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 antplatelet) 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 antplatelet 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 antplatelet 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 date of their first (earliest) hospitalisation until death or end of study (Dec 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 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%.


Atorvastatin was used in less than 4% of patients on PPIs at the end of the study in the same period, rabeprazole use was around 13%, and lansoprazole by 2007 to 31% in Dec 2011, omeprazole use decreased from 31% to 18% third of all PPI use, pantoprazole use increased from 20% in January (Figure 4) revealed that esomeprazole contributed for around one-

The majority of those using PPIs (one-third) received esomeprazole 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.

Discussion

Antithrombotic treatment is recommended to reduce the risk of
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. Further this 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