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Real-World On-Treatment and Initial Treatment Absolute Risk Differences for Dabigatran vs Warfarin in Older US Adults

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Abstract

Purpose: Trials and past observational work compared dabigatran and warfarin in patients with atrial fibrillation, but few reported estimates of absolute harm and benefit under real-world adherence patterns, particularly in older adults that may have differing benefit-harm profiles. We aimed to estimate risk differences for ischemic stroke, death, and gastrointestinal bleeding after initiating dabigatran and warfarin in older adults 1) when patients adhere to treatment and 2) under real-world adherence patterns.

Methods: In a 20% sample of nationwide Medicare claims from 2010–2015, we identified beneficiaries aged 66 years and older initiating warfarin and dabigatran. We followed individuals from initiation until death or October 2015 (initial treatment, IT) and separately censored individuals' follow-up after drug switches and gaps in supply (on-treatment, OT). We applied inverse probability of treatment and standardized morbidity ratio weights, as well as inverse probability of censoring weights, to estimate two-year risk differences (RDs) for dabigatran versus warfarin.

Results: We identified 10,717 dabigatran and 74,891 warfarin initiators. Weighted OT RDs suggested decreased ischemic stroke risk for dabigatran versus warfarin; IT RDs indicated increased or no change in ischemic stroke risk. Regardless of follow-up approach and weighting strategy, risk of death appeared lower and risk of gastrointestinal bleeding appeared higher when comparing dabigatran versus warfarin.

Conclusions: Dabigatran use was associated with lower risks of mortality and ischemic stroke in routine care when older adults stayed on treatment. IT analyses suggested that these benefits may be diminished under real-world patterns of switching and discontinuation.

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Past publication: This paper has not been published elsewhere. The results have, however, been previously presented at the 2019 International Conference on Pharmacoepidemiology and Risk Management in Philadelphia, Pennsylvania at a podium presentation. This research was conducted as part of a doctoral dissertation at the University of North Carolina at Chapel Hill. Grants from the National Institute on Aging (R01 AG056479) and National Institutes of Health (UL1TR002489, K01AI125087) provided indirect support for the work via coauthors' time.

Keywords

Anticoagulants; atrial fibrillation; stroke; older adults; dabigatran

INTRODUCTION

Patients with atrial fibrillation are at increased risk of ischemic stroke.[1,2] Warfarin, the historical standard of care for stroke prevention in atrial fibrillation, has a lengthy half-life and narrow therapeutic range; mismanagement can result in catastrophic bleeding events.[3] Direct oral anticoagulants are easier to dose and were approved after several trials demonstrated non-inferiority to warfarin.[4,5] The first direct oral anticoagulant to be approved in the United States, dabigatran, appeared to reduce the incidence of ischemic strokes vs. warfarin in the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) trial at the cost of increased gastrointestinal bleeding. An improvement in one secondary outcome of all-cause mortality was also observed.

Unfortunately, estimates of efficacy in clinical trials are imperfect estimates of benefits in clinical care.[6] Patients selected into trials tend to be younger with fewer comorbidities than the general population; as stroke risk is heavily associated with age and several comorbidities, trial estimates of benefit and harm may not generalize to many users of direct oral anticoagulants.[7] To address concerns about treatment effect modification in wider populations, studies have used insurance claims data to compare direct-acting oral anticoagulants with warfarin in clinical care.[8–15]

While these studies are generally well-conducted, gaps in knowledge remain. Most estimated treatment effects on the relative scale rather than the absolute scale, which makes it more difficult to directly contrast treatment benefits with harms; estimating numbers needed to treat, for example, is not possible with hazard or risk ratios.[16,17] In addition, most studies censored patients at treatment discontinuation and switching, ignoring whether this censoring differed by treatment. The fact that real-world adherence to these treatments is suboptimal[18] means these “best-case” results may not map directly to realized clinical benefits. Patients were also typically censored at death when analyzing stroke and bleeding outcomes, which can inflate estimates of risk in high-mortality populations.[19] More nuanced pharmacoepidemiologic analyses can help close these gaps, especially given the amount of information in large claims databases.

In this study, we aimed to use modern pharmacoepidemiologic methods in a large, real-world data set to estimate the absolute benefits and harms of dabigatran with respect to ischemic stroke, all-cause mortality, and gastrointestinal bleeding in a population of older adults, focusing separately on 1) perfect adherence to treatment and 2) real-world adherence patterns.

METHODS

Study Population

This study was performed in a 20% simple random sample of Medicare beneficiaries with at least one month of Medicare Parts A, B, and D that is maintained at UNC for use in approved research projects by faculty, staff, and students. The study included data from 2010–2015 as 2010 was the year dabigatran became available. Individuals were analysis-eligible after 365 days of continuous enrollment in Medicare A, B, and D given that they were over age 65. We also required at least one additional risk factor for ischemic stroke (analogous to a CHA_2DS_2 score of at least two): these risk factors included hypertension, diabetes, congestive heart failure, past stroke, past transient ischemic attack, and age over 75. Finally, individuals had to have a diagnosis code for non-valvular atrial fibrillation in the 180 days before or 7 days after treatment initiation.

To ensure patients were eligible for dabigatran treatment, individuals with diagnosis codes indicating prosthetic heart valves or valvular heart disease, endocarditis, primary diagnoses indicating cancer in the past 180 days, active liver disease in the past year, or chronic kidney disease were excluded. These inclusion and exclusion criteria parallel those used in RE-LY. Additionally, to ensure exposure preceded outcomes, those with an outcome on the day of initiation were excluded. All codes are listed in supplemental content.

Exposure

We used an active comparator new user study design,[20] defining “new use” or initiation as no days’ supply of any oral anticoagulant used for stroke prophylaxis in atrial fibrillation (warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban) for 60 days before filling a warfarin or dabigatran prescription. To ensure we were examining the dose of dabigatran from RE-LY, we limited analyses to the 150 mg dose. Each initiation was analyzed separately for eligibility criteria, allowing late entry if atrial fibrillation diagnoses occurred within 7 days after new use. The index date was defined as the date of their prescription indicating new use or the date of the atrial fibrillation diagnosis code within 7 days of new use if no diagnosis code was present in the 180 days prior. Only individuals’ first eligible initiation was included.

After identifying new users, we used two different follow-up strategies. First, we followed individuals until the end of the study period or the end of their Medicare Parts A, B, and D coverage, regardless of whether they continued use of their oral anticoagulant (an initial treatment, IT, analysis analogous to an intention-to-treat analysis in a randomized controlled trial).

Second, to capture the effect of remaining on therapy, we ended follow-up and censored individuals after a prescription for another oral anticoagulant or a gap in medication days’ supply of more than 30 days (dabigatran arm) or 45 days (warfarin arm) (an on-treatment, OT, analysis). We used comparatively longer gaps than previous observational work because we were less interested in biologic availability of the drug and more interested in engagement in clinical care, though we also explored shorter gap periods.[21] Procedure codes for anticoagulation management extended coverage in the warfarin arm for 30 days

to account for missing warfarin use in claims,[22] with the longer gap in the warfarin arm to accommodate dosage changes. Medication stockpiling was not allowed in either group as it would inaccurately estimate days' supply for warfarin users on multiple strengths; when patients had duplicate prescriptions on the same day the higher days' supply was used.

Outcomes

This study examined three outcomes: ischemic stroke, defined by previously validated[23] diagnosis codes; death, defined by the Medicare date of death; and gastrointestinal bleeding, defined by previously validated[23] diagnosis codes. Analyses were outcome-specific; that is, patients contributed person-time to gastrointestinal bleeding analyses even after an ischemic stroke. We also examined all strokes and major bleeds (including intracranial hemorrhages and hemorrhagic strokes) to compare with results of past studies. Codes for outcomes had to appear in the primary position of an inpatient encounter.

Covariates

In addition to the inclusion and exclusion criteria, we measured a number of baseline covariates via diagnosis codes[14] using a one-year lookback period from the date of initiation and estimated the predicted probability of frailty using a Medicare claims-based algorithm.[24] We constructed directed acyclic graphs[25] (see supplemental content) for the outcomes using expert opinion and a review of the literature to identify variables potentially associated with the treatment and outcome, as well as the causal relationships between each of those variables. If the assumptions behind the graphs are correct, our measured covariates remove any backdoor paths from treatment to the outcome and thus form a sufficient set for estimation of an unbiased effect of treatment on the outcome. Age and sex were available for all individuals; since our other covariates were defined by the presence of insurance claims, there was no missing data.

Statistical Analyses

For all individuals in our study population, we estimated the propensity of dabigatran (versus warfarin) initiation from multivariable logistic regression with our confounder set, modeling age and probability of frailty flexibly using restricted cubic splines with knots at the 20th, 40th, 60th, and 80th percentiles. These probabilities were used to construct inverse probability of treatment weighted (IPTW) dabigatran and warfarin cohorts (to estimate treatment effects in the total population) and a standardized mortality ratio weighted (SMR weighted) warfarin cohort (to estimate treatment effects in dabigatran initiators).[26] We checked covariate balance by assessing whether absolute standardized mean differences (ASMDs) between the groups after weighting were less than 0.1.[27] In OT analyses, we implemented inverse probability of censoring weights. These weights were estimated separately in each treatment arm to account for differential discontinuation and switching patterns in the two groups and are described further in supplemental content.[28]

After applying weights, we estimated risks in each treatment arm using a weighted Aalen-Johansen estimator to take into account the competing risk of death[29] at one- and two-years. We estimated standard deviations of the risk difference from 200 replicate bootstraps to calculate 95% confidence limits. Statistical analyses were conducted in SAS 9.4 for

Windows (Cary, NC, USA). This study was approved by the University of North Carolina at Chapel Hill's Institutional Review Board (approval number 18–1015).

Sensitivity Analyses

We conducted a variety of sensitivity analyses. First, we varied the allowable gap between prescriptions within a treatment episode to 7 or 60 days. Second, we ignored procedure codes for anticoagulation management. Because new use (and cohort eligibility) was defined by treatment episodes, these analyses impacted both OT estimates (because they changed when individuals were censored) and IT estimates (because more individuals qualified for the study with shorter gap periods or when ignoring procedure codes and fewer qualified for the study with longer gap periods). Third, we excluded individuals with any code for stroke in the primary position of an inpatient encounter in the past 6 months to emulate RE-LY's exclusion of those with severe strokes in that time period. Fourth, we excluded individuals with a predicted probability of frailty over 10%. This cut-point was chosen to be more aggressive than that from the score's initial validation[24] to remove those at higher risk of mortality from the study population. Finally, we explored the impact of 90, 180, and 365-day oral anticoagulant washout periods.

RESULTS

Figure 1 shows cohort inclusion and exclusion criteria. Of the 393,684 new use periods for dabigatran and warfarin, 231,680 had a recent code for non-valvular atrial fibrillation and 220,955 of those had a CHA_2DS_2 score of 2 or more. Of those, 18% had a recent cancer diagnosis, 8% had active liver disease, 27% had renal insufficiency, 23% had valvular heart disease or a valve replacement, and 0% (less than 100) had endocarditis. Eliminating those treatment episodes left 97,340 episodes, with 95,559 of those over 65 at the time of initiating dabigatran or warfarin. After restriction to individuals' first eligible initiation, we had a final cohort of 10,717 dabigatran new users and 74,891 warfarin new users for analysis. The distribution of various covariates in these individuals are listed in Table 1. Compared to warfarin new users, dabigatran new users were younger and less likely to be men, with lower predicted probability of frailty, fewer codes indicating past bleeds, and less past use of warfarin. New use of warfarin was also more common earlier in the study period. After IPTW or SMR weighting, baseline covariates were more balanced and standardized absolute mean differences for each measured covariate were all less than 0.1 (see Supplemental Figure I).

Table 2 reports rates and risks of ischemic stroke, all-cause mortality, and gastrointestinal bleeding across the populations of interest and adherence scenarios. Dabigatran users had shorter treatment duration, with 59% of dabigatran users stopping treatment and 16% switching treatment during the study period compared to 44% and 8% of warfarin users, respectively. Supplemental Figures II–III show the distribution of on-treatment follow-up time in the warfarin and dabigatran users and Supplemental Figure IV shows that a greater proportion of IT follow-up was covered by oral anticoagulants for the warfarin users than the dabigatran users.

Outcomes were common in the first two years of follow-up in the IT analyses with OT analyses showing lower rates for ischemic stroke and all-cause mortality. Figure 2 shows IPTW survival curves for ischemic stroke under IT and OT methodologies and illustrates the shift in risk for dabigatran patients with IT compared to OT; Supplemental Figures V–VIII contain survival curves for the two other outcomes.

Table 3 depicts two-year RRs and RDs under the OT and IT follow-up methods, both in the crude and after implementing the IPTW, SMR, and inverse probability of censoring weights. In OT analyses, initiating dabigatran compared with warfarin was associated with fewer ischemic strokes and lower mortality. There was an elevated risk of gastrointestinal bleeding, however.

In IPTW IT analyses, the association between dabigatran initiation and all-cause mortality was attenuated relative to the OT analyses and risk of ischemic stroke actually increased in dabigatran initiators. The increase in the risk of gastrointestinal bleeding was also attenuated compared to the OT analyses. SMR-weighted RDs were generally similar to those applying IPTW, though they were attenuated for OT gastrointestinal bleeding and farther from the null for the IT all-cause mortality.

RDs for the outcomes of all stroke and major bleeding are listed in Supplemental Table I. The all stroke outcome was similar to the ischemic stroke outcome, though farther from the null in OT analyses, while the major bleeding outcome showed increased risk of bleed in the IPTW OT analyses but no real difference in the SMR analyses; both estimates were fairly imprecise, however.

Changing the allowable gap in medication supply to 7 days resulted in less harmful RDs for gastrointestinal bleeding in the IPTW OT analyses. A smaller attenuation was observed in the IPTW OT gastrointestinal bleeding RD with the 60-day gap analysis. Removing the capacity for procedure codes for anticoagulation management to extend treatment episodes attenuated the apparent mortality benefit in IPTW OT analyses.

Exclusion of anyone with a stroke in the past six months diminished the favorable IPTW OT RD for ischemic stroke. Restricting the population to patients with a predicted probability of frailty of less than 10% at baseline excluded 42% of patients and reduced the magnitude of the OT all-cause mortality RD in both the IPTW and SMR analyses; IT all-cause mortality RDs were largely unaffected. Using more aggressive washout periods reduced the differences between the IPTW IT and OT estimates for mortality and ischemic stroke to similar in magnitude to those for the SMR analyses, with no real change in the SMR results. Full results from sensitivity analyses are listed in Supplemental Tables II–IV; Supplemental Figures IX–XI present the IPTW results graphically.

DISCUSSION

There is a shift in stroke prophylaxis for atrial fibrillation patients towards direct oral anticoagulants in the United States and around the world.[30] To put the benefits and risks of this shift into perspective, we estimated absolute effects of dabigatran compared to warfarin on all-cause mortality, ischemic stroke, and gastrointestinal bleeding in older adults

while comparing OT and IT estimates. To reduce bias in these estimates, we used inverse probability of censoring weights to account for differential switching by treatment arm in real-world patients (OT estimates) and performed analyses that did not censor the competing event of death (i.e. allowed patients to die).

That OT analyses showed decreased ischemic stroke risk and elevated gastrointestinal bleeding risk suggests a trade-off between a number needed to treat of 137 patients to prevent one stroke and a number needed to harm of 75 for one gastrointestinal bleed when patients stayed on treatment. On the other hand, IT analyses reversed or nullified estimated ischemic stroke benefits, making the trade-off considerably worse under observed patterns of adherence and discontinuation. Estimated benefits were greater and estimated harms less in dabigatran initiators compared with the entire population of initiators, suggesting patients that are good candidates for dabigatran treatment are being channeled towards dabigatran.

The OT results of this study are generally consistent with other non-experimental studies estimating relative scale treatment effects and censoring at treatment discontinuation. Our IPTW results for gastrointestinal bleeding (risk ratio: 1.48) aligned more closely with the hazard ratios from RE-LY (trial hazard ratio: 1.50), though SMR results (risk ratio: 1.15) and many of the sensitivity analyses were attenuated and more comparable to other observational studies. Notably, our OT results for stroke and gastrointestinal bleeding align better with RE-LY than the IT results, despite the trial analyses being intention-to-treat. This is not surprising given the better persistence and adherence in the trial relative to our study. Similar suboptimal treatment persistence after initiation has been observed in past non-experimental and population studies.[31,32]

Divergence between IT and OT estimates was particularly stark for ischemic stroke. This divergence persisted across a variety of sensitivity analyses, though it was attenuated when a longer washout was used. This, along with the fact that median time on treatment was much higher in warfarin than dabigatran patients, suggests suboptimal treatment persistence and adherence in dabigatran users. This may be a target for efforts to increase dabigatran adherence/persistence and future research estimating per-protocol treatment effects using medical records to assess when treatment discontinuation or switching to another medication is clinically appropriate.[33]

The magnitude of the protective association between treatment with dabigatran versus warfarin and all-cause mortality in IT and OT analyses is also noteworthy. This association has been observed in other studies in older adults.[34] Unfortunately, mortality may be subject to stronger unmeasured confounding by socioeconomic status or frailty, resulting in exaggerated estimates of treatment benefits.[35] Reduced mortality benefits in the analyses restricted to those with less than 10% predicted probability of frailty supports suggests potential confounding, though some of this may be due to lower overall risks in these patients resulting in less treatment benefit.

This study has several limitations to consider. Factors associated with treatment initiation and outcomes that we were not able to capture in claims data could bias treatment effect estimates if the assumptions behind our causal graphs were incorrect. In particular,

socioeconomic status and a reliable race indicator were not available.[36] Including Medicare's race variable shifted risk differences by at most by seven hundredths of a percent; as 91.5% of new users were white our findings may not generalize to minority populations.

Information bias due to misclassification of outcomes, treatment, or confounders could cause further issues; differential on-treatment time misclassification would be particularly problematic for OT analyses. Also, past studies have excluded patients with history of thrombosis rather than treating it as a confounder to avoid problems of differing indications between dabigatran and warfarin. When we removed these patients in a post-hoc analysis, results did not shift substantially. Finally, our results may not generalize to younger populations, populations outside the United States, or Medicare beneficiaries that enroll in managed care like Medicare Advantage whose prescription claims are unavailable; this is especially true of IT estimates, as differing cost sharing may be associated with differing treatment persistence.

CONCLUSIONS

The estimates from this study represent a step forward in understanding absolute effects of dabigatran versus warfarin treatment in older adults with atrial fibrillation. Based on our findings, dabigatran is associated with reduced risk of ischemic stroke compared to warfarin in older adults that remain on treatment (at the cost of an increase in gastrointestinal bleeding for some patients). If this trade-off is acceptable, the initial treatment analyses confirm that additional work is needed to improve adherence and persistence for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures:

While no funding for this project was received from Boehringer Ingelheim, who conducted the RE-LY trial for dabigatran, MWC and the authors are working on a related project using data from the trial (there is no financial compensation for the work). TS has research funding as a co-investigator from Novo Nordisk, and is a co-investigator in the Center for Pharmacoepidemiology (current members are GlaxoSmithKline, UCB BioSciences, Merck, and Takeda Pharmaceutical Company), and owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. JLL's spouse is a full-time paid employee of GlaxoSmithKline. CP also has faculty member support from the Center for Pharmacoepidemiology. RJS is a paid consultant to Merck, Pfizer, Amgen, and Regeneron on topics related to lipids, anticoagulation, and inflammatory drugs. JKE and MWC did not have any financial conflicts of interest.

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Key Points:

New users of dabigatran had lower ischemic stroke risk than new users of warfarin when both remained on treatment, even after applying inverse probability of censoring weights and controlling for confounding.

The results of IPTW and SMR analyses suggested that dabigatran is being channeled towards good candidates for dabigatran therapy.

Adherence and persistence to treatment appeared poorer for dabigatran new users than warfarin users.

These differences resulted in attenuation or even reversal of the protective ischemic stroke and mortality associations during initial treatment analyses.

Findings were similar in sensitivity analyses varying grace periods during treatment episodes and the length of the washout period used to exclude prevalent use.

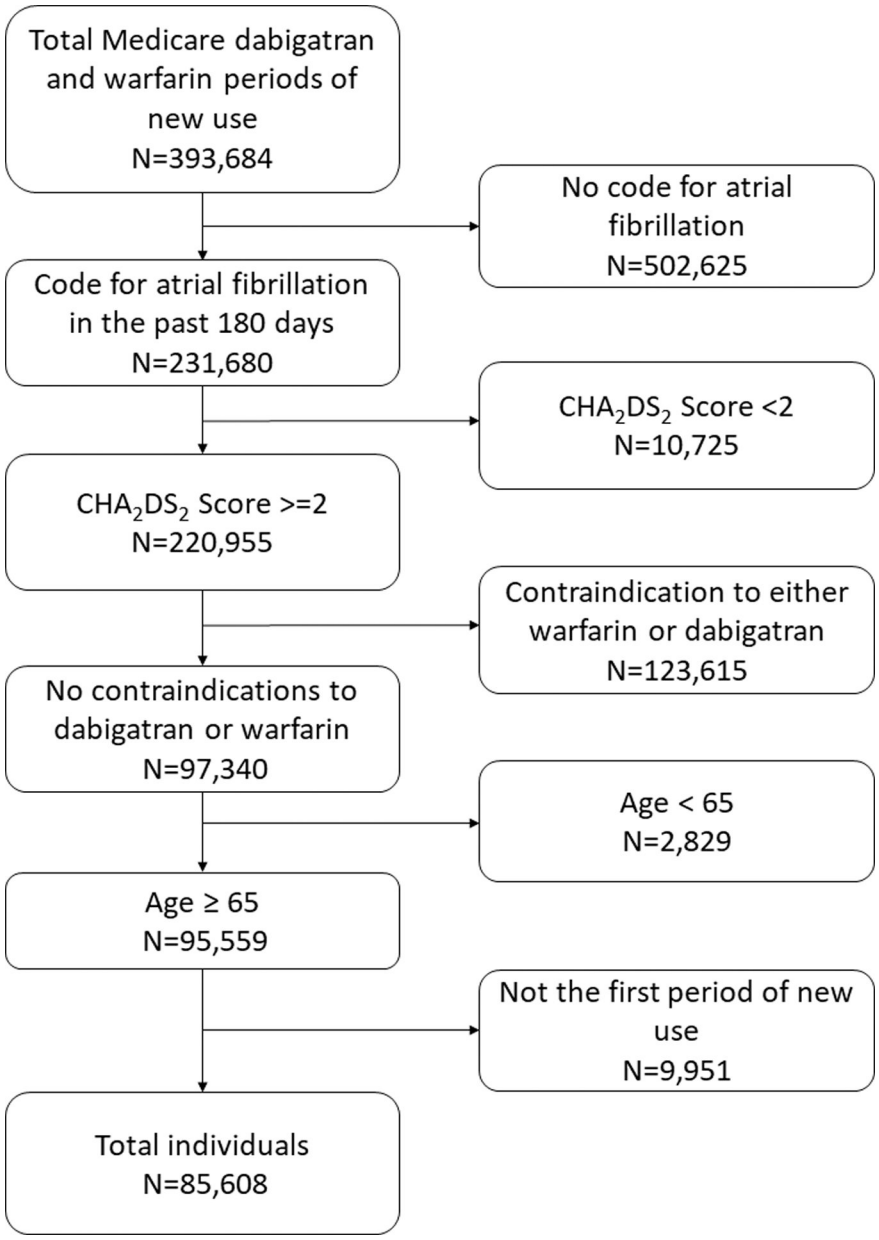

Figure 1:

Study flow diagram showing study inclusion and exclusion of new use periods identified in the Medicare 20% random sample. CHA_2DS_2 refers to the cardiovascular risk score. Contraindications include prosthetic heart valves or valvular heart disease, endocarditis, primary diagnoses indicating cancer in the past 180 days, active liver disease in the past year, and chronic kidney disease.

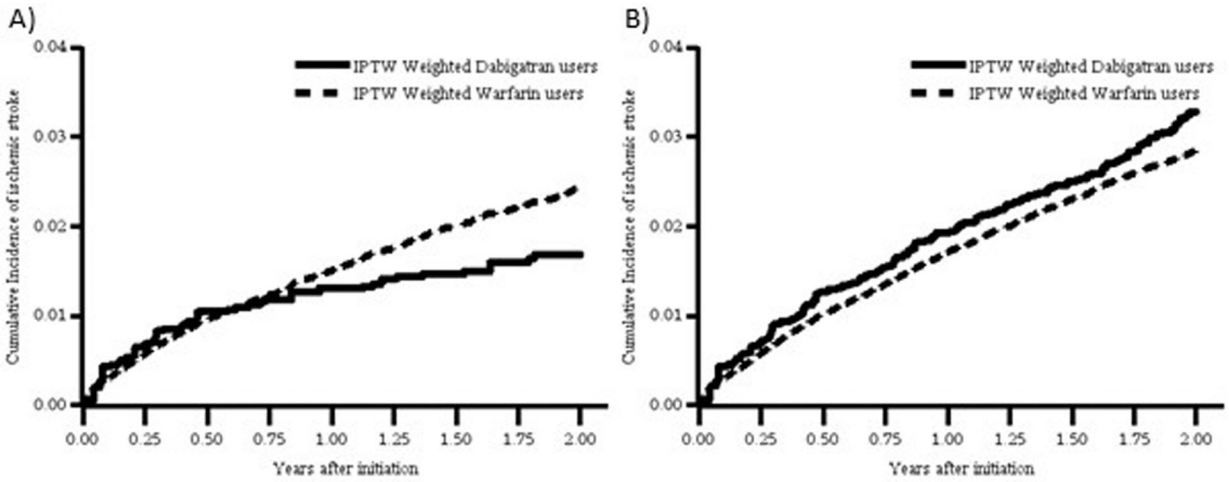

Figure 2:

Inverse probability of treatment weighted cumulative incidence curves for ischemic stroke comparing the on-treatment (panel A) and initial treatment (panel B) follow-up schemes. Incidence for dabigatran users is tracked with a solid line and incidence for warfarin users is tracked with a dashed line. The initial treatment risks are higher for both dabigatran and warfarin users.

Table 1:

Distributions of Key Covariates in New Users of Warfarin and Dabigatran in a Medicare Population

Covariate		Dabigatran new users[a] N=10,717 (%)		Warfarin new users[a] N=74,891 (%)		Standardized Absolute Mean Difference (SAMD)
Age						
	65–69	2249	21.0%	10295	13.7%	0.192
	70–74	2859	26.7%	15442	20.6%	0.143
	75–79	2514	23.5%	16666	22.3%	0.029
	80+	3095	28.9%	32488	43.4%	0.305
New Use Calendar Year						
	2010–2011	3864	36.1%	31938	42.7%	0.135
	2012–2013	4462	41.6%	23867	31.9%	0.202
	2014–2015	2391	22.3%	19076	25.5%	0.075
Male		5316	49.6%	32430	43.3%	0.127
Hypertension		10522	98.2%	73340	97.9%	0.018
Diabetes		3334	31.1%	24329	32.5%	0.030
Coronary Artery Disease		5178	48.3%	37389	49.9%	0.032
Congestive Heart Failure		3839	35.8%	30404	40.6%	0.098
Peripheral Vascular Disease		1626	15.2%	14829	19.8%	0.122
Past Stroke		2522	23.5%	19768	26.4%	0.066
Past TIA		900	8.4%	6276	8.4%	0.001
Hyperlipidemia		8973	83.7%	59521	79.5%	0.110
Atherosclerosis		4883	45.6%	35535	47.4%	0.038
Obesity		1348	12.6%	7960	10.6%	0.061
Smoking		739	6.9%	5149	6.9%	0.001
Cancer		1833	17.1%	11836	15.8%	0.035
Past Bleed		905	8.4%	9595	12.8%	0.142
Past Gastrointestinal Bleeding		537	5.0%	4863	6.5%	0.064
Acute Renal Dysfunction in the Past Year		317	3.0%	4303	5.7%	0.137
Alcohol Abuse		99	0.9%	677	0.9%	0.002
Ablation in the Last Year		209	2.0%	693	0.9%	0.086
Cardioversion in the Last Year		990	9.2%	3092	4.1%	0.206
Deep Vein Thrombosis		355	3.3%	8465	11.3%	0.311
Pulmonary Embolism		98	0.9%	4115	5.5%	0.262
Previous Warfarin Use (Ever)		2154	20.1%	26725	35.7%	0.353
Current Use of Proton Pump Inhibitors		3018	28.2%	21909	29.3%	0.024
CHA_2DS_2-VASc (median, P25-P755)		4	(3–5)	4	(3–5)	NA
Frailty Probability (median, P25-P75)		0.05	(0.03 – 0.11)	0.07	(0.04 – 0.23)	0.275
OT Follow-up[a] in Days (median, P25-P75)		152	(60–382)	259	(117 – 625)	NA
IT Follow-up[a] in Days (median, P25-P75)		980	(489–1,386)	846	(355–1,415)	NA

OT=on-treatment. IT=initial treatment. P25=25th percentile. P75 = 75th percentile.

[a] Follow-up for the all-cause mortality outcome.

Table 2:

Number of Events, Person-Years of Follow-Up, and Risks at One and Two Years By Treatment Group, Weighting Methodology, and Type of Follow-Up

Group	Person-years	Events	Incidence rate per 100 person-years	One-year risk	Two-year risk
Ischemic Stroke					
Dabigatran new users					
Crude, IT	17259	237	1.37	1.38%	2.57%
Crude, OT	7474	68	0.91	0.86%	1.29%
IPTW†, IT	17113	314	1.84	1.94%	3.29%
IPTW†, OT‡	7575	108	1.43	1.31%	1.68%
Warfarin new users					
Crude, IT	112263	1863	1.66	1.75%	2.91%
Crude, OT	70414	1095	1.56	1.54%	2.48%
IPTW†, IT	112676	1823	1.62	1.72%	2.85%
IPTW†, OT‡	70670	1068	1.51	1.51%	2.41%
SMR† weighted to Dabigatran, IT	16539	221	1.34	1.47%	2.41%
SMR† weighted to Dabigatran, OT‡	10260	127	1.24	1.27%	1.96%
All-Cause Mortality					
Dabigatran new users					
Crude, IT	17438	934	5.36	5.05%	10.24%
Crude, OT	7493	269	3.59	3.92%	6.82%
IPTW†, IT	17343	1476	8.51	8.29%	15.65%
IPTW†, OT‡	7599	484	6.37	6.37%	10.51%
Warfarin new users					
Crude, IT	113607	10807	9.51	9.37%	17.14%
Crude, OT	70918	5732	8.08	8.18%	14.02%
IPTW†, IT	114005	10385	9.11	8.97%	16.49%
IPTW†, OT‡	71167	5653	7.94	7.85%	13.49%
SMR† weighted to Dabigatran, IT	16714	1064	6.36	6.24%	11.89%
SMR† weighted to Dabigatran, OT‡	10326	570	5.52	5.47%	9.78%
Gastrointestinal Bleeding					
Dabigatran new users					
Crude, IT	17133	330	1.93	1.91%	3.55%
Crude, OT	7461	168	2.25	2.18%	4.00%
IPTW†, IT	16952	438	2.59	2.63%	4.55%
IPTW†, OT‡	7560	272	3.60	3.42%	5.51%
Warfarin new users					
Crude, IT	111617	2288	2.05	2.21%	3.54%
Crude, OT	70329	1597	2.27	2.27%	3.76%
IPTW†, IT	112028	2259	2.02	2.18%	3.50%

Group	Person-years	Events	Incidence rate per 100 person-years	One-year risk	Two-year risk
IPTW[†], OT[‡]	70574	1621	2.30	2.24%	3.72%
SMR[†] weighted to Dabigatran, IT	16445	294	1.79	1.97%	3.19%
SMR[†] weighted to Dabigatran, OT[‡]	10247	215	2.10	2.07%	3.49%

OT=on-treatment. IT=initial treatment. IPTW = inverse probability of treatment weighted. SMR=standardized morbidity ratio weighted.

[†]Weighted based upon logistic regression including frailty and age modeled with restricted cubic splines at the 20^{th}, 40^{th}, 60^{th}, and 80^{th} percentile, sex, diabetes, coronary artery disease, congestive heart failure, hypertension, stroke in the past year, transient ischemic attack, cancer, bleed and GI bleed history, past use of vitamin K antagonists, current use of proton pump inhibitors, alcohol abuse, acute renal problems, atherosclerosis, cardioversion in the past year, deep vein thrombosis in the past year, hyperlipidemia, obesity, pulmonary embolism in the past year, peripheral vascular disease and codes indicating smoking.

[‡]Weighted on-treatment analyses include time-varying inverse probability of censoring weights to account for differential censoring and switching across treatment arms by measured variables.

Table 3:

Risk Ratios and Risk Differences Comparing Dabigatran New Users to Warfarin New Users for Two-Year Risks By Outcome, Weighting Method, and Type of Follow-Up

	Two-year on-treatment‡:		Two-year initial treatment:	
Estimate	**Risk ratio (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
Ischemic Stroke				
Crude	0.52 (0.37, 0.74)	−1.19% (−1.67%, −0.71%)	0.88 (0.77, 1.02)	−0.34% (−0.71%, 0.02%)
IPTW†	0.70 (0.49, 1.03)	−0.73% (−1.40%, −0.06%)	1.15 (0.94, 1.41)	0.44% (−0.22%, 1.09%)
SMR† weighted to dabigatran	0.66 (0.48, 0.91)	−0.67% (−1.10%, −0.24%)	1.07 (0.93, 1.23)	0.16% (−0.20%, 0.52%)
All-cause Mortality				
Crude	0.49 (0.42, 0.56)	−7.20% (−8.13%, −6.27%)	0.60 (0.56, 0.63)	−6.90% (−7.59%, −6.21%)
IPTW†	0.78 (0.64, 0.95)	−2.98% (−5.05%, −0.91%)	0.95 (0.86, 1.04)	−0.84% (−2.39%, 0.72%)
SMR† weighted to dabigatran	0.70 (0.60, 0.81)	−2.96% (−3.97%, −1.95%)	0.86 (0.81, 0.91)	−1.65% (−2.32%, −0.98%)
Gastrointestinal Bleeding				
Crude	1.06 (0.87, 1.30)	0.24% (−0.49%, 0.98%)	1.00 (0.88, 1.13)	−0.00% (−0.43%, 0.44%)
IPTW†	1.48 (1.05, 2.09)	1.79% (−0.13%, 3.71%)	1.30 (1.05, 1.61)	1.05% (0.08%, 2.01%)
SMR† weighted to dabigatran	1.15 (0.93, 1.41)	0.51% (−0.30%, 1.31%)	1.11 (0.98, 1.26)	0.36% (−0.08%, 0.79%)

SMR = standardized morbidity ratio. IPTW = inverse probability of treatment weights.

†Weighted based upon logistic regression including frailty and age modeled with restricted cubic splines at the 20th, 40th, 60th, and 80th percentile, sex, diabetes, coronary artery disease, congestive heart failure, hypertension, stroke in the past year, transient ischemic attack, cancer, bleed and GI bleed history, past use of vitamin K antagonists, current use of proton pump inhibitors, alcohol abuse, acute renal problems, atherosclerosis, cardioversion in the past year, deep vein thrombosis in the past year, hyperlipidemia, obesity, pulmonary embolism in the past year, peripheral vascular disease and codes indicating smoking.

‡Weighted on-treatment analyses include time-varying inverse probability of censoring weights to account for differential censoring and switching across treatment arms by measured variables.