

# Serious Bleeding in Patients With Atrial Fibrillation Using Diltiazem With Apixaban or Rivaroxaban

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**IMPORTANCE** Diltiazem, a commonly prescribed ventricular rate-control medication for patients with atrial fibrillation, inhibits apixaban and rivaroxaban elimination, possibly causing overanticoagulation.

**OBJECTIVE** To compare serious bleeding risk for new users of apixaban or rivaroxaban with atrial fibrillation treated with diltiazem or metoprolol.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective cohort study included Medicare beneficiaries aged 65 years or older with atrial fibrillation who initiated apixaban or rivaroxaban use and also began treatment with diltiazem or metoprolol between January 1, 2012, and November 29, 2020. Patients were followed up to 365 days through November 30, 2020. Data were analyzed from August 2023 to February 2024.

**EXPOSURES** Diltiazem and metoprolol.

**MAIN OUTCOMES AND MEASURES** The primary outcome was a composite of bleeding-related hospitalization and death with recent evidence of bleeding. Secondary outcomes were ischemic stroke or systemic embolism, major ischemic or hemorrhagic events (ischemic stroke, systemic embolism, intracranial or fatal extracranial bleeding, or death with recent evidence of bleeding), and death without recent evidence of bleeding. Hazard ratios (HRs) and rate differences (RDs) were adjusted for covariate differences with overlap weighting.

**RESULTS** The study included 204 155 US Medicare beneficiaries, of whom 53 275 received diltiazem and 150 880 received metoprolol. Study patients (mean [SD] age, 76.9 [7.0] years; 52.7% female) had 90 927 person-years (PY) of follow-up (median, 120 [IQR, 59-281] days). Patients receiving diltiazem treatment had increased risk for the primary outcome (RD, 10.6 [95% CI, 7.0-14.2] per 1000 PY; HR, 1.21 [95% CI, 1.13-1.29]) and its components of bleeding-related hospitalization (RD, 8.2 [95% CI, 5.1-11.4] per 1000 PY; HR, 1.22 [95% CI, 1.13-1.31]) and death with recent evidence of bleeding (RD, 2.4 [95% CI, 0.6-4.2] per 1000 PY; HR, 1.19 [95% CI, 1.05-1.34]) compared with patients receiving metoprolol. Risk for the primary outcome with initial diltiazem doses exceeding 120 mg/d (RD, 15.1 [95% CI, 10.2-20.1] per 1000 PY; HR, 1.29 [95% CI, 1.19-1.39]) was greater than that for lower doses (RD, 6.7 [95% CI, 2.0-11.4] per 1000 PY; HR, 1.13 [95% CI, 1.04-1.24]). For doses exceeding 120 mg/d, the risk of major ischemic or hemorrhagic events was increased (HR, 1.14 [95% CI, 1.02-1.27]). Neither dose group had significant changes in the risk for ischemic stroke or systemic embolism or death without recent evidence of bleeding. When patients receiving high- and low-dose diltiazem treatment were directly compared, the HR for the primary outcome was 1.14 (95% CI, 1.02-1.26).

**CONCLUSIONS AND RELEVANCE** In Medicare patients with atrial fibrillation receiving apixaban or rivaroxaban, diltiazem was associated with greater risk of serious bleeding than metoprolol, particularly for diltiazem doses exceeding 120 mg/d.

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The direct factor Xa inhibitors apixaban and rivaroxaban are now the most frequently prescribed anticoagulants to prevent ischemic stroke in patients with atrial fibrillation,<sup>1</sup> the most common sustained cardiac arrhythmia.<sup>2</sup> Each drug's plasma concentration is influenced by hepatic cytochrome P450-3A4 (CYP3A4) enzymes, which promote metabolism and subsequent elimination, and the permeability glycoprotein multidrug transporter (P-gp), which facilitates intestinal, hepatic, and kidney efflux.<sup>3-6</sup>

Diltiazem, a calcium channel blocker commonly prescribed for ventricular rate control (hereafter, *rate control*) in patients with atrial fibrillation,<sup>7</sup> is a strong inhibitor of CYP3A4. It produced a 4.05-fold increase in the area under the plasma concentration-time curve (AUC) for the CYP3A4 substrate midazolam<sup>8</sup> and led to dose-dependent increases in the AUC for the substrates nifedipine<sup>9</sup> and ranolazine.<sup>10</sup> Diltiazem also may weakly inhibit P-gp; a study reported that concurrent use with the P-gp substrate digoxin increased the digoxin AUC by 22.4%.<sup>11</sup> Coadministration of diltiazem with apixaban increased the AUC for apixaban by 40%.<sup>12</sup>

Because the anticoagulant activity of direct factor Xa inhibitors is closely related to plasma concentrations,<sup>13</sup> concurrent use of diltiazem with apixaban or rivaroxaban could increase bleeding complications. Although there are case reports of hemorrhage in patients treated with diltiazem while receiving these anticoagulants,<sup>14-16</sup> the clinical impact of this potential drug-drug interaction is uncertain. Although both the US Food and Drug Administration labels for apixaban<sup>6</sup> and rivaroxaban<sup>5</sup> and the American College of Cardiology, American Heart Association, American College of Clinical Pharmacy, and Heart Rhythm Society guidelines for management of atrial fibrillation<sup>17</sup> acknowledge that anticoagulant management should consider drug-drug interactions, neither specifically mentions increased risk of bleeding as a potential consequence of diltiazem coadministration. Observational studies have had mixed findings,<sup>18-25</sup> but many of these were limited by relatively small sample size, lack of an active comparator, and incomplete control for confounding.

Because diltiazem is an effective and well-tolerated drug for rate control in patients with atrial fibrillation, particularly for those with chronic obstructive pulmonary disease,<sup>7,26,27</sup> a pro-hemorrhagic interaction with direct factor Xa inhibitors would have important clinical consequences for millions of patients. Thus, we conducted a retrospective cohort study involving Medicare beneficiaries with atrial fibrillation receiving apixaban or rivaroxaban to estimate the risk of serious bleeding associated with diltiazem treatment.

## Methods

### Design

The Vanderbilt University Medical Center institutional review board approved this cohort study prior to data access and determined that the study posed minimal risk to participants and thus waived informed consent. The study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

### Key Points

**Question** Do patients with atrial fibrillation receiving apixaban or rivaroxaban and concurrently treated for ventricular rate control with diltiazem have greater risk of serious bleeding than those treated with metoprolol?

**Findings** In this cohort study of 204 155 patients aged 65 years or older, those treated with diltiazem had a significantly greater risk of serious bleeding compared with those treated with metoprolol.

**Meaning** Among older adults with atrial fibrillation receiving apixaban or rivaroxaban, treatment with diltiazem was associated with increased risk of serious bleeding compared with metoprolol.

We compared patients with atrial fibrillation initiating apixaban or rivaroxaban use<sup>28</sup> who subsequently began diltiazem treatment with those who began metoprolol treatment, an alternative rate-control medication<sup>7</sup> not thought to inhibit either CYP3A4 or P-gp.<sup>29</sup> Although other  $\beta$ -blockers are appropriate for rate control, metoprolol is commonly prescribed for Medicare patients<sup>30</sup> and unlike carvedilol,<sup>23</sup> is not thought to inhibit direct oral anticoagulant elimination.<sup>29</sup> The study drugs are not interchangeable for many patients<sup>7</sup>; however, the metoprolol comparison group controlled for factors related to the decision to initiate a rate-control drug and should provide better management of confounding than either patients not using diltiazem<sup>19-21,24</sup> or those prescribed cardiovascular medications not recommended for rate control, such as amlodipine.<sup>22</sup>

This cohort study emulated a hypothetical target trial,<sup>31</sup> a large, simplified, pragmatic trial that used data from the Medicare program to identify and follow-up participants (eAppendix 1 and eTable 1 in Supplement 1). Because the risk of the diltiazem-anticoagulant interaction is only present while the patient receives both drugs, the estimand was while receiving treatment (eAppendix 1 in Supplement 1<sup>32</sup>).

### Data

Medicare provides health care insurance for persons 65 years or older and younger persons with disabilities.<sup>33</sup> Study data included the Medicare Master Beneficiary Summary File, which has enrollment status and identifies deaths for beneficiaries<sup>33</sup>; the Part D file for filled prescriptions (estimated 94% of prescriptions for covered medications included<sup>34</sup>); and claims files for hospital, outpatient, and nursing home services. The data resided in the Centers for Medicare & Medicaid Services Chronic Conditions Warehouse and were accessed through the Virtual Research Data Center, a cloud-based repository of deidentified Medicare files.<sup>35</sup> In accordance with Centers for Medicare & Medicaid Services policy, no table cells had fewer than 11 patients.

### Eligibility Criteria

Eligible patients (eAppendix 2 and eTable 2 in Supplement 1) were Medicare beneficiaries 65 years or older with continuous fee-for-service (Parts A and B) and prescription drug (Part D) coverage who filled a prescription for apixaban or rivaroxaban between January 1, 2012, and November 29, 2020.

They could not have filled any oral anticoagulant prescription in the past year, had to have a diagnosis of atrial fibrillation or flutter and an anticoagulant dose approved for atrial fibrillation, and could not have evidence of reversible atrial fibrillation or mitral valve stenosis. They also could not have had a bleeding-related hospitalization or stroke or systemic embolism in the past 30 days, as subsequent readmissions could be confused with new events. Patients entered the cohort if they had a filled prescription for diltiazem or metoprolol while receiving the study anticoagulant; for the first such prescription, there was no other study rate-control drug prescription in the past 365 days; and they had no evidence of terminal illness (deaths unlikely to be associated with study drug use) or long-term care (Medicare data may be incomplete<sup>33</sup>) in the past year. Treatment group was fixed at cohort entry, and time 0 was the day after the fill of the initial diltiazem or metoprolol prescription.

### Follow-Up

Follow-up (eAppendix 3 and eTable 3 in [Supplement 1](#)) began on time 0 and ended with the first of 365 days; November 30, 2020; loss of full Medicare enrollment; lapse of 30 days or more in dispensed days of supply for either the study anticoagulant or the rate-control medication; start of the other study rate-control treatment; start of a nonstudy oral anticoagulant; or the first study outcome. To assess potential exposure misclassification, follow-up was classified according to current use of the assigned treatment (eAppendix 3 in [Supplement 1](#)). Patients who left the cohort could not re-enter.

### Outcomes

The primary outcome was the composite of bleeding-related hospitalization<sup>36,37</sup> and death with recent evidence of bleeding.<sup>22,30,38</sup> Bleeding-related hospitalizations were identified from hospital principal discharge diagnosis codes by a previously validated algorithm (eAppendix 4A and eTables 4 and 5 in [Supplement 1](#))<sup>36,37</sup> and were further classified as intracranial or fatal (death within 30 days) extracranial bleeding or as nonfatal extracranial bleeding. Deaths with recent evidence of bleeding (eAppendix 4B in [Supplement 1](#)) had other evidence of hemorrhage in the 30 days preceding death: a secondary inpatient or any outpatient diagnosis of hemorrhage or an allogeneic transfusion.<sup>22,30,38</sup> Examples include terminal hospitalization with a principal diagnosis of sepsis and a secondary diagnosis of hemorrhage or intracranial hemorrhage in a patient presenting to the emergency department with death before hospital admission. Secondary outcomes were the components of the primary outcome, ischemic stroke or systemic embolism (eAppendix 4C and eTable 6 in [Supplement 1](#))<sup>39,40</sup>, major ischemic or hemorrhagic event (ischemic stroke, systemic embolism, intracranial or fatal extracranial bleeding, or death with recent evidence of bleeding), and death without recent evidence of bleeding.

### Statistical Analysis

#### Covariates

Study covariates (eAppendix 5A and eTable 7 in [Supplement 1](#)) were identified at cohort entry from the Medicare enrollment file, diagnoses from claims in the prior year, and

prescriptions filled in the past 90 days. Demographic characteristics included race and ethnicity (self-reported to Social Security Administration, fixed categories) because they are correlated with mortality.<sup>41</sup> Categories included Black, White, and other or unknown (Asian, Hispanic, North American Native, other, and unknown). Other covariates, chosen based on previous studies of anticoagulants,<sup>24,30,33,37,42,43</sup> included the specific anticoagulant and its dose (standard or reduced); time since anticoagulant initiation; risk factors for stroke<sup>44-47</sup> and bleeding<sup>37</sup>; indicators of frailty<sup>48</sup>; acute and chronic heart failure hospitalization history<sup>49</sup>; cardiovascular disease, including that for which low-dose aspirin prophylaxis is recommended; chronic kidney disease; respiratory illness<sup>7</sup>; neurologic conditions; cancer; medical care utilization; and prescribed medications, including inhibitors of either CYP3A4 or P-gp activity. Summary measures of risk for ischemic stroke or hemorrhage were claims-based versions of the CHA<sub>2</sub>DS<sub>2</sub>-VASC score (congestive heart failure; hypertension; age 65-74 years; age ≥75 years; diabetes; stroke, transient ischemic attack, or thromboembolism; vascular disease; and female sex)<sup>45-47</sup> and the HAS-BLED score (hypertension, kidney disease, liver disease, prior stroke, history of bleeding, age >65 years, use of aspirin and other antiplatelets, and alcohol use disorder, excluding labile international normalized ratio).<sup>45</sup> Covariate imbalances were assessed with standardized mean differences.<sup>50</sup>

#### Overlap Weights

The analysis adjusted for baseline covariate differences between treatment groups with overlap weights<sup>51,52</sup> estimated from the propensity score (eAppendix 5B and eTable 8 in [Supplement 1](#)). Overlap weights, the probability of belonging to the opposite treatment group, down-weight patients unlikely to be eligible for both treatments. Unlike other propensity score methods, the analysis includes all cohort members and is not unduly influenced by patients who are outliers. When the propensity score is estimated with logistic regression, overlap weights exactly balance covariate means across the treatment groups.

#### Risk Estimates

The measure of treatment association with outcomes was the hazard ratio (HR), estimated with weighted proportional hazards regression that used modified sandwich variance estimation<sup>53</sup> to correct for weighting-induced dependencies (eAppendix 5C in [Supplement 1](#)). The interaction of the HR with follow-up time was estimated. Adjusted incidence was estimated with a weighted Poisson regression piecewise exponential model<sup>54</sup> using generalized estimating equations to correct for weighting-induced dependencies (eAppendix 5D in [Supplement 1](#)), and the difference between the adjusted incidence rates for diltiazem and metoprolol (RD) was calculated.

#### Secondary Analyses

We performed a planned analysis according to whether the initial diltiazem dose was less than or equal to 120 mg/d, the study cohort median dose. Overlap weights were recalculated for each diltiazem dose, with all metoprolol-treated

patients serving as the controls. Because the clinical impact of a diltiazem interaction could be greatest in patients with elevated baseline bleeding risk, a planned analysis for the primary outcome estimated the RDs according to approximate tertiles of the HAS-BLED score and study anticoagulant (eAppendix 5E in Supplement 1). To assure covariate balance within these subgroups, overlap weights were recalculated with stratification by the grouping factor.

### Sensitivity Analyses

The sensitivity analyses (1) excluded 2020 data, the first year of the COVID-19 pandemic; (2) matched treatment groups according to propensity score; (3) restricted the cohort to patients starting diltiazem or metoprolol within 30 days of anticoagulant initiation, increasing the likelihood that treatment was for rate control; (4) limited follow-up to 180 days to assess the effect of nonproportional hazards; (5) included a modified intention-to-treat analysis in which follow-up was limited to 90 days and patients were not censored if they stopped or switched rate-control drugs; (6) censored if diltiazem dose changed during follow-up; (7) selected controls for diltiazem dose groups from those below or above the median metoprolol starting dose (25 mg/d); and (8) directly compared high- vs low-dose diltiazem treatment, including recalculating the overlap weights. We also performed a negative control outcome analysis<sup>55</sup> with fracture of the proximal femur as the falsification end point (eAppendix 5F in Supplement 1).<sup>56,57</sup>

Data were analyzed from August 2023 to February 2024. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc). Statistical significance was defined as a 95% CI that excluded 0 (RD) or 1 (HR).

## Results

### Cohort

Between January 1, 2012, and November 29, 2020, a total of 204 155 patients with atrial fibrillation initiated apixaban or rivaroxaban use and also began treatment with either diltiazem (n = 53 275) or metoprolol (n = 150 880) (eFigure 1 in Supplement 1). Cohort members had a mean (SD) age of 76.9 (7.0) years, 52.7% were female, 47.3% were male, 33.4% received rivaroxaban, 78.5% were taking the standard anticoagulant dose, and 48.6% of those receiving diltiazem treatment had a starting dose less than or equal to 120 mg/d. A total of 3.5% of patients were Black; 91.0%, White; and 5.6%, other or unknown (the low proportion of Black patients may be related to the substantially lower incidence of diagnosed atrial fibrillation in the Black population<sup>58</sup>). Prior to weighting, patients in the diltiazem group (Table 1 and eTable 7 in Supplement 1) were more likely to start rate-control treatment within 30 days of anticoagulant initiation (73.7% vs 62.3%) and to be female (59.3% vs 50.4%). Patients receiving diltiazem treatment were less likely to have had a myocardial infarction or revascularization, and fewer met the criteria for low-dose aspirin prophylaxis. However, they more frequently had a history of chronic obstructive pulmonary disease, used home oxygen, and had a recent hospital discharge. Both groups had

comparable CHA<sub>2</sub>DS<sub>2</sub>-VASc (4.2 vs 4.3) and HAS-BLED (3.0 vs 3.0) scores. After weighting (Table 1 and eTable 7 in Supplement 1), covariate means were balanced across the 2 groups.

### Follow-Up

Median duration of follow-up was 120 (IQR, 59-281) days in the entire cohort, 101 (IQR, 59-258) days in the diltiazem group, and 120 (IQR, 59-290) days in the metoprolol group (eTable 9 in Supplement 1). There was concurrent anticoagulant and rate-control drug use for 83.4% and 82.6% of follow-up days in the diltiazem and metoprolol groups, respectively. The most common reasons for ending follow-up were stopping the oral anticoagulant (31.4%) or rate-control drug (24.3%). Patients receiving diltiazem treatment less frequently stopped the rate-control drug (21.5% vs 25.2%) and more frequently switched treatments (14.3% vs 4.9%). For diltiazem treatment with starting doses of less than or equal to 120 mg/d or greater than 120 mg/d, doses during follow-up were concordant for 83.7% and 94.3% of prescriptions, respectively (eTable 10 in Supplement 1).

### Outcomes

During 90 927 person-years of follow-up, there were 5269 primary composite outcome events (57.9 per 1000 person-years of follow-up): 3869 bleeding-related hospitalizations (42.6 per 1000 person-years) and 1400 deaths with recent evidence of bleeding (15.4 per 1000 person-years). The adjusted rates for diltiazem and metoprolol were 60.3 vs 49.7 per 1000 person-years, an RD of 10.6 (95% CI, 7.0-14.2) per 1000 person-years (Table 2). The HR for diltiazem was 1.21 (95% CI, 1.13-1.29) (Figure 1), which was increased early in follow-up (days 1-180: HR, 1.24 [95% CI, 1.15-1.33]; days 181-365: HR, 1.09 [95% CI, 0.93-1.27]) (eTable 11 in Supplement 1). Patients receiving diltiazem treatment had increased risk for both components of the primary composite outcome compared with those receiving metoprolol (Table 2): bleeding-related hospitalization (HR, 1.22 [95% CI, 1.13-1.31]) and death with recent evidence of bleeding (HR, 1.19 [95% CI, 1.05-1.34]). There were no significant differences in the risk for ischemic stroke or systemic embolism (HR, 0.87 [95% CI, 0.74-1.03]), major ischemic or hemorrhagic events (HR, 1.06 [95% CI, 0.97-1.16]), or death without recent evidence of bleeding (HR, 1.04 [95% CI, 0.96-1.12]).

### Diltiazem Dose

The risk for the primary composite outcome increased with initial diltiazem dose. For patients treated with a dose of 120 mg/d or less, the HR was 1.13 (95% CI, 1.04-1.24) and the RD was 6.7 (95% CI, 2.0-11.4) per 1000 person-years (Figure 2A and Figure 3). The risk for bleeding-related hospitalizations increased significantly, but none of the HRs for the other secondary outcomes were significant. For patients treated with doses higher than 120 mg/d, the primary outcome HR was 1.29 (95% CI, 1.19-1.39) (Figure 2B and Figure 3) and the RD was 15.1 (95% CI, 10.2-20.1) per 1000 person-years, with significantly increased risk for both components of the primary outcome (Figure 3). The risk was significantly increased for major ischemic or hemorrhagic events (RD, 4.4 [95% CI, 0.7-8.0] per 1000 person-years; HR, 1.14 [95% CI, 1.02-1.27]). Risk for

Table 1. Unweighted and Weighted Demographics, Comorbidity, and Medications in the Cohort at Baseline

Covariate <sup>a</sup>	Unweighted <sup>b</sup>			Weighted <sup>b</sup>	
	Diltiazem	Metoprolol	SMD <sup>c</sup>	Diltiazem	Metoprolol
Patients, No.	53 275	150 880	NA	53 275	150 880
Rivaroxaban	34.7	33.0	0.035	34.1	34.1
Standard anticoagulant dose <sup>d</sup>	78.7	78.4	0.006	78.8	78.8
Started rate-control drug within 30 d of study anticoagulant	73.7	62.3	0.248	70.9	70.9
Diltiazem starting dose ≤120 mg/d	48.6	NA	NA	48.9	NA
Age, mean (SD), y	76.6 (6.9)	77.1 (7.0)	-0.072	76.7 (5.7)	76.7 (3.4)
Sex					
Female	59.3	50.4	0.180	57.2	57.2
Male	40.7	49.6	0.180	42.8	42.8
Race and ethnicity					
Black	3.3	3.6	-0.013	3.4	3.4
White	91.7	90.7	0.038	91.5	91.5
Other or unknown <sup>e</sup>	4.9	5.8	-0.037	5.2	5.2
Medicaid enrollee	14.9	13.9	0.028	14.3	14.3
Year of cohort entry	2017.1	2017.4	-0.127	2017.2	2017.2
Comorbidity, past year unless otherwise noted					
CHA <sub>2</sub> DS <sub>2</sub> -VASC score, mean (SD) <sup>f</sup>	4.2 (1.6)	4.3 (1.6)	-0.031	4.2 (1.3)	4.2 (0.7)
HAS-BLED score, mean (SD) <sup>g</sup>	3.0 (1.1)	3.0 (1.1)	-0.051	3.0 (0.9)	3.0 (0.5)
Hypertension	87.9	88.5	-0.016	87.8	87.8
Criteria for secondary prevention with low-dose aspirin <sup>h</sup>	40.5	46.6	-0.124	41.4	41.4
Inpatient stay past 30 d, any	43.4	32.3	0.232	39.0	39.0
Inpatient stay past 30 d, >7 d	7.1	5.9	0.047	6.3	6.3
Diabetes	32.7	33.9	-0.027	32.6	32.6
Anemia	31.9	32.9	-0.021	31.8	32.0
Chronic obstructive pulmonary disease	30.9	20.7	0.236	26.5	26.5
Cancer other than nonmelanoma skin cancer	18.7	18.8	-0.003	18.7	18.6
Chronic kidney disease, stage 3 or unspecified	17.2	18.9	-0.046	17.4	17.4
Chronic kidney disease, stage 4, 5, or end-stage	3.0	3.4	-0.023	3.0	3.0
Heart failure, chronic or unspecified only	17.4	17.2	0.004	16.7	16.7
Heart failure, acute	11.5	13.4	-0.059	11.4	11.4
Bleeding: gastrointestinal, intracranial, or at other sites	16.0	16.6	-0.016	16.1	16.1
Dysphagia or malnutrition	13.9	13.2	0.021	13.5	13.6
Fall	12.1	12.2	-0.003	12.1	12.1
Acute or unspecified kidney failure	12.0	12.5	-0.014	11.8	11.8
Cardioversion	10.5	12.2	-0.054	10.9	10.9
Percutaneous intervention	8.6	11.7	-0.103	8.9	8.9
Alzheimer disease and other dementias	7.5	8.1	-0.022	7.6	7.6
Ischemic stroke or systemic embolism	6.8	8.1	-0.049	7.1	7.1
Coronary artery bypass graft	5.5	9.0	-0.134	6.0	6.0
Myocardial infarction	5.0	8.1	-0.123	5.5	5.5
Transient ischemic attack	4.9	5.8	-0.039	5.1	5.1

(continued)

ischemic stroke or systemic embolism or death without recent evidence of bleeding was not significantly altered.

**HAS-BLED Score and Specific Anticoagulant Use**

The RDs for the primary composite outcome increased with diltiazem dose, increasing HAS-BLED scores, and rivaroxaban use (eFigure 2 in Supplement 1). For diltiazem doses exceeding 120 mg/d, the RD for patients with HAS-BLED scores of 1 or 2 was 9.8 (95% CI, 4.1-15.6) per 1000 person-years com-

pared with 22.0 (95% CI, 10.0-33.9) per 1000 person-years for scores of 4 or higher, and for patients receiving apixaban, the RD was 12.0 (95% CI, 6.1-17.9) per 1000 person-years compared with 21.2 (95% CI, 12.2-30.2) per 1000 person-years for patients receiving rivaroxaban.

**Sensitivity Analyses**

The diltiazem group had a dose-dependent increased risk of the primary composite outcome in all sensitivity analyses

Table 1. Unweighted and Weighted Demographics, Comorbidity, and Medications in the Cohort at Baseline (continued)

Covariate <sup>a</sup>	Unweighted <sup>b</sup>			Weighted <sup>b</sup>	
	Diltiazem	Metoprolol	SMD <sup>c</sup>	Diltiazem	Metoprolol
Prescriptions, past 90 d unless otherwise noted					
Angiotensin-converting enzyme inhibitor or receptor blocker	48.1	51.7	-0.073	48.8	48.9
Proton pump inhibitors	24.9	23.8	0.026	24.3	24.3
Diuretics, furosemide	18.7	20.1	-0.037	18.4	18.4
Diuretics, other loop	2.3	2.6	-0.021	2.3	2.3
Home oxygen (past year)	11.8	6.4	0.190	9.2	9.2
β-Blockers, carvedilol	10.6	5.0	0.209	8.2	8.2
β-Blockers, other	13.8	8.4	0.173	12.2	12.2
P2Y12 inhibitors or other antiplatelet drugs <sup>d</sup>	7.0	9.0	-0.073	7.1	7.1
Other PGP/3A4 inhibitors <sup>e</sup>	6.6	5.8	0.031	6.3	6.3
Amiodarone	6.9	11.0	-0.143	7.8	7.8
Flecainide	3.9	3.7	0.009	4.0	4.0
Sotalol	4.3	2.9	0.078	3.9	3.9
Medications in past year, mean (SD), No.	12.6 (6.0)	12.0 (5.7)	0.112	12.3 (4.7)	12.3 (2.9)

Abbreviations: NA, not applicable; SMD, standardized mean difference.

<sup>a</sup> Selected representative covariates (eTable 7 in Supplement 1 gives the complete set).

<sup>b</sup> Data are presented as percentage of patients unless otherwise indicated.

<sup>c</sup> The SMD (difference between variable means divided by pooled estimate of the SD) is a measure of balance of covariates between treatment groups, with values less than 0.1 considered to indicate good balance. After weighting, all SMDs were less than 0.01 and thus are not shown. By construction, overlap weighting produces equal means in the 2 groups if logistic regression is used to estimate the propensity score.<sup>51,52</sup> The weighted means of some variables have minor differences because they are composites of individual variables in the propensity score. For example, the propensity score contains individual terms for specific types of cancer; however, for conciseness, the table shows the composite of these individual covariates.

<sup>d</sup> The standard dose for apixaban is 5 mg twice daily and for rivaroxaban, 20 mg once daily.

<sup>e</sup> Includes Asian, Hispanic, North American Native, other, and unknown

<sup>f</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASC score for stroke risk stratification<sup>44</sup> gives 1 point for age 65

to 74 years, female sex, heart failure, hypertension, diabetes, vascular disease (myocardial infarction, peripheral artery disease, and aortic plaque) and 2 points for age 75 years or older and stroke, transient ischemic attack, or thromboembolism. The claims-based version of the score<sup>45-47</sup> was calculated from Medicare claims.

<sup>g</sup> The claims-based version of the HAS-BLED score for bleeding risk stratification<sup>45</sup> gives 1 point for hypertension, 1 point for age 65 years or older, 1 point for abnormal kidney function, 1 point for abnormal liver function, 1 point for stroke, 1 point for prior bleeding propensity, 1 point for antiplatelet or nonsteroidal anti-inflammatory drugs, and 1 point for alcohol use disorder. The original score also gives 1 point for labile International Normalized Ratio; however, this measure is not available in claims data.

<sup>h</sup> Acute myocardial infarction, coronary artery bypass graft, stent or angioplasty, ischemic stroke, transient ischemic attack, peripheral vascular disease, and carotid artery disease.

<sup>i</sup> P2Y12 inhibitors included clopidogrel, prasugrel, ticagrelor, and ticlopidine, and other drugs were cilostazol, dipyridamole, and vorapaxar.

<sup>j</sup> Erythromycin, clarithromycin, ciprofloxacin, and azole antifungals.

(eTable 12 in Supplement 1). The increased risk was present in the modified intention-to-treat analysis, which did not censor patients who stopped or switched rate-control medications. When patients receiving high-dose diltiazem treatment were directly compared with those receiving low-dose treatment, the HR was 1.14 (95% CI, 1.02-1.26). There was no evidence of increased risk for fracture of the proximal femur, the falsification end point (HR, 0.99 [95% CI, 0.82-1.20]) (eTable 13 in Supplement 1).

## Discussion

In this national cohort study of 204 155 Medicare beneficiaries aged 65 years or older with atrial fibrillation who initiated apixaban or rivaroxaban use and also began treatment with diltiazem or metoprolol, diltiazem treatment was associated with a significantly increased risk of serious bleeding, defined as a bleeding-related hospitalization or death with recent evidence of bleeding, compared with metoprolol treatment. The risk of the primary composite outcome for initial

diltiazem doses higher than 120 mg/d was greater than that for lower doses. Although neither diltiazem dose was associated with a significant change in the risk of ischemic stroke or systemic embolism or of death without recent evidence of bleeding, patients receiving doses higher than 120 mg/d had increased risk for major ischemic or hemorrhagic events.

The absolute risk of serious bleeding associated with diltiazem treatment increased with diltiazem doses higher than 120 mg/d; increased HAS-BLED score, which summarizes common risk factors for anticoagulant-related hemorrhage; and rivaroxaban use, which has been consistently associated with rates of serious bleeding greater than those for other direct oral anticoagulants.<sup>42,43,59,60</sup> For every 1000 person-years of treatment with diltiazem doses higher than 120 mg/d, there were an additional 15 cases of the primary composite outcome, which increased to 22 for patients with HAS-BLED scores of 4 or greater and 21 for patients who received rivaroxaban. Thus, measures to reduce the clinical impact of the interaction of diltiazem with study anticoagulants should target high-risk patients, including those with advanced age, history of bleeding, pro-hemorrhagic medication use, or rivaroxaban use.

Table 2. Study Outcomes

Outcome	Diltiazem (PY = 22 162)		Metoprolol (PY = 68 765)		Adjusted analysis <sup>a</sup>			
	Patients with event, No.	Rate, per 1000 PY	Patients with event, No.	Rate, per 1000 PY	Rate, per 1000 PY		Rate difference, per 1000 PY (95% CI)	Hazard ratio (95% CI)
					Diltiazem	Metoprolol		
Primary composite outcome and its components								
Serious bleeding	1560	70.4	3709	53.9	60.3	49.7	10.6 (7.0 to 14.2)	1.21 (1.13 to 1.29)
Bleeding-related hospitalization	1129	50.9	2740	39.8	44.8	36.6	8.2 (5.1 to 11.4)	1.22 (1.13 to 1.31)
Intracranial or fatal extracranial <sup>b</sup>	174	7.9	553	8.0	7.9	7.4	0.5 (−0.9 to 1.9)	1.07 (0.89 to 1.28)
Nonfatal extracranial	955	43.1	2187	31.8	36.6	29.0	7.6 (4.8 to 10.4)	1.25 (1.16 to 1.36)
Death, recent evidence of bleeding <sup>c</sup>	431	19.4	969	14.1	15.5	13.0	2.4 (0.6 to 4.2)	1.19 (1.05 to 1.34)
Secondary outcomes								
Ischemic stroke or systemic embolism	195	8.8	694	10.1	8.3	9.5	−1.2 (−2.6 to 0.3)	0.87 (0.74 to 1.03)
Major ischemic or hemorrhagic event <sup>d</sup>	800	36.1	2216	32.2	32.0	30.1	1.9 (−0.8 to 4.6)	1.06 (0.97 to 1.16)
Death without recent evidence of bleeding <sup>e</sup>	1064	48.0	2725	39.6	40.4	38.8	1.6 (−1.5 to 4.7)	1.04 (0.96 to 1.12)

Abbreviation: PY, person-years.

<sup>a</sup> Adjusted with overlap weighting. The variables used in the adjustment are shown in eTable 7 in Supplement 1.

<sup>b</sup> Death within 30 days of the date of the hemorrhage.

<sup>c</sup> In the 30 days preceding death, a secondary inpatient diagnosis or any outpatient diagnosis of hemorrhage or allogeneic blood transfusion.

<sup>d</sup> Composite of ischemic stroke, systemic embolism, intracranial bleeding, fatal bleeding-related hospitalization, and death with recent evidence of bleeding.

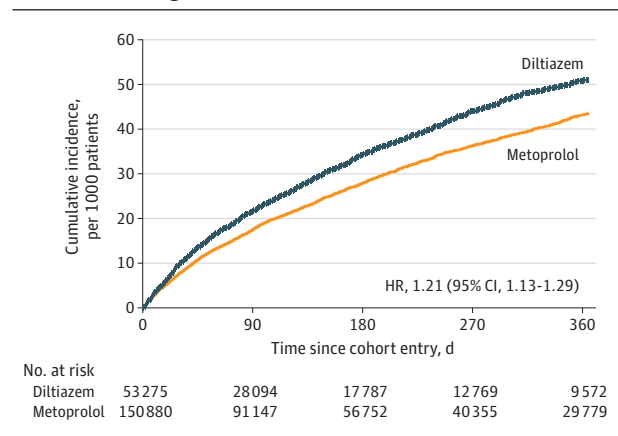
<sup>e</sup> Did not meet the definition for death with recent evidence of bleeding.

Although  $\beta$ -blockers, the primary alternative medications for rate control in atrial fibrillation, could be prescribed for high-risk patients, diltiazem has several advantages. It is not relatively contraindicated for those with chronic obstructive pulmonary disease and bronchospasm,<sup>7</sup> may provide better rate control and reduction of arrhythmia symptoms,<sup>61,62</sup> and is preferred for hypertension.<sup>63</sup> Consequently, many patients with atrial fibrillation and elevated risk of hemorrhage will continue to be treated with diltiazem and direct factor Xa inhibitors. If, as postulated, elevated anticoagulant plasma concentrations mediate the increased risk of serious bleeding associated with diltiazem, therapeutic drug monitoring could be studied in patients for whom diltiazem is indicated.

**Limitations**

There are several limitations. First, in this nonrandomized study, there may be confounding by unmeasured factors. Although Medicare files do not record aspirin use, the distribution of a surrogate—cardiovascular diagnoses for which aspirin prophylaxis is recommended—was balanced across study groups after propensity score adjustment for more than 200 covariates that reflected patient health across several domains. An investigation that linked claims data for direct oral anticoagulants with electronic health records reported that after propensity score adjustment, minimal differences remained between treatments in glomerular filtration rate, weight, low-dose aspirin use, and other factors.<sup>64</sup> Other unmeasured factors, including practitioner and patient preferences, could differ between treatment groups. However, if awareness of the potential diltiazem-factor Xa inhibitor in-

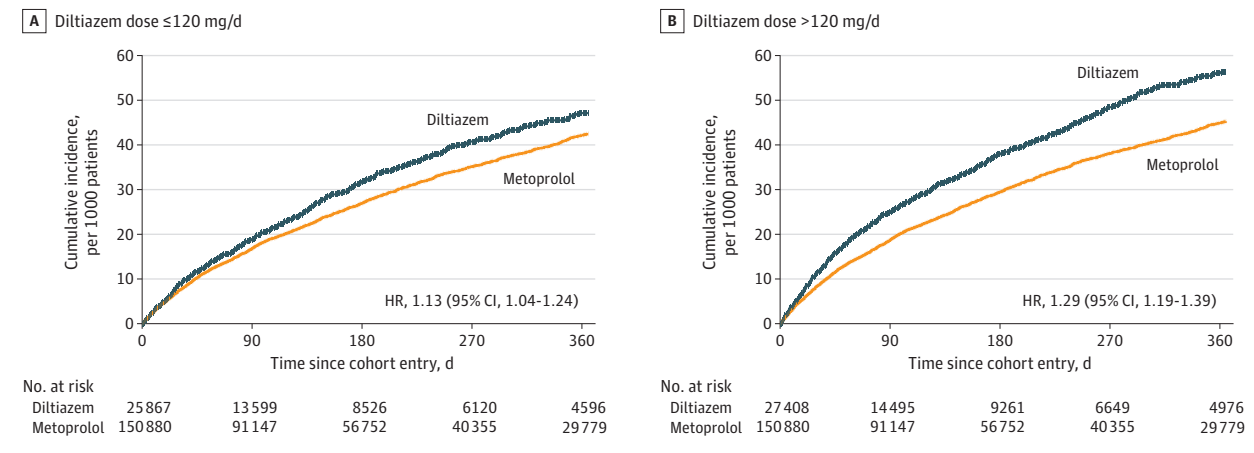
Figure 1. Adjusted Cumulative Incidence of the Primary Composite Outcome According to Rate Control Treatment



The primary composite outcome was a bleeding-related hospitalization or death with recent evidence of bleeding. Analysis was adjusted for the covariates listed in eTable 7 in Supplement 1 with overlap weighting (eAppendix 5C in Supplement 1). Cumulative incidence was calculated as 1 − S(t), where S is the survival function estimated in a weighted proportional hazards analysis stratified by study ventricular rate-control drug and with no terms in the model. The median length of follow-up was 101 (IQR, 59-258) days for diltiazem and 120 (IQR, 59-290) days for metoprolol.

teraction led to assignment of patients with greater risk of bleeding to metoprolol, the bias would be conservative. The absence of increased risk for major ischemic events and death with no recent evidence of bleeding, the dose-response relationship, and the negative outcome control analysis suggest that confounding does not explain study findings.

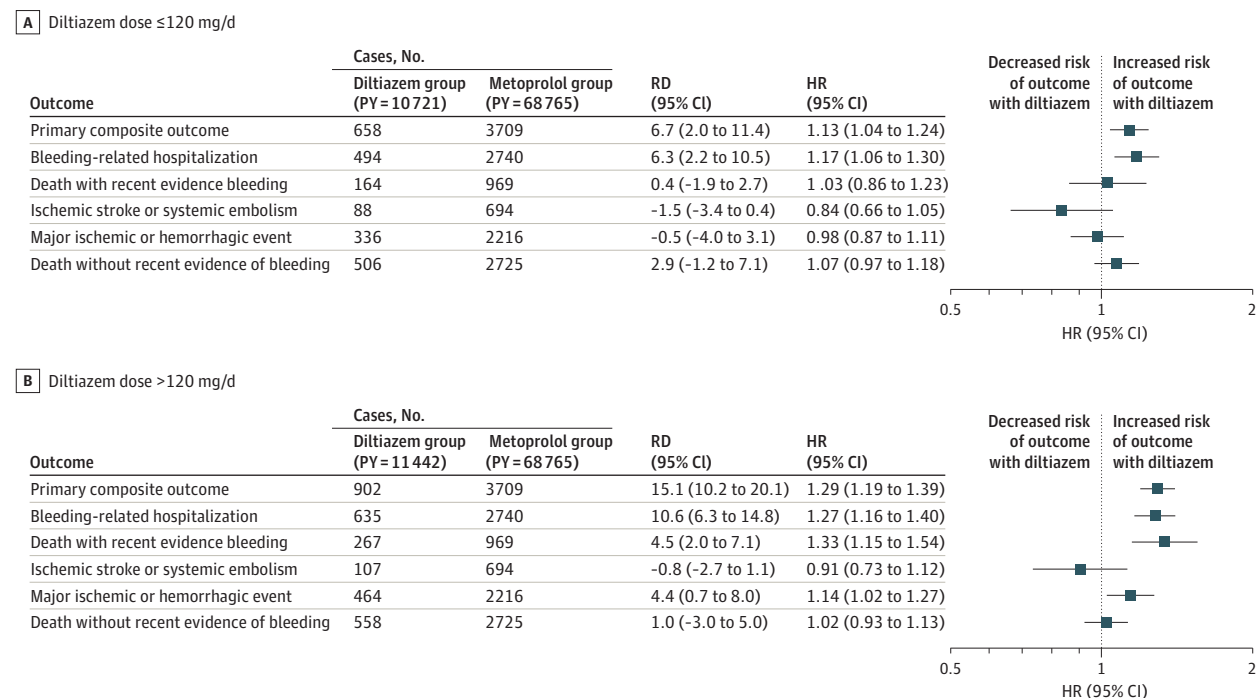
**Figure 2. Adjusted Cumulative Incidence of the Primary Composite Outcome According to Ventricular Rate-Control Treatment and Initial Diltiazem Dose**



The primary composite outcome was bleeding-related hospitalization or death with recent evidence of bleeding. Analysis was adjusted for the covariates listed in eTable 7 in Supplement 1 with overlap weighting (eAppendix 5C in Supplement 1). Cumulative incidence was calculated as  $1 - S(t)$ , where  $S$  is the survival function estimated in a weighted proportional hazards analysis

stratified by study rate control drug and with no terms in the model. The median length of follow-up for diltiazem was 100 (IQR, 59-253) days for doses of 120 mg/d or lower and 102 (IQR, 58-262) days for doses higher than 120mg/d and that for metoprolol was 120 (IQR, 59-290) days.

**Figure 3. Adjusted Risk of Study Outcomes According to Initial Diltiazem Dose**



Analysis was adjusted for the covariates listed in eTable 7 in Supplement 1 with overlap weighting. HR, indicates hazard ratio; PY, person-years; RD, rate difference.

Second, informative censoring could introduce bias, as patients in the diltiazem group changed treatment more frequently and thus were censored. However, if bleeding signs or symptoms led to ending diltiazem treatment, the bias would be conservative. Furthermore, a sensitivity analysis that did not censor patients who changed rate-control treatment had essentially identical findings.

Third, exposure, outcomes, and covariates were defined by data routinely collected in clinical practice and thus may be misclassified. Patients in both treatment groups had concurrent use of the prescribed anticoagulant and rate-control medication for 83% of follow-up days, indicating nondifferential exposure misclassification, which should bias toward the null. The definition for death with recent evidence of bleeding



used outpatient diagnoses and procedures and may have included deaths unrelated to hemorrhage.

Fourth, other effects of diltiazem and metoprolol may contribute to the differences in study outcomes. Case-control studies found associations of calcium channel blockers with increased gastrointestinal bleeding<sup>65</sup>; however, this finding was not confirmed by subsequent studies.<sup>66-68</sup> Nonselective  $\beta$ -blockers are associated with reduced bleeding from gastroesophageal varices in patients with cirrhosis,<sup>69</sup> but in more general populations,  $\beta$ -blockers are not associated with upper gastrointestinal bleeding.<sup>70</sup>

Fifth, generalizability was limited. Neither edoxaban, a factor Xa inhibitor,<sup>71</sup> nor verapamil, a rate-control medication<sup>7</sup>

that strongly inhibits CYP3A4 and p-GP,<sup>72,73</sup> were studied because of infrequent use. The cohort included only Medicare beneficiaries aged 65 years or older with both fee-for-service coverage and enrollment in the Part D program for prescription medications.

## Conclusions

In a cohort of Medicare patients with atrial fibrillation receiving apixaban or rivaroxaban, diltiazem was associated with greater risk of serious bleeding than metoprolol, particularly for diltiazem doses exceeding 120 mg/d.

### ARTICLE INFORMATION

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