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## Contraindications to Anticoagulation Therapy and Eligibility for Novel Anticoagulants in Older Patients With Atrial Fibrillation

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### Abstract

**Aims**—Oral anticoagulation therapy prevents stroke and improves survival in patients with atrial fibrillation, but the therapy is underutilized. We sought to identify the prevalence of contraindications for oral anticoagulation and the proportion of patients potentially eligible for different agents.

**Methods**—We identified patients with nonacute atrial fibrillation in a nationally representative 5% sample of 2009 Medicare data. We divided the population into patients ineligible for any oral anticoagulant, patients eligible for warfarin only, and patients eligible for any anticoagulant. We compared patient characteristics and the use of anticoagulation among the subgroups.

**Results**—Among 86,671 patients with atrial fibrillation, 1872 (2.2%) were ineligible for anticoagulation because of an absolute contraindication, most frequently a history of intracranial hemorrhage (60%). Patients ineligible for any anticoagulant were the same age as the overall group (mean age, 80.5 vs 80.4 years). However, they had higher rates of dementia (19% vs 8.6%) and heart failure (59% vs 43%) and higher mean CHADS<sub>2</sub> scores (3.8 vs 2.8). Of the remaining

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84,799 patients eligible for anticoagulation, 7146 (8.4%) had were eligible for warfarin only (most commonly because of mechanical heart valves [66%] and end-stage renal disease [12%]). Sixty-five percent of patients eligible for anticoagulation received warfarin, and the proportion was similar for patients with a relatively high risk of bleeding.

**Conclusions**—Older adults with atrial fibrillation rarely have absolute contraindications to oral anticoagulation therapy. Among patients without contraindications, most appeared to be eligible for any anticoagulant, and relatively high-risk features appeared not to influence warfarin use.

## Introduction

Treatment with oral anticoagulation has been demonstrated to significantly reduce stroke in patients with atrial fibrillation [1]. Guidelines recommend oral anticoagulation for patients with atrial fibrillation and additional risk factors for stroke [2,3]. However, historical data have shown underutilization of anticoagulation therapy, with approximately half of all patients with atrial fibrillation not receiving treatment [4-8]. Several reasons have been cited for undertreatment, including the prevalence of contraindications. However, contraindications to oral anticoagulation therapy are often relative and subject to provider interpretation. There remain few consistent, absolute contraindications to the use of anticoagulation therapy. In addition, oral vitamin K antagonist therapy, the historical mainstay of therapy, is a challenging treatment strategy, because the drugs require regular blood draws for monitoring and are associated with numerous drug and food interactions. Management challenges may be a factor in undertreatment. Several alternative agents have become available, yet it is not clear what proportion of patients is eligible for these drugs, which are approved for only a subset of patients with atrial fibrillation.

The objectives of the current study were to identify the proportion of older patients with atrial fibrillation who have absolute contraindications to oral anticoagulation; to identify the proportion of patients with atrial fibrillation who can only receive warfarin for anticoagulation; and to assess the use of anticoagulation therapy in eligible patients who have a relatively higher risk of bleeding.

## Methods

### Data Source

We obtained a nationally representative 5% sample of Medicare standard analytic files and corresponding denominator files from the US Centers for Medicare & Medicaid Services for 2009 through 2010. Inpatient files contain institutional claims for facility costs covered under Medicare Part A, and outpatient files contain claims from institutional outpatient providers. Carrier files contain noninstitutional provider claims for services covered under Medicare Part B. Denominator files contain beneficiary demographic characteristics and information about program eligibility and enrollment.

### Study Populations

We defined a 2010 cohort of beneficiaries with prevalent atrial fibrillation based on claims diagnoses in 2009. To establish a diagnosis of nonacute atrial fibrillation that was unlikely to

be due to a reversible cause, we required at least 2 diagnoses of atrial fibrillation (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31) in any position on separate inpatient or outpatient claims at least 6 months apart. We required at least 1 outpatient diagnosis to establish that beneficiaries were treated as outpatients. We required that beneficiaries were 65 years or older, were living in the United States on January 1, 2010, and had continuous enrollment in fee-for-service Medicare in the prior calendar year.

We defined 3 subpopulations of Medicare beneficiaries with prevalent atrial fibrillation: patients who were unlikely to be eligible for anticoagulation therapy because of absolute contraindications (“ineligible”); patients who were eligible for warfarin only because of absolute contraindications to novel anticoagulant use (“warfarin only”); and patients who were eligible for any oral anticoagulant. We searched Medicare inpatient, outpatient, and carrier claims files from 2009 for evidence of contraindications to anticoagulation therapy. We identified beneficiaries with absolute contraindications to any anticoagulation therapy based on diagnoses of intracranial hemorrhage (*ICD-9-CM* 430, 431, 432.x), intracranial mass (*ICD-9-CM* 191.x, 225.x, 239.6, 198.3), or end-stage liver disease using the algorithm from Goldberg et al [9] (see **Supplemental Material**). Patients with any contraindication to novel anticoagulant use were considered eligible for warfarin only. We defined these contraindications as valvular atrial fibrillation (ie, mitral stenosis [*ICD-9-CM* 394.0]; rheumatic mitral insufficiency [*ICD-9-CM* 394.1]; mitral stenosis with insufficiency [*ICD-9-CM* 394.2] or other and unspecified mitral valve diseases [*ICD-9-CM* 394.9]); presence of a mechanical valve (*ICD-9-CM* procedure codes 35.22 [10] or 35.24 or in situ diagnosis code V43.3); or end-stage renal disease (Medicare denominator file ESRD indicator, “Y”). Finally, the remaining patients not identified with contraindications were considered eligible for any anticoagulation therapy.

### Patient Characteristics

Demographic characteristics included age, sex, race, and state of residence. We used self-reported race categories “black” and “white” and combined all other categories as “other” [11]. On the basis of state of residence, we grouped beneficiaries into 4 geographic regions. We identified comorbid conditions using well-validated coding algorithms [12,13] and searched all claims in 2009 for dementia, diabetes mellitus, ischemic heart disease, peripheral vascular disease, heart failure, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, renal disease, stroke or transient ischemic attack, cancer, and valvular heart disease. We also searched for evidence of atrial flutter (*ICD-9-CM* code 427.32). We used the approach of Gage et al [14] to define the CHADS<sub>2</sub> score and Lip et al [15] to define the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. While these scores were not developed for patients with Rheumatic disease or mechanical valve replacements, they are used to risk-stratify patients with *non-valvular* AF for anticoagulation and can be useful markers of stroke risk in an overall AF population. We identified the existence of a pacemaker or implantable cardioverter-defibrillator on the basis of Current Procedural Terminology (CPT) and *ICD-9-CM* codes for device in situ, implantation, revision, or monitoring.

In addition to absolute contraindications for anticoagulation therapies, we examined the prevalence of high-risk characteristics or relative contraindications that may influence anticoagulation patterns (hereafter, “relative high risk”). We considered advanced age (85 years or older) [16-18], and also searched the prior year Medicare claims for evidence of dementia, gastrointestinal hemorrhage, thrombocytopenia, anemia, hematological malignancy, and traumatic intracranial hemorrhage [12,13,19].

## Medications

We examined medication use in the 90 days prior to January 1, 2010. We searched for evidence of international normalized ratio (INR) testing as a proxy for warfarin therapy. We searched carrier and outpatient facility claims for prothrombin time laboratory test (CPT 85610) or home INR monitoring instruction, equipment, or interpretation of results (Healthcare Common Procedure Coding System [HCPCS] codes G0248, G0249, G0250) [20]. We required 2 separate INR tests within 90 days to avoid misclassification related to routine INR testing in patients not on warfarin therapy. As a sensitivity analysis in the subset of beneficiaries enrolled in Medicare Part D, we searched Part D claims for a warfarin prescription claim (generic name “WARFARIN SODIUM”).

## Statistical Analysis

We describe the prevalence of contraindications using frequencies with percentages. To describe baseline characteristics of each study subpopulation, we present categorical variables as frequencies and continuous variables as means with SDs. We tested for differences between subgroups using  $\chi^2$  tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Among all patients eligible for any anticoagulation therapy, we describe rates of relative contraindications overall and by use of warfarin ascertained by prior INR testing. We tested for differences in relative contraindication rates between subgroups using  $\chi^2$  tests. As a sensitivity analysis, we compared rates of contraindications by warfarin use on the basis of prescription drug claims in the subgroup of beneficiaries enrolled in Medicare Part D.

We used SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina) for all analyses. We chose a 2-tailed  $\alpha$  threshold of 0.05 for statistical significance. The institutional review board of the Duke University Health System approved the study.

## Results

The study population consisted of 86,671 patients with atrial fibrillation. Of these patients, 1872 (2.2%) were ineligible for oral anticoagulation therapy; the most common reason for ineligibility was prior intracranial hemorrhage (n = 1120; 60%; **Figure 1**). We subsequently identified 7146 patients (8.2% overall) as candidates for warfarin only, most commonly due to the presence of a mechanical heart valve (n = 4730 [66%]) or end-stage renal disease (n = 869 [12%]). The remaining patients (n = 77,653 [90% overall]) were deemed potentially eligible for any oral anticoagulation therapy. A total of 43,818 patients (51% of the overall study population) were enrolled in Medicare Part D.

Demographic characteristics and medical history for the 3 subgroups are shown in **Table 1**. Differences in age and sex were modest. Compared with the overall population, patients who were ineligible for any anticoagulation therapy had the highest rates of dementia (19% vs 9%), diabetes mellitus (46% vs 36%), ischemic heart disease (67% vs 55%), peripheral vascular disease (42% vs 30%), heart failure (59% vs 43%), and prior stroke or transient ischemic attack (54% vs 20%). Mean CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were also highest in the ineligible group (mean CHADS<sub>2</sub> score, 3.8 vs 3.1 for warfarin only vs 2.8 for any anticoagulation;  $P < .001$ ).

Of the 84,799 patients without absolute contraindications, 39,592 (47%) represented groups that may be considered at higher risk for anticoagulation therapy or have relative contraindications. The details of these conditions are shown in **Table 2**. Age greater than 85 years ( $n = 22,451$  [27%]) and dementia ( $n = 7102$  [8.4%]) were the most common potentially high-risk features.

Among patients without absolute contraindications, 65% ( $n = 54,768/84,799$ ) were treated with warfarin according to INR testing. Rates of warfarin use among high-risk subgroups are shown in **Figure 2**. Warfarin use was lowest in patients with dementia (46%) and traumatic intracranial hemorrhage (47%), but ranged from 56% to 63% in the remaining groups (including advanced age, prior gastrointestinal bleeding, thrombocytopenia, anemia, and hematologic malignancy). Among patients at high risk of thromboembolism without absolute contraindications, 79% ( $n = 3,725/4,730$ ) of those with mechanical heart valves and 74% ( $n = 1,126/1,452$ ) of those with mitral valve disease were treated with warfarin. In sensitivity analyses in the Medicare Part D sample, 62% ( $n = 27,312/43,818$ ) were treated with warfarin based on prescription claims and rates of warfarin use among high-risk subgroups were similar (see **Supplemental Material**).

## Discussion

In our analysis of older patients with atrial fibrillation, we found that a minority had absolute contraindications to oral anticoagulation therapy, and as a group, they had a high risk of thromboembolic events. Of the remaining patients who were eligible for anticoagulation therapy, most appeared to be eligible for either warfarin or novel oral anticoagulants. However, whereas nearly half of eligible patients may have had characteristics placing them at higher risk of bleeding anticoagulation therapy, the majority of patients in these subgroups were prescribed warfarin and rates of warfarin use were only slightly lower than in the overall eligible study population. Our findings may have implications for improving the care of patients with atrial fibrillation.

Several prior studies have reported rates of anticoagulation contraindications from less than 20% to more than 50% [21-25]. There are many reasons for this variability. The identification of contraindications to anticoagulation therapy may be subjective, and often there is significant local practice variation [26]. In addition, many such conditions vary greatly in severity. For example, mild hepatic impairment may be a subjective contraindication, whereas decompensated hepatic failure with coagulopathy is a more consistent reason to withhold therapy. Finally, the severity of the contraindication must be

weighed against the underlying thromboembolic risk of the patient. Moderate relative contraindications may not be of sufficient risk to justify withholding anticoagulation from patients at substantial risk of stroke. Therefore, it is difficult to attribute undertreatment of a population to prevalence of significant contraindications.

Thus, we sought first to identify rates of comorbid conditions that are consistently considered absolute contraindications—major intracranial pathology (prior intracranial hemorrhage and/or intracranial masses) or decompensated liver disease. We found that a small minority of older patients meets these criteria. Importantly, patients at high risk for catastrophic bleeding on anticoagulation therapy also represent patients at high thromboembolic risk; on average, they had high CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and high rates of other cardiovascular comorbid conditions, compared with patients who did not have absolute contraindications to anticoagulation therapy. Therefore, it is imperative that providers carefully assess each of these risks to balance them and select the most beneficial treatment strategy overall.

The use of oral anticoagulation therapy is often based on a patient's stroke risk, relative to any comorbid conditions that might convey substantial risk for bleeding. Such features often are cited as relative contraindications, but they largely represent patient characteristics that put them at higher risk for bleeding and may lead to withholding of anticoagulation therapy, depending on its perceived benefit. Our data showed that among such subgroups, patients with dementia and traumatic intracranial hemorrhage had the lowest rates of warfarin use (46% and 47%, respectively). In contrast, the remaining groups (age 85 years or older, prior gastrointestinal bleeding, blood dyscrasias) had subtle variation in use anticoagulation therapy from the overall cohort (56%-63% vs 65%). Each represents a potential risk factor either for bleeding or for increased risk of adverse events in the setting of bleeding, yet such conditions appeared to have had little impact on warfarin use in the study population. Nevertheless, these data may also reflect the highly variable nature of such treatment patterns, without consistent criteria. Physicians are left to make highly subjective judgments of risk versus benefit [27], and likely benefit from shared decision-making models and aids [28].

The vast majority of patients eligible for anticoagulation therapy in our cohort did not have an identifiable condition that limited them to warfarin (ie, mechanical valve, severe renal disease, or valvular atrial fibrillation). These findings have important implications. Several newer oral anticoagulants have been approved, or are in development, for stroke prevention in patients with atrial fibrillation. However, these agents have not overtaken warfarin as the dominant strategy [29], and it remains unclear what proportion of patients should receive such agents. They have been demonstrated to be at least as effective as warfarin at preventing thromboembolism and have also demonstrated lower rates of bleeding [30-34]. Our data show a large proportion of patients with atrial fibrillation (90%) could be eligible and may benefit. Nevertheless, there may remain barriers including access, dosing, cost, reversibility, and interactions with concomitant medications.

Rates of oral anticoagulation therapy in the Medicare population have been previously reported to be approximately 56% and 59% using Medicare Part D data from 2006 and



2007, respectively [35]. We found a rate of 65% using INR data (62% using Part D data from 2010). There are likely several explanations for these differences. The prior data did not exclude patients with absolute contraindications, as ours did. Also, 2006-2007 was a period of still increasing enrollment in Medicare Part D, compared to 2010. Lastly, the higher rate in our study may reflect an overall increase in treatment rates in this population, as has been previously suggested [36].

Our study has limitations. The definitions of contraindications are subjective, perhaps even those we deemed “absolute.” Nevertheless, we used commonly accepted conditions in which most providers would not consider the use of anticoagulation therapy. In addition, our study was based on administrative claims data and thus was subject to the limitations inherent in such methods. These include diagnosis biases related to billing and the limitations of the coding schema, ascertainment bias of limited look-back, and exclusion of over-the-counter therapies such as aspirin. Furthermore, the severity of coded conditions could not be ascertained, which may be particularly relevant for renal disease in which medication dosing can vary by severity. Similarly, patient and provider preferences were not captured; we cannot attribute treatment decisions directly to the presence or absence of measured contraindications. Lastly, we did not have data on concomitant medications, which may also influence both rates of anticoagulation therapy (by using INR measurement as a surrogate) and the choice of whether to use anticoagulation therapy. However, the timing of the study predates the approval of any novel anticoagulant.

In conclusion, older patients with atrial fibrillation rarely have absolute contraindications to oral anticoagulation therapy, and those who do are also at high risk for thromboembolic events. Despite the infrequency of absolute contraindications, anticoagulation therapy is underutilized. Among eligible patients, the majority appeared to be medically eligible for any anticoagulant. These findings could provide an opportunity for improvement in the care of patients with atrial fibrillation, and additional studies are needed to identify the appropriate indications, if any, for withholding anticoagulation therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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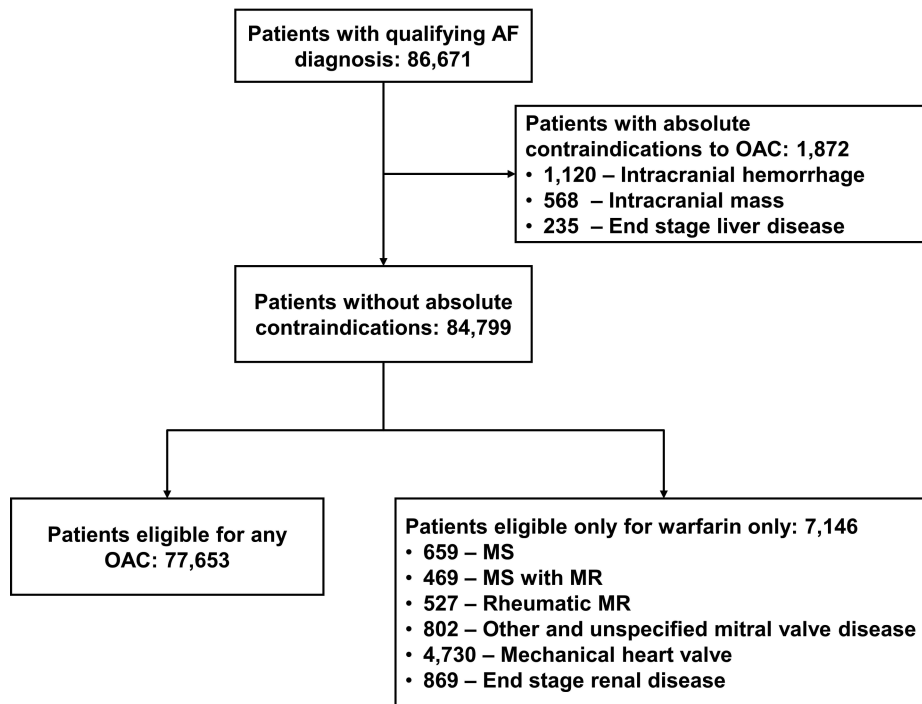
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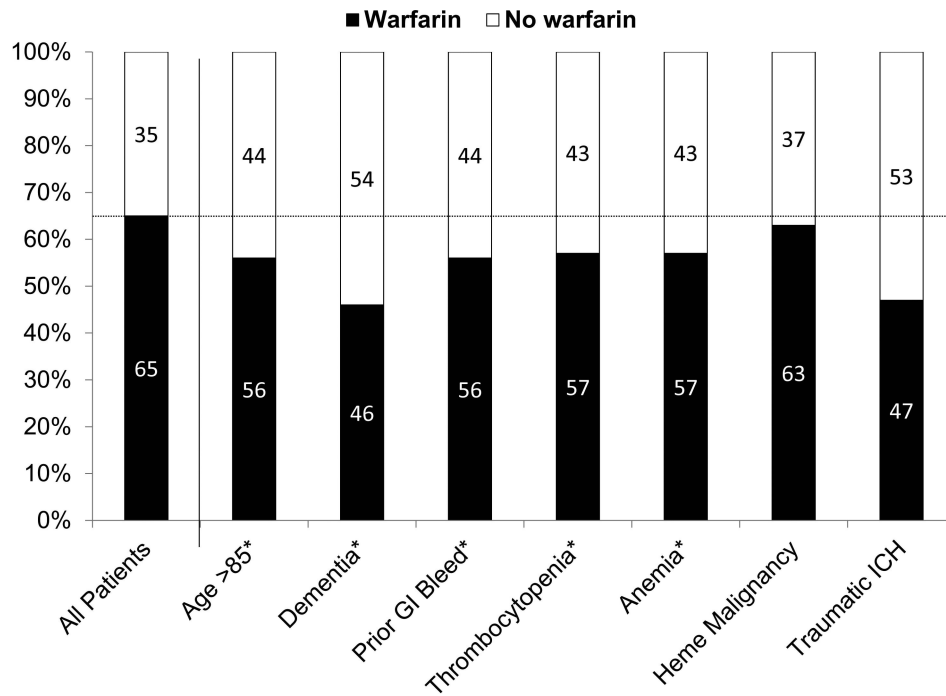


**Figure 1.**

Derivation of the Study Population

Abbreviations: AF, atrial fibrillation; MS, mitral stenosis; MR, mitral regurgitation; OAC, oral anticoagulation therapy.

Note: Subgroup numbers may not sum to totals due to overlap in diagnoses.



**Figure 2.** Among Patients Without Absolute Contraindications, Rates of Warfarin Use (Defined by INR Testing) Overall and Within Relatively High-Risk Patients  
Abbreviations: GI; gastrointestinal; ICH: intracranial hemorrhage; INR: international normalized ratio; OAC oral anticoagulation.

**Table 1**

Characteristics of the Study Population by Eligibility for Oral Anticoagulation Therapy

Characteristic	Eligibility				P Value
	Overall Population (N = 86,671)	Ineligible (n = 1872)	Warfarin Only (n = 7146)	Any Oral Anticoagulant (n = 77,653)	
Age, mean (SD), y	80.4 (7.4)	80.5 (7.3)	79.1 (6.9)	80.5 (7.4)	< .001
Age group, No. (%)					< .001
65-69 y	7607 (8.8)	156 (8.3)	777 (10.9)	6674 (8.6)	
70-74 y	12,912 (14.9)	285 (15.2)	1192 (16.7)	11,435 (14.7)	
75-79 y	17,978 (20.7)	378 (20.2)	1660 (23.2)	15,940 (20.5)	
80 y	48,174 (55.6)	1053 (56.3)	3517 (49.2)	43,604 (56.2)	
Women	49,764 (57.4)	1067 (57.0)	4067 (56.9)	44,630 (57.5)	.61
Race, No. (%)					< .001
Black	2741 (3.2)	77 (4.1)	246 (3.4)	2418 (3.1)	
White	81,847 (94.4)	1726 (92.2)	6686 (93.6)	73,435 (94.6)	
Other	2083 (2.4)	69 (3.7)	214 (3.0)	1800 (2.3)	
US geographic region, No. (%)					< .001
Midwest	21,671 (25.0)	412 (22.0)	1704 (23.8)	19,555 (25.2)	
Northeast	19,518 (22.5)	487 (26.0)	1966 (27.5)	17,065 (22.0)	
South	32,454 (37.4)	660 (35.3)	2378 (33.3)	29,416 (37.9)	
West	13,028 (15.0)	313 (16.7)	1098 (15.4)	11,617 (15.0)	
Comorbid conditions, No. (%)					
Atrial flutter	8463 (9.8)	274 (14.6)	1039 (14.5)	7150 (9.2)	< .001
Cancer	14,823 (17.1)	548 (29.3)	1248 (17.5)	13,027 (16.8)	< .001
Cerebrovascular disease	24,575 (28.4)	1447 (77.3)	2359 (33.0)	20,769 (26.7)	< .001
Stroke or TIA	16,953 (19.6)	1015 (54.2)	1524 (21.3)	14,414 (18.6)	< .001
COPD	30,168 (34.8)	863 (46.1)	3225 (45.1)	26,080 (33.6)	< .001
Dementia	7462 (8.6)	360 (19.2)	468 (6.5)	6634 (8.5)	< .001
Diabetes mellitus	30,862 (35.6)	865 (46.2)	2806 (39.3)	27,191 (35.0)	< .001
Heart failure	37,064 (42.8)	1095 (58.5)	4326 (60.5)	31,643 (40.7)	< .001
Hypertension	77,160 (89.0)	1771 (94.6)	6456 (90.3)	68,933 (88.8)	< .001
Ischemic heart disease	47,935 (55.3)	1253 (66.9)	5041 (70.5)	41,641 (53.6)	< .001
Peripheral vascular disease	26,118 (30.1)	785 (41.9)	2598 (36.4)	22,735 (29.3)	< .001
Renal disease	15,922 (18.4)	540 (28.8)	2268 (31.7)	13,114 (16.9)	< .001
Valvular heart disease	33,522 (38.7)	921 (49.2)	6722 (94.1)	25,879 (33.3)	< .001
CHADS <sub>2</sub> score, mean (SD)	2.8 (1.3)	3.8 (1.4)	3.1 (1.3)	2.8 (1.3)	< .001
0	1605 (1.9)	— <sup>a</sup>	129 (1.8)	1466 (1.9)	< .001
1	10,525 (12.1)	86 (4.6)	648 (9.1)	9791 (12.6)	< .001
2	74,541 (86.0)	1776 (94.9)	6369 (89.1)	66,396 (85.5)	< .001

Characteristic	Eligibility				P Value
	Overall Population (N = 86,671)	Ineligible (n = 1872)	Warfarin Only (n = 7146)	Any Oral Anticoagulant (n = 77,653)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean (SD)	5.1 (1.6)	6.2 (1.6)	5.4 (1.6)	5.0 (1.6)	< .001
1	587 (0.7)	— <sup>a</sup>	27 (0.4)	556 (0.7)	< .001
2	86,084 (99.3)	1868 (99.8)	7119 (99.6)	77,097 (99.3)	< .001
Implantable device, No. (%)					
ICD	5705 (6.6)	169 (9.0)	769 (10.8)	4767 (6.1)	< .001
Pacemaker	21,366 (24.7)	519 (27.7)	2433 (34.0)	18,414 (23.7)	< .001

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; TIA, transient ischemic attack.

<sup>a</sup>In accordance with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing 10 or fewer observations are not reported.

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**Table 2**

Among Patients Without Absolute Contraindications, Proportion With Conditions That Place Them at Relatively High Risk of Adverse Events With Anticoagulation

<b>Condition<sup>a</sup></b>	<b>Patients, No. (%) (N = 84,799)</b>
High risk for anticoagulation	39,592 (47.0)
Age > 85 years	22,451 (26.5)
Anemia	13,527 (16.0)
Prior gastrointestinal bleed	7973 (9.4)
Dementia	7102 (8.4)
Thrombocytopenia	2568 (3.0)
Hematological malignancy	1791 (2.1)
Traumatic intracranial hemorrhage	170 (0.2)

<sup>a</sup>Conditions are not mutually exclusive, and patients may be represented in more than 1 group.

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