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Co-prescribing of Warfarin with Statins and Proton Pump Inhibitors in Elderly Australians

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Abstract

Background: Comorbidity is common in individuals with atrial fibrillation (AF). The predominant treatment for AF is warfarin and medicine interactions with warfarin represent a challenge for optimising treatment of AF in older people with comorbidities. Statins and Proton Pump Inhibitors are commonly prescribed therapies and in both classes, there are medicines with greater or lesser potential to interact with warfarin.

Objective: The aim of this study was to examine use of antithrombotic treatment in elderly Australians, and the extent of concurrent use of interacting statins and proton pump inhibitors (PPIs) with warfarin.

Methods: A retrospective cohort study was conducted using data from the Australian Government Department of Veterans' Affairs. The cohort included all patients who had at least one hospitalisation with a primary diagnosis for AF between 2007 and 2011. Individuals contributed person-months from the date of first AF hospitalisation to death or end of study (December 2011). Monthly utilisation of antithrombotics was assessed. A sub-cohort of warfarin users was defined as those with AF who received warfarin as monotherapy and the proportions of those co-dispensed statins or PPIs were established.

Results: Around 70% of patients with AF were receiving antithrombotic treatment, with 35% dispensed warfarin, 17% aspirin, and 7% clopidogrel as monotherapy. In December 2011, 54% of patients with AF on warfarin monotherapy were co-dispensed a statin, with the statins with potential for interaction dispensed at highest rates; atorvastatin followed by simvastatin and rosuvastatin. At study end, 43% of the warfarin cohort were also dispensed PPIs, with one-third using esomeprazole, followed by pantoprazole, both of which have the potential to interact with warfarin.

Conclusion: 30% of patients with AF were not receiving antithrombotic treatment. In those receiving an antithrombotic agent, warfarin was the most commonly dispensed (35%). The most common statin and PPI co-prescribed with warfarin were agents with the potential to interact with warfarin, despite alternative agents being available. Raising awareness of the safer alternative for people with comorbidities may improve warfarin management.

Keywords: Atrial fibrillation; Statins; Proton pump inhibitors; Warfarin; Comorbidity

Introduction

Atrial Fibrillation (AF) is a common form of irregular heart rhythm increasing a person's risk for ischaemic stroke by about five-fold [1]. The condition affects around 1.1% of Australians [2] and the prevalence increases with age, more than half of all atrial fibrillation patients are aged over 75 years [2]. Antithrombotic (anticoagulation or antiplatelet) therapy is recommended to reduce the risk of stroke, with warfarin being the most commonly used oral anticoagulant in Australia [3]. Dose-adjusted-warfarin reduces stroke risk by 64%, while antiplatelet agents reduce risk by 22% [4].

Bleeding is the most common complication of warfarin therapy and the risk is related to factors such as advanced age, prior bleeding or stroke, and specific comorbidities [3,5]. Treatment for comorbid conditions may require medications which increase the probability of interactions with warfarin. Some drugs alter the pharmacokinetics or pharmacodynamics of warfarin which impacts on the bleeding risk; these include concomitant antiplatelet therapy [3,5], statins for lowering of high cholesterol [3,6], and Proton Pump Inhibitors (PPI) for reducing gastric acid production [7,8].

Warfarin is metabolised by liver enzymes from the Cytochrome P450 (CYP) family. S-warfarin is a CYP2C9 substrate, for which fluvastatin and rosuvastatin are also substrates [9,10]. R-warfarin is a substrate of CYP3A4, for which atorvastatin and simvastatin are also

substrates [9,10]. Only pravastatin is excreted predominantly by renal mechanisms and does not undergo significant metabolism via the CYP system [9,10]. The administration of statins (except pravastatin) to patients receiving warfarin could competitively inhibit warfarin metabolism causing potentiation of the anticoagulant effect [6], requiring a dosage adjustment.

PPI medications undergo considerable biotransformation in the liver before elimination [11]. Omeprazole, esomeprazole, pantoprazole and lansoprazole are extensively metabolised by CYP2C19 and CYP3A4 and as a consequence they also might interact with warfarin as it is also metabolised by the same hepatic CYP enzymes [8,11]. Only rabeprazole has primary nonenzymatic metabolism with an insignificant percent metabolised by CYP system [11]. Both statins and PPIs are among the

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most prescribed medicines in Australia [12] with significant potential to interact with warfarin.The extent to which prescribers are aware of these interactions and preferentially prescribe the medicines in the class least likely to interact with warfarin is unknown.

Aim of the study

The aim of this study was to examine use of antithrombotic treatments to manage atrial fibrillation, and the extent of concurrent use of interacting statins and proton pump inhibitors with warfarin.

Methods

Data sources

Data for this study were sourced from the Australian Government Department of Veterans' Affairs (DVA) administrative claims database [13]. The DVA administrative claims database contains details of all prescription medicines, medical and allied health services and hospitalisations provided to veterans, their spouses and dependants, as well as details on patient gender, date of birth and date of death. At study entry (2007), the data covered approximately 293,000 members of the veteran community, who had a mean age of 76 years [14]. Medicines are coded in the dataset according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system [15] and the Schedule of Pharmaceutical Benefits item codes [16]. Hospitalisations are coded according to the WHO International Classification of Diseases (ICD) [17].

Study population and statistical analysis

The study period was 1 January 2007 to 31 December 2011. The study cohort included all patients who have had at least one hospitalisation with a primary diagnosis for AF (identified by ICD code I48) during the study period. These patients contributed person-months from the date of their first (earliest) hospitalisation until death or end of study (Dec 2011). Overall monthly utilisation of antithrombotics was reported as the proportion of people dispensed the medicine(s) of interest in each month among the AF population in that month. Results were stratified by those using monotherapy or combination therapies. Medicine utilisation in a given month was determined using the dispensing date and the estimated prescription duration. The estimated prescription duration was calculated from the data for each medicine and was defined as the time period in which 75% of prescriptions for that medicine were refilled. It was assumed that a person continued to use the medicine from the dispensing date for the prescription duration.

A sub-cohort of warfarin users was defined as those with AF who received warfarin as monotherapy. The age-standardised monthly proportions of those co-dispensed Proton Pump Inhibitors (PPI), or statins were established.

Participants were censored at the time of death or end of study. Medicine utilisation rates were age-standardised using the veteran population in January 2007 as the standard population in five-year categories. Poisson regression models were used to calculate age-Standardised Rate Ratios (SRR) comparing the rate in one year to the previous year to test for linear trend over time in 2007-2011. Analyses were performed using a SAS 9.4 statistical package (SAS Institute, Cary NC, USA).

Definition of medicines included in the analyses

The medicines and ATC codes included in this study:

Antithrombotics

- Oral anticoagulants: warfarin (B01AA03). Note: the newer oral anticoagulants dabigatran and rivaroxaban for AF were subsidised after the end of study and were not analysed;

- Antiplatelets: clopidogrel (B01AC05), aspirin (B01AC06), dipyridamole (B01AC07), ticlopidine (B01AC05), aspirin plus dipyridamole (B01AC30–PBS code 8382E), aspirin plus clopidogrel (B01AC30 - PBS code 9296G);

Proton pump inhibitors: esomeprazole (A02BC05), lansoprazole (A02BC03), omeprazole (A02BC01), pantoprazole (A02BC02), rabeprazole (N02BC04).

Statins: simvastatin (C10AA01 and in fixed-dose combination (FDC)->C10BA02), atorvastatin (C10AA05 and in FDC-> C10BX03), pravastatin (C10AA03), fluvastatin (C10AA04), rosuvastatin (C10AA07).

Results

The AF cohort included 15,375 unique patients. Around 70% of the patients (Figure 1) were receiving antithrombotic treatment and the rate was stable over the years (SRR=0.998, 95% CI: 0.994-1.002, p=0.30). Stratification by the type of therapy (Figure 1) showed that the majority of patients were dispensed warfarin monotherapy (35%, SRR=1.002, 95% CI: 0.996-1.004, p=0.99), followed by aspirin monotherapy (17%, SRR=0.995, CI: 0.992-0.999, p=0.07) and clopidogrel monotherapy (7%, SRR=0.997, CI: 0.989-1.006, p=0.52). Dipyridamole and ticlopidine monotherapy had very limited use (below 0.1%). Nine percent of patients were managed on dual therapies (SRR=1.006, CI: 0.994, 1.016, p=0.37) and a further 2% on triple therapies (SRR=0.950, CI: 0.938-0.964, p=0.10). Of the patients with AF receiving dual therapy with antithrombotics, warfarin plus aspirin was the most commonly used (stable rate of 4.5%), followed by aspirin plus clopidogrel (around 3%), and aspirin plus dipyridamole (1.5%). Triple therapy of warfarin plus aspirin plus clopidogrel was dispensed for 0.5% of AF patients, while warfarin plus aspirin plus dipyridamole- for 0.1%.

Figure 2 presents concurrent use of statins and PPIs in patients with AF who were dispensed warfarin monotherapy. Overall statin use increased significantly from 41.6% in Jan 2007 to 54.2% in Dec 2011 (SRR=1.037, 95% CI: 1.031-1.042, p<0.0001) (Figure 2). Stratification by the type of statin (Figure 3) showed that atorvastatin was the most commonly dispensed in around half of the patients on any statin. Simvastatin use decreased over the study period (from 36% to 26%). Pravastatin use fell from 15% to 7%, while rosuvastatin increased from
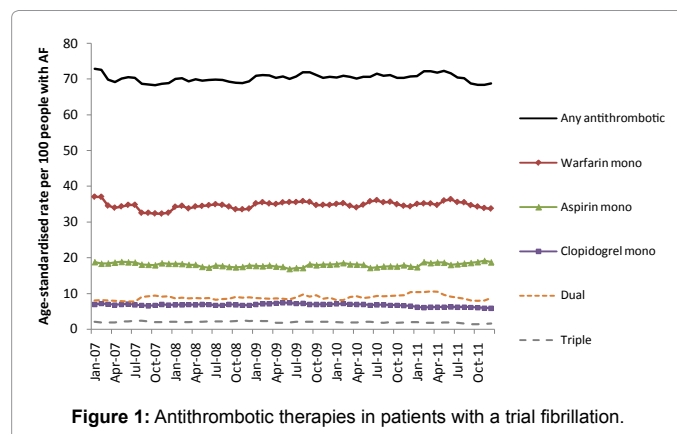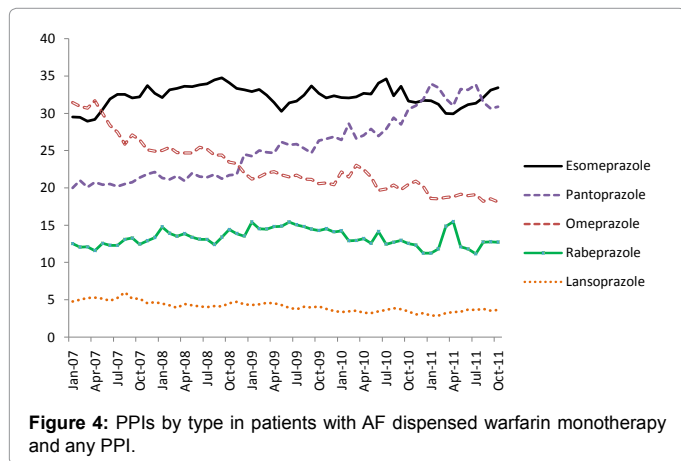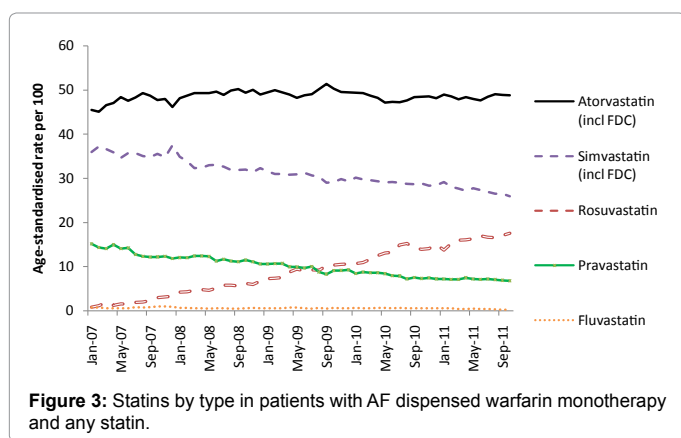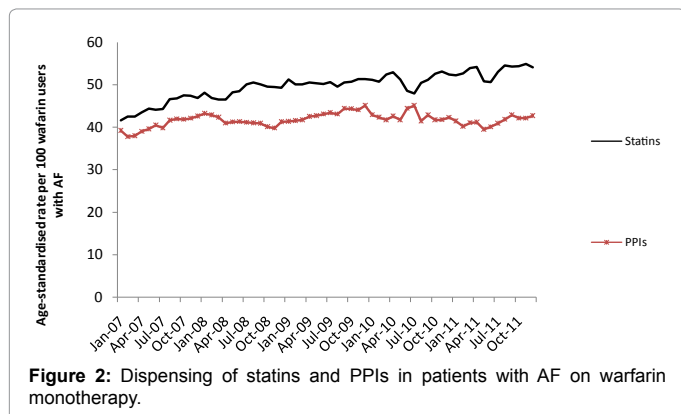

Figure 1: Antithrombotic therapies in patients with a trial fibrillation.

Figure 2: Dispensing of statins and PPIs in patients with AF on warfarin monotherapy.

Figure 3: Statins by type in patients with AF dispensed warfarin monotherapy and any statin.

Figure 4: PPIs by type in patients with AF dispensed warfarin monotherapy and any PPI.

1% to 18%. Fluvastatin had very limited use, below 1%.

Overall PPI use also increased from 39.3% to 42.7% (SRR=1.024, CI: 1.020-1.028, p<0.0001) (Figure 2). Stratification by the type of PPI (Figure 4) revealed that esomeprazole contributed for around one-third of all PPI use, pantoprazole use increased from 20% in January 2007 to 31% in Dec 2011, omeprazole use decreased from 31% to 18% in the same period, rabeprazole use was around 13%, and lansoprazole was used in less than 4% of patients on PPIs at the end of the study period.

Discussion

Antithrombotic treatment is recommended to reduce the risk of stroke in people with AF [3], with warfarin recommended in those who are at moderate to high risk of stroke, and aspirin when the risk is low [18,19], as warfarin has been shown to be significantly more effective than aspirin for stroke reduction [3]. Our results demonstrate that antithrombotics were dispensed in approximately 70% of patients with AF. Around 35% of patients received warfarin as sole treatment for atrial fibrillation, and another 17% received aspirin as monotherapy. The warfarin results are comparable with a US study reporting utilisation of warfarin by 42% of patients with high level of stroke, and by 44% with moderate stroke risk [20]. We did not measure individual stroke risk, however, our population may represent more severe disease as, by definition, all patients had had a prior hospitalisation for AF.

The combination of warfarin and aspirin is associated with increased incidence of major bleeding [21] and should be used with caution in elderly patients [22]. Our results showed that 4.5% of patients with AF were receiving aspirin concurrently with warfarin.

Comprehensive management of AF requires identification and treatment of predisposing factors and concomitant disorders (e.g. hypercholesterolemia) that increase the risk of stroke and other cardiovascular conditions [23]. In managing comorbid conditions, such as oesophageal reflux, practitioners also need to avoid therapies that may reduce the effectiveness of medicines for AF. Knowledge of the pharmacokinetic-pharmacodynamic properties of medicines that are prescribed for common comorbid conditions enables avoidance of drug interactions when concurrent therapy is necessary. However, our results suggest prescribers are not aware of some of these interactions and appropriate alternative therapies.

The administration of statins (except pravastatin) to patients receiving warfarin could competitively inhibit warfarin metabolism. We found that in Dec 2011 more than half the patients (54%) with AF dispensed warfarin as a monotherapy were also dispensed a statin, with atorvastatin dispensed at highest rates, followed by simvastatin and rosuvastatin. Case reports have shown a potentiation of the anticoagulant effect of warfarin when administered with fluvastatin [6] and that warfarin is a commonly co-administered medicine in cases of statin induced rhabdomyolysis [24]. A nested case-control study found no difference in risk of bleeding in warfarin users with recent statin use [25]. Conflicting results were found over the longer term use, however a healthy user effect may have confounded the longer term results [25]. Pravastatin, which is not metabolised by the CYP system and is not expected to interact with warfarin [6], was not widely prescribed with its use decreasing from 15% to 7% during the study; implying that prescribers might not be recognising the potential interactions between warfarin and statins.

Certain PPIs have been shown to reduce warfarin metabolism and clearance leading to increased warfarin concentration as they are metabolised by competing pathways [7]. Clinical evidence suggest significant hazard of over-anticoagulation for esomeprazole (HR 1.99, 95% CI 1.55-2.55) and lansoprazole (HR 1.49, 95% CI 1.05-2.10) when used concurrently with anticoagulant treatment [26]. A lower and non-significant risk increase was found for the other PPIs [26]. Patients on anticoagulants and PPIs should be monitored cautiously [7]. An Italian study on simultaneous use of warfarin and PPIs, found that 62% were using omeprazole, around 10% pantoprazole, and very few, rabeprazole [27]. Our data showed that overall 43% of patients with AF receiving warfarin as sole treatment were also dispensed a PPI in Dec 2011. The majority of those using PPIs (one-third) received esomeprazole followed by increasing use of pantoprazole. Rabeprazole, which has primarily nonenzymatic metabolism, had stable use in around 13%

of people on warfarin and PPIs, suggesting low awareness of potential differences in interactions in this class.

Our study had a number of limitations associated with use of administrative claims data. We used dispensing data as a surrogate for patient's use, however, we were unable to determine whether dispensed medicines were actually taken by the study participants. Also, as dose of prescribed medicines was not available in the data, dosage adjustment (e.g. warfarin dosage reduction) could not be established. We did not assess the length of co-dispensing and harm associated with those potentially interacting medicines. We could not account for other risk factors such as body weight, diet and genetics which may have had an impact on warfarin efficacy.

All subjects in this study receive subsidised medicines from the Department of Veterans' Affairs. Patient co-payments are $6.00 for all medicines and there is no price differential between the medicines for veterans, so pricing factors will not have influenced our results. Additionally, age is unlikely to have influenced our results as the veteran cohort is elderly, with a mean age of 76 years. The older age may make them even more vulnerable to interactions, as a result of age-related changes in kidney and liver function. This further highlights the need to encourage prescribers to be aware of potential pharmacokinetic interactions and consider alternative therapies for elderly people.

We analysed data from a national dataset of around 300,000 predominantly older Australian. The results are likely to reflect the general elderly Australian population, but may slightly over-estimate the utilisation rates as similar numbers of prescriptions per general practitioner visit are observed between the veteran population and the Australian population; however, because of the higher rate of GP visits, veterans receive slightly more prescriptions annually than other Australians (rate ratio 1.13; p<0.05) [13]. Veterans with no service related disability have similar levels of use to other Australians [13].

Conclusion

This study has identified that 30% of patients with AF were not receiving antithrombotic treatment. In those receiving an antithrombotic agent, warfarin was the most commonly dispensed (35%). In December 2011, above half of those with AF who were managed on warfarin as a sole therapy were co-dispensed statins, and around 43% were co-dispensed PPIs. The most common statin and PPI co-prescribed with warfarin were agents with the potential to interact with warfarin, despite alternative agents being available. Raising awareness of the safer alternative for people with comorbidities may improve warfarin management.

References

1. Wolf PA, Abbott RD, Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22: 983-988.

2. Atrial Fibrillation Association (2010) The economic cost of atrial fibrillation,Australia.

3. Hart RG, Benavente O, McBride R, Pearce LA (1999) Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 131: 492-501.

4. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, et al. (2013) An update of consensus guidelines for warfarin reversal. Med J Aust 198: 198-199.

5. Department of Health, Western Australia. Quick reference guide: atrial fibrillation information for the health practitioners. Perth: Health networks branch, Department of Health, Western Australia; (2011)

6. Andrus MR (2004) Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. Pharmacotherapy 24: 285-290.

7. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, et al. (2013) Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J 34: 1708-1713, 1713a-1713b.

8. Sansom L (2012) Australian pharmaceutical formulary and handbook. (22nd edition), Pharmaceutical Society of Australia.

9. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, et al. (1999) New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther 84: 413-428.

10. Williams D, Feely J (2002) Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmacokinet 41: 343-370.

11. Hagymási K, Müllner K, Herszényi L, Tulassay Z (2011) Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics 12: 873-888.

12. Top 10 drugs in Australia (2013) Aust Prescr 36: 211.

13. Lloyd J, Anderson P (2008)Veterans' use of health services. Australian Institute of Health and Welfare, Australia.

14. http://www.dva.gov.au/Pages/home.aspx

15. World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Code Classification index with Defined Daily Doses.

16. Australian Government. The Schedule of Pharmaceutical Benefits. Department of Health and ageing.

17. World Health Organization (2007) International Statistical Classification of Diseases and Related Health Problems.

18. National Prescribing Service Limited (2009) Antiplatelet and anticoagulant therapy in stroke prevention. Prescribing Practice Review 44.

19. Amerena JV, Walters TE, Mirzaee S, Kalman JM (2013) Update on the management of atrial fibrillation. Med J Aust 199: 592-597.

20. Zimetbaum PJ, Thosani A, Yu HT, Xiong Y, Lin J, et al. (2010) Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? Am J Med 123: 446-453.

21. Dentali F, Douketis JD, Lim W,Crowther M (2007) Combined aspirin–oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med 167: 117-24.

22. Hart RG (2000) What causes intracerebralhemorrhage during warfarin therapy? Neurology 55: 907-908.

23. Lip GY, Tse HF, Lane DA (2012) Atrial fibrillation. Lancet 379: 648-661.

24. Omar MA, Wilson JP (2002) FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 36: 288-295.

25. Douketis JD, Melo M, Bell CM, Mamdani MM (2007) Does statin therapy decrease the risk for bleeding in patients who are receiving warfarin? Am J Med 120: 369.

26. Teichert M, van Noord C, Uitterlinden AG, Hofman A, Buhre PN, et al. (2011) Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment. Br J Haematol 153: 379-385.

27. Trifirò G, Corrao S, Alacqua M, Moretti S, Tari M, et al. (2006) Interaction risk with proton pump inhibitors in general practice: significant disagreement between different drug-related information sources. Br J Clin Pharmacol 62: 582-590.