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Thromboembolic and haemorrhagic events in patients with atrial fibrillation:

a prospective cohort study in UK primary and secondary care

Abstract

Background
Strong evidence on the long-term safety and efficacy of different types of anticoagulants would help clinicians to prevent thromboembolic events among patients with atrial fibrillation (AF) while minimising the risk of haemorrhages.

Aim
To estimate the risk of thromboembolic and haemorrhagic events for patients with AF on antiplatelets or anticoagulants.

Design and setting
This was a cohort study using routinely collected UK primary and secondary care clinical data from patients with AF, aged ≥18 years, and with an indication to receive anticoagulation before April 2012.

Method
The risk of ischaemic stroke or transient ischaemic attack (TIA), coronary heart disease (CHD), peripheral artery disease (PAD), or gastrointestinal (GI) haemorrhage, between 1 April 2012 and 1 April 2017, was estimated using multivariate Cox regression models for patients on antiplatelets only, a combination of antiplatelets and vitamin K antagonists (VKAs), or novel oral anticoagulants (NOACs), and compared with those on VKAs only.

Results
Compared with VKAs, antiplatelets were associated with a higher risk of stroke or TIA, hazard ratio (HR) 1.51, 95% confidence interval (CI) = 1.09 to 2.09, and GI haemorrhage, HR 1.79, 95% CI = 1.01 to 3.18. The risk of thromboembolic and haemorrhagic events was similar for those on a combination of antiplatelets and VKAs, or those on VKAs only. The risk was also similar for those on NOACs or VKAs, except for CHD, where it was higher for patients on NOACs, HR 2.07, 95% CI = 1.35 to 3.19.

Conclusion
Anticoagulants are associated with lower risk of thromboembolic and haemorrhagic events among patients with AF than antiplatelets. More research is required on the risk associated with VKAs or NOACs.

Keywords
anticoagulants; atrial fibrillation; gastrointestinal haemorrhage; myocardial ischaemia; primary health care; stroke.

INTRODUCTION

Atrial fibrillation (AF) is a leading cause of morbidity and mortality with 5 million incident cases a year and an increasing prevalence worldwide.[1] It is strongly associated with a higher risk of acute cardiovascular events, increased mortality, higher medical costs, and a reduced quality of life.[2–4] Treatment with anticoagulation is key to prevent thromboembolic events in patients with AF.[5] Traditionally, vitamin K antagonists (VKAs) have been the first-line anticoagulant agents for these patients. However, since 2010 the novel oral anticoagulants (NOACs) have become available to manage AF.[6]

A number of studies have compared the safety and efficacy of NOACs versus VKAs, with most focusing on the prevention of strokes, with other potential outcomes receiving less attention, and have reported conflicting results on the association with different thromboembolic and haemorrhagic events.[3,6–11] Factors associated with the choice of anticoagulation, such as socioeconomic status or estimates of thromboembolic risk, have not always been acknowledged in previous studies.[12] There are also some concerns regarding the safety of NOACs in real-world settings, where they are prescribed to a broad range of patients, particularly with respect to bleeding as there is a limited choice of expensive antidotes.[13,14] Although anticoagulants seem to have better safety and efficacy than antiplatelets in the prevention of thromboembolic events among those with AF, a significant proportion of patients are still on antiplatelets only.[15,16]

Therefore, the evidence on the long-term safety and efficacy of anticoagulation is still limited and not fully applied in clinical practice. Stronger evidence on the effects of different types of anticoagulants and antiplatelets would help clinicians to prevent thromboembolic events while minimising the risk of haemorrhagic episodes among patients with AF.

This study tests the hypothesis that the risk of thromboembolic and haemorrhagic events varies for those treated with different anticoagulants or antiplatelets, and that the estimated thromboembolic risk, and socioeconomic status, may affect these differences. The risk of ischaemic stroke (IS) or transient ischaemic attack (TIA), coronary heart disease (CHD), peripheral artery disease (PAD), and gastrointestinal (GI) haemorrhage, was estimated over a period of 5 years for patients with AF treated with antiplatelets, a combination of antiplatelets and VKAs, or NOACs, and compared with those taking only VKAs.[3,17]

METHOD

The study conformed to the STROBE study design recommendations.[18]

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How this fits in

A number of studies have compared the safety and efficacy of different anticoagulants in patients with AF, with most focusing on the prevention of strokes, with other potential outcomes receiving less attention, and have reported conflicting results on the association with different thromboembolic and haemorrhagic events. In the present study, compared with vitamin K antagonists (VKAs), antiplatelets were associated with a higher risk of transient ischaemic attack (TIA) or stroke and gastrointestinal (GI) haemorrhage; the risk was similar for those on a combination of antiplatelets and VKAs; the risk was also similar for those on novel oral anticoagulants (NOAC), except for coronary heart disease (CHD), where patients had an increased risk. This evidence suggests lower risk of TIA or strokes and GI bleeds for anticoagulants than for antiplatelets, but does not support prioritising VKAs or NOACs. More research is required on the risk and efficacy of VKAs and NOACs.

It was a prospective cohort study, including patients aged ≥18 years, with at least 1-year registration in the area of study, with a diagnosis of AF, and a risk of thromboembolic events high enough to have indication to receive anticoagulation[19] (CHA_2DS_2-VASc[20] score ≥2) before 1 April 2012.

All data were collected from routinely recorded clinical notes from the East London primary care database, which has records of all patients registered in 140 practices in three contiguous boroughs of London, and the Secondary Uses Service, which has clinical data on the outcomes observed in this study from the hospitals in those same areas. Primary and secondary care records data were linked using pseudo-anonymised identifiers. Sociodemographic variables included age and sex. The English Index of Deprivation was recorded as a measure of socioeconomic status.[21] Clinical data included estimated risk of thromboembolic outcomes, measured with the CHA_2DS_2-VASc before 1 April 2012,[20] and the first diagnoses between 1 April 2012 and 1 April 2017 of TIA or IS, CHD, PAD, and GI haemorrhage. Clinical data were defined using the Read codes from the Quality and Outcomes Framework ruleset when collected from primary care.[22] Clinical data from secondary care were defined using the 10th version of the International Classification of Diseases.[23] All data from primary and secondary care had been entered by clinicians during routine care. Data on treatments were extracted for each drug according to their classification as antiplatelets, NOACs, or VKAs in the *British National Formulary*.[24] Data on each treatment category were taken from the earliest prescription of each treatment category, or from 1 April 2012 if the earliest prescription was before that date.

The risk of having TIA or IS, CHD, PAD, or GI haemorrhage, between 1 April 2012 and 1 April 2017, was estimated using Cox regression models for those who were on antiplatelets only during the follow-up, a combination of antiplatelets and VKAs, or NOACs, and compared with those who were only on VKAs. All models were first adjusted for age and sex, and later for variables that could affect choice of anticoagulation and risk of different outcomes: socioeconomic status and risk for thromboembolic events (CHA_2DS_2-VASc score).[12,20,25,26]

Patients were censored when they left the area of study (moving somewhere else or dying), they experienced their first outcome, or they stopped the treatment of interest (last prescription was issued). Patients were categorised as having the outcomes of interest when the diagnosis had been recorded either in primary or secondary care. When outcomes had been recorded both in primary and secondary care, the date of the first record was used to censor the patient. The risk for different outcomes was estimated independently, with a different model. The whole sample was treated as a single cohort as patients were all living in the same area of London where there is free access to health care for everyone, health care is standardised, and all patients were treated independently within the cohort.

RESULTS

Initially, 4943 patients with AF were identified in the database. Of those, 465 were excluded as their AF had been resolved before the beginning of the study, and 607 because their CHA_2DS_2-VASc score was <2. Finally, 3871 patients with AF diagnosed before 2012 were included in the study. The mean age of the study group was 76.99 years (SD 10.44) and 1925 (49.7%) of them were female. All of the participants had their risk for thromboembolic outcomes measured and the median CHA_2DS_2-VASc score was 4 (interquartile range [IQR] 3–5). The socioeconomic status was measured in 3646 of the participants and their median English Index of Deprivation score was 42.7 (IQR 36.6–49.2).

A description of participants who took each drug during the study period and their outcomes are presented in Table 1.

Patients who took only antiplatelets had higher risk of having a TIA or IS, with HR 1.51, 95% CI = 1.09 to 2.09, $P = 0.014$, and GI haemorrhages HR 1.79, 95% CI = 1.01 to 3.18, $P = 0.047$, than those on VKAs only. The risk of having all outcomes was similar for both those on a combination of VKAs and antiplatelets, and for those on VKAs only. Patients on NOACs had a higher risk of having CHD than those on VKAs, HR 2.07, 95% CI = 1.35 to 3.19, $P = 0.001$, and a similar risk for all other outcomes. These associations did not change when models were further adjusted for CHA_2DS_2-VASc and socioeconomic status (Table 2).

DISCUSSION

Summary

In the present study, patients with AF who took only antiplatelets had a higher risk of thromboembolic and haemorrhagic events than those on VKAs, those on a combination of VKAs and antiplatelets had a similar risk compared with those on VKAs only, and finally those on NOACs also had a similar risk, except for CHD where the risk was increased, compared with those on VKAs. The socioeconomic status and risk for thromboembolic outcomes made no difference to these associations.

Table 1. Participant characteristics, conditions and outcomes in each therapy category[a]

Participant characteristics and outcomes	Therapy			
	Antiplatelets (*N* = 901)	VKA (*N* = 1450)	Antiplatelets plus VKA (*N* = 576)	NOACs (*N* = 439)
Age, years				
Mean (SD)	79.6 (10.3)	75.3 (10.3)	74.6 (9.4)	75.5 (9.6)
Sex				
Female, *n* (%)	460 (51.1)	739 (51.0)	223 (38.7)	226 (51.5)
CHA_2DS_2-VASc score	4	4	4	4
Median (IQR)	(3–5)	(3–5)	(3–5)	(3–5)
English Index of Deprivation Score (*N* = 3646)	43.4	42.1	42.7	41.8
Median (IQR)	(37.6–49.8)	(36.2–48.8)	(36.6–49.4)	(35.3–48.3)
Exposure, days				
Mean (SD)	897 (633)	1288 (616)	764 (623)	438 (407)
TIA or IS				
n (%)	117 (13.0)	132 (9.1)	30 (5.2)	14 (3.2)
CHD				
n (%)	189 (21.0)	256 (17.7)	162 (28.1)	27 (6.2)
PAD				
n (%)	32 (3.6)	39 (2.7)	20 (3.5)	6 (1.4)
GI haemorrhage				
n (%)	36 (4.0)	43 (3.0)	17 (3.0)	7 (1.6)

[a]*Data show the participants who took each drug. Those who took no drugs at all, or took combinations that were not of interest in the study, that is, VKA+NOACs, are not presented. CHD = cardiovascular disease. GI = gastrointestinal. IQR = interquartile range. IS = ischaemic stroke. NOACs = novel oral anticoagulants. PAD = peripheral artery disease. SD = standard deviation. TIA = transient ischaemic attack. VKA = vitamin K antagonists.*

Strengths and limitations

An important limitation of the present study was the lack of information on patient adherence to prescribed drugs, which may have led to possible misclassifications of exposure. Although most patients attending practices in the study area would attend the local hospitals, some patients may have been seen elsewhere and thus these outcome data may have been missed. The East London database captures all prescriptions issued by the general practice team and there is evidence showing that 97% of cardiovascular medications are dispensed as prescribed.[27] However, non-adherence to dispensed drugs may have still contributed to an underestimation of both the efficacy of the drugs in the prevention of IS, and the risk for haemorrhagic outcomes. It should be noted that the absence of adherence data is a limitation that affects most observational studies using large clinical databases.[28] The low number of outcomes registered in some treatment categories is one of the limitations of the present study. Although the sample size was reasonably large, some interesting clinical events, such as haemorrhagic strokes, could not be included in the analysis, and others such as TIA and ischaemic strokes had to be categorised together owing to the low number of cases in the dataset. The older age of those on antiplatelets compared with those on VKAs, can also represent a limitation of this study. Although the authors' models were adjusted for confounders, including age and sex, there is always a degree of residual confounder left. Future studies with a larger sample size could investigate these outcomes separately, and also how they are affected by comorbidities and other medication. The use of alternative statistical methods to deal with confounding, such as propensity score matching, can also be considered in future research.

The long follow-up and the adjustment for factors associated with choice of anticoagulation and thromboembolic events are strengths of this study.[12,20,25,26] Furthermore, all data were entered into the

Table 2. Risk of outcomes in each treatment category compared with those taking VKAs only during the study period

Outcome	Covariates included in the models	Therapy: Antiplatelets HR (95% CI)	*P*-value	Antiplatelets and VKA HR (95% CI)	*P*-value	NOACs HR (95% CI)	*P*-value
TIA or IS	Age and sex	1.51 (1.09 to 2.09)	0.014	1.42 (0.93 to 2.17)	0.102	1.00 (0.54 to 1.84)	0.997
	Age, sex, socioeconomic status, and CHA_2DS_2-VASc score	1.53 (1.08 to 2.16)	0.015	1.38 (0.89 to 2.14)	0.153	0.98 (0.53 to 1.80)	0.941
CHD	Age and sex	1.06 (0.83 to 1.35)	0.651	1.05 (0.84 to 1.31)	0.678	2.07 (1.35 to 3.19)	0.001
	Age, sex, socioeconomic status, and CHA_2DS_2-VASc score	1.05 (0.81 to 1.35)	0.717	1.06 (0.84 to 1.32)	0.636	2.15 (1.34 to 3.44)	0.001
PAD	Age and sex	1.26 (0.68 to 2.36)	0.461	1.33 (0.67 to 2.64)	0.411	1.82 (0.68 to 4.82)	0.230
	Age, sex, socioeconomic status, and CHA_2DS_2-VASc score	1.13 (0.58 to 2.20)	0.726	1.68 (0.83 to 3.41)	0.150	2.67 (0.88 to 8.11)	0.082
GI haemorrhage	Age and sex	1.79 (1.01 to 3.18)	0.047	1.46 (0.74 to 2.91)	0.276	1.56 (0.63 to 3.85)	0.334
	Age, sex, socioeconomic status, and CHA_2DS_2-VASc score	1.77 (0.95 to 3.29)	0.070	1.49 (0.70 to 3.16)	0.294	1.34 (0.49 to 3.64)	0.565

CHD = cardiovascular disease. CI = confidence interval. GI = gastrointestinal. HR = hazard ratio. IS = ischaemic stroke. NOACs = novel oral anticoagulants. PAD = peripheral artery disease. TIA = transient ischaemic attack. VKA = vitamin K antagonists.

medical record prospectively, minimising the risk of recall bias or inaccurate self-reporting. The authors also applied a minimum of exclusion criteria to describe real-world effects with maximum external validity. The use of structured data entry templates, and clinical facilitation in the East London practices studied, enabled routine entry of high-quality data using agreed code sets for recording atrial fibrillation and cardiovascular risk factors. All data included in the East London Primary Care Database are audited on a quarterly basis by a data analyst at Queen Mary University of London, where the data is held, to ensure data quality. Finally, the diagnoses of atrial fibrillation, cardiovascular risk factors, and the medication prescribed are routinely reviewed by local clinicians as part of their national Quality and Outcomes Framework audit returns that provide further validation of data quality.[22]

Comparison with existing literature

The similar risk of TIA or IS for those on NOACs and VKAs is consistent with the results of two systematic reviews of observational studies and a recent large cohort study.[6,10,28] However, another two systematic reviews of observational studies have reported a lower risk of IS for those on rivaroxaban compared with VKAs.[9,29] The results of the present study, and part of the previous observational literature, differ from the results of randomised controlled trials (RCTs), where NOACs are associated with lower risk of IS and CHD than warfarin.[6,10,30] This may be because in most trials the participants were different from the present study's real-world AF population.

The higher risk of CHD among those on NOACs, observed in the present study, differs from the results of a systematic review of observational studies that reported similar risk for both therapies.[10] However, two recent observational studies have reported a higher risk of CHD for those on NOACs than for those on VKAs.[8,31] The higher risk of CHD for those on NOACs may be explained by the low dose of NOACs that many patients with AF receive to reduce the risk of bleeding, and the intensive follow-up from anticoagulation clinics, which those on VKAs, but not those on NOACs, receive.[8]

An increased risk of GI bleed has been reported by systematic reviews of observational studies, and a recent large cohort study, for those on rivaroxaban,[9,10,28] or dabigatran[6,10] compared with patients on VKAs. However, apixaban was associated with a lower risk of major bleed than warfarin.[28] No differences in risk of GI bleed were observed in the present study for any treatment category. This may be because of the low number of patients with GI haemorrhages included in the cohort, the analysis of all NOACs as a single category, or the genuine absence of the association in the present study population.

Implications for research and practice

The conflicting results of the present study and the previous literature make

it difficult to produce definitive clinical recommendations and would support the current guidelines recommending that treatment with anticoagulants should be individualised depending on patients' adherence to prescribed therapy, comorbidities, other prescribed drugs, and lifestyle factors.[17,32,33] The available evidence suggests better safety and efficacy of anticoagulants over antiplatelets but does not support prioritising VKAs or NOACs.

It seems, that the risk for different outcomes may vary for those on different NOACs compared with those on VKAs. Therefore, further research is required, using different NOACs, and observing a number of outcomes with their associated mortality and quality of life. The thromboembolic risk is likely to change over time and how this variation affects the incidence of each of the outcomes in patients exposed to different anticoagulation could also be addressed in new studies. The adherence to different anticoagulants and its impact on any beneficial or adverse effects can also be addressed in future research. Though observational studies like the one presented here, where participants were not randomised, are more prone to selection bias than RCTs, well-designed observational studies can provide good generalisability to real-world practice.[6,34] The combination of evidence from RCTs and observational research should lead to clear clinical recommendations about specific drugs in different groups of patients, and ultimately result in more effective and safer prevention of thromboembolic events in patients with AF.

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Ethical approval

All data were anonymised and managed according to the UK NHS information governance requirements. Ethical approval was not required for the use of routinely collected anonymised data in this observational study.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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