-reactive protein, interleukin-6 and tumour necrosis factor-α were measured in serum and carotid ultrasound images were obtained for the measurement of carotid intima media thickness (IMT) and plaque assessment. Medical history, behavioural and lifestyle information were obtained by interview.

Results: inflammatory markers, IMT and plaque were not associated with the 10-year cumulative incidence of olfactory impairment in adjusted Cox proportional hazard models. Among those <60 years, the mean IMT [hazard ratio (HR) = 4.35, 95% confidence interval (CI) = 1.69–11.21, tertile 3 versus tertile 1] and the number of sites with plaque (HR = 1.56, 95% CI = 1.17–2.08, per site) were associated with an increased risk of developing an olfactory impairment at follow-up.

Conclusion: subclinical atherosclerosis at a younger age may be a risk factor for the development of olfactory impairment.

Keywords: olfaction, atherosclerosis, inflammation, population-based, epidemiology, older people