Risk of Thromboembolism in Heart Failure

An Analysis From the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

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Background—In patients with heart failure, rates of clinically apparent stroke range from 1.3% to 3.5% per year. Little is known about the incidence and risk factors in the absence of atrial fibrillation. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 2521 patients with moderate heart failure were randomized to receive amiodarone, implanted cardioverter-defibrillators (ICDs), or placebo.

Methods and Results—We determined the incidence of stroke or peripheral or pulmonary embolism in patients with no history of atrial fibrillation (n=2114), predictors of thromboembolism and the relationship to left ventricular ejection fraction. Median follow-up was 45.5 months. Kaplan-Meier estimates (95% CIs) for the incidence of thromboembolism by 4 years were 4.0% (3.0% to 4.9%), with 2.6% (1.1% to 4.1%) in patients randomized to amiodarone, 3.2% (1.8% to 4.7%) in patients randomized to ICD, and 6.0% (4.0% to 8.0%) in patients randomized to placebo (approximate rates of 0.7%, 0.8%, and 1.5% per year, respectively). By multivariable analysis, hypertension ($P=0.021$) and decreasing left ventricular ejection fraction ($P=0.023$) were significant predictors of thromboembolism; treatment with amiodarone or ICD treatment was a significant predictor of thromboembolism-free survival ($P=0.014$ for treatment effect; hazard ratio [95% CI] versus placebo, 0.57 [0.33 to 0.99] for ICD; 0.44 [0.24 to 0.80] for amiodarone). Inclusion of atrial fibrillation during follow-up in the multivariable model did not affect the significance of treatment assignment as a predictor of thromboembolism.

Conclusions—In the SCD-HeFT patient cohort, which reflects contemporary treatment of patients with moderately symptomatic systolic heart failure, patients experienced thromboembolism events at a rate of 1.7% per year without antiarrhythmic therapy. Those treated with amiodarone or ICDs had lower risk of thromboembolism than those given placebo. Hypertension at baseline and lower ejection fraction were independent predictors of risk. **(*Circulation*. 2007; 115:2637-2641.)**

Key Words: thromboembolism ■ thrombosis ■ heart failure

Despite the large number of patients with heart failure (HF) and the importance of stroke and thromboembolism as clinical events, little is known about the incidence of thromboembolism in patients with HF who do not have atrial fibrillation (AF) or a prosthetic heart valve. In clinical trials of HF treatment, in which antithrombotic therapy was generally not a controlled variable, rates of clinically apparent stroke ranging from 1.3% to 3.5% per year have been reported,[1–4] but the long-term cumulative risk of thromboembolism and its relationship to other clinical parameters in patients with HF remains unclear. The major objective of the present analysis of data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was to determine the incidence of and risk factors for thromboembolism in stable, moderately symptomatic patients with systolic heart failure without a history of AF or atrial flutter.

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Methods

The design and results of SCD-HeFT have been reported previously.[5] In brief, 2521 patients with New York Heart Association functional class II or III HF and left ventricular (LV) ejection fraction (EF) ≤35% were randomly assigned to treatment with an implantable cardioverter-defibrillator (ICD), amiodarone, or placebo, in addition to state-of-the-art medical therapy. The primary end point was death due to any cause. The protocol required investigators to maintain optimum medical therapy as recommended in prevailing practice guidelines, including β-adrenergic antagonist, angiotensin-converting enzyme inhibitor, and aldosterone antagonist drugs.

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Identical-appearing amiodarone (200 mg; Wyeth-Ayerst Pharmaceuticals, Madison, NJ) or placebo tablets were administered in a double-blind fashion. The dose was based in part on body weight: After a loading dose of 800 mg daily for 1 week followed by 400 mg daily for 3 weeks, patients weighing >200 lb (90.9 kg) received 400 mg daily, those weighing 150 to 200 lb (68.2 to 90.9 kg) received 300 mg daily (1.5 tablets), and patients weighing <150 lb (68.2 kg) received 200 mg of amiodarone daily or the corresponding number of placebo tablets.

ICD therapy consisted of shock-only, single-lead devices programmed to detect tachycardia exceeding 188 bpm for 18 of 24 intervals. Neither dual-chamber nor biventricular devices were used.

Patients were seen at 1 week, 1 month, and 3 months after randomization and every 3 months thereafter. Patients with past history of AF or atrial flutter were excluded from the present analysis. For the purposes of the present analysis, all investigator-reported stroke or peripheral or pulmonary arterial embolic events that occurred in the remaining patients during follow-up were considered as thromboembolism events. Stroke severity was not evaluated formally. The occurrence of transient ischemic attacks was not included in this analysis, to increase the specificity for actual neurological events.

Statistical Analysis

Hazard ratios (HRs) are given with 95% CIs. Plots of time to event by randomized therapy and by level of EF were created with Kaplan-Meier estimates. Systolic blood pressure at baseline and last follow-up visit was compared between randomized treatment groups with a Kruskal-Wallis test for any difference; where the test was significant, pairwise Wilcoxon rank sum tests were used to identify differences.

Candidate baseline predictors for thromboembolism were randomized therapy (as defined by intention-to-treat); ischemic or nonischemic origin of HF; New York Heart Association class; gender; history of myocardial infarction, diabetes mellitus, hypertension, or tobacco smoking; age; EF; 6-minute walk performance; and angiotensin-converting enzyme inhibitor therapy. Antithrombotic therapy was determined on the basis of medication use reported at each follow-up visit; patients were classified as taking warfarin (with or without aspirin), taking aspirin without warfarin, or taking neither at each interval. All potential predictors were included in a multivariable Cox proportional hazards regression model with time to first thromboembolism as the response.

Antithrombotic therapy was included within the model as a time-dependent covariate, which allowed patients to change antithrombotic therapy status over time. The occurrence of AF during follow-up was also added to the multivariable model as a time-dependent covariate to determine whether any difference in thromboembolism risk between the randomized therapies could be attributed to differences in the incidence of AF.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Among the 2521 randomized patients, the present analysis was based on the 2114 patients with no history of documented AF or flutter at baseline (Table 1). Overall, 71 patients (3.4%) experienced thromboembolism over a median follow-up of 45.5 months. The 4-year Kaplan-Meier event rate was 4.0% (95% CI, 3.0% to 4.9%), which yielded an approximate annual rate of 1.0%. Among the 3 randomized treatment arms, 2.1% of patients in the amiodarone arm, 2.9% in the ICD arm, and 5.0% in the placebo arm experienced thromboembolism (Table 2). The 4-year Kaplan-Meier event rates (95% CIs) were 2.6% (1.1% to 4.1%) for amiodarone, 3.2% (1.8% to 4.7%) for ICD, and 6.0% (4.0% to 8.0%) for placebo, which yielded approximate annual rates of 0.7%, 0.8%, and 1.5% per year, respectively. The rates of thromboembolism were comparable across treatment groups during the first year, with the excess rate in the placebo arm emerging only after 1 year of follow-up, when accrual rates in the amiodarone and ICD arms slowed, whereas that in the placebo arm was maintained (Figure 1).

In the multivariable Cox model, randomized treatment assignment was a significant independent predictor of throm-

TABLE 1. SCD-HeFT: Baseline Characteristics Among Patients Without History of AF

Characteristic	Amiodarone (n=710)	Placebo (n=723)	ICD (n=681)
Age, y	59 (51, 66)	59 (50, 67)	59 (51, 68)
Female	25 (177)	25 (178)	26 (176)
Nonwhite race	24 (171)	25 (181)	23 (160)
EF, %	25 (20, 30)	25 (20, 30)	24 (19, 30)
Diabetes mellitus	29 (208)	32 (230)	30 (205)
Hypertension	54 (383)	55 (398)	54 (370)
Nonsustained ventricular tachycardia	22 (155)	20 (144)	25 (171)
Electrophysiology study	17 (119)	14 (99)	15 (103)
Systolic blood pressure, mm Hg	118 (106, 130)	120 (108, 131)	118 (104, 132)
Diastolic blood pressure, mm Hg	70 (62, 80)	70 (62, 80)	70 (62, 80)
Heart rate, bpm	72 (64, 82)	74 (64, 84)	75 (66, 84)
Serum sodium, mEq/L	139 (137, 141)	139 (137, 141)	139 (137, 141)
Serum creatinine, mg/dL	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Prior myocardial infarction	43 (307)	46 (332)	44 (297)
Prior stroke	6 (41)	7 (50)	5 (37)
Smoker			
Current	16 (111)	17 (123)	19 (126)
Past	56 (400)	61 (437)	53 (362)

Continuous variables are shown as median (25th, 75th percentiles). Categorical variables are shown as percent (n).

TABLE 2. Thromboembolic Events in Patients Without Documented AF or Flutter

Arm	No.	Stroke	Peripheral Embolism	Pulmonary Embolism	Any Thrombo-embolic Event
Amiodarone	710	12	1	2	15
Placebo	723	30	4	2	36
ICD	681	14	2	4	20
Total	2114	56	7	8	71

boembolism ($P=0.014$ for an overall test of difference between both treatments and placebo). Patients in the ICD and amiodarone groups had approximately half the thromboembolism risk of those in the placebo arm (HR, 0.57 [95% CI, 0.33 to 0.99] for ICD versus placebo and 0.44 [0.24 to 0.80] for amiodarone versus placebo; Table 3). In addition, hypertension at the time of randomization was a significant predictor ($P=0.021$; HR, 1.86 [95% CI, 1.10 to 3.13], as was LV EF ($P=0.023$; HR, 0.82 [95% CI, 0.69 to 0.97] per 5% increase in EF). No other variables (cause of HF, functional class, age, gender, diabetes mellitus, smoking, 6-minute walk test, and angiotensin-converting enzyme inhibitor therapy) added significant predictive value (all $P>0.2$).

There were no differences between groups in blood pressure at entry (overall $P=0.84$). Patients assigned to treatment with amiodarone had slightly but significantly higher systolic blood pressure at the last follow-up visit (median [25th, 75th percentiles]=120 mm Hg [108, 134]) than those in either the ICD (118 mm Hg [104, 130]) or placebo (116 mm Hg [100, 130]) groups ($P=0.001$ for each comparison). There was no significant difference in blood pressure at last follow-up between those in the ICD and placebo groups. The 4-year Kaplan-Meier rate (95% CI) of thromboembolism was 3.5% (1.8% to 5.1%) in patients with LV EF of at least 30% but ≤35%, 3.6% (1.9% to 5.3%) in those with EF >20% but <30%, and 4.6% (3.0% to 6.2%) in those with EF 20% or less, which yielded approximate annual rates of 0.9%, 0.9%, and 1.2%, respectively (Figure 2).

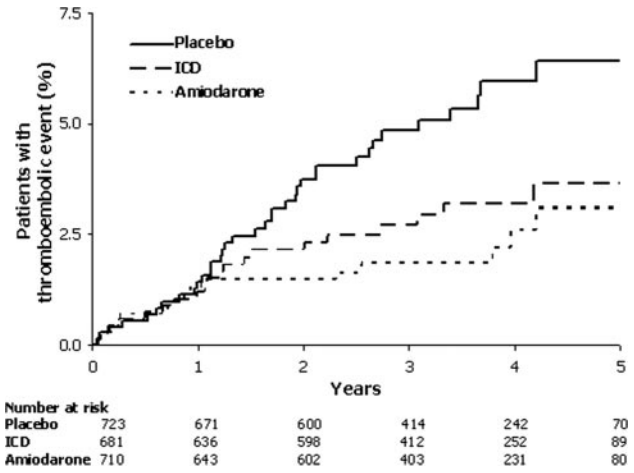

Figure 1. Proportion of patients with a thromboembolic event in each of the treatment arms (placebo, amiodarone, and ICD) in SCD-HeFT. Time zero is the day of randomization.

At baseline, 28% of patients (589) were taking warfarin, and 59% (1255) were taking aspirin. Antithrombotic therapy changed during follow-up, however, with 42% of patients who were not taking an anticoagulant at baseline beginning therapy subsequently, 13% of those taking an anticoagulant at entry discontinuing therapy, and 14% switching from 1 antithrombotic agent to another over the course of the study (Table 4). In the Cox model, warfarin was not significantly associated with reduced thromboembolism risk ($P=0.22$, HR, 0.62, 95% CI, 0.29 to 1.33), nor was aspirin therapy ($P=0.81$).

Postrandomization AF was detected in 9% of patients (189) and was less common in the amiodarone group (5% [39]) than in the ICD (12% [84]) or placebo (9% [66]) groups. When added to the Cox model, AF developed during the course of the trial was a significant predictor of thromboembolism ($P=0.008$, HR, 3.00, 95% CI, 1.33 to 6.75). Estimates for the treatment comparisons did not change materially with AF in the model (HR for ICD, 0.55; for amiodarone, 0.44 versus placebo), however, which indicates that a differential incidence of AF does not entirely explain the observed differences in thromboembolism based on treatment group assignment.

Discussion

The present analysis represents the most extensive published experience enumerating thromboembolism events in stable patients with moderately symptomatic systolic HF undergoing contemporary medical therapy. The most notable findings were as follows: (1) The incidence of thromboembolism in patients without AF or flutter was ≈1% per year; (2) the risk of thromboembolism was lower in patients randomized to treatment with amiodarone or an ICD device than in a control group otherwise comparably treated; and (3) there was a significant relationship between LV EF and thromboembolism.

The annual thromboembolism rate of 1.0% we observed is consistent with observations in other trials, in which ≈15% of patients had AF or atrial flutter.[6,7] In the population-based Framingham Heart Study, the risk of stroke was 4.1% per year in men and 2.8% per year in women with HF.[2] Among patients not treated with warfarin, the incidence of thromboembolism was 2.7% per year during 1068 patient-years in the Vasodilator Heart Failure Trial (V-HeFT) I and 2.1% per year during 1188 patient-years in V-HeFT II.

In the present large subset of the SCD-HeFT population, treatment with an ICD or amiodarone, hypertension at baseline, and LV EF were significant predictors of lower throm-

TABLE 3. Significant Predictors of Thromboembolism by Multivariable Model

Variable	*P*	HR (95% CI)
Treatment group	0.014*	0.57 (0.33 to 0.99) ICD vs placebo
		0.44 (0.24 to 0.80) Amiodarone vs placebo
Hypertension	0.021	1.86 (1.10 to 3.13)
LV EF	0.023	0.82 (0.69 to 0.97) per 5% increase
Warfarin therapy	0.22	0.62 (0.29 to 1.33)

*For a single overall test of any difference between either ICD or amiodarone and placebo.

boembolism risk. In V-HeFT, patients experiencing thromboembolism had lower peak exercise oxygen consumption ($P<0.03$ in V-HeFT I and $P<0.001$ in V-HeFT II), and EF was not a significant predictor ($P=0.10$ in V-HeFT I and $P=0.07$ in V-HeFT II). Among survivors of myocardial infarction in the Survival And Ventricular Enlargement (SAVE) study, however, the increased risk of stroke with declining EF was more impressive in women than in men.[3,8] A similar interaction with gender was observed in the Studies Of Left Ventricular Dysfunction (SOLVD), in which the relative risk for thromboembolism increased from 1.0 among women with EF ≥30% to 4.2 when EF was ≤10%.[2] When all participants in these studies are considered together, the risk of stroke appears to increase when the EF is <30%.

The incidence of thromboembolism in SCD-HeFT was significantly higher in the placebo group than in patients treated with amiodarone or shock-only defibrillation devices. After randomization, documented AF developed less often in the amiodarone group than in the placebo group, although self-limited episodes of paroxysmal AF may have gone undetected in patients treated with amiodarone. It is possible that amiodarone might reduce the risk of thromboembolism by preventing paroxysmal AF or promoting conversion to sinus rhythm.[9] Similarly, AF may have been detected more often in patients with cardioverter-defibrillators, and "inappropriate" shocks were sometimes delivered when AF was associated with a rapid rate of ventricular response. Early termination of episodes of AF may have contributed to a lower risk of thromboembolism in the ICD group. In other trials, however, strategies of rhythm control were not associated with reduced rates of thromboembolism in patients with AF.[7,8] Alternatively, given the relatively large number of patients in the present trial, this may be a finding of statistical significance whose clinical relevance needs to be assessed in another study.

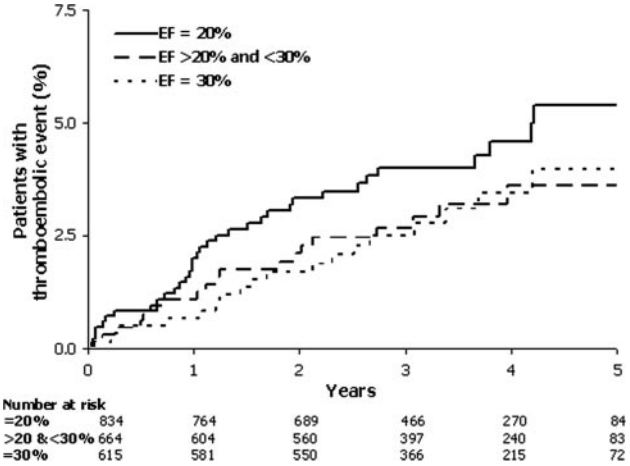

Figure 2. Proportion of patients with thromboembolic event in 3 strata of baseline EFs: ≤20%, between 20% and 30%, and 30% to 35%.

In theory, diseased ventricular myocardium might predispose to mural thrombus formation through mechanisms related to stasis or endocardial thrombogenesis, as is thought to occur in the dilated left atrium or dysfunctional atrial appendage of patients with AF. We found a significant relationship between EF and risk of thromboembolism; however, when transient ischemic attack was included as an end point, this relationship no longer existed (data not shown). It is therefore possible that ischemic stroke in patients with cardiomyopathy may be related to hypertension, atherosclerosis, and other disorders of the cerebral vasculature, rather than to cardiogenic embolism alone.[10]

Several potential limitations should be considered in the interpretation of these results. Determination of the incidence of thromboembolism was not a primary objective of SCD-

TABLE 4. Rates of Warfarin Use and AF by Treatment Group and by Year of Follow-Up

	Year of Follow-Up				
	1	2	3	4	5
Amiodarone					
n	708	592	498	322	157
Warfarin	34 (240)	29 (173)	28 (141)	29 (93)	30 (47)
ASA	68 (480)	66 (392)	65 (323)	61 (197)	61 (95)
AF/AFl	2 (11)	1 (8)	3 (14)	4 (13)	3 (5)
Placebo					
n	720	614	516	345	178
Warfarin	32 (229)	32 (195)	33 (170)	36 (123)	35 (63)
ASA	67 (483)	65 (398)	62 (319)	61 (209)	61 (108)
AF/AFl	3 (21)	4 (24)	5 (25)	3 (11)	3 (6)
ICD					
n	681	621	564	363	210
Warfarin	31 (214)	31 (194)	29 (166)	32 (115)	35 (74)
ASA	67 (458)	64 (398)	63 (355)	62 (224)	60 (127)
AF/AFl	5 (32)	4 (25)	5 (31)	4 (14)	7 (14)

Values are expressed as percent (n) as appropriate. ASA indicates aspirin; AFl, atrial flutter.

HeFT, and the findings must be considered exploratory. Criteria for diagnosis of thromboembolism events were not standardized; reported events were not subjected to blinded review and are therefore subject to diagnostic bias. Despite these constraints, we did not find important differences among the participating institutions in rates of diagnosis of stroke or other thromboembolism event. The occurrence of paroxysmal AF was incompletely characterized, and differences in observed rates of thromboembolism between treatment groups might be explained in part by differences in the frequency or duration of episodes of this arrhythmia. Finally, the relatively small number of events makes it likely that some predictors of thromboembolism in patients with HF could not be detected by multivariable analysis.

Conclusions

In the SCD-HeFT cohort of patients with stable, moderately symptomatic HF and EF ≤0.35%, the incidence of clinical thromboembolism events was low and dependent on the level of LV dysfunction at baseline. Rates of thromboembolism were lower in patients randomized to amiodarone or ICD devices than in those randomized to placebo. Although some trends are evident in the data to suggest that rates of thromboembolism are lower in patients who do not develop AF over time, this factor did not account for the observed treatment group differences in thromboembolism rates.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The overall risk of thromboembolism in chronic heart failure is poorly defined. Similarly, risk factors for thromboembolism in chronic heart failure in the absence of atrial fibrillation are poorly defined. This analysis of 2114 patients with no history of documented atrial fibrillation or flutter at baseline who were part of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial demonstrates that the risk of thromboembolism (stroke or pulmonary or peripheral embolization) is ≈1% per year. Patients in SCD-HeFT who were randomized to an implantable cardioverter defibrillator or amiodarone had a significantly lower incidence of thromboembolic events, and there was a significant relationship of thromboembolism and lower ejection fraction. This is the only analysis of thromboembolism events in a chronic heart failure cohort to demonstrate these relationships. Optimal preventive strategies are currently being studied in the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial.

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