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'Real-world' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand☆

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ABSTRACT

Background: Anticoagulants such as warfarin and dabigatran can significantly reduce the risk of stroke in individuals with atrial fibrillation that may lead to increased risk of bleeding, especially in older people. Evidence for bleeding risks with anticoagulants within the context of doses, multimorbidity and impaired renal function in real world setting is lacking.

Therefore we aimed to assess and compare real world bleeding risks with warfarin and dabigatran. Secondary analyses involved examining risk of fatal haemorrhages.

Methods and results: We formed two inception cohorts of propensity score (PS) matched older patients (≥65 years), who initiated dabigatran or warfarin between July 2011 and December 2012. A total of 4835 dabigatran users were matched to 4385 warfarin users in dose independent binary PS matching. A dose dependent PS matching resulted in 2383 warfarin, 2153 dabigatran 150 mg and 3395 dabigatran 110 mg users. In the first cohort, compared to warfarin, the hazard ratios (95% confidence intervals) for dabigatran were 0.45 (0.37–0.55) for any haemorrhage; 1.16 (0.87–1.56) for gastrointestinal haemorrhage; and 0.29 (0.09–0.86) for intracerebral haemorrhage. Similar associations were observed in the first 30 days of treatment. In dose dependent matched cohort, the risk of any haemorrhage was lower in individuals receiving dabigatran 110 mg (HR; 95% CI: 0.40 (0.31–0.52)) and 150 mg (HR; 95% CI: 0.29 (0.19–0.41)) compared to warfarin.

Conclusions: The risk of any haemorrhage and intracerebral haemorrhage was lower in dabigatran users compared to warfarin users. Importantly no increased risk of gastrointestinal haemorrhage was found in dabigatran users. The incidence rates for any haemorrhage were found to be higher in first 30 days of any anticoagulant treatment, but hazard ratios remained similar during the study period.

1. Introduction

Atrial fibrillation (AF), most common cardiac arrhythmia prevalent in older people carries an increased risk of stroke [1]. Anticoagulants including warfarin and dabigatran can significantly reduce the risk of stroke in individuals with AF [2–4], but is associated with a risk of major haemorrhage [5–11]. The relative risk of major haemorrhage reported in clinical trials with dabigatran compared to warfarin is between 0.69%–0.93%, and more specifically for intracranial bleeding is between 0.19%–0.59% [6,7]. However, these risks may not reflect real-world population based estimates [8–17]. Clinical trials typically include small number of selected individuals, exclude frail older people, and thus differ from real world population characteristics [18].

The effect of warfarin on reducing thromboembolic events associated with AF has been extensively reported [5–7,11–17]. The rates of major haemorrhage reported in clinical trial settings for warfarin range between 2% and 4% per-person year, while in routine clinical practice the reported rate of haemorrhages is higher (between 3% and 7% per-person year). In people aged over 80 years, bleeding rates may be higher at 13% during their first year of anticoagulation. Rates of up to 23% in older people in the 6 months after an acute hospital admission have been reported [9,11–16].

Dabigatran was the first new oral anticoagulant to be approved for prevention of stroke and systemic embolism in patients with non-valvular AF [19]. The prevalence of haemorrhage rates reported in clinical trials for dabigatran appears to be lower than warfarin [7]. However, data from recent observational studies and case reports show that dabigatran

Abbreviations: AF, atrial fibrillation; GI, gastrointestinal; NHI, National Health Index; DHB, District Health Board; CDS, chronic disease score.

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is associated with significant risk of haemorrhage [9,12,15,17,20–23]. Other large observational studies have found that dabigatran is associated with a higher risk of gastrointestinal (GI) bleeds and lower intracranial bleeding than warfarin [12,15]. Early reports from New Zealand have described a case series of serious haemorrhagic events, particularly in older patients with low body weight and impaired renal function [8, 24].The RE-LY study have reported lower risk of major haemorrhage in both dabigatran doses compared to warfarin and no significant risk of major haemorrhage between dabigatran doses [7]. Some studies have reported higher GI bleeding risk with 150 mg bd dabigatran users compared to warfarin while others have reported no significant difference in GI bleeds [7,12,15]. These data may indicate the need for dose individualization and monitoring guidance for dabigatran users [25–27].

In light of the uncertainty of bleeding risks outlined above, we need reliable population level evidence for safety of drug treatments in older people within the context of varying doses, multimorbidity and impaired renal function. To pursue this research, our study aims are to:

a. Examine the risk of haemorrhage in a large population-based cohort of older individuals with AF who recently commenced treatment with warfarin or dabigatran.
b. Compare the risk of haemorrhage with varying doses of dabigatran with warfarin, controlling for comorbidities.

2. Methods

2.1. Data sources

The diagnostic information was extracted from the National Minimum Dataset (NMDS) [28]. The NMDS is the national collection of all public and private hospital discharge information, including coded clinical data for inpatients and day patient stays. The recorded diagnoses were coded using the International classification of Diseases and Related Health Problems Tenth Revision, Australian Modification (ICD-10-AM) [29].

We linked multiple data sets supplied by the Ministry of Health, New Zealand. The specifications included prescription, diagnostic and mortality data. National Health Index (NHI) is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand [30]. The NHI was used to identify the individuals with the first dispensing during the period. The Pharmaceutical Collection contains prescription details about pharmaceutical dispensing claims for dabigatran and warfarin along with other prescribed medicines as well as information on sex, date of birth, age, ethnicity, District Health Board (DHB), daily dose, frequency and quantity dispensed during the study period. For the NHIs identified in Pharms data base, National Minimum Dataset (NMDS) contained all the inpatient hospitalisation details with an admission date, discharge date and all diagnoses on or after dispensings up to 31st December 2012 [31]. We used the national mortality collection (MORT) dataset to obtain death registration details with a date of death up to 31st December 2012 [32].

The study was approved by the University of Otago Human Ethics Committee (HD14/14).

2.2. Study population and new user design

A new user design was selected to reduce bias that can occur with including prevalent users as the bleeding rates are different between warfarin and dabigatran during the early course of therapy [33]. In addition, the new user design allows capturing all events after the start of treatment. We identified individuals prescribed dabigatran or warfarin for atrial fibrillation during the period of 1st July 2011 and 31st December from the Pharmaceutical Collections. To create an inception cohort, we excluded individuals' dispensed warfarin 18 months prior to the study. The same was not necessary for dabigatran since it was approved in New Zealand from 1st July 2011, and there were no prevalent users for the study period. For each individual, we identified the first date of dispensing as the date of entry to the cohort. We then excluded individuals who switched from either dabigatran or warfarin during the study period. The study population is shown in Fig. 1.

2.3. Propensity score matching

Propensity score matching was used to minimise the effects of covariates in the evaluation of the association between warfarin, dabigatran and bleeding rates. We created two new-user propensity-score matched cohorts from the source population (Fig. 1) based on drug type and dose.

2.3.1. Binary matching

First cohort was created based on dabigatran users (independent of dose) and warfarin users. In order to identify the comorbidities, we excluded individual without any hospital admission for past 5 year (Fig. 2). We identified age, sex, ethnicity, chronic disease score (CDS), impaired renal function, other comorbidities and medication use as potential confounding factors. We used binary logistic regression models to estimate the propensity scores. We matched propensity scores of dabigatran users to warfarin users in 1:1 ratio. Age, prevalence of liver disease and renal disease were higher in the warfarin group compared to dabigatran group prior to matching. Following matching, the covariates were well balanced in both groups.

2.3.2. Non-binary matching (TriMatch)

In order to match three groups, we used the method of non-binary treatment matching using propensity score (TriMatch) [34]. This second cohort was formed based on drug type and dabigatran dose, creating two groups of dabigatran users (dose dependent — 110 mg bd and 150 mg bd) and one group of warfarin users (Fig. 3). Individuals dispensed Dabigatran 75 mg bd were few and excluded from this cohort. We considered dabigatran 110 mg twice daily (bd) category as the treatment group 1, dabigatran 150 mg bd as the treatment group 2 and warfarin as the control group. We estimated propensity scores using three separate logistic regression models, dabigatran 110 mg bd with warfarin, dabigatran 150 mg bd with warfarin and dabigatran 110 mg bd with dabigatran 150 mg bd. Individuals with similar propensity scores were matched using maximum treatment method [34].

2.4. Comorbidity

In our study comorbidities were defined using the chronic disease score (CDS). The CDS is a risk-adjustment metric based on dispensed drugs, commonly used in routinely collected administrative datasets [35].The CDS was computed to impute the comorbidity data for all individuals included in the study [36,37]. We calculated chronic disease score for each patient in the cohort using information from NMDS and pharmaceutical collections for the study period [30,35] (Supplemental Table A.1).

We extracted the diagnostic codes for renal disease using the International classification of Diseases and Related Health Problems Tenth Revision, Australian Modification (ICD-10-AM). We analysed ICD-10-AM codes: N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, and N25 to identify patients with renal disease.

2.5. Medication exposure

We defined a standard dabigatran dose in accordance with the New Zealand Formulary [38]. The dabigatran standard dose is as follows: 150 mg twice a daily, unless aged ≥80 years when dose is 110 mg twice daily or 75 mg no more than twice daily. The duration of dabigatran and warfarin prescription funded by the Pharmaceutical Management Agency New Zealand is 30 days and 90 days respectively [39,40]. We defined continuous therapy as refills for prescriptions