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Comparing Stroke and Bleeding with Rivaroxaban and Dabigatran in Atrial Fibrillation: Analysis of the US Medicare Part D Data

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Abstract

Background—No studies have directly compared the effectiveness and safety of dabigatran and rivaroxaban using US Medicare data. The objective of the study was to compare the effectiveness and safety between rivaroxaban 20mg/dabigatran 150mg, or rivaroxaban 15mg/dabigatran 75mg among atrial fibrillation (AF) patients.

Methods—Using 2010–2013 US Medicare Part D data, we selected AF patients initiating dabigatran 150/75mg or rivaroxaban 20/15mg between November 4, 2011 (when rivaroxaban was approved) and December 31, 2013. Our sample included 7,322 dabigatran 150mg users, 5,799 rivaroxaban 20mg users, 1,818 dabigatran 75mg users and 2,568 rivaroxaban 15mg users. We followed them until stroke, other thromboembolic events, bleeding, discontinuation or switch of an anticoagulant, death, or December 31, 2013. We constructed Cox Proportional Hazard Models with propensity score weighting to compare clinical outcomes between groups.

Results—There was no difference in the risk of stroke between dabigatran 150mg and rivaroxaban 20mg (hazard ratio [HR] 1.05, 95%CI 0.97–1.13) or between dabigatran 75mg and rivaroxaban 15mg (HR1.05, 95%CI 0.94–1.18). Compared to dabigatran 150mg, rivaroxaban 20mg was associated with higher risk of other thromboembolic events (HR1.28, 95%CI 1.14–1.44), major bleeding (HR1.32, 95%CI 1.17–1.50), and death (HR1.36, 95% CI 1.19–1.56). The risk of thromboembolic events other than stroke (HR1.37, 95%CI 1.15–1.62), major bleeding (HR1.51, 95%CI 1.25–1.82) and death (HR1.21, 95% CI 1.04–1.41) was also higher for rivaroxaban 15mg than dabigatran 75mg.

Conclusions—There was no difference in stroke prevention between rivaroxaban and dabigatran; however, rivaroxaban was associated with higher risk of thromboembolic events other than stroke, death and bleeding.

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Compliance with Ethical Standards

Conflicts of interest

None

Keywords

Anticoagulants; Atrial Fibrillation; Hemorrhage; Stroke

INTRODUCTION

Dabigatran 150mg and 75mg were approved by the US Food and Drug Administration (FDA) in October 2010 for the prevention of stroke among non-valvular atrial fibrillation (AF) patients, with 75mg indicated for patients with creatinine clearance lower than 30ml/min.[1] Rivaroxaban 20mg and 15mg gained the FDA approval for the same indication in November 2011, with 15mg indicated for patients with creatinine clearance lower than 50ml/min.[2] Both doses of dabigatran are administered twice-a-day, whereas rivaroxaban follows a once-a-day regimen.[1, 2] The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) clinical trial found that dabigatran 150mg was similar to warfarin in the risk of bleeding, but superior in the prevention of stroke;[3] the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) showed that rivaroxaban 20mg/15mg was similar to warfarin in both the risk of bleeding and the prevention of stroke.[4, 5] Since the approval of rivaroxaban, two new nonvitamin K antagonist oral anticoagulants (NOACs) have gained FDA approval for the same indication: apixaban in December 2012 and edoxaban in January 2015. [6, 7]

Because no clinical trials have directly compared NOACs, previous researchers have used the results of the RE-LY[3] and ROCKET-AF trials[4] to compare the effectiveness and safety of dabigatran and rivaroxaban.[8, 9] In these indirect comparisons, rivaroxaban 20mg/15mg was predicted to be less effective in the prevention of stroke and systemic embolism than dabigatran 150mg, but similar in the risk of bleeding.[8, 9] Because the validity of indirect comparisons is limited by inter-trial population differences, and the subjects enrolled in the ROCKET-AF trial were considerably sicker than those in the RE-LY trial,[3, 4] it is important to perform direct analyses to compare the effectiveness and safety of dabigatran and rivaroxaban using the same population.

Although several observational studies have compared the real-world effectiveness and safety of dabigatran or rivaroxaban with those of warfarin,[10–15] only one study has directly compared the risk of bleeding between dabigatran and rivaroxaban, finding no differences in the risk of bleeding with two oral anticoagulants.[16] However, the authors used medical records from only two hospitals and did not examine the risk of bleeding by dose of anticoagulant separately.[16] Because the risk of bleeding varies by the strength of anticoagulant, it is also necessary to separately examine the risk of bleeding by dose.[17–19] To the best of our knowledge, no observational studies have compared head-to-head the effectiveness of dabigatran and rivaroxaban in the prevention of stroke in AF.

In this paper, we used 2010–2013 pharmacy and medical claims data from a 5% random sample of Medicare beneficiaries with AF to compare the risk of stroke, other thromboembolic events, death and bleeding following the initiation of dabigatran and

rivaroxaban, separately for high-dose (dabigatran 150mg and rivaroxaban 20mg) and low-dose initiators (dabigatran 75mg and rivaroxaban 15mg).

METHODS

Data Source and Study Population

We obtained 2010–2013 pharmacy and medical data for a 5% random sample of US Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS). First, we identified patients who filled a prescription for dabigatran or rivaroxaban between November 4, 2011 (the approval date for rivaroxaban) and December 31, 2013 (n=44,621) (Figure 1). The index date was defined as the day of the first prescription filled for dabigatran or rivaroxaban in this time window. Second, we required that patients had a diagnosis of AF any time before the index date according to the CMS Chronic Condition Warehouse definition of AF (n=22,292).[20] Third, we excluded patients who had a claim for dabigatran or rivaroxaban in the three months before the index date to make sure that we identified patients who initiated dabigatran or rivaroxaban treatment during our study period, when the risk of bleeding is higher.[21] We used a three-month wash-out period because anticoagulants used in AF are usually prescribed as 30-day or 90-day supply prescriptions. Our final sample included 7,322 dabigatran 150mg users, 5,799 rivaroxaban 20mg users, 1,818 dabigatran 75mg users and 2,568 rivaroxaban 15mg users. In our study, we did not include rivaroxaban 10 mg users because this dose has not been approved for the prevention of stroke and systemic embolism in AF.[2] Since apixaban was approved in December 2012, the follow-up period available for this treatment group in our data set was shorter than one year and therefore, we did not include apixaban in our study.

We followed each individual from the index date until discontinuation of treatment, defined as a gap in anticoagulant treatment for over 60 days, switch of an anticoagulant or dose, death, or December 31, 2013.[13] This study was approved by the Institutional Review Board at the University of Pittsburgh.

Outcomes

Effectiveness outcomes included ischemic stroke, other thromboembolic events and all-cause mortality. Ischemic stroke was defined as having one inpatient, emergency room or outpatient claim with primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) codes 433, 434 or 436.[22, 23] Other thromboembolic events included inpatient, emergency room or outpatient claims for systemic embolism (ICD-9=444), transient ischemic attack (ICD-9=435) and pulmonary embolism (ICD- 9=415.1).[22, 23] Safety outcomes included any bleeding event and major bleeding; we also reported specifically safety outcomes for two anatomical locations: intracranial hemorrhage, and gastrointestinal bleeding. Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency room stays for gastrointestinal, hematuria, or not otherwise specified hemorrhage (Supplemental Table 1).[13]

Covariates

We adjusted for demographic variables and clinical characteristics, all of which were measured on the index date. Demographic variables included age, race and Medicaid eligibility. Clinical characteristics included CHADS2 score,[24] chronic kidney disease, hypertension, a history of stroke or transient ischemic attack (TIA), prior acute myocardial infarction, diabetes, congestive heart failure, acquired hypothyroidism, number of other CMS priority comorbidities (list in Table 1), a history of bleeding, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), and concomitant use of antiplatelet drugs (definitions are listed in Table 1).

Statistical Analysis

We compared patient characteristics between dabigatran 150mg initiators and rivaroxaban 20mg initiators, and between dabigatran 75mg initiators and rivaroxaban 15mg initiators using chi-square tests. To compare the unadjusted cumulative incidence of effectiveness and safety outcomes at 1 year follow-up, we constructed Kaplan-Meier time-to-event curves.

One of the limitations from using observational data to conduct comparative effectiveness studies is that individuals in one treatment group may not be comparable to individuals in the other group. To mitigate this problem, we used propensity score weighting, which was conducted in two steps. First, we constructed a logistic regression controlling for all covariates listed in the Covariates Section to calculate the probability of initiating rivaroxaban (propensity score). We used the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) in statistical software R to find the best logistic regression model to calculate the propensity score. We calculated standardized differences in covariate means between two treatment groups to evaluate whether covariates were balanced between treatment groups after propensity score weighting.[25] Standardized differences with absolute values below 10% indicate a good balance between treatment groups.[26] Second, we constructed Cox Proportional Hazards models to compare effectiveness and safety outcomes between groups, using the inverse of the propensity score for each individual as a weight. Cox models included one indicator variable for rivaroxaban initiation, as well as all pre-defined covariates listed in the Covariates Section. Because one of the limitations of this methodology is the presence of large weights, we checked the distribution of weights and found that none of the subjects had weights larger than 10. For all time-to-event analyses except for the ones that compared the risk of all-cause mortality between treatment groups, the time at risk was censored at the end of the study period (December 31, 2013), or at switch of anticoagulant or dose, discontinuation of anticoagulant therapy, or death. Time-to-event analyses built to compare the risk of all-cause mortality between treatment groups had the same censoring events except death. All analyses were conducted with statistical software SAS 9.4 (Cary, NC).

We further compared the effectiveness and safety of dabigatran and rivaroxaban among three subgroups of patients: those older than 75 years, with chronic kidney disease, or with at least 7 CMS priority conditions other than AF.[27] For each subgroup identified, we re-calculated the propensity score, and constructed Cox models to compare effectiveness and safety outcomes following the same methodology as with the overall sample.

Sensitivity Analyses

One may argue that some of our study participants may have initiated anticoagulation therapy for an indication other than AF. To examine whether this may have affected our results, we re-run our analyses after excluding study participants who had claims in the three months before the index date with a diagnosis of venous thromboembolism, pulmonary embolism, phlebitis, and hip or knee replacement surgery. Subjects who used warfarin before the initiation of dabigatran or rivaroxaban may have had remaining warfarin at the time of dabigatran or rivaroxaban initiation, which may have affected the occurrence of bleeding events soon after the initiation of dabigatran or rivaroxaban. To analyze whether our results for safety outcomes were affected by this problem, we ran our analyses after excluding subjects who filled a prescription for warfarin six months before index date. Because in patients with a history of stroke it is difficult in some occasions to differentiate new events from prior diagnoses of strokes, we conducted sensitivity analyses by including and excluding \ patients who had a history of stroke or TIA before the index date. Finally, we also examined the robustness of our results after excluding patients who filled a prescription for NSAIDs or antiplatelet agents after index date.

RESULTS

Patient Characteristics

The mean follow-up period was 385 days for dabigatran 150mg users, 251 days for rivaroxaban 20mg users, 357 days for dabigatran 75mg users, and 239 for rivaroxaban 15mg users (Supplemental Table 2). Before propensity score weighting, rivaroxaban 20mg initiators were more likely to be also eligible for Medicaid benefits, have chronic kidney disease and acquired hypothyroidism than dabigatran 150mg initiators (Table 1). The mean age of dabigatran 150mg users was 75.64, and the mean age of rivaroxaban 20mg users was 75.44. Dabigatran 75mg users and rivaroxaban 20mg were 82.0 and 81.71 years old on average, respectively. Although low-dose dabigatran and rivaroxaban are only indicated in AF patients with reduced kidney function, only 52.6% of patients on dabigatran 75mg and 51.5% of those on rivaroxaban 15mg had a diagnosis of chronic kidney disease. After propensity score weighting, all patient characteristics were balanced between rivaroxaban and dabigatran groups for both high and low dose initiators.

Unadjusted Incidence of Effectiveness and Safety Outcomes

Before adjustment, dabigatran 150mg was associated with lower risk of all-cause mortality, major bleeding, gastrointestinal bleeding and any bleeding events than rivaroxaban 20 mg (Table 2). The unadjusted incidence of clinical outcomes did not differ between dabigatran 75mg and rivaroxaban 15mg initiators except for any bleeding event, which was higher with rivaroxaban 15mg than dabigatran 75mg.

Adjusted Hazard Ratio of Effectiveness and Safety Outcomes

Figure 2 shows the adjusted hazard ratios for effectiveness and safety outcomes after propensity score weighting. The risk of ischemic stroke did not differ between rivaroxaban 20 mg and dabigatran 150mg (hazard ratio [HR] 1.05; 95% CI 0.97–1.13); however,

rivaroxaban 20mg was associated with higher risk of other thromboembolic events (HR 1.28; 95%CI 1.14–1.44) and all-cause mortality (HR 1.36; 95% CI, 1.19–1.56) than dabigatran 150mg. The risk of major bleeding (HR 1.32; 95% CI, 1.17–1.50), any bleeding event (HR 1.17; 95% CI, 1.10–1.24) and gastrointestinal bleeding (HR 1.19; 95% CI, 1.03–1.30) was also higher among patients initiating rivaroxaban 20mg than those initiating dabigatran 150 mg. The risk of intracranial hemorrhage did not differ between high-dose dabigatran and rivaroxaban.

Our results for the comparative risk of effectiveness and safety outcomes among low-dose initiators are consistent with the findings from high-dose initiators: There was no difference in the risk of ischemic stroke and intracranial bleeding between rivaroxaban 15mg and dabigatran 75mg; however, the risk of other thromboembolic events (HR 1.37; 95%CI, 1.15–1.62), all-cause mortality (HR 1.21; 95% CI, 1.04–1.41), major bleeding (HR 1.51; 95% CI, 1.25–1.82), any bleeding event (HR 1.39; 95% CI, 1.27–1.53) and gastrointestinal bleeding (HR 1.25; 95% CI, 1.09–1.44) was higher with rivaroxaban 15mg than dabigatran 75mg.

Subgroup and Sensitivity Analyses

For patients with more than 7 CMS priority chronic conditions other than AF, we found that the risk of ischemic stroke was higher with rivaroxaban 20 mg than dabigatran 150 mg (HR 1.12; 95%CI, 1.01–1.25) (Figure 3). Other results for selected effectiveness and safety outcomes in three high-risk subgroups are consistent with the findings from the overall sample. After excluding patients with a diagnosis of an indication for anticoagulation other than AF, there was no difference in the risk of thromboembolic events other than stroke between rivaroxaban and dabigatran, but other outcomes were similar as those from the overall sample (Supplemental Table 3). After the exclusion of recent warfarin-experienced subjects from the study sample, the hazard ratios of bleeding events did not vary much (Supplemental Table 4). The exclusion of patients with a history of stroke or TIA did not impact our results for the comparative risk of effectiveness outcomes between two anticoagulants (Supplemental Table 5). Our results were also consistent after the exclusion of patients who used NSAIDs or antiplatelet agents after index date (Supplemental Table 6).

DISCUSSION

To the best of our knowledge, our study is the first to compare effectiveness and safety outcomes between dabigatran and rivaroxaban, separately by dose, among Medicare patients with AF. Our study yielded two main findings. First, we found no differences in stroke prevention between dabigatran and rivaroxaban; however, rivaroxaban was associated with higher rates of thromboembolic events other than stroke and all-cause mortality than dabigatran. Second, we observed that the risk of major bleeding, gastrointestinal bleeding and any bleeding events was higher with rivaroxaban than dabigatran, but there was no difference in the risk of intracranial bleeding between dabigatran and rivaroxaban.

Previous researchers have conducted indirect comparisons of the results from the RE-LY and ROCKET-AF trials, predicting that dabigatran would be associated with a lower combined risk of stroke and systemic embolism than rivaroxaban (HR 1.35; 95% CI 1.02–1.78), but with a similar risk of ischemic stroke (HR 1.33; 95% CI 0.98–1.78), and a similar risk of

bleeding (HR 1.12; 95% CI 0.92– 1.37).[8, 9] We found no difference in the risk of ischemic stroke with two NOACs (HR 1.05; 95% CI, 0.97–1.13), but we observed that the risk of thromboembolic events other than stroke (HR 1.28; 95% CI, 1.14–1.44) and of bleeding (HR 1.32; 95% CI, 1.17–1.50) was higher with rivaroxaban. The differences between our results for the comparative risk of bleeding with two NOACs and those reported in indirect comparisons may be explained by the difference in patient characteristics of subjects enrolled in two clinical trials.[8, 9] For example, 55% and 62% of the subjects enrolled in the ROCKET-AF trial had a prior stroke/TIA and heart failure, compared to 20% and 35% of those enrolled in the RE-LY trial, respectively.[3, 4] Using US commercial insurance data, Laliberte et al. compared the effectiveness and safety of rivaroxaban and warfarin, estimating the annual risk of major bleeding on rivaroxaban at 3.3%.[10] Our estimate for the rate of major bleeding on rivaroxaban 20mg (5%) is higher than the estimate reported by Laliberte and colleagues, partially because of the higher prevalence of risk factors for bleeding among our study sample. For instance, 28.6 % of our study participants on rivaroxaban 20mg had a diagnosis of kidney disease, whereas only 7.5% of those included in the study by Laliberte et al. did.[10] To the best of our knowledge, only one study has directly compared the risk of bleeding with dabigatran and rivaroxaban. In doing so, Sherid et al. used medical records from two community hospitals and did not find differences in the risk of bleeding with two NOACs.[16] However, the sample size of this study was very small (227 dabigatran users and 147 rivaroxaban users), which may have prevented the authors from finding significant differences.

Our study is subject to six main limitations. First, propensity score weighting did not adjust for unobserved patient characteristics, such as the result of laboratory tests, because they are not available in Medicare claims data. Thus, some unobserved risk factors for clinical outcomes may have been unbalanced between treatment groups, such as creatinine clearance. However, we balanced the proportion of patients with chronic kidney disease between treatment groups using propensity score weighting, and we also included this as a covariate in our Cox Proportional Hazards models. Second, because of the unavailability of data on INR, we could not calculate the HAS-BLED risk score, which is a prediction tool of the risk of bleeding.[28, 29] Nevertheless, we balanced all components of HAS-BLED score except for labile INR between treatment groups, and included them as separate covariates in our analytical models as well. Third, in our study, we used 2010–2013 Medicare data, so our study period represents the first two years after rivaroxaban entered the US market. Prescribing patterns of NOACs may change over time as prescribers become more familiar with these agents.[18, 19] Fourth, our study did not include apixaban, which was approved in December 2012, because we would not have enough follow-up period to study effectiveness outcomes. As a result, it will be informative to repeat our analyses as newer Medicare Part D data becomes available, and compare the effectiveness and safety of dabigatran and rivaroxaban to those of apixaban. Fifth, we censored patients when they switched anticoagulation treatments or they discontinued anticoagulation for over 60 days; however, there may have been short interruptions of anticoagulation that were not captured in our analysis. In addition, we observed that the rates of discontinuation and switching during our study period were higher on the dabigatran groups than the rivaroxaban groups, which may be partially due to the longer follow-up time available for the dabigatran cohorts.

Nevertheless, these differences in discontinuation and switching rates should not affect our results, because for each of the outcomes analyzed, we used a time to first event analysis. Sixth, claims data do not capture information on patients' adherence to therapy, which may have been higher in the rivaroxaban groups because of the once-a-day regimen. In fact, a recent analysis of US commercial insurance claims data found that rivaroxaban users were more adherent than patients on dabigatran.[30] However, this is not especially concerning because our study aimed to compare effectiveness and safety outcomes under real-world conditions, where adherence to rivaroxaban is likely to be higher. In doing so, we found no difference in the prevention of stroke with two new oral anticoagulants, yet rivaroxaban was associated with higher risk of bleeding. This implies that despite of the twice-a-day regimen, dabigatran still presents a better benefit/risk ratio in the real-world clinical practice than rivaroxaban.

Rivaroxaban 15mg and dabigatran 75mg are indicated in the prevention of stroke or systemic embolism in renally impaired patients with AF; however, we observed that half of the study participants who initiated rivaroxaban 15mg or dabigatran 75mg did not have a diagnosis of chronic kidney disease. Even though our study did not specifically examine the off-label use of low-dose dabigatran and rivaroxaban, we hypothesize that these low doses of anticoagulants were prescribed off-label in 2011–2013 for patients with normal kidney function who had however other risk factors for bleeding, such as hypertension, a history of stroke or a history of bleeding. These prescribing patterns may have been motivated by the concerns of severe bleeding events with NOACs, the unavailability of dabigatran 110mg in the US, and the lack of an antidote to reverse the anticoagulation effects of rivaroxaban and dabigatran in case of emergency in 2011–2013, the period that our study represents. Idarucizumab, the specific antidote for dabigatran, was approved in October 2015.[31] In the future, it will be informative to further characterize this off-label use of low-dose anticoagulants, and analyze how it has changed over time as clinicians become more familiar with NOACs. In addition, it will be relevant to compare post-hemorrhage outcomes of patients who bled on rivaroxaban and dabigatran in future analyses. These outcomes are likely to differ between two drugs because, in addition to idarucizumab, there is another strategy available to revert the effects of dabigatran that is not available for rivaroxaban: hemodialysis.[32] Evaluating how post-hemorrhage outcomes compare between two drugs would specially be relevant for subgroups at high-risk of bleeding events, such as patients older than 75 years or with kidney disease.[29, 24].

In conclusion, we found that dabigatran was superior in safety to rivaroxaban; however, we did not find differences in stroke prevention between two oral anticoagulants. Our findings have important implications to the use of NOACs among AF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Food and Drug Administration. Pradaxa Prescribing Information. 2015 <http://www.accessdata.fda.gov/drugsatfdadocs/label/2015/022512s0281bl.pdf> Accessed January 12 2016.
- Food and Drug Administration. Prescribing information for Xarelto. 2015 <http://www.accessdata.fda.gov/drugsatfdadocs/label/2015/022406s0121bl.pdf> Accessed May 14 2015.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12): 1139–51. [PubMed: 19717844]
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–91. [PubMed: 21830957]
- Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2014;63(9):891–900. [PubMed: 24315894]
- Food and Drug Administration. Prescribing information for Eliquis. 2015 <http://www.accessdata.fda.gov/drugsatfdadocs/label/2015/202155s0111bl.pdf> Accessed January 12 2016.
- Food and Drug Administration. Prescribing information for Savaysa. 2015 <http://www.accessdata.fda.gov/drugsatfdadocs/label/2015/206316s0021bl.pdf> Accessed January 12 2016.
- Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. *Thromb Haemost*. 2012;108(9):476–84. [PubMed: 22740145]
- Lip GY, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2012;60(8):738–46. [PubMed: 22575324]
- Laliberte F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin*. 2014;30(7):1317–25. [PubMed: 24650301]
- Chang HY, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *Bmj*. 2015;24(350).
- Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M et al. Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated with Dabigatran or Warfarin for Non-Valvular Atrial Fibrillation. *Circulation*. 2015;131 (2) :157–64. [PubMed: 25359164]
- Hernandez I, Baik SH, Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med*. 2015;175(1):18–24. [PubMed: 25365537]
- Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M et al. Efficacy and safety of dabigatran etexilate and warfarin in “real-world” patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol*. 2013;61(22):2264–73. [PubMed: 23562920]
- Maura G, Blotiere PO, Bouillon K, Billionnet C, Ricordeau P, Alla F et al. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity- matched cohort study. *Circulation*. 2015; 132(13): 1252–60. [PubMed: 26199338]
- Sherid M, Sifuentes H, Sulaiman S, Samo S, Husein H, Tupper R et al. Risk of Gastrointestinal Bleeding with Dabigatran: A Head-to-Head Comparative Study with Rivaroxaban. *Digestion*. 2014;90(2): 137–46. [PubMed: 25278002]
- Liu S, Kim CO, Lucyk SN. Dosage of dabigatran as a risk factor for bleeding in atrial fibrillation. *JAMA Intern Med*. 2015;175(7):1244–5.

18. Miyares MA. One-year risk of bleeding with dabigatran in patients with atrial fibrillation: Placing real-world results into perspective. *JAMA Intern Med.* 2015;175(7):1242–3. [PubMed: 26146916]
19. Hernandez I, Zhang Y. Risk of bleeding with dabigatran in 2010–2011 Medicare data. *JAMA Intern Med.* 2015; 175(7): 1245–7.
20. Center for Medicare and Medicaid Services Chronic Conditions Data Warehouse. 27 Chronic Condition Algorithm. 2014 <https://www.ccwdata.org/cs/groups/public/documents/document/ccwconditioncategories.pdf> Accessed July 8 2015.
21. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation.* 2007;115(21):2689–96. [PubMed: 17515465]
22. Thigpen JL, Dillon C, Forster KB, Henault L, Quinn EK, Tripodis Y et al. Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circ Cardiovasc Qual Outcomes.* 2015;8(1):8–14. [PubMed: 25587093]
23. Lichtman JH, Jones SB, Watanabe E, Allen NB, Wang Y, Howard VJ et al. Elderly women have lower rates of stroke, cardiovascular events, and mortality after hospitalization for transient ischemic attack. *Stroke.* 2009;40(6):2116–22. [PubMed: 19228857]
24. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke. *J Am Med Assoc.* 2001;285(22):2864–70.
25. d'Agostino RB. Tutorial in biostatistics: propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998;17(19):2265–81. [PubMed: 9802183]
26. Cohen J Statistical power analysis. *Cur Dir Psychol Sci.* 1992;1(3):98–101.
27. Medicare Beneficiary Prevalence for Chronic Conditions for 2002 Through 2011 <https://www.ccwdata.org/cs/groups/public/documents/document/wlsucm1-000774.pdf> Accessed January 5 2015.
28. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc.* 2013;2(3):000250.
29. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS- BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010; 138(5): 1093–100. [PubMed: 20299623]
30. McHorney CA, Crivera C, Laliberte F, Nelson WW, Germain G, Bookhart B et al. Adherence to non- vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure. *Curr Med Res Opin.* 2015;31(12):2167–73. [PubMed: 26393483]
31. Pollack CV Jr., Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S et al. Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. *Thromb Haemost.* 2015;114(1).
32. Fawole A, Daw HA, Crowther MA. Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban. *Cleve Clin J Med.* 2013;80(7):443–51. [PubMed: 23821689]

Key Points

- We used 2010–2013 Medicare Part D data for atrial fibrillation patients to compare the effectiveness and safety of two doses of dabigatran and rivaroxaban.
- We found no difference in stroke prevention between rivaroxaban and dabigatran; however, the risk of bleeding and the risk of thromboembolic events other than stroke were higher with rivaroxaban.
- In conclusion, dabigatran showed a superior benefit/risk ratio than rivaroxaban in the prevention of stroke among a sample of Medicare beneficiaries with atrial fibrillation.

Figure 1.
Selection of the Study Sample.

NOTES:

Abbreviations: AF=Atrial Fibrillation.

Figure 2.

Hazard Ratios for Effectiveness and Safety Outcomes, by Treatment and Dose.

NOTES:

Hazard ratios were estimated with Cox Proportional Hazard Models with propensity score weighting that controlled for treatment, age, gender, race, Medicaid eligibility, CHADS2 score, chronic kidney disease, hypertension, previous stroke or transient ischemic attack, acute myocardial infarction, diabetes mellitus, congestive heart failure, acquired hypothyroidism, number of other CMS priority conditions, a history of bleeding, use of NSAIDs, and use of antiplatelet agents.

Figure 3.

Hazard Ratios for Effectiveness and Safety Outcomes, by Subgroup, Treatment and Dose.

NOTES:

Hazard ratios were estimated with Cox Proportional Hazard Models with propensity score weighting that controlled for all the covariates listed in the Covariates Section except for the one defining the subgroup.

Table 1.
Baseline Characteristics of the Study Cohorts, Before and After Propensity Score Weighting, by Treatment and Dose.

Variable (%)	Before Propensity Score Weighting				After Propensity Score Weighting			
	High Dose		Low Dose		High Dose		Low Dose	
	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)	P- Value	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)	P- Value	D	R
Age			0.005			0.565		
<65	5.0	6.3		1.9	1.9		5.5	5.6
65-74	39.3	38.4		14.4	15.5		38.9	38.9
75	55.7	55.3		83.7	82.5		55.6	55.5
Male sex	49.5	45.9	<0.001	34.7	32.5	0.132	48.0	47.9
Race			0.058			0.894		
White	87.5	86.3		86.4	86.5		87.3	87.3
Black	5.4	5.5		5.6	5.1		5.4	5.3
Asian	1.8	1.8		2.7	2.9		1.7	1.7
Hispanic	3.9	5.1		4.3	4.7		4.3	4.4
Native American	0.3	0.3		0.3	0.3		0.2	0.2
Other	1.2	1.1		0.7	0.6		1.1	1.1
Medicaid eligibility	20.0	22.7	<0.001	27.3	25.9	0.314	21.0	20.9
CHADS2 score [*] --mean (SD)	3.28 (1.30)	3.29 (1.32)	0.961	3.87 (1.29)	3.79 (1.30)	0.039	3.28 (1.75)	3.28 (1.96)
CMS priority comorbidities								
CKD	26.3	28.6	0.003	52.6	51.5	0.469	27.2	27.2
Hypertension	92.9	92.8	0.976	96.9	96.6	0.577	92.9	92.9
Previous stroke or TIA	22.7	23.4	0.302	34.7	33.7	0.505	22.9	23.0
AMI	6.5	7.4	0.044	11.1	11.1	0.989	6.8	6.8
Diabetes mellitus	43.4	44.4	0.258	50.0	50.0	0.992	43.8	43.9
CHF	51.8	50.8	0.219	72.5	66.6	<0.001	51.3	51.3
Acquired hypothyroidism	26.0	29.6	<0.001	38.2	39.5	0.410	27.6	27.7
No. of other CMS			<0.001			0.074		
							3.83 (1.99)	3.83 (1.68)
							51.9	51.8
							96.9	96.8
							34.3	34.1
							10.8	11.0
							50.1	50.0
							69.3	69.1
							39.3	39.1
							-0.1	-0.1
							0.0	0.0
							0.0	0.0
							0.5	0.5
							0.3	0.3

Variable (%)	Before Propensity Score Weighting					After Propensity Score Weighting				
	High Dose		Low Dose			High Dose		Low Dose		
	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)	P- Value	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)	P- Value	D	R	Standardized Difference in Covariate Means	Standardized Difference in Covariate Means
priority comorbidities [†]										
0-3	22.4	21.5		8.8	7.0		22.0	21.9	0.2	7.8
4-6	41.5	38.1		30.1	31.2		40.0	40.0	0.0	30.5
7	36.2	40.4		61.1	61.8		38.0	38.0	-0.2	61.7
History of bleeding	19.2	20.2	0.145	25.4	24.7	0.579	19.6	19.5	0.1	24.8
Use of NSAIDs [§]	15.9	11.4	<0.001	13.1	9.9	0.001	13.9	13.7	0.6	11.1
Use of antiplatelets ^{//}	7.1	6.1	0.017	9.5	6.9	0.002	6.6	6.4	0.5	7.7

NOTES:

Abbreviations: D=Dabigatran; R=Rivaroxaban, CKD=Chronic kidney disease; AMI=Acute Myocardial Infarction; TIA= Transient Ischemic Attack; CHF= Congestive Heart Failure; CMS= Centers for Medicare and Medicaid Services; NSAIDs=Non-Steroidal Anti-inflammatory Drug.

* CHADS2 score is a prediction measure of the risk of stroke in patients with atrial fibrillation. In the calculation of the CHADS2 score, CHF, hypertension, age of 75 years or older and diabetes are assigned one point and a history of previous stroke or TIA is assigned two points; CHADS2 score is calculated as the sum of all points.[24]

[†]The number of other CMS priority comorbidities was calculated as the sum of previous a history of Alzheimer's disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer and endometrial cancer.

[‡]A history of bleeding was defined as having one claim with ICD-9 codes for any bleeding event in the year before the index date.

[§]Concurrent use of NSAIDs was defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin after the index date.

^{//}Concurrent use of antiplatelet drugs was defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamol, ticlopidine or ticagrelor after the index date.

High dose includes dabigatran 150mg and rivaroxaban 20mg initiators, and low dose includes dabigatran 75mg and rivaroxaban 15mg initiators. Standardized differences in covariate means measure the balance of covariates between groups, differences lower than 10% indicate balance between treatment groups.

Table 2.

Number of Events and Cumulative Incidence Rates at 1 Year Follow-up of Clinical Outcomes, by Treatment Group and Dose.

	Number of events (%)		Cumulative Incidence At 1 year (95% CI)	
	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)
High Dose				
Effectiveness Outcomes				
Ischemic Stroke	1036 (14.2)	580 (10.0)	0.12 (0.11 , 0.13)	0.12 (0.11 , 0.14)
Other Thromboembolic events	386 (5.3)	250 (4.3)	0.041 (0.036 , 0.046)	0.053 (0.046 , 0.061)
All-Cause Mortality	247 (3.4)	229 (3.9)	0.032 (0.030 , 0.039)	0.050 (0.043 , 0.056)
Safety Outcomes				
Major Bleeding	349 (4.8)	229 (4.0)	0.034 (0.029 , 0.038)	0.050 (0.043 , 0.058)
Any Bleeding	1658 (22.6)	1008 (17.4)	0.19 (0.18 , 0.20)	0.22 (0.21 , 0.23)
Intracranial Bleeding	88 (1.2)	33 (0.6)	0.008 (0.006 , 0.010)	0.007 (0.004 , 0.009)
Gastrointestinal Bleeding	722 (9.9)	439 (7.6)	0.08 (0.07 , 0.08)	0.10 (0.09 , 0.11)
Low Dose				
	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)
Effectiveness Outcomes				
Ischemic Stroke	316 (17.4)	315 (12.3)	0.16 (0.14 , 0.18)	0.17 (0.15 , 0.19)
Other Thromboembolic events	130 (7.2)	161 (6.3)	0.07 (0.06 , 0.08)	0.08 (0.07 , 0.09)
All-Cause Mortality	146 (8.0)	191 (7.4)	0.087 (0.073 , 0.101)	0.099 (0.085 , 0.114)
Safety Outcomes				
Major Bleeding	107 (5.9)	139 (5.4)	0.053 (0.041 , 0.064)	0.073 (0.060 , 0.087)
Any Bleeding	429 (23.6)	518 (20.2)	0.21 (0.19 , 0.23)	0.27 (0.24 , 0.29)
Intracranial Bleeding	26 (1.4)	29 (1.1)	0.013 (0.007 , 0.018)	0.018 (0.011 , 0.025)
Gastrointestinal Bleeding	206 (11.3)	229 (8.9)	0.10 (0.08 , 0.11)	0.12 (0.10 , 0.13)

NOTES:

Bold denotes statistical significant results.

High dose includes dabigatran 150mg and rivaroxaban 20mg initiators, and low dose includes dabigatran 75mg and rivaroxaban 15mg initiators. Cumulative incidence rates at 1 year follow up were estimated with Kaplan-Meier time to event curves.