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Association of Multimorbidity with Cardiovascular Endpoints and Treatment Effectiveness in Patients 75 years and older with Atrial Fibrillation

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Abstract

Background: The burden imposed by multimorbidity on outcomes and on the effectiveness of atrial fibrillation therapies in elderly adults with atrial fibrillation is unknown.

Methods: Patients with non-valvular atrial fibrillation ≥75 years in the MarketScan Medicare Supplemental database from 2007–2015. Prevalence of 14 chronic conditions at the time of atrial fibrillation diagnosis were obtained and classified as cardiometabolic or non-cardiometabolic. Cox regression estimated the associations of the number and type of conditions with stroke, severe bleeding, and heart failure hospitalizations. Tests for interaction were assessed between atrial fibrillation treatments and multimorbidity.

Results: Among 275,617 patients with atrial fibrillation (mean age 83 years, 51% women), the mean (SD) number of conditions per participant was 3.0 (2.1). Over a mean follow-up of 23 months, 7,814 strokes, 13,622 severe bleeds, and 19,252 heart failure events occurred. After adjustment, an increase in the number of cardiometabolic conditions was associated with greater risk of stroke (HR=1.07,95%CI 1.05–1.10), severe bleeding (HR=1.09,95%CI 1.07–1.11), and heart failure (HR=1.19,95%CI 1.18–1.20). In contrast, number of non-cardiometabolic conditions had weak or null associations with risk of cardiovascular endpoints. Overall, the effectiveness of atrial fibrillation treatment on stroke and heart failure were similar across multimorbidity status,

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but bleeding risk associated with atrial fibrillation treatments was higher in patients with overall and subgroup multimorbidity.

Conclusion: Cardiometabolic multimorbidity was associated with worse outcomes and modified bleeding risk in AF patients. These findings underscore the impact of cardiometabolic conditions on atrial fibrillation outcomes and highlights the need to incorporate multimorbidity management in atrial fibrillation treatment guidelines.

Keywords

Atrial Fibrillation; Multimorbidity; Elderly; Cardiovascular Disease

Introduction

Atrial fibrillation affects 2.7–6.1 million individuals in the United States,[1] and is projected to affect 12 million by 2050.[2] The prevalence of atrial fibrillation dramatically increases with age, ranging from 0.1% among adults younger than 55 years to more than 1 in 10 individuals 70 years and older to approximately 1 in 6 in persons 85 years and older.[3,4] Advancing age is often accompanied by a higher burden of multiple chronic conditions, polypharmacy, and frailty.[5,6] With considerable growth expected in the older population in the U.S., projections suggest that adults aged 65 and over will make up 21% (estimated 84 million adults) of the population by 2050.[7] This changing demography has serious implications on the future of healthcare management and delivery.

Multimorbidity is defined as the coexistence of two or more chronic conditions.[8] Its prevalence increases steeply with age, with approximately three in four individuals age 65 and older having multiple chronic conditions.[9,10] Multimorbidity is common in atrial fibrillation, affecting the vast majority of patients. It is estimated that approximately 98% of patients with atrial fibrillation have one additional chronic condition.[11,12] Despite a high prevalence of multimorbidity in older adults with atrial fibrillation, current atrial fibrillation treatment guidelines do not specifically consider the management of multiple chronic conditions and their impact on atrial fibrillation-specific treatments.[1,13] Atrial fibrillation is associated with increased morbidity, especially stroke[14] and heart failure,[15] with older age being a strong determinant of the risk of adverse outcomes in atrial fibrillation.[16–18] In addition, the greater prevalence of co-occurring diseases in the elderly population adds further complexity to the care and management of patients with atrial fibrillation. To date, however, there is little evidence on the impact of multimorbidity or comorbidity type on atrial fibrillation outcomes and the effectiveness of atrial fibrillation treatment in adults ≥75 years and older. Therefore, the primary objectives of the study were to determine 1) the effect of the number and type of conditions (cardiometabolic or non-cardiometabolic) on cardiovascular outcomes (i.e., stroke, severe bleeding, and heart failure) and 2) whether the effectiveness of treatments on outcome differs by multimorbidity status.

Methods

Study Population

We used health care claims data from the Truven Health MarketScan® Medicare Supplemental and Coordination of Benefits Database[19] (Truven Health Analytics Inc., Ann Arbor, MI, USA) from January 1, 2007 through September 30, 2015. Details about the database are included in the online supplement.

The analysis was restricted to individuals with a history of non-valvular atrial fibrillation, defined in the online supplement. Furthermore, patients were required to have at least six months of continuous enrollment before their initial atrial fibrillation diagnosis and be aged ≥75 years at the time of atrial fibrillation diagnosis. The Institutional Review Board at Emory University reviewed and approved this study, and waived the need for patient consent.

Definition of Multimorbidity

Comorbidities were defined using ICD-9-CM codes from inpatient and outpatient claims prior to or at the time of atrial fibrillation diagnosis. Two occurrences of a code for a given condition (either the same code or two different codes for the given condition) separated by more than 30 days were required to confirm diagnosis. The selection of comorbidities were guided by the 20 chronic conditions identified by the US Department of Health and Human Services (DHHS) for studying multimorbidity.[20] We excluded autism spectrum disorder and human immunodeficiency virus infection due to low prevalence in the general elderly population,[11] hepatitis, schizophrenia, and substance abuse disorders due to low prevalence in our data, and cardiac arrhythmias because the entire cohort has atrial fibrillation, resulting in 14 chronic conditions. More information on the ICD-9-CM codes used to define each chronic condition is provided in Supplementary Table I.

For this paper, we examined overall multimorbidity (defined as 2 or more chronic conditions) as well as conditions characterized into two categories: cardiometabolic conditions and non-cardiometabolic conditions. Cardiovascular diseases and cardiovascular risk factors were used to define cardiometabolic conditions and included heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, and diabetes mellitus. Non-cardiometabolic conditions included arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis. In the primary analysis, we explored the complexity of multimorbidity by focusing on the number of comorbidities within each category.

Definition of Outcome Variables

Outcomes of interest included a hospitalization for an ischemic stroke or systemic embolism, severe bleeding, or heart failure. Each outcome was defined by presence of ICD-9-CM codes as the primary discharge diagnosis in any inpatient claim after atrial fibrillation date. Additional details are provided in the Supplemental Methods.

Covariates

Covariates were defined based on inpatient and outpatient claims during the enrollment period prior to or at the time of atrial fibrillation diagnosis. Demographic characteristics, comorbidities, procedures, and pharmacy fills were ascertained. A frailty index was defined using a published algorithm developed from inpatient and outpatient claims using ICD-9 codes found in Supplementary Table II.[21] ICD-9-CM codes for arthritis, stroke and dementia were excluded from the frailty algorithm due to overlap with the main exposure variable. A list of prescription medications included is available in the Supplemental Methods.

Treatment Variables

Anticoagulant use—All prescriptions for oral anticoagulants (OAC; warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban) within 30 days of atrial fibrillation diagnosis were identified. Although there is no information available on the validity of claims for direct OAC prescriptions, the validity of warfarin claims in administrative databases is excellent (positive predictive value >99%).[22]

Rate and Rhythm control—atrial fibrillation control therapies were defined based on inpatient, outpatient, and outpatient pharmacy claims within 30 days of atrial fibrillation diagnosis from June 30, 2007 to September 30, 2015. Precise definitions and codes used to define rate and rhythm control therapies are provided in the supplemental methods. Patients receiving both rate and rhythm control therapy were categorized as rhythm control.

Statistical analysis

Baseline characteristics are presented as frequencies and mean (SD) for the entire cohort and across cardiometabolic/non-cardiometabolic comorbidity categories. Follow-up started at the date of the AF diagnosis and continued until a hospitalization for the outcome of interest occurred, September 30, 2015, or patient health plan disenrollment, whichever occurred earlier. Cox proportional hazards regression was used to determine associations between the number of comorbidities within each category of conditions with each outcome (ischemic stroke or systemic embolism, severe bleeding, or heart failure). Models were initially adjusted for age, sex, and the number of conditions of the other comorbidity group [Model 1], with subsequent adjustments for frailty index [Model 2] and medications [Model 3].

We tested for interactions between treatments for atrial fibrillation and any multimorbidity to determine whether the effect of treatment on outcomes differs by multimorbidity status. Interactions were assessed separately for each of the three outcomes. The overall multimorbidity variable incorporated all comorbidities (defined as 2 or more chronic conditions). Cardiometabolic and non-cardiometabolic multimorbidity variables were defined as 2 or more chronic conditions within the given type. Multiplicative interaction was assessed by including multimorbidity by treatment product terms in the models and performing stratified analyses. Treatment comparisons included no anticoagulation vs. oral anticoagulation and rate vs. rhythm control therapy. The proportional hazard assumption was tested using time dependent covariates in a cox model and Schoenfeld residuals and found to be valid. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Results

Of the 275,617 individuals with atrial fibrillation 75 years and older, 90% had at least one or more additional chronic condition. The most prevalent conditions were hypertension, coronary artery disease, hyperlipidemia, and diabetes mellitus (Table 1). Of the 14 chronic conditions evaluated, the overall mean (SD) number of comorbid conditions per patient was 3 (2.1); the mean (SD) number of cardiometabolic and non-cardiometabolic conditions were 2.4 (1.2) and 1.7 (0.9), respectively. The mean (SD) age of the cohort was 83.2 (5.4) years, with an average CHA_2DS_2-VASc score of 4.1.

Over a mean follow up of 1.9 years, 7,814 ischemic stroke and systemic embolism, 19,252 heart failure, and 13,622 severe bleeding events occurred. Adjusted hazard ratios (HR) by condition category and outcome are presented in Table 2. An increase of one cardiometabolic condition was associated with a stronger increased risk of outcomes compared to an increase in one non-cardiometabolic condition. Results were similar when stratified by age (Supplemental Table III). After adjustment for age, sex, the number of conditions of the other type, frailty, and medications, there was a 7% increased rate of stroke per increase of one cardiometabolic condition (HR = 1.07, 95% confidence interval (CI): 1.05–1.10). For an increase of one non-cardiometabolic condition, the rate of stroke was reduced by 7% (HR = 0.93, 95% CI = 0.90–0.95). The rate of severe bleeding per increase of one cardiometabolic condition was 9% (HR = 1.09) and the rate per increase of one non-cardiometabolic conditions was 4% (HR = 1.04). The rate of heart failure per increase of one cardiometabolic condition was 19% (HR = 1.19) and the rate per increase of one non-cardiometabolic conditions was not associated with heart failure (HR = 1.00). We also observed a dose response relationship between multimorbidity burden and each outcome (Supplemental Table IV). Those with 4 or more conditions were at highest risk of disease compared to those with < 2 conditions.

The tests for interaction between treatments for atrial fibrillation and multimorbidity burden (overall, cardiometabolic, or non-cardiometabolic) show that, for most of the comparisons, the effectiveness of atrial fibrillation treatment on cardiovascular outcomes of stroke, major bleeding, and heart failure, does not differ by multimorbidity status (Tables 3–4 & Supplementary Table V – VI). However, there were four comparisons where we observed a significant multiplicative interaction. First, presence of overall multimorbidity, defined as 2 or more chronic conditions, modified the association of OAC use (vs. none) with major bleeding. Specifically, the association of OAC use with bleeding was stronger in those with overall multimorbidity (HR 1.27, 95% CI 1.21–1.33) than those without (HR 1.11, 95% CI 1.03–1.19, p for interaction = 0.01) (Table 3). Second, rhythm control (vs. rate control) treatment was associated with reduced rate of major bleeding in those without multimorbidity (HR 0.80, 95%CI 0.70–0.93) but not among those with multimorbidity (HR 1.00, 95%CI 0.93–1.07, p for interaction = 0.004) (Table 4). Finally, OAC use (vs. none) was associated with slightly increased risk of bleeding in those with cardiometabolic multimorbidity (HR 1.29, 95%CI 1.20–1.39) and non-cardiometabolic multimorbidity (HR 1.30, 95%CI 1.22–1.37) compared to those without multimorbidity (HR 1.20, 95%CI 1.15–1.26 for no cardiometabolic multimorbidity and HR 1.23, 95%CI 1.17–1.30 for no non-cardiometabolic multimorbidity) (Supplementary Table III).

Discussion

In this analysis, we found that individuals with atrial fibrillation aged 75 years and older have, on average, 3 additional chronic conditions, with hypertension being the most prevalent condition. Cardiometabolic comorbidity was associated with a higher risk of stroke, heart failure, and bleeding compared to non-cardiometabolic comorbidity. Our findings also indicate that multimorbidity did not modify the effectiveness of atrial fibrillation treatments (i.e., anticoagulation, rhythm therapy) on risk of stroke and heart failure. However, there was some evidence that multimorbidity status modified the association of atrial fibrillation treatments with bleeding risk. These results have important implications on the healthcare delivery and management of elderly adults with atrial fibrillation.

We found that 90% of atrial fibrillation patients 75 years and older had at least one additional comorbidity, which is consistent with findings in other populations.[11] A high prevalence of multiple chronic conditions is common among the elderly. The burden of multimorbidity in individuals over 65 years has been well documented, with estimates between 67% and 92%.[23,24] In individuals with atrial fibrillation, the burden of multiple chronic diseases are predominantly from cardiovascular-related diseases, including hypertension, heart failure, coronary heart disease, and diabetes.[12,25,26] This high burden of cardiovascular multimorbidity is likely responsible for the elevated rates of hospitalization among patients with atrial fibrillation.[11,26,27] Understanding the patterns of multimorbidity in atrial fibrillation patients and characterizing their impact on atrial fibrillation-related endpoints is, therefore, key to improving the overall management and outcomes of these patients.

The management of atrial fibrillation focuses on two major goals: first, to reduce thromboembolic risk (predominantly strokes) and second, to improve quality of life and outcomes by reducing and controlling symptoms and, when possible, restoring sinus rhythm. The first goal is achieved using OACs. The American guidelines for the management of patients with atrial fibrillation recommends the use of OACs for stroke risk reduction in individuals with a CHA_2DS_2VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Prior Stroke or TIA or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category) score of 2 or greater.[1] Although anticoagulation therapy is effective in stroke risk reduction, the decision to begin anticoagulation cannot be fully evaluated without consideration of the increased risk of treatment-related severe bleeding. Several risk scores that quantify bleeding risk exist;[17,28,29] however, like the CHA_2DS_2VASc score, these scores may be insufficient in characterizing risk in patients ≥ 75 years where the combination of chronic conditions may be more important that traditional clinical risk factors.[5] Our study shows that individuals who are prescribed an OAC are less likely to have a stroke compared to those not prescribed an OAC and that this association did not differ by an individual's multimorbidity status. However, the risk of bleeding associated with OAC was significantly higher among those with multimorbidity. Although literature suggests that the net clinical benefit of OACs, balancing stroke prevention and bleeding risk, is crucial in older adults,[30–32] our results suggest that considering multimorbidity status when evaluating risk scores may inform decisions around anticoagulation in atrial fibrillation.

The second goal in the management of individuals with atrial fibrillation is achieved by using rate or rhythm control. In older adults, a rate control strategy is often the preferred first choice,[33,34] but there is conflicting evidence regarding the superiority of one strategy over the other.[34–36] In our analysis, rhythm control was associated with better outcomes than rate control, but the comparative effectiveness of rhythm versus rate control was modified by multimorbidity status, particularly for the major bleeding endpoint. Though we recognize that these results are likely confounded, they highlight the role that multimorbidity may have in affecting outcomes of rhythm control approaches.

The high prevalence of multimorbidity in atrial fibrillation patients 75 years and older and the impact of multimorbidity on the effectiveness of atrial fibrillation treatments underscores the need to factor in multimorbidity status in the management of these patients. Clinical guidelines, including the atrial fibrillation treatment guidelines,[1] prioritize single disease care, with limited consideration of presence of multiple comorbidities. However, net benefit and harm of any atrial fibrillation treatment is likely to be modified by coexisting conditions and their accompanying treatments. Therefore, evaluating the interaction between atrial fibrillation treatments and multimorbidity, particularly among those aged ≥75, is a necessary step to improve atrial fibrillation outcomes.

Strengths & Limitations

This study has several strengths, including being a real-world analysis that focuses on important cardiovascular outcomes in atrial fibrillation and the effect of atrial fibrillation treatment across multimorbidity status among individuals ≥ 75, a population for which evidence on the management of atrial fibrillation is limited. Second, we evaluate associations across cardiometabolic and non-cardiometabolic conditions, providing evidence about the type of conditions that may have a stronger impact on the management of elderly atrial fibrillation individuals.

We acknowledge the following limitations: Foremost, study findings rely on our ability to accurately ascertain outcomes, chronic conditions, and covariates using diagnostic codes in administrative data. Validated algorithms were used to ascertain events of interest and it is likely that any misclassification is non-differential. To identify chronic conditions, we required two occurrences of a diagnostic code separated by more than 30 days to reduce false-positive diagnoses. Second, we did not consider an extensive list of chronic conditions. We instead focused on the DHHS 20 chronic conditions selected for the study of multiple chronic conditions. Third, residual confounding may exist. Baseline confounding factors that contribute to treatment decisions may be only accounted for partially. Also, geriatric conditions and frailty contribute to the complexity of multimorbidity with outcomes in this population and may not be well defined in a claims database. Fourth, the estimates in this analysis may be affected by lack of mortality data in the database and the definition of our outcomes, which were limited to ICD-9-CM codes with high positive predictive values in an inpatient hospital claim. It is possible that individuals died before developing one of our events of interest or the event occurred outside the hospital setting and not included in the analysis. Finally, due to the nature of the database, we lacked information on race/ethnicity and information on atrial fibrillation types.

In conclusion, multimorbidity is common among older atrial fibrillation patients, and a higher number of cardiometabolic comorbidities was more strongly associated with stroke, heart failure, and major bleeding than non-cardiometabolic comorbidities. Multimorbidity was not associated with differential effectiveness of atrial fibrillation treatments (i.e., anticoagulation, rhythm therapy) on risk of stroke and heart failure. However, multimorbidity status modified the association of atrial fibrillation treatments with bleeding risk. These data underscore the importance of cardiometabolic conditions on cardiovascular outcomes and highlights that multimorbidity status may impact the effectiveness of atrial fibrillation treatment on bleeding risk in a population where multimorbidity is pervasive and health care delivery is complex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Patient characteristics and prevalence of comorbidities overall and among those with at least one additional comorbidity at the time of AF diagnosis, MarketScan 2007–2015

	Entire Population	≥1 Cardiometabolic conditions†	≥1 Non-Cardiometabolic conditions†
N	275,617	228,700	172,374
Age (years), mean (SD)	83.2 (5.4)	83.2 (5.4)	83.4 (5.4)
Women, %	50.7	50.4	50.3
CHA_2DS_2-VASc, mean (SD)	4.1 (1.5)	4.5 (1.4)	4.4 (1.5)
Cardiometabolic comorbidities, %			
Coronary artery disease	36.0	43.4	41.0
Diabetes mellitus	25.4	30.6	28.6
Heart failure	24.0	29.0	29.6
Hyperlipidemia	31.1	37.4	35.6
Hypertension	61.6	74.3	69.3
Stroke or transient ischemic attack	17.7	21.3	21.0
Non-cardiometabolic comorbidities, %			
Arthritis	21.4	23.5	34.2
Asthma	4.7	5.1	7.5
Cancer	23.9	25.2	38.2
Chronic kidney disease	19.6	22.5	31.4
Chronic obstructive pulmonary disease	17.6	19.2	28.1
Dementia	9.8	10.7	15.7
Depression	4.9	5.4	7.8
Osteoporosis	4.9	5.3	7.8
No. of comorbidities, mean (SD)	3.0 (2.1)	2.4 (1.2)	1.7 (0.9)
No. of comorbidities, median (IQR)	3 (1,4)	2 (1,3)	1 (1,2)
No. of comorbidities, N (%)			
0	27,687 (10.1)		
1	44,343 (16.1)		
2	51,051 (18.5)		
3	48,827 (17.7)		
4	40,233 (14.6)		
5	28,910 (10.5)		
6	17,808 (6.5)		
≥ 7	16,758 (6.1)		
Frailty, %	54.9	59.7	67.8

† **Cardiometabolic conditions:** heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, and diabetes mellitus.

†† **Non-cardiometabolic conditions:** arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis.

Table 2.

Hazard ratios for stroke, severe bleeding, and heart failure per increase of one additional condition by comorbidity group, MarketScan 2007–2015.

	Cardiometabolic conditions*	Non- Cardiometabolic conditions**
	HR (95% CI)	**HR (95% CI)**
Ischemic stroke and systemic embolism		
Model 1†	1.10 (1.08, 1.12)	0.93 (0.91, 0.96)
Model 2††	1.09 (1.07, 1.11)	0.92 (0.90, 0.94)
Model 3‡	1.07 (1.05, 1.10)	0.93 (0.90, 0.95)
Severe bleeding		
Model 1†	1.13 (1.12, 1.14)	1.07 (1.05, 1.09)
Model 2††	1.12 (1.11, 1.13)	1.06 (1.04, 1.08)
Model 3‡	1.09 (1.07, 1.11)	1.04 (1.02, 1.06)
Heart failure		
Model 1†	1.30 (1.29, 1.31)	1.03 (1.02, 1.04)
Model 2††	1.30 (1.29, 1.32)	1.03 (1.02, 1.05)
Model 3‡	1.19 (1.18, 1.20)	1.00 (0.99, 1.02)

*Cardiometabolic conditions: heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, and diabetes mellitus.

**Non-cardiometabolic conditions: arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis.

†Model 1: age, sex, number of conditions of the other type

††Model 2: Model 1 and frailty index

‡Model 3: Model 2 and lipid lowering medications, calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, loop diuretics, thiazides and related diuretics, other diuretics, anticoagulants, thyroid hormones, gastrointestinal drugs, cardiac drugs, antidepressant, potassium supplement, antiplatelets, antiarrhythmics, oral antidiabetics, insulin, sulfonylureas, thiazolidinediones, eye/ear/nose/throat miscellaneous medications, adrenals medications, statins, and digoxin.

Table 3.

Adjusted hazard ratios (95% confidence intervals) for the association of oral anticoagulation use with selected cardiovascular endpoints by multimorbidity status, MarketScan 2007–2015.

	No Multimorbidity		Multimorbidity*	
	No oral anticoagulation use	**Oral anticoagulation use**	**No oral anticoagulation use**	**Oral anticoagulation use**
Stroke				
Number of Events	1,594	682	3,645	1,372
Adjusted Hazard Ratio (95% CI)	1 (ref)	0.91 (0.83–1.00)	1 (ref)	0.90 (0.84–0.96)
p-value for interaction	*0.93*			
Major Bleeding				
Number of Events	2,187	1,180	6,093	3,299
Adjusted Hazard Ratio (95% CI)	1 (ref)	1.11 (1.03–1.19)	1 (ref)	1.27 (1.21–1.33)
p-value for interaction	*0.01*			
Heart Failure				
Number of Events	2,607	1,340	9,386	4,446
Adjusted Hazard Ratio (95% CI)	1 (ref)	1.02 (0.95–1.09)	1 (ref)	1.05 (1.02–1.09)
p-value for interaction	*0.13*			

*Multimorbidity is defined as having 2 or more of the following chronic conditions: heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, diabetes mellitus, arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis.

Models were adjusted for age, sex, rate control, rhythm control, frailty, lipid lowering medications, calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, loop diuretics, thiazides and related diuretics, other diuretics, thyroid hormones, gastrointestinal drugs, cardiac drugs, antidepressant, potassium supplement, antiplatelets, oral antidiabetics, insulin, sulfonylureas, thiazolidinediones, eye/ear/nose/throat miscellaneous medications, adrenals medications, statins, and digoxin.

Table 4.

Adjusted hazard ratios (95% confidence intervals) for the association of rhythm control versus rate control with selected cardiovascular endpoints by multimorbidity status, MarketScan 2007–2015.

	No Multimorbidity		Multimorbidity*	
	Rate Control	**Rhythm Control**	**Rate Control**	**Rhythm Control**
Stroke				
Number of Events	1,045	137	2,348	434
Adjusted Hazard Ratio (95% CI)	1 (ref)	0.75 (0.62–0.90)	1 (ref)	0.77 (0.70–0.86)
p-value for interaction	*0.76*			
Major Bleeding				
Number of Events	1,520	231	4,084	1,085
Adjusted Hazard Ratio (95% CI)	1 (ref)	0.80 (0.70–0.93)	1 (ref)	1.00 (0.93–1.07)
p-value for interaction	*0.004*			
Heart Failure				
Number of Events	1,784	342	6,277	1,768
Adjusted Hazard Ratio (95% CI)	1 (ref)	1.12 (1.00–1.26)	1 (ref)	1.13 (1.07–1.19)
p-value for interaction	*0.52*			

* Multimorbidity is defined as having 2 or more of the following chronic conditions: heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, diabetes mellitus, arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis.

Models were adjusted for age, sex, oral anticoagulants, frailty, lipid lowering medications, calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, loop diuretics, thiazides and related diuretics, other diuretics, thyroid hormones, gastrointestinal drugs, cardiac drugs, antidepressant, potassium supplement, antiplatelets, oral antidiabetics, insulin, sulfonylureas, thiazolidinediones, eye/ear/nose/throat miscellaneous medications, adrenals medications, statins, and digoxin.