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Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009

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ABSTRACT

Objective To assess use of thromboprophylaxis in UK general practise among patients with atrial fibrillation (AF); to investigate whether elderly patients are less likely to receive anticoagulation therapy than younger patients.

Design Retrospective cohort study

Setting UK General Practice Research Database (GPRD)

Patients Aged ≥ 60 years with a new diagnosis of AF (2000–2009).

Interventions None.

Main outcome measures The main outcome measure was initiation of warfarin in the first year following diagnosis. Patients were categorised by stroke risk (CHADS₂ score) and bleeding risk (HAS-BLED score).

Results 81 381 patients were identified (21% aged 60–69 years, 37% aged 70–79 years, 42% aged 80+ years). Patients aged 80+ years were significantly less likely to be initiated on warfarin than younger patients, adjusted for gender, practice and comorbidities; 32% of patients aged 80+ years received warfarin compared with 57% aged 60–69 years ($p < 0.0001$), and 55% aged 70–79 years ($p < 0.0001$). For all strata of CHADS₂/HASBLED scores, patients aged 80+ years were significantly less likely to be treated with warfarin than younger patients. Logistic regression showed that female sex, low Basal Metabolic Index (BMI), age over 80 years, increasing HAS-BLED score and dementia were independently associated with reduced use of warfarin. Stroke/Transient Ischaemic Attack (TIA), hypertension, heart failure and left ventricular systolic dysfunction were associated with increased use. Patients with HAS-BLED > CHADS₂ were less likely to be initiated on warfarin. Higher CHADS₂ scores were associated with increased anticoagulation use.

Conclusions Anticoagulation is being under-used in patients with AF aged 80+ years, even after taking into account increased bleeding risk in this age group.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is associated with high morbidity and mortality, with stroke being the most significant complication.¹ AF increases the risk of stroke 5-fold, and accounts for around 15% of all strokes.² While AF can affect adults of any age, the prevalence increases with age: 3.8% among people aged >60 years rising to 9.0% among those aged >80 years.³ AF is a growing problem, projected to increase with the ageing population and the increased survival of patients with chronic cardiac

disorders, such as ischaemic heart disease and congestive heart failure (CHF) that predispose to AF.⁴

Oral anticoagulation treatment with a vitamin K antagonist, traditionally warfarin, has been demonstrated to be highly effective, reducing the relative risk of stroke in patients with AF by around two-thirds, with a typical absolute annual risk reduction of 2.7%.⁵ Guidelines recommend that the decision to use anticoagulation is primarily based around an assessment of stroke risk in atrial fibrillation.⁶ Older age is recognised as one of the key risk factors. With regard to the two risk stratification schemes in common use, the CHA₂DS₂-VASc score recommends that all people in AF age ≥ 75 years should be anticoagulated, and the CHADS₂ score that anticoagulation is considered for all people in this age group, but is recommended in the presence of an additional risk factor.⁷ However, recent studies have found that warfarin prescription was unrelated to CHADS₂ score.^{8,9}

Recent National Institute for Health & Clinical Excellence (NICE) guidance recommends use of anticoagulation for all people aged ≥ 75 years in AF.¹⁰ Despite this, less than half the patients aged over 80 years receive warfarin among both hospitalised and outpatient populations.^{10–16} A UK study found that between 1994 and 2003, patients with AF aged 85 years and above were five times less likely to be treated with anticoagulants than patients aged 55–64 years.¹⁷

Bleeding risk is often cited as a reason for non-use of warfarin among elderly patients, in which case, aspirin is often used as an alternative.^{11–14} However, the Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial showed that in patients aged 80–89 years there were significantly more adverse events including bleeding in patients treated with aspirin compared with warfarin.¹⁸ This is consistent with the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study which found no significant difference in risk of major haemorrhage between warfarin and aspirin in people aged ≥ 75 years.¹⁹

In the light of the stronger evidence base for using anticoagulation in the elderly,¹⁹ the development of scores to quantify bleeding risk in atrial fibrillation,²⁰ and the emergence of new anticoagulants, it is timely to examine whether the underuse of anticoagulation in the elderly persists, and the extent to which this can be explained by risk of bleeding. This study sought to examine anticoagulation treatment of elderly patients (80+ years) compared with younger

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patients (60–69 years, 70–79 years) within a cohort of patients with AF from the UK population, and to determine the extent to which any differences in treatment prescribing among different age groups might be explained by bleeding risk.

METHODS

Study design

This was a cohort study of patients from the General Practice Research Database (GPRD)²¹ with a first diagnosis of AF, between 2000 and 2009. The GPRD includes approximately three million residents in the UK registered with over 600 general practitioners (GPs). The database includes demographics, medical diagnoses, referrals and prescriptions. AF diagnoses were identified using the GPRD Read codes (see appendix 1).

To be eligible, patients had to be flagged as having data of an acceptable quality (as defined by GPRD), and be registered with practices whose data quality met the criteria for an 'up-to-standard' practice. Each patient had to have at least 12 months of data between registering with the practice and their first diagnosis of AF. Patients had to be over the age of 60 years at the time of first diagnosis of AF.

From this cohort, patients who were initiated on warfarin in the year following the AF diagnosis were identified. Warfarin initiation was defined as at least one prescription for warfarin within the first year following AF diagnosis (see appendix 2 for warfarin codes).

Data analysis

Descriptive statistics were recorded at baseline for the AF cohort at first diagnosis of AF, and for the cohort of patients treated with warfarin at first prescription for warfarin (if within 12 months of diagnosis). Comorbid conditions were defined using GPRD Read codes (see Appendix 1). Patients were split into three age groups: 60–69 years, 70–79 years, and 80+ years based upon age at AF diagnosis. Differences between groups were tested using χ^2 tests, with the group of patients aged 80+ years as the reference group.

Patients were split between warfarin-treated and warfarin-untreated, based on whether they were initiated on warfarin within their first year following AF diagnosis.

Patients within the AF cohort were categorised into risk groups at baseline using two commonly used risk scores: CHADS₂ and CHA₂DS₂-VASc. CHADS₂ score allocates one point each for CHF, hypertension, age >75 years, diabetes mellitus and two points for a prior stroke/TIA. The CHADS₂ score was used to stratify patients within the analysis, as this method is most widely used. The CHA₂DS₂-VASc score incorporates the additional risk factors of vascular disease, age 65–74 years, and female gender, and gives two points each to age ≥75 years and prior stroke/TIA/thromboembolism, and one point each to all other factors.

The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio (INR), elderly (>65 years), drugs/alcohol) is recommended to assess the bleeding risk of patients with AF when deciding whether to prescribe anticoagulation.²² Hypertension was defined as a diagnosis of hypertension, or a systolic blood pressure reading of at least 160 mmHg in the last year. Abnormal renal function required a patient to have a Read code for chronic dialysis, renal transplant, chronic kidney disease stage 5, or a serum creatinine level of 200 mmol/l or above. Abnormal liver function included chronic hepatic disease, cirrhosis or significant hepatic derangement. Bleeding history or predisposition was defined as patients with a record of a serious bleed or anaemia in the previous year, and a labile INR required that the patient was prescribed warfarin in the

year prior to AF diagnosis, and had a time in therapeutic range lower than 60% in that year. Drugs refer to Non-steroidal Anti-inflammatory Drugs (NSAID) or antiplatelet use, and patients were allocated one point if they had at least two prescriptions for either of these in the latest year, and another point for a diagnosis of alcoholism in the latest year.

Pisters *et al* proposed that if HAS-BLED score is greater than CHADS₂ score in patients with CHADS₂ ≥2, then anticoagulation should not be given due to risk of bleeding.²² The percentage of patients treated with warfarin in each age group was split by HAS-BLED > CHADS₂ and HAS-BLED ≤ CHADS₂.

Logistic regression was used to identify the factors which affected whether patients were initiated on warfarin. Results were found to be significantly different between sexes, so men and women were modelled separately in order to produce clinically useful estimates. The results were adjusted for practice, to take into account differential prescribing practices between practices, as well as regional variation, by including dummy variables for each practice in the model. Logistic regression models were fitted using SAS software, V9.2 (SAS Institute Inc, Cary, North Carolina, USA) using PROC LOGISTIC.

Further logistic regression models were used to investigate whether stroke risk (measured using CHADS₂ score) had an effect on whether men and women were treated with warfarin, adjusted for age and practice.

RESULTS

Patients

A cohort of 81 381 patients with AF was identified, of whom 17 054 (21%) were aged 60–69 years, 30 350 (37%) were aged 70–79 years, and 33 977 (42%) were aged 80+ years. Just over half the cohort (52%; n=42 318) were women. More patients with AF were female in the older age group (≥80 years; 63% female), while patients in the youngest age group were predominantly men (60–69 years; 63% male) (table 1).

Warfarin treatment

Patients aged 80+ years were significantly less likely to be initiated on warfarin in the first year following AF diagnosis than younger patients; 32% of patients aged 80+ years received warfarin compared with 55% aged 70–79 years, $\chi^2(1, n=64\ 327)=3453$ ($p<0.0001$), and 57% aged 60–69 years, $\chi^2(1, n=51\ 031)=2883$ ($p<0.0001$) (table 1). This remained true in all subgroups of patients with comorbidities. Men were more likely to be initiated on warfarin than women in all age groups (table 1).

Over the 10-year study period (2000–2009), there was a trend towards increased prescribing of warfarin in patients with AF, which was consistent across the three age groups. The proportion of patients aged 80+ years initiated on warfarin following AF diagnosis increased from 25% to 37% between 2000 and 2009, but was still much lower than the proportion in younger patients (48% to 61% in patients aged 70–79 years, and 54% to 55% in patients aged 60–69 years).

Logistic regression models of whether warfarin was initiated in the year following AF diagnosis are presented (table 2). For both men and women, age was the strongest independent predictor of warfarin use. A patient aged 60–69 years, or 70–79 years, was more than twice as likely to be initiated on warfarin following a diagnosis of AF, than a patient with the same BMI, gender and comorbidities aged ≥80 years (table 2). Having adjusted for other factors, patients with BMI <20 kg/m² were significantly less likely to receive warfarin treatment than patients with BMI 20–25 kg/m². Patients with higher BMIs were

Table 1 Frequency of comorbidities in total atrial fibrillation patient population and among those treated with warfarin

| Age group | 60–69 years | | | | | 70–79 years | | | | 80+ years (reference group) | |
|--|--------------------|----------------|--------------------------------------|-----------------|----------|----------------|--------------------------------------|-----------------|----------|-----------------------------|--------------------------------------|
| | All patients n (%) | Patients n (%) | Patients treated with warfarin n (%) | χ^2 Value* | p Value* | Patients n (%) | Patients treated with warfarin n (%) | χ^2 Value† | p Value† | Patients n (%) | Patients treated with warfarin n (%) |
| Number of patients | 81 381 | 17 054 | 9648 (57) | 2883 | <0.0001 | 30 350 | 16 641 (55) | 3453 | <0.0001 | 33 977 | 10 830 (32) |
| Women | 42 318 (52) | 6300 (37) | 3268 (52) | 1094 | <0.0001 | 14 315 (47) | 7433 (52) | 1849 | <0.0001 | 21 300 (63) | 6246 (29) |
| Men | 39 063 (48) | 10 754 (63) | 6380 (59) | 1254 | <0.0001 | 16 035 (53) | 9208 (57) | 1283 | <0.0001 | 12 677 (37) | 4584 (36) |
| BMI, mean (SD) | 27.1 (5.2) | 29.0 (5.9) | 29.5 (6.1) | | | 27.6 (5.2) | 28.0 (5.2) | | | 25.8 (4.7) | 26.5 (4.6) |
| % with non-missing BMI | | 85 | 87 | | | 74 | 87 | | | 74 | 82 |
| Hypertension (diagnosed) | 44 841 (55) | 8362 (49) | 4951 (59) | 1461 | <0.0001 | 17 328 (57) | 9692 (56) | 1694 | <0.0001 | 19 151 (56) | 6603 (34) |
| Diabetes | 10 022 (12) | 2233 (13) | 1333 (60) | 377 | <0.0001 | 4291 (14) | 2358 (55) | 355 | <0.0001 | 3498 (10) | 1175 (34) |
| LVEF <40% | 2719 (3) | 723 (4) | 529 (73) | 109 | <0.0001 | 1165 (4) | 797 (68) | 92 | <0.0001 | 831 (2) | 391 (47) |
| Coronary heart disease | 19 860 (2) | 3531 (2) | 2088 (59) | 588 | <0.0001 | 8052 (27) | 4592 (57) | 794 | <0.0001 | 8277 (24) | 2901 (35) |
| Congestive heart failure | 21 075 (26) | 3094 (18) | 2152 (70) | 1277 | <0.0001 | 7401 (24) | 4490 (61) | 1296 | <0.0001 | 10 580 (31) | 3549 (34) |
| Stroke | 8142 (10) | 1264 (7) | 807 (64) | 369 | <0.0001 | 3084 (10) | 1760 (57) | 394 | <0.0001 | 3794 (11) | 1259 (33) |
| Stroke/TIA | 10 763 (13) | 1567 (9) | 1029 (66) | 496 | <0.0001 | 3928 (13) | 2299 (59) | 543 | <0.0001 | 5268 (16) | 1797 (34) |
| Alzheimer's/dementia | 5382 (7) | 187 (1) | 95 (51) | 121 | <0.0001 | 1519 (5) | 617 (41) | 294 | <0.0001 | 3676 (11) | 664 (18) |
| Thromboembolism‡ | 4619 (6) | 803 (5) | 554 (69) | 132 | <0.0001 | 1729 (6) | 1109 (64) | 137 | <0.0001 | 2087 (6) | 943 (45) |
| Vascular disease‡ | 12 389 (15) | 2 225 (13) | 1353 (61) | 418 | <0.0001 | 4997 (16) | 2847 (57) | 487 | <0.0001 | 5167 (15) | 1816 (35) |
| CHADS ₂ score | | | | | | | | | | | |
| 0 | 10 241 (13) | 6243 (37) | 3072 (49) | – | – | 3998 (13) | 2038 (51) | – | – | 0 (0) | 0 (0) |
| 1 | 24 859 (31) | 6701 (39) | 3925 (59) | 1514 | <0.0001 | 9865 (33) | 5297 (54) | 1310 | <0.0001 | 8293 (24) | 2249 (27) |
| 2+ | 46 281 (57) | 4110 (24) | 2651 (65) | 1458 | <0.0001 | 16 487 (56) | 9306 (56) | 2181 | <0.0001 | 25 684 (76) | 8581 (33) |
| CHA ₂ DS ₂ -VASC score | | | | | | | | | | | |
| 0 | 1620 (2) | 1620 (9) | 798 (49) | – | – | 0 (0) | 0 (0) | – | – | 0 (0) | 0 (0) |
| 1 | 6276 (8) | 4348 (25) | 2292 (53) | – | – | 1928 (6) | 1028 (53) | – | – | 0 (0) | 0 (0) |
| 2+ | 73 485 (90) | 11 086 (65) | 6 558 (59) | 2625 | <0.0001 | 28 422 (94) | 15 613 (55) | 3370 | <0.0001 | 33 977 (100) | 10 830 (32) |
| HAS-BLED | | | | | | | | | | | |
| 0–1 | 31 522 (39) | 10 337 (61) | 5805 (56) | 1169 | <0.0001 | 10 445 (34) | 5857 (56) | 1167 | <0.0001 | 10 740 (32) | 3518 (33) |
| 2+ | 49 859 (61) | 6717 (39) | 3843 (57) | 1478 | <0.0001 | 19 905 (66) | 10 784 (54) | 2271 | <0.0001 | 23 237 (68) | 7312 (31) |

* χ^2 tests comparing the proportion of patients treated with warfarin in the 60–69 years age group compared with the 80+ years age group.

† χ^2 tests comparing the proportion of patients treated with warfarin in the 70–79 years age group compared with the 80+ years age group.

‡Diagnostic codes used to define are shown in appendix S1.

BMI, body mass index; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

increasingly likely to be treated with warfarin than patients with BMI 20–25 kg/m². Increasing bleeding risk, as measured using HAS-BLED score, reduced the probability that a patient was treated with warfarin.

In men and women, hypertension, heart failure, reduced left ventricular ejection fraction, thromboembolism and a history of stroke or TIA, all independently increased the likelihood that a patient received warfarin. Paradoxically, men with diabetes were less likely to be anticoagulated, and presence of diabetes was not associated with use of anticoagulation in women. In both sexes, dementia halved the chance that warfarin was used.

Stroke and bleeding risk analysis

As would be anticipated, CHADS₂ scores rise with age, with 76% of patients aged 80+ years having a CHADS₂ score of 2 or above compared with 56% of patients aged 70–79 years, and 24% of patients aged 60–69 years.

Patients in the 80+ years age group had higher HAS-BLED scores than patients aged 60–69 years; 68% of patients aged 80+ years had a HAS-BLED score ≥ 2 compared with 39% of patients aged 60–69 years (and 66% patients aged 70–79 years) (table 1).

Patients with HAS-BLED > CHADS₂ were slightly less likely to be initiated on warfarin. This effect was greater in patients with CHADS₂ ≥ 2 , and in patients aged 60–69 years (table 3). For all strata of CHADS₂/HAS-BLED scores in table 3 (bar one,

due to small numbers), patients in the 80+ years age group were significantly less likely to be treated with warfarin than those of younger ages.

Logistic regression models investigating CHADS₂ (table 4) found evidence in both men and women of a significant increase in the chance of being prescribed warfarin as CHADS₂ score increased, when adjusted for age group and practice.

DISCUSSION

Patients with AF, aged 80 years or over, are much less likely to be treated with warfarin than younger patients. This holds true if the data are adjusted to take into account factors that might deter a clinician from prescribing warfarin, such as frailty (indicated by low BMI), bleeding risk and Alzheimer's disease. While the proportion of people over 80 years treated with warfarin has increased moderately over the study period (2000–2009), it remains substantially lower than the proportion treated in the younger age groups. Logistic regression analysis demonstrated that a patient aged 60–79 years is more than twice as likely to be initiated on warfarin following a diagnosis of AF, than a patient with the same gender, BMI, comorbidities and bleeding risk aged over 80 years (table 2).

Our finding of low warfarin use among elderly patients in the UK is consistent with findings of US studies in hospitals and in primary care, which found warfarin prescribed in only

Table 2 Logistic regression models

| Variable | Unadjusted OR§ | 95% CI | p Value | Adjusted OR§ | 95% CI | p Value |
|------------------|----------------|--------------|---------|-----------------------------|--------------|---------|
| Men | | | | | | |
| Age 60–69* | 2.55 | 2.4 to 2.72 | <0.0001 | 2.15 | 2.01 to 2.29 | <0.0001 |
| Age 70–79* | 2.32 | 2.19 to 2.45 | <0.0001 | 2.20 | 2.08 to 2.33 | <0.0001 |
| BMI <20† | 0.56 | 0.49 to 0.65 | <0.0001 | 0.60 | 0.52 to 0.70 | <0.0001 |
| BMI 25–<30† | 1.43 | 1.35 to 1.51 | <0.0001 | 1.30 | 1.23 to 1.38 | <0.0001 |
| BMI 30–<35† | 1.75 | 1.63 to 1.87 | <0.0001 | 1.46 | 1.36 to 1.57 | <0.0001 |
| BMI 35+† | 2.30 | 2.07 to 2.55 | <0.0001 | 1.73 | 1.55 to 1.93 | <0.0001 |
| Hypertension | 1.17 | 1.11 to 1.22 | <0.0001 | 1.24 | 1.18 to 1.3 | <0.0001 |
| Heart Failure | 1.34 | 1.27 to 1.41 | <0.0001 | 1.41 | 1.33 to 1.49 | <0.0001 |
| LVEF | 2.09 | 1.86 to 2.35 | <0.0001 | 1.72 | 1.52 to 1.94 | <0.0001 |
| Diabetes | 1.08 | 1.01 to 1.15 | <0.0001 | 0.94 | 0.88 to 1.00 | 0.05650 |
| Stroke/TIA | 1.15 | 1.07 to 1.23 | <0.0001 | 1.56 | 1.44 to 1.68 | <0.0001 |
| Dementia | 0.47 | 0.42 to 0.53 | <0.0001 | 0.59 | 0.52 to 0.66 | <0.0001 |
| Vascular Disease | 1.10 | 1.04 to 1.17 | 0.0006 | 1.10 | 1.03 to 1.16 | 0.00260 |
| Thromboembolism | 1.59 | 1.44 to 1.76 | <0.0001 | 1.59 | 1.44 to 1.77 | <0.0001 |
| HAS-BLED 2 | 0.82 | 0.78 to 0.87 | <0.0001 | 0.8 | 0.76 to 0.85 | <0.0001 |
| HAS-BLED 3 | 0.69 | 0.65 to 0.74 | <0.0001 | 0.612 | 0.57 to 0.66 | <0.0001 |
| HAS-BLED 4 | 0.55 | 0.5 to 0.61 | <0.0001 | 0.432 | 0.38 to 0.49 | <0.0001 |
| p | | | | | | |
| Goodness-of-fit‡ | 0.79 | | | | | |
| Women | | | | | | |
| Age 60–69* | 2.29 | 2.14 to 2.44 | <0.0001 | 1.95 | 1.82 to 2.10 | <0.0001 |
| Age 70–79* | 2.43 | 2.31 to 2.55 | <0.0001 | 2.29 | 2.17 to 2.41 | <0.0001 |
| BMI <20† | 0.63 | 0.58 to 0.70 | <0.0001 | 0.69 | 0.62 to 0.76 | <0.0001 |
| BMI 25–<30† | 1.35 | 1.28 to 1.43 | <0.0001 | 1.25 | 1.18 to 1.32 | <0.0001 |
| BMI 30–<35† | 1.55 | 1.45 to 1.66 | <0.0001 | 1.33 | 1.24 to 1.42 | <0.0001 |
| BMI 35+† | 1.96 | 1.81 to 2.13 | <0.0001 | 1.46 | 1.34 to 1.59 | <0.0001 |
| Hypertension | 1.14 | 1.09 to 1.19 | <0.0001 | 1.23 | 1.17 to 1.3 | <0.0001 |
| Heart Failure | 1.18 | 1.12 to 1.24 | <0.0001 | 1.28 | 1.21 to 1.35 | <0.0001 |
| LVEF | 1.82 | 1.58 to 2.11 | <0.0001 | 1.55 | 1.33 to 1.80 | <0.0001 |
| Diabetes | 1.00 | 0.94 to 1.07 | 0.93 | Not included in final model | | |
| Stroke/TIA | 1.16 | 1.08 to 1.24 | <0.0001 | 1.49 | 1.38 to 1.60 | <0.0001 |
| Dementia | 0.41 | 0.37 to 0.46 | <0.0001 | 0.51 | 0.46 to 0.57 | <0.0001 |
| Vascular disease | 0.96 | 0.89 to 1.03 | 0.22 | Not included in final model | | |
| Thromboembolism | 1.74 | 1.58 to 1.91 | <0.0001 | 1.72 | 1.56 to 1.90 | <0.0001 |
| HAS-BLED 2 | 0.85 | 0.81 to 0.9 | <0.0001 | 0.83 | 0.79 to 0.88 | <0.0001 |
| HAS-BLED 3 | 0.78 | 0.73 to 0.83 | <0.0001 | 0.71 | 0.66 to 0.76 | <0.0001 |
| HAS-BLED 4 | 0.61 | 0.55 to 0.68 | <0.0001 | 0.51 | 0.45 to 0.57 | <0.0001 |
| p | | | | | | |
| Goodness-of-fit‡ | 0.43 | | | | | |

*Age: reference group=Age 80+ years;

†BMI: reference group=BMI 20–<25;

‡Hosmer and Lemeshow goodness-of-fit test.

§ OR, unadjusted is crude OR adjusted for practice only, adjusted is OR from multivariable model adjusted for practice and all other variables included in the final model.

40%–45% of patients with AF, with age increasing the risk of not being treated.^{11–14} Our findings are also consistent with an earlier analysis of patients with AF from the GPRD database in 1996 that found among potential candidates for anticoagulation, only 22% of those aged 70+ years were prescribed warfarin compared with 49% among patients aged 40–60 years.²³ While a trend towards increasing warfarin prescribing practice in recent years has been demonstrated in our study, the results show that current prescribing practice is not in step with the current evidence base, and that anticoagulation therapy is particularly under-used in elderly patients. This is important, since there is now a clear evidence base that anticoagulation is effective for stroke prevention in elderly people in atrial fibrillation.¹⁹ Indeed, a recent non-randomised study found that warfarin use

in this age group not only was associated with reduced stroke risk, but also with improved life expectancy.⁹

This study found that in the UK, women with AF are less likely to be prescribed warfarin than men with the same risk factors for stroke, even though female sex has been associated with increased risk of stroke in AF.⁴ This is consistent with findings in Scotland that women with AF were 25% less likely to receive warfarin than men,²⁴ and a Canadian study which showed that women were 54% less likely to receive warfarin, but only in the subgroup of patients aged ≥ 75 years.²⁵ However, a more recent Canadian study found no evidence of reduced usage of warfarin in women compared with men.²⁶

It is difficult to explain the disparity of use of anticoagulation in women as compared with men. Gender inequalities have been

Table 3 Warfarin treatment by HAS-BLED and CHADS₂ score

| CHADS ₂ | Age group | 60–69 years | | | | 70–79 years | | | | 80+ years (reference group) | |
|--------------------|-------------------------------|-------------|------------------------------------|-----------------|----------|-------------|------------------------------------|-----------------|----------|-----------------------------|------------------------------------|
| | | Patients n | Patients treated with warfarin (%) | χ^2 Value* | p Value* | Patients n | Patients treated with warfarin (%) | χ^2 Value† | p Value† | Patients n | Patients treated with warfarin (%) |
| 0 | HAS-BLED > CHADS ₂ | 4265 | 49 | – | – | 3998 | 51 | – | – | 0 | – |
| | HAS-BLED ≤ CHADS ₂ | 1978 | 49 | – | – | 0 | – | – | – | 0 | – |
| 1 | HAS-BLED > CHADS ₂ | 2880 | 56 | 692 | <0.0001 | 5556 | 52 | 697 | <0.0001 | 3801 | 25 |
| | HAS-BLED ≤ CHADS ₂ | 3821 | 60 | 814 | <0.0001 | 4309 | 56 | 640 | <0.0001 | 4492 | 29 |
| 2 | HAS-BLED > CHADS ₂ | 512 | 55 | 130 | <0.0001 | 2296 | 52 | 266 | <0.0001 | 3286 | 30 |
| | HAS-BLED ≤ CHADS ₂ | 2137 | 65 | 772 | <0.0001 | 6997 | 58 | 1022 | <0.0001 | 10596 | 33 |
| 3 | HAS-BLED > CHADS ₂ | 128 | 52 | 31 | <0.0001 | 419 | 53 | 71 | <0.0001 | 526 | 26 |
| | HAS-BLED ≤ CHADS ₂ | 965 | 69 | 419 | <0.0001 | 4157 | 58 | 554 | <0.0001 | 6524 | 34 |
| 4+ | HAS-BLED > CHADS ₂ | 7 | 57 | 3 | 0.0762 | 62 | 53 | 13 | 0.0004 | 111 | 26 |
| | HAS-BLED ≤ CHADS ₂ | 361 | 66 | 129 | <0.0001 | 2556 | 57 | 286 | <0.0001 | 4641 | 36 |

* χ^2 tests comparing the proportion of patients treated with warfarin in the 60–69 years age group compared with the 80+ years age group.

† χ^2 tests comparing the proportion of patients treated with warfarin in the 70–79 years age group compared with the 80+ years age group.

observed in use of therapies in other areas of cardiovascular medicine.²⁷ These have been attributed to a possible perceived lower risk of cardiovascular disease in women compared with men, leading to under-recording of risk factors and lower rates of prophylactic treatment in women. It may be that the same factors apply in the use of anticoagulation in patients with AF.

The factors that determine whether warfarin is prescribed in clinical practice are complex, and our study was not designed to investigate the reasons behind clinical decision making. Physicians often avoid anticoagulation in elderly patients due to fear of bleeding, fall risk, non-adherence and monitoring concerns.^{13–15} While the efficacy of warfarin in stroke prevention is established, warfarin has many limitations, including a narrow therapeutic index, slow onset and offset of action, multiple drug and food interactions, and a requirement for close laboratory monitoring of coagulation via the International Normalised Ratio (INR) and subsequent dose adjustments.²⁸ Close monitoring necessitates regular clinic visits with increased financial burden and inconvenience to patients; thus, many eligible patients choose not to use warfarin.²⁹ However, patient education and self-monitoring may promote better compliance and INR control among elderly patients with AF.³⁰

Unlike recent Swedish and Canadian studies, in this study, CHADS₂ scores predicted anticoagulation use in a British

population.^{8,9} The difference between these findings may reflect international variation in practice, or may be related to issues of study design: for instance, the present study was restricted to patients aged 60 years and over; and the Swedish study was smaller, so it cannot exclude associations of a similar magnitude to the present study.

The recent development of new anticoagulants, such as dabigatran, rivaroxaban and apixaban, represent potential new therapies for patients with AF that may circumvent many of the inconveniences of warfarin, such as regular INR checks, dietary restrictions and drug interactions. How new agents will be used in the management of elderly patients with AF in everyday practice remains to be established; however, recent NICE guidance recommends the use of dabigatran in atrial fibrillation under the licensed indication, which includes patients aged >75 years, and those aged >65 years with an additional risk factor.¹⁰

Study limitations

In this study, patients with at least one prescription for warfarin in their GP record were assumed to have been initiated on warfarin. The GPRD records prescriptions issued rather than dispensed, thus, it would not be possible to confirm whether a patient was taking the medication from an initial prescription alone. However, as this study aimed to investigate the

Table 4 Logistic regression models- CHADS₂

| Variable | Unadjusted OR* | 95% CI | p Value | Adjusted OR* | 95% CI | p Value |
|-------------------------|----------------|--------------|---------|--------------|--------------|---------|
| Men | | | | | | |
| CHADS ₂ =2† | 0.98 | 0.93 to 1.03 | 0.47 | 1.30 | 1.23 to 1.38 | <0.0001 |
| CHADS ₂ =3† | 0.98 | 0.92 to 1.05 | 0.62 | 1.35 | 1.26 to 1.45 | <0.0001 |
| CHADS ₂ =4+† | 0.97 | 0.90 to 1.06 | 0.53 | 1.44 | 1.32 to 1.57 | <0.0001 |
| Goodness-of-fit‡ | | | | | | 0.952 |
| Women | | | | | | |
| CHADS ₂ =2† | 0.88 | 0.83 to 0.92 | <0.0001 | 1.21 | 1.14 to 1.28 | <0.0001 |
| CHADS ₂ =3† | 0.93 | 0.87 to 0.99 | 0.03 | 1.32 | 1.23 to 1.42 | <0.0001 |
| CHADS ₂ =4+† | 0.89 | 0.82 to 0.96 | 0.004 | 1.34 | 1.23 to 1.46 | <0.0001 |
| Goodness-of-fit‡ | | | | | | 0.575 |

*OR, unadjusted is crude OR adjusted for practise only, adjusted is OR from multivariable model adjusted for practise and age.

†CHADS₂: Reference group CHADS₂=0/1.

‡Hosmer and Lemeshow goodness-of-fit test.

prescribing decision rather than the treatment, this will not have introduced major misclassification.

As discussed above, clinical practice is driven by other factors than are in the clinical guidelines such as patient preference, that may affect the decision as to whether warfarin is initiated, which are not recorded in GPRD. It might be that these factors have confounded the associations that we observed between age and sex and use of warfarin. Socioeconomic factors were not taken into account in our analysis, however, an earlier analysis of anticoagulation use in AF using general practice data suggests that these were not significant confounders of any association with anticoagulation use.¹⁷

While this study was able to look at the extent to which warfarin use was influenced by bleeding risk, as assessed using the HAS-BLED score, this tool does have limitations in terms of accuracy.²⁰ Therefore, it is possible that we have not fully accounted for bleeding risk in our models. Nevertheless, we did find that higher HAS-BLED scores were associated with lower use of warfarin, suggesting that this tool does have reasonable utility as a means of adjusting for bleeding risk in this analysis.

CONCLUSIONS

Our analysis has demonstrated that age is much the strongest single predictor of whether or not anticoagulation is used in AF. The low use of warfarin in people aged 80 years is not explained by increased comorbidity or increased bleeding risk, since marked differences in use of warfarin were observed when we compared use in people aged 80+ years with other ages, after we stratified by these factors, or adjusted for them. This suggests that there is genuine under-use of anticoagulation in the elderly. Strategies need to be developed to improve the uptake of anticoagulation in this age group.

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