ORIGINAL RESEARCH

Outcomes of Patients With Atrial Fibrillation Newly Recommended for Oral Anticoagulation Under the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline

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***Background*—**In March 2014, the American Heart Association updated their guidelines for the management of oral anticoagulation (OAC) in atrial fibrillation, recommending OAC for all patients with CHA_2DS_2-VASc ≥2. Previously, only patients with $CHADS_2$ ≥2 were recommended for anticoagulation. This study compared effectiveness and safety outcomes of OAC among patients who would receive OAC using the 2014 guidelines but not the 2011 guidelines.

***Methods and Results*—**Using claims data from a 5% sample of 2013–2014 Medicare beneficiaries, we identified patients with initially diagnosed atrial fibrillation between 2013 and 2014 and selected those who would receive OAC under the 2014 guidelines but not the 2011 guidelines (those with CHA_2DS_2-VASc score ≥2 or $CHADS_2$ score <2). Patients were categorized according to their use of OAC after first atrial fibrillation diagnosis (2937 users and 2914 nonusers). Primary outcomes included the composite of ischemic stroke, systemic embolism and death, and any bleeding event. Cox proportional hazard models were constructed to compare the risk of primary outcomes between the 2 groups, while controlling for patient demographic and clinical characteristics. There was no difference in the combined risk of stroke, systemic embolism, and death between the treatment groups (hazard ratio, 1.00; 95% confidence interval, 0.84–1.20). The risk of bleeding was higher for patients receiving OAC than for patients not receiving OAC (hazard ratio, 1.70, 95% confidence interval, 1.46–1.97).

***Conclusions*—**The benefit of OAC is not well defined in this patient population, and new studies that minimize residual confounding are needed to fully understand the risk/benefit of OAC in patients with atrial fibrillation and low to moderate stroke risk. **(*J Am Heart Assoc*. 2018;7:e007881. DOI: 10.1161/JAHA.117.007881.)**

Key Words: anticoagulant • atrial fibrillation • hemorrhage • stroke

Atrial fibrillation (AF) is associated with a 5-fold increase in stroke and thromboembolism risk.[1] Oral anticoagulation has been shown to reduce this risk by ≈60%[2]; however, anticoagulation therapy increases the risk of bleeding. Although the benefits of stroke prevention outweigh the risk of bleeding in patients with moderate to high risk of stroke,[3] the benefit/risk ratio of anticoagulation in patients with low risk remains unclear. In March 2014, the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) updated their guidelines for the use of anticoagulation in patients with AF, recommending oral anticoagulation therapy for patients with CHA_2DS_2-VASc ≥2.[3] Before 2014, only patients with $CHADS_2$ ≥2 were recommended for anticoagulation.[4] $CHADS_2$ and CHA_2DS_2-VASc are 2 validated scores that predict the risk of stroke in patients with AF: $CHADS_2$ score is calculated as the sum of 6 points: 1 for congestive heart failure, hypertension, diabetes mellitus, and age older than 75 years, and 2 for a history of stroke or transient ischemic attack.[5] In addition to these factors, female sex, vascular disease, and age 65 to 74 years are assigned 1 point in the calculation of the CHA_2DS_2-VASc score, and age older than 75 years is assigned 2, for a possible sum of 9 points.[5]

The objective of the updated 2014 guidelines was to better distinguish between patients with moderate and those with

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Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/7/1/e007881/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The use of oral anticoagulation in patients with atrial fibrillation newly recommended for anticoagulation under the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines (those with CHA_2DS_2-VASc score ≥2 and those with $CHADS_2$ score <2) did not result in a reduction in the composite risk of stroke, systemic embolism, and death; however, it was associated with an increased risk of any bleeding event and gastrointestinal bleeding.
- Among patients on anticoagulation, the combined risk of stroke, systemic embolism, and death was lower for patients taking nonvitamin K antagonist oral anticoagulants than those taking warfarin.

What Are the Clinical Implications?

- Our results do not support the use of oral anticoagulation with either warfarin or nonvitamin K antagonist oral anticoagulants in patients with CHA_2DS_2-VASc score ≥2 and $CHADS_2$ score <2.
- Because our study is based on claims data, it is particularly subject to residual confounding.
- Further research is needed to evaluate the benefit/risk ratio of oral anticoagulation in this low to moderate risk cohort.

low risk,[6] which means that many more patients are recommended to receive anticoagulation now than before 2014. Specifically, two thirds of patients not recommended for anticoagulation under the 2011 guidelines are recommended for anticoagulant therapy under the 2014 guideline.[6] For example, all women older than 64 years are recommended for therapy now regardless of risk profile.[6] This guideline update was highly controversial because previous studies that evaluated the benefit/risk ratio of oral anticoagulation therapy in patients with low or low to moderate risk have yielded conflicting results: several studies have demonstrated the benefit of anticoagulation in men with CHA_2DS_2-VASc score 1 and women with CHA_2DS_2-VASc score 2,[7–9] whereas others have found that oral anticoagulation did not reduce the risk of stroke in this low-risk group, but did increase the risk of bleeding.[10] For this reason, the publication of this guideline, which was based mostly on expert opinion rather than quantitative data, was followed by concerns on the strength of the evidence supporting this guideline update and the potential increase in the incidence of bleeding in this population.[11]

To the best of our knowledge, no prior study has specifically evaluated the benefit/risk ratio of oral anticoagulation therapy in a cohort of US patients who are newly recommended for anticoagulation under the 2014 AHA/ACC/HRS guideline. To address this gap in literature, we used claims data from a 5% random sample of Medicare Part D beneficiaries for patients with newly diagnosed AF who are recommended to receive oral anticoagulation under the 2014 guideline but who were not under the 2011 guideline, ie, those with CHA_2DS_2-VASc score ≥2 and $CHADS_2$ score <2. This study sample was used to compare the combined risk of stroke, systemic embolism (SE) and death, and the risk of bleeding between patients who used oral anticoagulation and those who did not use oral anticoagulation therapy.

Methods

Data Source and Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because Medicare claims data were obtained under a Data User Agreement that does not allow data sharing. We obtained 2013–2014 pharmacy and medical claims data for a 5% random sample of Medicare beneficiaries from the Centers for Medicare & Medicaid Services (CMS) and identified patients with Medicare Parts A and B fee-for-service coverage who were diagnosed with AF for the first time between January 1, 2013, and December 31, 2014 (Figure 1). According to the CMS Chronic Condition Warehouse, AF was defined as having one inpatient or 2 outpatient claims with primary or secondary *International Classification of Diseases, Ninth Revision* (*ICD-9*), code 427.31.[12] After excluding beneficiaries without continuous Part D enrollment, we collected pharmacy claims for oral anticoagulant agents (warfarin, dabigatran, rivaroxaban, and apixaban) filled after the date of the first diagnosis of AF. For patients who had at least one prescription for an oral anticoagulant agent (oral anticoagulant users), we defined the index date as the date of the first prescription filled for an oral anticoagulant. We performed frequency matching to define the index date for the patients who did not use oral anticoagulation. Specifically, we calculated the time from first AF diagnosis to the index date for oral anticoagulant users, and modeled the distribution of this variable. Then, the index date for each of the patients who did not use anticoagulation was defined as the sum of a number obtained from this distribution and the date of first AF diagnosis. This methodology enabled us to make sure baseline characteristics and outcomes were defined for a similar time window for the 2 treatment groups. We calculated the CHA_2DS_2-VASc and the $CHADS_2$ scores for the study sample as of the index date (further details on the definition of each of these risk factors can be found in

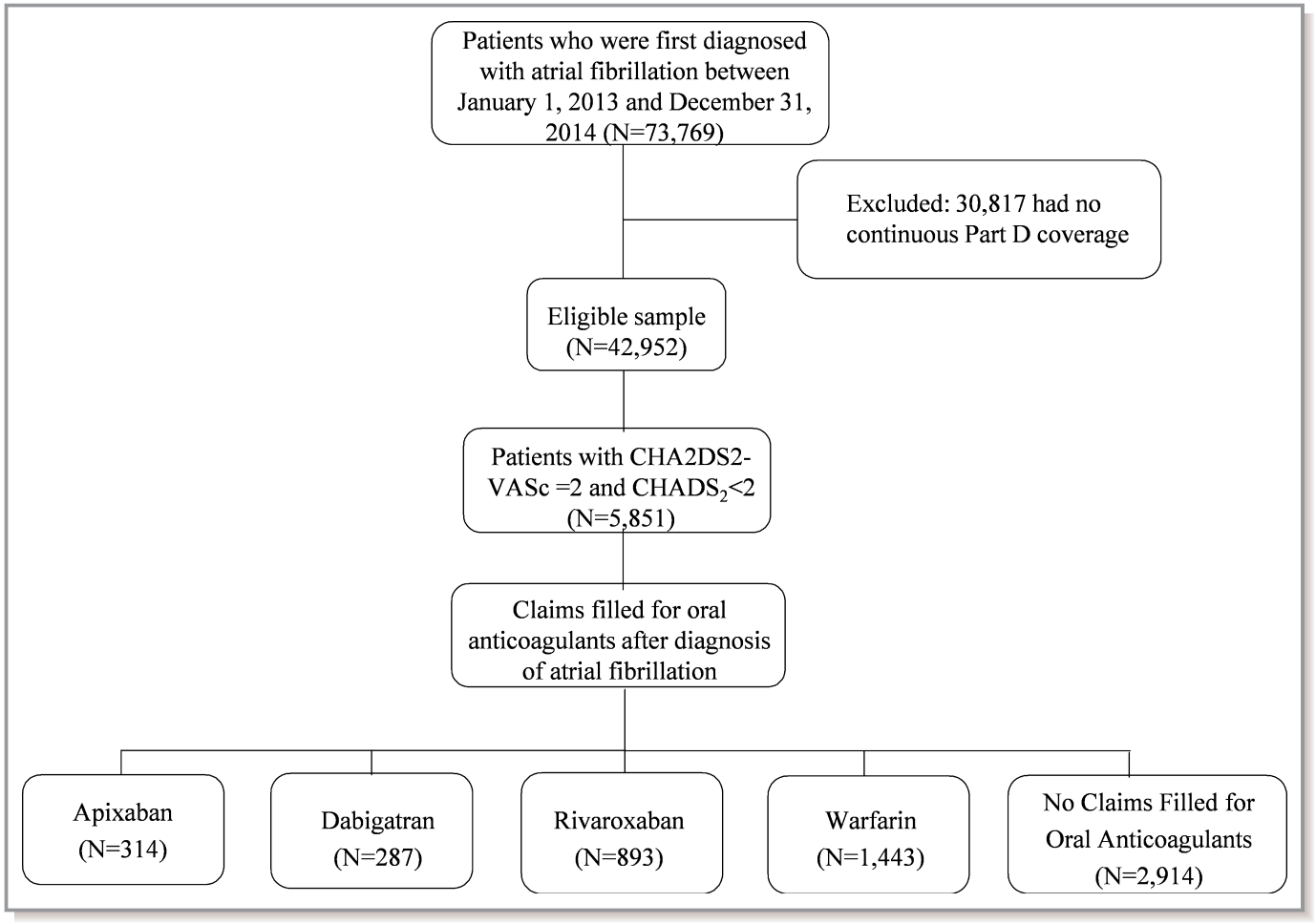

Figure 1. Selection of the study sample. Using a 5% sample of Medicare claims data, we selected all patients with newly diagnosed atrial fibrillation between January 1, 2013, and December 31, 2014. We then excluded patients who were not continuously enrolled in a part D plan during this period and selected those who had CHA_2DS_2-VASc score ≥2 and $CHADS_2$ score <2. We collected their claims for oral anticoagulants and classified them according to their use of oral anticoagulation.

Table 1) and selected patients with CHA_2DS_2-VASc score ≥2 and $CHADS_2$ score <2, because they represent the subgroup of patients with AF recommended for oral anticoagulation therapy under the 2014 AHA/ACC guideline but not under the 2011 guideline. Our sample included 2937 oral anticoagulant users and 2914 patients who did not use oral anticoagulation. All individuals were followed from the index date until death, or December 31, 2014. This study was approved by the institutional review board at the University of Pittsburgh as exempt.

Outcomes

Our primary outcomes include: the composite risk of ischemic stroke (ICD-9 codes 433, 434, 436), systemic embolism (ICD-9 code 444), and all-cause mortality, the risk of any bleeding event, the risk of intracranial bleeding and the risk of gastrointestinal bleeding. Secondary outcomes included ischemic stroke, all-cause mortality, and bleeding events other than GI and intracranial bleeding. Bleeding outcomes were defined using a previously published list of *ICD-9* codes.[13–15] Following previously published definitions, we used inpatient and outpatient claims in defining these outcomes, and there was no restriction on the position of *ICD-9* codes for outcomes within the claims.[13–15]

Covariates

We evaluated how demographics and clinical characteristics differed between treatment groups. All baseline characteristics were defined on the index date. Demographics included age, sex, race, and eligibility for Medicaid. Clinical characteristics included $CHADS_2$ score,[16] CHA_2DS_2-VASc score,[5] modified HAS-BLED score,[17] chronic kidney disease, hypertension, acute myocardial infarction, diabetes mellitus, congestive heart

Table 1. Baseline Characteristics of the Study Sample by Treatment Group

Variable	No Anticoagulation (n=2914)	Any Anticoagulation (n=2937)	*P* Value
Age, mean (SD), y	70.7 (6.7)	71.1 (6.2)	0.056
Male sex, No. (%)	1203 (41.3)	1344 (45.7)	0.001
Race, No. (%)			0.021
White	2573 (88.3)	2641 (89.9)	
Black	128 (4.4)	101 (3.4)	
Hispanic	69 (2.4)	84 (2.9)	
Other	144 (4.9)	111 (3.8)	
Medicaid eligibility, No. (%)	514 (17.6)	462 (15.7)	0.050
CHA_2DS_2-VASc score, mean (SD)	2.55 (0.6)	2.54 (0.6)	0.698
CHA_2DS_2-VASc=2, No. (%)	1477 (50.7)	1477 (50.3)	
CHA_2DS_2-VASc=3, No. (%)	1275 (43.7)	1326 (45.2)	
CHA_2DS_2-VASc=4, No. (%)	162 (5.6)	134 (4.6)	
Components of CHA_2DS_2-VASc, No. (%)			
Congestive heart failure	104 (3.6)	171 (5.8)	<0.001
Hypertension	1958 (67.2)	1956 (66.6)	0.629
Age 65 to 74 y	2386 (81.9)	2400 (81.7)	0.870
Age ≥75 y	375 (12.9)	422 (14.4)	0.095
Diabetes mellitus	80 (2.8)	101 (3.4)	0.126
Stroke	0	0	–
Vascular disease, No. (%)	450 (15.4)	423 (14.4)	0.264
Female sex, No. (%)	1711 (58.7)	1593 (54.2)	0.001
HAS-BLED score—INR, mean (SD)*	2.99 (0.8)	2.92 (0.8)	<0.001
CMS priority comorbidities, No. (%)†			
CKD	444 (15.2)	345 (11.8)	<0.001
AMI	98 (3.4)	71 (2.4)	0.031
No. of other CMS priority comorbidities, mean (SD)‡	3.75 (2.3)	3.34 (2.2)	<0.001
History of bleeding, No. (%)§	343 (11.8)	331 (11.3)	0.549
Use of antiplatelet agents, No. (%)‖	218 (7.5)	170 (5.8)	0.009
Use of NSAIDs, No. (%)¶	368 (12.6)	296 (10.1)	0.002

We do not show the proportion of patients who had a history of stroke or transient ischemic attack on index date because, by definition, our sample did not include patients with a history of stroke or transient ischemic attack. This is because a history of stroke or transient ischemic attack is assigned 2 points in the calculation of the $CHADS_2$ score and hence everyone with a history of stroke or transient ischemic attack would not be captured in our sample because we only selected patients with $CHADS_2$ <2. AMI indicates acute myocardial infarction; CKD, chronic kidney disease.

*The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score is a prediction of the risk of bleeding and it is calculated as the sum of 8 characteristics, including age 65 years or older, labile international normalized ratio (INR), kidney disease, liver disease, hypertension, history of stroke, history of major bleeding, alcohol or drug use, and antiplatelet or nonsteroidal anti-inflammatory drug (NSAID) use. We calculated a modified HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score, including all factors except for labile INR, because claims data do not contain information on INR levels.

†We used Centers for Medicare & Medicaid Services (CMS) Chronic Condition Warehouse definitions to calculate each of the CMS priority conditions.[12]

‡Other CMS priority conditions included Alzheimer disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, depression, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer, and endometrial cancer.

§A history of bleeding was defined as having a claim or bleeding events in the year before index date. The list of *International Classification of Diseases, Ninth Revision*, codes used to define a history of major bleeding is the same list as the one used to define the primary outcome of any bleeding event.

‖NSAID use was defined as filling at least one prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid, or indomethacin in the 6 months before index date.

¶Antiplatelet use was defined as filling at least one prescription for aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine, or ticagrelor in the 6 months before index date.

failure, other CMS priority comorbidities, a history of bleeding, and antiplatelet and nonsteroidal anti-inflammatory drug (NSAID) use (definitions in Table 1).

Statistical Analysis

We compared patient characteristics at baseline between treatment groups using ANOVA for continuous variables and chi-square for categorical variables. To compare the incidence rates of primary outcomes at 1 year follow-up between treatment groups, we constructed Kaplan–Meier time-to-event curves. To further control for potential confounders, we constructed Cox proportional hazard models. Cox proportional hazard models controlled for age, sex, race, eligibility for Medicaid, chronic kidney disease, hypertension, acute myocardial infarction, diabetes mellitus, congestive heart failure, other CMS priority comorbidities, history of bleeding, and antiplatelet and NSAID use. We did not control for $CHADS_2$, CHA_2D_S2-VASc, and HAS-BLED scores because we adjusted for the individual components included in the calculation of these scores. For Kaplan–Meier curves and Cox models, time 0 was the index date, and the time at risk was censored at death or the end of the study period (December 31, 2014). Time-to-event analyses that compared the composite risk of ischemic stroke, SE, and death were not censored at death, because death was the outcome event of interest in these models. All analyses were conducted with statistical software SAS 9.4 (SAS Institute Inc), and Stata 14 (StataCorp).

Subgroup Analysis

In subgroup analysis, we evaluated how the comparative risk of primary outcomes with oral anticoagulation and with no anticoagulation differed between patients with a CHA_2DS_2-VASc score of 2 and those with a CHA_2DS_2-VASC score of 3 or 4. We also evaluated how primary outcomes differed between patients who did not use any oral anticoagulation therapy and those who used warfarin or nonvitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban. In doing so, we followed the methodology described above, but we included 2 indicator variables for treatment groups. We performed 3 pairwise comparisons to directly compare outcomes between each pair of treatment groups (warfarin versus no oral anticoagulation, NOACs versus no oral anticoagulation, and NOACs versus warfarin).

Sensitivity Analysis

Patients in the oral anticoagulation treatment group may have discontinued oral anticoagulation therapy before the occurrence of outcome events. To examine how this may have affected our results, we re-ran our analysis after censoring patients in the oral anticoagulation group when they discontinued oral anticoagulation therapy (defined as a gap in therapy of at least 60 days). In addition, we re-ran our analysis controlling for CHA_2DS_2-VASc, instead of each of the independent risk factors that are included in the calculation of this score.

Results

Baseline Characteristics

The mean follow-up period of our study was 287 days (SD=204 days). The prevalence of chronic kidney disease, congestive heart failure, and antiplatelet or NSAID use was higher for patients who did not use anticoagulation therapy than for those who used oral anticoagulants (Table 1). For example, the prevalence of chronic kidney disease was 15.2% in the no oral anticoagulation group, compared with 11.8% in the oral anticoagulation group ($P<0.001$). HAS-BLED score was higher for patients who did not use oral anticoagulation (2.99) than for those who did (2.92) ($P<0.001$). There were no differences in the prevalence of a history of bleeding between treatment groups. Table S1 shows patient characteristics by the oral anticoagulant agent used.

Effectiveness of Oral Anticoagulation Therapy

In the anticoagulation group, 218 (7.4%) patients presented with the primary effectiveness outcome of stroke, SE, or death, compared with 200 (6.9%) in the no anticoagulation treatment group (Table 2). The unadjusted cumulative incidence rate of stroke, SE, and all-cause mortality at 1 year did not differ between patients who did not receive anticoagulation (0.09; 95% confidence interval [CI], 0.08–0.11) and those who did receive oral anticoagulation (0.10; 95% CI, 0.08–0.11) (Table 2). After adjustment for potential confounders, there were no differences in the combined risk of stroke, SE, and all-cause mortality between the 2 treatment groups (hazard ratio [HR] 1.00; 95% CI, 0.84–1.20) (Table 2).

Safety of Oral Anticoagulation Therapy

In the anticoagulation group, 406 (13.8%) patients presented with any bleeding event, 125 (4.3%) with GI bleeding, and 9 (0.3%) with IC bleeding, compared with 218 (7.5%), 86 (3.0%), and 10 (0.3%) in the no anticoagulation treatment group, respectively (Table 2). The unadjusted cumulative incidence rates of any bleeding (0.18; 95% CI, 0.16–0.19) were higher for patients taking oral anticoagulants than for those who did not take oral anticoagulants (0.11; 95% CI, 0.10–0.13)

Table 2. Unadjusted Cumulative Incidence Rates and Adjusted HRs for Primary Effectiveness and Safety Outcomes

Outcome	Events, No. (%)		Unadjusted Cumulative Incidence at 1 y (95% CI)*		Adjusted HR for Anticoagulation vs No Anticoagulation†
	No Anticoagulation	Any Anticoagulation	No Anticoagulation	Any Anticoagulation	
Stroke, SE, or death	200 (6.9)	218 (7.4)	0.09 (0.08–0.11)	0.10 (0.08–0.11)	1.00 (0.84–1.20)
Any bleeding event	218 (7.5)	406 (13.8)	0.11 (0.10–0.13)	0.18 (0.16–0.19)	1.70 (1.46–1.97)
GI bleeding	86 (3.0)	125 (4.3)	0.04 (0.04–0.05)	0.06 (0.05–0.07)	1.37 (1.06–1.77)
IC bleeding	10 (0.3)	9 (0.3)	0.005 (0.002–0.009)	0.004 (0.002–0.008)	1.07 (0.51–2.24)

CI indicates confidence interval; GI, gastrointestinal; IC, intracranial; SE, systemic embolism.
*Unadjusted cumulative incidence rates were obtained from Kaplan–Meier curves.
†Adjusted hazard ratios (HRs) were obtained from Cox proportional hazard models that controlled for patient demographics including age, sex, race, eligibility for Medicaid, and clinical characteristics including hypertension, acute myocardial infarction, diabetes mellitus, congestive heart failure, other Centers for Medicare & Medicaid Services priority comorbidities, a history of bleeding, antiplatelet use, and nonsteroidal anti-inflammatory drug use.

(Table 2). Results from adjusted analyses were consistent with this observation: the risk of any and GI bleeding were higher for patients on any oral anticoagulation therapy than for those who did not use anticoagulation (HR, 1.70; 95% CI, 1.46–1.97 for any bleeding, and HR 1.37; 95% CI, 1.06–1.77 for GI bleeding) (Table 2). There were no differences in the risk of intracranial bleeding between treatment groups. The risk of bleeding events other than intracranial and GI bleeding was also higher for patients taking anticoagulants than for those not taking anticoagulants (Table S2).

Results of Subgroup Analyses

Table S3 shows the results of subgroup analysis after stratifying the sample into 2 groups according to CHA_2DS_2-VASc. The results from these subgroup analyses were consistent with the results from the overall sample: for the 2 subgroups, the combined risk of stroke, SE, and death did not differ between patients on anticoagulation therapy and those who did not use any oral anticoagulation therapy (HR, 1.07; 95% CI, 0.82–0.41 for a CHA_2DS_2-VASc score of 2, and HR, 0.93; 95% CI, 0.75–1.18 for a CHA_2DS_2-VASc score of 3 or 4). However, the risk of any bleeding was higher for patients on oral anticoagulation (HR, 1.76; 95% CI, 1.41–2.19 for a CHA_2DS_2-VASc score of 2; HR, 1.61; 95% CI, 1.30–1.99 for a CHA_2DS_2-VASc score of 3 or 4).

Figure 2 shows the results of subgroup analysis by oral anticoagulant agent. The combined risk of stroke, SE, and death did not differ between patients taking NOACs and those who did not use any oral anticoagulation therapy (HR, 0.86; 95% CI, 0.68–1.08) or between patients taking warfarin and those who did not use any oral anticoagulation therapy (HR, 1.13; 95% CI, 0.92–1.39). However, the combined risk of stroke, SE, and death was lower for patients taking NOACs than those taking warfarin (HR, 0.76; 95% CI, 0.59–0.98).

Consistent with the results from our main analysis, the risk of any bleeding event was higher for patients taking NOACs (HR, 1.73; 95% CI, 1.45–2.07) or warfarin (HR, 1.65; 95% CI, 1.39–1.97) than those who did not use any oral anticoagulation. The risk of any bleeding (HR, 1.04; 95% CI, 0.87–1.25) or GI bleeding (HR, 1.09; 95% CI, 0.79–1.51) did not differ between patients taking NOACs and warfarin. There were no significant differences in intracranial bleeding between the treatment groups, which may have been attributable to the relatively small size of our study sample to evaluate this outcome.

Results of Sensitivity Analyses

Our results for the comparative effectiveness and safety of oral anticoagulation therapy did not vary much when we censored oral anticoagulant users at discontinuation of treatment (Table S4). Our results did not change appreciably after controlling for CHA_2DS_2-VASc instead of for each of the covariates included in the calculation of this score (Table S5).

Discussion

To the best of our knowledge, our study is the first to use data from a nationally representative sample of Medicare fee-for-service beneficiaries with Part D coverage to evaluate the effectiveness and safety of oral anticoagulation therapy in a cohort of patients with AF who were newly recommended to receive oral anticoagulation by the 2014 AHA/ACC/HRS updated guideline. We found that the use of oral anticoagulation in this cohort was associated with an increased risk of any bleeding and GI bleeding but not with a reduction in the combined risk of stroke, SE, and death.

Several European studies have demonstrated the benefit of anticoagulation in men with a CHA_2DS_2-VASc score of 1 and women with a CHA_2DS_2-VASc score of 2.[7–9] In addition, using a Taiwanese database, Chao et al[18] showed that warfarin therapy in patients newly recommended for anticoagulation under the 2014 AHA/ACC/HRS guidelines was associated

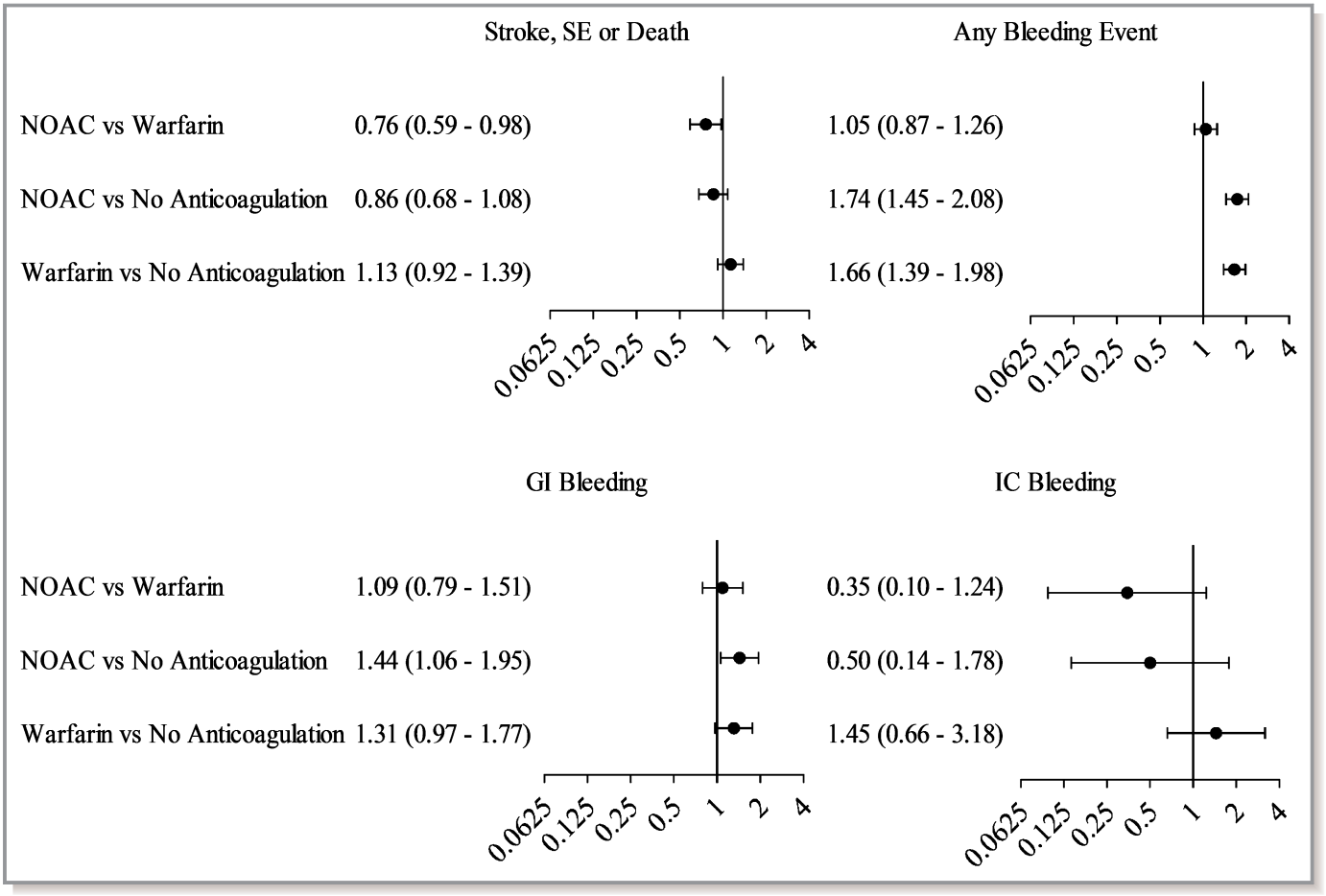

Figure 2. Adjusted hazard ratios for primary effectiveness and safety outcomes by oral anticoagulant agent. Hazard ratios were obtained from Cox proportional hazard models after controlling for age, sex, race, eligibility for Medicaid, chronic kidney disease, hypertension, acute myocardial infarction, diabetes mellitus, congestive heart failure, other Centers for Medicare & Medicaid Services priority comorbidities, history of bleeding, antiplatelet use, and nonsteroidal anti-inflammatory drug use. GI indicates gastrointestinal; IC, intracranial; NOAC, nonvitamin K antagonist oral anticoagulant; SE, systemic embolism.

with an 11% reduction in the composite risk of stroke, bleeding, and mortality. In contrast, our results are consistent with a recent study by Golive and colleagues, who used data from a US integrated health system and found no significant reduction in the risk of stroke or transient ischemic attack with anticoagulation in a sample of patients with AF who had a $CHADS_2$ score of <2.[10] The apparently conflicting results of these studies may be attributable to higher time in the therapeutic range with oral anticoagulation therapy in Europe than in the United States,[19] as well as differences in patient characteristics between the 2 continents.

Our study constitutes an important contribution to this existing literature because, using recent data from a US nationally representative sample of patients with AF, it is the first to evaluate safety and effectiveness outcomes of anticoagulation therapy in the cohort of patients with AF newly recommended for anticoagulation as a result of the 2014 AHA/ACC/HRS guideline update. In doing so, we found that oral anticoagulation therapy did not significantly reduce the combined risk of stroke, SE, and death in this population with low to moderate risk. Our findings reinforce the need for systematically evaluating the benefit/risk ratio of anticoagulation in this population using data or study designs that minimize the risk of residual confounding.[11,20] Understanding the benefit/risk ratio of treating patients with AF at low and moderate risk with oral anticoagulation is increasingly important because the standards of care for these patients have evolved as a result of the approval of NOACs.[21,22]

Study Limitations

Our study has several limitations to acknowledge. First, our study uses Medicare claims data from 2013 to 2014, and the 2014 AHA guidelines were released in March of 2014.[3] However, potential changes in prescription patterns following the guidelines are unlikely to have affected our results

because previous studies have shown little change in prescription patterns following the release of the guideline, as small as 2%.[22] Second, one may argue that our average follow-up period may be too short to compare the incidence of stroke between treatment groups, particularly because our cohort included patients at low risk. Third, in this study, we used Medicare claims data, so we were not able to control for potential confounders not captured in claims, such as results from laboratory or diagnostic tests or use of over-the-counter antiplatelet and NSAID agents, which may have been unbalanced between treatment groups. For example, unobserved differences in the prevalence of over-the-counter NSAID use between those who used oral anticoagulation and those who did not use anticoagulation could partially explain the increased risk of GI bleeding observed among oral anticoagulant users. Fourth, our study included Medicare beneficiaries newly diagnosed with AF in 2013–2014, and it is unknown how applicable our results will be to other populations. Finally, in defining outcomes, we followed previously published definitions and did not restrict the position of *ICD-9* codes for outcomes within the claims.[13–15] For this reason, our definitions may have lower positive predictive values than definitions based solely on primary diagnosis codes.[23–25] However, stroke definitions based on primary and secondary codes like ours have not only higher sensitivity and negative predictive value than those based only on primary codes but also a higher κ statistic.[25]

Conclusions

We found that the use of oral anticoagulation therapy in patients with AF newly recommended for anticoagulation under the 2014 AHA/ACC/HRS guidelines did not result in a reduction in the composite risk of stroke, SE, and death; yet, it was associated with an increased risk of bleeding. These results do not support the changes to anticoagulant therapy recommended by the 2014 guidelines; however, further research is needed to evaluate the benefit/risk ratio of oral anticoagulation in this cohort with low to moderate risk.

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Disclosures

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References

1. Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res*. 2006;118:321–333.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
4. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA III, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, Fuster V, Ryden LE, Cannom DS, Le Heuzey JY, Crijns HJ, Olsson SB, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Guyton RA, Tarkington LG, Yancy CW. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;57:223–242.
5. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
6. O'Brien EC, Kim S, Hess PL, Kowey PR, Fonarow GC, Piccini JP, Peterson ED. Effect of the 2014 atrial fibrillation guideline revisions on the proportion of patients recommended for oral anticoagulation. *JAMA Intern Med*. 2015;175:848–850.
7. Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol*. 2015;65:1385–1394.
8. Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GY. Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the Loire Valley Atrial Fibrillation Project. *Chest*. 2016;149:960–968.
9. Fauchier L, Clementy N, Bisson A, Ivanes F, Angoulvant D, Babuty D, Lip GY. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated? *Stroke*. 2016;47:1831–1836.
10. Golive A, May HT, Bair TL, Jacobs V, Crandall BG, Cutler MJ, Day JD, Mallender C, Osborn JS, Stevens SM, Weiss JP, Woller SC, Bunch TJ. The population-based long-term impact of anticoagulant and antiplatelet therapies in low-risk patients with atrial fibrillation. *Am J Cardiol*. 2017;120:75–82.
11. Fang MC. Implications of the new atrial fibrillation guideline. *JAMA Intern Med*. 2015;175:850–851.
12. CMS Chronic Conditions Data Warehouse. 27 chronic condition algorithm. Available at: https://www.ccwdata.org/web/guest/condition-categories. Accessed April 26, 2017.
13. Hernandez I, Baik SH, Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med*. 2015;175:18–24.
14. Hernandez I, Zhang Y, Brooks MM, Chin PK, Saba S. Anticoagulation use and clinical outcomes after major bleeding on dabigatran or warfarin in atrial fibrillation. *Stroke*. 2017;48:159–166.
15. Hernandez I, Zhang Y, Saba S. Comparison of the effectiveness and safety of apixaban, dabigatran, rivaroxaban and warfarin in newly diagnosed atrial fibrillation. *Am J Cardiol*. 2017;120:1813–1819.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA*. 2001;285:2864–2870.
17. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (has-bled) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. *Chest*. 2010;138:1093–1100.
18. Chao T-F, Liu C-J, Tuan T-C, et al. Impact on Outcomes of Changing Treatment Guideline Recommendations for Stroke Prevention in Atrial Fibrillation: A Nationwide Cohort Study. *Mayo Clinic Proceedings* 2016;91:567–74.
19. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, Halperin JL, Becker RC, Breithardt G, Hankey GJ, Hacke W, Nessel CC, Patel MR, Califf RM, Fox KA. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *J Am Heart Assoc*. 2013;2:e000067. DOI: 10.1161/JAHA.112.000067.
20. Barnett AS, Lewis WR, Field ME, Fonarow GC, Gersh BJ, Page RL, Calkins H, Steinberg BA, Peterson ED, Piccini JP. Quality of Evidence Underlying the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines on the Management of Atrial Fibrillation. *JAMA Cardiol*. 2017;2:319–323.

21. Katz DF, Maddox TM, Turakhia M, Gehi A, O'Brien EC, Lubitz SA, Turchin A, Doros G, Lei L, Varosy P, Marzec L, Hsu JC. Contemporary Trends in Oral Anticoagulant Prescription in Atrial Fibrillation Patients at Low to Moderate Risk of Stroke After Guideline-Recommended Change in Use of the CHADS2 to the CHA2DS2-VASc for Thromboembolic Risk Assessment: Analysis From the National Cardiovascular Data Registry's Outpatient Practice Innovation and Clinical Excellence Atrial Fibrillation Registry. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003476. DOI: 10.1161/CIRCOUTCOMES.116.003476.

22. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2017;69:2475–2484.

23. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, Goldberg RJ, Gurwitz JH. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(Suppl 1):100–128.

24. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20:560–566.

25. Lakshminarayan K, Larson JC, Virnig B, Fuller C, Allen NB, Limacher M, Winkelmayer WC, Safford MM, Burwen DR. Comparison of Medicare claims versus physician adjudication for identifying stroke outcomes in the Women's Health Initiative. *Stroke*. 2014;45:815–821.

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