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PROGRESSION OF STROKE RISK IN ATRIAL FIBRILLATION: COHORT STUDY IN GENERAL PRACTICE

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ABSTRACT

Background: Due to new technologies, more people with atrial fibrillation (AF) are likely to be diagnosed under the age of 65 years.

Aim: To investigate risk of someone diagnosed with AF aged <65 developing an indication for anticoagulation before they reach 65.

Design and setting: Population based cohort study of patients from English practices using a primary care database of electronic medical records, the Clinical Practice Research Data Link (CPRD).

Method: Patients aged <65 newly diagnosed with AF were included. The CHA2DS2-VASc score was derived at time of diagnosis based on patients’ medical records. Patients not eligible for anticoagulation were followed up until they became eligible or turned 65 years old. The primary outcome of interest was development of a risk factor for stroke in AF.

Results: Among 18,178 patients diagnosed with AF aged <65, 9,188 (51%) were eligible for anticoagulation at time of diagnosis. Among 8,990 ineligible, 1,688 (23%) developed a risk factor during follow up before turning 65 or leaving the cohort for other reasons, at a rate of 6.1 per 100 patient-years. Hypertension and heart failure were the most common risk factors to occur, with rates of 2.51 (95% CI 2.25-2.59) and 2.41 (95% CI 1.38-1.64) per 100 patient years respectively. Rate of new diabetes was 0.93 (95% CI 0.83-1.04) per 100 patient years.

Conclusion: People aged <65 with AF are at higher risk of developing hypertension, heart failure and diabetes than the general population, so may warrant regular review to identify new occurrence of such risk factors.

KEY WORDS

atrial fibrillation; stroke risk; primary care; anticoagulation; risk factors

HOW THIS FITS IN

New technologies are likely to result in younger people being diagnosed with atrial fibrillation who do not require anticoagulation treatment at diagnosis. There are few data to inform follow up of such people. Risk of development of hypertension and heart failure was found to be high in this group (indications for anticoagulation), suggesting that more frequent review is required as compared to the general population.
INTRODUCTION

Atrial fibrillation (AF) is a rhythm disturbance of the heart that becomes increasingly common as people age(1). AF is a strong risk factor for stroke(2), but this risk can be substantially reduced by treatment with anticoagulation(3). Recognising that such treatment is not without hazard (of bleeding), guidelines recommend that treatment with anticoagulation is offered on the basis of risk of stroke(4). A widely used score to assess risk of stroke in AF is the CHA2DS2-VASc score(5). The guidelines recommend that anticoagulation should be considered or offered to all patients with AF except those under the age of 65 with no risk factors other than their sex(4). This raises the question as to how frequently patients should be reviewed who fall into this category (under age 65 with no risk factors), so that anticoagulation can be considered should their risks change.

In the UK, the Quality and Outcomes Framework (QOF) encourages annual review of such patients(6), but there is little evidence to inform this aspect of clinical practice. A cohort study in Denmark of people aged 30-65 with atrial fibrillation confirmed the utility of the CHA2DS2-VASc score in this population, and that all the individual risk factors remained independent predictors of stroke in this age group(7). With regard to risk of development of the individual CHA2DS2-VASc risk factors in people with AF, a systematic review of cohort studies showed that AF is associated with increased future risk of heart failure and peripheral vascular disease(8). For hypertension and diabetes mellitus, the focus has been on the risk of AF in association with these conditions, rather than the other way round(9, 10). Thus, there is only limited evidence on the risk of development of risk factors for stroke in people who have AF. This is likely to be a growing issue in the future due to the increased use of wearable devices that can incidentally detect AF (11, 12). Therefore, in this analysis of a cohort of people in general practice newly diagnosed with AF under the age of 65, we sought to quantify the proportion that had an indication for anticoagulation, and for those that did not, the risk of developing an indication for anticoagulation prior to their 65th birthday, and the risk of development of the individual CHA2DS2-VASc risk factors.

METHODS

Data sources
The Clinical Practice Research Datalink (CPRD) GOLD is a database of electronic primary care records in the UK, based on patients attending GP practices which use the Vision computer system. CPRD has been shown to be a nationally representative sample corresponding to about 7% of the UK population in 2013(13). The data includes coded information on medical diagnoses, referrals, tests and all prescriptions issued at the practice.

Study population
We used a cohort included in a previous study(1). This cohort included patients from English practices newly diagnosed with AF between the 1st January 2004 and 31 December 2018, identified using diagnostic codes for AF. For the current study we considered only patients that were under 65 at time of AF diagnosis (Figure 1).

CHA2DS2-VASc risk score
We used the CHA2DS2-VASc score to determine the patients’ eligibility for anticoagulation. We calculated the risk score directly for each patient, rather than relying on the coding of the CHA2DS2-VASc itself in the patient record again based on diagnostic codes in clinical records for each
condition. The code lists for these diagnoses were developed as part of a project on the epidemiology of multimorbidity(14, 15) – see supplementary table. For hypertension, diagnostic codes were used rather than blood pressure level.

**Statistical analysis**

We calculated the proportion of AF patients under 65 that are eligible for anticoagulation at time of diagnosis based on current guidelines that anticoagulation should not be offered to people in this age group with AF and no risk factors other than their sex (i.e., a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0 for men or 1 for women)(4).

For those that were ineligible for anticoagulation at diagnosis we then calculated the rate at which they become eligible through the development of relevant conditions (from the CHA\textsubscript{2}DS\textsubscript{2}-VASc score). The start of follow-up was the date of AF diagnosis and the end of follow-up was the earliest of: the last day the patient was registered at the practice, date of death, the last day the practice contributed to CPRD, 31 December 2018 (our end of study date) or the date the patient turned 65 years old. Our primary outcome was development of the first CHA\textsubscript{2}DS\textsubscript{2}-VASc risk factor. As secondary outcomes we looked at the risk of each risk factor occurring separately (heart failure; hypertension; diabetes; stroke/TIA/systemic embolism and vascular disease), independently of another risk factor having already occurred during follow up. In the latter analysis we included all conditions developed during follow up instead of just the first one, and individual time at risk takes into account when each risk factor occurred.

Incidence rates were calculated as the number of patients who develop relevant conditions during follow-up (numerator) divided by the total person-years at risk (denominator). The numerator includes only patients who develop relevant conditions during follow up and excludes those that become eligible when turning 65 years old. The denominator is the sum of the person-years at risk from all eligible patients. Stratified incidence rates by age group were calculated through the use of a Lexis expansion where each person time at risk was split according to their age group(16). We report 95% confidence intervals using the Poisson distribution.

As a post-hoc analysis, we show the evolution of risk factors over the first 10 years after AF diagnosis in a Kaplan-Meier graph. This graph shows the estimated probability of having no risk factors (estimated survival function) for the primary and secondary outcomes.

**RESULTS**

During the time period 2004-2018, 18,178 new cases of AF were identified in people under the age of 65 (18.2% of all new cases), as shown in figure 1(1). A little over half of these (50.5%) had a pre-existing risk factor for AF, and so were immediately eligible for anticoagulation. Presence of at least one risk factor was more likely in older patients, with 60.7% of people aged 60-64 years having a risk factor, as compared to 29.1% of people aged 40-49 years (table 1). Hypertension was the most common risk factor (present in 39%), and heart failure the least common (6%). Prevalence of all risk factors rose with age. In each age stratum, a higher proportion of men than women had a risk factor, but this difference was not substantial. The distribution of total CHA\textsubscript{2}DS\textsubscript{2}-VASc score was similar in men and women, with the women’s score shifted to the right by one – a feature of the assignment of a point for sex (figure 2).
The majority of the 8,990 participants without an indication for anticoagulation were men (68%) reflecting their higher prevalence of AF (table 1). Over the period of follow up, 1,688 (23%) participants developed a risk factor at a rate of 6.1 (95% CI 5.8-6.4) per 100 patient years prior to reaching the age of 65 or leaving the cohort for other reasons (table 2). The rate was lowest (4.8, 95% CI 4.2-5.4 per 100 patient years) in people aged 40-49 years, and highest (7.1, 95%CI 6.6-7.6 per 100 patient years) in people aged 60 to 64. Men developed a risk factor at a higher rate than women (6.75 per 100 patient years versus 4.85 per 100 patient years).

Hypertension was the most common risk factor to develop in the study cohort without an initial indication for anticoagulation with an incidence of 2.65 (95% CI 2.47-2.84) per 100 patient years, followed by heart failure (1.58 per 100 person years , 95% CI 1.45-1.72), and diabetes (0.95 per 100 person years (0.85-1.06)). The incidence of stroke and vascular disease was 0.71 per 100 person years (0.62-0.81) and 0.34 per 100 person years (0.29-0.41) respectively. Development of these risk factors over time is shown in figure 3 (and supplementary table 2). The risks of a new risk factor being identified are particularly high in the first year following the diagnosis of AF. This is driven largely by new diagnoses of hypertension and heart failure.

**DISCUSSION**

**Summary**

Half of people diagnosed with AF under the age of 65 have an indication for anticoagulation. The remaining half become eligible for anticoagulation at a rate of 6% per annum, most commonly because of development of hypertension or heart failure.

**Strengths and limitations**

To our knowledge, this is the first study to look at risk of development of risk factors for stroke in people with AF. We included just under 9,000 participants who did not have a risk factor at baseline, so were able to report risks with reasonable precision in terms of width of confidence interval. This cohort, while representative of UK primary care, will have had their AF largely diagnosed through traditional methods (namely 12 lead ECG) since wearable devices such as apple watches and fitbits did not have the AF detection function enabled outside trials in the UK by 2018, and NICE only recognised the use of other ECG technology to diagnose paroxysmal AF in 2021. We do not know if these people will be representative of people with AF in the future, who will be increasingly diagnosed with novel technologies. Validity of our analysis depends upon the accuracy of GP coding of both AF and the risk factors for AF, which is prone to error(17, 18). For example, if we had used blood pressure in addition to hypertension codes, we would have increased our sensitivity to hypertension, but with a loss of specificity. It is possible that the association between diagnosis of AF and development of heart failure and hypertension in the first months following diagnosis reflects reverse-causality. In this analysis, we cannot distinguish to what extent the risks of development of risk factors for stroke relate to the AF, or to other factors such as obesity and socio-economic deprivation which are associated both with AF and risk factors for stroke. Over half of our participants left the cohort before reaching the age of 65. While this was mostly due to their practice leaving CPRD, it is plausible that this might have affected the observed rates of risk factor occurrence, if practices that left CPRD were systematically different from practices that stayed in it.
Since detection of risk factor occurrence depends upon GP diagnosis, the true risks are likely to be higher.

**Comparison with existing literature**

The low risk of stroke in this population is below that observed for people with a CHA$_2$DS$_2$-VASc score of 0 or 1 in a Danish cohort(5), thus confirming that it is not appropriate to offer anticoagulation to such people. It is difficult to estimate what would be the incidence rates of the risk factors in people not in AF, due to lack of studies of incidence in these risk factors in equivalent populations over a similar time period. Nevertheless, we observed a high incidence of heart failure compared to those not in AF in this age group(19) consistent with the five fold increase in risk of heart failure in AF observed in observational studies(8). Our observed incidence of diabetes was about twice what would be expected in a similar aged population without AF(20). Similarly, our incidence of hypertension was approximately double the rate of new hypertension diagnosed through health checks(21).

**Implications for research and/or practice**

While there is guidance on the symptomatic management of AF in people under the age of 65(4), there is only limited evidence as to how to follow up stroke risk in people diagnosed with AF who do not meet the threshold for anticoagulation treatment. We conducted this cohort study of just under 9,000 such people to inform this issue. The risk of developing heart failure, hypertension or diabetes in this population seems higher than would be expected in the non-AF population, particularly in the case of heart failure. This suggests that standard care should include regular assessment for these risk factors so that they can be managed and anticoagulation to prevent stroke can be started promptly. This is consistent with the current QOF indicator that rewards re-assessing stroke risk annually for people with AF whose CHA$_2$DS$_2$-VASc score is less than 2, though it does not prompt active case finding of any of the CHA$_2$DS$_2$-VASc risk factors(6). More formal epidemiological studies of the association of atrial fibrillation with these risk factors would enable firmer recommendations to be made.

**FUNDING**

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**ETHICAL APPROVAL**

This study was approved by the Independent Scientific Advisory Board for Medicines and Healthcare products Regulatory Agency research (protocol reference number 17_079R). No further ethics approval is required.

**COMPETING INTERESTS**

All authors report grants from the NIHR School of Primary Care Research, during the conduct of the study. JL reports grants from the Wellcome Trust and the National Institute for Health Research,
outside the submitted work. JM is on an advisory board for BMS/Pfizer on an AF screening trial, and is chief investigator of an NIHR funded programme grant on screening for atrial fibrillation. DE is a co-investigator on this same NIHR programme.

ACKNOWLEDGEMENTS

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. JM is an NIHR Senior Investigator.

DATA AVAILABILITY STATEMENT

The study uses data from the Clinical Practice Research Datalink (CPRD). CPRD does not allow the sharing of patient-level data. The code lists used in this study is part of a set of lists made available at https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/.

REFERENCES

Figure 1: Flowchart showing the number of patients included for each analysis aim, starting from the number of patients included in Mendonça et al. 2020.

(1) There is overlap in the categories specified.
**Table 1:** Presence of risk factors for stroke by age and sex in 18,178 participants aged under 65 at time of diagnosis

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No risk factors</th>
<th>At least one risk factor</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Vascular disease</th>
<th>Stroke/TIA</th>
<th>congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td>8,990 &amp; 49.5</td>
<td>9,188 &amp; 50.5</td>
<td>7,062 &amp; 38.8</td>
<td>2,155 &amp; 11.9</td>
<td>1,425 &amp; 7.84</td>
<td>1,231 &amp; 6.77</td>
<td>1,107 &amp; 6.09</td>
</tr>
<tr>
<td>Age group</td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
</tr>
<tr>
<td>40-49</td>
<td>1,928 &amp; 70.9</td>
<td>792 &amp; 29.1</td>
<td>570 &amp; 3.14</td>
<td>173 &amp; 0.95</td>
<td>87 &amp; 0.48</td>
<td>93 &amp; 0.51</td>
<td>106 &amp; 0.58</td>
</tr>
<tr>
<td>50-59</td>
<td>4,014 &amp; 52.0</td>
<td>3,698 &amp; 48.0</td>
<td>2,821 &amp; 15.52</td>
<td>919 &amp; 5.06</td>
<td>532 &amp; 2.93</td>
<td>442 &amp; 2.43</td>
<td>455 &amp; 2.50</td>
</tr>
<tr>
<td>60-64</td>
<td>3,048 &amp; 39.3</td>
<td>4,698 &amp; 60.7</td>
<td>3,671 &amp; 20.19</td>
<td>1,063 &amp; 5.85</td>
<td>806 &amp; 4.43</td>
<td>696 &amp; 3.83</td>
<td>546 &amp; 3.00</td>
</tr>
<tr>
<td>Female</td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
</tr>
<tr>
<td>40-49</td>
<td>532 &amp; 75.1</td>
<td>176 &amp; 24.9</td>
<td>129 &amp; 0.71</td>
<td>40 &amp; 0.22</td>
<td>13 &amp; 0.07</td>
<td>22 &amp; 0.12</td>
<td>26 &amp; 0.14</td>
</tr>
<tr>
<td>50-59</td>
<td>1,293 &amp; 55.6</td>
<td>1,034 &amp; 44.4</td>
<td>818 &amp; 4.50</td>
<td>230 &amp; 1.27</td>
<td>96 &amp; 0.53</td>
<td>149 &amp; 0.82</td>
<td>109 &amp; 0.60</td>
</tr>
<tr>
<td>60-64</td>
<td>1,066 &amp; 41.7</td>
<td>1,490 &amp; 58.3</td>
<td>1,234 &amp; 6.79</td>
<td>299 &amp; 1.64</td>
<td>144 &amp; 0.79</td>
<td>221 &amp; 1.22</td>
<td>129 &amp; 0.71</td>
</tr>
<tr>
<td>Male</td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
<td> </td>
</tr>
<tr>
<td>40-49</td>
<td>1,396 &amp; 69.4</td>
<td>616 &amp; 30.6</td>
<td>441 &amp; 2.43</td>
<td>133 &amp; 0.73</td>
<td>74 &amp; 0.41</td>
<td>71 &amp; 0.39</td>
<td>80 &amp; 0.44</td>
</tr>
<tr>
<td>50-59</td>
<td>2,721 &amp; 50.5</td>
<td>2,664 &amp; 49.5</td>
<td>2,003 &amp; 11.02</td>
<td>689 &amp; 3.79</td>
<td>436 &amp; 2.40</td>
<td>293 &amp; 1.61</td>
<td>346 &amp; 1.90</td>
</tr>
<tr>
<td>60-64</td>
<td>1,982 &amp; 38.2</td>
<td>3,208 &amp; 61.8</td>
<td>2,437 &amp; 13.41</td>
<td>764 &amp; 4.20</td>
<td>662 &amp; 3.64</td>
<td>475 &amp; 2.61</td>
<td>417 &amp; 2.29</td>
</tr>
</tbody>
</table>

TIA: Transient Ischaemic Attack
Figure 2: Distribution of CHA$_2$DS$_2$-VASc risk score at time of AF diagnosis in patients under 65, stratified by gender.

NOTE: 1 point is assigned in CHA$_2$DS$_2$-VASc for being female, hence no females have risk score of 0.
Table 2: Risk of becoming eligible for anticoagulation in the subsample (n=8,990) that was diagnosed with AF under 65 years and was low risk at diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Total person-years</th>
<th>Number(%) of patients that become eligible for anticoagulation during follow up</th>
<th>Rate of becoming eligible for anticoagulation during follow up (per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>27,524</td>
<td>1688 (18.8)</td>
<td>6.13 (5.85-6.43)</td>
</tr>
<tr>
<td>Male</td>
<td>18,522</td>
<td>1251 (20.5)</td>
<td>6.75 (6.39-7.14)</td>
</tr>
<tr>
<td>Female</td>
<td>9,002</td>
<td>437 (15.1)</td>
<td>4.85 (4.42-5.33)</td>
</tr>
<tr>
<td>Age group*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>4,796</td>
<td>228</td>
<td>4.75 (4.18-5.41)</td>
</tr>
<tr>
<td>50-59</td>
<td>12,718</td>
<td>749</td>
<td>5.89 (5.48-6.33)</td>
</tr>
<tr>
<td>60-64</td>
<td>10,011</td>
<td>711</td>
<td>7.10 (6.60-7.64)</td>
</tr>
</tbody>
</table>

*Age group in which the risk factor was diagnosed
Figure 3: Kaplan-Meier graph showing the evolution of risk factors over the first 10 years after AF diagnosis. Summary statistics from this graph are shown in Supplementary Table 2.