

# Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke

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## Aims

Atrial fibrillation increases the risks of stroke, heart failure, and death, and anticoagulation therapy increases the risk of gastrointestinal haemorrhage. However, the relative event rates for these outcomes are not well described. We sought to define the risks of major clinical events in older adults after a new diagnosis of atrial fibrillation.

## Methods and results

We undertook a population-based, retrospective cohort study of a nationally representative sample of fee-for-service Medicare beneficiaries 65 years or older with incident atrial fibrillation diagnosed between 1999 and 2007. The main outcome measures were mortality and hospitalization or emergency department care for heart failure, myocardial infarction, stroke, or gastrointestinal haemorrhage. Among 186 461 patients with atrial fibrillation and no recent hospitalizations for heart failure, myocardial infarction, stroke, or gastrointestinal haemorrhage, mortality was the most frequent of these major clinical events (19.5% at 1 year; 48.8% at 5 years). By 5 years, 13.7% of patients were hospitalized for heart failure, 7.1% developed new-onset stroke, and 5.7% had gastrointestinal haemorrhage. Myocardial infarction was less frequent (3.9% at 5 years). Rates of mortality, heart failure, myocardial infarction, stroke, and gastrointestinal bleeding increased with older age and higher CHADS<sub>2</sub> scores. Among 44 479 patients with previous events, the 5-year risk of death was greatest among patients with recent bleeding events (70.1%) and stroke (63.7%) and lowest among those with recent myocardial infarction (54.9%).

## Conclusion

After the diagnosis of incident atrial fibrillation in older adults, mortality was the most frequent major outcome during the first 5 years. Among non-fatal cardiovascular events, heart failure was the most common event.

## Keywords

Atrial fibrillation • Heart failure • Outcome assessment (health care) • Mortality

## Introduction

Atrial fibrillation is a common problem among older adults,<sup>1</sup> and it is associated with increased risks of heart failure, stroke, and death.<sup>2</sup> The Institute of Medicine recently ranked the treatment of patients with atrial fibrillation among the highest priority topics for comparative effectiveness research.<sup>3</sup> Effective treatment of patients with atrial fibrillation includes not only rate control, rhythm control, and prevention of stroke, but also management of cardiovascular risk factors and comorbid illnesses. Although atrial fibrillation is

associated with increased risks of major cardiovascular events such as stroke and heart failure, the absolute and relative event rates of these competing outcomes are not well described. Optimal public health prioritization, clinical decision-making, and patient counselling require an understanding of the clinical course of disease states, including the potential risks of multiple subsequent clinical events. Therefore, we used survival analysis in a national sample of older adults to describe the incidence of death, heart failure, myocardial infarction, stroke, and gastrointestinal bleeding after the diagnosis of atrial fibrillation.

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## Methods

### Study population

Using a 5% national sample of fee-for-service Medicare beneficiaries 65 years or older, we identified beneficiaries who received a diagnosis of incident atrial fibrillation between 1 January 1999 and 30 September 2007. We described our identification of the study population in detail previously.<sup>1</sup> In brief, we considered beneficiaries to have incident atrial fibrillation if they had a single inpatient claim or two outpatient or physician claims with an atrial fibrillation diagnosis [*International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code 427.31] in any position on the claim after two or more years of enrolment in fee-for-service Medicare with no atrial fibrillation diagnosis. Because of the requirement of prior enrolment without atrial fibrillation, beneficiaries in the study population were 67 years or older. For the purpose of our analyses, we excluded patients with atrial fibrillation initially diagnosed during a terminal hospitalization.

### Data sources

For patients in the study population, we obtained inpatient, outpatient, and carrier claims and the corresponding denominator files from 1 January 1998 to 31 December 2009, from the US Centers for Medicare & Medicaid Services. The inpatient files contain institutional claims for inpatient services. The outpatient files contain institutional claims for outpatient services. The carrier files contain physician and other non-institutional claims for services. All files include service dates and *ICD-9-CM* diagnosis codes. The denominator files contain beneficiary demographic characteristics, date of death (if applicable), and Medicare enrolment information. All analyses were limited to periods of Medicare fee-for-service enrolment.

### Events

The outcomes of interest were death and hospitalization or emergency department care for heart failure, myocardial infarction, stroke, or gastrointestinal haemorrhage in the 5 years after a diagnosis of incident atrial fibrillation. We used the Medicare denominator files to identify deaths. We identified all other outcomes by searching for inpatient or emergency department claims containing a primary diagnosis of stroke (*ICD-9-CM* codes 430, 431, 433.x1, 434.x1, 435.x, 436), heart failure (428.x, 402.x1, 404.x1, 404.x3), myocardial infarction (410.x1), or gastrointestinal haemorrhage (456.0, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x). If a hospitalization or emergency department visit resulted in death, we classified the event as a death regardless of the associated primary diagnosis. In a sensitivity analysis, we counted these hospitalizations and emergency department visits towards the other outcomes, when applicable.

### Study cohorts

Within the study population, we defined a primary study cohort and several secondary cohorts on the basis of events in the 3 months before the atrial fibrillation diagnosis. We treated these groups separately, because we expected recent events to have a strong effect on subsequent outcome trajectories. The recent events of interest were the same as those described above except death (i.e. heart failure, myocardial infarction, stroke, and gastrointestinal haemorrhage). The primary study cohort included patients who had no recent events. The secondary study cohorts included patients who had one or more recent events—heart failure alone, myocardial infarction alone, stroke alone, gastrointestinal haemorrhage alone, or multiple events.

### Statistical analysis

For the primary study cohort, we described demographic characteristics (age, sex, and race), comorbid conditions (cancer, cerebrovascular disease, chronic obstructive pulmonary disease, coronary heart disease, dementia, diabetes mellitus, heart failure, hypertension, peripheral vascular disease, renal disease, and valvular heart disease), devices in place at the time of diagnosis (implantable cardioverter-defibrillator and pacemaker), and the setting of the atrial fibrillation diagnosis (inpatient or outpatient). We identified comorbid conditions using diagnoses from both inpatient and outpatient claims and previously validated coding algorithms.<sup>4,5</sup> To summarize risk, we used both the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scores.<sup>6,7</sup> For categorical variables, we report frequencies and percentages. For continuous variables, we report means and SDs.

For all study cohorts, we used Kaplan–Meier methods to estimate mortality rates. We treated death as a competing risk for all other events and used the cumulative incidence function to estimate rates for each event. We censored data at the time of disenrolment from fee-for-service Medicare or at the end of data availability (31 December 2009), if applicable. We also plotted cumulative incidence curves for each cohort. In the primary cohort, we summarized the observed cumulative incidence rates for a number of subgroups, defined according to age, sex, setting of diagnosis, and CHADS<sub>2</sub> score.

We used SAS version 9.2 (SAS Institute, Inc.) for all analyses.

## Results

The study population included 230 940 Medicare beneficiaries with incident atrial fibrillation. The primary study cohort included 186 461 patients (81%) who did not have any of the clinical events of interest during the preceding 3 months. The 44 479 patients (19%) who did have a recent event were included in the secondary study cohorts. The median follow-up was 4.4 years (inter-quartile range, 4.1–5.0). *Table 1* shows the baseline characteristics of the primary cohort. Most patients (60.1%) were first diagnosed with atrial fibrillation in inpatient settings. The mean age was 79.5 (SD: 7.3) years, 44.6% of the patients were men, and 92.0% were white. The mean CHADS<sub>2</sub> score was 2.8 (SD: 1.4) and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 5.0 (SD: 1.7).

*Figure 1* shows the cumulative incidence of each event over 5 years after the diagnosis of atrial fibrillation. Mortality was the most common event after the diagnosis of atrial fibrillation, with a cumulative incidence of 19.5% at 1 year and 48.8% at 5 years. At 5 years, 13.7% of the patients with incident atrial fibrillation had a hospitalization or emergency department visit for heart failure, 7.1% developed new-onset stroke, and 5.7% had gastrointestinal bleeding (*Table 2*). Myocardial infarction was the least frequent event, with a cumulative incidence of 1.2% at 1 year and 3.9% at 5 years. In a sensitivity analysis that considered all hospitalizations and emergency department visits, regardless of subsequent inpatient mortality, the findings were similar.

*Figure 1* and *Table 2* also show the incidence of clinical events among patients with recent heart failure, myocardial infarction, stroke, gastrointestinal haemorrhage, or multiple events in the secondary study cohorts. Among patients with recent heart failure, the cumulative incidence of heart failure hospitalization was 37.0% at 5 years and the cumulative incidence of death was 73.1% at 5 years (*Table 2*). In patients with recent stroke, the most frequent non-fatal event after a diagnosis of atrial fibrillation was recurrent stroke (17.7% at 5 years). Among patients with any recent events, the

**Table 1** Characteristics of the primary study cohort of Medicare beneficiaries with incident atrial fibrillation

Characteristic	Patients (n = 186 461)
Age, mean (SD), year	79.5 (7.3)
Male, n (%)	83 079 (44.6)
Race, n (%)	
Black	9852 (5.3)
White	171 579 (92.0)
Other/unknown	5030 (2.7)
Comorbid conditions, n (%)	
Cancer	38 509 (20.7)
Cerebrovascular disease	53 047 (28.4)
Chronic obstructive pulmonary disease	71 093 (38.1)
Coronary heart disease	101 299 (54.3)
Dementia	17 320 (9.3)
Diabetes mellitus	54 659 (29.3)
Heart failure	72 746 (39.0)
Hypertension	149 673 (80.3)
Peripheral vascular disease	51 021 (27.4)
Renal disease	20 684 (11.1)
Valvular heart disease	69 905 (37.5)
Risk scores, n (%)	
CHADS <sub>2</sub> , mean (SD)	2.8 (1.4)
CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean (SD)	5.0 (1.7)
Devices, n (%)	
Implantable cardioverter-defibrillator	1636 (0.9)
Pacemaker	9666 (5.2)
Clinical setting of diagnosis, n (%)	
Inpatient	112 097 (60.1)
Outpatient	74 364 (39.9)

cumulative incidence of death at 5 years was greatest among patients with multiple events (78.1%) and lowest among those with prior myocardial infarction (54.9%).

When we analysed rates of events by the setting of the atrial fibrillation diagnosis, the cumulative incidence of mortality was higher among patients diagnosed in inpatient settings. For example, 1-year cumulative incidence of mortality was 55.7% among patients with an inpatient diagnosis, compared with 38.4% among those with an outpatient diagnosis. The cumulative incidence rates of heart failure, myocardial infarction, stroke, and gastrointestinal bleeding were similar between patients diagnosed in inpatient and outpatient settings (Figure 2). Table 3 shows the cumulative incidence rates of mortality, heart failure, myocardial infarction, stroke, and gastrointestinal bleeding in other subgroups. All outcome rates increased with older age and higher CHADS<sub>2</sub> scores.

## Discussion

Clinicians have several important treatment goals for patients with atrial fibrillation, including prevention of stroke, heart rate control, rhythm control, and improving quality of life. Counselling patients

and prescribing therapies require knowledge of the risks of various clinical events, including cardiovascular events, gastrointestinal bleeding due to anticoagulation therapy, and mortality. We examined rates and risk factors for clinical events among 230 940 Medicare beneficiaries after a diagnosis of incident atrial fibrillation.

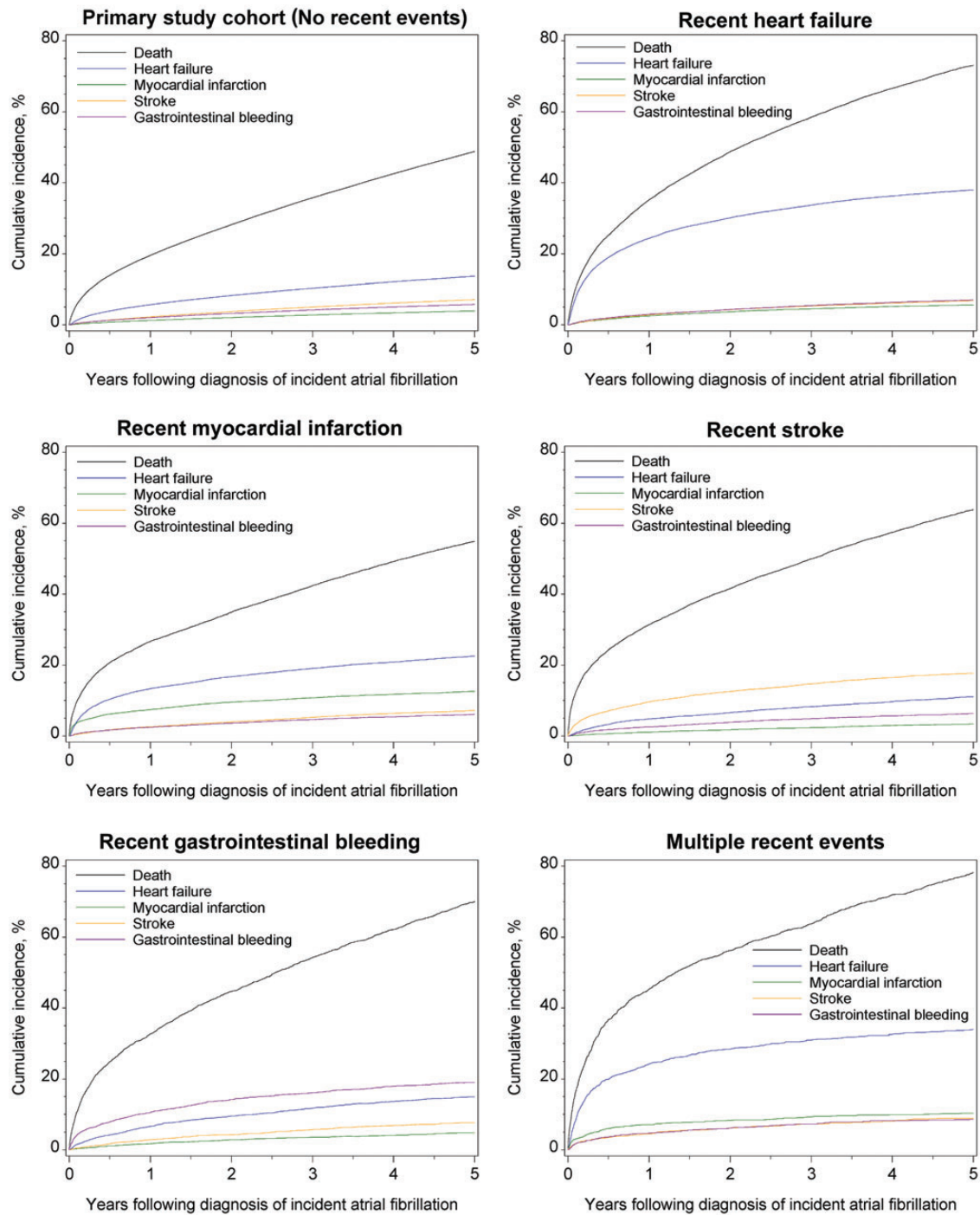
As may be expected in an older cohort, mortality rates were high. Nearly half of the primary study cohort, those without a major cardiovascular or bleeding event in the 3 months before the diagnosis of atrial fibrillation, died in the 5 years after the diagnosis of atrial fibrillation. Rates were higher in the secondary study cohorts, which consisted of beneficiaries who had experienced one or more recent events in the 3 months before the diagnosis of atrial fibrillation.

Among the major nonfatal events we examined—hospitalization or emergency department visit for heart failure, myocardial infarction, stroke, and gastrointestinal bleeding—heart failure was most common and myocardial infarction was the least common in the primary cohort. In the secondary cohorts, non-fatal event rates varied depending on which recent event a patient had experienced. In general, risk of heart failure hospitalization was still high, eclipsed only by the risk of stroke among patients with a recent stroke and the risk of gastrointestinal bleeding among patients with a recent bleeding event.

Despite effective pharmacological prophylaxis, stroke remains an important complication of atrial fibrillation.<sup>8</sup> However, in terms of absolute risk, older patients with atrial fibrillation are twice as likely to develop heart failure as to develop stroke.<sup>9–12</sup> Although the importance of stroke prevention cannot be overemphasized, our findings highlight the disproportionate burden of heart failure in patients with atrial fibrillation. Given the high risk of incident heart failure among patients with atrial fibrillation, and the poor outcomes of patients with both conditions,<sup>9,10</sup> prevention and management of heart failure in patients with atrial fibrillation requires attention. Ours and other studies suggest that prevention of heart failure should be elevated alongside stroke prevention as a key priority in the management of patients with atrial fibrillation.<sup>2,12</sup>

Data from a variety of observational studies have shown that atrial fibrillation is associated with greater mortality,<sup>8</sup> regardless of the presence or absence of previous cardiovascular disease.<sup>13</sup> Furthermore, the risk of death is greatest in the first year after a new diagnosis of atrial fibrillation. The overall risk of death 1 year after diagnosis approaches 25% and is higher in critically ill patients, such as those with sepsis.<sup>1,14,15</sup> In our primary cohort of older patients with incident atrial fibrillation and no recent events, the risk of death was more than three-fold greater than the occurrence of heart failure and seven-fold greater than the occurrence of stroke. In addition, the risk of death was higher among patients diagnosed with atrial fibrillation in inpatient settings, despite relatively similar risks of incident heart failure, stroke, and myocardial infarction. Our data suggest that, regardless of the mechanism, incident atrial fibrillation is a powerful marker for 1-year and 5-year mortality in older adults.

In the secondary cohorts of patients with recent cardiovascular or gastrointestinal bleeding events, those who developed incident atrial fibrillation also had a high risk of death in intermediate and long-term follow-up. These poor outcomes are consistent with prior observations in patients with concomitant atrial fibrillation and heart failure.<sup>16</sup> In general, patients with recent cardiovascular or bleeding events were at a high risk of a recurrent event after their first diagnosis of atrial fibrillation, particularly in the case of



**Figure 1** Observed cumulative incidence of events in the 5 years after the diagnosis of incident atrial fibrillation by study cohort. Numbers of patients at risk of death over time.

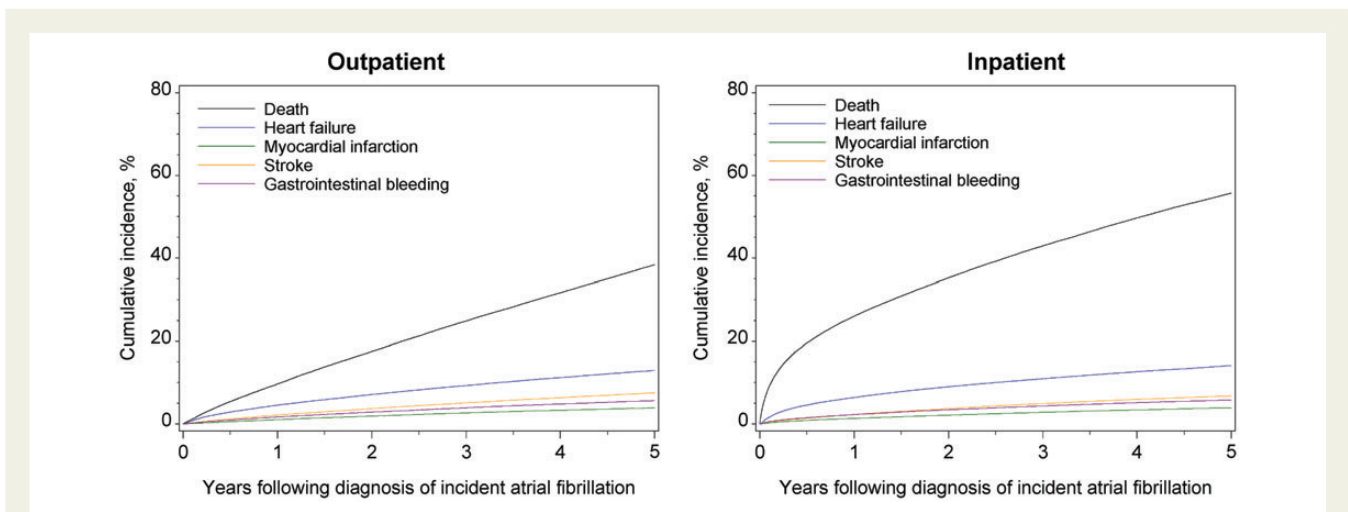
heart failure. Consistent with other studies of populations with atrial fibrillation, patients with previous myocardial infarction had a higher risk of myocardial infarction, and patients with previous bleeding events a higher risk of subsequent bleeding events.<sup>17,18</sup> Taken together, these findings confirm that mortality is common among older patients with recent cardiovascular and bleeding events and that future events tend to mirror the patient's recent medical history.

Our study has several limitations. First, the data are from a Medicare population, so the findings may not be generalizable to younger populations. Secondly, Medicare beneficiaries who accessed health care through other programmes before enrolling in Medicare may have been incorrectly classified as having incident atrial fibrillation if a previous diagnosis was not documented during the Medicare enrolment examination. Also, Medicare data do not include information on cause of death. Our analysis cannot shed light on the

**Table 2** Observed cumulative incidence of events over 1, 2, and 5 years after the diagnosis of incident atrial fibrillation by study cohort

Outcome	Study cohort					
	No recent events (n = 186 461) <sup>a</sup>	Recent heart failure (n = 17 928) <sup>a</sup>	Recent myocardial infarction (n = 12 408) <sup>a</sup>	Recent stroke (n = 8801) <sup>a</sup>	Recent gastrointestinal bleeding (n = 3633) <sup>a</sup>	Multiple recent events (n = 1709) <sup>a</sup>
1 year, n (%)						
Death	36 153 (19.5)	6260 (35.2)	3286 (26.6)	2748 (31.4)	1181 (32.7)	770 (45.3)
Heart failure	10 499 (5.7)	4329 (24.3)	1649 (13.4)	419 (4.8)	240 (6.7)	411 (24.2)
Myocardial infarction	2272 (1.2)	444 (2.5)	915 (7.4)	95 (1.1)	62 (1.7)	121 (7.1)
Stroke	4122 (2.2)	495 (2.8)	317 (2.6)	842 (9.6)	104 (2.9)	78 (4.6)
Gastrointestinal bleeding	3751 (2.0)	526 (3.0)	303 (2.5)	225 (2.6)	382 (10.6)	80 (4.7)
2 years, n (%)						
Death	51 778 (28.2)	8595 (48.7)	4274 (34.9)	3611 (41.5)	1601 (44.6)	949 (56.2)
Heart failure	15 170 (8.3)	5320 (30.0)	2048 (16.7)	571 (6.6)	341 (9.5)	481 (28.4)
Myocardial infarction	3723 (2.0)	646 (3.7)	1169 (9.5)	151 (1.7)	102 (2.9)	141 (8.3)
Stroke	6825 (3.7)	751 (4.3)	486 (4.0)	1092 (12.6)	154 (4.3)	104 (6.2)
Gastrointestinal bleeding	5912 (3.2)	762 (4.3)	441 (3.6)	338 (3.9)	509 (14.2)	103 (6.1)
5 years, n (%)						
Death	82 917 (48.8)	12 183 (73.1)	6314 (54.9)	5194 (63.7)	2345 (70.1)	1252 (78.1)
Heart failure	23 389 (13.7)	6509 (37.9)	2650 (22.6)	890 (11.1)	503 (15.0)	560 (33.9)
Myocardial infarction	6597 (3.9)	934 (5.6)	1486 (12.6)	270 (3.4)	159 (4.8)	169 (10.3)
Stroke	11 920 (7.1)	1124 (6.8)	814 (7.2)	1462 (17.7)	255 (7.7)	142 (8.9)
Gastrointestinal bleeding	9748 (5.7)	1156 (7.0)	700 (6.1)	517 (6.4)	654 (19.1)	139 (8.6)

<sup>a</sup>Recent events were events within 3 months before the diagnosis of atrial fibrillation.



**Figure 2** Observed cumulative incidence of events in the 5 years after the diagnosis of incident atrial fibrillation by setting of diagnosis in the primary study cohort. Numbers of patients at risk of death over time.

distribution of underlying causes of death in patients with atrial fibrillation. Finally, claims data are inherently limited with respect to clinical characteristics, because comorbid conditions are often not coded uniformly. As with any retrospective analysis, unmeasured covariates likely influenced the outcomes.

In summary, among non-fatal clinical events in patients with incident atrial fibrillation, heart failure was the most common event. After a new diagnosis of atrial fibrillation, the risk of heart failure hospitalization was more than two-fold greater than the risk of stroke over 5 years. Given the frequency and consequences of heart

**Table 3** Observed cumulative incidence of events over 5 years after the diagnosis of incident atrial fibrillation by the subgroup of the primary study cohort

Subgroup	No. of patients	Cumulative incidence, n (%)				
		Mortality	Heart failure	Myocardial infarction	Stroke	Gastrointestinal bleeding
Sex						
Female	103 382	46 105 (49.0)	13 233 (14.0)	3482 (3.7)	7456 (8.0)	5579 (5.9)
Male	83 079	36 812 (48.5)	10 156 (13.3)	3115 (4.2)	4464 (6.0)	4169 (5.5)
Age group						
67–69 year	16 294	4211 (28.8)	1626 (11.0)	471 (3.3)	728 (5.0)	644 (4.4)
70–74 year	37 153	10 876 (32.3)	4082 (12.1)	1199 (3.6)	1902 (5.7)	1652 (4.9)
75–79 year	44 396	16 155 (40.1)	5401 (13.3)	1538 (3.9)	2749 (6.9)	2375 (5.9)
80–84 year	41 450	19 603 (52.1)	5710 (15.1)	1611 (4.3)	3023 (8.1)	2402 (6.4)
85–89 year	28 657	17 526 (67.0)	4179 (15.8)	1161 (4.4)	2324 (8.9)	1741 (6.6)
≥ 90 year	18 511	14 546 (84.3)	2391 (13.7)	617 (3.6)	1194 (6.9)	934 (5.4)
Setting of incident diagnosis of atrial fibrillation						
Outpatient setting	74 364	25 276 (38.4)	8756 (13.0)	2602 (3.9)	5009 (7.5)	3778 (5.7)
Inpatient setting	112 097	57 641 (55.7)	14 633 (14.1)	3995 (3.9)	6911 (6.8)	5970 (5.8)
CHADS <sub>2</sub> score						
0–1	35 719	10 124 (31.0)	2039 (6.3)	859 (2.7)	1594 (4.9)	1229 (3.8)
2–4	125 351	57 294 (50.4)	16 883 (14.7)	4455 (4.0)	8261 (7.3)	6860 (6.0)
5–6	25 391	15 499 (66.9)	4467 (19.1)	1283 (5.6)	2065 (9.0)	1659 (7.2)

failure in patients with incident atrial fibrillation, greater emphasis on primary prevention of heart failure in patients with atrial fibrillation may be warranted.

## Additional contributions

Damon M. Seils, MA, Duke University, provided editorial assistance. Mr Seils did not receive compensation for his assistance apart from his employment at the institution where the study was conducted.

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## CARDIOVASCULAR FLASHLIGHT

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### Incomplete isolated cleft of the anterior mitral valve: first reported as triangular defect

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A 16-year-old girl with a 12 year history of systolic murmur at the apex presented with mitral regurgitation. Two-dimensional echocardiography in the parasternal long-axis view showed the part of the anterior mitral valve (AMV) which near the root was thin without echo drop-out (Panel A, arrowhead). The parasternal short-axis view showed a cleft on AMV (Panel B, arrowhead) and moderate-severe regurgitation through the cleft (Panel C, Supplementary material online, Video S1). Continuous ultrasound scanning from mitral valve tip to root showed the cleft was incomplete (Supplementary material online, Video S2). Three-dimensional echocardiography revealed a better view of the cleft which is a triangular shape without thickening and edge retraction in the A2 region (Panel D). Three-dimensional echocardiography also helped us to measure the width and depth of the cleft. Intra-operative findings confirmed the echocardiography diagnosis (Panel E). One week after the surgery in which the mitral valve was repaired without a patch, three-dimensional echocardiography showed that the AMV was integrated (Panel F).

Incomplete isolated cleft of the AMV without any other heart defects even prolapse diagnosed by echocardiography is not reported yet. Preoperative diagnosis is useful for surgical planning.

(Panel A) Two-dimensional echocardiography in the parasternal long-axis view showed the part of the anterior mitral valve (AMV) which near the root was thin without echo drop-out (Panel A, arrowhead).

(Panel B) The parasternal short-axis view showed a cleft on the AMV (Panel B, arrowhead). (Panel C) The parasternal short-axis view showed moderate-severe regurgitation through the cleft (Panel C). (Panel D) Three-dimensional echocardiography revealed a better view of the cleft which is a triangular shape without thickening and edge retraction in the A2 region (Panel D). (Panel E). Intra-operative findings confirmed the echocardiography diagnosis (Panel E). (Panel F) Post-operative three-dimensional echocardiography showed the AMV was integrated (Panel F). LA, left atrium; LV, left ventricle; RV, right ventricle; PMV, posterior mitral valve.

Supplementary material is available at *European Heart Journal* online.

