**Thromboembolic and haemorrhagic events in atrial fibrillation patients; a prospective cohort study.**

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**Abstract**

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

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

Design and setting: Cohort study. Routinely collected primary and secondary care clinical data from AF patients, aged ≥18, and indication to receive anticoagulation, prior to April 2012, were used

Methods: The risk of Ischaemic Stroke or Transient Ischaemic Attack (TIA), Coronary Heart Disease (CHD), Peripheral Artery Disease, or Gastrointestinal (GI) haemorrhage, between April 2012 and 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), compared to those on VKAs only.

Results: Compared to VKAs, antiplatelets were associated with a higher risk of stroke or TIA, Hazard Ratio (HR): 1.51, 95% Confidence interval (CI): (1.09-2.09), and GI haemorrhage, HR (95% CI): 1.79 (1.01-3.18). 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 increased for patients on NOACs, HR (95% CI): 2.07 (1.35-3.19).

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

**Key Words**: Atrial Fibrillation, Primary Health Care, Anticoagulants, Stroke, Gastrointestinal Haemorrhage, Myocardial Ischaemia.

**How this fits in**:

A number of studies have compared the safety and efficacy of different anticoagulants in AF patients, most of them have focused 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 our study, compared to Vitamin K antagonists (VKA), antiplatelets were associated with a higher risk of TIA or stroke, and gastroentitestinal 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, except for coronary heart disease, where patients had an increased risk.

This evidence suggests lower thromboembolic and haemorrhagic risk of anticoagulants over antiplatelets but does not support prioritizing VKAs or NOACs. More research is required on the risk and efficacy of VKAs and NOACs.

**Introduction**

Atrial fibrillation (AF) is a leading cause of morbidity and mortality, with five 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 AF patients.[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, most of them have focused 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 or thromboembolic events, 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]

Despite the better safety and efficacy of anticoagulants over antiplatelets in the prevention of thromboembolic events among those with AF, a significant proportion of patients are still on antiplatelets only.

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

AF patients.

This study tests the hypothesis that 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), CHD, PAD, and gatrointestinal (GI) haemorrhage, is estimated over a period of five years, for patients with AF treated with antiplatelets, a combination of antiplatelets and VKAs, or NOACs, compared to those taking only VKAs.[3, 15]

**Methods**

The study conformed to the STROBE study design recommendations.[16]

Prospective cohort study, including patients aged ≥18, with at least one 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[17] (CHA2DS2VASc[18] score ≥2), prior to the 1st of April 2012.

All data were collected from routinely recorded clinical notes from the East London Primary care database, that has records of all patients registered in 140 practices in three contiguous boroughs of London, and The Secondary Uses Service, that has clinical data from the hospitals in those same areas. Primary and secondary care records data were linked using pseudoanonymised identifiers. Sociodemographic variables included age, and gender. The English Index of Deprivation was recorded as a measure of socioeconomic status.[19] Clinical data included risk of thromboembolic outcomes, measured with the CHA2DS2VASc score,[18] and the first diagnoses between 1st April 2012 and 1st April 2017 of TIA or IS, CHD, PAD, and GI haemorrhage. When clinical data were collected from primary care they were defined

using the read codes from the Quality and Outcomes Framework ruleset entered by doctors in the medical records.[20] Clinical data from secondary care were defined using the tenth version of the International Classification of Diseases.[21] Data on treatments were extracted for each drug according to their classification as antiplatelets, NOACs or VKAs in the British National Formulary.[22] Data on each treatment category were taken from the earliest prescription of each treatment category, or from the 1st of April 2012, if the earliest prescription was before that date.

The risk of having TIA or IS, CHD, PAD, or GI haemorrhage, between 1st of April 2012 and the 1st of 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, compared to those who were only VKAs. All models were first adjusted for age and gender, and later for variables that can affect choice of anticoagulation and risk of different outcomes: socioeconomic status, and risk for thromboembolic events (CHA2DS2VASc score).[12, 18, 23, 24]

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). 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 standardized, and all patients were treated as independent within the cohort.

**Results**

A total of 4943 AF patients were initially identified in the database. 465 of them were excluded, as they had got AF resolved before the beginning of the study, and 607

because their CHA2DS2VASc score was<2. Finally, 3871 patients with AF diagnosed before 2012, with mean age 76.99 (SD: 10.44), 1925 (49.7%) of them women, were included in the study. All of them had their risk for thromboembolic outcomes measured and the median and interquartile range CHA2DS2VASc score was 4 (3-5). The socioeconomic status was measured in 3646 of them and their median and interquartile range English Index of Deprivation score was 42.7 (36.6-49.2)

The description of participants who took each drug during the study period, and the outcomes they had, are presented in table one.

Patients who took only antiplatelets had higher risk of having a TIA or IS, and GI haemorrhages, than those on VKAs. The risk of having all outcomes was similar for those on VKAs and antiplatelets, than for those on VKAs only. Patients on NOACs had higher risk of having CHD than those on VKAs, and similar risk for all other outcomes. These associations did not change when models were further adjusted for CHA2DS2VAc and socioeconomic status (table two).


**Discussion**

Summary:

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

Strengths and limitations:

An important limitation for our study is the lack of information on patient adherence

to their prescribed drugs, which may have lead to a possible misclassifications of exposure. The east London database captures all prescriptions issued by the general practice team and there is evidence showing that 97% of cardiovascular medications dispensed as prescribed 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.[25] The low number of outcomes registered in some treatment categories is one of the limitations of our study. While the sample size was reasonable 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 categorized together, due to the low number of cases in the dataset. Future studies with larger sample size could investigate these outcomes separately, and how are they are affected by comorbidities and other medication.

The long follow up and the adjustment for factors associated with choice of anticoagulation and thromboembolic events, is a strength of this study.[12, 18, 23, 24] Furthermore all data were entered into the medical record prospectively, minimizing the risk of recall bias or inaccurate self-report. We 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 CVR factors.  Finally, the diagnoses of atrial fibrillation, CVR factors, and the medication prescribed is  routinely reviewed by local clinicians as part of their national Quality and Outcome Framework audit returns which provides further validation of data quality..

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, 25] However, another two systematic reviews of observational studies have reported a lower risk of IS for those on Rivaroxaban compared to VKAs.[9, 26] The results of our study, and part of the previous observational literature, differs from the results of randomised controlled trials, where NOACs are associated with lower risk of IS and CHD than warfarin.[6, 10, 27] This may be because in most trials the participants are different from our real-world AF population.

The higher risk of CHD among those on NOACs, observed in our 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, 28] The higher risk of CHD for those on NOACs may be explained by the low dose of NOACs that many AF patients receive to reduce the risk of bleeding, and the intensive follow up from anticoagulation clinics, that 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, 25] or dabigatran[6, 10] compared to patients on VKAs. However, apixaban was associated with a lower risk of major bleed than warfarin.[25] No differences in risk of GI bleed were observed in our study for any treatment category. This can 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 association in our study population.

Implications for clinical practice and future research:

The conflicting results of our study, and the previous literature, make difficult to produce definitive clinical recommendations and would support the current guidelines that recommend that treatment with anticoagulation should be individualized depending on patients' adherence to prescribed therapy, comorbidities, other prescribed drugs, and lifestyle factors.[17, 29, 30] The available evidence suggests better safety and efficacy of anticoagulants over antiplatelets but does not support prioritizing VKAs or NOACs.

It seems, that the risk for different outcomes may vary for those on different NOACs compared to 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 adherence to different anticoagulants and its impact on any beneficial or adverse effects can also be addressed in future studies. Although observational studies are more prone to selection bias than RCTs, well-designed observational studies can provide good generalizability to real-world practice.[6, 31] 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.

study.

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