Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

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Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134,414 patients with 37,587 person-years of follow-up, there were 2,715 primary outcome events. The hazard ratios (95% confidence intervals) comparing dabigatran with warfarin (reference) were as follows: ischemic stroke, 0.80 (0.67–0.96); intracranial hemorrhage, 0.34 (0.26–0.46); major gastrointestinal bleeding, 1.28 (1.14–1.44); acute myocardial infarction, 0.92 (0.78–1.08); and death, 0.86 (0.77–0.96). In the subgroup treated with dabigatran 75 mg twice daily, there was no difference in risk compared with warfarin for any outcome except intracranial hemorrhage, in which case dabigatran risk was reduced. Most patients treated with dabigatran 75 mg twice daily appeared not to have severe renal impairment, the intended population for this dose. In the dabigatran 150 mg twice daily subgroup, the magnitude of effect for each outcome was greater than in the combined-dose analysis.

Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran.

Key Words: anticoagulant ■ pharmacoepidemiology ■ safety ■ thrombin inhibitor ■ warfarin

Clinical Perspective on p 164

Dabigatran is a competitive direct thrombin inhibitor approved in the United States to reduce the risk of stroke and systemic embolization in patients with nonvalvular AF. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, patients with AF were randomized to dabigatran doses of 110 or 150 mg twice daily or adjusted-dose warfarin. At the dose subsequently approved in the United States (150 mg twice daily), dabigatran reduced the risk of stroke and intracranial hemorrhage and increased the risk of major gastrointestinal hemorrhage compared with warfarin. Although dabigatran...
has a favorable net clinical benefit compared with warfarin, it lacks a validated assay by which to monitor anticoagulation intensity, and there is no proven method of rapidly reversing its effect.

Given that AF primarily affects the elderly and that the safety profile of dabigatran may be different in general practice versus controlled trial settings, we compared the risk of stroke, major gastrointestinal and intracranial bleeding, acute myocardial infarction (AMI), and mortality in elderly Medicare beneficiaries with nonvalvular AF who initiated therapy with warfarin or dabigatran.

Methods

Study Population

Medicare provides health insurance coverage to ≈42 million persons aged ≥65 years as well as nearly 9 million persons aged <65 years with end-stage kidney disease or who are disabled. This study was restricted to the ≈21 million beneficiaries aged ≥65 years enrolled in fee-for-service Medicare Part A (hospitalization), Part B (office-based medical care), and Part D (prescription drugs) because claims from these sources were necessary for research purposes. For each beneficiary, we linked claims from all settings of care to create a longitudinal record of their health encounters, diagnoses, and drug prescriptions.

A new-user retrospective cohort design was used to compare patients initiating dabigatran or warfarin for the treatment of nonvalvular AF. We identified all patients with any inpatient or outpatient diagnoses of AF or atrial flutter based on International Classification of Diseases, Ninth Revision coding who also filled at least 1 prescription for either drug from October 19, 2010 (US dabigatran approval date) through December 31, 2012, the study end date. Patients were excluded if they had <6 months of enrollment in Medicare before their index dispensing, were aged <65 years, received prior treatment with a study medication or rivaroxaban or apixaban (anticoagulants approved during the study), were in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription. Patients were also excluded if they had a hospitalization that extended beyond the index dispensing date. Patients discharged from the hospital on the same day as their index dispensing were included. Patients undergoing dialysis and kidney transplant recipients were also excluded. Additionally, because warfarin is approved for indications other than AF, we excluded patients with diagnoses indicating the presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement surgery in the preceding 6 months.

Baseline Covariates and Cohort Follow-Up

Claims data on chronic medical conditions, cardiovascular risk factors, risk factors for bleeding events, and healthcare utilization were collected for each patient during the 6 months preceding their cohort-qualifying prescription fill. We also collected data on prescriptions for medications used for treatment of cardiovascular disease and other chronic medical conditions, as well as potentially interacting medications that might alter warfarin or dabigatran pharmacokinetics. Finally, to the extent possible using claims data, we calculated the CHADS2 score, which predicts the risk of stroke in patients with AF, and the HAS-BLED score, which predicts the risk of bleeding in patients with AF treated with warfarin.

To reduce confounding due to imbalance in study covariates, propensity score matching was used. Unconditional logistic regression was used to estimate the predicted probability of patients initiating dabigatran therapy given their sociodemographic characteristics, baseline medical comorbidities, medications used during the preceding 6 months, prescriber characteristics, and other potentially relevant variables (Table 1 and Table I in the online-only Data Supplement). Dabigatran users were propensity score matched to warfarin users in a 1:1 ratio with the use of a greedy matching algorithm. The balance of measured covariates between the matched cohorts was assessed with the standardized mean difference, a measure not influenced by sample size and thus useful for comparing cohorts in large observational studies. A standardized mean difference of ≥0.1 indicates a negligible difference in the measured variables between groups.

Follow-up began on the day after the first qualifying anticoagulant prescription fill and continued until disenrollment from Medicare, occurrence of a study outcome, a gap in anticoagulant days of supply >3 days, a prescription fill for a different anticoagulant, initiation of dialysis or kidney transplantation, admission to a skilled nursing facility or nursing home, transfer to hospice care, or the end of the study period, whichever came first. We chose a 3-day gap in anticoagulant therapy to increase the likelihood that patients were therapeutically anticoagulated given the short half-life of dabigatran, estimated at 14 hours. We censored patients for admission to a skilled nursing facility or nursing home because of concerns about incomplete capture of prescription fills and outcomes in these settings. We also censored patients transferred to hospice care because most deaths in these patients were expected and therefore unlikely to be related to anticoagulant use.

Study Outcomes

The primary outcomes were ischemic stroke, major bleeding with specific focus on intracranial and gastrointestinal bleeding, and AMI. Secondary outcomes were all hospitalized bleeding events and mortality. The International Classification of Diseases, Ninth Revision, Clinical Modification codes used to define these outcomes are listed in Table II in the online-only Data Supplement. The codes defining ischemic stroke have a positive predictive value (PPV) of 88% to 95%, and major bleeding was defined as a fatal bleeding event, a hospitalized bleeding event requiring transfusion, or hospitalization with hemorrhage into a critical site (ie, intracranial, intraspinal, intraarticular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome). Intracranial hemorrhage was defined with the use of codes for atraumatic hemorrhage, with a PPV of 89% to 97%, and codes for hemorrhage with closed head trauma, which have not been validated. We included these codes to capture situations in which a bleeding event preceded by a fall may have been coded as trauma related. The codes for gastrointestinal hemorrhage have a PPV of 86% to 88%, and those defining all hospitalized bleeding have a PPV of 89%. The codes for AMI have a PPV between 89% and 97% in a variety of administrative claims databases.

Out-of-hospital death occurring within 1 day of an emergency department visit for acute ischemic heart disease was also classified as an AMI. Death was ascertained by linkage to the Social Security Master Beneficiary Record database, which provides the date, but not cause, of death and captures >95% of deaths for US residents aged ≥65 years. Our death outcome included deaths not preceded by a study outcome plus deaths within 30 days after hospitalization for an outcome event.

Statistical Analysis

Analyses were performed on the propensity score–matched cohorts, thereby accounting for the potential confounding factors shown in Table 1 and in the online-only Data Supplement. Incidence rates were estimated with the use of event counts and exposure follow-up time. Kaplan–Meier plots were generated to characterize the contour of risk over time for each outcome. Cox proportional hazards regression was used to compare time to event in dabigatran compared with warfarin (reference) cohorts. Incidence rates and Cox models were also generated to examine risk during predefined intervals of time on therapy (1–90, 91–180, >180 days) because bleeding risks with warfarin may be greatest during the first 3 months after initiation.
Table 1. Sociodemographic Factors, Medical Conditions, and Medication Use at Baseline in Propensity Score–Matched Medicare Beneficiaries Initiating Dabigatran or Warfarin for Atrial Fibrillation, 2010–2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran, % (n=67207)</th>
<th>Warfarin, % (n=67207)</th>
<th>Standardized Mean Difference</th>
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Table 1. Continued

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<th>Warfarin, % (n=67207)</th>
<th>Standardized Mean Difference</th>
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Additional factors included in the propensity score model are shown in the online-only Data Supplement. ACEI/ARB indicates angiotensin converting-enzyme inhibitor/angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; and SSRI, selective serotonin reuptake inhibitor.

*The CHADS2 score assigns points for the presence of congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, stroke, or transient ischemic attack.11

†The HAS-BLED score assigns points for the presence of hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age ≥65 y, and antiplatelet drug or alcohol use.12,13 Labile international normalized ratio could not be determined from claims data and was excluded from our scoring.

‡Days supply of use overlapped with the date of first prescription for warfarin or dabigatran.
was determined with 95% confidence intervals and 2-tailed \( P \) values (\( P < 0.05 \)).

Subgroup analyses were performed in categories defined by age, sex, hospitalization within 30 days before anticoagulant initiation, and chronic kidney disease. We also examined subgroups with concomitant use of selective serotonin reuptake inhibitor antidepressants or prescription antipatelet agents at anticoagulant initiation because they may increase bleeding risks with anticoagulants. Finally, we examined outcome risk by dabigatran dose (150 or 75 mg twice daily). Lower-dose dabigatran (75 mg twice daily) was approved in the United States for patients with severe renal impairment (creatinine clearance \( 15–30 \) mL/min) on the basis of pharmacokinetic modeling.5

We performed sensitivity analyses using different definitions of cohort follow-up to assess whether the main analyses were affected by misclassification of exposed time. We did this by (1) restricting the analysis to patients with initial prescriptions of \( \leq 30 \) days' duration, (2) restricting the analysis to patients with at least 2 prescription fills of a study drug, and (3) increasing the gap allowance between anticoagulant prescriptions from 3 to 14 days.

This study was performed as part of the SafeRx Project, a joint initiative of the Centers for Medicare & Medicaid Services and the US Food and Drug Administration. It was approved by the Research in Human Subjects Committee of the Food and Drug Administration’s Center for Drug Evaluation and Research. Analyses were performed with the use of R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc, Cary, NC).

Results
A total of 67,494 dabigatran-treated and 273,920 warfarin-treated patients were eligible for study inclusion. Dabigatran users tended to be younger, were less likely to have chronic kidney disease, and were more likely to be treated by a cardiologist and to have received antiarrhythmics and prescription antipatelet agents. A propensity score match was obtained for 67,207 new dabigatran users (99.6%), resulting in cohorts closely balanced for all baseline covariates (Table I and Table I in the online-only Data Supplement). Dabigatran patients contributed 18,205 person-years of on-therapy follow-up time, and warfarin users contributed 19,382 person-years. Of note, 52.0% of dabigatran users and 50.2% of warfarin users filled only a single prescription of their anticoagulant.

During follow-up, there were 2,715 primary outcome events including 475 ischemic strokes, 1,628 major bleeding events, and 612 AMIs. Compared with warfarin, dabigatran use was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality and with an increased risk of major gastrointestinal bleeding (Table 2). There were no differences between cohorts in risk of AMI or all hospitalized bleeding events. The absolute incidence rates of ischemic stroke, major gastrointestinal bleeding, intracranial hemorrhage, and death were substantially higher during the first 90 days of therapy than during later time periods for both dabigatran and warfarin (Figure I in the online-only Data Supplement). However, the point estimates of the hazard ratios did not vary substantively over intervals of 1 to 90, 91 to 180, or \( >180 \) days of continuous anticoagulant use, although the confidence intervals widened because of lower numbers of events in the later intervals (Table III in the online-only Data Supplement). Kaplan–Meier plots showed early separation of survival curves for ischemic stroke with slightly later separation for intracranial hemorrhage, major gastrointestinal bleeding, and death (Figure).

Subgroup analyses stratified by age and sex showed that risk of major gastrointestinal bleeding with dabigatran was increased for women aged \( \geq 75 \) years and for men age \( \geq 85 \) years compared with warfarin (Table 3 and Tables IV and V in the online-only Data Supplement). Below these ages, gastrointestinal bleeding risk was comparable for both anticoagulants. The point estimate for the risk of death with dabigatran compared with warfarin was reduced in all strata except women aged \( \geq 85 \) years, where it was increased compared with younger women (\( P_{interaction} = 0.004 \)). There were no interactions for ischemic stroke or intracranial hemorrhage. Results in other subgroups defined by chronic kidney disease, use of prescription antiplatelet agents or selective serotonin reuptake inhibitors antidepressants, or hospitalization in the 30 days before anticoagulant use was started were similar to results in the main analysis.

The magnitude of effect for each outcome was greater in the subgroup treated with dabigatran 150 mg twice daily compared with the main analysis, which included patients treated with the 150- and 75-mg doses (Table 4 and Table VI in the online-only Data Supplement). Approximately 16% of patients received dabigatran 75 mg twice daily, and among these, none of the outcome comparisons were statistically significantly different from warfarin except for a lower risk of intracranial hemorrhage with dabigatran (Table 4). Only 33% of patients treated with the lower dose of dabigatran had a diagnosis of chronic kidney disease within the preceding 6 months, and, of these, coding explicitly indicated severe renal impairment in only 20%. Lower-dose recipients were more likely to be older, to be receiving home healthcare or home oxygen, and to have higher CHADS2, and HAS-BLED scores (Table VII in the online-only Data Supplement). Sensitivity analyses yielded results similar to those of the primary analysis.

Discussion
In a large cohort of elderly Medicare beneficiaries with nonvalvular AF, risk of ischemic stroke, intracranial hemorrhage, and mortality was reduced and risk of major gastrointestinal bleeding was increased in patients treated with dabigatran compared with warfarin. The levels of risk were similar in direction and magnitude to those observed in the randomized trial RE-LY, in which dabigatran 150 mg twice daily was compared with adjusted-dose warfarin therapy.6 The absolute incidence of outcome events for both dabigatran and warfarin was greatest during the first 90 days of treatment, although the hazard ratios for these outcomes were constant over time. Our results for gastrointestinal bleeding differed from those of a Mini-Sentinel Modular Program analysis that found a 2-fold increase in incidence for warfarin compared with dabigatran.30 Modular programs were unadjusted for any confounding factors and included substantial numbers of younger patients, in whom bleeding risks may be lower. Our results also differed from those of 2 small observational studies from Denmark. In the first, no difference in thromboembolic or hospitalized bleeding risk
was noted in 765 new users of dabigatran compared with warfarin. In the second study, no difference in stroke or gastrointestinal bleeding risk was noted in 2239 patients initiating dabigatran compared with warfarin.

In our study, the increased risk of major gastrointestinal bleeding with dabigatran appeared to be restricted to women aged ≥75 years and to men aged ≥85 years. The beneficial effect of dabigatran on mortality was not present in women.

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score-Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>No. of Events</th>
<th>Incidence Rate per 1000 Person-Years</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Primary outcomes</td>
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<td></td>
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<td></td>
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<tr>
<td>Ischemic stroke</td>
<td>205/270</td>
<td>11.3/13.9</td>
<td>0.80 (0.67–0.96)</td>
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<td>Major hemorrhage</td>
<td>777/851</td>
<td>42.7/43.9</td>
<td>0.97 (0.88–1.07)</td>
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<td>Gastrointestinal</td>
<td>623/513</td>
<td>34.2/26.5</td>
<td>1.28 (1.14–1.44)</td>
<td>&lt;0.001</td>
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<tr>
<td>Intracranial</td>
<td>60/186</td>
<td>3.3/9.6</td>
<td>0.34 (0.26–0.46)</td>
<td>&lt;0.001</td>
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<tr>
<td>Intracerebral</td>
<td>44/142</td>
<td>2.4/7.3</td>
<td>0.33 (0.24–0.47)</td>
<td>&lt;0.001</td>
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<tr>
<td>Acute myocardial infarction</td>
<td>285/327</td>
<td>15.7/16.9</td>
<td>0.92 (0.78–1.08)</td>
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<tr>
<td>Secondary outcomes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalized bleeds</td>
<td>1079/1139</td>
<td>59.3/58.8</td>
<td>1.00 (0.92–1.09)</td>
<td>0.97</td>
</tr>
<tr>
<td>Mortality*</td>
<td>603/744</td>
<td>32.6/37.8</td>
<td>0.86 (0.77–0.96)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% confidence interval [CI]) was 0.89 (0.79–1.00; P=0.051), whereas for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98; P=0.03).
Ischemic stroke reported. In RE-LY, and analyses of age and mortality were not presented. The number of women aged ≥85 years than in other age/sex groups. Although many subgroups were examined in this analysis, it should be noted that in RE-LY, an interaction was observed that the benefit/risk profile of dabigatran may be less favorable in women aged ≥85 years, in whom there was a trend for a higher risk of death with dabigatran compared with warfarin. This shift in hazard ratio between younger and older women represented a statistically significant interaction and suggests that the benefit/risk profile of dabigatran may be less favorable in women aged ≥85 years than in other age/sex groups. Although many subgroups were examined in this analysis, it should be noted that in RE-LY, an interaction was observed between treatment and age for major gastrointestinal bleeding but not stroke or intracranial hemorrhage, similar to our findings here.33,34 The number of women aged ≥85 years was small in RE-LY, and analyses of age and mortality were not reported. Of note, the 75-mg dose of dabigatran was approved for use in patients with severe renal impairment on the basis of pharmacokinetic modeling rather than a randomized trial in patients. Our study represents the largest examination of the clinical effect of dabigatran 75 mg twice daily. Although we lacked laboratory data on creatinine clearance and are uncertain of the accuracy of kidney disease coding, our results suggest that many patients treated with this lower dose may not have had severe renal impairment, in which case, on the basis of current product labeling, they should have been treated with the 150-mg dose. In the setting of moderate, mild, or no renal impairment, off-label use of the 75-mg dose might result in patients being underdosed and could explain why we found no difference in risk of ischemic stroke, major gastrointestinal bleeding, or mortality between warfarin and the lower dose of dabigatran. On the other hand, if most of the patients treated with the 75-mg dose actually had severe renal impairment, this would suggest that dabigatran dosing based on pharmacokinetic modeling was suboptimal. This raises the question of whether patients treated off-label with the 75-mg dose would have experienced improved outcomes for ischemic stroke and mortality had they been treated with the 150-mg dose instead. We cannot answer this question with certainty because our comparison across dose levels was indirect and was not based on a head-to-head analysis. Of possible relevance here, the RE-LY trial suggested that a 110-mg twice daily dose of dabigatran was less effective than the 150-mg dose, and, as a result, this lower dose was not approved for marketing in the United States.

This study had several limitations. It was observational and may be subject to confounding from factors not adjusted for in the analysis, such as over-the-counter aspirin or nonsteroidal anti-inflammatory drug use. To reduce this possibility, we included an extensive number of variables in our propensity score model, including prescription antiplatelet agents, and a close balance for these factors was achieved. Nonetheless, residual confounding by unmeasured factors cannot be excluded. Medicare data do not capture laboratory results, and therefore we had no basis on which to assess the quality of warfarin anticoagulation. It is possible that the favorable effects of dabigatran on ischemic stroke and mortality and its adverse effect on major gastrointestinal bleeding in our study were at least partly due to low time in the therapeutic range. Of note, the 75-mg dose of dabigatran was approved for use in patients with severe renal impairment on the basis of pharmacokinetic modeling rather than a randomized trial in patients. Our study represents the largest examination of the clinical effect of dabigatran 75 mg twice daily. Although we lacked laboratory data on creatinine clearance and are uncertain of the accuracy of kidney disease coding, our results suggest that many patients treated with this lower dose may not have had severe renal impairment, in which case, on the basis of current product labeling, they should have been treated with the 150-mg dose. In the setting of moderate, mild, or no renal impairment, off-label use of the 75-mg dose might result in patients being underdosed and could explain why we found no difference in risk of ischemic stroke, major gastrointestinal bleeding, or mortality between warfarin and the lower dose of dabigatran. On the other hand, if most of the patients treated with the 75-mg dose actually had severe renal impairment, this would suggest that dabigatran dosing based on pharmacokinetic modeling was suboptimal. This raises the question of whether patients treated off-label with the 75-mg dose would have experienced improved outcomes for ischemic stroke and mortality had they been treated with the 150-mg dose instead. We cannot answer this question with certainty because our comparison across dose levels was indirect and was not based on a head-to-head analysis. Of possible relevance here, the RE-LY trial suggested that a 110-mg twice daily dose of dabigatran was less effective than the 150-mg dose, and, as a result, this lower dose was not approved for marketing in the United States.

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with warfarin. However, this would not explain the reduced risk of intracranial hemorrhage with dabigatran. More importantly, whether warfarin management in our study was or was not adequate, it reflects the quality of anticoagulation likely to be experienced by patients treated with warfarin in the general practice setting in the United States. In that context, our study results suggest that dabigatran is associated with generally better patient outcomes. In addition, >50% of patients in each cohort received only a single prescription of their study anticoagulant. This represents the ambulatory care experience in Medicare. However, the constancy of hazard ratios in the time period beyond 180 days of use and the results of our sensitivity analysis restricted to patients receiving ≥2 prescriptions suggest that bias was not introduced by this limited persistence of use.

In summary, in elderly Medicare beneficiaries with non-valvular AF, dabigatran was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality and an increased risk of major gastrointestinal bleeding compared with warfarin. These associations were strongest for the 150-mg dabigatran dose, whereas the 75-mg dose was associated only with a reduced risk of intracranial hemorrhage.

Acknowledgments
The authors are employees or contractors of the Centers for Medicare & Medicaid Services or the US Food and Drug Administration; however, other officials at the Centers for Medicare & Medicaid Services and the US Food and Drug Administration had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. The manuscript was subject to administrative review before submission, but the content was not altered by this review. The views expressed are those of the authors and not necessarily those of the Department of Health and Human Services, the Centers for Medicare and Medicaid Services and the US Food and Drug Administration. Dr Macurdy had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures
None.

References
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Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, Marsha E. Reichman, Michael Wernecke, Rongmei Zhang, Mary Ross Southworth, Mark Levenson, Ting-Chang Sheu, Katrina Mott, Margie R. Goulding, Monika Houstoun, Thomas E. MaCurdy, Chris Worrall and Jeffrey A. Kelman

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### SUPPLEMENTAL MATERIAL

Table 1. Distribution of additional baseline sociodemographic and medical factors in propensity score matched Medicare beneficiaries initiating dabigatran or warfarin for atrial fibrillation from 2010-2012.

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Dabigatran (n=67,207)</th>
<th>Warfarin (n=67,207)</th>
<th>Standardized mean difference</th>
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<td>21</td>
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<td>Geographic region</td>
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<td>8</td>
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<tr>
<td>Chronic liver disease</td>
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<tr>
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<td>20</td>
<td>0.01</td>
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<td>Hospitalizations in past 31-183 days (n)</td>
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Table 2. International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) codes used to define study outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICD-9 Codes</th>
<th>Position</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>410 (all)</td>
<td>1st or 2nd</td>
<td>IP only</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>433.x1, 434.x (except subcode: x0), 436</td>
<td>1st</td>
<td>IP only</td>
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<tr>
<td>All bleeding events</td>
<td>A bleeding event is defined as a definite bleeding code, or a possible bleeding code (primary) supported by a definite bleeding code (secondary); without a corresponding trauma (as defined in Cunningham et al*)</td>
<td>1st</td>
<td>IP only</td>
</tr>
<tr>
<td></td>
<td>Definite bleeding: 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 455.8, 456.0, 456.20, 530.7, 530.82, 578.0, 455.2, 455.6, 455.8, 562.02, 562.60, 562.12, 562.13, 568.81, 569.3, 569.85, 578.1, 578.9, 593.81, 599.7, 623.8, 626.2, 626.6, 430, 431, 432, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0, 423.0, 459.0, 568.81, 719.1x, 784.7, 784.8, 786.3</td>
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<td></td>
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<td>Possible bleeding: 531.1, 531.3, 531.5, 531.7, 531.9, 532.1, 532.3, 532.5, 532.7, 532.9, 533.1, 533.3, 533.5, 533.7, 533.9, 534.1, 534.3, 534.5, 534.7, 534.9, 535.00, 535.10, 535.20, 535.30, 535.40, 535.50, 535.60, 455.x, 562.00, 562.01, 562.10, 562.11, 530.1, 280.0, 285.1, 285.9, 790.92</td>
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<td>Major bleeding events</td>
<td>Major bleeding is defined as a bleeding event with (i) a critical site code, (ii) a transfusion, or (iii) death, as described in Cunningham et al.</td>
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<tr>
<td></td>
<td>Critical site: 430, 431, 432, 852.0, 852.2, 852.4, 853.0, 336.1, 363.6, 372.72, 376.32, 377.42, 379.23, 719.1, 729.92, 729.97, 423.0, 593.81, 772.5, 866.01, 866.02, 866.11, 866.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transfusions: a) ICD-9 PRC: 9903, 9904, 9905, 9906, 9907, 9909, b) HCPC: P9010, P9011, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031-P9040, P9044, P9051 - P9060, c) Revenue Center Codes: 0380-0392, 0399, d) Additional Value Codes: 37, 38, 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major GI bleeding events</td>
<td><strong>Major GI bleeding is defined as a major bleeding event at a GI site</strong></td>
<td>N/A</td>
<td>IP only</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>430, 431, 432, 852.0, 852.2, 852.4, 853.0</td>
<td>1st</td>
<td>IP only</td>
</tr>
</tbody>
</table>

*Adapted from Cunningham AW, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database definition for serious bleeding due to oral anticoagulant use. Pharmacoepidemiol Drug Saf 2011; 20:560-66
Table 3. Adjusted hazard ratios with 95% confidence intervals by intervals of follow-up during continuous use in propensity score matched new user cohorts of dabigatran and warfarin treated for non-valvular atrial fibrillation. Warfarin served as the reference group. This was a combined dose analysis that included patients treated with dabigatran 150 mg or 75 mg twice daily.

<table>
<thead>
<tr>
<th></th>
<th>1-90 days</th>
<th>91-180 days</th>
<th>≥ 181 days</th>
<th>≥ 91 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.82 (0.67-1.00)</td>
<td>0.72 (0.42-1.22)</td>
<td>0.82 (0.44-1.54)</td>
<td>0.76 (0.51-1.14)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.31 (1.14-1.50)</td>
<td>1.13 (0.84-1.52)</td>
<td>1.37 (0.92-2.02)</td>
<td>1.21 (0.96-1.54)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.34 (0.24-0.48)</td>
<td>0.42 (0.22-0.83)</td>
<td>0.29 (0.14-0.62)</td>
<td>0.36 (0.22-0.59)</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>0.31 (0.20-0.48)</td>
<td>0.48 (0.24-0.99)</td>
<td>0.26 (0.10-0.63)</td>
<td>0.37 (0.21-0.64)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.96 (0.80-1.15)</td>
<td>0.96 (0.61-1.51)</td>
<td>0.63 (0.38-1.05)</td>
<td>0.80 (0.57-1.12)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalized bleeds</td>
<td>1.04 (0.94-1.14)</td>
<td>0.88 (0.71-1.10)</td>
<td>0.92 (0.71-1.19)</td>
<td>0.90 (0.76-1.06)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.89 (0.79-1.01)</td>
<td>0.81 (0.60-1.10)</td>
<td>0.73 (0.53-0.99)</td>
<td>0.77 (0.62-0.96)</td>
</tr>
</tbody>
</table>
### Table 4. Incidence rates and event counts for selected outcomes in the dabigatran cohort, stratified by age and gender.

<table>
<thead>
<tr>
<th>Age-group (n)</th>
<th>Men Dabigatran incidence rate per 1,000 years (#events)</th>
<th>Women Dabigatran incidence rate per 1,000 years (#events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,999)</td>
<td>5.9 (26)</td>
<td>9.5 (30)</td>
</tr>
<tr>
<td>75-84 (28,563)</td>
<td>11.1 (39)</td>
<td>14.4 (62)</td>
</tr>
<tr>
<td>≥ 85 (10,645)</td>
<td>13.2 (12)</td>
<td>18.9 (62)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,999)</td>
<td>2.0 (9)</td>
<td>0.9 (3)</td>
</tr>
<tr>
<td>75-84 (28,563)</td>
<td>3.4 (12)</td>
<td>5.4 (23)</td>
</tr>
<tr>
<td>≥ 85 (10,645)</td>
<td>5.5 (5)</td>
<td>4.2 (8)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,999)</td>
<td>15.2 (67)</td>
<td>22.4 (71)</td>
</tr>
<tr>
<td>75-84 (28,563)</td>
<td>33.2 (117)</td>
<td>42.1 (181)</td>
</tr>
<tr>
<td>≥ 85 (10,645)</td>
<td>62.7 (57)</td>
<td>68.4 (130)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,999)</td>
<td>23.1 (103)</td>
<td>19.6 (63)</td>
</tr>
<tr>
<td>75-84 (28,563)</td>
<td>34.0 (122)</td>
<td>29.0 (127)</td>
</tr>
<tr>
<td>≥ 85 (10,645)</td>
<td>57.1 (53)</td>
<td>69.5 (135)</td>
</tr>
</tbody>
</table>

### Table 5. Incidence rates and event counts for selected outcomes in the warfarin cohort, stratified by age and gender.

<table>
<thead>
<tr>
<th>Age-group (n)</th>
<th>Men Warfarin incidence rate per 1,000 years (#events)</th>
<th>Women Warfarin incidence rate per 1,000 years (#events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,762)</td>
<td>8.3 (39)</td>
<td>11.6 (40)</td>
</tr>
<tr>
<td>75-84 (28,782)</td>
<td>11.5 (44)</td>
<td>16.0 (72)</td>
</tr>
<tr>
<td>≥ 85 (10,663)</td>
<td>15.0 (15)</td>
<td>32.0 (60)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,762)</td>
<td>6.4 (30)</td>
<td>7.2 (25)</td>
</tr>
<tr>
<td>75-84 (28,782)</td>
<td>12.8 (49)</td>
<td>9.1 (41)</td>
</tr>
<tr>
<td>≥ 85 (10,663)</td>
<td>11.0 (11)</td>
<td>16.0 (30)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,762)</td>
<td>17.8 (84)</td>
<td>22.6 (78)</td>
</tr>
<tr>
<td>75-84 (28,782)</td>
<td>32.1 (123)</td>
<td>28.2 (127)</td>
</tr>
<tr>
<td>≥ 85 (10,663)</td>
<td>41.1 (41)</td>
<td>32.0 (60)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 (27,762)</td>
<td>28.0 (134)</td>
<td>27.1 (95)</td>
</tr>
<tr>
<td>75-84 (28,782)</td>
<td>46.7 (182)</td>
<td>35.4 (162)</td>
</tr>
<tr>
<td>≥ 85 (10,663)</td>
<td>62.0 (63)</td>
<td>56.4 (108)</td>
</tr>
</tbody>
</table>
Table 6. Adjusted hazard ratios with 95% confidence intervals by intervals of follow-up during continuous use in propensity score matched new user cohorts of dabigatran and warfarin treated for non-valvular atrial fibrillation. Warfarin served as the reference group. Analysis restricted to patients treated with dabigatran 150 mg twice daily.

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>1-90 days</th>
<th>91-180 days</th>
<th>≥ 181 days</th>
<th>≥ 91 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.70 (0.56-0.88)</td>
<td>0.76 (0.40-1.45)</td>
<td>0.56 (0.28-1.15)</td>
<td>0.66 (0.41-1.07)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>1.51 (1.30-1.76)</td>
<td>1.60 (1.12-2.29)</td>
<td>1.35 (0.86-2.11)</td>
<td>1.50 (1.13-1.98)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.30 (0.20-0.44)</td>
<td>0.37 (0.15-0.95)</td>
<td>0.26 (0.11-0.61)</td>
<td>0.30 (0.16-0.57)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.28 (0.17-0.46)</td>
<td>0.35 (0.13-0.95)</td>
<td>0.16 (0.06-0.47)</td>
<td>0.23 (0.11-0.48)</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>0.88 (0.71-1.08)</td>
<td>0.92 (0.55-1.55)</td>
<td>0.55 (0.31-0.97)</td>
<td>0.72 (0.49-1.06)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.13 (1.01-1.26)</td>
<td>1.06 (0.82-1.36)</td>
<td>0.93 (0.69-1.26)</td>
<td>1.00 (0.83-1.22)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalized bleeds</td>
<td>0.80 (0.69-0.93)</td>
<td>0.64 (0.46-0.90)</td>
<td>0.64 (0.44-0.92)</td>
<td>0.64 (0.50-0.82)</td>
</tr>
</tbody>
</table>

Table 7. Comparison of selected demographic and baseline medical characteristics of elderly Medicare patients treated with dabigatran 75 mg or 150 mg twice daily for non-valvular atrial fibrillation.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 75 mg (%; n=10,522)</th>
<th>Dabigatran 150 mg (%; n=56,576)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 85 years</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>COPD</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Home health care</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Home oxygen use</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>CHADS$_2$ ≥ 4</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>HAS-BLED ≥ 4</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>
Figure 1. Incidence rates of ischemic stroke, major gastrointestinal bleeding, intracranial hemorrhage, and mortality by time-period of follow-up in patients treated with dabigatran and warfarin. Days 1-90 ( ), days 91-180 ( ), days >180 ( ).
Riesgos cardiovasculares, de hemorragias y de mortalidad en pacientes de edad avanzada con seguro médico estatal Medicare tratados con dabigatran o warfarina para fibrilación auricular no valvular

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PharmD, MPH; Thomas E. MaCurdy, PhD; Chris Worrell, BS; Jeffrey A. Kelman, MD, MMSc

Antecedentes — Aún no se ha establecido la seguridad comparativa de dabigatran con relación a warfarina para el tratamiento de fibrilación auricular no valvular en pacientes de edad avanzada.

Métodos y resultados — Formamos cohortes de nuevos usuarios con pacientes de edad avanzada ajustados por puntuación de propensión inscriptos en Medicare que comenzaron con dabigatran o warfarina para el tratamiento de fibrilación auricular no valvular entre octubre de 2010 y diciembre de 2012. En 134 414 pacientes con 37 587 personas/años de seguimiento, hubo 2715 resultados primarios. Los hazard ratios (intervalos de confianza de 95%) al comparar dabigatran con warfarina (referencia) fueron los siguientes: accidente cerebrovascular isquémico: 0,80 (0,67–0,96); hemorragia intracraneal: 0,34 (0,26–0,46); hemorragia gastrointestinal grave: 1,28 (1,14–1,44); infarto agudo de miocardio: 0,92 (0,78–1,08) y muerte: 0,86 (0,77–0,96). En el subgrupo tratado con dabigatran 75 mg dos veces al día, no hubo diferencia en el riesgo comparado con warfarina para ninguno de los resultados excepto hemorragia intracraneal; en este caso el riesgo de dabigatran se redujo. La mayoría de los pacientes tratados con dabigatran 75 mg dos veces al día no presentaron insuficiencia renal grave, la población destinataria para esta dosis. En el subgrupo de dabigatran 150 mg dos veces al día, la magnitud del efecto para cada resultado fue mayor que en el análisis de dosis combinadas.

Conclusiones — En la práctica clínica, dabigatran se asoció con un menor riesgo de accidente cerebrovascular isquémico, hemorragia intracraneal y muerte, y con un mayor riesgo de hemorragia gastrointestinal grave comparado con warfarina en pacientes de edad avanzada con fibrilación auricular no valvular. Estas asociaciones fueron más pronunciadas en pacientes tratados con dabigatran 75 mg dos veces al día, mientras que la asociación de 75 mg dos veces al día con resultados de estudios fue imperceptible para warfarina excepto por un menor riesgo de hemorragia intracraneal con dabigatran.

(Circulation. 2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.)

Palabras clave: anticoagulante ■ farmacoepidemiología ■ seguridad ■ inhibidor de trombina ■ warfarina

L a warfarina, un antagonista de la vitamina K, es un anticoagulante comúnmente usado en pacientes con fibrilación auricular (FA). Los meta-análisis de ensayos clínicos aleatorizados han demostrado que reduce el riesgo de accidente cerebrovascular embólico en 40% a 80% y de mortalidad en ≈30%, pero también duplica el riesgo de hemorragia intracraneal y aumenta el riesgo de hemorragia extracraneal en alrededor de 66%.1-3 Puede ser difícil mantener a los pacientes en el rango terapéutico (índice internacional normalizado de 2-3). Un meta-análisis halló que los pacientes tratados con warfarina se encontraban dentro del rango terapéutico 61% del tiempo.4 En este estudio, un índice internacional normalizado < 2 se asoció con un aumento 5 veces mayor en riesgo de accidente cerebrovascular, y un índice internacional normalizado > 3 se asoció con un aumento 3 veces mayor en el riesgo de hemorragias.4
Dabigatran es un inhibidor competitivo directo de trombina aprobado en los Estados Unidos para reducir el riesgo de accidente cerebrovascular y embolización sistémica en pacientes con FA no valvular. En el ensayo clínico Evaluación Aleatorizada de Terapia Anticoagulante a Largo Plazo (RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy), los pacientes con FA fueron aleatorizados para recibir dosis de dabigatran de 110 o 150 mg dos veces al día o dosis ajustadas de warfarina. Con la dosis posteriormente aprobada en los Estados Unidos (150 mg dos veces al día), dabigatran redujo el riesgo de accidente cerebrovascular y hemorragia intracraneal, y aumentó el riesgo de hemorragia gastrointestinal grave comparado con warfarina. Aunque dabigatran presenta un beneficio clínico neto favorable comparado con warfarina, carece de un ensayo validado para revertir rápidamente su efecto.

Dado que la FA afecta principalmente a personas de edad avanzada y que el perfil de seguridad de dabigatran sería diferente en la práctica clínica comparado con ensayos clínicos controlados, comparamos el riesgo de accidente cerebrovascular, hemorragia gastrointestinal grave y hemorragia intracraneal, infarto agudo de miocardio (IAM) y mortalidad en beneficiarios de Medicare de edad avanzada con FA no valvular que comenzaron el tratamiento con warfarina o dabigatran.

Métodos

Población del estudio

Medicare proporciona cobertura de seguro médico a ≈42 millones de personas ≥ 65 años de edad y a alrededor de 9 millones de personas < 65 años de edad con enfermedad renal en etapa terminal o que se encuentran discapacitadas. Este estudio se limitó a los ≥21 millones de beneficiarios ≥ 65 años de edad inscriptos en el sistema de pago por servicios de Medicare Parte A (hospitalización), Parte B (atención médica en consultorios) y Parte D (fármacos de venta bajo receta) ya que las declaraciones de estas fuentes eran necesarias a los efectos de la investigación. Para cada beneficiario, relacionamos las declaraciones de todos los ámbitos de atención para crear un registro longitudinal de sus encuentros en el ámbito de la salud, diagnósticos y prescripciones de fármacos.

Se usó un diseño de cohorte retrospectiva de nuevos usuarios para comparar pacientes que comenzaban con dabigatran o warfarina para el tratamiento de FA no valvular. Identificamos a todos los pacientes hospitalizados o ambulatorios con algún diagnóstico de FA o aletcea auricular según la codificación de la Clasificación Internacional de Enfermedades, Novena Revisión que también completaran al menos 1 prescripción para cualquiera de los fármacos desde el 19 de octubre de 2010 (fecha de aprobación de dabigatran en Estados Unidos de América) hasta el 31 de diciembre de 2012, fecha de finalización del estudio. Los pacientes eran excluidos si tenían < 6 meses de inscripción en Medicare antes de la dispensación de su tratamiento, si eran menores de 65 años, si habían recibido tratamiento previo con alguno de los medicamentos del estudio o rivaroxaban o apixaban (anticoagulantes aprobados durante el estudio), si se encontraban en un centro de enfermería especializada u hogar de ancianos, o si estaban recibiendo cuidados paliativos en la fecha de la prescripción de su clasificación en la cohorte. Los pacientes también eran excluidos si tenían una hospitalización que se extendía más allá de la fecha de dispensación del tratamiento. Los pacientes dados de alta del hospital en la misma fecha que su dispensación inicial del tratamiento fueron incluidos en el estudio. Los pacientes en diálisis y receptores de trasplante de riñón también fueron excluidos. Además, debido a que warfarina está aprobada para otras indicaciones además de FA, excluimos pacientes con diagnósticos que indicaban la presencia de enfermedad de válvula mitral, reparación o reemplazo de válvula cardíaca, trombosis venosa profunda, embolia pulmonar o cirugía de reemplazo articular en los 6 meses previos.

Covariables basales y seguimiento de la cohorte

Los datos de las declaraciones sobre condiciones médicas crónicas, factores de riesgo cardiovascular, factores de riesgo para hemorragias y utilización de atención sanitaria fueron recopilados para cada paciente durante los 6 meses previos a que se los asignara en cada cohorte. También recopilamos datos sobre prescripciones para medicamentos usados para el tratamiento de enfermedad cardiovascular y otras afecciones médicas crónicas, y también medicamentos con potencial interacción que alterarían la farmacocinética de warfarina o dabigatran. Por último, en la medida en que fuera posible usar los datos de las declaraciones, calculamos la puntuación CHADS <sub>2</sub>, que pronostica el riesgo de accidente cerebrovascular en pacientes con FA, y la puntuación HAS-BLED, que pronostica el riesgo de hemorragia en pacientes con FA tratados con warfarina.

Para reducir factores de confusión debidos al desequilibrio en covariables de estudios, se usó ajuste de puntuación de propensión. Se usó regresión logística no condicional para estimar la probabilidad pronosticada de pacientes que comenzaban con terapia con dabigatran dadas sus características sociodemográficas, comorbilidades médicas basales, medicamentos usados durante los 6 meses previos, características de los prescriptores y otras variables potencialmente relevantes (Tabla 1 y Tabla I del Suplemento de Datos solamente online). A los usuarios de dabigatran se les realizó ajuste de puntuación de propensión con respecto a los usuarios de warfarina en una proporción 1:1 con el uso de un algoritmo de coincidencia exigente. El equilibrio de covariables medidas entre las cohortes ajustadas fue evaluado con la diferencia promedio estandarizada, una medida no influenciada por el tamaño de la muestra y, por lo tanto, útil para comparar cohortes en estudios observacionales amplios. El seguimiento comenzó el día después de la primera prescripción clasificada del anticoagulante y continuó hasta la baja de Medicare, la aparición de un resultado en el estudio, una brecha en días del anticoagulante de suministro > 3 días, una prescripción para un anticoagulante diferente, el inicio de diálisis o trasplante de riñón, admisión a un centro de enfermería especializada u hogar de ancianos, transferencia a cuidados paliativos o la finalización del período de estudio, lo que ocurriera primero. Elegimos una brecha de 3 días en terapia anticoagulante para aumentar la posibilidad de que los pacientes estuvieran terapéuticamente anticoagulados dada la vida media corta de dabigatran, estimada en 14 horas. Excluimos pacientes para admisión en centros de enfermería especializada u hogar de ancianos debido a una posible recopilación incompleta de prescripciones y resultados en estos ámbitos. También excluimos pacientes transferidos a cuidados paliativos debido a que en estos pacientes se esperaba la mayoría de las muertes y, en consecuencia, era improbable que estuvieran relacionadas con el uso de anticoagulantes.

Resultados del estudio

Los resultados primarios fueron accidente cerebrovascular isquémico, hemorragia grave con foco específico en hemorragia intracraneal y gastrointestinal, e IAM. Todos los resultados secundarios fueron hemorragias en internación y mortalidad. Los códigos de la Clasificación Internacional de Enfermedades, Novena Revisión, Modificación...
Tabla 1. Factores sociodemográficos, afecciones médicas y uso de medicamentos a nivel basal en beneficiarios de Medicare con ajuste de puntuación de propensión que comenzaron con dabigatran o warfarina para fibrilación auricular, 2010–2012

<table>
<thead>
<tr>
<th>Característica</th>
<th>Dabigatran, % (n = 67)</th>
<th>Warfarina, % (n = 67)</th>
<th>Diferencia promedio estandarizada</th>
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<tr>
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<tr>
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<td>Últimos 1–30 d</td>
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<tr>
<td>Accidente cerebrovascular</td>
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<td></td>
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</tr>
<tr>
<td>Últimos 1–30 d</td>
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<td>2</td>
<td>0,00</td>
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<tr>
<td>Últimos 31–183 d</td>
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<td>0,00</td>
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<tr>
<td>Otra enfermedad cerebrovascular</td>
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<td>Ataque isquémico transitorio</td>
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<td>Uso de caminador (walker)</td>
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<tr>
<td>Puntuación CHADS₂*</td>
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</tbody>
</table>

Los factores adicionales incluidos en el modelo de puntuación de propensión se muestran en el Suplemento de Datos solamente online. *La puntuación de CHADS₂ asigna puntos por la presencia de insuficiencia cardíaca congestiva, hipertensión, edad ≥ 75 años, diabetes mellitus, accidente cerebrovascular o ataque isquémico transitorio.  
†La puntuación de HAS-BLED asigna puntos por la presencia de hipertensión, funciones renal o hepática anormales, accidente cerebrovascular, antecedentes de hemorragia, índice internacional normalizado de la coagulación, edad ≥ 65 años y uso de fármacos antiplaquetarios o consumo de alcohol.  
‡Cobertura del uso superpuesto con la fecha de la primera prescripción para warfarina o dabigatran.
Clinica usados para definir estos resultados se enumeran en la Tabla II del Suplemento de Datos solamente online. Los códigos que definen accidente cerebrovascular isquémico tienen un valor pronóstico positivo (VPP) de 88% a 95%. Hemorragia grave se definió como un evento hemorrágico fatal, un evento hemorrágico en internación que requirió transfusión, u hospitalización con hemorragia en un sitio crítico (es decir, intracraneal, intraespinal, intra-articular, intracocular, pericárdica, retroperitoneal o intramuscular con síndrome compartimental). Hemorragia intracraneal se definió con el uso de códigos para hemorragia no traumática, con un VPP de 89% a 97%. Los códigos para hemorragia con trauma craneal cerrado, que no han sido validados. Incluimos estos códigos para capturar situaciones en las que una hemorragia precedida por una caída habría sido codificada como relacionada con el traumatismo. Los códigos para hemorragia gastrointestinal tienen un VPP de 86% a 88%. Los códigos que definen todas las hemorragias en internación tienen un VPP de 89%. Los códigos para IAM tienen un VPP entre 89% y 97% en varias bases de datos de declaraciones administrativas. La muerte fuera del hospital que ocurriera dentro del lapso de 1 día de una visita al departamento de emergencias por enfermedad cardiaca isquémica aguda fue también clasificada como un IAM. La muerte fue determinada por la condición con la base de datos del Registro Principal de Beneficiarios de Seguridad Social, que proporciona la fecha, pero no la causa, de la muerte y capta > 95% de las muertes para los residentes de Estados Unidos mayores de 65 años de edad. Nuestro resultado relacionado con las muertes incluyó muertes no precedidas por un resultado del estudio más muertes dentro de los 30 días posteriores a la hospitalización para un resultado.

Análisis estadístico

Los análisis fueron realizados sobre las cohortes con ajuste de puntuación de propensión, justificando por lo tanto los factores de confusión potenciales que se enumeran en la Tabla I y en el Suplemento de Datos solamente online. Los índices de incidencia fueron estimados con el uso de recuentos de eventos y tiempo de exposición del seguimiento. Se generaron gráficos de Kaplan-Meier para caracterizar el perfil de riesgo con el transcurso del tiempo para cada resultado. Se usó la regresión de riesgos proporcionales de Cox para comparar tiempo con evento en las cohortes de dabigatran comparado con warfarina (referencia). Los índices de incidencia y los modelos de Cox también se generaron para evaluar el riesgo durante intervalos predefinidos de tiempo en tratamiento (1–90, 91–180, > 180 días) debido a que los riesgos de hemorragias con warfarina serían mayores durante los primeros 3 meses posteriores al inicio. La importancia estadística se determinó con intervalos de confianza del 95% y valores P bilaterales (P ≤ 0,05).

Los análisis de subgrupos se realizaron en categorías definidas por edad, sexo, hospitalización dentro de los 30 días antes del inicio con anticoagulantes y enfermedad renal crónica. También examinamos subgrupos con uso concomitante de antidepresivos inhibidores selectivos de la recapitación de serotonina o agentes antiplaquetarios de venta baja receta al inicio de anticoagulantes debido a que podrían aumentar los riesgos de hemorragia con los anticoagulantes. Finalmente, evaluamos el riesgo del resultado por dosis de dabigatran (150 o 75 mg dos veces al día). Dabigatran en dosis más bajas (75 mg dos veces al día) fue aprobado en los Estados Unidos para pacientes con insuficiencia renal grave (clearance de creatinina: 15–30 mL/min) sobre la base de los modelos farmacocinéticos.

Realizamos análisis de sensibilidad usando diferentes definiciones de seguimiento de cohortes para evaluar si los análisis principales se veían afectados por una clasificación errónea del tiempo de exposición. Lo hicimos mediante (1) restricción del análisis a pacientes con prescripciones iniciales de ≤ 30 días de duración, (2) restricción del análisis a pacientes con, al menos, 2 prescripciones de un fármaco de estudio y (3) aumento del margen de brecha entre prescripciones de anticoagulantes de 3 a 14 días.

Este estudio se realizó como parte del Proyecto SafeRx, una iniciativa conjunta de los Centros para Medicare & Medicaid Services y la Food and Drug Administration (FDA) de EUA. Fue aprobado por el Comité de Investigación en Seres Humanos del Centro de la FDA para Evaluación e Investigación de Fármacos. Los análisis se realizaron con el uso de R 3.0.2 (Fundación R para Computación Estadística, Viena, Austria) y SAS 9.2 (Instituto SAS Inc, Cary, NC).

Resultados

En total, 67 494 pacientes tratados con dabigatran y 273 920 pacientes tratados con warfarina fueron seleccionados para su inclusión en el estudio. Los usuarios de dabigatran tendían a ser más jóvenes, con menos probabilidades de presentar enfermedad renal crónica y con más probabilidades de ser tratados por un cardiólogo y de haber recibido antiarrítmicos y agentes antiplaquetarios de venta bajo receta. Se obtuvo un ajuste de puntuación de propensión para 67 207 nuevos usuarios de dabigatran (99,6%), lo que resultó en cohortes muy equilibradas para todas las covariables basales (Tabla I y Tabla I en el Suplemento de Datos solamente online). Los pacientes de dabigatran aportaron 18 205 personas/años de tiempo de seguimiento en terapia, y los usuarios de warfarina aportaron 19 382 personas/años. Cabe destacar que 52,0% de los usuarios de dabigatran y 50,2% de los usuarios de warfarina completaron solo una única prescripción de su antiagulante.

Durante el seguimiento, hubo 2715 resultados primarios incluyendo 475 accidentes cerebrovasculares isquémicos, 1628 hemorragias graves y 612 IAM. Comparado con warfarina, el uso de dabigatran se asoció con una reducción del riesgo de accidente cerebrovascular isquémico, hemorragia intracranal y mortalidad, y con un aumento del riesgo de hemorragia gastrointestinal grave (Tabla 2). No hubo diferencias entre las cohortes en riesgo de IAM o todas las hemorragias en internación. Los índices de incidencia absoluta de accidente cerebrovascular isquémico, hemorragia gastrointestinal grave, hemorragia intracranal y muerte fueron considerablemente mayores durante los primeros 90 días de tratamiento que durante periodos posteriores tanto para dabigatran como para warfarina (Figura I en el Suplemento de Datos solamente online). Sin embargo, las estimaciones precisas de los hazard ratios no variaron considerablemente durante los intervalos de 1 a 90, 91 a 180 o > 180 días de uso continuo de anticoagulantes, aunque los intervalos de confianza se ampliaron debido a la menor cantidad de eventos en los intervalos posteriores (Tabla III en el Suplemento de Datos solamente online). Los gráficos de Kaplan-Meier mostraron una separación temprana de las curvas de sobrevida para accidente cerebrovascular isquémico con una separación poco después para hemorragia intracranal, hemorragia gastrointestinal grave y muerte (Figura).

Los análisis de subgrupos estratificados por edad y sexo mostraron que el riesgo de hemorragia gastrointestinal grave
Tabla 2. Recuentos de resultados, índices de incidencia e índices de riesgo ajustados con IC de 95% que comparan cohortes de nuevos usuarios ajustados por puntuación de propensión de dabigatran y warfarina tratados para fibrilación auricular no valvular, con warfarina como grupo de referencia

<table>
<thead>
<tr>
<th>Nº de eventos</th>
<th>Índice de incidencias cada 1000 personas/año</th>
<th>Hazard ratio ajustado (IC 95%)</th>
<th>Valor P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Warfarina</td>
<td>Dabigatran</td>
</tr>
<tr>
<td><strong>Resultados primarios</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Accidente cerebrovascular isquémico</td>
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<td>270</td>
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<tr>
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<td>15,7</td>
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<td><strong>Resultados secundarios</strong></td>
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<td></td>
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<td>Todas las hemorragias en internación</td>
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<td>1139</td>
<td>59,3</td>
</tr>
<tr>
<td>Mortalidad*</td>
<td>603</td>
<td>744</td>
<td>32,6</td>
</tr>
</tbody>
</table>

*Para 1064 muertes no precedidas por un resultado primario del estudio, el hazard ratio ajustado (intervalo de confianza [IC]: 95%) fue de 0,89 (0,79–1,00; P = 0,051), mientras que para 283 muertes producidas dentro de los 30 días después de un resultado primario, el hazard ratio ajustado (IC 95%) fue de 0,77 (0,61–0,98; P = 0,03).

con dabigatran aumentaba para mujeres ≥ 75 años y para hombres ≥ 85 años comparado con warfarina (Tabla 3 y Tablas IV y V en el Suplemento de Datos solamente online). Para pacientes menores de las edades mencionadas, el riesgo de hemorragia gastrointestinal fue comparable para ambos anticoagulantes. La estimación precisa para el riesgo de muerte con
dabigatran comparado con warfarina se redujo en todos los estratos excepto en mujeres ≥ 85 años, donde se vio aumentado comparado con mujeres más jóvenes (*Pinteraction = 0.004). No hubo interacciones para accidente cerebrovascular isquémico o hemorragia intracranal. Los resultados en otros subgrupos definidos por enfermedad renal crónica, uso de agentes antiplaquetarios de venta bajo receta o antidepresivos inhibidores selectivos de la recapitación de serotonina, u hospitalización en los 30 días antes de que se comenzara con el uso del anticoagulante fueron similares a los resultados del análisis principal.

La magnitud del efecto para cada resultado fue mayor en el subgrupo tratado con dabigatran 150 mg dos veces al día comparado con el análisis principal, que incluía pacientes tratados con las dosis de 150 y 75 mg (Tabla 4 y Tabla VI en el Suplemento de Datos solamente online). Aproximadamente 16% de los pacientes recibió dabigatran 75 mg dos veces al día y dentro de este grupo, ninguna de las comparaciones de resultados fue en forma considerable estadísticamente diferente de warfarina excepto por un menor riesgo de hemorragia intracranal con dabigatran (Tabla 4). Solamente 33% de los pacientes tratados con la dosis más baja de dabigatran presentaron un diagnóstico de enfermedad renal crónica dentro de los 6 meses previos y, de estos, la codificación indicó claramente insuficiencia renal grave solamente en el 20%. Es más probable que aquellos pacientes que recibieron dosis más bajas fueran mayores, estuvieran recibiendo atención domiciliaria u oxígeno en sus hogares, y que tuvieran puntuaciones más elevadas de CHADS2 y HAS-BLED (Tabla VII en el Suplemento de Datos solamente online).

Discusión

En una amplia cohorte de beneficiarios de Medicare de edad avanzada con FA no valvular, el riesgo de accidente cerebrovascular isquémico, hemorragia intracranal y mortalidad se redujo, y el riesgo de hemorragia gastrointestinal grave aumentó en pacientes tratados con dabigatran comparados con warfarina. Los niveles de riesgo fueron similares en dirección y magnitud a aquellos observados en el ensayo clínico aleatorizado RE-LY, donde dabigatran 150 mg dos veces al día fue comparado con terapia con warfarina con dosis ajustadas. La incidencia absoluta de resultados para dabigatran y warfarina fue mayor durante los primeros 90 días de tratamiento, aunque los hazard ratios para estos resultados fueron constantes con el transcurso del tiempo. Nuestros resultados para hemorragia gastrointestinal difirieron de aquellos de un análisis del Mini-Sentinel Modular Program que halló un aumento 2 veces mayor en incidencia para warfarina comparado con dabigatran. Los programas modulares no se ajustaron por ningún factor de confusión e incluyeron cantidades considerables de pacientes más jóvenes, en quienes los riesgos de hemorragias serían menores. Nuestros resultados también difieren de los de 2 estudios observacionales pequeños de Dinamarca. En el primero, no se observaron diferencias en el riesgo de hemorragias

| Tabla 3. Efecto de edad y sexo sobre el riesgo de accidente cerebrovascular isquémico, hemorragia intracranal, hemorragia gastrointestinal grave, y mortalidad en cohortes ajustadas por puntuación de propensión tratadas con dabigatran o warfarina para fibrilación auricular no valvular, con warfarina como grupo de referencia* |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Grupo etario (n) | Hombres, hazard ratio (IC 95%) | Mujeres, hazard ratio (IC 95%) | Hombres, hazard ratio (IC 95%) |
| Accidente cerebrovascular isquémico | | | |
| 65–74 (55 761) | 0,69 (0,42–1,14) | 0,81 (0,51–1,31) | |
| 75–84 (57 345) | 0,98 (0,64–1,51) | 0,89 (0,64–1,26) | |
| ≥ 85 (21 308) | 0,89 (0,41–1,90) | 0,60 (0,40–0,91) | |
| Hemorragia intracranal | | | |
| 65–74 (55 761) | 0,32 (0,15–0,68) | 0,13 (0,04–0,44) | |
| 75–84 (57 345) | 0,27 (0,14–0,50) | 0,59 (0,35–0,98) | |
| ≥ 85 (21 308) | 0,51 (0,18–1,48) | 0,26 (0,12–0,56) | |
| Hemorragia gastrointestinal grave | | | |
| 65–74 (55 761) | 0,83 (0,60–1,14) | 0,99 (0,72–1,37) | |
| 75–84 (57 345) | 1,02 (0,79–1,31) | 1,50 (1,20–1,88) | |
| ≥ 85 (21 308) | 1,55 (1,04–2,32) | 2,18 (1,61–2,97) | |
| Mortalidad | | | |
| 65–74 (55 761) | 0,81 (0,62–1,05) | 0,72 (0,52–0,99) | |
| 75–84 (57 345) | 0,73 (0,58–0,92) | 0,82 (0,65–1,03) | |
| ≥ 85 (21 308) | 0,92 (0,64–1,33) | 1,24 (0,96–1,60) | |

IC indica intervalo de confianza.

*Índices de incidencia específicos de edad/sexo de resultados para las cohortes de dabigatran y warfarina se muestran en las Tablas IV y V en el Suplemento de Datos solamente online.

| Tabla 4. Efecto de la dosis diaria de dabigatran sobre el riesgo de accidente cerebrovascular isquémico, hemorragia gastrointestinal grave, hemorragia intracranal y mortalidad comparado con el tratamiento con warfarina para fibrilación auricular no valvular* |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Accidente cerebrovascular isquémico, hazard ratio (IC 95%) | Hemorragia gastrointestinal grave, hazard ratio (IC 95%) | Hemorragia intracranal, hazard ratio (IC 95%) | Mortalidad, hazard ratio (IC 95%) |
| 75 mg dos veces al día (n = 10 522) | 0,88 (0,60–1,27) | 1,01 (0,78–1,31) | 0,46 (0,26–0,81) | 0,95 (0,78–1,16) |
| 150 mg dos veces al día (n = 56 576) | 0,70 (0,57–0,85) | 1,51 (1,32–1,73) | 0,30 (0,21–0,42) | 0,76 (0,67–0,86) |

IC indica intervalo de confianza.

*Debido a los desequilibrios de las covariables entre las cohortes de dabigatran y warfarina después de la estratificación por dosis, los pacientes fueron re-emparejados dentro de los estratos definidos por dosis diaria de dabigatran, lo que dio como resultado un total de 67 098 pacientes en cada cohorte en lugar de 67 207 del análisis primario.
tromboembólicas o en internación en 765 nuevos usuarios de dabigatran comparado con warfarina. En el segundo estudio, no se observaron diferencias en el riesgo de accidente cerebrovascular o hemorragia gastrointestinal en 2239 pacientes que comenzaron con dabigatran comparado con warfarina.

En nuestro estudio, el aumento del riesgo de hemorragia gastrointestinal grave con dabigatran se limitó a mujeres ≥ 75 años y a hombres ≥ 85 años. El efecto beneficioso de dabigatran sobre la mortalidad no se presentó en mujeres ≥ 85 años, en quienes hubo una tendencia para un mayor riesgo de muerte con dabigatran comparado con warfarina. Este cambio en el hazard ratio entre mujeres más jóvenes y mujeres mayores representó una interacción estadísticamente significativa y sugiere que el perfil de riesgo/beneficio de dabigatran sería menos favorable en mujeres ≥ 85 años que en otros grupos de edad/sexo. Aunque se evaluaron muchos subgrupos en este análisis, debe destacarse que en RE-LY, se observó una interacción entre tratamiento y edad para hemorragia gastrointestinal grave, pero no accidente cerebrovascular o hemorragia intracranial, similar a nuestros hallazgos en el presente estudio. La cantidad de mujeres ≥ 85 años de edad fue pequeña en RE-LY, y los análisis de edad y mortalidad no fueron informados.

Cabe destacar que la dosis de 75 mg de dabigatran fue aprobada para su uso en pacientes con insuficiencia renal grave sobre la base del modelo farmacocinético en vez de un ensayo clínico aleatorizado en pacientes. Nuestro estudio representa la evaluación más amplia del efecto clínico de dabigatran 75 mg dos veces al día, aunque los datos fueron de laboratorio sobre clearance de creatinina y no tenemos certeza sobre la precisión de la codificación de las enfermedades renales, nuestros resultados sugieren que muchos pacientes tratados con esta dosis más baja no deben haber tenido insuficiencia renal grave, en cuyo caso, sobre la base del rótulo actual del producto, se debieron haber tratado con la dosis de 150 mg. En el marco de insuficiencia renal moderada o leve o en ausencia de insuficiencia renal, el uso fuera de etiqueta de la dosis de 75 mg resultaría en pacientes que son subdosificados y podría explicar por qué no encontramos diferencias en el riesgo de accidente cerebrovascular isquémico, hemorragia gastrointestinal grave o mortalidad entre warfarina y la dosis más baja de dabigatran. Por otro lado, si la mayoría de los pacientes tratados con la dosis de 75 mg realmente tenían insuficiencia renal grave, esto sugeriría que la dosificación de dabigatran basada en los modelos farmacocinéticos estaba incorrecta. Esto genera el interrogante con respecto a si los pacientes tratados fuera de etiqueta con la dosis de 75 mg hubieran experimentado mejorías para accidente cerebrovascular isquémico y mortalidad si se los hubiera tratado con la dosis de 150 mg. No podemos responder a este interrogante con certeza porque nuestra comparación entre niveles de dosis fue indirecta y no se basó en un análisis de comparación directa. Probablemente sea relevante destacar en este aspecto que el estudio RE-LY sugeró que una dosis de 110 mg dos veces al día de dabigatran era menos efectiva que la dosis de 150 mg y, en consecuencia, esta dosis más baja no estaba aprobada para su comercialización en los Estados Unidos.

Este estudio tuvo varias limitaciones. Fue observacional y estaría sujeto a confusión por factores no ajustados en el análisis, tales como el uso de aspirina de venta libre o anti-inflamatorios no esteroides. Para reducir esta posibilidad, incluimos una extensa cantidad de variables en nuestro modelo de puntuación de propensión, incluso agentes antiplaquetarios de venta bajo receta, y se alcanzó un estricto equilibrio para estos factores. No obstante, no pueden excluirse las confusiones restantes por factores no medidos. Los datos de Medicare no capturaron los resultados de laboratorio y, en consecuencia, no tuvimos una base para evaluar la calidad de la anticoagulación de warfarina. Es posible que los efectos favorables de dabigatran sobre accidente cerebrovascular isquémico y mortalidad, y su efecto adverso sobre hemorragia gastrointestinal grave en nuestro estudio se debieran, al menos en parte, al breve tiempo en el rango terapéutico con warfarina. Sin embargo, esto no explicaría la reducción del riesgo de hemorragia intracranial con dabigatran. Más importante aún, si el tratamiento con warfarina en nuestro estudio fue o no adecuado, refleja la calidad de anticoagulación que probablemente experimentan los pacientes tratados con warfarina en la práctica clínica en los Estados Unidos. En ese contexto, los resultados de nuestro estudio sugieren que dabigatran está asociado con resultados generalmente mejores en los pacientes. Además, ≈50% de los pacientes de cada cohorte recibieron solamente una única prescripción del anticoagulante del estudio. Esto representa la experiencia de Medicare en atención ambulatoria. Sin embargo, la constancia de los hazard ratios en el tiempo más allá de los 180 días de uso y los resultados de nuestro análisis de sensibilidad limitado a pacientes que recibían ≥ 2 prescripciones, sugieren que el sesgo no se introdujo por esta limitada persistencia de uso.

En síntesis, en los beneficiarios de edad avanzada de Medicare con FA no valvular, dabigatran se asoció con una reducción del riesgo de accidente cerebrovascular isquémico, hemorragia intracranial y mortalidad, y un aumento del riesgo de hemorragia gastrointestinal grave comparado con warfarina. Estas asociaciones fueron más fuertes para la dosis de dabigatran de 150 mg, mientras que la dosis de 75 mg se asoció solamente con una reducción del riesgo de hemorragia intracranial.

Reconocimientos

Los autores son empleados o contratistas de los Centros para Medicare & Medicaid Services o la Food and Drug Administration de EUA; sin embargo, otros funcionarios en los Centros de Medicare & Medicaid Services y la Food and Drug Administration de EUA no tuvieron ninguna función en el diseño y conducción del estudio, la recopilación, análisis e interpretación de los datos, o la preparación, revisión o aprobación del manuscrito. El manuscrito estuvo sujeto a revisión administrativa antes de su presentación, pero el contenido no fue alterado por esta revisión. Los puntos de vista expresados son los de los autores y no necesariamente los del Departamento de Salud y Servicios al Ser Humano, los Centros para Medicare & Medicaid Services o Food and Drug Administration de EUA. El Dr. MaCurdy tuvo total acceso a todos los datos del estudio y asume la responsabilidad por la integridad de los datos y la precisión del análisis de datos.
**Declaraciones**

Ninguna.

**Bibliografía**


En 2010, el primer anticoagulante oral no antagonista de la vitamina K, dabigatran, fue aprobado en los Estados Unidos para su uso en pacientes con fibrilación auricular no valvular. En un amplio estudio observacional de los beneficiarios de Medicare ≥ 65 años de edad con fibrilación auricular no valvular, dabigatran se asoció con una reducción en el riesgo de accidente cerebrovascular, hemorragia intracraneal y muerte, y con un aumento del riesgo de hemorragia gastrointestinal grave comparado con warfarina. Con la dosis de dabigatran más comúnmente usada, 150 mg dos veces al día, la magnitud del efecto para estos resultados fue mayor que cuando los usuarios de dosis de 150 mg y 75 mg fueron incluidos en el análisis. Con la dosis de 75 mg dos veces al día, aprobada específicamente para su uso en pacientes con insuficiencia renal grave (clearance de creatinina 15–30 mL/min), dabigatran no fue diferente de warfarina excepto por una reducción del riesgo de hemorragia intracraneal. La mayoría de los pacientes tratados con la dosis de 75 mg no tenían un diagnóstico que indicara insuficiencia renal grave, esto sugiere que habrían sido tratados fuera de etiqueta con la dosis más baja y posiblemente subdosificados. La asociación de dabigatran con hemorragia gastrointestinal grave varió dependiendo de la edad y sexo del paciente (efecto del medicamento). El aumento del riesgo con dabigatran se observó en mujeres ≥ 75 años de edad y en hombres ≥ 85 años de edad, pero no en individuos más jóvenes. No hubo efecto aparente de edad/sexo en el riesgo de accidente cerebrovascular o hemorragia intracraneal. Si bien dabigatran se asoció con una reducción de la mortalidad en el análisis principal, el riesgo posiblemente aumentó en mujeres ≥ 85 años. Serían de utilidad más investigaciones para orientar una terapia óptima con dabigatran.