Causes of death in patients with atrial fibrillation anticoagulated with rivaroxaban: a pooled analysis of XANTUS

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Abstract

Aims. Anticoagulation can prevent stroke and prolong lives in patients with atrial fibrillation (AF); However, anticoagulated patients with AF remain at risk of death. The aim of this study was to investigate the causes of death and factors associated with all-cause and cardiovascular death in the XANTUS population.

Methods and results. Causes of death occurring within a year after rivaroxaban initiation in patients in the XANTUS program studies were adjudicated by a central adjudication committee and classified following international guidance.

Baseline characteristics associated with all-cause or cardiovascular death were identified. Of 11,040 patients, 187 (1.7%) died. Almost half of these deaths were due to cardiovascular causes other than bleeding (*n* = 82, 43.9%), particularly heart failure (*n* = 38, 20.3%) and sudden or unwitnessed death (*n* = 24, 12.8%). Fatal stroke (*n* = 8, 4.3%), which was classified as a type of cardiovascular death, and fatal bleeding (*n* = 17, 9.1%) were less common causes of death. Independent factors associated with all-cause or cardiovascular death included age, AF type, body mass index, left ventricular ejection fraction, hospitalization at baseline, rivaroxaban dose, and anaemia.

Conclusion. The overall risk of death due to stroke or bleeding was low in XANTUS. Anticoagulated patients with AF remain at risk of death due to heart failure and sudden death. Potential interventions to reduce cardiovascular deaths in anticoagulated patients with AF, require further investigation, e.g. early rhythm control therapy and AF ablation.

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Keywords

Rivaroxaban • Stroke • Mortality • Heart failure • Sudden death

Graphical Abstract

Adjudicated causes of death in the XANTUS programme. Patients with atrial fibrillation treated with rivaroxaban were enrolled and followed for 12 months. All deaths were centrally adjudicated. The majority of deaths were cardiovascular, with deaths due to heart failure and sudden deaths the most common causes of death. The findings call for additional interventions, e.g. early rhythm control, to reduce the burden of death due to heart failure and sudden death

What´s new?

There is a shift towards a more systematic use of rhythm control therapy in patients with atrial fibrillation based on outcome reduction in recent controlled trials. The burden of cardiovascular mortality in unselected anticoagulated patients with AF is not known. This report based on adjudicated causes of death in the XANTUS programme finds that the majority (53%) of deaths in anticoagulated patients with AF remain cardiovascular. Death due to stroke and death due to bleeding are rare, while death due to heart failure and sudden death emerge as the most common causes of cardiovascular death. These findings highlight an unmet clinical need to improve treatment of heart failure and to prevent sudden death, potentially through early rhythm control, holistic heart failure therapy, and identification of common causes of AF and sudden death, e.g. inherited cardiomyopathies.

Introduction

Atrial fibrillation (AF) is associated with increased mortality,[1, 2] and stroke is a common cause of death in patients with AF.[3, 4] Oral anticoagulation with vitamin K antagonists or non-vitamin K antagonists oral anticoagulants (NOACs) can reduce the risk of stroke as well as mortality in patients with AF.[3, 5] However, even when receiving anticoagulation therapy, patients with AF enrolled into controlled clinical trials remain at risk of cardiovascular death, calling for further treatments to improve outcomes.[6-8]

The XANTUS program collected 1-year outcomes in more than 11 000 unselected patients with AF from 47 countries who were anticoagulated with the NOAC rivaroxaban.[9, 10] Centrally adjudicated causes of death and a description of factors associated with all-cause death and cardiovascular death in the XANTUS population are reported.

Methods

The data underlying this article will be shared on reasonable request to the corresponding author. The XANTUS program has been described previously. This analysis included data from the XANTUS (NCT01606995), XANTUS-EL (NCT01800006), and XANAP (NCT01750788) studies.[11-13] These three observational studies included patients with AF treated with rivaroxaban. Follow-up was planned for one year. To enable capture of a wide range of patients receiving rivaroxaban in clinical care, there were hardly any exclusion criteria and sites were encouraged to enrol consecutive patients. All causes of death in patients with AF in the first year after initiating rivaroxaban therapy were adjudicated by a central adjudication committee. A single committee consisting of five members adjudicated all events across the prospective, observational XANTUS program,[10] which enrolled patients from different geographic regions (XANTUS: Western

Europe, Canada, and Israel[11]; XANAP: Asia-Pacific[12]; XANTUS-EL: the Middle East, Eastern Europe, Africa, and Latin America[13]). Each event was independently adjudicated by two adjudication committee members, and a third member was involved if there was any disagreement. All patients included in the analysis provided informed, written consent.

The main outcomes of interest in this analysis were all-cause death and cardiovascular death. Cardiovascular death included death due to intracranial and extracranial bleeding, stroke, and other cardiovascular causes, as listed in *Table 1*, other XANTUS outcomes were defined in previous publications.[11-13] Non-cardiovascular death included death due to cancer, infectious disease, or other known causes (*Table 1*). For some patients, multiple causes of death were adjudicated. If one of these causes was cardiovascular, the death was categorized as 'cardiovascular death'. If the cause of death was 'other' with a non-cardiovascular cause specified, the death was categorized as non-cardiovascular, and if no further specification was given, the death was categorized as 'unknown' (*Figure 1*).

Statistical analysis

Statistical evaluation was performed using the Statistical Analysis System (release 9.2 or higher). All patients who received at least one dose of rivaroxaban during the observation period were analyzed. One site with Good Clinical Practice violations in the XANTUS study was excluded from the analysis (81 patients were affected). Cumulative incidence functions for cardiovascular and non-cardiovascular deaths were calculated using the Aalen–Johansen estimator. Other causes of death were considered as competing risks for the respective curve.[14]

In addition, an analysis to determine baseline characteristics associated with all-cause death and cardiovascular death was performed. For each outcome, the analysis was conducted in the following steps. Firstly, a descriptive analysis of potential factors associated with outcomes was performed based on medical judgment and previous reports in the literature. Thereafter, univariate Cox models were fitted with the outcome as the response variable and only one feature at a time. Features with a *P* value < 0.10 were candidates for inclusion in the multivariable model, and Kendall's Tau was used to assess correlations between covariates. Factors that were categorized and had very low numbers of events in a category were excluded or combined with another category. The proportional hazards assumption of the covariates was checked. In the third step, multivariable Cox regression models including the previously selected factors were fitted using backward elimination. At each stage, the variable with the highest *P* value was excluded from the model until all variables in the model were significant (*P* value < 0.10). Finally, discrimination of the multivariable models was assessed using Harrell's C statistic.[15] Because data on creatinine clearance (CrCl) were missing in 37% of patients, these patients were grouped with patients who had CrCl ≥ 50 ml/min. These two groups had similar baseline characteristics and were generally healthier than patients with CrCl < 50 ml/min. A sensitivity analysis, from which patients with missing CrCl values were excluded, was also performed.

Results

Of 11 040 patients receiving rivaroxaban treatment for a median duration of 366 (interquartile range 329–379) days, the majority survived (10 853 [98.3%]), 187 (1.7%) died, and 87 fatal or non-fatal strokes and 172 fatal or non-fatal major bleeding events occurred, these were defined in line with previous XANTUS publications[11, 12, 16]. The mean age of the population of patients who survived was 70.4 ± 10.4 years and 76.7 ± 10.4 years in the population who died. The mean

CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category [female]) score was 3.5 ± 1.7 in the survival population and 4.4 ± 1.7 in the population who died.

Among the patients who died, 98 (52.4%) died of cardiovascular causes (1.0 event per 100 patient-years; 95% confidence interval [CI] 0.8–1.2), 68 (36.4%) died of other causes (0.7 events per 100 patient-years; 95% CI 0.5–0.9), and the remaining 21 (11.2%) died of unknown causes (0.2 events per 100 patient-years; 95% CI, (0.1–0.3) (*Table 1, Figures 2 and 3*). Deaths occurred at a steady rate during the 1-year follow-up period (*Figure 3*). Deaths were most often due to heart failure (*n* = 38), sudden or unwitnessed death (*n* = 24), cancer (*n* = 26), or infectious diseases (*n* = 24). Causes of death in the subcategory 'other' (*n* = 23) included respiratory, renal, and multi-system failure. Regional differences in cause of death are summarized in *Table S1*.

Compared with survivors, patients who died were older, with a lower body mass index (BMI), and were more likely to suffer from persistent forms of AF and to have a history of stroke/transient ischaemic attack or non-central nervous system systemic embolism, heart failure, diabetes, or myocardial infarction (MI; *Table 2*). In addition, patients who died were more often hospitalized at baseline and, if enrolled as outpatients, more often managed by general physicians. They were also more often anaemic or treated with doses other than those recommended in the label. Baseline characteristics were generally more similar between patients who died of cardiovascular or non-cardiovascular causes compared with those with unknown causes of death (*Table S2*). Patient sex, dosing according to label, AF type, hypertension, prior MI, active cancer at baseline, and type of treating physician differed according to the cause of death.

Factors associated with all-cause death and cardiovascular death were selected from the available baseline characteristics using Cox proportional hazards regression (*Figure S1*) and included in the multivariable Cox regression model. The multivariable Cox regression models are shown in *Figure 4*. This exploratory analysis suggested that age, anaemia, left ventricular ejection fraction (LVEF), hospitalization at baseline, AF type, BMI, diabetes, congestive heart failure, active cancer, and rivaroxaban dose independently affected the risk of all-cause death. Similarly, age, anaemia, or reduced haemoglobin, LVEF, hospitalization at baseline, AF type, BMI, and rivaroxaban dose were independently associated with cardiovascular death. A sensitivity analysis assessing the effect of excluding patients with missing CrCl values showed generally similar results (*Figure S2*).

Discussion

This study explored the causes of death in patients with AF anticoagulated with rivaroxaban in routine care. Overall, mortality was low. Cardiovascular death, especially due to heart failure and sudden or unwitnessed death, was the most common cause of death and accounted for nearly half of deaths, comparable with reports from the Global Anticoagulant Registry in the FIELD Atrial Fibrillation (GARFIELD-AF).[17] Deaths due to stroke were uncommon, as were deaths due to bleeding (*Table 1, Figure 3*). Several factors were independently associated with an increased risk of all-cause or cardiovascular death. These factors included age, AF pattern, LVEF, hospitalization at baseline, rivaroxaban dose, and comorbidities such as anaemia or reduced haemoglobin, diabetes, congestive heart failure, and active cancer.

The association of heart failure with an increased risk of death observed in our analysis is of particular interest. Similar results have been reported in other studies. In the prospective GARFIELD-AF Registry,[2] approximately half of deaths were due to cardiovascular causes, and congestive heart failure and cancer were the two most common causes of death overall, whereas sudden or unwitnessed death was the second most common cause of cardiovascular death. Congestive heart failure and other characteristics, such as diabetes and older age, were also associated with an increased risk of death.[2] In several contemporary observational data sets including Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)[18], Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation (GLORIA-AF), EURObservational Research Programme in Atrial Fibrillation (EORP-AF), and Fushimi AF Registry, [19-21], and a French retrospective database study[22] and the Loire Valley study [23, 24] all found that presence of heart failure and other comorbidities increased the risk of cardiovascular death. To reduce AF-related mortality, it is important for clinicians to treat comorbid conditions alongside heart failure and any anticoagulation.[20, 25] Subanalyses of the EAST-AFNET 4 trial[26] and recent trials of AF ablation[27] all support the early use of rhythm control therapy and AF ablation in patients with AF and heart failure. It is possible that a more intensive and earlier use of rhythm control could have reduced sudden deaths and heart failure-related deaths in this population.

The phase III NOAC trials also found a high rate of death due to heart failure or sudden death: In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, the most common cause of cardiovascular death was sudden cardiac death, the risk of which was increased in patients with low ejection fraction, heart failure, or prior MI at baseline.[28] The rate of fatal

bleeding observed here is comparable to findings in the approval trials of the NOACs[28, 29] and in recent controlled trials of NOACs in patients with device-detected AF.[30, 31] A meta-analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), RE-LY, ENGAGE AF-TIMI 48, and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) studies also showed that the most common causes of death were sudden death or dysrhythmia and heart failure, with fatal bleeding or ischaemic stroke being the cause of death in only a small proportion of patients.[29] Finally, a meta-analysis of these phase III trials showed that patients with heart failure and AF had an increased risk of death, a lower risk of bleeding, and a similar risk of stroke or systemic embolism compared with patients who did not have heart failure, whereas the efficacy and safety of NOACs versus warfarin treatment were similar regardless of comorbid heart failure.[32] Overall, our data support the notion that death due to heart failure and sudden death are the main drivers of mortality in anticoagulated patients with AF.

The evidence that patients with AF remain at risk of death despite anticoagulation, as well as the evidence that causes of death other than stroke play an important role in the risk of mortality in AF, contributed to the European Society of Cardiology (ESC) and Asia Pacific Heart Rhythm Society (APHRS) guideline recommendations for a more holistic and integrated approach to care with the Atrial Fibrillation Better Care (ABC) pathway.[25, 33] This pathway has three key components: Avoid stroke, Better symptom control and treatment of Comorbidities.[25, 33] The recently published ACC/AHA/HRS guidelines on AF add a new therapeutic goal to the management of AF, reduction of AF burden.[34] A call for a broader use of rhythm control came also out of the 9th AFNET/EHRA consensus document.[35] Our data illustrate the potential for

rhythm control interventions, and for holistic AF care, to further reduce cardiovascular events in anticoagulated patients with AF.

Events in XANTUS underwent a similar adjudication process as events in controlled clinical trials, rendering causes of death comparable. Mortality in XANTUS was lower than in historic cohorts of patients with AF not receiving anticoagulation.[36-38] In addition, we observed very few deaths due to stroke or bleeding, underpinning the efficacy and safety of NOACs such as rivaroxaban for stroke prevention in patients with AF.[29] Despite this effect, which can be attributed to anticoagulation, cardiovascular deaths due to heart failure or sudden, presumably arrhythmic death remained common.

The association of anaemia or low haemoglobin at baseline with all-cause death and cardiovascular death is also of interest. Anaemia was four times more frequent at baseline in patients who died (*n* = 24, 12.8%) compared with survivors (*n* = 346, 3.2%), and there was a trend towards a higher frequency of anaemia in patients who died of cardiovascular (*n* = 17, 17.3%) versus non-cardiovascular causes (*n* = 7, 10.3%). Previously, low haemoglobin levels were identified as a predictor of death and hospitalization for heart failure in patients with AF in a prospective, single-centre cohort study,[39] and anaemia was a predictor of death and rehospitalization in a US claims database analysis of elderly patients with AF.[40] In addition to heart failure, death due to bleeding, and death due to non-cardiovascular causes associated with anaemia, such as cancer, may have contributed to these trends. Our cohort is too small to draw a conclusion on this topic. Of the 24 patients with anaemia or reduced haemoglobin at baseline who died, the most common adjudicated cause of death was cardiac decompensation or heart failure (*n* = 11). Cancer (*n* = 2), intracranial haemorrhage (*n* = 1), and extracranial haemorrhage

(n = 1) were identified as the adjudicated cause of death in very few of these patients. The remainder of these patients died of infectious disease (n = 3), non-haemorrhagic stroke (n = 2), multi-organ failure (n = 1), MI (n = 1), respiratory failure (n = 1), or sudden or unwitnessed death (n = 1). The effect of investigating or treating anaemia in patients with AF on the risk of mortality requires further study. Our results highlight that a low haemoglobin can help to identify patients with AF at risk.

The identification of rivaroxaban dose as a feature associated with death and cardiovascular death is probably linked to measured and unmeasured underlying comorbidities and their real or perceived severity. This is especially true for patients with malignancies. The fact that a proportion of patients did not receive the indicated dose of rivaroxaban is discussed in full in the original XANTUS publication[10] and will, therefore, not be covered in detail here.

To further reduce the risk of death in patients with AF, treatments other than anticoagulation are needed. Our exploratory analysis suggested that targeting heart failure, sudden death, and AF could improve survival in this setting. The recently published Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST–AFNET 4)[41] and its subanalyses[26, 42, 43] suggests that early rhythm control therapy could reduce cardiovascular complications, including cardiovascular death, in anticoagulated patients with recently diagnosed AF. Current ESC guidelines state that consideration of rhythm control therapy as an early intervention step and as part of the 'B' element of the ABC pathway may be appropriate for patients with symptomatic AF for both quality of life and symptom improvement.[25] Heart failure and AF frequently occur together.[44] Rhythm control therapy[26] and especially AF ablation[27, 45] have the potential to reduce outcomes in patients with AF and heart failure with reduced ejection fraction. Patients with non-

ischaemic cardiomyopathy resulting from genetic and other disorders may present with a combination of AF and heart failure, and studies on these disorders are being conducted for an improved understanding of the mechanisms underlying the complex association between heart failure and AF, as well as between AF and sudden death.[46-48] Implementation of a dynamic, interdisciplinary approach to AF management is expected to lead to further improved outcomes, but strategies to further improve adherence are needed.

One third of the deaths recorded in XANTUS were due to non-cardiovascular causes. Our analyses identify anaemia and active cancer as features associated with death. The association of AF, newly detected AF, and cancer[49, 50] and the association of anaemia with death in patients with AF[51-53] have recently been reported by others. Both associations warrant further mechanistic research. Reducing these deaths will require comprehensive assessment of patients with AF and treatment of their comorbidities as highlighted in AF guidelines as comprehensive care [54, 55] or, in an earlier iteration, integrated care of patients with AF.[56] The findings in XANTUS call for validation. At face value, they suggest that attention should be paid to anaemia and to detection of cancer as part of the comprehensive care of patients with AF. In addition, infections contributed to non-cardiovascular deaths in this cohort. Their timely detection and therapy can help to reduce this mortality. These should be considered in a holistic approach to patients with AF.[57, 58]

Limitations

The limitations of the XANTUS program have been described previously.[10, 11] Treatment with rivaroxaban was a requirement for inclusion. Selection bias could have resulted if patients

considered their risk of stroke or bleeding when deciding whether to participate in the study, and physicians may have included patients with intact cognitive function preferentially. Patients included in XANTUS were also heterogeneous in terms of the time from their first diagnosis of AF. Nevertheless, the large study population, regional spread across five continents, central endpoint adjudication, and prospective design are important strengths of the study. The associations reported here cannot be used to infer causality. Not all therapies were captured during follow-up. Therefore, influence of rhythm control and comorbidity treatment could not reliably be assessed in this data set.

Conclusions

The overall rate of stroke and death is low in anticoagulated patients with atrial fibrillation. The remaining deaths are predominantly cardiovascular and often due to heart failure and sudden death. These results underpin the effectiveness of current stroke prevention strategies but also highlight that management of patients with AF needs to encompass other cardiovascular treatments to mitigate heart failure and sudden death. Further research is needed to understand the mechanisms underlying the association between the clinical features identified in this study and death and cardiovascular death, including further evaluation of rhythm control therapy and AF ablation.

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Data access and analysis

All authors had full access to all the data in the study and were involved in the drafting and reviewing of this manuscript. All authors take responsibility for the integrity of the data and the data analysis.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures

Figure 1. Causes of death of patients included in the XANTUS registry program.

Figure 2 Causes of death in the pooled XANTUS studies.[a]

[a] patient could have more than one adjudicated cause of death but could only be included in one of the categories of cardiovascular death or non-cardiovascular death.

CV, cardiovascular, VTE, venous thromboembolism.

Figure 3 Cumulative incidence of death according to (*A*) cardiovascular and non-cardiovascular death and (*B*) sudden or unwitnessed death, and death due to non-haemorrhagic stroke, myocardial infarction, or cardiac decompensation or heart failure. Aalen–Johansen estimates are shown for the cumulative incidence functions, including all other deaths as competing risks. For all-cause death, Kaplan–Meier estimates are shown. cardiovascular, cardiovascular.

Figure 4 Multivariable Cox proportional hazards regression of risk factors for (*A*) all-cause death and (*B*) cardiovascular death. cardiovascular, cardiovascular. [a] Harrell's C statistic was 0.782 for A and 0.798 for B.

BMI, body mass index; CI, confidence interval; CV, cardiovascular; HR, hazard ratio, LVEF, left ventricular ejection fraction.

First diagnosed AF was chosen as comparator as it reflects the first presenting pattern of AF.

Tables

Table 1 Summary of causes of death

Category, n (%)	Adjudicated cause of death	Number of patients who died (*n* = 187), n (%)
Cardiovascular death, 98 (52.4)[a]	Bleeding	17 (9.1)
	Extracranial haemorrhage	6 (3.2)
	Intracranial haemorrhage	11 (5.9)
	Cardiovascular other than bleeding	82 (43.9)[b]
	Cardiac decompensation/heart failure	38 (20.3)
	Sudden or unwitnessed death[c]	24 (12.8)
	Myocardial infarction	8 (4.3)
	Non-haemorrhagic stroke	8 (4.3)
	Other vascular event	3 (1.6)
	Dysrhythmia	2 (1.1)
	Venous thromboembolism	1 (0.5)
	Systemic embolism	0 (0)
Non-cardiovascular death, 68 (36.4)[a]	Cancer	26 (13.9)

	Infectious disease	24 (12.8)
	Other (reason specified)[d]	23 (12.3)
Unknown, 21 (11.2)[a]	Other (no reason given)	3 (1.6)
	Unexplained[e]	22 (11.8)

cardiovascular, cardiovascular.

[a] A patient could have more than one adjudicated cause of death but could only be included in one of the categories of cardiovascular death, non-cardiovascular death, and unknown.

[b] Two patients had two cardiovascular causes of death (other than bleeding) each.

[c] Sudden or unwitnessed deaths were assessed as cardiovascular deaths.

[d] Reasons included respiratory, renal, and multi-system failure.

[e] Of the 22 patients with unexplained causes of death, one had an additional cardiovascular cause of death and was included in the cardiovascular death category.

Table 2 Baseline characteristics according to survival

Potential risk factor	Patients who survived (*n* = 10 853)	Patients who died (*n* = 187)	*P* value
Age, yrs, mean ± SD	70.4 ± 10.4	76.7 ± 10.4	< 0.0001
Age			< 0.0001
< 75 yrs	6712 (61.8)	70 (37.4)	
≥ 75 yrs	4141 (38.2)	117 (62.6)	
Male	6207 (57.2)	101 (54.0)	0.3811
CHA_2DS_2-VASc score, mean ± SD	3.5 ± 1.7	4.4 ± 1.7	< 0.0001
HAS-BLED score, mean ± SD	2.0 ± 1.1	2.5 ± 1.2	< 0.0001
Rivaroxaban dose			< 0.0001
20 mg od	7997 (73.7)	102 (54.5)	
15 mg od	2665 (24.6)	76 (40.6)	

Potential risk factor	Patients who survived (*n* = 10 853)	Patients who died (*n* = 187)	*P* value
Other doses (including missing)[a]	191 (1.8)	9 (4.8)	
Dosing according to label			< 0.0001
Yes	5397 (49.7)	83 (44.4)	
No	1518 (14.0)	48 (25.7)	
Unknown[b]	3938 (36.3)	56 (29.9)	
First available CrCl, ml/min, median (IQR)	68.8 (55.1–87.0)	60.0 (42.0–71.0)	0.3350
First available CrCl			< 0.0001
< 50 ml/min	1215 (11.2)	47 (25.1)	
≥ 50 ml/min	5647 (52.0)	82 (43.9)	
Unknown	3991 (36.8)	58 (31.0)	

Potential risk factor	**Patients who survived (*n* = 10 853)**	**Patients who died (*n* = 187)**	***P* value**
BMI, kg/m^2, mean ± SD	28.0 ± 5.1	27.0 ± 6.3	0.0232
First available weight, kg, mean ± SD	80.0 ± 17.7	75.6 ± 20.0	0.0021
AF type			< 0.0001
First diagnosed	1997 (18.2)	41 (21.9)	
Paroxysmal	4066 (37.5)	36 (19.3)	
Persistent	1756 (16.2)	40 (21.4)	
Permanent	3012 (27.8)	69 (36.9)	
Missing	42 (0.4)	1 (0.5)	
Prior stroke/TIA/non-CNS SE	2274 (21.0)	55 (29.4)	0.0049
Congestive heart failure	2276 (21.0)	76 (40.6)	< 0.0001
LVEF			< 0.0001
< 40%	1075 (9.9)	45 (24.1)	

Potential risk factor	Patients who survived (*n* = 10 853)	Patients who died (*n* = 187)	*P* value
≥ 40%	8619 (79.4)	105 (56.1)	
Unknown[b]	1159 (10.7)	37 (19.8)	
Hypertension	8262 (76.1)	143 (76.5)	0.9128
Diabetes	2405 (22.2)	57 (30.5)	0.0067
Prior MI	956 (8.8)	29 (15.5)	0.0014
Vascular disease	2964 (27.3)	67 (35.8)	0.0097
Active cancer at baseline	129 (1.2)	6 (3.2)	0.0127
Anaemia/reduced haemoglobin	346 (3.2)	24 (12.8)	< 0.0001
Hospitalized at baseline			< 0.0001
Yes	2004 (18.5)	60 (32.1)	
No	8848 (81.5)	127 (67.9)	
Missing	1 (< 0.1)	0 (0.0)	

Potential risk factor	**Patients who survived (*n* = 10 853)**	**Patients who died (*n* = 187)**	***P* value**
Patient treated by			0.0040
GP	668 (6.2)	13 (7.0)	
Office cardiologist	5388 (49.6)	76 (40.6)	
Office neurologist	218 (2.0)	4 (2.1)	
In-hospital physician	4438 (41)	88 (47.1)	
Other	140 (1.3)	6 (3.2)	
Missing	1 (< 0.1)	0 (0.0)	
Prior antithrombotic therapy			0.6100
Yes	7413 (68.3)	131 (70.1)	
No	3440 (31.7)	56 (29.9)	
Concomitant antiplatelet or NSAID			0.7721
Yes	2285 (21.1)	41 (21.9)	

Potential risk factor	Patients who survived (*n* = 10 853)	Patients who died (*n* = 187)	*P* value
No	8568 (78.9)	146 (78.1)	
Alcohol use			0.0002
Abstinent	5830 (53.7)	124 (66.3)	
Light	3952 (36.4)	47 (25.1)	
Medium or heavy	878 (8.1)	10 (5.3)	
Missing	193 (1.8)	6 (3.2)	
Smoking			0.6081
Never	6956 (64.1)	114 (61.0)	
Former	3056 (28.2)	58 (31.0)	
Current	698 (6.4)	11 (5.9)	
Missing	143 (1.3)	4 (2.1)	

Values are n (%) unless specified otherwise.

AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, age 65–74 years, Sex category (female); CNS, central nervous system; CrCl, creatinine clearance; GP, general practitioner; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; od, once daily; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack; yrs, years.

[a] Three patients had missing doses, 190 patients received doses < 15 mg od, and seven patients received doses > 20 mg od.

[b] These missing values were included in the category 'unknown' in the multivariable Cox regression model.

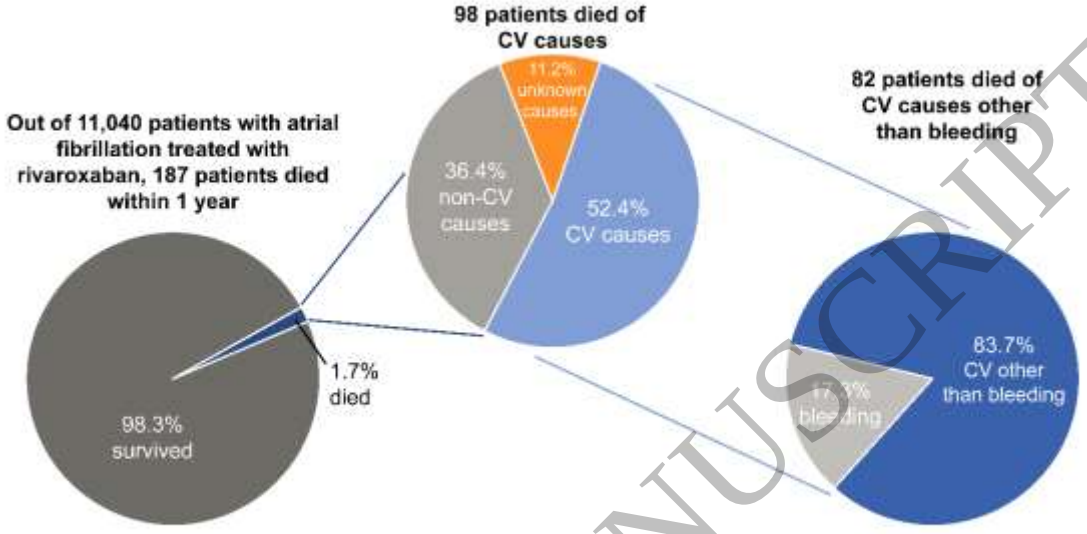

Figure 1
147x102 mm (x DPI)

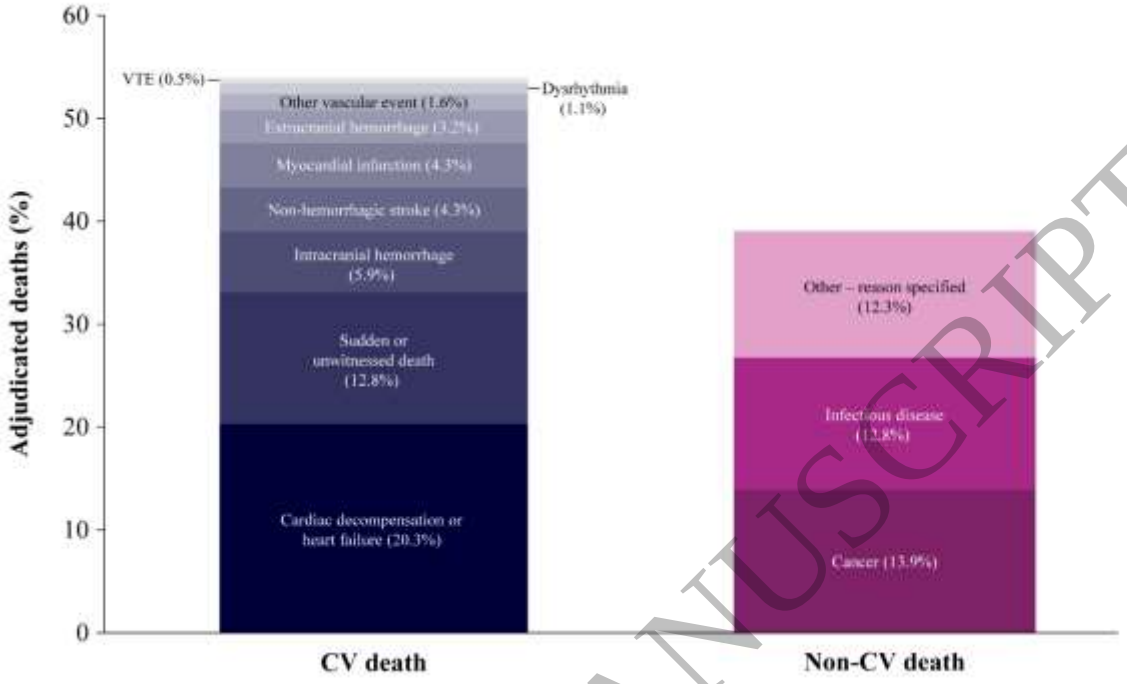

Figure 2
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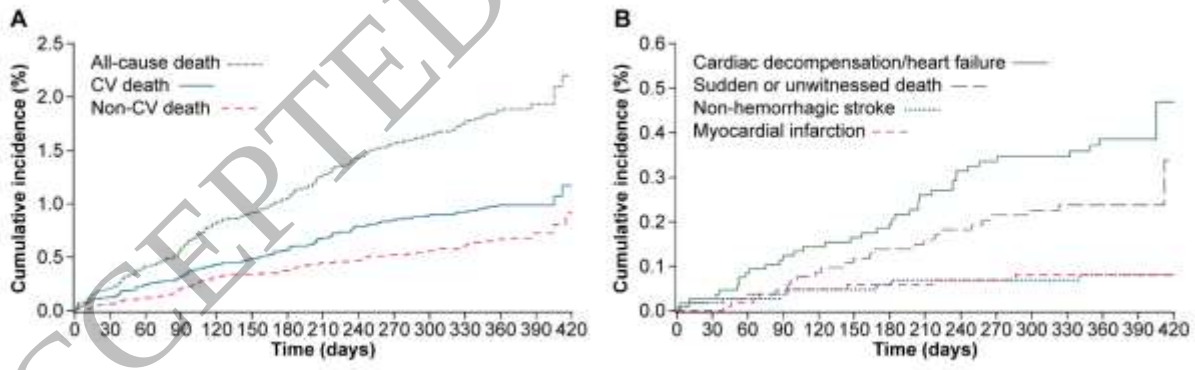


Figure 3
160x62 mm (x DPI)

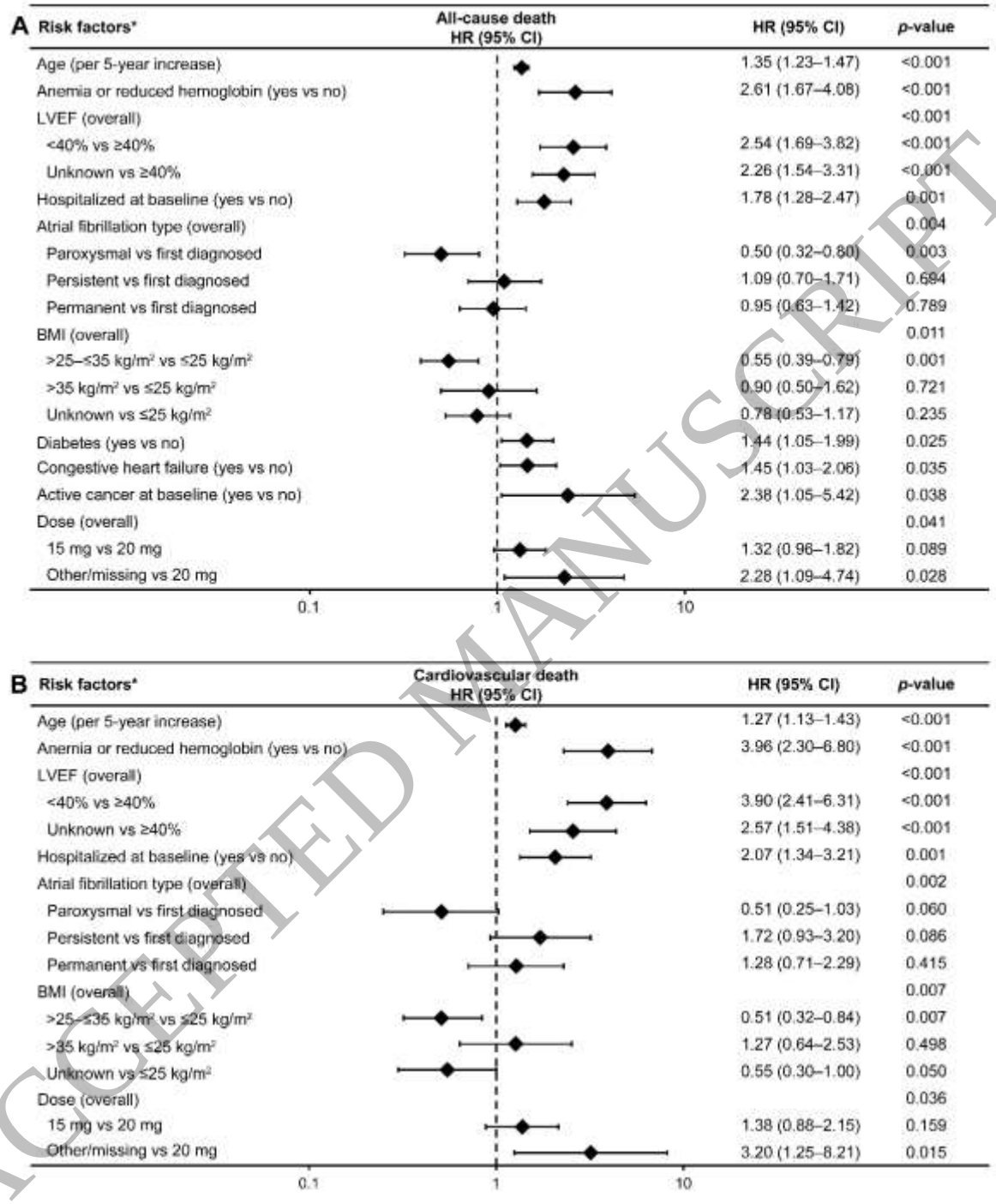
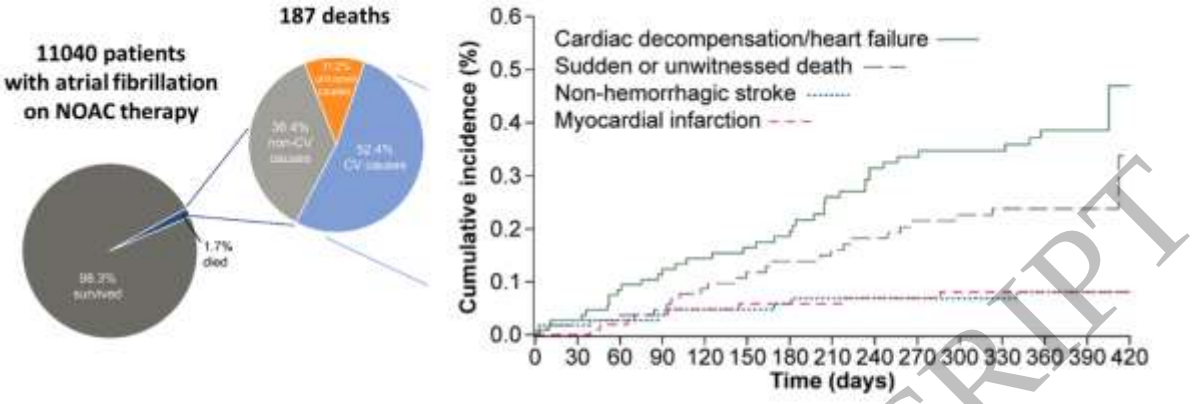


Figure 4
160x195 mm (x DPI)



1. Deaths in anticoagulated patients with AF are often cardiovascular
2. Cardivoascular deaths are commonly due to heart failure or sudden death.
3. Holistic care and early rhythm control may further reduce these deaths.

Graphical Abatract
161x81 mm (x DPI)