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Dual-antithrombotic therapy and gastroprotection in atrial fibrillation: An observational primary care study

Charis Xuan Xie[1] (MRes, MSc; Wellcome Trust PhD student), John Robson[2] (MD, FRCGP; Reader), Crystal Williams[2] (MSc; Senior data analyst), Chris Carvalho[1,2] (MD; General Practitioner and NIHR research fellow), Stuart Rison[1,2] (MD; General Practitioner and research fellow), Zahra Raisi-Estabragh[3,4] (MD, PhD; Cardiology registrar and NIHR Clinical Lecturer)

1. Wolfson Institute of Population Health, Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Yvonne Carter Building, 58 Turner Street, London, E1 2AB
2. North East London Integrated Care System, Unex Tower, 5 Station Street, London E15 1DA
3. Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, EC1A 7BE, London
4. William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, Charterhouse Square, London, EC1M 6BQ, UK

Email list: charis.xie@qmul.ac.uk; j.robson@qmul.ac.uk; crystal.williams@qmul.ac.uk; chris.carvalho@nhs.net; s.rison@qmul.ac.uk; z.r.raisi-estabragh@qmul.ac.uk

Corresponding author: Dr Zahra Raisi-Estabragh; Address: William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, Charterhouse Square, London, EC1M 6BQ, UK; Tel: +44 (20) 37658766; E-mail: z.r.raisi-estabragh@qmul.ac.uk

Abstract

Background: Patients with both atrial fibrillation (AF) and cardiovascular disease (CVD) may receive dual-antithrombotic therapy (DAT) with both an anticoagulant and one or more antiplatelet agents. Avoiding prolonged duration of therapy and use of gastroprotective therapies reduces bleeding risk.

Aim: To describe the extent and duration of DAT and use of gastroprotection in a primary care cohort of patients with AF.

Design and Setting: Observational study in 1.2 million people registered with general practitioners across four east London Clinical Commissioning Groups, covering prescribing from January 2020 to June 2021.

Methods: In patient with AF, we characterised factors associated with DAT prescription, prolonged DAT prescription (>12 months), and gastroprotective prescription using logistic regression.

Results: There were 8,881 patients with AF of whom 4.7% (416) were on DAT. Of these, 65.9% (274) were prescribed DAT for >12 months and 84.0% (351) were prescribed concomitant gastroprotection. Independent of all other factors, women with AF were less likely to receive DAT than men [OR=0.61 (0.49-0.77)]. Similarly, older (≥75 years) individuals [OR=0.79 (0.63-0.98)]) were less likely to receive DAT than younger patients. Amongst those with AF on DAT, people with CVD [OR=3.33 (1.71-6.47)] or South Asian ethnicity [OR=2.70 (1.15-6.32)] were associated with increased gastroprotection prescriptions. Gastroprotection prescription [OR=1.80 (1.01-3.22)] was associated with prolonged DAT prescription.

Conclusion: Almost two thirds of patients with AF on DAT were prescribed prolonged durations of therapy. Prescription of gastroprotection therapies was suboptimal in 1 in 6 patients. Treatment decisions varied by sex, age, ethnicity, and comorbidity. Duration of DAT and gastroprotection in patients with AF requires improvement.

Keywords: dual-antithrombin therapy, anticoagulation, antiplatelets, atrial fibrillation, cardiovascular disease, gastroprotection, bleeding risk, population health.

How this fits in:

Patients with atrial fibrillation (AF) and cardiovascular disease may be treated with dual antithrombotic therapy (DAT). Associated bleeding risk may be reduced using gastroprotective therapies and by avoiding prolonged DAT durations. In this large population-based cohort of AF patients, amongst those on DAT, two thirds of patients received treatment for excessive durations and use of gastroprotection therapies was suboptimal. Treatment decisions varied by sex, age, ethnicity, and comorbidity. Our findings highlight urgent need for directed strategies to optimise medication management of AF patients treated with DAT.

Introduction

Ageing populations[1] are leading to greater burdens from chronic age-related illnesses, among which atrial fibrillation (AF) and coronary artery disease (CAD) are the most common cardiovascular diseases (CVDs).[2,3] These conditions share multiple risk factors and commonly co-exist, presenting clinical challenges.[4]

Patients with CAD may be prescribed antiplatelets for event prevention in stable disease.[5] In the setting of an acute coronary syndrome or after percutaneous coronary intervention (PCI), there is strong evidence for dual antiplatelet therapy to prevent myocardial infarction and, for those undergoing PCI, stent thrombosis.[6] High risk patients with chronic stable coronary artery disease also warrant antiplatelet therapy to prevent myocardial infarction or after elective PCI to prevent stent thrombosis.[6] The typical duration of dual antiplatelet therapy after PCI is 12 months; however, there is increasing evidence to suggest that shorter durations of therapy are adequate for newer generation drug eluting stents and may be considered for patients at high bleeding risk.[6]

Treatment decisions are further complicated in CAD patients with co-existent AF, who have an indication for anticoagulation to prevent thromboembolic stroke.[4] In these individuals, a short period (1-3 months) of "triple therapy" (combining dual antiplatelet therapy with anticoagulation) may be recommended, followed by dual anti-thrombotic therapy (DAT), comprising a single antiplatelet agent and an anticoagulant, for a further 3-11 months.[6] Similar clinical challenges are encountered in patients with ischaemic cerebrovascular events with requirement for antiplatelet therapy; these individuals often have co-existent AF, which not infrequently has precipitated the cerebral event. Although durations of DAT vary, it is very rarely indicated for more than a year and for many the appropriate duration is less than 6 months.[4]

Concomitant use of multiple antithrombotic therapies is accompanied by increased risk of serious bleeding complications, most commonly upper gastrointestinal bleeding (UGIB). Routine use of gastroprotection therapies and avoiding excessive durations of DAT are important considerations for minimising DAT-related bleeding complications.[5–7] However, the frequency with which such simple strategies are adopted in clinical practice is unclear. As most patients with stable chronic diseases are discharged to the community, it is important for both primary care and hospital clinicians to be vigilant to these issues.

Upper gastrointestinal bleeding is the commonest cause of hospital admission for an adverse drug related event of which antiplatelet use, anticoagulant use, and particularly the combination of the two in conjunction with older age are substantive causes.[8] A variety of evidence and guidelines now

recommend PPI in people at high risk of bleeding on antiplatelet therapy particularly in combination with anticoagulant therapy.[6,9–12]

We sought to evaluate factors associated with suboptimal bleeding risk mitigation in patients with AF using routine health data in a community setting. This work is particularly timely as the new national Network Contract Directed Enhanced Service Investment and Impact Fund 2020/21 addresses medicines safety area and includes dual anticoagulant and antiplatelet therapy as a quality indicator for general practitioners in England.[13]

We present a population-based study of patients with AF, describing demographic, physiologic, and clinical factors associated with DAT, and, amongst those on DAT, prolonged DAT (> 12 months) and the prescription of gastroprotective therapies.

Methods

Setting and study population

The study population included individuals registered with a general practitioner (GP) in one of four east London Clinical Commissioning Groups (CCGs: Waltham Forest, City and Hackney, Tower Hamlets and Newham), covering a total of 1.2 million people. This population comprises individuals who are, on average, younger, more ethnically diverse, and less affluent than the general UK population.[14] The CCGs have above national average performance in cardiovascular risk management.[14] We limited the study to adults age 18 years or more. We excluded individuals who were registered with GPs for less than 12 months from the date of data extraction. We included individuals with a record of diagnosed AF or atrial flutter as per standardised SNOMED codes (Supplementary Table 1). We excluded patients with a record of "Atrial fibrillation resolved".

Data source

De-identified health data were provided by the Clinical Effectiveness Group at Queen Mary University of London who centrally extracted pseudonymised data from the general practice systems (EMIS) in June 2021, covering prescribing in the period from January 2020 to June 2021. Data analysis was conducted in July 2021. Cases, demographic and other risk factors and medication were identified using SNOMED codes and routinely collected data.

DAT and gastric protection medications

We defined DAT as concomitant prescription of one or more antiplatelet medications (aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor) and an anticoagulant (warfarin, phenindione, acenocoumarol, apixaban, dabigatran, edoxaban, rivaroxaban) within the preceding six months. We identified individuals prescribed DAT for longer than 12 months using an algorithm identifying prescription of both an anticoagulant and an antiplatelet medicine at both 18 months and within six months prior to data extraction. We additionally noted prescription of gastroprotection medications in the preceding six months, specifically, proton pump inhibitors (PPIs: pantoprazole, rabeprazole, omeprazole, esomeprazole) or H2 receptor antagonists (H2RAs: ranitidine, cimetidine, famotidine).

Risk factor indicators

We considered two age categories of above and below 75 years, sex defined as male or female, and five ethnic groups aligned with the Office for National Statistics (ONS) 2001 census ethnicity classification[15]: 1) White (British, Irish, other White), 2) Black (Caribbean, African, Other Black), 3) South Asian (Indian, Pakistani, Bangladeshi), 4) Other ethnic groups including mixed ethnic groups and Chinese, and 5) those with no record of coded ethnic group.[16] Deprivation was measured by the Index of Multiple Deprivation (IMD) 2015 and individuals were grouped into locally derived quintiles, from least (IMD=1) to most (IMD=5) deprived.[17]

Smoking history was classified as current smoker, ex-smoker, or never smoked (ever recorded). Body mass index (BMI) was directly extracted or calculated from records of height and weight. We categorised BMI into World Health Organisation categories of obesity: < 20kg/m^2 (underweight), 20-29 kg/m^2 (Reference level), ≥ 30 kg/m^2 (obese). Systolic blood pressure was extracted from recorded office measurements and classified into above and below 140mmHg. All characteristics considered were based on the latest record within the last three years.

We included the following conditions, selected on their likely influence on clinical decisions regarding anti-thrombotic and gastroprotection therapies: ischemic heart disease (IHD), stroke/ transient ischemic attack, diabetes (Type1 or Type2), chronic kidney disease (CKD), previous UGIB. Disease definitions were based on relevant SNOMED codes (Supplementary Table 1).

Statistical analysis

Statistical analyses were conducted using Stata SE (version 17.0; StataCorp). We estimated association of clinical, physiological, and demographic factors with DAT prescription amongst patients with AF. We used logistic regression models with DAT status (Yes/No) set as the model outcome and participant characteristics set as the exposures of interest. We additionally examined, amongst patients with AF on DAT, association of factors with prescription of gastroprotective therapy using logistic regression models, setting the model outcome as gastroprotection (Yes/No) and inserting participant characteristics as the exposures of interest. Analyses were performed first in univariable and then in multivariable models with mutual adjustment for all exposures (age, sex, ethnicity, deprivation, CVD (IHD, stroke, TIA), diabetes or stage 3-5 CKD, UGIB, systolic blood pressure, smoking, BMI). Subgroup analysis was performed in patients prescribed DAT for 6 months and > 12 months. Missing fields were treated as a separate category 'unknown' in the univariable and multivariable logistic regression models without losing this information. Where the number of patients with missing data was very small (i.e., less than five) these patients were excluded from the model and indicated in the footnotes. We report odds ratios (ORs) with 95% confidence intervals (CIs) and the corresponding p-values. Statistical significance level was set at 5%. The study conformed to the STROBE criteria.[18]

Results

Sample characteristics

We included 8,881 patients with AF in the analysis (Table 1, Supplementary Figure 1). Almost half the patients (4300/8881, 48.4%) were aged ≥ 75 years old. There were slightly more men than women (5024/8881, 56.6%). The degree of ethnic diversity was greater than in the national UK population with 36.6% (3253/8881) of patients from ethnic minority backgrounds, most commonly from Black (1186/8881, 13.4%) and South Asian (1069/8881, 12.0%) ethnicities. There was high prevalence of comorbidities, with diabetes or CKD recorded in 49.4% (4389/8881) and CVD (IHD, stroke, or TIA) in 35.8% (3177/8881). There was record of obesity (BMI ≥ 30 kg/m^2) in 33.8% (3002/8881) of individuals. The sample included 8.9% (792/8881) current smokers and 30.9% (2742/8881) ex-smokers. Latest recorded systolic blood pressure measurement was above 140 mmHg for 14.2% (1262/8881) of patients.

A total of 416 (4.7%) patients were on DAT. The majority had documented CVD (340/416, 81.7%). Patients on DAT had substantially poorer cardiometabolic profile and more demographic and other vascular risk factors than the rest of the cohort (Table 1). Amongst those on DAT, 65.9% (274/416) were issued prescriptions for more than 12 months. Amongst those on DAT, 84.0% (351/416) were on gastroprotection therapies; the proportion of these patients on DAT with a history of UGIB did not appear markedly different to the rest of the AF cohort not on DAT (1.4% (6/416) vs 1.2% (105/8465).

DAT

In fully adjusted multivariable logistic regression models (Table 2), male sex, younger age, South Asian ethnicity, CVD, diabetes or CKD, current smoking, and obesity (BMI ≥ 30kg/m^2) were all independently associated with greater likelihood of DAT. Individuals with CVD were over 8-fold (OR=8.01; 95% CI=6.17, 10.39; p-value≤0.001) more likely to receive DAT compared to those without CVD. Independent of all other factors, women with AF were significantly less likely to receive DAT than men (OR=0.61; 95% CI=0.49, 0.77; p-value=<0.001), as were older individuals, (OR=0.79; 95% CI=0.63, 0.98; p-value=0.032), compared to younger patients.

Prolonged DAT

Most AF patients on DAT had a record of dual prescriptions for more than 12 months (274/416, 65.9%). Patient characteristics stratified by DAT duration are displayed in Supplementary Table 2. Amongst those on prolonged DAT, there was a disproportionate number of men (200/274,73.0% vs 86/142, 60.6%), younger individuals (147/274, 53.7% vs 70/142, 49.3%), and individuals from South Asian ethnic backgrounds (67/284, 24.5% vs 26/142, 18.3%). Those with CVD were more likely to be on prolonged DAT (85.0% (233/274) vs 75.4% (107/142). The rates of UGIB did not differ amongst those on prolonged DAT compared to those on shorter DAT durations (1.5% (4/274) vs 1.4% (2/142).

In multivariable linear regression models (Table 3), prescription of gastroprotection therapies (PPI or H2RAs) was significantly associated with DAT duration of 12 months or more (OR=1.80; 95% CI=1.01, 3.22; p-value=0.048). We did not observe statistically significant associations between any of the other exposures and DAT duration in univariable or multivariable models.

Gastric protection

Amongst the 416 atrial fibrillation patients on DAT, 84.4% (351) were prescribed gastroprotection (PPIs or H2RAs); of these 346 (98.6%) were prescribed PPI and 5 (1.4%) patients were prescribed H2RA alone. The characteristics of this subset is presented in Supplementary Table 3. Those receiving gastroprotection, were more likely to be women (31.9% (112/351) vs 27.7% (18/66)), from ethnic minority backgrounds (48.7% (171/351) vs 35.4% (23/66)), and to have co-morbidities including CVD, diabetes, CKD, or previous UGIB (Supplementary Table 3).

In fully adjusted models (Table 4), those with CVD were over 3-fold more likely to receive gastroprotection (OR=3.33; 95% CI: 1.71, 6.47; p-value ≤0.001), compared to those without CVD. Similarly, independent of all other exposures, individuals of South Asian ethnicity were significantly more likely to receive PPI/H2RA prescriptions (OR 2.70; 95% CI: 1.15, 6.32; p-value=0.023) compared to those from White ethnic backgrounds.

Discussion

Summary

In this large population-based cohort of 8,881 patients with AF, 4.7% (416) were on DAT. Male sex, younger age, South Asian ethnicity, cardiovascular disease, diabetes or CKD, current smoking, and obesity were all independently associated with greater likelihood of DAT. Independent of all other factors, women and older patients with AF were significantly less likely to receive DAT than men and younger patients. Amongst patients with AF on DAT, almost two thirds [65.9% (274/416)] received prescriptions for more than 12 months, which indicates an inappropriately prolonged duration. Greater use of PPI/H2RA was the only factor significantly linked to prolonged DAT prescription. Amongst patient with AF on DAT, 84.0% (351/416) were on gastroprotective therapies (PPI/H2RAs). The presence of CVD (IHD, stroke, TIA) was associated with greater likelihood of PPI/H2RA.

Strengths and Limitations

This large-scale epidemiologic study of routine primary care health data allowed examination of treatment practices in an ethnically diverse population cohort. The use of standardised disease codes and complete prescription records supported reliable ascertainment of case and treatment status across a large, unselected sample. Use of routine data may have some limitations. Ascertainment of AF cases may be limited by misdiagnoses or coding errors. Furthermore, we defined DAT and PPI/H2RA use based on primary care prescription records, without assessment of medication adherence. It is possible that a small minority patients were using medications obtained from sources other than primary care or were using medications issued outside of our analysis window, such individuals would not be captured in our study but are unlikely to be in numbers to appreciably alter our results. We assumed that concurrent prescription of medications indicates concurrent usage. Whilst for most people this would be correct, it is possible that some people were categorised as DAT users but had in fact discontinued taking their antiplatelet medicine. Our definition of prolonged DAT (> 12 months) does not account for individuals who may have stopped and restarted DAT for an appropriate indication. Finally, very uncommonly, extended DAT may be appropriate. We were unable to view individual patient records and could not distinguish patients on appropriate prolonged DAT or who received DAT prescriptions but did not actually take the medication. However, the number of such individuals is likely to be small and would not explain the large proportion of patients on prolonged DAT in our cohort (274, 65.9% of those on DAT). Our study did not consider the further duration of therapy beyond 12 months as for the vast majority this is clearly an excessive duration. Future work considering more granular risk would be informative but information electronically coded in UK GP records is limited to the issue of a prescription and there is no adequate record of patients not completing prescriptions.

There are many factors that may influence bleeding risk, in this paper we aimed to provide broad characterisation of individuals who were prescribed DAT; the clinical factors considered in this study are not exhaustive. A key outcome in evaluating DAT is the frequency of UGIB. The few UGIB events in our sample precluded comparisons with this outcome. Finally, our sample from east London has greater ethnic diversity, deprivation, and comorbidities than the national UK population. Similar evaluations at a national level would provide further insight on the topic.

Comparison with existing literature

The risk factors associated with DAT in our study are consistent with previous reports.[19–22] Amongst AF patients on DAT, 81.7% (340/416) had co-existent CVD (IHD, stroke, TIA). There were 76 patients (18.3%) who were on DAT, but without documented CVD; we noted that these individuals were significantly less likely to receive PPI/H2RA than those with record of CVD. It is possible that CVDs were present but are not correctly coded for these patients or that they have alternative, less common, indications for antiplatelet therapy such as, peripheral arterial disease or haematological diseases. Either way, our findings suggest that for these patients the indication for DAT was unclear and associated with lower rates of gastroprotection prescription.

We found a record of DAT in 4.7% (416) of our study sample. This is lower than in previous studies and indicates a decreasing contemporary trend when compared with other nationwide studies dating from more than 10 years earlier. Previous reports from UK data between 1998-2010 indicate that 11% of patients with AF and IHD were on DAT.[23] In a similar population of patients with AF and IHD between 2010-2011, rates of DAT were reported at 27%.[24] Corresponding figures from Japan[25] (2016-2018) and Italy[26] (2018-2019) are 15.1% and 8.8% respectively. A key difference between our studies and these reports is that the latter are all limited to individuals with AF and IHD, in whom guideline recommendations for DAT are generally well-defined. Our study included all patients with AF patients and as such a lower proportion on DAT would be expected. Other potential explanations include differences in study populations, more contemporary results and differences in national practices.

Amongst AF patients on DAT, 84.0% (351) were prescribed a PPI/H2RA, which is higher than reported by other cohort studies (11%-63%).[25,27,28] We achieved a relatively high figure possibly by virtue of a local incentive program promoting the use of PPI optimization, or simply because contemporary guidance and research is more likely to endorse the use of PPI co-therapy with antithrombic medicines. Indeed, a recent European Society of Cardiology guidance update highlighted bleeding risk reduction as a key priority area including recommendation for routine use of PPI in combined uses of antiplatelet agents with either another antiplatelet drug or an anticoagulant.[6] As

indicated in the above discussion, prescription of DAT was significantly higher in patients with documented CVD, indicating that perhaps these patients had clearer healthcare plans.

Independent of all other demographic and clinical factors, women with AF had significantly lower rates of DAT prescription than men (5.7% vs. 3.4%), which may suggest undertreatment of women. Previous work has demonstrated greater underdiagnosis[29], undertreatment, and delayed treatment of women with CVD compared to men.[30,31] Poorer risk factor profile and IHD patterns associated with higher thrombotic risk[32–35], were not evaluated in our study, and may be driving greater use of DAT in men. Additionally, greater perception of bleeding risk in women may be driving a reluctance for DAT in women. Indeed, amongst women prescribed DAT, we observed greater use of gastric protection therapies than men (31.9% vs 27.7%), although this difference was not statistically significant. There are likely to be other factors influencing sex-differentials which would be a subject for further research.

Despite very few indications for prolonged DAT beyond 6 months, we found that almost two-thirds of the patients (65.9%) on DAT received prolonged therapy beyond 12 months.[4,36] Although we observed higher rates of PPI/H2RA prescription in those on prolonged DAT, further research is indicated to investigate the efficacy of PPI/H2RA in prolonged duration of DAT.

Implications for research and practice

Our findings underline several key management considerations. Amongst patients with AF 4.7% were receiving DAT, of these, over 65% were prescribed DAT for inappropriately prolonged durations. This highlights the importance of clear documentation of indications for DAT and its duration, with a requirement for continuing regular review of any DAT use beyond 6 months. Secondly, 16% of patients on DAT were not prescribed PPI/H2RA. Gastroprotection therapy should be routinely recommended for older patients receiving multiple anti-thrombotic agents or those with other UGIB risk factors.[37,38] Finally, we observed that women were significantly less likely to receive DAT, even when all other patient-related factors were accounted for; possible undertreatment of women warrants further study.

Ethical approval

This study is based on de-identified information obtained from routinely compiled general practitioner electronic health records and did not require ethics committee approval.

Patient and public involvement

There was no involvement from patients or the public in the design, conduct, or outcome of this work.

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Contributions

CX and JR conceived the study. CW conducted the data extraction. CW, CX and ZRE supported the analysis. ZRE, CX, and JR wrote the manuscript. All authors contributed to the planning of the study and the manuscript.

Competing interests. None.

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