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ORIGINAL RESEARCH

Anticoagulation for the prevention of stroke in non-valvular AF in general practice: room for improvement

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Abstract

Objective: Our aim was to assess whether the recommendations and guidelines for thromboprophylaxis in patients with atrial fibrillation (AF) have been adopted in general practice (GP).

Methods: We conducted a retrospective study using the GP computer database (Hatfield, UK) on all 9400 patients to assess the quality of anticoagulation in patients with a recorded diagnosis of AF.

Results: Of the 180 patients with a diagnosis of AF, 107 (59.4%) were treated with warfarin, 19 (10.6%) with a novel oral anticoagulant (NOAC), 31 (17.2%) with aspirin or clopidogrel, and 23 (12.8%) received none. Thirty-seven patients (34.6%) who were taking warfarin had a time in the therapeutic range (TTR) of less than 65%. Forty-five (27.6%) of the 163 patients who had a CHA2DS2VASc score of two or more were not prescribed a vitamin K antagonist (VKA) or a NOAC. None had a HAS-BLED greater than the CHA2DS2VASc score.

Conclusion: Our study demonstrates that one in four patients with non-valvular AF, at risk of a stroke, is not being adequately treated with an oral anticoagulant in primary care. The majority were treated with warfarin, a third of which had a low TTR. A high proportion of patients are prescribed antiplatelet therapy instead. This is despite overwhelming evidence that VKAs and NOACs, and not aspirin or clopidogrel, improve outcome in patients with non-valvular AF. We suggest that a review of GP practice databases should be considered to identify patients with non-valvular AF, at risk of a disabling or fatal event, and measures taken to initiate anticoagulant therapy.

Keywords: cardiovascular, arrhythmias, atrial fibrillation, warfarin, apixaban, dabigatran, rivaroxaban, general practice, stroke.

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Introduction

Atrial fibrillation (AF) is by far the most common arrhythmia occurring in 1–2% of the population and the incidence doubles with each decade after 50 years of age and approaches 10% in those over the age of 80. It is a major risk factor for stroke (which is usually more disabling than stroke from other causes), cognitive dysfunction, heart failure, and premature death [1–6].

A number of well-conducted clinical trials have confirmed that use of vitamin K antagonists (VKAs), like warfarin, significantly reduce the risk of stroke in patients with non-valvular AF [7–9]. The development of novel oral anticoagulants (NOACs) have been shown to be at least as effective and safe as VKAs without the need for anticoagulation monitoring and dose adjustment [10–13]. However, there have been wide variations in the adherence to evidence-based guidelines with a suggestion of suboptimal implementation leaving patients with AF at risk of a fatal or severe disabling event [14].

We assessed whether the recommendations and guidelines for thromboprophylaxis in patients with non-valvular AF have been implemented in a general practice in the UK [9,15].

Methods

We performed a retrospective study in a primary care setting to assess whether or not patients with non-valvular AF were treated with warfarin (with a time in therapeutic range (TTR) >65%), or a NOAC, in line with the recommendations and guidelines published by the European Society of Cardiology in 2012 and by NICE in 2014. A large practice in Hertfordshire, UK (6 general practitioners, 9400 patients) agreed to participate in the study, and the case notes from the computer database

were used to identify all the patients with a recorded diagnosis of AF. The data collected included patient demographics, risk factors for stroke (which allowed us to calculate individual CHA2DS2VASc scores), risk factors for bleeding (which allowed us to calculate individual HAS-BLED scores), and data regarding the type of anticoagulation that was being prescribed and INR results for patients being treated with warfarin to allow calculation of the TTR. Results are expressed as mean±SD or as a percentage. As a survey report using clinically collected, non-identifiable data, this work does not fall under the remit of National Health Service Research Ethics Committees.

Results

A total of 180 patients (mean age 77.1±11.4 years; eGFR 73.6±23.4 mls/min/1.73 m^2) were identified. Of these 104 (57.8%) were male, 177 were Caucasian, and three were of Asian descent. One hundred and forty one (78.3%) of the patients identified had a diagnosis of chronic AF and 39 (21.7%) paroxysmal AF. Twenty-three (12.8%) of these patients were known to have cardiac valvular disease. Seventeen had mitral regurgitation, three of whom underwent valve replacement or repair; six had mitral stenosis, two of whom underwent valve replacement. One hundred and seventeen (65.0%) were on treatment for hypertension, 23 (12.8%) for congestive cardiac failure, 53 (29.4%) for ischaemic heart disease, and 32 (17.8%) for diabetes mellitus.

Thirty patients (16.7%) had a history of an embolic cerebral event (23 embolic stroke; 7 transient ischaemic attack). Eleven of these patients had a diagnosis of AF prior to having an event, only three of whom were anticoagulated at the time (all with warfarin). Two of these patients had an INR within therapeutic range at the time of the stroke and one did not (INR=1.5). One patient was taking warfarin, but this was withheld, as he was due to undergo a mitral valve replacement. One patient was taking aspirin, and three patients were previously anticoagulated with warfarin, but at the time of the stroke, their warfarin had been discontinued due to labile INR. Three out of the eight patients who were not anticoagulated had a diagnosis of paroxysmal AF and were in sinus rhythm at the time of their stroke (confirmed by a resting electrocardiogram that occurred immediately on admission to hospital). Ten patients were diagnosed with AF at the time of the event (three of whom were commenced on a NOAC and the rest on warfarin). Nine patients were diagnosed with AF subsequently.

Of the 180 patients with a diagnosis of chronic or paroxysmal AF, 126 (70.0%) were prescribed regular anticoagulation (106 warfarin, 1 warfarin and enoxaparin, 10 apixaban, 7 rivaroxaban, and 2 dabigatran) (Table 1). All 19 (15.1%) patients taking NOACs had their anticoagulation initiated in a hospital setting (17 by a cardiologist, 1 in a TIA clinic, and 1 in A&E). Of the patients taking warfarin thirty-seven (34.6%) had a time in the therapeutic range (TTR) of less than 65%, and of these only 11 patients would not have been suitable for a NOAC due to the presence of mitral valve disease.

Only 13 (10.3%) out of all the patients on regular anticoagulation were known to have had a recorded conversation informing them of the advantages and disadvantages of NOACs over warfarin, and all of these consultations took place in a secondary care setting. This is despite 151 (83.9%) patients being referred for assessment in secondary care. Of these patients, 71 had a 24-hour Holter analysis to assess rate control. For the remainder of the patients, the diagnosis was confirmed on a resting ECG.

Fifty-four patients (30.0%; mean age 74.7±13.8 years; eGFR 78.0±25.7 mL/min/1.73 m^2) were not prescribed regular anticoagulation therapy. Out of these patients, 28 had a history of falls, 5 excessive alcohol intake (none of whom had LFTs twice the normal range), 2 epistaxis, and 1 subdural hemorrhage.

Thirty-one patients (17.2%) were taking antiplatelet agents (26 aspirin, 5 clopidogrel; none were taking dual antiplatelet therapy), and 23 (12.8%) patients were not taking either anticoagulation or an antiplatelet agent. Out of these patients, two had a history of dyspepsia and one had thrombocytopenia (platelets <150 × 109/L).

Table 1. The CHA2DS2VASc score of patients with chronic or paroxysmal AF and the prescribed stroke prophylaxis.

	CHA2DS2VASc score for patients with chronic or paroxysmal AF									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Warfarin	1	4	11	28	28	18	13	2	2	107
NOAC	3	0	3	5	4	2	2	0	0	19
Aspirin only (no anticoagulation)	2	1	5	8	7	2	0	0	1	26
Clopidogrel only (no anticoagulation)	0	0	1	1	0	3	0	0	0	5
No anticoagulation or antiplatelet agent	5	1	4	5	4	1	2	1	0	23
Total	11	6	24	47	43	26	17	3	3	180

Of the total number of patients, 163 had a CHA2DS2VASc score of two or more, and 45 (27.6%) of these patients were not prescribed an anticoagulant drug. In three of these patients, the CHA2DS2VASc score was equal to the HAS-BLED score; however, in the rest (42 patients), the CHA2DS2VASc score was at least one greater than the HAS-BLED score. One patient had a previous history of a subdural hemorrhage, but there were no other recorded contraindications to anticoagulation (Table 1).

Discussion

The clinical decision making on the initiation of oral anticoagulant therapy is based on the stroke risk assessed using the CHA2DS2VASc scoring system (cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65–74 years, and female sex category) balanced against the risk of bleeding currently assessed using the HAS-BLED scoring system (hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol). Currently there is no official guidance as to how the HAS-BLED score should be interpreted; however, studies suggest that if the HAS-BLED score is greater than the CHA2DS2VASc score, then anticoagulation should be withheld, and vice versa. Any patient who scores two or more in the CHA2DS2VASc should be considered for anticoagulation [16,17].

Despite the above guidelines, our results clearly show that one in four patients diagnosed with non-valvular AF and who are at risk of a thromboembolic event are not receiving anticoagulation with either a VKA or a NOAC. A high proportion of patients are being prescribed aspirin or clopidogrel as monotherapy for stroke prophylaxis (in fear of falls, bleeding, or inability to comply with the logistics of anticoagulation monitoring). This occurred despite these patients having a greater risk of ischaemic stroke than bleeding and is concerning considering the lack of antiplatelet efficacy when compared with conventional anticoagulation therapy; therefore, treating physicians are missing a vital opportunity to prevent a stroke with devastating consequences [18,19]. Our data are consistent with other studies that have demonstrated that despite the overwhelming evidence proving VKAs and NOACs, and not aspirin, improve outcome, many patients with non-valvular AF are not being anticoagulated appropriately.

A vast number of patients being anticoagulated with warfarin had a suboptimal TTR and would be best treated with a NOAC. NOACs consist of two groups of agents: direct thrombin inhibitors (such as dabigatran) and direct factor X_a inhibitors (such as rivaroxaban and apixaban). Their development has been shown to be superior to warfarin, with more consistent and predictable anticoagulation and without the need for regular INR monitoring and dose adjustment. In patients with at least one risk factor for stroke, the use of NOACs, as compared to warfarin, reduced the risk of strokes or systemic embolisation further and also the risk of bleeding. These benefits are even more pronounced in those who struggle to maintain an INR within therapeutic range [10–13].

Despite this there is still a low level of NOAC uptake, which is unlikely to be unique to this general practice. We can only speculate on why this is the case. Warfarin has been the drug of choice for many years; therefore, general practitioners may feel a sense of familiarity when prescribing the above anticoagulant. NOACs are significantly more expensive than VKAs. However, when analysing financial implications, one must also consider the added cost of repeated monitoring and dose adjustment that is required for patients taking VKAs [20]. Due to the lack of long-term follow up, use of NOACs may seem daunting. This is likely to be confounded at present by a lack of fast reversibility in all but dabigatran [21], which the longer acting warfarin does offer. NOACs have a much shorter action, making patient compliance with pharmacological therapy of paramount importance. It would, however, appear that clinicians in secondary care are more confident in the initiation and the use of NOACs.

Interestingly, there is increasing evidence to suggest that in other European countries NOACs have been adopted to a much greater extent than in the UK. Our results are at variance with those obtained in large cross-sectional studies from Europe or the United States, where the use of NOACs has long overtaken the use of VKAs for the prevention of strokes in patients with non-valvular AF [20,22].

The PREFER in AF study enrolled seven European countries including the UK and registered 7243 patients between January 2012 to January 2013 who were diagnosed with AF. It demonstrated that over 80% of patients were treated with VKA (66.3%) or a NOAC (6.1%); furthermore, 9.9% of patients were treated with a combination of VKA and antiplatelet agents, 11.2% with antiplateletet agents as monotherapy, and 6.5% received no antithrombotic or antiplatelet therapy [14].

Previous registries yielded similar results to our study, where only 70% of eligible patients received oral anticoagulation. Despite the PREFER in AF study demonstrating better prescribing practices, the authors believe there still exists scope for improvement [14,23].

Over the past decade, there is increasing evidence to suggest that age-related public health problems like AF and heart failure may be increasing and in some cases may remain underdiagnosed [24]. The ability to establish an early diagnosis and the initiation of effective treatment is likely to improve cardiovascular outcome and prevent a cascade of adverse events on the cardiovascular system. Patients with AF are five-fold more likely to have an embolic stroke than patients in sinus rhythm, and the risk of AF-related death from stoke is doubled**.** VKAs reduce the risk of embolic stroke by 40–80% and of mortality by 30% in patients with non-valvular AF [25–27].

VKAs, however, have a slow onset of action, a narrow therapeutic index, and multiple drug interactions. The risk of bleeding is increased, and regular anticoagulation monitoring and dose adjustment is required. Their safe use depends upon the quality of the anticoagulation control as assessed by the TTR. A TTR of >70% for the efficacy and safety of warfarin is

now generally accepted but, as shown by our study, can be difficult to achieve [9]. Patients with poor anticoagulation control are more at risk of adverse cardiovascular events like major bleeding and a severe or fatal embolic event [28,29].

Our study does have some limitations. The data were collected from a GP database, which relies on the record keeping of the clinicians. Some of the contraindications to the use of anticoagulant therapy as well as discussions regarding patient preferences on the type of anticoagulation therapy may not have been recorded. Furthermore, we studied a predominantly white population without any other ethnic groups, which is one of the risk factors for poor outcome due to the low TTR [30].

In conclusion, our study clearly demonstrates that one in four patients with non-valvular AF is not being treated with oral anticoagulants, putting the patient at risk of stroke. A high proportion of these patients are being prescribed aspirin or clopidogrel instead. This is despite overwhelming evidence that VKAs and NOACs, and not aspirin, improve outcome in patients with non-valvular AF. Of those patients who were anticoagulated, the majority were prescribed warfarin despite sufficient evidence suggesting the risk of a thromboembolic event and bleeding would be lower if prescribed a NOAC instead, more so in those patients with a low TTR. We suggest therefore that a review of GP practice databases should be considered to identify those patients with non-valvular AF and at risk of a disabling or fatal embolic event and measures taken to initiate anticoagulant therapy. This is likely to lead to a substantial reduction in cardiovascular morbidity and mortality in the UK.

Contributions: All four authors (Dr Adam Ioannou, Dr Sofia Metaxa, Dr George Kassianos, and Dr Constantinos Missouris) contributed to the manuscript. All were involved in the design of the study, collection of data, and analysis and interpretation of data. All authors were involved in drafting the manuscript, and all authors approved a final version of the manuscript before it was sent to be published.

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Ethics approval: As a survey report using clinically collected, non-identifiable data, this work does not fall under the remit of National Health Service Research Ethics Committees and does not require ethics approval. Consent was not obtained but the presented data are anonymised and there is minimal risk of identification.

Clinical trial registration: Due to this trial not requiring ethics approval, it was not registered.

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