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Typical, Atypical, and Asymptomatic Presentations of New-Onset Atrial Fibrillation in the Community: Characteristics and Prognostic Implications

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Abstract

Background—The prognostic significance of the clinical presentation of atrial fibrillation (AF) is poorly defined.

Objective—We aimed to determine the frequency, associations, and prognostic impact of different clinical presentations of new-onset AF.

Methods—One thousand patients with incident AF in Olmsted County, MN, were randomly selected (2000–2010). Patients with AF that was complicated at presentation [heart failure (n=71), thromboembolism (n=24)], provoked (n=346), or unable to determine symptoms (n=83) were excluded. In the remaining patients, characteristics and prognosis associated with different types of symptoms were examined.

Results—Among 476 patients, 193 had typical (palpitations), 122 had atypical (other non-palpitation symptoms), and 161 had asymptomatic AF presentation. Patients with typical presentation had lower CHA₂DS₂-VASc scores (mean 2.3±2) compared to atypical and asymptomatic presentation (mean 3.2±1.8 and 3.3±1.9, respectively; p<0.001). Fifty-nine cerebrovascular events (CVE) and 149 deaths (n=49 cardiovascular) were documented over median 5.6 and 6.0 years, respectively. Atypical and asymptomatic AF conferred higher risks of CVE compared to typical AF after adjustment for CHA₂DS₂-VASc score and age (hazard ratio

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(HR) 3.51, 95% confidence interval (CI) 1.65-7.48 and HR 2.70, 95% CI 1.29-5.66, respectively), and associations remained statistically significant after further adjustments including comorbidities and warfarin use. Asymptomatic AF was associated with an increased risk of cardiovascular (HR 3.12, 95% CI 1.50-6.45) and all-cause mortality (HR 2.96, 95% CI 1.89-4.64) compared to typical AF after adjustment for CHA₂DS₂-VASc score and age.

Conclusion—The type of clinical presentation may have important implications for the prognosis of new-onset AF in the community.

Keywords

atrial fibrillation; palpitations; clinical presentations; stroke; prognosis

Introduction

Palpitations are considered the hallmark symptom of AF but other presentations without palpitations or without symptoms whatsoever¹ are commonly encountered in clinical practice. Studies have previously focused on the presence or absence of symptoms in AF.²⁻⁴ However, the frequency and associations of typical (i.e. palpitations) and atypical symptomatic presentations (i.e. fatigue, dyspnea, lightheadedness, etc.) are not well established.

The clinical presentation of new-onset AF may provide additional prognostic information beyond the widely used CHA₂DS₂-VASc score.⁵ Investigations on asymptomatic versus symptomatic AF have, however, shown mixed results. A recent analysis by Rienstra et al. suggested that asymptomatic patients carry a lower risk of adverse outcomes,² whereas an Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) substudy and a meta-analysis showed no effect of the presence or absence of symptoms on outcomes.^{4, 6} In these analyses, however, the specific nature of symptoms (palpitations vs. atypical symptoms) was not taken into consideration. Also, cases of secondary AF (in the setting of other acute concurrent conditions) were included which may have made AF-related symptoms difficult to discern.

We aimed to characterize clinical presentations of new-onset AF in the community, distinguishing specifically between typical and atypical symptoms, to identify patient characteristics associated with different presentations, and to assess the prognostic impact of these presentations on the risk of cerebrovascular events (CVE) and cardiovascular and all-cause mortality.

Methods

Study population

The study population was derived from the Rochester Epidemiology Project (REP) records-linkage system, which allows complete capture of health care utilization in Olmsted County, MN residents.⁷ This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes 427.31 and 427.32 from all providers in the REP, and Mayo Clinic electrocardiograms (ECGs) indicating AF or atrial flutter were obtained among Olmsted County, MN, residents aged 18 from 2000-2010.⁸ Patient records were reviewed by trained abstractors and evidence of AF or atrial flutter of any duration on 1 of the following was required to validate AF: 1) ECG or rhythm strip, 2) Holter monitor, event monitor, or telemetry, 3) emergency room or intensive care unit monitor, 4) ECG during an echocardiogram, 5) pacemaker interrogation, or 6) physician diagnosis. AF occurring 30 days of cardiac or large thoracic vessel surgery was excluded. If AF recurred >30 days after surgery, the episode was eligible for inclusion. As described previously,⁸ 83% of those screened for AF were validated, the majority (88%) of which had documented evidence on 12-lead ECG confirming AF diagnosis. From the eligible patient population with AF (n=3344), we selected randomly 1,000 patients that comprised our study population.

Clinical presentations of AF

The medical records of each patient were reviewed by one investigator (KCS) who was blinded to the outcomes to determine symptoms at the time of the first documented AF episode. We excluded patients with a concurrent condition that could be the cause or trigger of AF (sepsis, acute coronary syndrome, post-operative state (<7 days after surgery), etc.)⁹ because it is difficult to discern whether symptoms are due to AF or the concurrent condition as well as patients presenting with a complication possibly attributable to AF (thromboembolism, heart failure) because of their distinct prognostic implications. Cases where the clinical presentation could not be fully ascertained or attributed to AF (inadequate, ambiguous, contradicting documentation) and patients with severe cognitive impairment due to advanced dementia or developmental delay who were unable to provide history of symptoms were also excluded. For the remaining cases, presentation was categorized as: 1) typical (palpitations with or without other concomitant symptoms), 2) atypical (fatigue, shortness of breath, chest pain, lightheadedness, syncope, decreased exercise tolerance, etc., without palpitations), 3) asymptomatic (AF detected incidentally during routine physical examination, preoperative evaluation, emergency department or clinic visit for unrelated problem, etc.). We further documented whether there was rapid or slow ventricular response at the time of presentation (defined as ventricular rate >100 and <60 beats per minute, respectively). For atypical presentations, we ensured that symptoms were not due to other concomitant etiology. Asymptomatic AF during routine monitoring before, during, or after minor procedures under conscious sedation (such as gastrointestinal endoscopy) was considered incidental and not due to peri-operative state.

Data collection

Comorbid conditions at baseline were ascertained by retrieving ICD-9 codes and requiring 2 occurrences of a code within the 5 years prior to the index AF, as described previously.⁸ The estimated glomerular filtration rate was calculated using the closest serum creatinine within 90 days of AF diagnosis¹⁰. Warfarin use after the index AF diagnosis was collected from outpatient prescription records. Novel oral anticoagulant use was not collected as they were not in use during the time period of our study except for dabigatran, which received FDA approval in the last few months of 2010. International normalized ratios (INRs) were

obtained and time in therapeutic range was calculated using the following rules: On days where multiple INRs were measured, we used an average value for the INR. An INR was calculated for each day during follow-up using linear interpolation for the days between INR measurements. For each day during follow-up, we calculated the cumulative proportion of time spent in subtherapeutic (INR <2), therapeutic (INR 2-3), or supratherapeutic (INR >3) categories.

Clinical events

Outcomes were ascertained through December 31, 2013. Information on deaths was obtained from death certificates from the state of Minnesota and the Mayo Clinic registration office. Deaths were classified as cardiovascular (ICD-9 codes 390-459, ICD-10 codes I00-I99) based on American Heart Association classifications¹¹ when the cause of death was available from a death certificate (98.7% of deaths). Diagnostic codes identified ischemic strokes (ICD-9 433-434 and 436) and transient ischemic attacks (TIAs) (ICD-9 435); events were validated by trained abstractors using established diagnostic criteria.^{12, 13}

Statistical analyses

Analysis of variance (ANOVA) and chi-square or Fisher's Exact tests determined differences in patient characteristics across AF presentation categories. The distributions of clinical presentation were presented by CHA₂DS₂-VASc score categories.⁵ Cumulative incidence curves for warfarin use across AF presentation categories were constructed treating death as a competing risk¹⁴ and tested using the methods developed by Gray.¹⁵ Cumulative incidence curves were constructed to plot event-free survival by type of AF presentation for CVE and cardiovascular mortality treating death and non-cardiovascular death, respectively, as competing risks. Kaplan-Meier curves were constructed for all-cause mortality. Cox proportional hazards regression assessed the associations between type of AF presentation and outcomes. Unadjusted, partially adjusted models for the CHA₂DS₂-VASc score and age, and fully adjusted models that also included baseline variables that were significantly different between AF presentation groups were run. Age was included separately as a continuous variable to control for residual confounding since it is modeled categorically in the CHA₂DS₂-VASc score. Models were also adjusted for warfarin use, which was modeled as a time-dependent variable, and time in therapeutic range for warfarin.

For all outcomes, we calculated the concordance index (c-statistic), a measure of discrimination, before and after the addition of AF presentation type to the models containing the CHA₂DS₂-VASc score. The 95% confidence interval (CI) for the c-statistics were estimated using approximate jackknife methods.¹⁶ To compare the discrimination between the models with and without AF presentation type, we created 1,000 bootstrap samples, sampling individuals with replacement, and estimated a 95% CI for the difference in c-statistics between the 2 models. Analysis was performed using SAS 9.2 (SAS Institute, Inc.; Cary, NC).

Results

Study population and frequency of AF presentations

Among 1,000 randomly selected cases whose medical records were reviewed, 524 (52%) were excluded for various reasons (Figure A1). Among the remaining 476 cases, 193 (40%) had typical, 122 (26%) had atypical and 161 (34%) had asymptomatic presentation based on the symptoms at the time of the first AF diagnosis. The 5 most frequent clinical settings of incidental diagnoses are shown in Table A1. Patients who were excluded were older, and had greater prevalence of cardiovascular disease, cerebrovascular disease, diabetes, and other chronic comorbidities and higher mean CHA₂DS₂-VASc scores (3.9 versus 2.9, $p<0.001$) compared to those included in the analysis (Table A2).

Characteristics associated with typical, atypical and asymptomatic presentation

The mean age at the time of AF diagnosis was 69.2 ± 15.7 years. Men comprised 53.2% of the cohort and were younger than women at the time of first AF occurrence (mean age 65.3 versus 73.7, $p<0.001$). One hundred thirty-four (28.2%) and 185 (38.9%) patients had CHA₂DS₂-VASc scores 0-1 and 4 at baseline, respectively. Most patients presented with rapid ventricular response (66.2%) while a minority had slow ventricular rates at presentation (4.4%).

There was male gender predominance for asymptomatic presentation (61.5%) (Table 1). The mean age at the time of AF diagnosis was significantly younger for patients with typical (mean 62 ± 17 years) compared to atypical and asymptomatic presentation (both with mean 74 ± 13 years). Diabetes was more frequent among asymptomatic patients and COPD was more common among patients with atypical symptoms.

Among patients with typical and atypical symptoms, rapid ventricular rates were more common than normal or slow rates (85% versus 15% in typical AF, and 65% versus 35% in atypical AF, respectively), whereas asymptomatic patients more commonly had normal or slow rates (56%) than rapid rates (44%) (overall $p<0.001$ for difference between the 3 groups).

Baseline thromboembolic risk

Patients with typical AF presentation had significantly lower CHA₂DS₂-VASc scores (2.3 ± 2) compared to atypical (3.2 ± 1.8) and asymptomatic presentations (3.3 ± 1.9) (Table 1 and Figure 1A). Among patients with CHA₂DS₂-VASc score 0-2, more than 50% had typical presentation while about 25% had asymptomatic presentation. In contrast, among patients with scores 3, asymptomatic presentation represented the majority of cases while typical presentation was less common (Figure 1B).

Utilization of warfarin

Use of warfarin was less common in patients presenting with typical AF ($n=115$, 59.6%) than those with atypical ($n=87$, 71.3%) or asymptomatic ($n=112$, 70%) AF (Figure 2). Although a similar proportion of patients with atypical and asymptomatic AF received warfarin, those with atypical AF were initiated on warfarin sooner (median days from AF to

warfarin initiation 5 and 19 days for atypical and asymptomatic, respectively). Patients with typical AF were initiated on warfarin at a median of 17 days after diagnosis.

Cerebrovascular events

A total of 59 (12%) CVEs occurred over a median follow-up of 5.6 years. Compared to typical presentation, those with atypical and asymptomatic presentations experienced a greater risk of CVE (Figure 3A). After adjusting for CHA₂DS₂-VASc score and age, those with atypical and asymptomatic presentation experienced a 3.5-fold (HR 3.51, 95% CI 1.65-7.48) and 2.7-fold (HR 2.70, 95% CI 1.29-5.66) increased risk of CVE, respectively, compared to those with typical presentation (Table 2). Approximately 3-fold risks of CVE for atypical and asymptomatic AF were observed after further adjustment for comorbidities and warfarin treatment. The c-statistic for prediction of CVE was 0.71 (95% CI 0.64-0.77) for the CHA₂DS₂-VASc score. With the addition of type of presentation in the model, the c-statistic increased to 0.74 (95% CI 0.68-0.80); however, the difference in c-statistics was not statistically significant.

Cardiovascular and all-cause mortality

Over a median follow-up of 6.0 years, 49 (10%) patients died of cardiovascular causes (Figure 3B). Atypical AF presentation conferred an increased risk for cardiovascular death compared to typical presentation in the unadjusted analysis (HR 2.38, 95% CI 1.03-5.51) but this effect was eliminated after serial adjustments (Table 2). Asymptomatic presentation was associated with increased risk of cardiovascular death after adjustment for CHA₂DS₂-VASc score and age (HR 3.12, 95% CI 1.50-6.45) and after additional adjustment for comorbidities and warfarin treatment. The c-statistic for cardiovascular mortality was 0.78 (95% CI 0.70-0.84) for the CHA₂DS₂-VASc score and increased to 0.80 (95% CI 0.74-0.86) after adding type of AF presentation to the model; the difference in c-statistics was statistically significant.

One hundred and forty nine (31%) deaths from any cause were documented. There were strong associations between both atypical and asymptomatic presentation and mortality compared to typical presentation (Figure 3C and Table 2). These remained significant after adjustment for CHA₂DS₂-VASc score and age (HR 2.75, 95% CI 1.71-4.41 and HR 2.96, 95% CI 1.89-4.64 for atypical and asymptomatic AF, respectively) and after serial adjustments for comorbidities and warfarin treatment. Addition of the type of AF presentation to the model with CHA₂DS₂-VASc score resulted in a statistically significant increase in the c-statistic from 0.72 (95% CI 0.68-0.76) to 0.76 (95% CI 0.72-0.79).

Discussion

This analysis demonstrated that among patients with new-onset non-provoked and yet uncomplicated AF (1) typical presentation with palpitations was less common than atypical or asymptomatic presentation, (2) patient characteristics differed by presenting symptoms as typical AF was associated with younger age and lower CHA₂DS₂-VASc scores, and asymptomatic AF was associated with male gender and diabetes, and (3) the presenting symptoms have important prognostic implications. Patients with atypical and asymptomatic

AF presentation at the time of their first AF diagnosis had higher rates of stroke/TIAs and mortality compared to typical presentation even after adjustment for the CHA₂DS₂-VASc score, other risk factors, and anticoagulation therapy.

Characteristics of presentation types

The distinction between asymptomatic and symptomatic AF has gained attention.^{2, 3, 6, 17, 18} However, there is a spectrum of symptomatic AF presentations. In our study, typical AF represented only a minority of all AF presentations. This observation may have significant implications for the early recognition of AF by both patients and healthcare providers, which is one of the research priorities set forth by the National Heart, Lung, and Blood Institute.¹⁹ For myocardial infarction, symptom perception can determine how quickly patients seek medical care^{20, 21}; such evidence is limited in AF. A recent study suggested that most patients with new-onset AF do not readily identify their symptoms as cardiac and may delay seeking care.²² This may be more prominent among patients with atypical symptoms. Notably, approximately 1 in 10 patients presented with a complication as the first manifestation of AF, either thromboembolism or heart failure. We did not investigate whether these patients had preceding AF symptoms but this observation highlights the importance of AF symptom awareness and has implications for population screening among high-risk groups.²³

The relationship between patient characteristics and presenting symptoms has not been consistent across studies. In Boriani et al., older age was associated with asymptomatic AF³ whereas the converse was true in a RAtE Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) substudy² and there was no association in an AFFIRM substudy.⁶ Herein, by further defining the symptom characteristics (rather than just symptomatic versus asymptomatic), we show that patients with typical symptoms at their first AF diagnosis tend to be younger compared to both atypical and asymptomatic presentation. Consistent with previous investigations,^{2, 3} asymptomatic presentation was more common in men. Both the RACE and AFFIRM studies showed that asymptomatic patients had fewer comorbidities; however this was not the case in Boriani et al. In our study, symptomatic patients had an overall better risk profile; however, there were significant differences depending on whether symptoms were typical or atypical. Thus, the variation observed in previous studies may be explained by the inclusion of heterogeneous “symptomatic” patients.

Association of presentation type with outcomes

In addition to being associated with a favorable risk profile, typical AF also had a more favorable prognosis. Other studies, however, have demonstrated that symptomatic AF confers comparable⁶ or even less favorable prognosis for cardiovascular morbidity and mortality, including thromboembolism,² in comparison to asymptomatic AF. The patient populations in these studies differed from our population. The AFFIRM study included patients aged >65 years or with other risk factors for adverse outcomes. The RACE study included patients with established permanent AF, aged <80 years, resting heart rate >80 beats per minute, and current use of oral anticoagulation therapy. In contrast, we employed no restrictions with regards to age, baseline risk profile or duration of symptoms. In both the

RACE and AFFIRM studies, symptom status was assessed at the time of enrollment rather than the time of AF diagnosis. Symptoms at the time of AF onset may differ from subsequent symptoms. Most importantly, in this study we differentiated between types of presentation, and typical and atypical symptoms had distinct effects on thromboembolic and mortality risk. Typical AF represented a more benign clinical phenotype even after adjustments for established risk factors in AF.

What mediates such favorable prognosis in typical AF is not entirely clear. It is possible that patients with typical symptoms seek medical attention earlier compared to patients with no or atypical symptoms. In the myocardial infarction paradigm, the delay in recognition and delivery of treatments has been recognized as the mediator of adverse outcomes in patients with atypical ischemic symptoms.²⁴ One could presume that the increased risk of cerebrovascular events with asymptomatic AF observed in our study could be due to delay in initiation of anticoagulation therapy or lack thereof but this was accounted for in the adjusted analyses. Rhythm or rate control strategies may be utilized more or less frequently with different presentations but are unlikely to mediate any of the associations seen herein as their effects on major AF outcomes are generally neutral. Finally, as the typical AF population had an overall lower risk profile, it is possible that the more favorable outcomes reflect the cardiovascular and general health fitness that statistical adjustments are not able to account for (due to unmeasured confounders).

The favorable effects of typical AF over atypical and asymptomatic AF were of large magnitude, with adjusted hazard ratios in excess of 3 for stroke/TIA. In comparison, adjusted odds ratios of the CHA₂DS₂-VASc components for thromboembolic events did not exceed 2.53 in the Euro Heart Survey for AF cohort.⁵ The large effect sizes and the ease of use in daily practice render AF symptomatology an appealing risk variable. Whether incorporation of the type of symptoms in the risk stratification calculations may improve their prognostic ability is of interest. Current prediction schemes incorporate common demographic and comorbidity variables but none consider phenotypic AF characteristics such as symptoms.²⁵ Herein, addition of the type of AF presentation to the guideline-recommended CHA₂DS₂-VASc scheme⁹ improved the c-statistic for cerebrovascular events. This change was not statistically significant, which is likely due to power limitations because of the relatively small number of events. The changes in discrimination were significant for both cardiovascular and all-cause mortality but it should be acknowledged that the CHA₂DS₂-VASc score was developed for stroke rather than mortality risk stratification in AF.

Limitations and strengths

This is a retrospective evaluation where determination of AF presentation was based on available medical record documentation. We included only cases where the type of presentation was clear but deficits in documentation of symptoms cannot be completely excluded. We included information on symptoms only at the time of the initial diagnosis of AF and were not able to capture information on whether symptoms or presentation of subsequent AF paroxysms may have had an effect on outcomes. Similarly, consistent and reliable information on the paroxysmal, persistent, or permanent nature of AF cases was not

available. Recent evidence suggests that the AF pattern may be an important prognostic factor²⁶ and it is possible that certain symptoms are more likely with different AF patterns. Finally, as in any epidemiologic study, residual confounding in our estimates may exist due to the inability to adjust for unmeasured confounding.

Our study has several strengths. To our knowledge, this is the first study to examine specifically the characteristics and prognostic implications of different symptomatic presentations rather than symptomatic versus asymptomatic AF. Second, it is a population-based study that included patients of all ages and with AF occurring in a community setting. Ascertainment of index AF diagnoses, AF-related symptoms and validation of clinical events was done on a case-by-case basis and a large number of events over several years of follow-up were available.

Conclusions

More than half of patients with AF in the community present with atypical or no symptoms. Patients presenting with palpitations were younger and had lower CHA₂DS₂-VASc scores than those with atypical or asymptomatic AF. Notably, AF presenting with palpitations may be a more benign phenotype with regards to major clinical endpoints. It is possible that the ability of CHA₂DS₂-VASc score-based schemes to discriminate between low, intermediate, and high-risk patients can be improved by consideration of AF symptoms. This could also have implications for population-based screening methods for AF detection and stroke prevention. Future studies should validate our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
CVE	cerebrovascular events
HR	hazard ratio

Clinical Perspectives

New-onset AF may present with a variety of symptoms, including typical (palpitations), atypical (other non-palpitation symptoms) or no symptoms at all. The different types of presentations are associated with certain patient characteristics, such as asymptomatic presentation with male gender and diabetes, and typical presentation with younger age. Even after adjustment for established thromboembolic risk factors and warfarin therapy, patients with atypical and asymptomatic presentations have significantly higher risk of cerebrovascular events compared to those with typical presentation. Typical presentation may also confer a more favorable prognosis compared to asymptomatic and atypical presentations with regards to cardiovascular and all-cause mortality. Since AF is a very common arrhythmia with considerable public health burden and potentially detrimental effects when gone unnoticed for long periods of time, increasing interest for population screening approaches and early detection has emerged. Our findings can be important in this context by helping identify patient profiles more likely to present with certain symptoms or no symptoms and can help increase AF symptom awareness by patients. The consideration of the type of symptoms at arrhythmia onset in prognostic schemes may also improve risk stratification and affect decisions for the initiation of anticoagulation and intensity of follow-up in patients with a new diagnosis of AF.

Figure 1. Estimated baseline stroke risk in the cohort: (A) distribution of CHA₂DS₂-VASc scores by type of atrial fibrillation presentation and (B) frequency of type of atrial fibrillation presentation among CHA₂DS₂-VASc score categories

Figure 2. Cumulative incidence curves of warfarin use treating death as a competing risk by type of atrial fibrillation presentation

Figure 3. 1-Cumulative incidence curves for (A) stroke or transient ischemic attack treating death as a competing risk and (B) cardiovascular death treating non-cardiovascular death as a competing risk, and Kaplan-Meier curves for (C) all-cause death by type of atrial fibrillation presentation

Table 1
Patient Characteristics by Type of Atrial Fibrillation Presentation

Characteristic	Total (n=476)	Typical (n=193)	Atypical (n=122)	Asymptomatic (n=161)	P-value
Female	223 (46.8%)	101 (52.3%)	60 (49.2%)	62 (38.5%)	0.029
Age, years	69.2 (15.7)	61.9 (16.9)	74.2 (12.6)	74.3 (12.6)	<0.001
BMI, kg/m ²	29.6 (6.5)	28.6 (5.7)	29.6 (6.0)	30.8 (7.6)	0.008
Current or former smoking	218 (46%)	76 (39.4%)	71 (58.2%)	71 (44.7%)	0.004
Prior CHF	63 (13.2%)	13 (6.7%)	19 (15.6%)	31 (19.3%)	0.002
Prior MI	42 (8.8%)	13 (6.7%)	9 (7.4%)	20 (12.4%)	0.138
Prior peripheral vascular disease	23 (4.8%)	6 (3.1%)	6 (4.9%)	11 (6.8%)	0.266
Prior diabetes	88 (18.5%)	24 (12.4%)	21 (17.2%)	43 (26.7%)	0.002
Prior cerebrovascular disease	62 (13.0%)	17 (8.8%)	22 (18.0%)	23 (14.3%)	0.051
Prior dementia	31 (6.5%)	3 (1.6%)	11 (9.0%)	17 (10.6%)	0.001
Prior renal disease	12 (2.5%)	2 (1.0%)	3 (2.5%)	7 (4.3%)	0.137
Prior COPD	52 (10.9%)	12 (6.2%)	24 (19.7%)	16 (9.9%)	0.001
Prior malignancy	58 (12.2%)	14 (7.3%)	16 (13.1%)	28 (17.4%)	0.014
Prior liver disease	2 (0.4%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0.065
Estimated glomerular filtration rate, * mL/min per 1.73 m ²	64.5 (21.0)	68.9 (22.3)	61.0 (20.4)	62.1 (18.7)	0.001
CHA ₂ DS ₂ -VASc score	2.9 (2.0)	2.3 (2.0)	3.2 (1.8)	3.3 (1.9)	<0.001

Values are shown as mean (standard deviation) or n (%).

Abbreviations: BMI, body mass index; CHF, congestive heart failure; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease

* Excludes 26 patients who did not have creatinine measured within 90 days of atrial fibrillation diagnosis.

Table 2

Unadjusted and Serially Adjusted Hazard Ratios (95% Confidence Intervals) for the Risk of Stroke/Transient Ischemic Attack, Cardiovascular and All-Cause Death for Atypical and Asymptomatic Atrial Fibrillation Presentation Compared to Typical Presentation

	Stroke/TIA		Cardiovascular death		All-cause death	
	Atypical	Asymptomatic	Atypical	Asymptomatic	Atypical	Asymptomatic
Unadjusted	5.24 (2.48-11.05)	4.04 (1.95-8.40)	2.38 (1.03-5.51)	4.07 (2.01-8.22)	4.35 (2.72-6.95)	4.27 (2.74-6.67)
Adjusted [†]	3.51 (1.65-7.48)	2.70 (1.29-5.66)	1.59 (0.68-3.76)	3.12 (1.50-6.45)	2.75 (1.71-4.41)	2.96 (1.89-4.64)
Adjusted [‡]	3.77 (1.66-8.56)	2.72 (1.21-6.13)	1.24 (0.51-3.02)	2.61 (1.23-5.55)	2.42 (1.47-3.99)	3.27 (2.03-5.26)
Adjusted [§]	4.12 (1.71-9.94)	2.90 (1.23-6.84)	1.26 (0.50-3.16)	2.80 (1.28-6.10)	2.52 (1.46-4.35)	3.63 (2.24-5.89)
Adjusted [*]	3.12 (1.27-7.66)	2.60 (1.10-6.11)	1.56 (0.53-4.60)	3.40 (1.30-8.90)	3.19 (1.78-5.71)	4.01 (2.32-6.91)

[†] Adjusted for CHA₂DS₂-VAsC score and age.

[‡] Adjusted for CHA₂DS₂-VAsC score, age, body mass index, smoking status, chronic obstructive pulmonary disease, estimated glomerular filtration rate, dementia, and malignancy.

[§] Adjusted for CHA₂DS₂-VAsC score, age, body mass index, smoking status, chronic obstructive pulmonary disease, estimated glomerular filtration rate, dementia, malignancy, and warfarin use modeled as a time-dependent variable.

^{*} Adjusted for CHA₂DS₂-VAsC score, age, body mass index, smoking status, chronic obstructive pulmonary disease, estimated glomerular filtration rate, dementia, malignancy, warfarin use modeled as a time-dependent variable, and time in therapeutic range.

Abbreviations: TIA, transient ischemic attack