ORIGINAL RESEARCH

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Sudden Cardiac Death in Patients With Atrial Fibrillation: Insights From the ENGAGE AF-TIMI 48 Trial

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Background—Recent findings suggest that atrial fibrillation is associated with sudden cardiac death (SCD). We examined the incidence, characteristics, and factors associated with SCD in patients with atrial fibrillation.

Methods and Results—SCD was defined as witnessed death ≤60 minutes from the onset of new symptoms or unwitnessed death 1 to 24 hours after being observed alive, without another known cause of death. Predictors of SCD were examined using multivariate competing risks models. Over 2.8 years (median), 2349 patients died (40.5 per 1000 patient-years), of which 1668 (71%) were cardiovascular deaths. SCD was the most common cause of cardiovascular death (n=749; median age 73 years; 70.6% male). Most SCD events occurred out of hospital (92.8%) and without prior symptoms (66.0%). Predictors of SCD included low ejection fraction, heart failure, and prior myocardial infarction (P<0.001 for each). Additional significant baseline predictors of SCD, but not of other causes of death, included male sex, electrocardiographic left ventricular hypertrophy, higher heart rate, nonuse of beta blockers, and use of digitalis. The latter was associated with SCD in patients with or without heart failure (adjusted hazard ratio 1.55 [95% CI 1.29–1.86] and 1.56 [95% CI 1.14–2.11], respectively; $P_{interaction}$=0.73). The rate of SCD was numerically but not statistically lower with edoxaban (1.20% per year with lower dose edoxaban; 1.28% per year with higher dose edoxaban) compared with warfarin (1.40% per year).

Conclusion—SCD is the most common cause of cardiovascular death in patients with atrial fibrillation and has several distinct predictors, some of which are modifiable. These findings may be considered in planning research and treatment strategies for patients with atrial fibrillation.

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Key Words: atrial fibrillation • sudden cardiac death

Atrial fibrillation (AF) is the most common arrhythmia, affecting >33 million people worldwide, and its prevalence is expected to rise by 2- to 3-fold by 2050.[1] AF is associated with an increased risk of stroke, heart failure (HF), and all-cause mortality.[2,3] Recent data suggest that AF is also independently associated with an increased risk of sudden cardiac death (SCD).[4–7] In patients with established AF treated with anticoagulation, SCD accounts for >20% of all deaths.[8] In addition, patients with AF have, on average, a 2.5-fold increased risk of SCD or ventricular fibrillation compared with patients without AF.[4]

The mechanism underlying this possible causal association is not completely understood.[9] Although AF and SCD share common risk factors such as HF or coronary artery disease, the association between AF and SCD does not seem to be entirely dependent on these risk factors,[10] and the identification of other factors that are unique to patients with AF would be of interest.

We examined the incidence, characteristics, and factors associated with SCD in a contemporary large cohort of patients with AF and the treatment interaction between edoxaban and warfarin with regard to SCD.

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Methods

This study represents an analysis from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. The ENGAGE AF-TIMI 48 trial was a 3-group, randomized, double-blind, double-dummy, multinational trial that compared 2 dosing regimens of the oral factor Xa inhibitor edoxaban with warfarin in 21 105 patients with AF (ClinicalTrials.gov identifier NCT00781391).[11] The study population and study design were described in detail previously.[12] In brief, eligible patients were aged ≥21 years and had electrocardiographic evidence of AF within 12 months prior to randomization, a $CHADS_2$ score ≥2, and planned anticoagulation. Key exclusion criteria were AF due to a reversible cause, presence of a mechanical valve or moderate-severe mitral stenosis, increased risk of bleeding, recent acute coronary syndrome or stroke within 30 days prior to randomization, severe renal insufficiency (creatinine clearance <30 mL/min), and life expectancy <12 months. Patients were randomly assigned to receive warfarin with continual dose adjustment to achieve an International Normalized Ratio of 2.0 to 3.0, edoxaban 60 mg once daily (higher dose edoxaban), or edoxaban 30 mg once daily (lower dose edoxaban). For patients in either edoxaban group, the dose was halved if ≥1 characteristic associated with anticipated increased drug exposure was present.[12] The protocol and amendments were approved by the ethics committee at each participating center. All patients provided written informed consent.

In the ENGAGE AF-TIMI 48 trial, treatment with edoxaban was noninferior to well-managed warfarin for the risk of stroke and systemic embolic events and was associated with significantly less bleeding. In addition, compared with warfarin, edoxaban significantly reduced the rate of cardiovascular death.[11] Higher dose edoxaban is currently approved for clinical use in the United States, Europe, and Asia to reduce the risk of stroke and systemic embolic events in patients with AF.

SCD Definition

All deaths in the ENGAGE AF-TIMI 48 trial were adjudicated by an independent clinical end point committee without knowledge of treatment assignment. SCD was predefined as an unexpected death that was either witnessed (occurring within 60 minutes from the onset of new symptoms in the absence of a clear cause other than cardiovascular) or unwitnessed (within 24 hours of being observed alive in the absence of preexisting progressive circulatory failure or other noncardiovascular causes of death). All but 1 patient in the ENGAGE AF-TIMI 48 trial had a known vital status at the end of follow-up. Causes of death were further categorized to SCD, other cardiovascular death, and noncardiovascular death. Complete definitions of causes of death were described previously.[11,12]

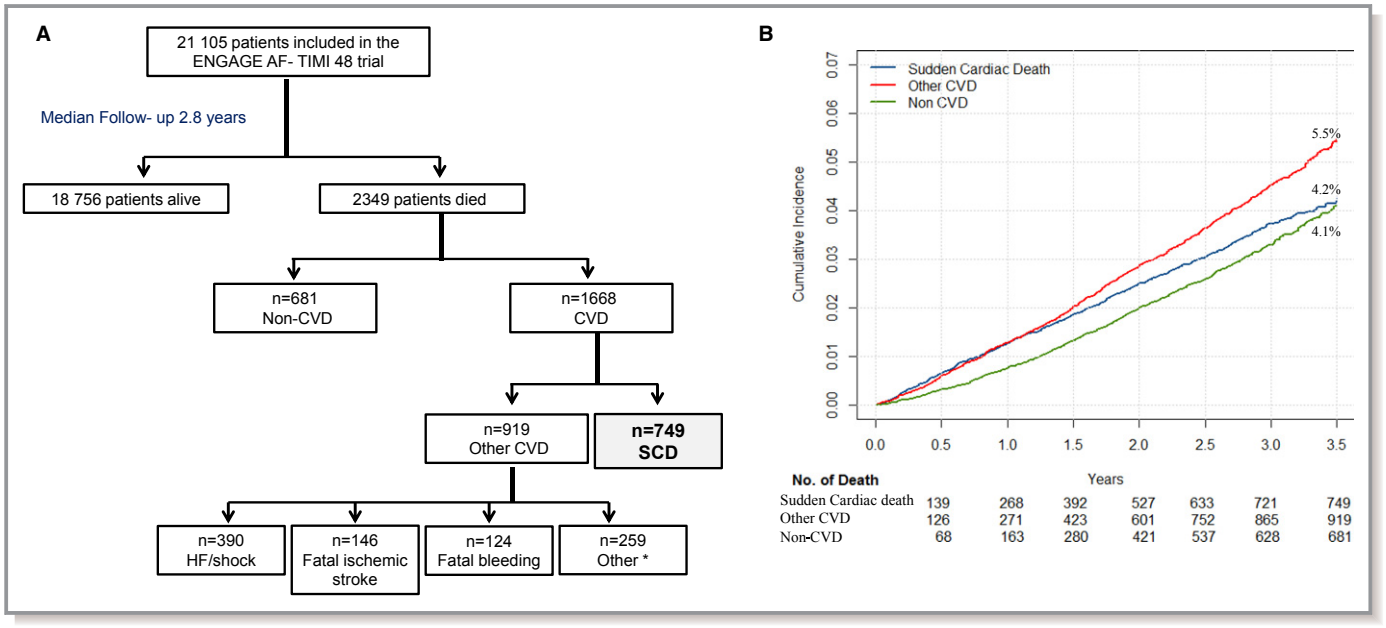

Figure 1. Causes of deaths (A) and their cumulative incidence (B) in the ENGAGE AF-TIMI 48 trial. Deaths are categorized as SCD, other CVD, and non-CVD. *Other CVD: atherosclerotic vascular disease excluding coronary (n=25); directly related to coronary revascularization (n=12); dysrhythmia (n=51); pulmonary embolism (n=17); systemic embolic event (n=8); unknown (n=146). CVD indicates cardiovascular death; HF, heart failure; SCD, sudden cardiac death.

Table 1. Characterization of SCD Events

Category	Yes	No	Unknown
Witnessed	257 (34.3)	357 (47.7)	135 (18.0)
During sleep	215 (28.7)	323 (43.1)	211 (28.2)
Out of hospital	695 (92.8)	49 (6.5)	5 (0.7)
Immediate preceding symptoms	130 (17.3)	494 (66.0)	125 (16.7)
Dyspnea	55	—	—
Chest pain	33	—	—
Weakness/dizziness	16	—	—
Nausea/vomiting/diarrhea	8	—	—
Seizures	3	—	—
Other	15	—	—
Resuscitation by medical personnel	179 (23.9)	538 (71.8)	32 (4.3)
First reported arrhythmia	86 (11.5)	645 (86.1)	18 (2.4)
Asystole	38	—	—
Ventricular fibrillation/ tachycardia	37	—	—
Pulseless electrical activity	8	—	—
Other (bradycardia, nonshockable)	3	—	—
Autopsy	38 (5.1)	707 (94.4)	4 (0.5)
IHD/atherosclerosis	20	—	—
Myocardial infarction	11	—	—
Other (aortic stenosis or regurgitation, pulmonary edema, natural cause, not reported)	7	—	—

Data shown are n or n (%). The denominator of each % is all sudden cardiac death events (n=749). IHD indicates ischemic heart disease; SCD, sudden cardiac death.

SCD Characterization

To describe the characteristics of SCD events, source documents of patients were reviewed by a single investigator (A.E.) using a prospectively designed data collection tool. Each SCD event was characterized as follows: witnessed (yes or no), occurred during sleep (yes or no), occurred out of hospital (yes or no), immediately preceded by clinical symptoms (yes or no; type of symptom), resuscitation performed by medical personnel (yes or no), first arrhythmia reported (yes or no; type of arrhythmia), and autopsy (yes or no; autopsy findings). In case the data were insufficient to decide, the category was defined as unknown.

Statistical Analysis

Baseline characteristics of patients were compared between groups, using chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. For the cause-specific death rate, we used the cumulative incidence function.[13,14] Predictors of SCD, other cardiovascular death, and noncardiovascular death were examined using the Gray test[13] based on the proportional subdistribution hazard model, which is a Cox regression hazards model used in competing risks situations. Independent predictors of SCD were also examined using a cause-specific hazard model, which is a specific method used in competing risks analysis.[14] Variables in the multivariable models included baseline characteristics with $P<0.1$ in the univariate model for mortality, omitting colinear variables, and adding variables that were judged to be of clinical importance. All multivariable analyses were adjusted for the following baseline variables: age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking (current or past), mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or transient ischemic attack, prior myocardial infarction, New York Heart Association functional class, pattern of AF (persistent or permanent versus paroxysmal), prior electrical cardioversion, race, use of vitamin K antagonists ≥60 days prior to baseline, class II antiarrhythmics (beta blockers), class III antiarrhythmics, digitalis use, electrocardiographic left ventricular hypertrophy, heart rate, randomization group, lipid-lowering drugs, and renin–angiotensin–aldosterone system inhibitors. The impact of the randomized treatment (edoxaban versus warfarin) on the risk of SCD was examined with the use of a Cox proportional hazards model in the intention-to-treat population during the overall study period, including all first events between randomization and the end of the study treatment period, whether occurring on or off the study drug. Results are presented as hazard ratios (HRs) with 95% CIs, with $P<0.05$ considered significant.

Results

Over a median follow-up of 2.8 years, 2349 patients died (40.5 per 1000 patient-years), with 1668 (71%) classified as cardiovascular death and 681 (29%) as noncardiovascular death (Figure 1). SCD (n=749; 12.9 per 1000 patient-years) was the most common cause of cardiovascular death, accounting for 31.7% of all deaths and for 44.9% of all cardiovascular deaths (Figure 1). Other common causes of cardiovascular death included HF or shock (n=390, 23.4%), fatal ischemic stroke (n=146, 8.8%), and fatal bleeding (n=124, 7.4%).

SCD Characterization

Most commonly, SCD occurred out of the hospital (92.8%), was unwitnessed (47.7%), and was not preceded by symptoms (66.0%). In the 16.7% of cases in which immediately

preceding symptoms were reported, dyspnea and chest pain were the most common (11.7%) (Table 1). A documented arrhythmia was reported in a minority of SCD events (11.5%). The most common arrhythmias were asystole (5.0%) and ventricular fibrillation or tachycardia (4.9%). Autopsy was performed in 38 patients (5.1%), and among them, chronic ischemic heart disease was the most common cause of death (52.7%). Further categorization of SCD events is depicted in Figure 2.

Patients who experienced SCD were predominantly male (70.6%), with a median age of 73 years (interquartile range 65–79 years). The majority had persistent or permanent AF (82.9%), HF symptoms at baseline (72.9%), a CHA_2DS_2-VASc score ≥4 (75.4%), and lower ejection fraction. SCD was most frequent in Eastern Europe (Table 2),[15–17] and the use of class I antiarrhythmics was not common among patients who experienced SCD (2.1%) (Table 2). During follow-up, 23 patients (3.1%) in the SCD group had a pacemaker implantation compared with 726 patients (3.6%) in the non-SCD group (P=0.47). Similarly, there was no difference between the groups in the number of patients who had an implantable cardioverter-defibrillator during follow-up (4 patients [0.5%] versus 200 patients [1.0%], respectively; P=0.22).

Compared with patients who experienced other cardiovascular deaths, patients who experienced SCD were younger and were more likely to be male, have a lower CHA_2DS_2-VASc score, have a higher heart rate at baseline, and to be treated with digitalis at baseline (Table 3).[15–17] Compared with patients who experienced noncardiovascular death, patients with SCD were significantly younger; had more HF symptoms, lower ejection fraction, higher heart rate at baseline, and more frequent signs of electrocardiographic left ventricular hypertrophy; and were more likely to be treated with digitalis at baseline (Table 3).

Predictors of SCD

vIn a multivariate competing risks analysis using the subdistribution hazard model accounting for other cardiovascular death and for noncardiovascular death, independent predictors of SCD were identified. Among these were older age, ejection fraction <50%, New York Heart Association functional class III–IV, and prior myocardial infarction (P<0.001 for each) (Table 4). Additional significant predictors of SCD, but not for other cardiovascular deaths or noncardiovascular deaths, included male sex, peripheral arterial disease, left ventricular hypertrophy per electrocardiogram, heart rate >80 beats per minute, nonuse of vitamin K antagonists ≥60 days prior to baseline, nonuse of beta blockers, and digitalis use (Tables 4 through 6). Notably, digitalis use was associated with SCD among patients with HF (adjusted HR 1.55, 95% CI 1.29–1.86, P<0.001) and among patients without HF (adjusted HR 1.56, 95% CI 1.14–2.11, P=0.005) with no significant interaction by HF status ($P_{interaction}$=0.73). A graded risk of SCD was observed when patients were stratified by the use of digitalis and beta blockers at baseline, with the highest rate of SCD observed in patients treated with digitalis and not treated with beta blockers (adjusted HR 1.82, 95% CI 1.45–2.27, P<0.001) (Figure 3). White race and diabetes mellitus were significant predictors of other cardiovascular death and noncardiovascular death but were not significant predictors of SCD (Tables 5 and 6). Using a cause-specific multivariate model, the same predictors of SCD as in the subdistribution hazard model were identified, with qualitatively consistent results (Table 7).

SCD and Randomized Treatment

The annual rate of SCD was 1.40% in patients treated with warfarin, which was numerically but not statistically lower with higher dose edoxaban (1.28%; HR versus warfarin 0.91,

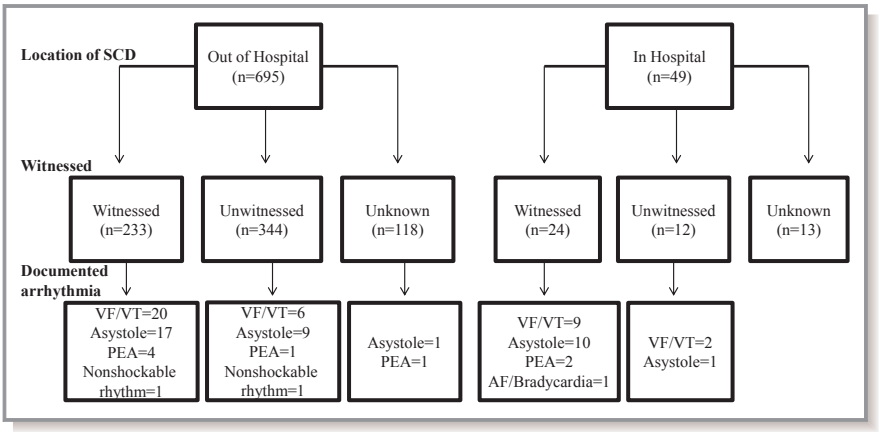

Figure 2. Characterization of sudden cardiac death events by the location of death, whether it was witnessed, and whether an arrhythmia was documented. AF indicates atrial fibrillation; PEA, pulseless electrical activity; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. Baseline Characteristics by SCD

Characteristic	SCD (n=749)	No SCD (n=20 356)	*P* Value	Total ENGAGE AF-TIMI 48 (n=21 105)
Age, y				
Median (IQR)	73 (65–79)	72 (64–78)	0.002	72 (64–78)
Female sex	220 (29.4)	7820 (38.4)	<0.001	8040 (38.1)
Weight, kg				
Mean (SD)	80.4 (20.6)	84.0 (20.2)	<0.001	83.9 (20.2)
Region			<0.001	
North America	127 (17.0)	4554 (22.4)		4681 (22.2)
Latin America	148 (19.8)	2513 (12.3)		2661 (12.6)
Western Europe	97 (13.0)	3139 (15.4)		3236 (15.3)
Eastern Europe	231 (30.8)	6913 (34.0)		7144 (33.8)
Asia Pacific and South Africa	146 (19.5)	3237 (15.9)		3383 (16.0)
White race	566 (75.6)	16 501 (81.1)	0.001	17 067 (80.9)
Type of AF			<0.001	
Paroxysmal	128 (17.1)	5238 (25.7)		5366 (25.4)
Persistent	204 (27.3)	4664 (22.9)		4868 (23.1)
Permanent	416 (55.6)	10 449 (51.3)		10 865 (51.5)
Qualifying risk factor				
Congestive heart failure	546 (72.9)	11 578 (56.9)	<0.001	12 124 (57.4)
Hypertension requiring treatment	702 (93.7)	19 052 (93.6)	0.89	19 754 (93.6)
Age ≥75 years	328 (43.8)	8146 (40.0)	0.04	8474 (40.2)
Diabetes mellitus	254 (33.9)	7370 (36.2)	0.20	7624 (36.1)
Prior stroke or transient ischemic attack	210 (28.0)	5763 (28.3)	0.87	5973 (28.3)
$CHADS_2$ score*				
4 to 6	208 (27.8)	4560 (22.4)	<0.001	4768 (22.6)
Mean (SD)	3.0 (1.0)	2.8 (1.0)	<0.001	2.8 (1.0)
CHA_2DS_2-VASc score*				
4 to 9	565 (75.4)	14 354 (70.5)	0.004	14 919 (70.7)
Mean (SD)	4.5 (1.4)	4.3 (1.4)	<0.001	4.3 (1.4)
HAS-BLED score*				
≥3	407 (54.3)	9395 (46.2)	<0.001	9802 (46.4)
Mean (SD)	2.7 (1.0)	2.5 (1.0)	<0.001	2.5 (1.0)
Coronary artery disease	313 (41.8)	6710 (33.0)	<0.001	7023 (33.3)
Prior myocardial infarction	148 (19.8)	2285 (11.2)	<0.001	2433 (11.5)
Ejection fraction†				
<30%	77 (10.3)	705 (3.5)	<0.001	782 (3.7)
<50%	319 (42.6)	4852 (23.8)	<0.001	5171 (24.5)
NYHA III, IV‡	175 (32.1)	2460 (21.2)	<0.001	2635 (21.8)
Peripheral arterial disease	54 (7.2)	787 (3.9)	<0.001	841 (4.0)
Former/current smoker	333 (44.4)	8315 (40.9)	0.04	8648 (41.0)
Mitral valve disease	288 (38.5)	6960 (34.2)	0.02	7248 (34.3)
Aortic valve disease	181 (24.2)	4258 (20.9)	0.03	4439 (21.0)
Prior electrical cardioversion for AF	99 (13.2)	3692 (18.1)	<0.001	3791 (18.0)

Continued

Table 2. Continued

Characteristic	SCD (n=749)	No SCD (n=20 356)	*P* Value	Total ENGAGE AF-TIMI 48 (n=21 105)
Heart rate, bpm, mean (SD)	77.1 (14.3)	74.1 (14.0)	<0.001	74.3 (14.0)
Left ventricular hypertropy per ECG	180 (24.3)	3257 (16.1)	<0.001	3437 (16.4)
Vitamin K antagonist experienced[§]	369 (49.3)	12 072 (59.3)	<0.001	12 441 (59.0)
Medication at randomization				
Aspirin	258 (34.4)	5922 (29.1)	0.002	6180 (29.3)
Lipid lowering	314 (41.9)	9768 (48.0)	0.001	10 082 (47.8)
Antiarrhythmics				
Class I	16 (2.1)	877 (4.3)	0.004	893 (4.2)
Class II (beta blockers)	472 (63.0)	13 512 (66.4)	0.06	13 984 (66.3)
Class III	122 (16.3)	3012 (14.8)	0.26	3134 (14.8)
Class IV	57 (7.6)	1848 (9.1)	0.17	1905 (9.0)
Digitalis	333 (44.5)	5994 (29.4)	<0.001	6327 (30.0)
Diuretics	541 (72.2)	12 115 (59.5)	<0.001	12 656 (60.0)
RAAS inhibitor	499 (66.6)	13 407 (65.9)	0.67	13 906 (65.9)
Creatinine clearance, mL/min				
Median (IQR)	62 (47–86)	71 (54–92)	<0.001	70 (54–92)
Dose reduction at randomization	291 (38.9)	5065 (24.9)	<0.001	5356 (25.4)

Data shown are n (%) unless otherwise indicated. AF indicates atrial fibrillation; bpm, beats per minute; IQR, interquartile range; NYHA, New York Heart Association functional class; RAAS, renin–angiotensin–aldosterone system; SCD, sudden cardiac death.

*References are provided for $CHADS_2$ score,[15] CHA_2DS_2-VASc score,[16] and HAS-BLED score.[17]

†Ejection fraction was unknown for 169 patients with SCD and for 5372 patients with no SCD.

‡NYHA class at baseline was reported only for patients with heart failure.

§Vitamin K antagonist experience denotes ≥60 consecutive days of treatment with a vitamin K antagonist at any time prior to enrollment.

95% CI 0.77–1.08) and with lower dose edoxaban (1.20%; HR versus warfarin 0.85, 95% CI 0.71–1.01). Kaplan–Meier curves for SCD in each treatment arm are depicted in Figure 4.

Discussion

In the current analysis from a large international cohort of patients with AF, SCD was the single most common cause of death and accounted for about a third of all deaths and nearly half of all cardiovascular deaths. We described several clinical characteristics of SCD and identified independent predictors that were associated with SCD in patients with AF. These included HF and prior cardiovascular disease as well as other unique factors for SCD that were not associated with other causes of death, including male sex, higher heart rate, left ventricular hypertrophy, digitalis use, and nonuse of beta blockers. To our knowledge, this study is the first to specifically examine the association between baseline features and SCD in stable patients with established AF.

Several studies have suggested a causal association between incident AF and SCD.[4–7] The association between them is complex and may involve several mechanisms.[9,10] AF and SCD share common pathophysiological etiologies including HF and coronary artery disease.[9,10] In addition, AF may also be a marker of more advanced disease with a greater extent of underlying structural heart disease.[18] AF may have proarrhythmic effects including myocardial ischemia induced by rapid AF, reduction of ventricular refractoriness during rapid AF, and electrical remodeling of the atria, characterized by shorter action potential duration and refractoriness, with similar changes that might also occur in ventricular myocytes.[5,19] In this analysis, the rate of SCD was higher than the rate of SCD observed in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (n=305, 22.2% of 1371 deaths[8]), which might be attributed to the higher risk population included in the ENGAGE AF-TIMI 48 trial (mean $CHADS_2$ score 2.8±1.0 versus 2.1±1.1 in the RE-LY trial). Nevertheless, SCD was also the most common cause of cardiovascular death in the RE-LY trial. These findings highlight the need to identify risk factors for SCD in patients with AF and perhaps to examine treatment modalities in addition to anticoagulation to reduce SCD rates in these patients with AF.

Table 3. Baseline Characteristics by Type of Death: SCD, Other CVD, Non-CVD, Non-SCD, CVD, and All Death

Characteristic	SCD (n=749)	Other CVD (n=919)	*P* Value (Other CVD vs SCD)	Non-CVD (n=681)	*P* Value (Non-CVD vs SCD)	Non-SCD (n=1600)	*P* Value (Non-SCD vs SCD)	CVD* (n=1668)	All Death* (n=2349)
Age, y, median (IQR)	73 (65–79)	76 (69–81)	<0.001	76 (70–81)	<0.001	76 (69–81)	<0.001	75 (67–80)	75 (68–80)
Female sex	220 (29.4)	342 (37.2)	<0.001	222 (32.6)	0.18	564 (35.3)	0.005	562 (33.7)	784 (33.4)
Weight, kg, mean (SD)	80.4 (20.6)	78.7 (18.6)	0.10	80.8 (19.6)	0.59	79.6 (19.2)	0.44	79.5 (19.6)	79.8 (19.7)
Region			<0.001		<0.001		<0.001		
North America	127 (17.0)	230 (25.0)		192 (28.2)		422 (26.4)		357 (21.4)	549 (23.4)
Latin America	148 (19.8)	164 (17.8)		125 (18.4)		289 (18.1)		312 (18.7)	437 (18.6)
Western Europe	97 (13.0)	133 (14.5)		102 (15.0)		235 (14.7)		230 (13.8)	332 (14.1)
Eastern Europe	231 (30.8)	261 (28.4)		169 (24.8)		430 (26.9)		492 (29.5)	661 (28.1)
Asia Pacific and South Africa	146 (19.5)	131 (14.3)		93 (13.7)		224 (14.0)		277 (16.6)	370 (15.8)
White race	566 (75.6)	740 (80.5)	0.02	556 (81.6)	0.02	1296 (81.0)	0.004	1306 (78.3)	1862 (79.3)
Type of AF			0.35		0.08		0.11		
Paroxysmal	128 (17.1)	176 (19.2)		142 (20.9)		318 (19.9)		304 (18.2)	446 (19.0)
Persistent	204 (27.3)	226 (24.6)		157 (23.1)		383 (23.9)		430 (25.8)	587 (25.0)
Permanent	416 (55.6)	517 (56.3)		382 (56.1)		899 (56.2)		933 (56.0)	1315 (56.0)
Qualifying risk factor									
Congestive heart failure	546 (72.9)	642 (69.9)	0.17	396 (58.1)	<0.001	1038 (64.9)	<0.001	1188 (71.2)	1584 (67.4)
Hypertension requiring treatment	702 (93.7)	849 (92.4)	0.29	624 (91.6)	0.13	1473 (92.1)	0.15	1551 (93.0)	2175 (92.6)
Age ≥75 y	328 (43.8)	519 (56.5)	<0.001	400 (58.7)	<0.001	919 (57.4)	<0.001	847 (50.8)	1247 (53.1)
Diabetes mellitus	254 (33.9)	348 (37.9)	0.09	255 (37.4)	0.16	603 (37.7)	0.08	602 (36.1)	857 (36.5)
Prior stroke or transient ischemic attack	210 (28.0)	300 (32.6)	0.04	212 (31.1)	0.20	512 (32.0)	0.05	510 (30.6)	722 (30.7)
$CHADS_2$ score†									
4 to 6	208 (27.8)	322 (35.0)	0.001	205 (30.1)	0.33	527 (32.9)	0.01	530 (31.8)	735 (31.3)
Mean (SD)	3.0 (1.0)	3.2 (1.1)	<0.001	3.1 (1.1)	0.17	3.2 (1.1)	0.002	3.1 (1.1)	3.1 (1.1)
CHA_2DS_2-VASc score†									
4 to 9	565 (75.4)	761 (82.8)	<0.001	549 (80.6)	0.018	1310 (81.9)	<0.001	1326 (79.5)	1875 (79.8)
Mean (SD)	4.5 (1.4)	4.9 (1.5)	<0.001	4.7 (1.4)	0.005	4.8 (1.4)	<0.001	4.7 (1.5)	4.7 (1.4)
HAS-BLED score†									
≥3	407 (54.3)	519 (56.5)	0.38	391 (57.4)	0.24	910 (56.9)	0.25	926 (55.5)	1317 (56.1)
Mean (SD)	2.7 (1.0)	2.7 (0.9)	0.16	2.7 (1.0)	0.16	2.7 (1.0)	0.11	2.7 (1.0)	2.7 (1.0)
Coronary artery disease	313 (41.8)	403 (43.9)	0.39	266 (39.1)	0.29	669 (41.8)	0.98	716 (43.0)	982 (41.8)
Prior myocardial infarction	148 (19.8)	173 (18.8)	0.64	99 (14.5)	0.009	272 (17.0)	0.11	321 (19.3)	420 (17.9)
Ejection fraction‡									
<30%	77 (10.3)	81 (8.8)	0.29	30 (4.4)	<0.001	111 (6.9)	<0.001	158 (9.5)	188 (8.0)
<50%	319 (42.6)	343 (37.3)	0.06	165 (24.3)	<0.001	508 (31.8)	<0.001	662 (39.7)	827 (35.2)
NYHA III, IV§	175 (32.1)	202 (31.5)	0.65	72 (18.2)	<0.001	274 (26.4)	0.13	377 (31.7)	449 (28.4)
Peripheral arterial disease	54 (7.2)	59 (6.4)	0.52	34 (5.0)	0.08	93 (5.8)	0.19	113 (6.8)	147 (6.3)
Former/current smoker	333 (44.4)	397 (43.3)	0.28	339 (49.8)	0.04	736 (46.1)	0.15	730 (43.9)	1069 (45.6)
Mitral valve disease	288 (38.5)	357 (38.8)	0.87	257 (37.7)	0.78	614 (38.4)	0.97	645 (38.7)	902 (38.4)
Aortic valve disease	181 (24.2)	231 (25.1)	0.65	146 (21.4)	0.22	377 (23.6)	0.75	412 (24.7)	558 (23.8)

Continued

Table 3. Continued

Characteristic	SCD (n=749)	Other CVD (n=919)	*P* Value (Other CVD vs SCD)	Non-CVD (n=681)	*P* Value (Non-CVD vs SCD)	Non-SCD (n=1600)	*P* Value (Non-SCD vs SCD)	CVD* (n=1668)	All Death* (n=2349)
Prior electrical cardioversion for AF	99 (13.2)	110 (12.0)	0.44	107 (15.7)	0.18	217 (13.6)	0.82	209 (12.5)	316 (13.5)
Heart rate, bpm, mean (SD)	77.1 (14.3)	75.1 (13.9)	<0.001	74.5 (14.4)	<0.001	74.8 (14.1)	<0.001	76.0 (14.1)	75.6 (14.2)
Hypertrophy per ECG	180 (24.3)	188 (20.6)	0.07	94 (14.0)	<0.001	282 (17.8)	<0.001	368 (22.2)	462 (19.9)
Vitamin K antagonist experienced‖	369 (49.3)	523 (56.9)	0.002	414 (60.8)	<0.001	937 (58.6)	<0.001	892 (53.5)	1306 (55.6)
Medication at randomization									
Aspirin	258 (34.4)	309 (33.6)	0.72	191 (28.0)	0.009	500 (31.3)	0.12	567 (34.0)	758 (32.3)
Lipid lowering	314 (41.9)	408 (44.4)	0.31	314 (46.1)	0.11	722 (45.1)	0.15	722 (43.3)	1036 (44.1)
Antiarrhythmics									
Class I	16 (2.1)	15 (1.6)	0.45	14 (2.1)	0.92	29 (1.8)	0.59	31 (1.9)	45 (1.9)
Class II (beta blockers)	472 (63.0)	605 (65.8)	0.23	421 (61.8)	0.64	1026 (64.1)	0.60	1077 (64.6)	1498 (63.8)
Class III	122 (16.3)	122 (13.3)	0.08	104 (15.3)	0.60	226 (14.1)	0.17	244 (14.6)	348 (14.8)
Class IV	57 (7.6)	84 (9.1)	0.26	79 (11.6)	0.01	163 (10.2)	0.05	141 (8.5)	220 (9.4)
Digitalis	333 (44.5)	340 (37.0)	0.002	226 (33.2)	<0.001	566 (35.4)	<0.001	673 (40.3)	899 (38.3)
Diuretics	541 (72.2)	657 (71.5)	0.74	453 (66.5)	<0.001	1110 (69.4)	0.16	1198 (71.8)	1651 (70.3)
RAAS inhibitor	499 (66.6)	573 (62.4)	0.07	411 (60.4)	0.01	984 (61.5)	0.02	1072 (64.3)	1483 (63.1)
Creatinine clearance, mL/min									
Median (IQR)	62 (47–86)	56 (43–74)	<0.001	59 (46–80)	0.07	57 (44–77)	<0.001	58 (44–79)	59 (45–79)
Dose reduction at randomization	291 (38.9)	396 (43.1)	0.08	270 (39.6)	0.76	666 (41.6)	0.20	687 (41.2)	957 (40.7)

Data shown are n (%) unless otherwise indicated. The Non-SCD category includes Other CVD and Non-CVD, the CVD category includes SCD and Other CVD, and the All Death category includes SCD, Other CVD, and Non-CVD. AF indicates atrial fibrillation; bpm, beats per minute; CVD, cardiovascular death; IQR, interquartile range; NYHA, New York Heart Association functional class; RAAS, renin–angiotensin–aldosterone system; SCD, sudden cardiac death.

**P* values (vs SCD) are not available for CVD and All Death because these categories include SCD.

†References are provided for $CHADS_2$ score,[15] CHA_2DS_2-VASc score,[16] and HAS-BLED score.[17]

‡Ejection fraction was unknown for 169 patients with SCD, 230 patients with other CVD, 205 patients with non-CVD.

§NYHA class at baseline was reported only in patients with heart failure.

‖Vitamin K antagonist experienced denotes ≥60 consecutive days of treatment with a vitamin K antagonist at any time prior to enrollment.

In our study, SCD and other cardiovascular deaths shared several known predictors (Tables 4 and 5).[19,20] These included low ejection fraction, HF symptoms, and prior myocardial infarction. Using competing risks models, which accounted for the different types of deaths, several distinct predictors of SCD in patients with AF were identified. Interestingly, some of these predictors are modifiable and might have important clinical implications. The use of digitalis in patients with AF with or without HF has long been debated.[21–23] An analysis from the 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) trial demonstrated an increased risk of all-cause death, vascular death, and SCD with digitalis use.[23] In the current study, we also observed an increased risk of SCD among patients treated with digitalis. Interestingly, among the patients who were treated with digitalis in the ENGAGE AF-TIMI 48 trial, 28.8% did not have HF symptoms and presumably were treated with digitalis for ventricular rate control. We demonstrated that digitalis is associated with SCD regardless of HF status, and this adds to the concern regarding digitalis treatment in patients with AF with or without HF.[23] In addition, we observed that nonuse of beta blockers was an independent predictor of SCD (Table 4); however, it is not clear whether the pharmacological treatment (use of digitalis, nonuse of beta blockers) and/or the underlying condition responsible for the treatment (eg, HF) was responsible for the SCD.[24]

The relationship among hypertension, electrocardiographic evidence of left ventricular hypertrophy, and SCD is complex. Okin et al reported that in hypertensive patients with left ventricular hypertrophy, patients who developed AF during follow-up compared with those who did not had a >3-fold increased risk of SCD.[6] In the ENGAGE AF-TIMI 48 trial, 93.6%

Table 4. Multivariate Cox Proportional Subdistribution Hazard Model of Significant Predictors of SCD (Competing Risks Analysis) in the ENGAGE AF-TIMI 48 Trial

	SCD		
Variable	Adjusted sHR (95% CI)*	Chi-square	*P* Value
Ejection fraction <50%	1.71 (1.45–2.02)	39.7	<0.001
Digitalis use†	1.51 (1.29–1.77)	26.9	<0.001
NYHA III–IV	1.85 (1.44–2.37)	23.6	<0.001
Creatinine (per 10-μmol/L increase)	1.06 (1.03–1.08)	22.4	<0.001
Prior myocardial infarction	1.55 (1.27–1.88)	19.1	<0.001
VKA naive†	1.40 (1.20–1.60)	18.9	<0.001
Weight (per 5-kg decrease)	1.05 (1.03–1.08)	17.3	<0.001
Age ≥75 y	1.35 (1.15–1.59)	12.9	<0.001
Peripheral arterial disease†	1.68 (1.26–2.24)	12.4	<0.001
Male†	1.38 (1.15–1.65)	11.7	0.001
NYHA I–II	1.37 (1.12–1.67)	9.4	<0.001
Heart rate at baseline ≥80 bpm†	1.26 (1.08–1.47)	8.7	0.003
Persistent or permanent AF	1.32 (1.07–1.63)	6.8	0.009
Left ventricular hypertrophy (per ECG)†	1.25 (1.04–1.50)	5.5	0.02
Nonuse of beta blockers†	1.21 (1.03–1.42)	5.4	0.02

AF indicates atrial fibrillation; bpm, beats per minute; CVD, cardiovascular death; NYHA, New York Heart Association functional class; SCD, sudden cardiac death; sHR, subdistribution hazard ratio; VKA, vitamin K antagonist.
*Adjusted for age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking, mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or transient ischemic attack, prior myocardial infarction, NYHA class, type of AF, prior electrical cardioversion, race, previous use of VKA for ≥60 days, class II antiarrhythmics, class III antiarrhythmics, digitalis use, left ventricular hypertrophy per ECG, heart rate, randomization group, lipid-lowering drugs, renin–angiotensin–aldosterone system inhibitors.
†Independent predictors of SCD but not of other CVD or non-CVD (see Tables 5 and 6).

Table 5. Multivariate Analysis Using Subdistribution Hazard Model of Significant Predictors of Other CVD Using a Competing Risks Analysis in the ENGAGE AF-TIMI 48 Trial

	Other CVD	
Variable	Adjusted sHR (95% CI)*	*P* Value
Ejection fraction <50%	1.51 (1.30–1.76)	<0.001
Creatinine (per 10 μmol/L increase)	1.10 (1.07–1.12)	<0.001
NYHA III–IV	2.38 (1.91–2.97)	<0.001
NYHA I–II	1.57 (1.33–1.86)	<0.001
Prior myocardial infarction	1.39 (1.16–1.67)	<0.001
Weight (per 5 kg decrease)	1.09 (1.05–1.11)	<0.001
Age ≥75 y	2.02 (1.75–2.33)	<0.001
Persistent/permanent AF	1.23 (1.03–1.48)	0.02
Diabetes mellitus	1.41 (1.23–1.63)	<0.001
Prior stroke/TIA	1.42 (1.23–1.63)	<0.001
Prior electrical cardioversion	0.67 (0.55–0.83)	<0.001
White race	1.27 (1.05–1.54)	0.01
Lipid-lowering therapy	0.86 (0.74–0.99)	0.04
RAAS inhibitor	0.81 (0.71–0.93)	0.003

AF indicates atrial fibrillation; CVD, cardiovascular death; NYHA, New York Heart Association functional class; RAAS, renin–angiotensin–aldosterone system; sHR, subdistribution hazard ratio; TIA, transient ischemic attack.
*Adjusted for age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking, mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or TIA, prior myocardial infarction, NYHA class, type of AF, prior electrical cardioversion, race, previous use of vitamin K antatgonist for ≥60 days, class II antiarrhythmics, class III antiarrhythmics, digitalis use, left ventricular hypertrophy per ECG, heart rate, randomization group, lipid-lowering drugs, RAAS inhibitors.

of the patients had hypertension requiring treatment, and almost a quarter of the patients who died from SCD showed left ventricular hypertrophy on baseline electrocardiograms. Indeed, left ventricular hypertrophy was identified as an independent predictor of SCD in this study, but it remains unclear whether hypertrophy is the substrate for SCD or perhaps only a marker of longstanding hypertension that could be related to SCD.[6] It should be emphasized that these observations are hypothesis generating only and should be examined prospectively in future trials. In addition, in the absence of a control group of patients without AF, the extent to which these predictors are specific for patients with AF also remains to be elucidated.

In the current study, we examined the characteristics of all SCD events that occurred in the ENGAGE AF-TIMI 48 trial. These descriptive data were not reported in other recent large AF trials.[8,23,25,26] Interestingly, resuscitation by a medical team was attempted in the minority (23.9%) of patients who had SCD, and documentation of the responsible arrhythmia was rare.

Compared with warfarin treatment, the rate of SCD was numerically but not statistically lower in patients treated with edoxaban. The reason for this observation remains unclear. In the ENGAGE AF-TIMI 48 trial, compared with warfarin, edoxaban reduced the rates of hemorrhagic stroke. It is possible that some of the unwitnessed deaths that were categorized as SCD in the ENGAGE AF-TIMI 48 trial were actually caused by hemorrhagic stroke and thus were numerically lower with edoxaban.[11]

This study has several clinical implications. Some of the predictors of SCD in patients with AF may be modifiable by careful considerations of pharmacological treatment (digoxin,

Table 6. Multivariate Analysis Using Subdistribution Hazard Model of Significant Predictors of Non-CVD Using a Competing Risks Analysis in the ENGAGE AF-TIMI 48 Trial

	Non-CVD	
Variable	Adjusted sHR (95% CI)*	*P* Value
Creatinine (per 10 μmol/L increase)	1.07 (1.04–1.10)	<0.001
NYHA I to II	1.29 (1.07–1.54)	0.006
Weight (per 5 kg decrease)	1.04 (1.02–1.08)	0.002
Age ≥75 y	2.05 (1.72–2.44)	<0.001
Persistent/permanent AF	1.29 (1.05–1.58)	0.015
Diabetes mellitus	1.29 (1.09–1.52)	<0.001
Prior stroke/TIA	1.28 (1.08–1.51)	0.005
White race	1.32 (1.04–1.66)	0.02
RAAS inhibitor	0.84 (0.72–0.99)	0.038
Current or prior smoking	1.38 (1.17–1.62)	<0.001

AF indicates atrial fibrillation; CVD, cardiovascular death; NYHA, New York Heart Association functional class; RAAS, renin–angiotensin–aldosterone system; sHR, subdistribution hazard ratio; TIA, transient ischemic attack.
*Adjusted for age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking, mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or TIA, prior myocardial infarction, NYHA class, type of AF, prior electrical cardioversion, race, previous use of vitamin K antagonist for ≥60 days, class II antiarrhythmics, class III antiarrhythmics, digitalis use, left ventricular hypertrophy per ECG, heart rate, randomization group, lipid-lowering drugs, RAAS inhibitors.

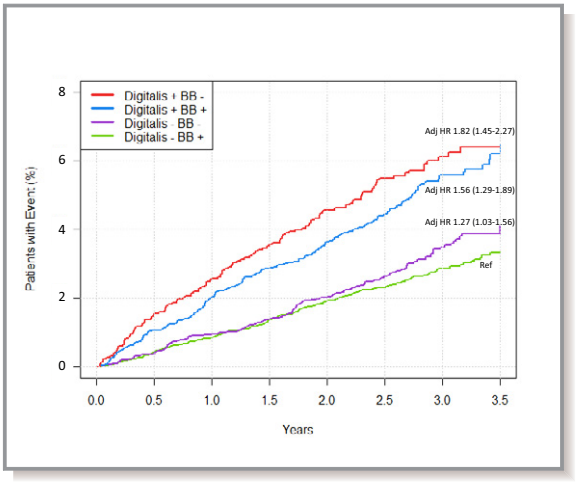

Figure 3. SCD stratified by the use of digitalis and BBs at baseline. The risk of SCD was the highest among patients who were treated with digitalis and were not treated with BBs at baseline (red line). Adjustment variables: age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking, mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or transient ischemic attack, prior myocardial infarction, New York Heart Association class, type of atrial fibrillation, prior electrical cardioversion, race, previous use of vitamin K antagonists for ≥60 days, class II antiarrhythmics, class III antiarrhythmics, digitalis use, left ventricular hypertrophy per ECG, heart rate, randomization group, lipid-lowering drugs, renin–angiotensin–aldosterone system inhibitors. Adj HR indicates adjusted hazard ratio; BB, beta blocker; SCD, sudden cardiac death.

beta blockers), better control of heart rate, and treatment of hypertension, which is an important cause of left ventricular hypertrophy. Because our findings are observational, future prospective studies should examine whether these modifications in treatment can reduce the risk of SCD in patients with AF. In addition, this study demonstrated that SCD is more common than fatal stroke as a cause of death in patients with AF who are treated with anticoagulation; therefore, future research is needed to examine treatment modalities, perhaps other than anticoagulation, that could curtail this risk.

Limitations

This study has several limitations. Cause-specific mortality in many cases is unclear and often multifactorial. Nevertheless, SCD was predefined and adjudicated by a clinical end points committee. SCD categorization was performed using a predefined approach by a single investigator, but autopsies were infrequent, and specific details were not always provided; therefore, these findings should be interpreted with caution. Baseline data on pacemakers and implantable cardioverter-defibrillators were unavailable. With regard to SCD, several important factors were not available in this study including family history of SCD, physical activity status, and genetic tests.

Conclusion

SCD is the most common cause of cardiovascular death in patients with AF and has several distinct predictors, some of which are modifiable. These findings may be considered in planning treatment strategies and future research for patients with AF.

Disclosures

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Table 7. Multivariate Cause-Specific Hazard Model of Significant Predictors of Sudden Cardiac Death in the ENGAGE AF-TIMI 48 Trial

Variable	Adjusted HR (95% CI)*	Chi-square	*P* Value
Ejection fraction <50%	1.74 (1.48–2.06)	42.7	<0.001
NYHA III–IV	1.93 (1.51–2.46)	27.9	<0.001
Digitalis use	1.52 (1.30–1.77)	27.6	<0.001
Creatinine (per 10-μmol/L increase)	1.06 (1.04–1.09)	26.3	<0.001
Weight (per 5-kg decrease)	1.06 (1.03–1.09)	22.8	<0.001
Prior myocardial infarction	1.57 (1.30–1.91)	21.0	<0.001
VKA naive	1.40 (1.20–1.64)	18.5	<0.001
Age ≥75 y	1.40 (1.19–1.64)	16.5	<0.001
Peripheral arterial disease	1.72 (1.29–2.28)	13.9	<0.001
Male	1.38 (1.15–1.66)	11.7	0.001
NYHA I–II	1.40 (1.15–1.70)	11.4	<0.001
Heart rate at baseline ≥80 bpm	1.27 (1.09–1.47)	9.4	0.002
Persistent or permanent AF	1.33 (1.08–1.63)	7.4	0.007
Nonuse of beta blockers	1.22 (1.04–1.43)	6.0	0.014
Left ventricular hypertrophy (per ECG)	1.24 (1.04–1.49)	5.7	0.014

AF indicates atrial fibrillation; bpm, beats per minute; HR, hazard ratio; NYHA, New York Heart Association functional class; VKA, vitamin K antagonist.
*Adjusted for age, sex, weight, creatinine, ejection fraction <50%, hypertension, diabetes mellitus, smoking, mitral valve disease, aortic valve disease, peripheral arterial disease, prior stroke or transient ischemic attack, prior myocardial infarction, NYHA class, type of AF, prior electrical cardioversion, race, previous use of VKA for ≥60 days, class II antiarrhythmics, class III antiarrhythmics, digitalis use, left ventricular hypertrophy per ECG, heart rate, randomization group, lipid-lowering drugs, renin–angiotensin–aldosterone system inhibitors.

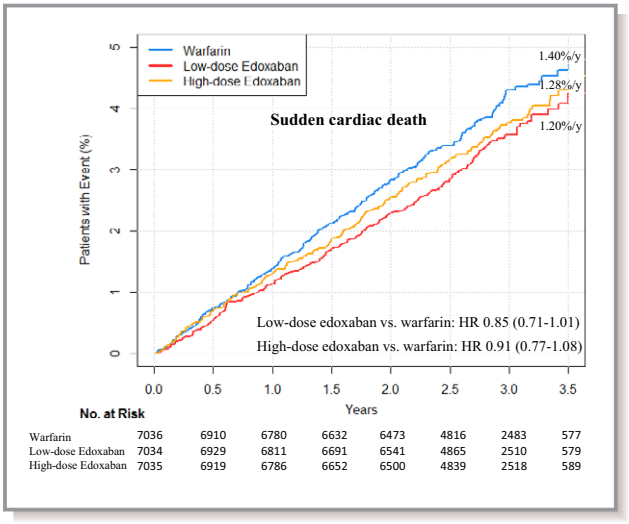

Figure 4. Kaplan–Meier curves of sudden cardiac death by treatment arm. HR indicates hazard ratio.

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