Research Paper

JRSM Cardiovascular Disease
Volume 9: 1–5

DOI: 10.1177/2048004020915406
journals.sagepub.com/home/cvd
SAGE

Changing trends in the use of novel oral anticoagulants and warfarin for treating non-valvular atrial fibrillation

Alexander Birkinshaw[1], Christopher H Fry[2], David Fluck[1], Pankaj Sharma[3] and Thang S Han[3]

Abstract

Background: Prevention of thromboembolism by novel oral anticoagulants is increasing, whilst use of vitamin K antagonists is on the decline. We assessed changes in the use of these anticoagulants in treating non-valvular atrial fibrillation between 2014 and 2018.

Methods: One-hundred and sixty-two consecutive patients (95 men, 67 women) with non-valvular atrial fibrillation, mean age 72.3 years (standard deviation = 11.0), underwent cardiac assessment in a single cardiac unit. Use of anticoagulants at the time of investigation was documented: overall 83 (51.2%) patients were prescribed novel oral anticoagulants and 79 (48.8%) warfarin treatment. Trends in treatment rates with either anticoagulant class over time were characterised by calculating the average annual percentage change using a Joinpoint Regression Program 4.7.0.0.

Results: There were diverging trends in anticoagulant treatment from 2014 to 2018 without join points: yearly increase in novel oral anticoagulant treatment (41.9, 45.5, 53.7, 53.1 and 72.7%, average annual percentage change = 16.2%, 95% confidence interval = 5.8% to 27.5%, $p < 0.001$), and decrease in warfarin treatment (57.1, 54.5, 46.3, 46.9 and 27.3%, average annual percentage change = −14.4%, 95% confidence interval = −25.2% to −2.1%, $p < 0.001$).

Conclusions: Changing trends in treatment with anticoagulants for patients with non-valvular atrial fibrillation observed within less than two years provide important information to healthcare services to estimate future pharmaco-economic costs for such treatments.

Keywords

Pharmaco-economics, thromboembolism, vitamin K antagonists

Date received: 1 September 2019; revised: 6 February 2020; accepted: 25 February 2020

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with excess cardiovascular morbidity and mortality.[1–3] The prevalence of AF rises with advancing age, from about 0.5–1% at age 50–59 years to 10–15% at age 80 years and over.[4,5] It is estimated that there will be up to 12 million people in the US and 18 million people in Europe living with AF in 40 to 50 years from now.[6–8]

Since their introduction in the UK and the rest of Europe in 2008,[9] novel oral anticoagulants (NOACs) are increasingly being used to prevent thromboembolism in a number of conditions such as AF, myocardial infarction, ischaemic stroke and pulmonary embolism.[10,11] Consequently, the use of vitamin K antagonists (VKAs), primarily warfarin, has declined progressively.[12,13] The decision to select NOACs as treatment of choice for non-valvular atrial fibrillation (NVAF) has been supported by a number of clinical

[1]Department of Cardiology, Ashford & St Peter's Foundation Trust, Chertsey, UK
[2]School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
[3]Institute of Cardiovascular Research, Royal Holloway, University of London, Egham, UK

Corresponding author:
Thang S Han, FRCP, Institute of Cardiovascular Research, Royal Holloway, University of London, Egham, UK.
Email: thang.han@rhul.ac.uk

trials favouring their effectiveness and safety of NOACs over Warfarin.[14] Guidelines for management of NVAF with NOACs have been published by the European Heart Rhythm Association (EHRA) since 2013[15] with continual update (www.NOACfor AF.eu), and also influence the use of NOACs. It is important to continue to monitor the use of these anticoagulants in order to provide evidence-based information to healthcare services for resource requirements. In this study, we aimed to assess the changing trends in the use of these anticoagulants to treat NVAF between 2014 and 2018.

Methods

Participants

We studied 162 patients (95 men, 67 women) with NVAF, mean age 72.3yrs ($SD = 11.0$, range 37.4–89.2), who underwent cardiac assessment in a single Cardiac Unit. Patients were referred by physicians and surgeons from acute admissions and outpatient clinics. There was a variety of reasons for referral including symptoms of chest pain and shortness of breath, newly diagnosed AF, paroxysmal AF with recurrent transient ischaemic attacks, and abdominal aortic aneurysm repairs. The use of anticoagulants at the time of their original investigation for each year between 2014 and 2018 was documented: 83 patients were treated with NOACs and 79 with warfarin. None of the patients had a history of major bleeding.

Statistical analysis

Trends in treatment rates with either anticoagulant class over time were examined using the Joinpoint Regression Program 4.7.0.0 (surveillance.cancer.gov/joinpoint/). This technique allows detection of join points in data sets and calculates the annual percentage change (APC) for individual linear segments (i.e. different slopes) if one or more join points exist, as well as average annual percentage change (AAPC) for the entire period of study. If no join points exist then APC is the same as AAPC. Results are expressed as percentage (%) change either each year or over the whole period, the latter includes the 95% confidence interval (CI).

Results

A total of 83 patients were on NOAC treatment with mean age of 71 years (*SD* 12) and similar sex distribution. There were 14 patients (16.9%) aged 85 years or older. Rivaroxaban was the most popular choice of NOAC treatment (54%) (Table 1).

Table 1. Demographic characteristics and numbers of patients with non-valvular atrial fibrillation (NVAF) treated with different types of novel oral anticoagulants (NOACs), mean age 71.4 years ($SD = 12.0$).

	Number of patients ($n = 83$)[a]	Proportions (%)
Men: women	43: 40	51.8: 48.2
Older patients (≥85 years)	14	16.9
Types of NOACs		
Rivaroxaban	45	54.2
Edoxaban	20	24.1
Apixaban	14	16.9
Dabigatran	4	4.8

[a]The numbers are small therefore further verification is needed.

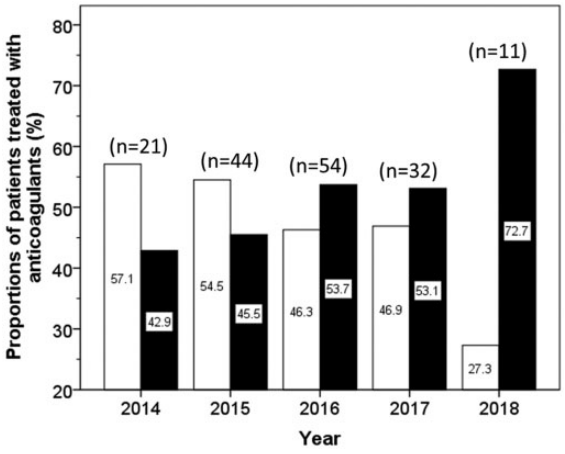

Figure 1. Proportions of patients with NVAF treated with NOACs (black bars) or with warfarin (white bars) between 2014 and 2018.

There were diverging trends in anticoagulant treatment from 2014: with year-on-year increase in NOAC use (42.9, 45.5, 53.7, 53.1 and 72.7%) and a decrease in warfarin treatment (57.1, 54.5, 46.3, 46.9 and 27.3%) (Figure 1). By 2016, the use of NOACs had surpassed that of warfarin and continued to rise into 2018.

Joinpoint regression analysis did not detect any join points for either NOACs (slope = 0.150) or warfarin (slope = −0.156) indicating a single curvilinear relationship between the use of anticoagulants and period of study was adequate (Figure 2). Trends in treatment rates over time increased progressively for NOACs: AAPC of 16.2% (95% CI = 5.8–27.5%, $p < 0.001$) (Figure 2(a)), and decline for Warfarin: AAPC of −14.4% (95% CI = −25.2% to −2.1%, $p < 0.001$) (Figure 2(b)).

Except for the first year of study (2014) when there was none of these older individuals being treated with

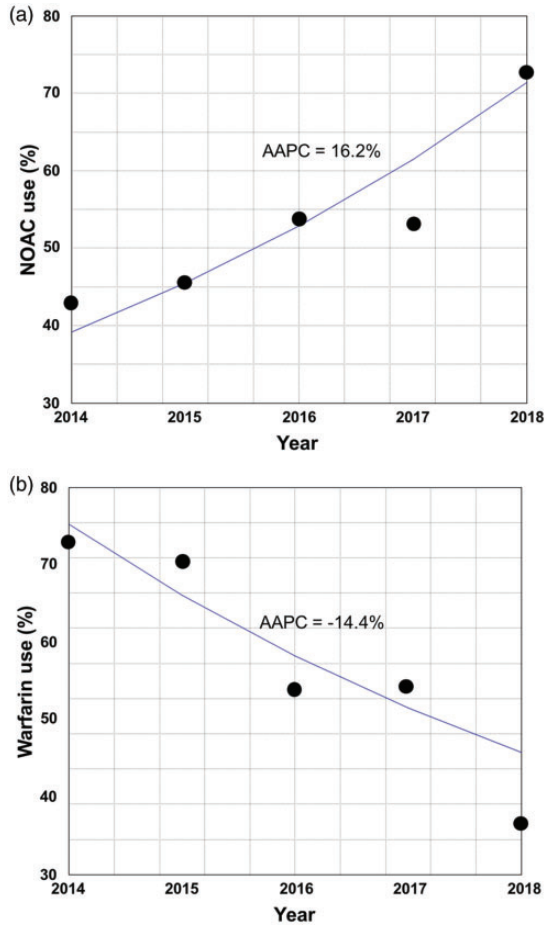

Figure 2. Trends in NVAF treatment with NOACs (a) or with warfarin (b) between 2014 and 2018.

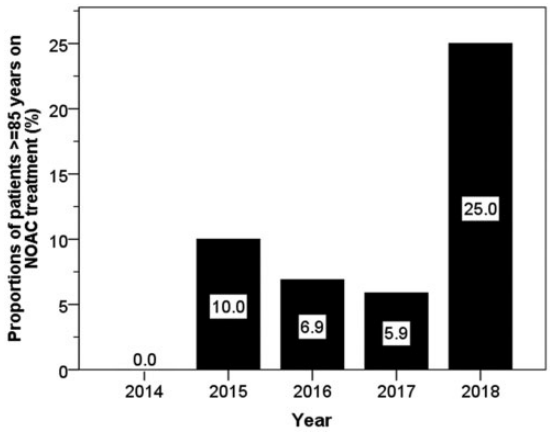

Figure 3. Proportions of older patients (≥85 years) on NOAC treatment in within each year of study between 2014 and 2018.

an NOAC, the proportions of older patients (≥85) on NOAC treatment within each year were 10%, 7% and 6% in 2015, 2016 and 2017 respectively, but rose to 25% in 2018 (Figure 3).

Discussion

This study shows that NOACs are now the anticoagulant of choice for NVAF treatment. Our study is consistent with a number of reports on the use of these agents over recent years for treatment of AF, myocardial infarct and cerebral ischaemic episodes.[10,12,16,17] This information provides important information to healthcare services when planning resource distributions owing to the rising trends in prevalence and incidence of AF.[18,19]

These changes are due to a number of advantages of NOACs over VKAs: NOACS are more effective in prevention of ischaemic disease while less likely to associate with intracranial bleeding, and no worse in gastric bleeding.[11,20] The elimination of regular blood test monitoring (international normal ratio (INR) for warfarin) is beneficial both to patients and healthcare systems. In addition, NOACs such as Rivaroxaban can be reversed almost immediately using prothrombin complex concentrates[21] while the anticoagulant effect of dabigatran has been shown to be completely reversed by the specific antidote Idarucizumab (a humanised monoclonal antibody fragment)[22] which is important in emergency situations such as haemorrhage or surgery. However, warfarin remains an essential drug, as NOAC treatment is not suitable for all patients, including those who have an allergy to these agents, potential interactions with other drugs, or those with kidney impairment[14] or valvular AF.[23] Given the ever increasing numbers of people living with AF, projected to 1.8 million in the UK alone[24] and up to 30 million in Europe and US by 2060,[6–8] INR monitoring for those who require warfarin treatment will continue to incur a substantial cost to healthcare resources.

Our observations of the curvilinear relationship between NOAC treatment and years of study may be explained by the publication of the European Society Cardiology guidelines in 2016[25] and EHRA position statement on NOAC treatment of AF in 2018.[15] These guidelines also encourage the use of NOACs in older patients, which coincide with the sudden rise in the proportions of older individuals (≥85 years) on NOAC treatment seen in our study.

This study is limited by its relatively small number of patients; therefore, the association of the changing proportions of patients treated with anticoagulants each year of study may not be the same as the trends observed in this study. This will lead to some uncertainty in the estimation of future uses of these different drug classes, or when their use attains a new steady state. This relationship may also be influenced by the endorsement from published guidelines (see above). In addition it should be stressed that this study was restricted to NVAF patients. Our study focussed on

the prevalence of treatment at the time when patients were undergoing cardiac assessment, rather than new cases. It is possible that bias was introduced since some patients might already have switched from one type of anticoagulant to another,[26] or discontinued treatment, to suit their treatment tolerability.[27] The increasing trend in NOAC treatment and declining trend in warfarin treatment therefore represents net year-on-year prevalence. An alternative method would be to compare unselected consecutive patients in each year and record new patients being prescribed each class of anticoagulant, but would require a different (prospective) study design. We did not collect data on the history of stroke but this would be expected to be high. Our recent study of 2643 patients admitted with an acute ischaemic stroke showed that there were 666 patients (20.1%) with a history of AF and 171 patients (6.5%) with newly diagnosed AF.[17]

In conclusion, changing trends in treatment with anticoagulants of NVAF observed in the present study provide important information to healthcare services for evaluating future pharmacological healthcare costs.

Acknowledgements

We would like to thank patients who underwent cardiac investigations and treatment in the present study and colleagues from Department of Cardiology, Ashford & St Peter's NHS Foundation Trust.

Contributorship

TSH wrote the first draft and analysed the data. CHF and TSH edited the manuscript. AB Collected additional data on anticoagulation treatment. DF and PS commented on the paper. All authors read and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

None.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Guarantor

TSH.

ORCID iD

Thang S Han https://orcid.org/0000-0003-2570-0938

Provenance

Invited contribution.

References

1. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; 31: 2369–2429.
2. Freedman B, Potpara TS and Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016; 388: 806–817.
3. Han TS, Fry CH, Fluck D, et al. Evaluation of anticoagulation status for atrial fibrillation on early ischaemic stroke outcomes: a registry-based, prospective cohort study of acute stroke care in Surrey, UK. *BMJ Open* 2017; 7: e019122.
4. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; 82: 2N–9N.
5. Naccarelli GV, Varker H, Lin J, et al. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009; 104: 1534–1539.
6. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; 114: 119–125.
7. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013; 34: 2746–2751.
8. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; 129: 837–847.
9. Khoo CW, Tay KH, Shantsila E, et al. Novel oral anticoagulants. *Int J Clin Pract* 2009; 63: 630–641.
10. Hicks T, Stewart F and Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open Heart* 2016; 3: e000279.
11. Bengtson LG, Lutsey PL, Chen LY, et al. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol* 2017; 69: 868–876.
12. Loo SY, Dell'Aniello S, Huiart L, et al. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol* 2017; 83: 2096–2106.
13. Loo SY, Coulombe J, Dell'Aniello S, et al. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. *BMJ Open* 2018; 8: e019638.
14. Capodanno D, Capranzano P, Giacchi G, et al. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. *Int J Cardiol* 2013; 167: 1237–1241.
15. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013; 34: 2094–2106.

16. Weitz JI, Semchuk W, Turpie AG, et al. Trends in prescribing oral anticoagulants in Canada, 2008–2014. *Clin Ther* 2015; 37: 2506–2514.
17. Han TS, Fry CH, Fluck D, et al. Anticoagulation therapy in patients with stroke and atrial fibrillation: a registry-based study of acute stroke care in Surrey, UK. *BMJ Open* 2018; 8: e022558.
18. Guo Y, Tian Y, Wang H, et al. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest* 2015; 147: 109–119.
19. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015; 386: 154–162.
20. Verdecchia P, Angeli F, Aita A, et al. Why switch from warfarin to NOACs? *Intern Emerg Med* 2016; 11: 289–293.
21. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. *Circulation* 2011; 124: 1573–1579.
22. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet* 2015; 386: 680–690.
23. Molteni M, Polo Friz H, Primitz L, et al. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. *Europace* 2014; 16: 1720–1725.
24. Lane DA, Skjøth F, Lip GY, et al. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *J Am Heart Assoc* 2017; 6: e005155.
25. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016; 50: e1–88.
26. Guimarães PO, Kaatz S and Lopes RD. Practical and clinical considerations in assessing patients with atrial fibrillation for switching to non-vitamin K antagonist oral anticoagulants in primary care. *Int J Gen Med* 2015; 8: 283–291.
27. Martinez C, Katholing A, Wallenhorst C, et al. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. *Thromb Haemost* 2016; 115: 31–39.