Bleeding-Related Hospital Admissions and 30-Day Re-Admissions in Patients with Nonvalvular Atrial Fibrillation Treated with Dabigatran versus Warfarin

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Abstract

Essentials

- Bleeding is a common cause of hospital admission and re-admission in oral anticoagulant users.
- Patients with dabigatran and warfarin were included to assess hospital admission risk.
- Dabigatran users had a higher risk of 30-day re-admission with bleeding versus warfarin users.
- Close monitoring following hospital discharge for dabigatran-related bleeding is warranted.

Summary

Background: Reducing 30-day hospital re-admission is a policy priority worldwide. Warfarin-related bleeding is among the most common cause of hospital admissions due to adverse drug events. Compared to warfarin, dabigatran achieve full anticoagulation effect more quickly following its initiation, hence may lead to early-onset bleeds.

Objectives: To compare the incidence of bleeding-related hospital admissions and 30-day re-admissions with dabigatran versus warfarin in patients with nonvalvular atrial fibrillation (NVAF).

Methods: Retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF from 2010 through 2014 and prescribed dabigatran or warfarin were 1:1 matched by propensity score. The incidence rate of hospital admission with bleeding (a composite of gastrointestinal bleeding, intracranial hemorrhage, and bleeding at other sites) was assessed.

Results: Among the 51946 patients with NVAF, 8309 users of dabigatran or warfarin were identified, with 5160 patients matched by propensity score. The incidence of first hospitalized bleeding did not differ significantly between groups (incidence rate ratio: 0.92; 95% confidence interval[CI]: 0.66-1.28). Among patients who were continuously prescribed with their initial anticoagulants upon discharge, dabigatran use was associated with a higher risk of 30-day re-admission with bleeding over warfarin (adjusted hazard ratio: 2.87; 95%CI: 1.10-7.43).

Conclusion: When compared to warfarin, dabigatran was associated with a comparable incidence of first hospital admission but a higher risk of 30-day re-admission with respect to bleeding. Close early monitoring of patients initiated on dabigatran following hospital discharge for bleeding is warranted.

Keywords: re-admission; atrial fibrillation; dabigatran; warfarin; anticoagulant; bleeding.

Introduction

Bleeding is a major complication of oral anticoagulants that leads to serious morbidity and substantial burden on healthcare resources. In the United States (US), the annual cost of hospitalization associated with warfarin-related bleeding was estimated at US$24 347-41 903 per patient.[1] With the rapid development of non-vitamin K antagonist oral anticoagulants (NOACs), the burden of bleeding related to these agents is expected to rise. Dabigatran is the first NOAC approved as an alternative treatment to warfarin in patients with nonvalvular atrial fibrillation (NVAF).[2] At present, dabigatran remains the most frequently used NOAC and there is an increasing trend for its use.[3] However, several cases of serious hospitalized bleeds associated with dabigatran have been reported.[4-7] When comparing dabigatran to warfarin, the literature provides inconsistent results as some studies found a higher risk of hospitalized bleeding with dabigatran over warfarin,[8-10] while some studies reported no increased risk.[11-13] Indeed, dabigatran works rapidly following its initiation,[14] hence may lead to more early-onset bleeds. In contrast, warfarin may take weeks to achieve anticoagulation stability following its initiation,[14] resulting in less bleeding. Further investigation of bleeding risk with dabigatran over warfarin is therefore needed.

Since oral anticoagulants might precipitate bleeding from pre-existing lesions,[15] early recurrence is plausible after resuming treatment. Early re-admission is costly and particularly common among the high-risk and older patients,[16] who are the typical users of oral anticoagulants. In the US, reducing early hospital re-admissions (i.e. 30 days) is a policy priority aimed at improving health care quality and is considered as a pay-for-performance indicator of inpatient services by policymakers.[16,17] Approximately two thirds of hospitals in the US received penalties due to excessive 30-day re-admission rates in 2013.[18] Of note, antithrombotic drugs are one of the most common medications implicated in hospital admissions, with bleeding as the major cause of admission.[19,20] However, there is limited information about the rate of 30-day re-admission with bleeding related to dabigatran and warfarin use.

With a view to address these knowledge gaps, this study was conducted to compare the incidence of bleeding-related hospital admission and 30-day re-admission in patients with NVAF treated with dabigatran versus warfarin.

Materials and methods

Data source

This study used the population-wide electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA), which is the sole public-funded healthcare provider of Hong Kong. HA is serving a population of over seven million through healthcare facilities including hospitals, specialist clinics, and general outpatient clinics.[21] Electronic patient records, such as demographics, date of registered death, date of consultation, drug dispensing records, date of hospital admission and discharge, diagnoses, procedures, and laboratory tests of the HA are centralized in CDARS for research and audit purpose. Data in CDARS have been extensively used for various epidemiological studies.[22-30] Previous studies have demonstrated the high coding accuracy in CDARS, including the diagnosis records for AF, gastrointestinal bleeding, intracranial hemorrhage, and ischemic stroke with positive predictive values of 90-100%.[23,24,26] Detailed descriptions of CDARS were previously published.[24,28,31]

Patient records in CDARS are anonymized to protect patient identity. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital

Authority Hong Kong West Cluster (reference number: UW13-468). Informed patient consent was not required as the data used in this study were anonymized.

Study design and Study population

This was a population-based retrospective cohort study. Patients who had their first recorded AF (i.e. newly diagnosed with AF) between January 1, 2010 and December 31, 2014 were selected from CDARS based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Supplemental Table 1). In order to identify patients with NVAF, patients diagnosed with valvular heart disease or hyperthyroidism, or underwent valve replacement (ICD-9-CM; Supplemental Table 1) at or prior to their first AF occurrence were excluded. Patients with transient AF (ICD-9-CM; Supplemental Table 1), missing date of birth or sex information, aged<18 years, or died at first AF occurrence were also excluded. Index date was defined as the date of the first recorded prescription of dabigatran/warfarin following AF diagnosis. To select new users of dabigatran and warfarin, patients who were exposed to either drug within 180 days prior to index date were excluded. Patients with a history of bleeding were also excluded to eliminate any residual effect of previous bleeding on subsequent bleeding risk after commencement of dabigatran or warfarin (Figure 1).

The follow-up for each patient commenced from the index date until the end of study period (September 30, 2015), death, switching to other oral anticoagulants (among apixaban, dabigatran, rivaroxaban, and warfarin), or discontinuation of treatment (defined as >5 days of gap between consecutive prescription refill), whichever came first. We used a 5-day permissible medication gap to determine discontinuation of treatment because this was the mean time interval between prescription refills of dabigatran and warfarin in our cohort.

Sensitivity analyses were conducted to examine the robustness of the study results using different permissible medication gaps.

Outcome definitions

The outcomes of interest were the first and 30-day recurrent bleeding that required inpatient admission since commencement of dabigatran and warfarin. Bleeding was defined as a composite endpoint of gastrointestinal bleeding (GIB), intracranial hemorrhage (ICH), and other bleeding, which included epistaxis, haematuria, haemarthrosis, hemopericardium, haemoptysis, and hemorrhage from kidney, throat, and vagina.[26,32] Information for hospitalization with bleeding was identified from discharge diagnosis records in CDARS using ICD-9-CM codes (Supplemental Table 1). Hospitalizations nested within 24 hours were regarded as the same episode. The total length of stay was calculated as the time interval between the admission date and discharge date. For patients who survived after the first hospitalized bleeding and were continuously prescribed with their initial anticoagulants upon discharge (i.e. no medication gap of >5 days between consecutive prescription refill), we examined the risk of 30-day re-admission with bleeding in respective treatment groups. Re-admission with bleeding was defined as subsequent inpatient admission with a discharge diagnosis of bleeding within 30 days of discharge from the first bleeding episode.[33]

Propensity score matching

Propensity score (PS) matching was used to account for the potential selection bias in treatment allocation.[34] The PS was estimated by logistic regression based on age, sex, index year, number of hospitalization(s) within one year prior to index date, medical history (yes/no) of congestive heart failure, hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack/systemic embolism, vascular disease, myocardial infarction, renal disease, pneumonia, fall; Charlson Comorbidities Index; recent use (≤90 days prior to index date) of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, amiodarone, dronedarone, aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs (NSAIDs), histamine type-2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs), statins, and selective serotonin reuptake inhibitors. Baseline medical history of each patient was identified from all diagnosis records in CDARS dated before their individual index date (ICD-9-CM; Supplemental Table 1). Dabigatran and warfarin cohorts were 1:1 matched by the greedy matching algorithm, which has been demonstrated to perform well in both actual and simulation studies.[35] Standardized differences were calculated to assess the balance on baseline characteristics between treatment groups. A standardized difference of <0.1 was considered negligible.[36]

Statistical analysis

Baseline characteristics were expressed as mean ± standard deviation and frequencies (percentages) for continuous and categorical variables respectively. To account for the excess zero counts in hospital admissions, zero-inflated negative binomial regression model was used to compare the incidence rate of first hospitalized bleeding between dabigatran and warfarin users.[37] The risk of re-admission with bleeding in respective treatment groups were illustrated by Kaplan-Meier curves and compared using Cox proportional hazards regression model with adjustment for the length of stay and type of bleeding (GIB, ICH, or other bleeding) in the initial bleeding episode (Figure 2). Cox proportional hazards regression model would have been used for all statistical analyses if the model assumptions were satisfied. As the hazard rates of the first hospitalized bleeding with dabigatran and warfarin were not proportional and thus did not satisfy the proportional-hazard assumption in Cox model, a negative binomial regression model was used as an alternative. A two-sided p-value <0.05 was considered as statistical significant. Statistical analyses were independently conducted by WCYL and KKCM as quality assurance. SAS (version 9.3; SAS Institute, Inc, Cary, NC) was used for statistical analyses.

Additional analyses

Subgroup analyses were conducted by stratifying bleeding into three subtypes: GIB, ICH, and other bleeding. Further analysis was conducted for dabigatran 110 mg BID only, which is the most common dosage of dabigatran prescribed in Asian countries.[24,38] In our main analysis, discontinuation of treatment was defined as >5 days of gap between consecutive prescription refill. Sensitivity analyses were conducted using varying 10-day and 20-day permissible medication gaps to define discontinuation of treatment. Finally, since warfarin can take up to six weeks to achieve full anticoagulation effect,[14] we studied the risk of re-admission in 60 days of discharge to capture any later bleeding in additional analyses.

In post hoc analysis, we stratified patients into aged<75y and aged ≥75y; and patients on warfarin into having good and poor international normalized ratio (INR) control using the Rosendaal method,[39] where INR was aimed at 2.0-3.0. Intervals between INR records that were ≥8 weeks were not interpolated.[40] INR records measured in the first 28 days of warfarin or during hospitalization were excluded as they were unlikely to reflect the actual quality of anticoagulation control.[26] Good INR control was defined as time in therapeutic range (TTR)≥65%.[41]

Results

Baseline characteristics

There were 51,946 patients newly diagnosed with AF identified in CDARS from January 1, 2010 through December 31, 2014. Following patient exclusion, 8,309 new dabigatran and warfarin users were eligible for PS-matching (Figure 1). The most common dosage of dabigatran was 110 mg BID (n=1,992; 75%), followed by 150 mg BID (n=331; 12%), and 75 mg BID (n=237; 9%).

Among warfarin users, 4,055 (72%) had at least one INR test record available. The mean time interval between two INR tests was 46 days (standard deviation=35 days). There were 3,559 warfarin users with valid INR test interval(s) for calculation of TTR and of these, 26% had TTR≥65%. Among patients who had TTR<65%, 85% of their out-of-range INR records were below 2.0.

After PS-matching, 5,160 patients were included in the analysis. All baseline characteristics were balanced between treatment groups (Table 1). The mean follow-up of the PS-matched cohort was 425 ± 434 days.

First hospital admission with bleeding

After PS matching, there were 151 (5.9%) and 172 (6.7%) patients hospitalized with bleeding in the dabigatran and warfarin group respectively. The mean INR of warfarin users at discharge was 1.8 (standard deviation=0.6).

The incidence rates of hospital admission were comparable between dabigatran and warfarin users (5.0 vs. 5.8 per 100 patient-years; IRR: 0.92, 95%CI: 0.66-1.28) (Table 2), irrespective of the quality of INR control (Supplemental Table 2). Subgroup analyses for bleeding subtypes showed that dabigatran use was associated with a higher admission rate of GIB (2.9 vs. 2.1 per 100 patient-years; IRR: 2.21, 95%CI: 1.28-3.83), but a lower rate of ICH (0.5 vs. 1.4 per 100 patient-years; IRR: 0.26, 95%CI: 0.12-0.55) and a comparable rate of other bleeding (1.7 vs. 2.5 per 100 patient-years; IRR: 0.67, 95%CI: 0.43-1.04) when compared to warfarin. The results were consistent for patients who received 110 mg BID of dabigatran. The use of dabigatran 110 mg BID was associated with a comparable risk of any bleeding

(IRR: 1.04, 95%CI: 0.71-1.54) and other bleeding (IRR: 0.68, 95%CI: 0.43-1.09); an increased risk for GIB (IRR: 2.76, 95%CI: 1.43-5.33) and a reduced risk of ICH (IRR: 0.31, 95%CI: 0.12-0.77) when compared to warfarin (Supplemental Table 3). Sensitivity analyses using different medication gaps also yielded similar results (Supplemental Table 4). Post hoc analysis showed that dabigatran was associated with a lower rate of bleeding compared to warfarin in patients aged<75y (IRR: 0.59, 95%CI: 0.35-0.97) but not in those aged≥75y (IRR: 1.29, 95%CI: 0.83-2.01) (p-value for interaction: 0.02) (Supplemental Table 5).

Thirty-day re-admission with bleeding

There were 13.5% of dabigatran patients and 5.1% of warfarin patients re-admitted to hospital with bleeding within 30 days of discharge respectively (Table 3). The KM curve of re-admission is illustrated in Figure 2. Over the 30 days of discharge from the first episode, a total of 28 patients on dabigatran and 21 patients on warfarin were censored either due to death (n=2 vs. n=0), discontinuation of treatment (n=23 vs. n=21), or reaching the end of study period (n=3 vs. n=0), respectively. Cox regression analysis showed that dabigatran use was significantly associated with a higher risk of 30-day re-admission (HR: 2.87, 95%CI: 1.10-7.43) compared to warfarin. The hazard ratio for dabigatran 110 mg BID was similar but did not reach statistical significance (HR: 2.15, 95%CI: 0.74-6.26) (Supplemental Table 6). Subgroup analysis for bleeding subtypes indicated dabigatran tended to have a higher risk of re-admission with dabigatran against warfarin for GIB (HR: 1.89, 95%CI: 0.39-9.20) and other bleeding (HR: 2.67, 95%CI: 0.78-9.11), yet the differences did not reach statistical significance (Table 3). The results were robust to all sensitivity analyses (Supplemental Table 7). No significant differences in re-admission were observed between patients aged<75y and ≥75y (p-value for interaction=0.77) (Supplemental Table 5). Further analysis revealed that the risk of re-admission between dabigatran and warfarin became statistically non-significant in 60 days of discharge (HR: 1.89; 95%CI: 0.89-4.04) (Table 3).

Discussion

Bleeding is a primary complication of oral anticoagulant that is also associated with the risk of recurrence.[42] In this population-based cohort study, we found that dabigatran use was associated with a comparable rate of first hospital admission but a higher risk of 30-day re-admission with respect to bleeding when compared to warfarin. Stratified analyses of bleeding subtypes revealed that dabigatran use was associated with a higher incidence of GIB, yet a lower incidence for ICH over warfarin. The results are consistent for low-dose dabigatran at 110 mg BID and robust to all sensitivity analyses.

Oral anticoagulants are among the most common class of medications implicated in hospital admissions due to adverse drug events.[43,44] Patients who experienced complications of anticoagulants are at high risk of hospital re-admissions,[44] which have been reported to occur most commonly within the first 30 days of discharge, involve longer stays and higher management costs than the initial episode in patients with AF.[45] Therefore, there is a pressing need for reducing early re-admission rates in AF patients. In the US, the Centers for Medicare and Medicaid Services began penalizing hospitals for excessive rate of 30-day re-admission in October 2012.[17] To date, over 2000 hospitals have been penalized, resulting in an estimated USD 280 million penalties in the fiscal year 2013.[46] Similarly, a non-payment policy for 30-day re-admissions was introduced in the United Kingdom in April 2011, where commissioners will not pay for a proportion of 30-day acute re-admissions that are judged to have been avoidable.[47] These policies highlight the value of data for re-admission both from the perspective of the patient and the healthcare system as a whole. A higher risk of 30-day re-admission for bleeding was observed for dabigatran compared to warfarin in patients with NVAF and this finding bares important implications to clinical practice and healthcare policies.

Our findings that dabigatran was associated with a higher risk of 30-day re-admission with bleeding may be explained by several factors. Firstly, dabigatran achieves full anticoagulation effect more quickly than warfarin. While it takes approximately 2 to 3 days for dabigatran to reach steady-state levels, it could take up to 6 weeks for warfarin to achieve full anticoagulation effect.[14] Therefore, dabigatran might lead to more early-onset bleeds compared to warfarin. Consistent with this hypothesis, we noted that the difference in the risk of re-admission between dabigatran and warfarin became statistically non-significant in 60 days of discharge. Secondly, there is limited guidance on prevention of recurrent bleeding with dabigatran. Dosing adjustment based on INR has been the traditional strategy to prevent warfarin-related bleeding[48]; however, routine monitoring of dabigatran is not yet recommended and there are no approved means to monitor anticoagulation level of dabigatran.[49] Existing coagulation tests for dabigatran, including calibrated dilute thrombin time (dTT) and Ecarin Clotting Time (ECT), are not approved by the US Food and Drug Administration as a reliable measure of dabigatran concentrations.[49,50] There is also no consensus on the optimal therapeutic range of dabigatran plasma level.[51,52] As a result, effective dose adjustment of dabigatran to prevent re-bleeding is challenging.

In contrast, warfarin has well-established means for monitoring. The correlation between INR outside therapeutic range (typically 2.0-3.0 in patients with NVAF)[53] and clinical outcomes with warfarin has been demonstrated in meta-analyses and population-based studies.[26,54,55] The ability to monitor anticoagulation in warfarin might facilitate the assessment of the readiness for discharge from hospital, as well as dosing management to minimize bleeding risk after discharge when required. Our study found that the mean INR of warfarin users at discharge was close to 2.0, which might reflect a conservative strategy to reduce bleeding risk in this cohort of Chinese patients, who are perceived to have a high risk of bleeding.[56] However, the necessity of drug monitoring in dabigatran remains under strong debate.[50,52]

Another potential factor to consider is the substantial variability of dabigatran concentrations across individuals.[52] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, patients on fixed dose of dabigatran 150 mg BID had a wide range of plasma concentration from 2.3 to 1000 ng/mL.[52] The risk of major bleeding was reported to increase rapidly with dabigatran plasma concentration, from 2-3% at 50 ng/mL to over 9% at 300 ng/mL.[52] Since oral anticoagulants may exacerbate bleeding from pre-existing lesions, this variability of plasma concentration could affect the likelihood of early re-bleeding with dabigatran.[57]

In this study, we noted a higher incidence of hospitalized GIB with dabigatran versus warfarin, which is consistent with previous meta-analyses of randomized controlled trials[15] and observational studies.[58] Importantly, we observed an increased risk for GIB with dabigatran 110 mg BID compared with warfarin, in contrast to the RE-LY trial that reported a comparable risk.[2] However, in the subgroup analysis of patients aged ≥75 years in the RE-LY trial, dabigatran 110 mg BID was associated with a 40% higher risk of GIB compared to warfarin.[59] Given that the mean age of this cohort was 74 years (standard deviation=10 years), our results consistently reflect a higher risk of GIB with dabigatran compared to warfarin in an older population, who are the common users of oral anticoagulants. Post hoc we also found an interaction between treatment and age on bleeding risk, where dabigatran compared with warfarin was associated with a lower risk of overall bleeding in patients aged<75 years, but a trend towards a higher risk in those aged≥75 years, consistent with the RE-LY trial.[59] The lower incidence of ICH with dabigatran irrespective of age has been consistently reported in the literature, with a risk ratio of approximately from 0.2 to 0.4,[2,13,60,61] in line with our study findings. In addition, our findings suggest that GIB remains the most common type of bleeding associated with dabigatran use. GIB has been the key complication in the use of dabigatran since pre-marketing stage.[2] Concerns for GIB heightened following the release of safety announcement from the US Food and Drug Administration in 2014, which suggested dabigatran is associated with a higher risk of GIB compared with warfarin.[62] Although the reversal agent of dabigatran was approved in October 2015,[63] there is lack of high-level evidence of its effectiveness and safety in real-life setting. Therefore, continual post-marketing surveillance on the risk of bleeding is warranted in dabigatran users.[5,62]

To our knowledge, no population-based studies have yet been conducted to compare the re-admission rate for bleeding with dabigatran and warfarin in the real-life practice. We utilized the large electronic patient record database of the HA in Hong Kong, which has recognized strengths in providing high-quality data for large-scale post-marketing surveillance studies.[22-29] We applied new user design to eliminate the residual effect of previous exposure on the study outcomes. Patients with a history of outcome were also excluded to minimize residual confounding. To further account for the potential confounding factors, our study cohort was matched by PS with respect to patient characteristics, comorbidities and concurrent medications, where all the characteristics were balanced between groups after PS matching.

Several limitations are worthy of mention. Similar to other healthcare databases, CDARS does not capture over-the-counter medications such as aspirin, hence we cannot control for the effect of such medications in our analyses. However, HA is the only source of public healthcare services in Hong Kong, of which the service is highly subsidized (85%-98%) by the government.[64] As a result, patients with chronic illness requiring long-term treatment care, such as AF, commonly opt for the service of HA instead of purchasing full-cost medications from elsewhere.[64] Therefore, the impact of uncaptured medications on our results is anticipated to be minimal. We accounted for important confounding factors and conducted sensitivity analyses to test for the robustness of the results, and the results were found to be consistent in all analyses. However, by nature of pharmacoepidemiological studies, we cannot exclude the possibility of unmeasured residual confounding effect. Similar to the case of other epidemiological healthcare databases, we used ICD codes to identify bleeding events, of which the coding accuracy has been shown to be high in CDARS (PPV=95% to 100%).[24,26] However, we are unable to classify bleeding by severity using the International Society on Thrombosis and Haemostasis (ISTH) bleeding definition, because information such as the extent of haemoglobin level drop and the number of units of blood used in transfusion are not available in CDARS. Finally, as the sample size was reduced in the stratification analyses for bleeding subtypes and the power is therefore reduced, the stratified analyses might not be statistically powerful enough to detect a significant difference. Further study is needed to confirm these results. Areas for future research may include development of predictive tools for re-admission among NVAF patients prescribing different types of oral anticoagulants,[65,66] and effective measures on prevention for 30-day re-admission among oral anticoagulant users.

Conclusion

When compared to warfarin, dabigatran was associated with a comparable incidence of hospital admission but a higher risk of 30-day re-admission with respect to bleeding. Considering that dabigatran achieves full anticoagulation more rapidly compared to warfarin, close early monitoring of patients initiated on anticoagulation following hospital discharge and strategies to reduce bleeding recurrence with dabigatran are warranted.

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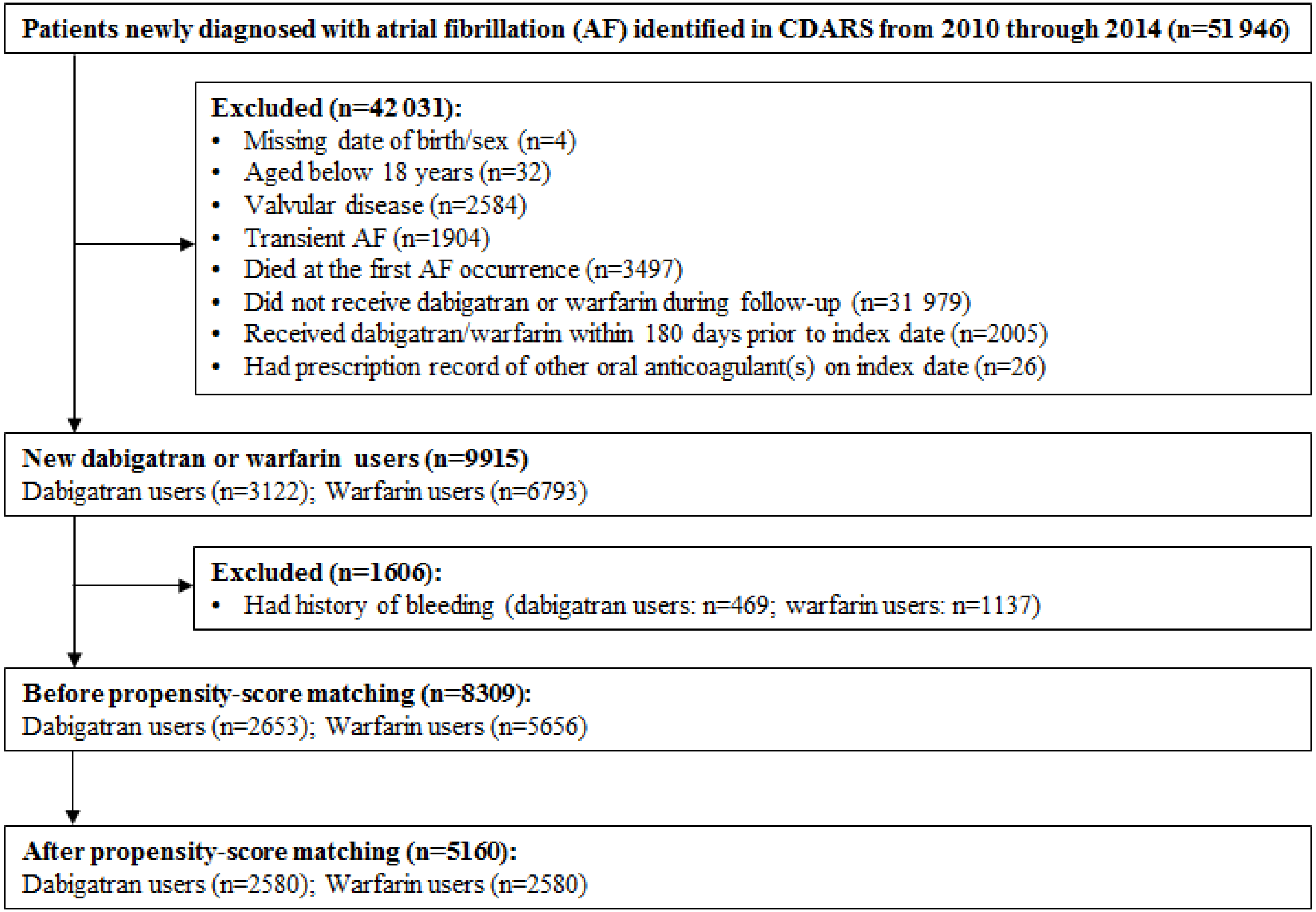

Figure 1. Selection of patients.

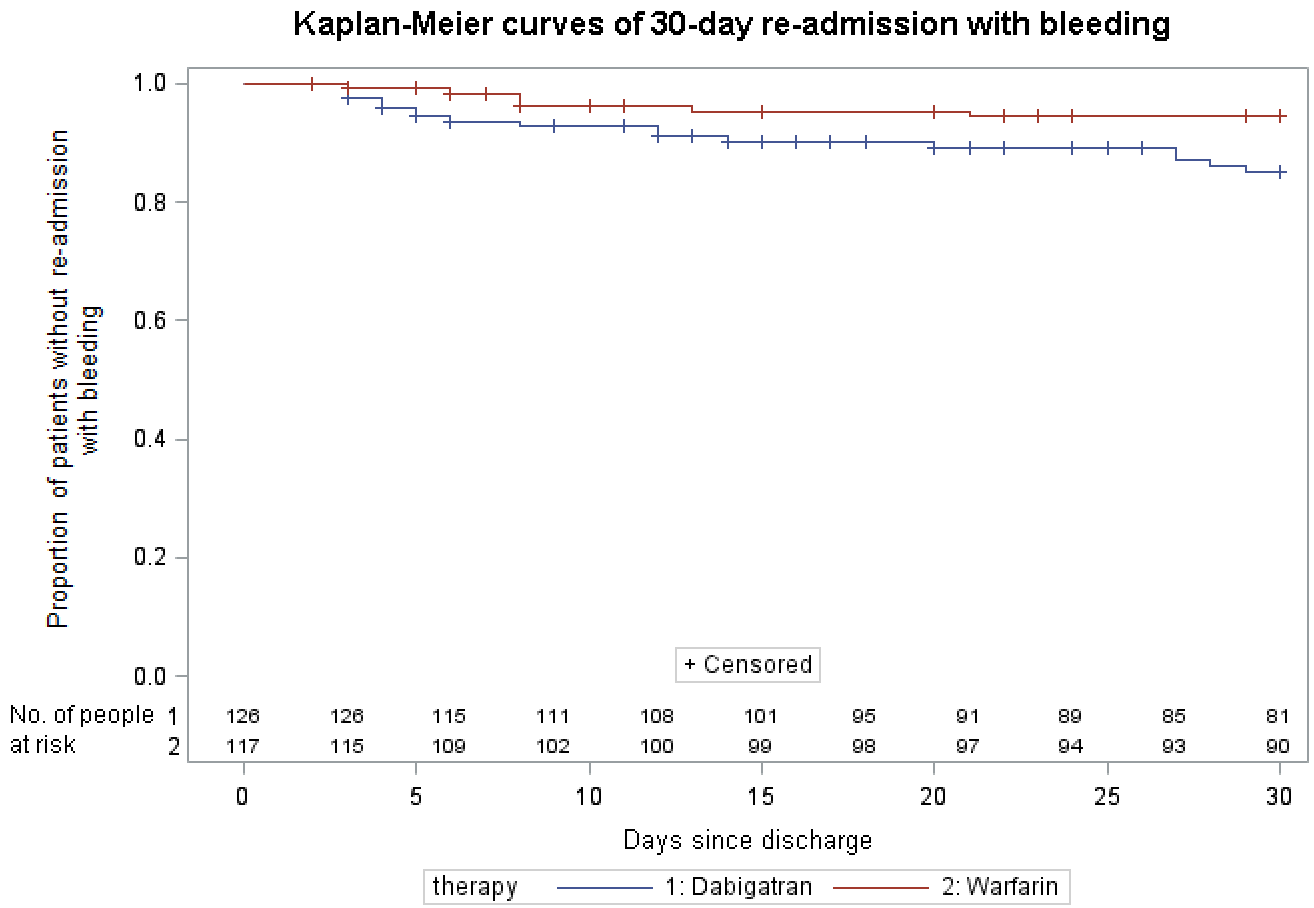

Figure 2. Kaplan-Meier curves of 30-day re-admission with bleeding in patients treated with dabigatran and warfarin.

Table 1. Patient characteristics.

	Before PS matching			After PS matching		
	Dabigatran (n=2653)	Warfarin (n=5656)	Standardized difference†	Dabigatran (n=2580)	Warfarin (n=2580)	Standardized difference†
Age, mean (SD)	74.0 (10.2)	71.6 (11.7)	0.21	73.9 (10.2)	73.8 (10.6)	0.002
Female (%)	1400 (52.8)	2639 (46.7)	0.12	1349 (52.3)	1350 (52.3)	-0.001
Baseline medical conditions						
CHADS2, mean (SD)	2.1 (1.5)	2.0 (1.5)	0.03	2.1 (1.5)	2.0 (1.6)	0.01
CHA2DS2-VASc, mean (SD)	3.3 (2.2)	3.2 (2.2)	0.05	3.3 (2.2)	3.3 (2.2)	0.01
Charlson comorbidity index, mean (SD)	1.3 (1.3)	1.5 (1.5)	0.15	1.3 (1.3)	1.2 (1.3)	0.02
Congestive heart failure	527 (19.9)	1747 (30.9)	-0.26	526 (20.4)	520 (20.2)	0.01
Hypertension	1410 (53.1)	2832 (50.1)	0.06	1364 (52.9)	1379 (53.4)	-0.01
Diabetes mellitus	655 (24.7)	1308 (23.1)	0.04	626 (24.3)	636 (24.7)	-0.01
Prior ischemic stroke/TIA/SE	858 (32.3)	1682 (29.7)	0.06	829 (32.1)	806 (31.2)	0.02
Vascular disease	497 (18.7)	1313 (23.2)	-0.11	488 (18.9)	491 (19.0)	-0.003
Myocardial infarction	119 (4.5)	436 (7.7)	-0.14	118 (4.6)	101 (3.9)	0.03
Renal disease	129 (4.9)	579 (10.2)	-0.20	129 (5)	137 (5.3)	-0.01
Pneumonia	273 (10.3)	752 (13.3)	-0.09	273 (10.6)	262 (10.2)	0.01
History of fall	395 (14.9)	700 (12.4)	0.07	374 (14.5)	379 (14.7)	-0.01
Recent drug use						
ACEI/ARB	1226 (46.2)	2625 (46.4)	-0.004	1183 (45.9)	1196 (46.4)	-0.01
Beta-blocker	1632 (61.5)	3242 (57.3)	0.09	1582 (61.3)	1592 (61.7)	-0.01
Amiodarone	279 (10.5)	758 (13.4)	-0.09	275 (10.7)	268 (10.4)	0.01
Dronedarone	23 (0.9)	29 (0.5)	0.04	22 (0.9)	20 (0.8)	0.01
Aspirin	1888 (71.2)	4043 (71.5)	-0.01	1841 (71.4)	1811 (70.2)	0.03
Clopidogrel	173 (6.5)	423 (7.5)	-0.04	171 (6.6)	160 (6.2)	0.02
NSAIDs	142 (5.4)	336 (5.9)	-0.03	139 (5.4)	130 (5.0)	0.02
Histamine type-2 receptor antagonist	1567 (59.1)	3059 (54.1)	0.10	1517 (58.8)	1494 (57.9)	0.02
Proton-pump inhibitor	575 (21.7)	1226 (21.7)	0	555 (21.5)	528 (20.5)	0.03
Statins	1376 (51.9)	2371 (41.9)	0.20	1318 (51.1)	1302 (50.5)	0.01
SSRIs	68 (2.6)	116 (2.1)	0.03	64 (2.5)	55 (2.1)	0.02

Abbreviations: PS, propensity score; SD, standard deviation; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism (doubled); CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); TIA, transient ischemic attack; SE, systemic embolism; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. †Standardized difference is the mean difference in dabigatran group versus warfarin group divided by the pooled standard deviation.

Table 2. Incidence of hospital admission with bleeding among dabigatran and warfarin users.

	Before PS matching					After PS matching				
	Dabigatran (N=2653)		Warfarin (N=5656)		Dabigatran vs. Warfarin	Dabigatran (N=2580)		Warfarin (N=2580)		Dabigatran vs. Warfarin
Hospital admissions	n	Incidence/ 100 py	n	Incidence/ 100 py	Crude IRR (95% CI)	n	Incidence/ 100 py	n	Incidence/ 100 py	Adjusted IRR (95% CI)‡
All Bleeding	153	4.9	412	5.5	0.90 (0.75-1.08)	151	5.0	172	5.8	0.92 (0.66-1.28)
Gastrointestinal bleeding	89	2.8	145	1.9	1.50 (1.15-1.95)*	88	2.9	63	2.1	2.21 (1.28-3.83)*
Intracranial hemorrhage	16	0.5	104	1.3	0.38 (0.22-0.64)*	15	0.5	43	1.4	0.26 (0.12-0.55)*
Other bleeding†	53	1.7	188	2.5	0.68 (0.50-0.93)*	53	1.7	74	2.5	0.67 (0.43-1.04)

Abbreviations: PS, propensity score; py, patient-years; IRR, incidence rate ratio; CI, confidence interval.
†other bleeding includes epistaxis, haematuria, haemarthrosis, hemopericardium, haemoptysis, and hemorrhage from kidney, throat, and vagina.
‡adjusted IRR's were obtained using zero-inflated negative binomial regression to account for excess zero counts in hospital admissions.
*p<0.05.

Table 3. Re-admission with bleeding among dabigatran and warfarin users.

	Before PS matching					After PS matching				
	Dabigatran		Warfarin		Dabigatran vs. Warfarin	Dabigatran		Warfarin		Dabigatran vs. Warfarin
	n	%	n	%	HR (95% CI)	n	%	n	%	HR (95% CI)
30-day re-admissions										
All Bleeding	17/127	13.4	19/294	6.5	2.23 (1.13-4.38)*	17/126	13.5	6/117	5.1	2.87 (1.10-7.43)*
Gastrointestinal bleeding	7/74	9.5	6/103	5.8	1.54 (0.51-4.66)	7/73	9.6	2/42	4.8	1.89 (0.39-9.20)
Intracranial hemorrhage	2/9	22.2	1/35	2.9	7.62 (0.69-84.7)	2/9	22.2	0/13	0	-‡
Other bleeding†	7/47	14.9	11/172	6.4	2.50 (0.97-6.45)	7/47	14.9	4/67	6.0	2.67 (0.78-9.11)
60-day re-admissions										
All Bleeding	20/127	15.7	28/294	9.5	1.88 (1.04-3.41)*	20/126	15.9	11/117	9.4	1.89 (0.89-4.04)
Gastrointestinal bleeding	8/74	10.8	8/103	7.8	1.33 (0.49-3.59)	8/73	11.0	4/42	9.5	1.14 (0.34-3.82)
Intracranial hemorrhage	2/9	22.2	1/35	2.9	7.62 (0.69-84.7)	2/9	22.2	0/13	0	-‡
Other bleeding†	9/47	19.1	18/172	10.5	2.02 (0.91-4.50)	9/47	19.1	7/67	10.4	2.05 (0.76-5.52)

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval.

Values are expressed as: number of patients re-hospitalized within 30 day of discharge/total number of hospitalized patients.

†other bleeding includes epistaxis, haematuria, haemarthrosis, hemopericardium, haemoptysis, and hemorrhage from kidney, throat, and vagina.

‡unable to estimate hazard ratio as there were no warfarin patients re-hospitalized with intracranial hemorrhage.

*$p<0.05$.