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Causes of deaths and influencing factors in patients with atrial fibrillation

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Short title. Causes of Death in Atrial Fibrillation Patients

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Clinical significance

- Cardiovascular events were the most common cause of death (54% of cases) in a large study of hospitalized patients with atrial fibrillation.
- Fatal stroke or fatal bleeding each accounted for 7% of all deaths.
- The strongest predictors of overall death were permanent atrial fibrillation, heart failure (whether with decreased or with preserved ejection fraction), previous bleeding and renal failure.
- Oral anticoagulant use was independently associated with a lower risk of all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality.

ABSTRACT

Background: Atrial fibrillation is associated with a higher mortality, but causes of death of atrial fibrillation patients and their specific predictors have been less well defined. We aimed to identify the causes of death among atrial fibrillation patients and secondly, clinical predictors for the different modes of deaths.

Methods: Patients diagnosed with atrial fibrillation in a four-hospital institution between 2000 and 2010 were identified. During a follow-up of 929±1082 days (median 456, interquartile 10-1584), 1253 deaths were recorded (yearly rate 5.5%).

Results: Cardiovascular deaths accounted for 54% and non-cardiovascular in 43%. The three main causes of death were heart failure (29%), infection (18%) and cancer (12%). Fatal stroke or fatal bleeding each accounted for 7% of all deaths. On multivariate analysis, the strongest predictors of death were permanent atrial fibrillation, heart failure (whether with decreased or with preserved ejection fraction), previous bleeding and renal failure, which were independently associated with an increase in the risk of all cause mortality (35%, 78%, 42% and 79% respectively), cardiovascular mortality (43%, 129%, 46% and 93%) and non-cardiovascular mortality (21%, 45%, 40% and 50%). Oral anticoagulant use was independently associated with a lower risk of all-cause mortality (hazard ratio[HR] 0.62, 95% confidence interval [CI] 0.54-0.71, p<0.0001), cardiovascular mortality (HR 0.60, 95%CI 0.49-0.72, p<0.0001), and non-cardiovascular mortality (HR 0.60, 95%CI 0.49-0.74, p<0.0001).

Conclusions: The majority of deaths were related to a cardiovascular origin and heart failure was the most common cause of death in atrial fibrillation patients. Despite the high risk of stroke associated with atrial fibrillation, only 7% died from stroke. Optimization of management of any underlying heart disease and associated comorbidities should be a relevant therapeutic target to reduce total mortality in atrial fibrillation patients.

Key words: atrial fibrillation, death, heart failure, stroke, oral anticoagulation.

INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia and significantly increases mortality and morbidity, and impairs quality of life. Strategies to reduce overall atrial fibrillation-related mortality are focused on the prevention of thromboembolism. Indeed, oral anticoagulation with the Vitamin K antagonists (VKA, eg. warfarin) significantly reduce stroke and systemic embolism by 64% compared to placebo or control, although all-cause mortality is also significantly reduced by 26% [1]. The development of non vitamin-K oral anticoagulants (NOACs) which are simpler to use, and at least as effective and safe as vitamin K antagonist (VKA) may provide additional reductions in morbidity and mortality in this population [2].

However, patients with atrial fibrillation often have several cardiovascular risk factors, structural heart disease, and comorbidities, all of which can increase mortality [3–7]. Thus, besides the risk of fatal hemorrhage conferred by anti-thrombotic therapy, the causes of death (and their predictors) in patients with atrial fibrillation are less well defined. Identifying causes of death and their predictors in patients with atrial fibrillation is crucial in enabling the development of effective targeted interventions and reducing overall mortality in this population. The objective of this study was to identify the causes of death among atrial fibrillation patients and secondly, clinical predictors for the different modes of deaths.

METHODS

We included all patients with a diagnosis of atrial fibrillation seen in the cardiology department in our institution between January 2000 and December 2010[8]. Atrial fibrillation was defined on the electrocardiogram by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, often rapid ventricular response. Patients' characteristics were obtained from the records of our institution's computerized codification system for each patient. Extensive information was collected on date of admission, discharge, diagnosis, clinical presentation, comorbidities, medication and subsequent hospitalization or outpatient visit. Patients entered into the study on their first cardiology encounter during the study period with atrial fibrillation. For each patient, the thromboembolic risk was estimated at the time of entry into the study using the CHA_2DS_2-VASc (acronym for Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes, Stroke/TIA/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65-74 years, Sex category [female]) score and the haemorrhagic risk using the HAS-BLED (acronym for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) bleeding risk score. The SAMe TT_2R_2 (acronym for Sex, Age <60 years; Medical history [at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease]; Treatment [interacting drugs, eg, amiodarone for rhythm control] [all 1 point]; current Tobacco use (2 points) and Race [non-Caucasian; 2 points]) score was used to predict poor INR control in patients with atrial fibrillation treated with VKA[9–13]. None of the patients were treated with NOAC during this study period.

During follow-up, deaths from all causes and events of interest were recorded whenever they occurred in our institution, which includes a total of 4 hospitals covering all medical and surgical specialties. Our hospital covers an area of 4000 km^2, and a population of 400.000 inhabitants and is the only public institution in the area. In addition, mortality data were obtained using a search tool from a dedicated website for the Région Centre (http://nrco.lanouvellerepublique.fr/dossiers/necro/index.php). The causes of death occurring in the University Hospital of Tours were collected through computerized hospitalization reports. For those that occurred outside our institution, they were collected by telephone from treating physicians, retirement homes or families. Mode of death was adjudicated based on medical reports and autopsy reports or death certificates when available. This information was reviewed by 2 investigators and causes of death were adjudicated after consideration of all the available information, and according to the following prespecified groups: cardiovascular, noncardiovascular, as well as unknown when the quality of the information could not allow the investigators to appropriately identify cause of death.

The study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital, on December 7, 2010 and registered as a clinical audit. Ethical review was therefore not required. Patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.

Statistical analysis

Patient characteristics are reported as percentages and the mean ± standard deviation (SD).

Comparisons between groups were made using chi-square tests for comparing categorical variables and the Student t test or non-parametric Kruskal Wallis test were appropriate for continuous variables. Cumulative incidence rates of events were calculated for all patients by subgroups of interest. A Cox proportional hazards regression model was used to calculate the hazard ratio (HR) of predictive factors and their 95% confidence interval (CI) for the incidence of events. The proportional hazard assumption was checked by plotting the log-log Kaplan Meier curves. A p-value < 0.05 was considered statistically significant. Statistical analysis was carried out with the Statview 5.0 software (Abacus Concepts, Berkley, CA, USA).

RESULTS

A total of 8,962 patients with atrial fibrillation were included between January 2000 and December 2010. During a follow-up of 929 ± 1082 days (median 456, interquartile 10-1584), 1294 patients died (14%, yearly rate of death 5.5%) and 97% of causes of death were identified.

Patient characteristics

Patients who died during follow-up were older, were more frequently with permanent atrial fibrillation and had higher CHA_2DS_2-VASc score, HASBLED score and $SAMeTT_2R_2$ score (Table 1).. Among patients with heart failure, 51% had ischemic etiology and among those with left ventricular ejection fraction measured in the 6 previous months with either echocardiography or angioscintigraphy, there were 34% with reduced left ventricular ejection fraction <40% and 24% with ejection fraction 40-49%. In patients with heart failure, 52% were treated with beta-blockers (59% in those with ejection fraction <40%, 57% in those with ejection fraction 40-49% and 43% in those with ejection fraction ≥50%. Among patients who died during the follow-up,

there was a higher prevalence of patients with various cardiovascular comorbidities, as well as alcohol abuse and active smoking. The proportion of patients with coronary artery disease, heart failure (whether with decreased or preserved ejection fraction) and those with a left ventricular ejection fraction <40% was higher among the patients dead at the end of follow-up Non-use of antithrombotic therapy was higher, and the proportion of patients on VKA was lower, among those who died during follow-up. The proportion of patients on beta-blockers was higher among the patients alive at the end of follow-up.

Causes of death and impact of prescription of VKA

Among the 1,294 causes of death identified, 699 (54%) were cardiovascular and 552 (43%) non-cardiovascular. Heart failure was the primary cause of cardiovascular deaths (29.2%) whereas infection (17.6%) was the primary cause of non-cardiovascular deaths (Figure 1, Table 2).

After adjustment for age, sex, characteristics of atrial fibrillation (permanent or non-permanent), comorbidities and treatments, the prescription of VKA was independently associated with a lower overall mortality, cardiovascular mortality and non-cardiovascular mortality (risk reduction of 38%, 40% and 40%) (Table 3). Among cardiovascular deaths, prescription of VKA was associated with a non-significantly lower risk of *fatal* stroke in our cohort. Central nervous system fatal hemorrhage was not independently linked with prescription of VKA. VKA use was also associated with a lower risk of vascular events such as fatal pulmonary embolism or fatal aortic syndrome.

Among non-cardiovascular death, prescription of VKA was independently associated with a higher risk of fatal trauma (245%). This higher risk was not significant for deaths from cerebral

trauma but was significant for other trauma-related deaths (Table 3).

Independent predictors of the main causes of death

Besides age and male gender, the presence of permanent atrial fibrillation, heart failure (whether with systolic dysfunction or with preserved ejection fraction, and with ischemic or non-ischemic etiology), previous major bleeding and renal failure were independently associated with an increase in the risk of overall mortality (35%, 78%, 42% and 79% respectively), cardiovascular mortality (43%, 129%, 46% and 93%) and non-cardiovascular mortality (21%, 45%, 40% and 50%) (Table 4).

Death due to heart failure was independently associated with permanent atrial fibrillation, coronary artery disease, previous heart failure (whether with decreased or with preserved ejection fraction), previous acute coronary syndrome, renal failure or left bundle branch block. Of note, use of beta-blockers was associated with a 22% decrease in the risk of death related to heart failure. Death due to sudden cardiac death was independently associated with older age, history of heart failure (whether with decreased or with preserved ejection fraction), and renal failure (Table 5).

There were more permanent atrial fibrillation patients who died due to a fatal stroke, and as expected, age and CHA_2DS_2-VASc scores were significant predictors of fatal stroke. For fatal bleeding, HASBLED score, age and renal failure were predictors on the unadjusted analysis, but only age was significant predictor for more fatal bleeds on adjustment. Patients with a prescription of VKA had lower risk of death from fatal bleeding (Table 6).

DISCUSSION

In our cohort, the three main causes of death were heart failure (29%), infections (18%) and cancer (12%), whilst stroke and hemorrhagic-related deaths each only contributed for approximately 7% of causes of death. Second, the presence of permanent atrial fibrillation, heart failure (whether with decreased or with preserved ejection fraction), previous bleeding and renal failure were all independently associated with an increase in the risk of all cause mortality, cardiovascular mortality and non-cardiovascular mortality. Third, oral anticoagulant use was independently associated with a lower risk of mortality.

Our work is the first to detail the causes of mortality and identified independent predictors of the main causes of death in a large population of unselected and well characterized patients with atrial fibrillation.

The identification of these predictors for the specific mode of death may help to develop effective targeted interventions in order to reduce overall atrial fibrillation-related mortality.

VKA use was independently associated with a decrease in overall mortality during follow-up, as was previously suggested for patients seen in randomized trials [1]. While 24% of patients who died did not receive thromboprophylaxis in our cohort, the distribution of causes of death in our cohort was different (with lower rates of cardiovascular deaths and fatal strokes) than that seen in the RE-LY analysis [14]. The latter was a selected clinical trial population in which all patients were receiving anticoagulant therapy.

Our work suggests that anticoagulation is perhaps not the only consideration amongst strategies

for the reduction of atrial fibrillation-related mortality, and we should also target comorbidities associated with atrial fibrillation. Indeed, we found that heart failure (whether with decreased or with preserved ejection fraction) increased risk of overall mortality (78%), cardiovascular mortality (129%), non-cardiovascular mortality (45%), heart failure-related mortality (178%) and sudden cardiac death (222%). These data are consistent with the RE-LY trial analysis, although a lower annual rate of death (3.8%) was seen [14]. Similarly, in the recent observational XANTUS study of atrial fibrillation patients treated with rivaroxaban, death occurred in 118 patients (yearly rate 1.9%) within the study treatment period, with the adjudicated cause of death due primarily to cardiovascular causes, mainly heart failure, followed by cancer [15]. Our findings clearly reflect the less selected 'real world' nature of our atrial fibrillation patients, given the annual rate of death was 5.5%.

In our cohort, only 52% of atrial fibrillation patients with heart failure (with decreased or with preserved ejection fraction) were treated with beta-blockers as in other studies [16]. We found that patients who died during follow-up had a significantly lower rate of prescription of beta-blockers. Of note, beta-blocker use was independently associated with a decrease of 22% in the risk of heart failure- related mortality while there was no association with a lower risk of sudden death in our patients. This is consistent with another large study from the Danish nationwide cohort study [17]. However, a recent individual patient metaanalysis of trial data suggests that the effect of beta-blockers on outcome in HF patients with reduced systolic LVEF who have atrial fibrillation may be less than in those who have sinus rhythm [18]. Although the subject is currently debated, increasing the rate of patients with atrial fibrillation and heart failure treated according to guidelines remains crucial, particularly for those with systolic heart failure, in order to decrease mortality in contemporary populations [19]. Patients not using beta-blockers may also have

hypotension or low rate permanent atrial fibrillation, selecting a population with a worse prognosis.

Renal failure increases the morbidity, overall mortality and cardiovascular mortality in populations that it affects [20–23]. Although deaths from renal failure-related death represented only 1.55% of all causes of death, renal failure also appeared to be a strongly associated with mortality amongst patients with atrial fibrillation. A similar finding was recently reported for atrial fibrillation patients dying in French hospitals, although there was no information on medication use [24]. After adjustment of potential confounding parameters, renal failure was independently associated with a higher risk of overall mortality (21%, which is consistent with the Danish Registry data on 132,372 patients with atrial fibrillation [25]), as well as cardiovascular mortality (93 %), non-cardiovascular mortality (50%), heart failure-related death (124%) and sudden cardiac death (145%). The result on total mortality was also consistent with the Danish Registry data on 132,372 patients with atrial fibrillation, although this did not analyze the mode of death [25]. By contrast, renal failure was not an independent predictor of occurrence of a fatal stroke or fatal hemorrhage on multivariate analysis.

Permanent atrial fibrillation was independently associated with an increased risk of overall mortality, cardiovascular mortality, non-cardiovascular mortality, heart failure-related death and fatal stroke, as previously reported for some of this findings [26–30]. However, our analysis is to our knowledge one of the first to report how permanent atrial fibrillation might be related to the *mode* of death. Nonetheless, a strategy of using drugs for rhythm control has not been found to be superior to rate control [31], and the impact of atrial fibrillation ablation catheter techniques on mortality is currently unknown. Our findings for permanent atrial fibrillation show association

and not causation. Rather than focus on rhythm control, our study suggests that the optimizing treatment of underlying heart disease which commonly complicates atrial fibrillation, or cardiac remodeling induced by atrial fibrillation, should be an important management consideration.

Study limitations

Our study was observational and not a randomized study, but this gives it the benefit of being a less biased reflection of events in a population of consecutive patients with atrial fibrillation. One needs to interpret associations with caution, and not attempt to infer causation. Permanent atrial fibrillation could be an expression of patients comorbidities with a worse overall state including a worse prognosis. It is plausible that the patients on VKA were younger and healthier, hence tolerated VKA and they may have had lower mortality rate because they were healthier. This possibly explains that patients with VKA had lower risk of death from fatal bleeding whilst one would not expect anticoagulation to actually reduce risk of bleeding. Quality of anticoagulation with time in therapeutic range was not available. Studies with a long-term follow-up as this one are often at risk of changes in treatment during the follow-up, which is impossible to make adjustments for in the multivariable analysis. It was also a monocentric study and our results should be interpreted with caution regarding the general population. Patients in different disease states were included (those with new-onset atrial fibrillation and those with multiple years of atrial fibrillation history) and this may hamper the interpretation of predictors. We did not differentiate between progressive heart failure and immediately lethal heart failure (myocardial infarction complicated by fatal cardiogenic shock for example). Finally, we did not have a control group (patients without atrial fibrillation) that would have allowed us to compare the distribution and predictors of each of the specific causes of mortality in patients with atrial fibrillation. The rate of cardiovascular deaths in hospitalized patients with atrial fibrillation (54.1%) could be

viewed as being somewhat higher than the rates reported for the general population in the United States (30.8%) [32] and in France (27.5%)[33]. As such, atrial fibrillation may not simply reflect cardiovascular ageing and would differ from general population trends.

CONCLUSION

In a large cohort of unselected patients with atrial fibrillation, the majority of deaths was not related to a fatal ischemic stroke or a fatal hemorrhage. The three main causes of death were heart failure-related death, infections and cancer. Despite the high risk of stroke associated with atrial fibrillation, only 7% died from stroke. Optimization of management of any underlying heart disease and associated comorbidities should be a relevant therapeutic target to reduce total mortality in atrial fibrillation patients.

Authorship: Drs Fauchier and Villejoubert made the primary contribution to data collection. Dr Fauchier contributed to the study conception and design. Drs Fauchier and Villejoubert performed the analyses and produced the initial manuscript. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content, and all approved the final manuscript. All authors had access to the data.

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Figure legend.

Figure 1. Cumulative mortality of patients with atrial fibrillation during the follow up.

Table 1: Characteristics of patients with atrial fibrillation alive or died at the end of the follow-up

Variable	Patients alive at the end of follow-up 7,668(86%)	Patients who died during the follow-up 1,294(14%)	*p*
Demographics			
Age (years), mean ± SD	70 ± 15	78 ± 10	<0.0001
Women, n(%)	2,975(39)	492(38)	0.60
Atrial fibrillation type and risk scores			
Permanent atrial fibrillation, n(%)	2,866(37)	629(49)	<0.0001
CHA_2DS_2-VASc score, mean ± SD	2.9 ± 1.7	3.9 ± 1.6	<0.0001
HASBLED score, mean ± SD	1.5 ± 1.1	2.0 ± 1.1	<0.0001
SAMe TT_2R_2, mean ± SD	1.46 ± 1.07	1.55 ± 1.16	0.007
Cardiovascular risk factors			
Hypertension, n(%)	3156(41)	587(45)	0.005
Diabetes mellitus, n(%)	1,134(15)	252(19)	<0.0001
Hyperlipidaemia, n(%)	1,513(20)	251(19)	0.08
Current tobacco use, n(%)	930(12)	223(17)	<0.0001
Alcohol abuse, n(%)	255(3)	63(5)	0.006
Cardiovascular Disease			
Heart failure, n(%)	3,958(52)	954(74)	<0.0001
Coronary artery disease, n(%)	2,189(29)	529(41)	<0.0001
Previous myocardial infarction, n(%)	991(13)	307(24)	<0.0001
Valvular heart disease, n(%)	1,659(22)	380(29)	<0.0001
NYHA III/IV (n=3,977), n(%)	902(27)	252(39)	<0.0001
LVEF (n=1,934), mean ± SD	48 ± 15	45 ± 17	0.01
LVEF <40% (n=1934), n(%)	464(31)	163(38)	<0.0001
LBBB, n(%)	402(5)	119(9)	<0.0001
Prior stroke/TIA, n(%)	588(8)	150(12)	<0.0001
Comorbidities			
Renal failure, n(%)	552(7)	256(20)	<0.0001
eGFR (n=7,569), ml/min/1.73m^2, mean ± SD	64 ± 24	56 ± 22	<0.0001
Pulmonary disease, n(%)	742(10)	209(16)	<0.0001
Thyroid disorder, n(%)	569(7)	128(10)	0.003
Previous major BARC bleeding, n(%)	360(5)	124(10)	<0.0001
Cancer, n(%)	130(2)	33(2)	0.04
Therapy at discharge or during follow-up			
Oral anticoagulation (VKA) (n=8,120), n(%)	4,062(58)	575(51)	<0.0001
APT (Aspirin or Clopidogrel) (n=7,969), n(%)	2,261(33)	419(38)	0.002
Dual APT (Aspirin and Clopidogrel)	467(7)	76(7)	0.97
No prevention of thromboembolic risk	1,264(19)	262(24)	0.0002
ACE inhibitor or ARB (n=8,671), n(%)	2,510(34)	539(44)	<0.0001
Beta-blocker (n=8,767), n(%)	3,427(46)	479(38)	<0.0001
Antiarrhythmic agent (n=8,362), n(%)	3,174(42)	519(41)	0.69
Digoxin (n=8,871), n(%)	1,751(23)	408(32)	<0.0001
Diuretic (n=8,224), n(%)	2,664(38)	694(57)	<0.0001
Pacemaker or ICD, n(%)	1,266(17)	266(21)	0.0003

ACE: angiotensin converting enzyme inhibitor; APT: antiplatelet therapy; ARB: angiotensin receptor blocker; eGFR : estimated glomerular filtration rate using the MDRD equation; ICD: implantable cardioverter defibrillator. LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; SD: standard deviation;TIA: transient ischemic attack; VKA: vitamine K antagosnist;

Table 2: Causes of death in patients with atrial fibrillation

Causes of death	**n**	**%**
Total death	1,294	100.0
Cardiovascular death	699	54.1
Cardiac	419	32.4
Sudden cardiac death	42	3.3
Progressive heart failure	377	29.2
Vascular death	196	15.2
Ischemic stroke	87	6.7
Fatal haemorrhage	87	6.7
CNS fatal haemorrhage	53	4.1
non-CNS fatal haemorrhage	34	2.6
Pulmonary embolism	12	0.9
Acute aortic syndrome	10	0.8
Other cardiovascular death	82	6.4
Non cardiovascular death	553	42.7
Cancer	153	11.8
Infection	227	17.6
Renal failure	20	1.6
Respiratory failure	41	3.2
Trauma	35	2.7
Cerebral trauma	18	1.4
Other trauma	18	1.4
Other non cardiovascular death	78	6.0
Undetermined death	42	3.2

CNS: central nervous system

Table 3: Effect of oral anticoagulation on incidences of different causes of death

Causes of death	no VKA n(%) 3,483(100%)	VKA n(%) 4,637(100%)	HR(95%CI) Non adjusted	HR(95%CI) Adjusted
Overall mortality	561(16.11)	575(12.40)	0.64(0.57-0.72) ‡	0.62(0.54-0.71) ‡
Cardiovascular death	304(8.73)	307(6.60)	0.63(0.54-0.74) ‡	0.60(0.49-0.72) ‡
Cardiac	180(5.17)	188(4.05)	0.65(0.53-0.78) ‡	0.56(0.44-0.71) ‡
Sudden cardiac death	19(0.55)	19(0.41)	0.62(0.33-1.17)	0.61(0.29-1.31)
Progressive heart failure	161(4.62)	169(3.64)	0.66(0.53-0.82) †	0.69(0.55-0.87) †
Vascular death	87(2.49)	90(1.94)	0.61(0.46-0.82) †	0.70(0.49-0.99)*
Ischemic stroke	36(1.03)	40(0.86)	0.70(0.44-1.09)	0.93(0.54-1.59)
Fatal haemorrhage	41(1.17)	40(0.86)	0.61(0.39-0.94)*	0.58(0.36-0.95)*
CNS fatal haemorrhage	22(0.63)	29(0.62)	0.80(0.46-1.40)	0.77(0.41-1.45)
non CNS fatal haemorrhage	19(0.54)	11(0.24)	0.37(0.18-0.78) †	0.36(0.16-0.81)†
Pulmonary embolism	3(0.09)	6(0.13)	0.84(0.80-0.88) ‡	0.84(0.80-0.89) ‡
Acute aortic syndrome	4(0.11)	4(0.09)	0.84(0.80-0.88) ‡	0.84(0.80-0.89) ‡
Other cardiovascular death	37(1.06)	29(0.62)	0.84(0.81-0.88) ‡	0.85(0.81-0.90) ‡
Non cardiovascular death	234(6.72)	253(5.46)	0.67(0.56-0.8) ‡	0.60(0.49-0.74) ‡
Cancer	70(2.01)	71(1.53)	0.62(0.45-0.87) †	0.48(0.33-0.70) ‡
Infection	100(2.87)	94(2.03)	0.59(0.44-0.78) †	0.55(0.39-0.76) †
Renal failure	6(0.17)	9(0.19)	0.93(0.33-2.61)	0.56(0.17-1.81)
Respiratory failure	20(0.57)	17(0.37)	0.52(0.27-1.00)*	0.30(0.15-0.60) †
Trauma	9(0.26)	24(0.52)	1.63(0.75-3.50)	3.45(1.39-8.33) †
Cerebral trauma	7(0.20)	11(0.24)	0.97(0.38-2.50)	1.25(0.42-3.68)
Other trauma	2(0.06)	13(0.28)	2.60(0.74-9.17)	12.35(2.51-62.5) †
Other non cardiovascular death	31(0.89)	38(0.82)	0.76(0.47-1.22)	0.84(0.80-0.88) ‡
Undetermined death	330(9.47)	346(7.46)	0.63(0.55-0.74) ‡	0.72(0.6-0.87) †

Adjustment for age, sex, characteristics of AF (permanent or non-permanent), comorbidities and treatments listed in table 1. VKA: vitamin K antagonist; HR: hazard ratio; CI: confidence interval; CNS: central nervous system;
* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.0001$

Table 4: Predictive factors for overall mortatily, cardiovascular death and non cardiovascular death

	HR(IC 95%) Non adjusted	***p***	**HR(IC 95%) Adjusted**	***p***
Overall mortality				
Age	1.06(1.05-1.07)	<0.0001	1.06(1.05-1.06)	<0.0001
Women	1.01(0.91-1.07)	0.80	0.78(0.68-0.89)	0.0003
Permanent atrial fibrillation	1.58(1.36-1.83)	<0.0001	1.35(1.19-1.52)	<0.0001
Previous heart failure	2.16(1.90-2.44)	<0.0001	1.78(1.53-2.06)	<0.0001
Previous myocardial infarction	1.69(1.49-1.92)	<0.0001	1.43(1.18-1.74)	0.0002
Prior stroke	1.49(1.19-1.87)	0.0005	1.21(1.00-1.47)	0.05
Renal failure	2.48(2.16-2.84)	<0.0001	1.79(1.53-2.08)	<0.0001
Pulmonary disease	1.45(1.25-1.68)	<0.0001	1.18(1.01-1.40)	0.04
Previous bleeding	1.88(1.56-2.26)	<0.0001	1.42(1.15-1.75)	0.001
VKA	0.64(0.57-0.72)	<0.0001	0.62(0.54-0.71)	<0.0001
APT	1.28(1.13-1.44)	<0.0001	0.78(0.67-0.91)	0.001
ß-blocker	0.75(0.66-0.84)	<0.0001	0.78(0.68-0.88)	0.0001
Cardiovascular death				
Age	1.06(1.06-1.07)	<0.0001	1.06(1.05-1.07)	<0.0001
Women	1.03(0.89-1.20)	0.60	0.79(0.66-0.96)	0.01
Permanent atrial fibrillation	1.58(1.36-1.83)	<0.0001	1.43(1.21-1.70)	<0.0001
Previous heart failure	2.75(2.30-3.30)	<0.0001	2.29(1.86-2.82)	<0.0001
Previous myocardial infarction	2.34(1.99-2.75)	<0.0001	1.80(1.40-2.31)	<0.0001
Prior stroke	1.49(1.19-1.87)	0.0005	1.33(1.03-1.71)	0.03
Renal failure	2.95(2.47-3.52)	<0.0001	1.93(1.58-2.35)	<0.0001
Previous bleeding	1.96(1.53-2.51)	<0.0001	1.46(1.11-1.93)	0.01
VKA	0.63(0.54-0.74)	<0.0001	0.60(0.49-0.72)	<0.0001
APT	1.31(1.11-1.54)	0.001	0.73(0.60-0.89)	0.002
Non cardiovascular death				
Age	1.05(1.04-1.06)	<0.0001	1.05(1.04-1.06)	<0.0001
Women	0.90(0.75-1.07)	0.20	0.71(0.58-0.87)	0.0009
Permanent atrial fibrillation	1.39(1.17-1.64)	<0.0001	1.21(1.00-1.45)	0.05
Alcohol abuse	1.53(1.09-2.16)	0.01	1.66(1.14-2.40)	0.01
Previous heart failure	1.72(1.44-2.06)	<0.0001	1.45(1.18-1.78)	0.0004
Renal failure	2.00(1.59-2.50)	<0.0001	1.50(1.17-1.91)	0.001
Pulmonary disease	1.90(1.55-2.34)	<0.0001	1.68(1.34-2.11)	<0.0001
Previous bleeding	1.74(1.30-2.34)	0.0002	1.40(1.02-1.94)	0.04
VKA	0.67(0.56-0.80)	<0.0001	0.60(0.49-0.74)	<0.0001
APT	1.23(1.02-1.49)	0.02	0.80(0.65-0.99)	0.04

APT: antipatelet therapy**;** CI: confidence interval; HR: hazard ratio; VKA: vitamin K antagonist.

Table 5: Predictive factors of heart failure death and sudden cardiac death

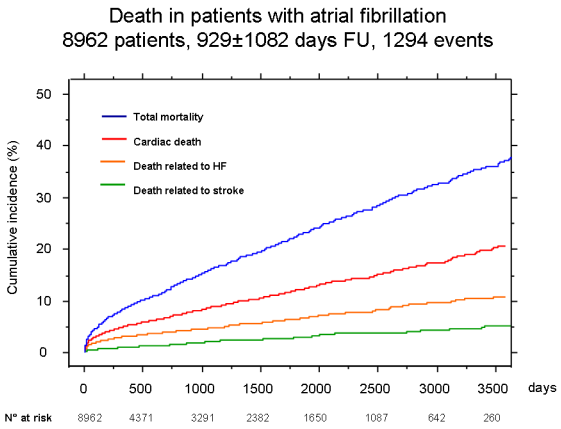
	HR(IC 95%) Non adjusted	***p***	**HR(IC 95%) Adjusted**	***p***
Heart failure death				
Age	1.06(1.05-1.07)	<0.0001	1.05(1.04-1.06)	<0.0001
Women	0.93(0.75-0.15)	0.50	0.83(0.64-1.07)	0.14
Permanent atrial fibrillation	1.43(1.17-1.75)	0.001	1.34(1.06-1.68)	0.01
Diabetes mellitus	1.55(1.20-1.95)	0.0006	1.12(0.85-1.47)	0.42
Current tobacco use	1.40(1.08-1.81)	0.009	1.05(0.78-1.42)	0.73
Coronary artery disease	3.07(2.50-3.77)	<0.0001	1.53(1.12-2.08)	0.01
Previous heart failure	4.29(3.24-5.68)	<0.0001	2.78(1.99-3.86)	<0.0001
Previous myocardial infarction	3.27(2.65-4.03)	<0.0001	1.88(1.38-2.57)	<0.0001
LBBB	2.08(1.55-2.79)	<0.0001	1.45(1.05-2.00)	0.02
Renal failure	3.77(3.01-4.74)	<0.0001	2.24(1.74-2.88)	<0.0001
VKA	0.66(0.53-0.82)	0.0002	0.69(0.55-0.87)	0.0002
ACE inhibitor or ARB	1.49(1.21-1.83)	<0.0001	0.98(0.77-1.24)	0.85
ß-blocker	0.91(0.74-1.12)	0.36	0.78(0.62-0.98)	0.03
Diuretic	2.60(2.10-3.23)	<0.0001	1.41(1.09-1.82)	0.01
Sudden cardiac death				
Age	1.04(1.01-1.07)	0.006	1.04(1.01-1.08)	0.02
Women	0.75(0.39-1.44)	0.40	0.44(0.19-1.00)	0.05
Previous heart failure	4.65(1.96-10.99)	0.0005	3.22(1.20-8.62)	0.02
Previous myocardial infarction	2.43(1.26-4.67)	0.008	1.64(0.77-3.46)	0.20
Renal failure	3.23(1.58-6.58)	0.001	2.45(1.15-5.21)	0.02
VKA	0.62(0.33-1.17)	0.13	0.61(0.29-1.31)	0.21
APT	2.16(1.12-4.15)	0.02	1.24(0.56-2.73)	0.60
ACE inhibitor or ARB	1.34(0.07-2.58)	0.005	1.87(0.92-3.80)	0.08
ß-blocker	1.56(0.84-2.89)	0.16	1.53(0.75-3.11)	0.24

ACE: angiotensin converting enzyme inhibitor; APT: antiplatelet therapy**;** ARB: angiotensin receptor blocker. CI: confidence interval; HR: hazard ratio; LBBB: left bundle branch block; VKA: vitamin K antagonist;

Table 6: Predictive factors of fatal ischemic stroke or fatal haemorrhage

	HR(IC 95%) Non adjusted	***p***	**HR(IC 95%) Adjusted**	***p***
Fatal ischemic stroke				
CHA_2DS_2VASc	1.59(1.42-1.79)	<0.0001	1.27(1.08-1.49)	0.003
Age	1.10(1.08-1.13)	<0.0001	1.08(1.04-1.11)	<0.0001
Permanent atrial fibrillation	2.65(1.68-3.98)	<0.0001	2.42(1.50-3.92)	0.0003
Renal failure	1.77(0.98-3.18)	0.05	1.24(0.65-2.36)	0.52
VKA	0.70(0.44-1.09)	0.11	0.93(0.54-1.59)	0.79
APT	2.00(1.26-3.14)	0.003	1.33(0.78-2.27)	0.29
Fatal haemorrhage				
CHA_2DS_2VASc	1.25(1.11-1.41)	0.0003	1.08(0.88-1.32)	0.48
HASBLED	1.44(1.20-1.72)	<0.0001	1.22(0.88-1.70)	0.23
Age	1.05(1.03-1.07)	<0.0001	1.05(1.03-1.08)	<0.0001
Renal failure	2.43(1.43-4.13)	0.001	1.71(0.88-3.32)	0.11
VKA	0.61(0.39-0.94)	0.02	0.58(0.36-0.95)	0.03
APT	1.19(0.75-1.87)	0.46	0.66(0.38-1.15)	0.14

APT: antiplatelet therapy; HR: hazard ratio; CI: confidence interval; VKA: vitamin K antagonist;



Clinical significance

- Cardiovascular events were the most common cause of death (54% of cases) in a large study of hospitalized patients with atrial fibrillation.
- Fatal stroke or fatal bleeding each accounted for 7% of all deaths.
- The strongest predictors of overall death were permanent atrial fibrillation, heart failure (whether with decreased or with preserved ejection fraction), previous bleeding and renal failure.
- Oral anticoagulant use was independently associated with a lower risk of all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality.