Anticoagulation in Heart Failure

고신의대

차 태준

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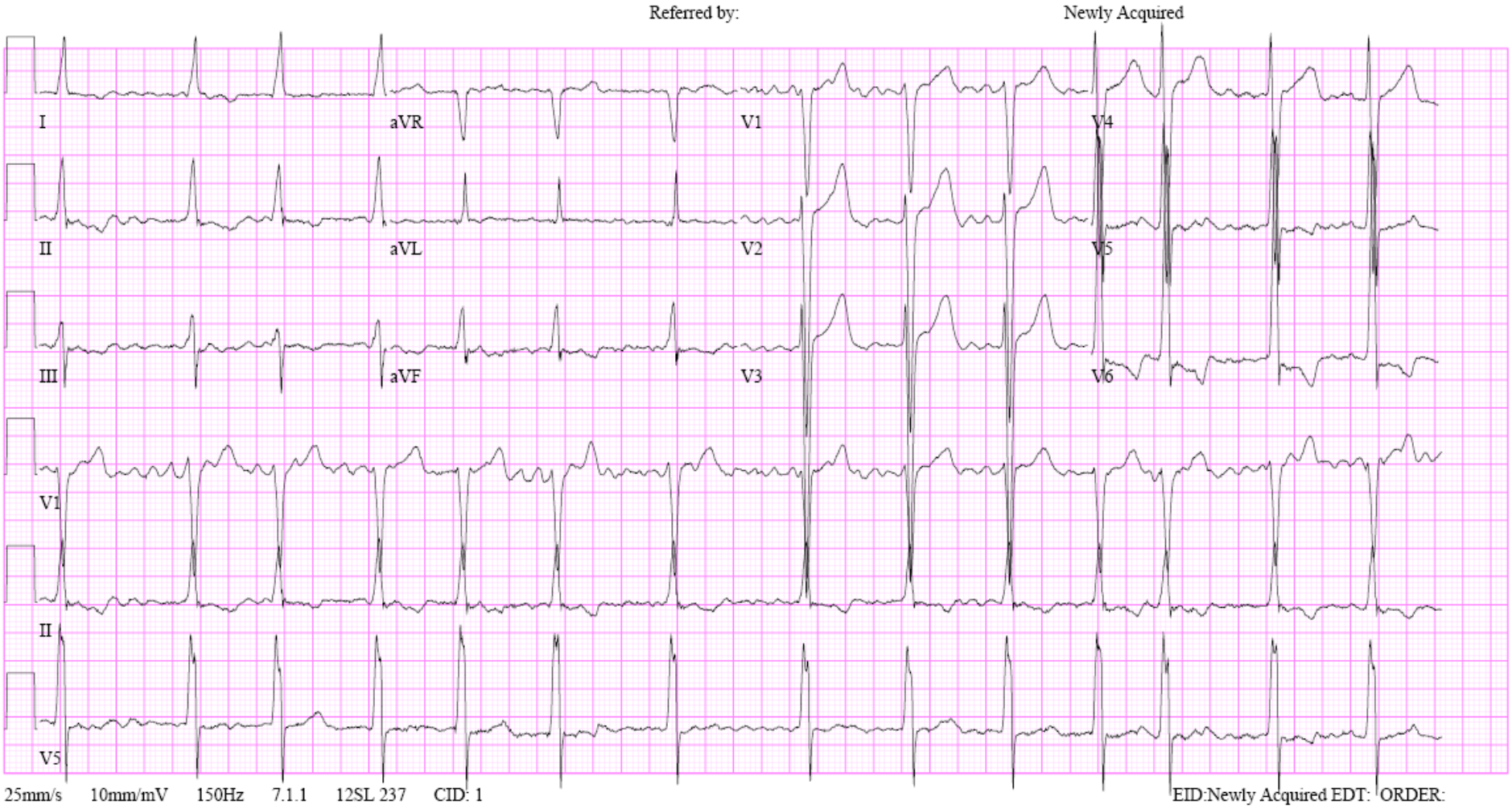
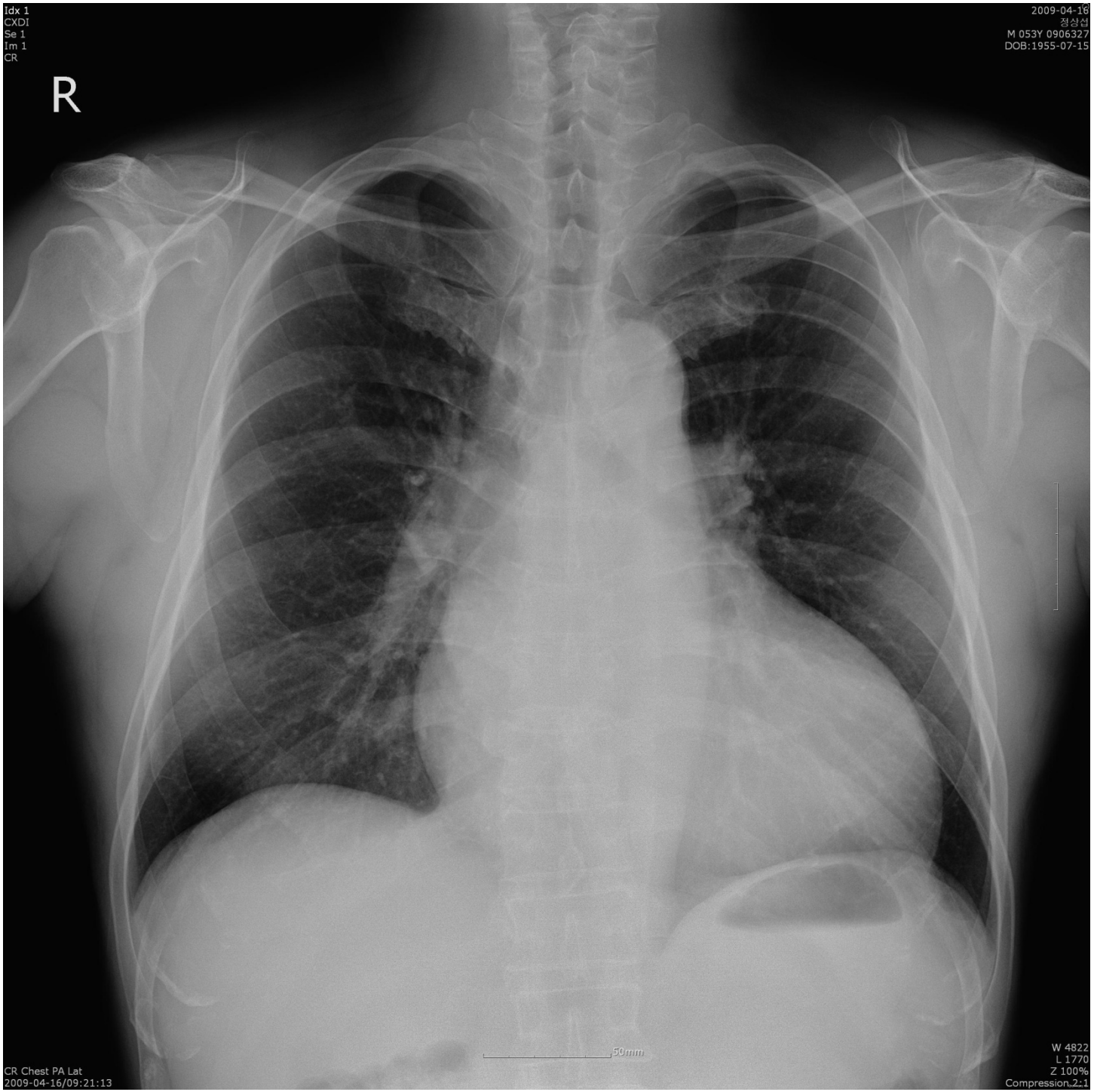
Apr/16/2009

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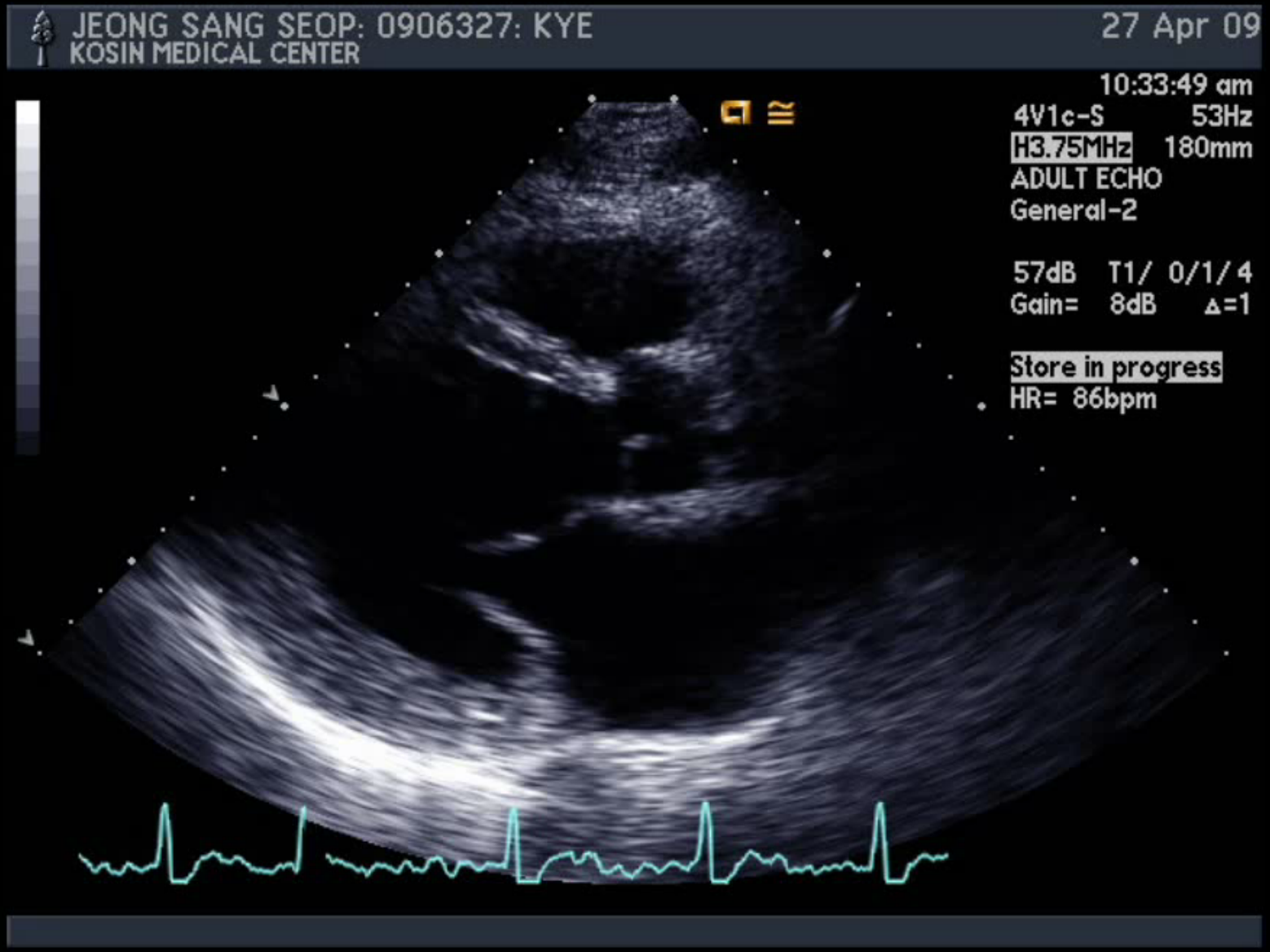

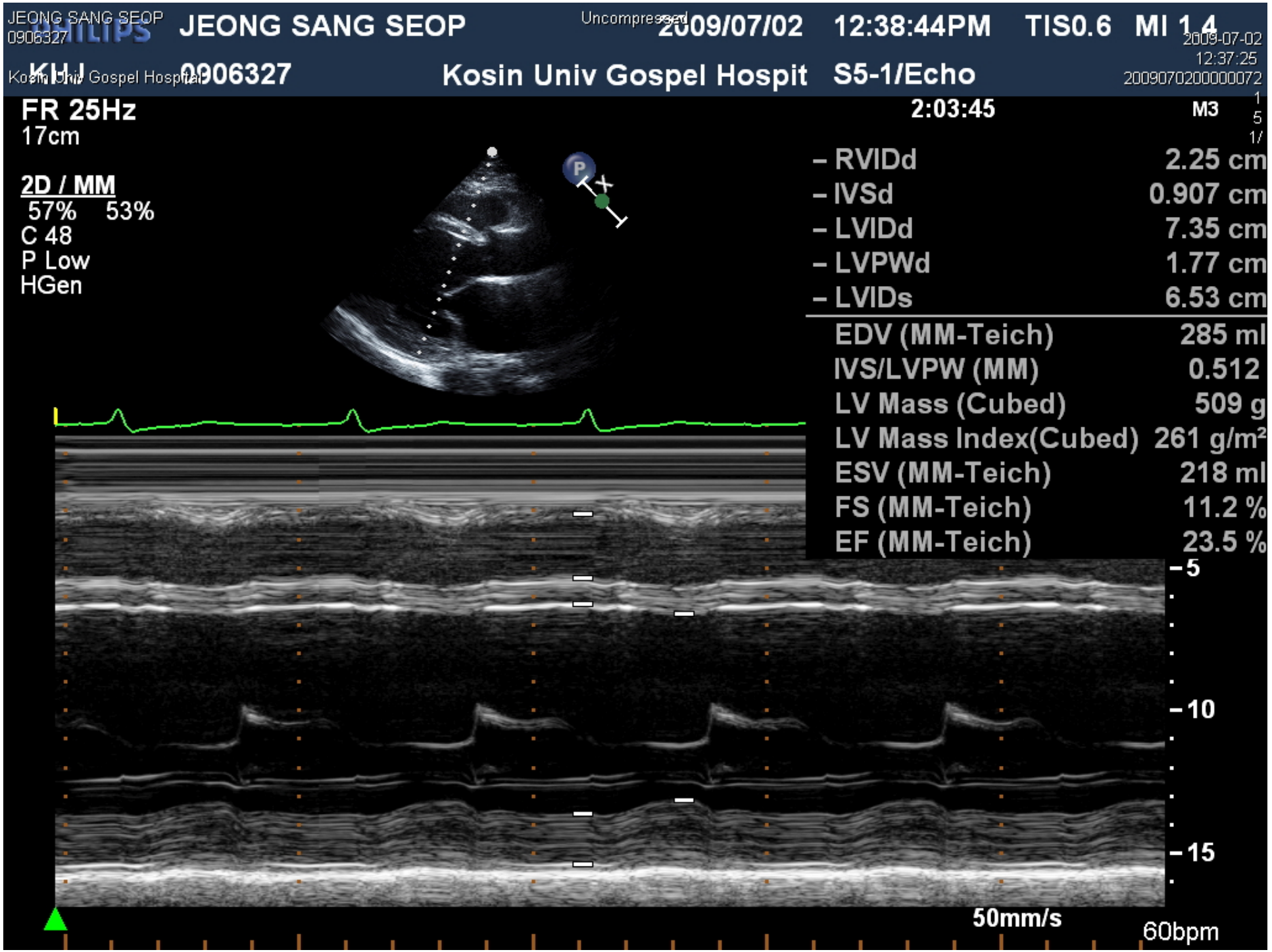
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– LVPWd 1.77 cm
– LVIDs 6.53 cm
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IVS/LVPW (MM) 0.512
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LV Mass Index(Cubed) 261 g/m²
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EF (MM-Teich) 23.5 %
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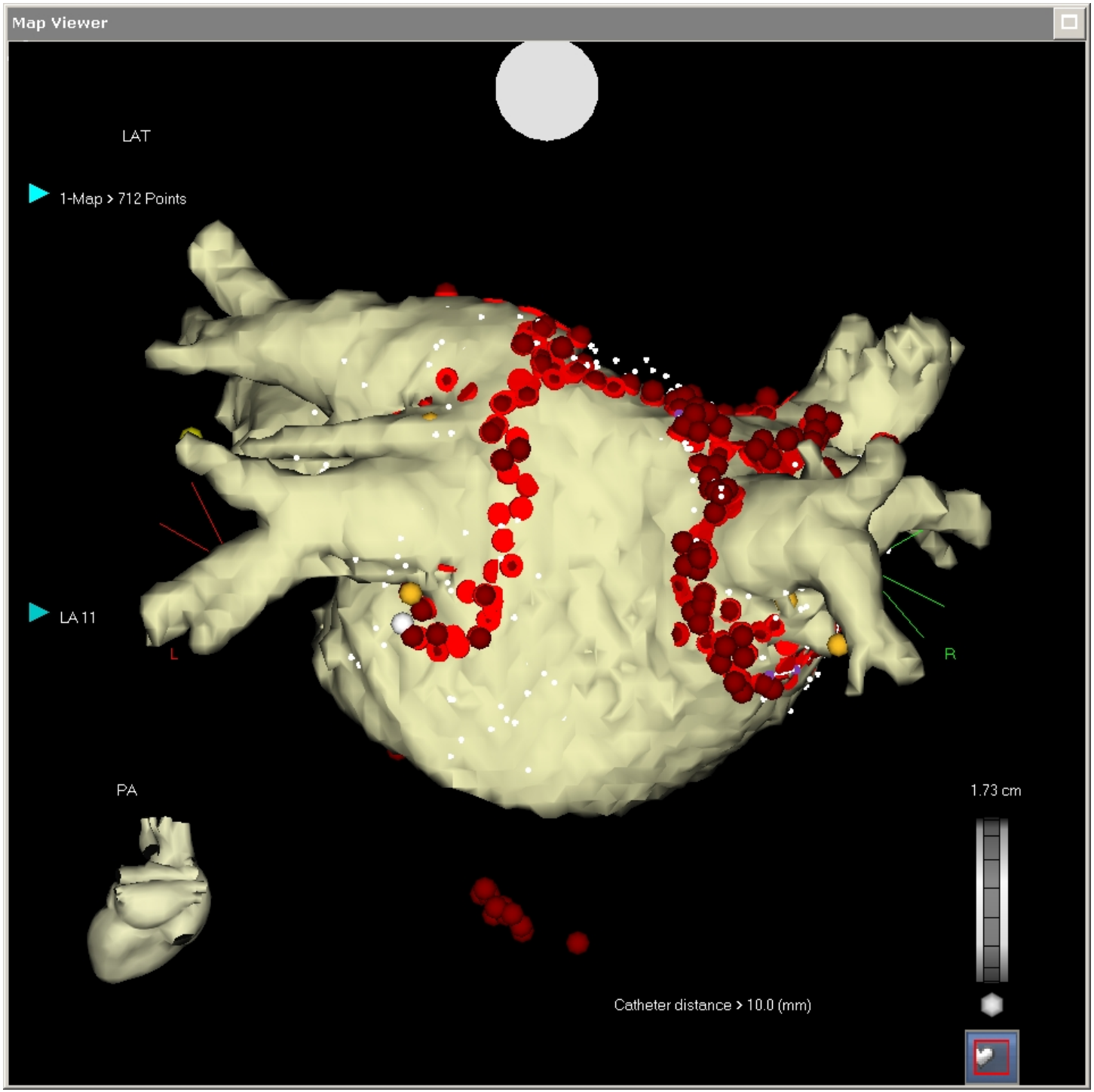
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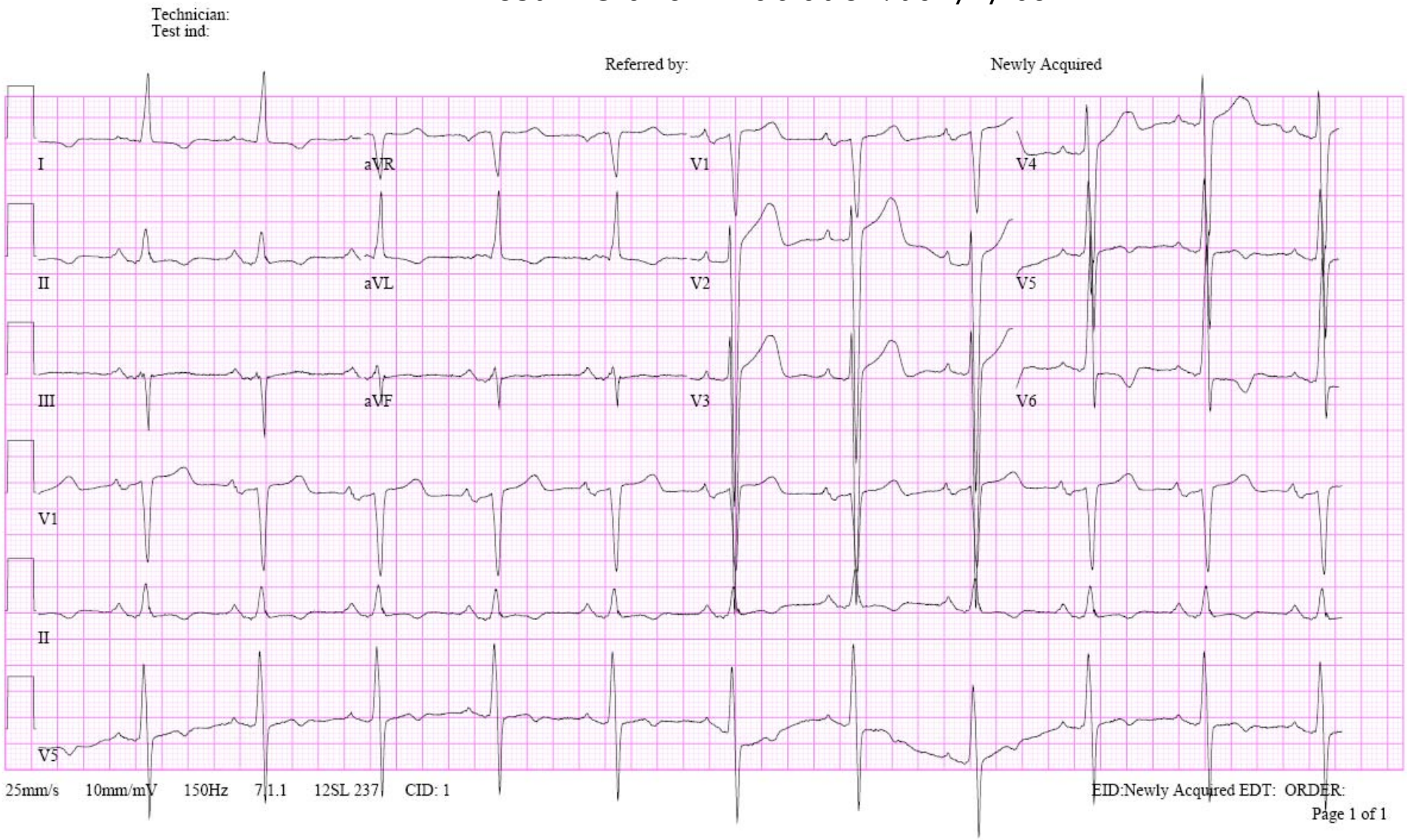

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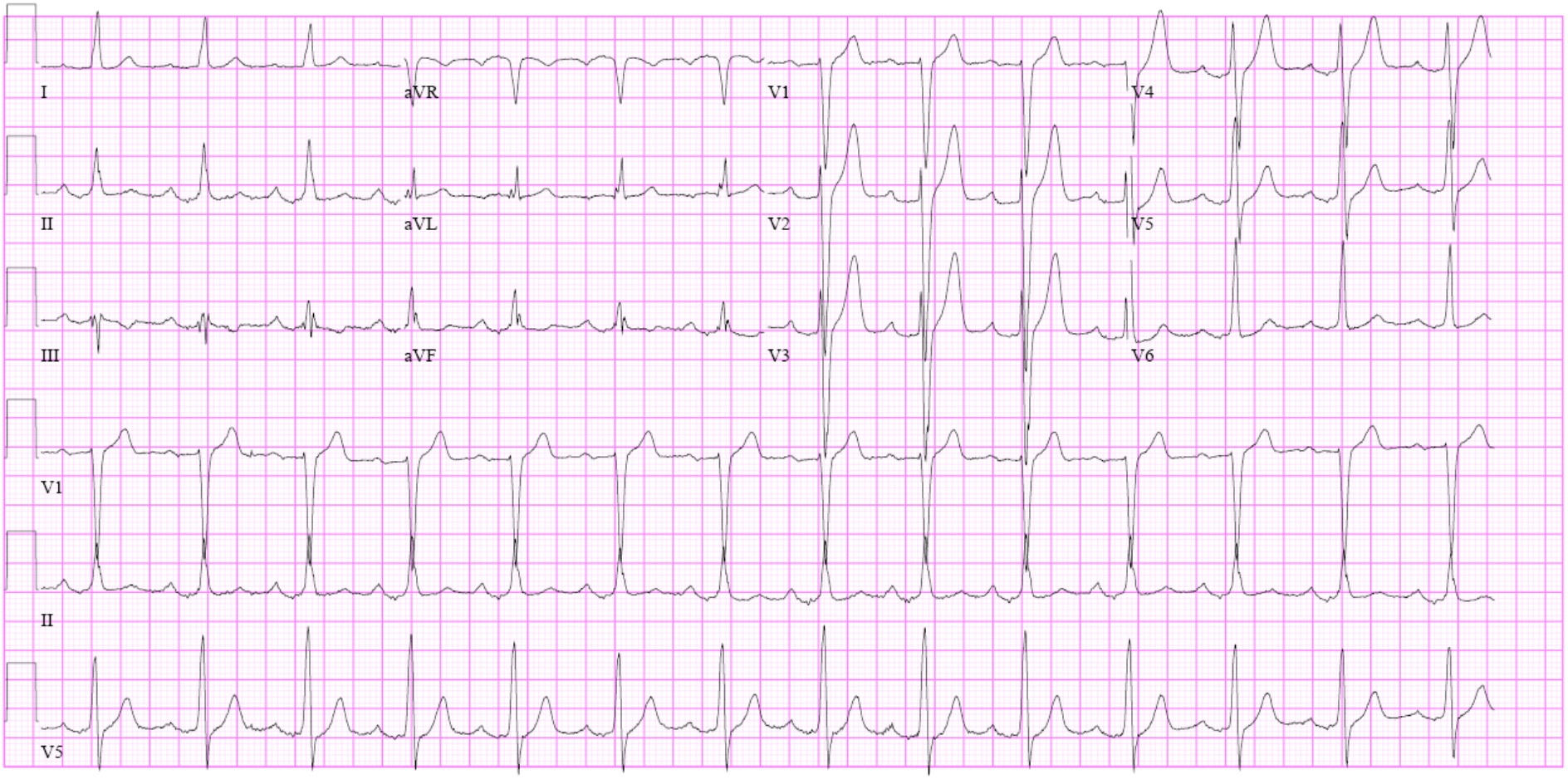

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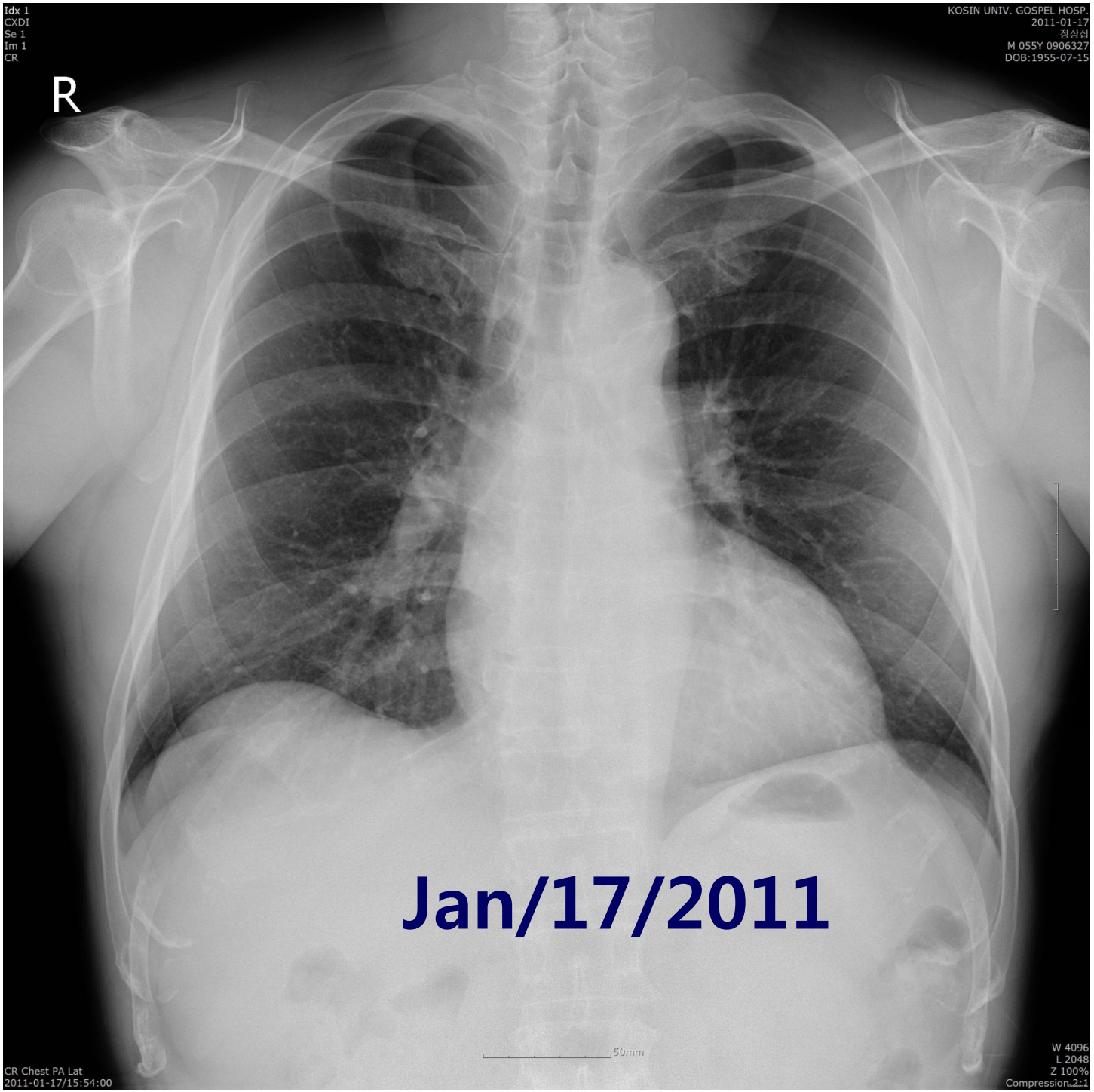
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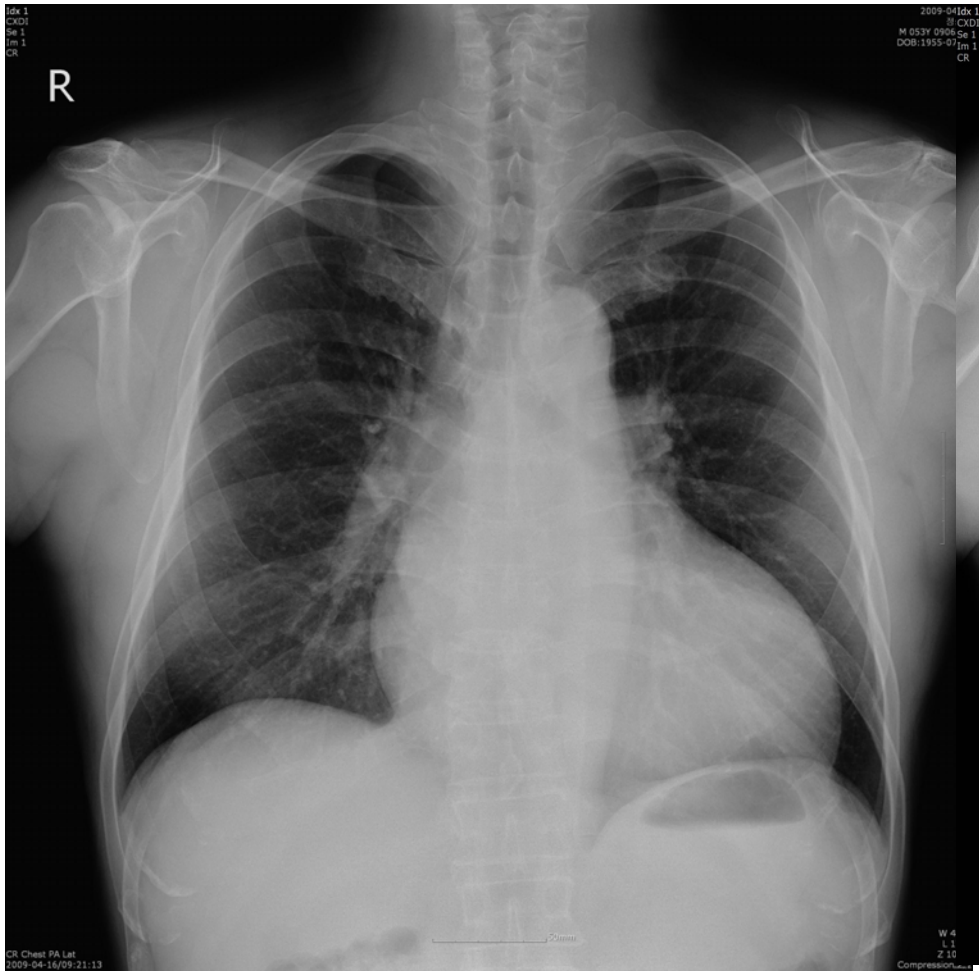

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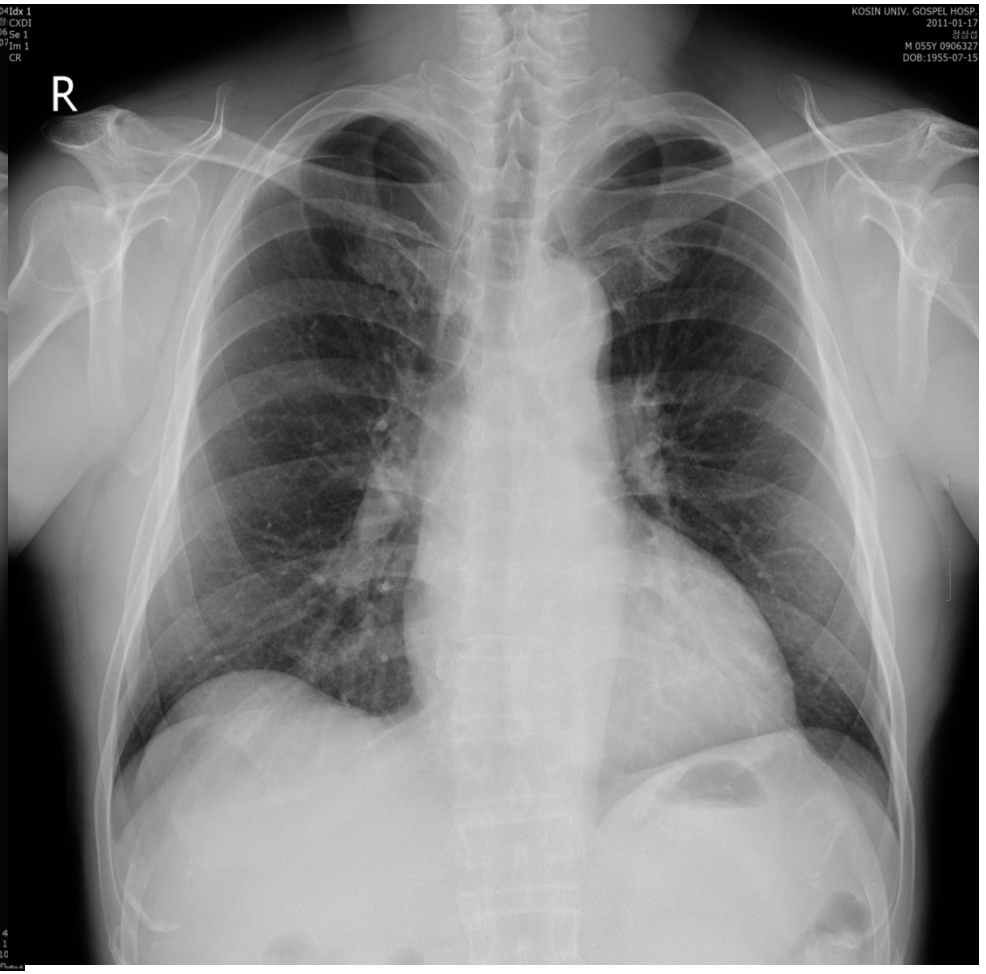

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- **With lifetime risks of one in four and one in five, respectively, nonvalvular atrial fibrillation (NVAF) and heart failure (HF) present major public health burdens in terms of morbidity, mortality, and cost to health systems, with future increase predicted.**

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March 15, 1998:749–53

Warfarin Anticoagulation and Survival: A Cohort Analysis From the Studies of Left Ventricular Dysfunction

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Boston, Massachusetts

Table 1. Baseline Clinical Characteristics and Drug Therapy of Warfarin Users and Nonusers in the Studies of Left Ventricular Dysfunction Combined Trial*

	Warfarin Users (n = 861)	Warfarin Nonusers (n = 5,652)	p Value
Randomization group (% randomized to enalapril)	48.6	50.2	0.4
Age (years)	58.5 ± 10.8	59.7 ± 10.1	< 0.0001
Men	87.0	85.4	0.2
EF (%)	26.2 ± 6.6	27.1 ± 6.2	< 0.0001
NYHA functional class			< 0.0001
I	41.8	46.3	
II	43.4	41.8	
III	13.2	11.3	
IV	1.5	0.5	
History of	28.9	36.3	0.0002
Atrial fibrillation	19.3	4.5	< 0.0001
Cerebrovascular disease	13.8	5.5	< 0.0001
Diabetes mellitus	14.6	20.0	0.0001
Hypertension	34.4	39.8	0.002
Smoking	78.2	78.3	0.9
Etiology			
Ischemic	67.6	80.6	< 0.0001
Nonischemic	32.4	19.4	< 0.0001
Baseline drug therapy			
Antiarrhythmic agents	24	16.7	< 0.0001
Antiplatelet agents	17.7	50.9	< 0.0001
Beta-blockers	13.3	18.6	< 0.0001
Digitalis	50.3	30.5	< 0.0001
Diuretic agents	48.8	41.8	<0.0001
Nitrates	32	35.1	0.07

*Two hundred eighty-four patients had missing baseline data. Data are presented as mean value ± SD or percentage of patients. EF = ejection fraction; NYHA = New York Heart Association.

Table 2. Unadjusted Risk and Adjusted Hazard Ratios for All-Cause Mortality and Death or Hospital Admission for Heart Failure in Warfarin Users Versus Nonusers in the Studies of Left Ventricular Dysfunction Combined Trial

End Point	W+ (%)	W− (%)	RR (95% CI)	p Value	HR (95% CI)	p Value
All-cause mortality	24.4	23.6	1.03 (0.91–1.17)	0.6	0.76 (0.65–0.89)	0.0006
Death or hospital admission for HF	35.5	33.8	1.05 (0.95–1.16)	0.3	0.82 (0.72–0.93)	0.002

CI = confidence interval; HF = heart failure; HR = adjusted hazard ratio; RR = relative risk; W+ = warfarin users; W− = warfarin nonusers.

Table 3. Unadjusted Relative Risk and Adjusted Hazard Ratios for Causes of Death in Warfarin Users Versus Nonusers in the Studies of Left Ventricular Dysfunction Combined Trial

End Point	W+ (%)	W− (%)	RR (95% CI)	p Value	HR (95% CI)	p Value
Cardiovascular deaths	20.6	20.9	0.99 (0.86–1.14)	0.9	0.72 (0.61–0.86)	0.0002
Sudden death not preceded by HF	5.2	6.3	0.83 (0.61–1.12)	0.2	0.66 (0.47–0.91)	0.01
Death associated with HF	10.9	9.8	1.12 (0.91–1.38)	0.3	0.77 (0.61–0.98)	0.03
Fatal MI	2.3	3.1	0.76 (0.48–1.20)	0.2	0.55 (0.34–0.90)	0.02
Noncardiac vascular deaths	1.6	1.2	1.33 (0.75–2.36)	0.3	0.99 (0.53–1.64)	1.00
Fatal stroke	0.8	0.6	1.28 (0.57–2.86)	0.6	0.80 (0.32–1.97)	0.6
Fatal pulmonary embolism	0.6	0.4	1.64 (0.62–4.37)	0.3	1.65 (0.57–4.78)	0.4
Other vascular deaths	0.2	0.2	1.01 (0.23–4.46)	1.0	0.77 (0.16–3.71)	0.7

MI = myocardial infarction; other abbreviations as in Table 2.

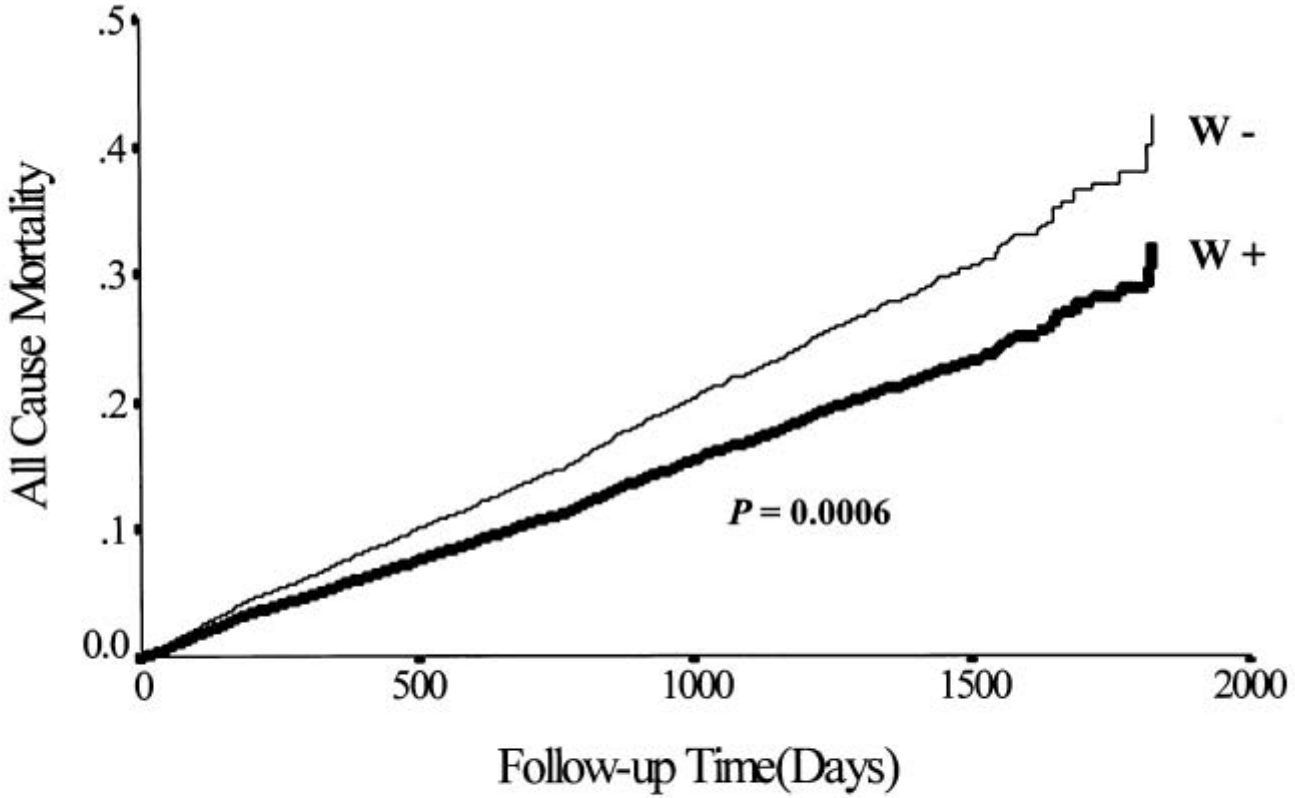


Figure 1. Adjusted all-cause mortality in warfarin users (W+) and nonusers (W−) in the combined SOLVD trial.

Risk of Thromboembolism in Heart Failure

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

Ronald S. Freudenberger, MD; Anne S. Hellkamp, MS; Jonathan L. Halperin, MD; Jeanne Poole, MD; Jill Anderson, BSN; George Johnson, BSEE; Daniel B. Mark, MD, MPH; Kerry L. Lee, PhD; Gust H. Bardy, MD; for the SCD-HeFT Investigators

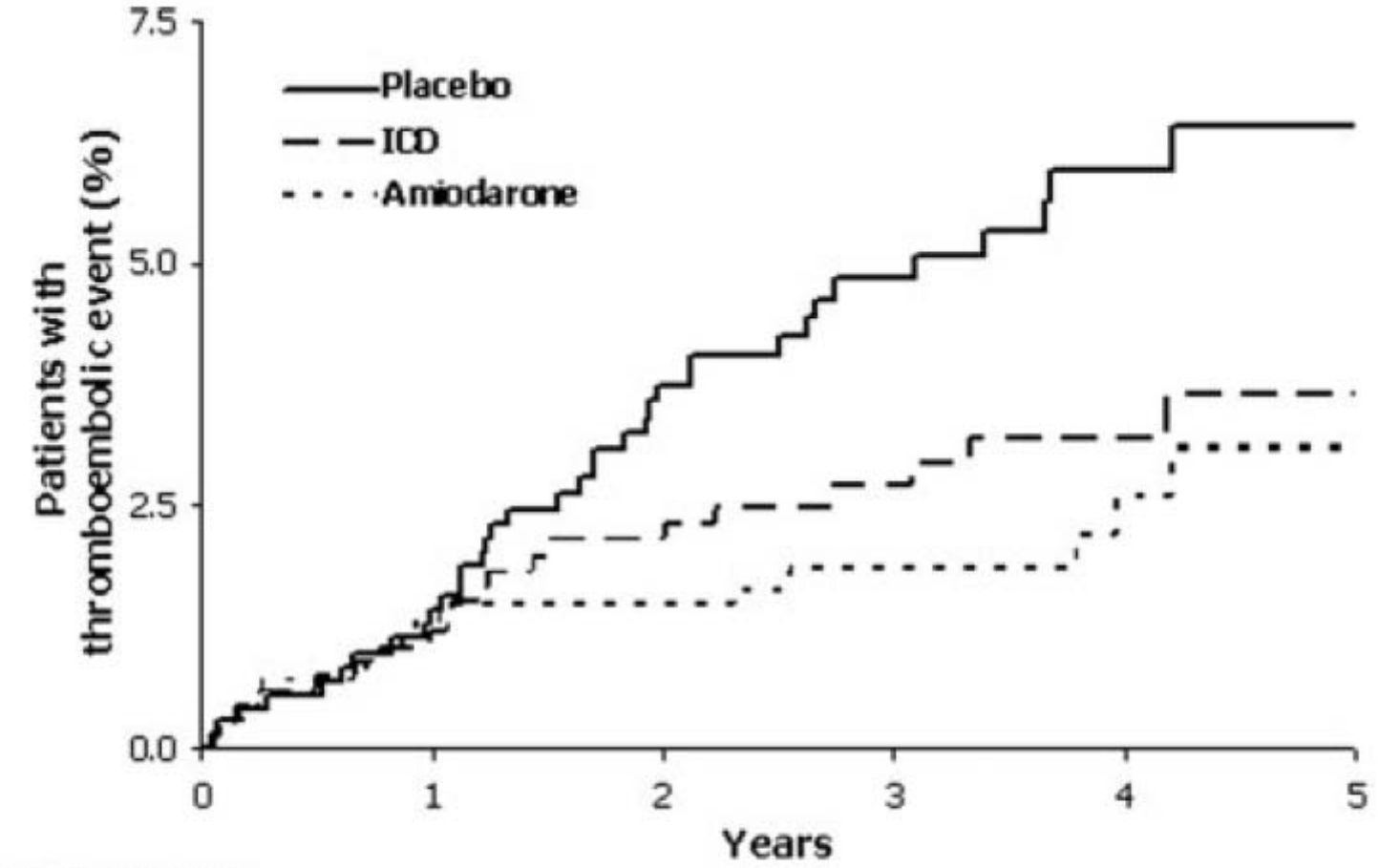
Background—In patients with heart failure, rates of clinically apparent stroke range from 1.3% to 3.5% per year. Little is known about the incidence and risk factors in the absence of atrial fibrillation. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 2521 patients with moderate heart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

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



Number at risk						
Placebo	723	671	600	414	242	70
ICD	681	636	598	412	252	89
Amiodarone	710	643	602	403	231	80

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.

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.

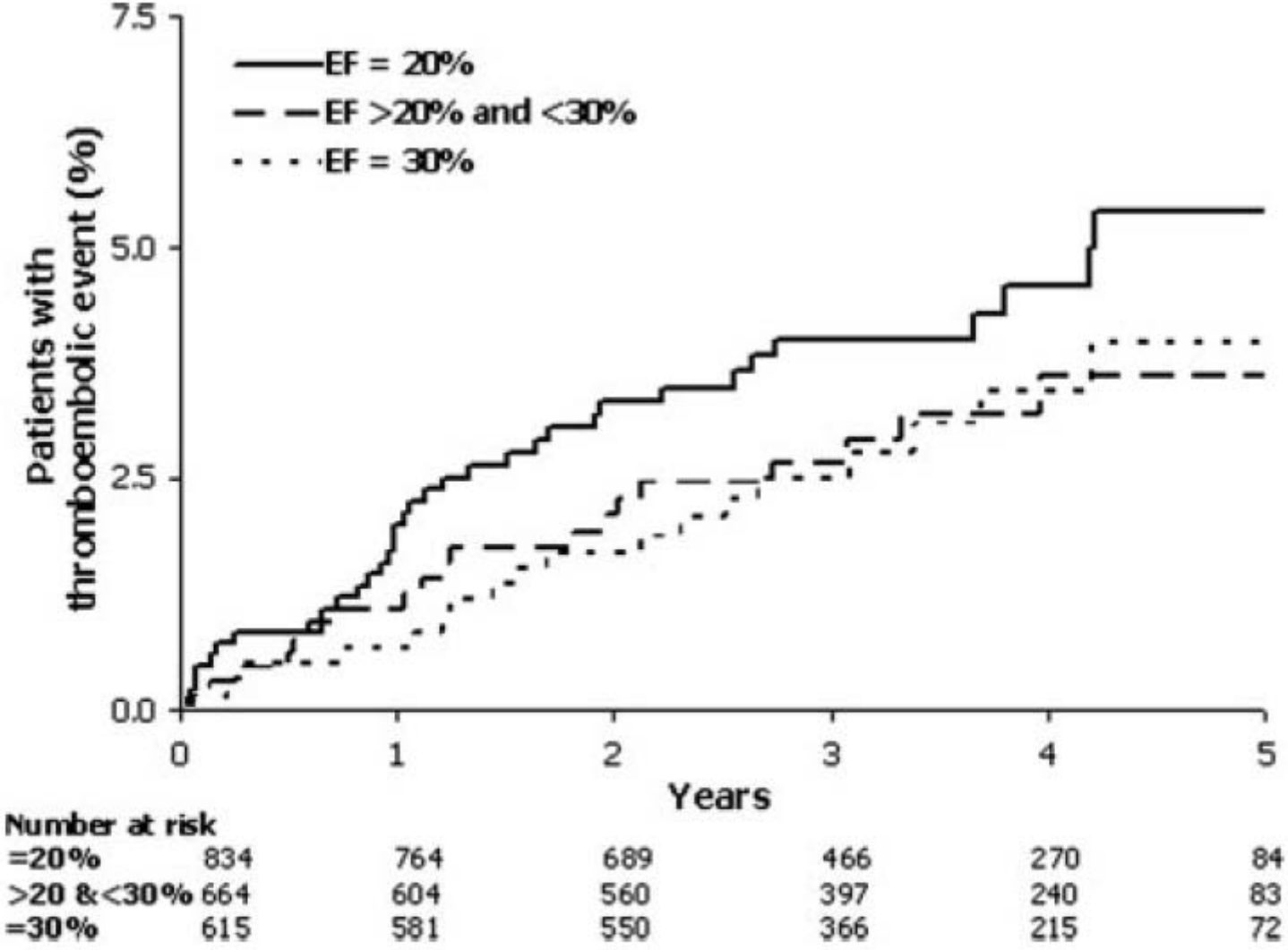


Figure 2. Proportion of patients with thromboembolic event in 3 strata of baseline EFs: ≤20%, between 20% and 30%, and 30% to 35%.

VENTRICULAR DYSFUNCTION AND THE RISK OF STROKE AFTER MYOCARDIAL INFARCTION

EVAN LOH, M.D., MARTIN ST. JOHN SUTTON, M.D., CHUAN-CHUAN C. WUN, PH.D., JEAN L. ROULEAU, M.D., GREG C. FLAKER, M.D., STEPHEN S. GOTTLIEB, M.D., GERVASIO A. LAMAS, M.D., LEMUEL A. MOYÉ, PH.D., SAMUEL Z. GOLDHABER, M.D., AND MARC A. PFEFFER, M.D., PH.D.

N Engl J Med 1997;336:251-7

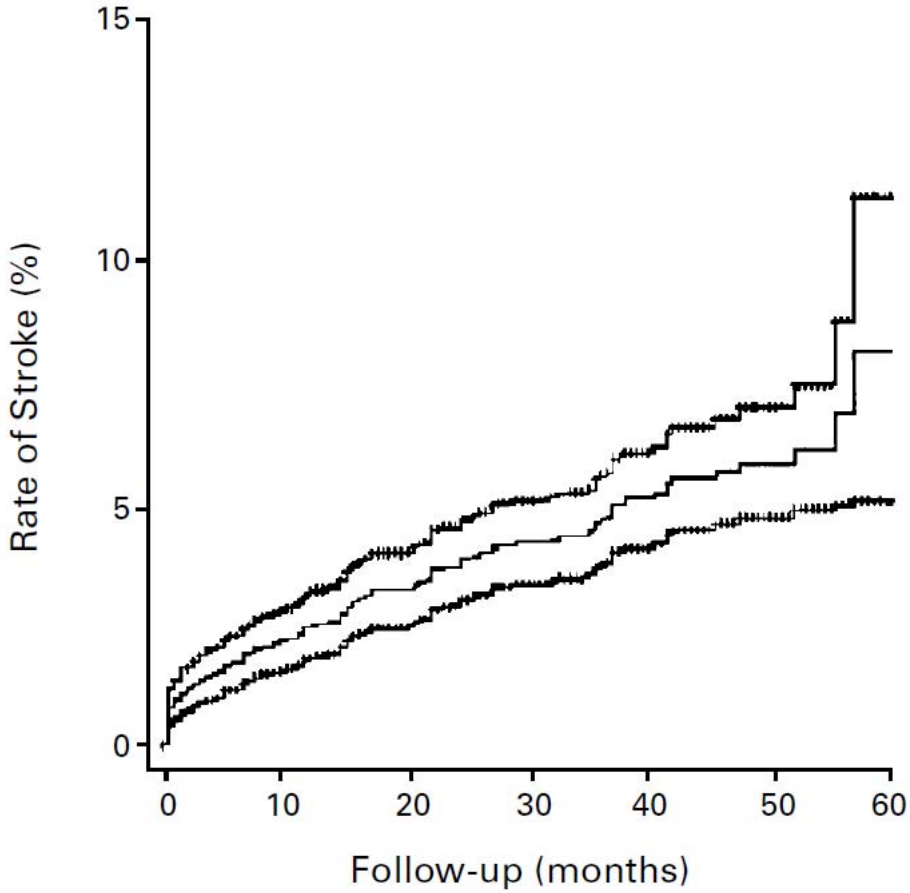


Figure 1. Kaplan–Meier Estimate of the Cumulative Rate of Stroke among 2231 Patients in the SAVE Trial.

A total of 103 patients (4.6 percent) had strokes during follow-up. The estimated cumulative rate of stroke over a five-year period was 8.1 percent. The annualized incidence was 1.5 percent per patient-year of follow-up. The top and bottom curves show the 95 percent confidence interval for the rate of stroke.

TABLE 1. BASE-LINE CLINICAL CHARACTERISTICS OF PATIENTS WHO SUBSEQUENTLY HAD STROKE AND THOSE WHO DID NOT.*

CHARACTERISTIC	WITH STROKE (N = 103)	WITHOUT STROKE (N = 2128)	P VALUE†
Age — yr	63 ± 9	59 ± 11	<0.001
LVEF — %	29 ± 7	31 ± 7	0.01
Male sex — no. (%)	83 (81)	1758 (83)	NS
History of diabetes — no. (%)	30 (29)	462 (22)	0.08
History of hypertension — no. (%)	44 (43)	793 (37)	NS
Current smoking — no. (%)	46 (45)	879 (41)	NS
Previous myocardial infarction — no. (%)	42 (41)	750 (35)	NS
Atrial fibrillation or flutter — no. (%)	17 (16)	210 (10)	0.03
Anticoagulant therapy — no. (%)	39 (38)	593 (28)	0.03
Aspirin use — no. (%)	47 (46)	1263 (59)	<0.01
Location of infarction — no. (%)			
Anterior Q-wave	59 (57)	1170 (55)	NS
Inferior Q-wave	18 (17)	376 (18)	NS
Anterior and inferior Q-wave	11 (11)	250 (12)	NS
Non–Q-wave	8 (8)	208 (10)	NS
Other	7 (7)	124 (6)	NS
Thrombolytic therapy — no. (%)	25 (24)	744 (35)	0.03

*Plus–minus values are means ±SD. Characteristics are listed as assessed at the time of randomization.

†P values were calculated by the two-sample t-test for age and LVEF and by the chi-square test for the other variables. NS denotes not significant.

TABLE 2. RISK FACTORS FOR STROKE IN THE MULTIVARIATE ANALYSIS.*

RISK FACTOR	RELATIVE RISK (95% CI)	WALD CHI-SQUARE	P VALUE†
LVEF (for each decrease of 5 percentage points)	1.18 (1.02–1.36)	4.71	0.03
Age (for each increase of 5 yr)	1.18 (1.05–1.33)	7.80	<0.001
Anticoagulant therapy during follow-up	0.19 (0.13–0.27)	81.95	<0.001
Aspirin use during follow-up	0.44 (0.29–0.65)	16.61	<0.001
Current smoking at randomization	1.40 (0.89–2.20)	2.12	NS
History of hypertension	1.12 (0.72–1.73)	0.25	NS
History of diabetes	1.34 (0.83–2.14)	1.44	NS
Previous myocardial infarction	0.97 (0.62–1.51)	0.02	NS
Recurrent myocardial infarction	0.87 (0.47–1.59)	0.22	NS
Assignment to captopril	1.28 (0.84–1.93)	1.27	NS
Atrial fibrillation or flutter before randomization	1.62 (0.93–2.78)	2.94	NS
Thrombolytic therapy	0.62 (0.37–1.02)	3.51	0.061

*The time-dependent covariates anticoagulant therapy, aspirin use, and recurrent myocardial infarction were assessed at the visit just before the stroke occurred. CI denotes confidence interval.

†P values were determined in the multivariate Cox regression analysis. NS denotes not significant.

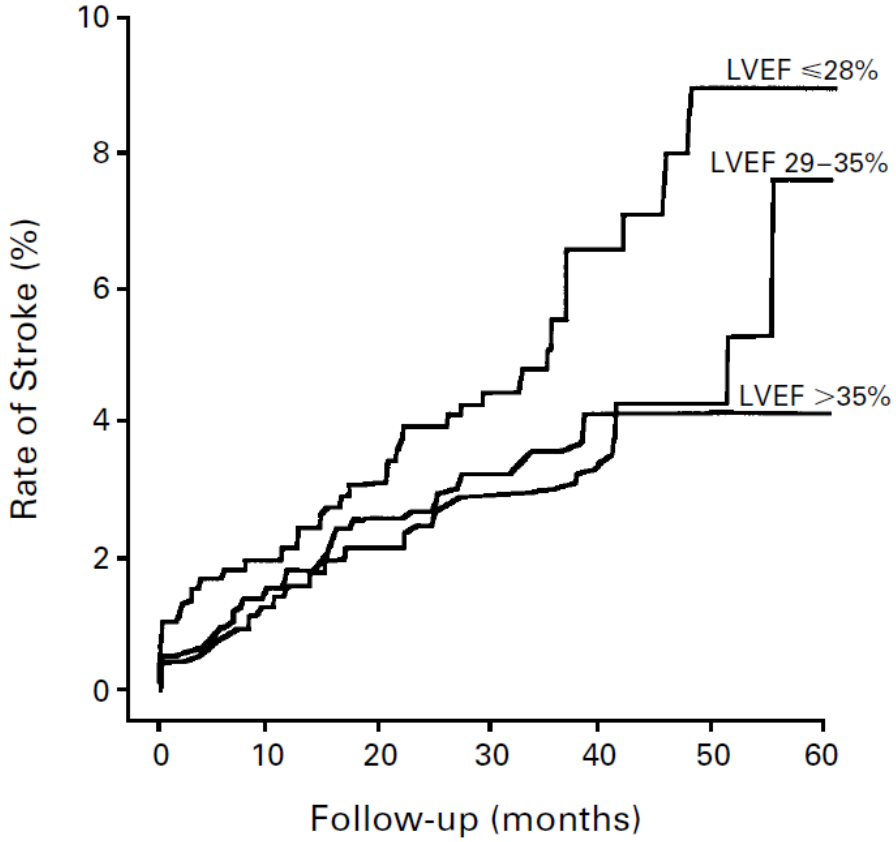


Figure 2. Cumulative Rate of Stroke in the SAVE Trial, According to the Left Ventricular Ejection Fraction (LVEF).

The patients were divided into three subgroups: those with an LVEF of ≤28 percent (n=724), those with an LVEF of 29 to 35 percent (n=817), and those with an LVEF >35 percent (n=690). The cumulative rates of stroke in these subgroups were 8.9 percent, 7.8 percent, and 4.1 percent, respectively. When the group with LVEF values above 35 percent was used as the reference category, the relative risk of stroke was 1.15 (95 percent confidence interval, 0.69 to 1.91; P not significant) for patients with LVEF values of 29 to 35 percent and 1.86 (95 percent confidence interval, 1.15 to 3.04; P=0.01) for patients with LVEF values of ≤28 percent.

The Warfarin/Aspirin Study in Heart failure (WASH): A randomized trial comparing antithrombotic strategies for patients with heart failure

J. G. F. Cleland, MD,[a] I. Findlay, MD,[b] S. Jafri, MD,[c] G. Sutton, MD,[d] R. Falk, MD,[e] C. Bulpitt, MD,[f] C. Prentice, MD,[g] I. Ford, MD,[h] Adele Trainer, MD,[h] and P. A. Poole-Wilson, MD[i] ***Hull, Paisley, London, Leeds, and Glasgow, United Kingdom, Detroit, Mich, and Boston, Mass***

Background Heart failure is commonly associated with vascular disease and a high rate of athero-thrombotic events, but the risks and benefits of antithrombotic therapy are unknown.

Methods The current study was an open-label, randomized, controlled trial comparing no antithrombotic therapy, aspirin (300 mg/day), and warfarin (target international normalized ratio 2.5) in patients with heart failure and left ventricular systolic dysfunction requiring diuretic therapy. The primary objective was to demonstrate the feasibility and inform the design of a larger outcome study. The primary clinical outcome was death, nonfatal myocardial infarction, or nonfatal stroke.

Results Two hundred seventy-nine patients were randomized and 627 patient-years exposure were accumulated over a mean follow-up time of 27 ± 1 months. Twenty-six (26%), 29 (32%), and 23 (26%) patients randomized to no antithrombotic treatment, aspirin, and warfarin, respectively, reached the primary outcome (ns). There were trends to a worse outcome among those randomized to aspirin for a number of secondary outcomes. Significantly ($P = .044$) more patients randomized to aspirin were hospitalized for cardiovascular reasons, especially worsening heart failure.

Conclusions The Warfarin/Aspirin Study in Heart failure (WASH) provides no evidence that aspirin is effective or safe in patients with heart failure. The benefits of warfarin for patients with heart failure in sinus rhythm have not been established. Antithrombotic therapy in patients with heart failure is not evidence based but commonly contributes to polypharmacy. (Am Heart J 2004;148:157–64.)

Table I. Patient characteristics

Analysis	No ATT	Aspirin	Warfarin
No.	99	91	89
Patient-years at risk (y)	217	211	199
Demography			
Age (y)	61	65	62
Weight (kg)	80	79	79
Female (%)	28	25	24
NYHA III/IV (%)	28/3	27/2	25/1
Principle cause of heart failure (%)			
Ischemic heart disease	60	63	56
Prior myocardial infarction	44	52	42
Dilated cardiomyopathy	11	15	20
Hypertensive heart disease	8	2	2
Uncertain etiology	12	14	17
Other	9	5	4
Concomitant disease (%)			
Atrial fibrillation	4	7	7
Diabetes	24	19	17
History of hypertension	37	30	34
Investigation			
Systolic/diastolic BP (mm Hg)	127/77	124/76	126/77
Serum sodium (mmol/L)	139	140	140
Serum creatinine (umol/L)	100	113	108
LV end-diastolic dimension (mm)	66	66	65
Fractional shortening (%)	16	15	16
Therapy (%)			
Loop diuretics	93	96	98
Thiazide diuretic	7	9	1
Digoxin	32	38	37
ACE inhibitors	94	88	90
β-Blockers	14	8	10
Calcium antagonist	18	15	20
Amiodarone	7	5	9
Baseline aspirin	46	42	56
Baseline warfarin	2	9	4

For the continuous variables the mean of each group is presented, with the exception of serum sodium and serum creatinine where the median of each group is presented. *No ATT,* No anti-thrombotic therapy.

Table II. Primary outcome cluster

Analysis	No ATT	Aspirin	Warfarin
Intention to treat analysis			
No.	99	91	89
Patient-years at risk	217	211	199
Patient-years alive	189 (87.1%)	181 (85.8%)	172 (86.4%)
Composite outcome	26 (26%)	29 (32%)	23 (26%)
Death†	21 [19]	27 [25]	22 [22]
Myocardial infarction†	7 [6]	8 [2]	3 [1]
Stroke†	2 [1]	2 [2]	0 [0]
Hazard ratio (95% CI)‡	0.96 (0.60, 1.54)	1.16 (0.74, 1.85)	0.88 (0.54, 1.43)
Intention to treat analysis, sinus rhythm patients only			
No.	94	80	80
Composite	24 (26%)	26 (33%)	21 (26%)
Death	19	24	20
Myocardial infarction†	7	7	3
Stroke†	2	2	0
On-therapy analysis*			
Patient-years exposure (and % of time alive)	152 (80%)	163 (90%)	140 (81%)
Composite	20 (20%)	20 (22%)	16 (18%)
Death	14 [14]	17 [17]	15 [15]
Myocardial infarction	6 [5]	7 [2]	3 [1]
Stroke	2 [1]	1 [1]	0 [0]
Hazard ratio (95% CI)‡	1.09 (0.63, 1.89)	1.02 (0.59, 1.75)	0.89 (0.50, 1.61)

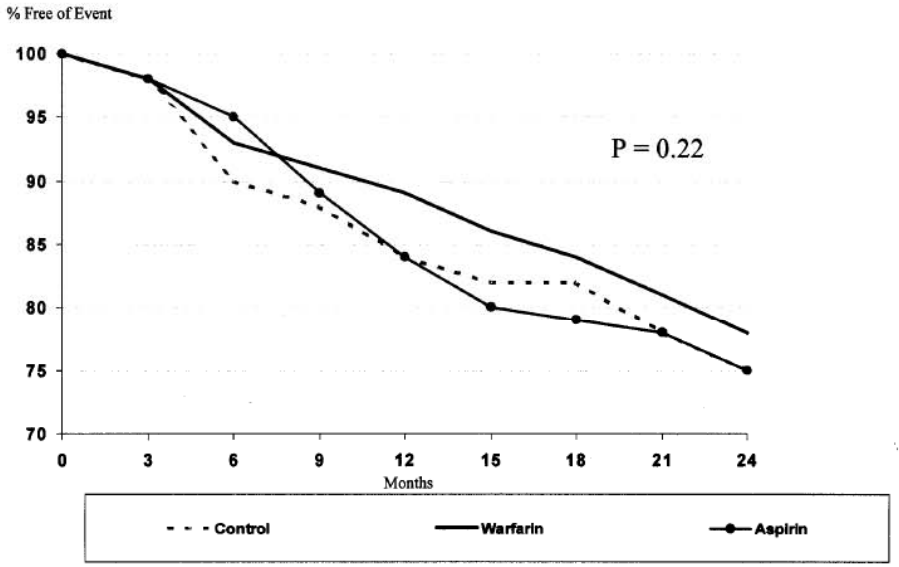
*Patients censored for further events 10 days after permanent discontinuation of randomized therapy.
†Figures are total number of patients with fatal and nonfatal events. Events that contributed to the composite outcome given in brackets [].
‡Hazard ratio is for group in column header versus the other 2 groups (ie, no ATT versus either aspirin or warfarin, aspirin versus no aspirin and warfarin versus no warfarin). The hazard ratio for the comparison of aspirin versus warfarin was 1.21 (0.70, 2.09) on the intention to treat analysis and 1.09 (0.57, 2.11) in the on-therapy analysis. Log rank tests of equality of hazard ratio across the three treatment groups showed no significant differences for intention-to-treat or on-therapy analyses.

Table III. Prespecified secondary outcomes

Analysis	No ATT	Aspirin	Warfarin	*P*
Death or CVS hospitalisation (including major hemorrhage)				
ITT	37 (37%)	45 (49%)	33 (37%)	.23†
On-therapy*	31 (31%)	39 (43%)	24 (27%)	.29†
Hazard ratio (95% CI)	0.88 (0.60, 1.32)	1.39 (0.95, 2.00)	0.81 (0.54, 1.20)	
Death or all-cause hospitalisation				
ITT	55 (56%)	63 (69%)	51 (57%)	.18†
On-therapy*	49 (49%)	58 (64%)	43 (48%)	.21†
Hazard ratio (95% CI)	0.88 (0.63, 1.20)	1.35 (0.98, 1.82)	0.85 (0.61, 1.18)	
All-cause hospitalisation				
Patients	48 (48%)	58 (64%)	42 (47%)	.044‡
Events and mean number per patient per year alive	108 (0.571)	131 (0.724)	102 (0.593)	.84§
Events on therapy*	73	118	78	na
Death, CVS hospitalisation (including major hemorrhage) or an increase in diuretic therapy for worsening heart failure				
ITT	47 (47%)	58 (64%)	45 (51%)	.16†
On-therapy*	41 (41%)	53 (58%)	36 (40%)	.23†
Hazard ratio (95% CI)	0.83 (0.59, 1.18)	1.39 (0.99, 1.92)	0.86 (0.61, 1.22)	

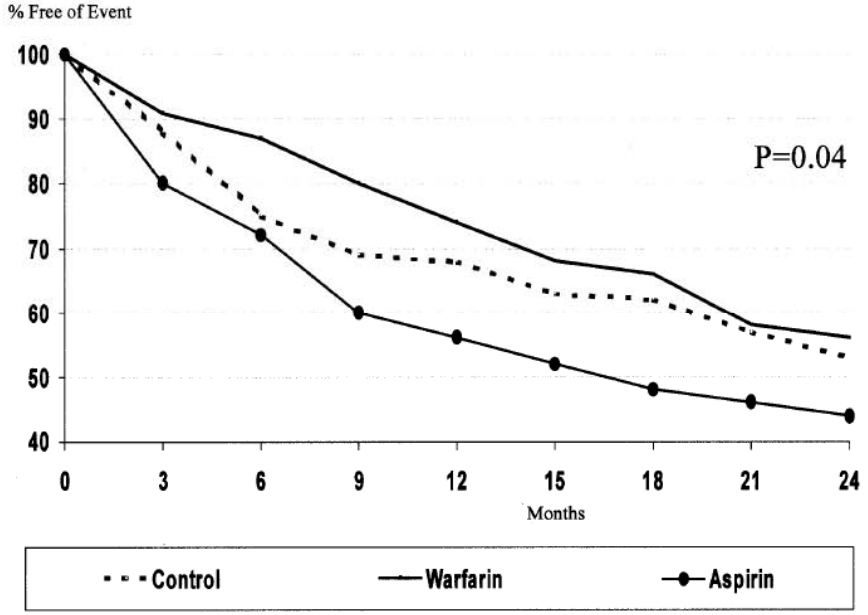
na, Statistical test not applied.
*Patients censored for further events 10 days after permanent discontinuation of randomised therapy.
†Log rank test.
‡χ^2 Test.
§Permutation test.

Figure 1



Kaplan-Meier plot for the primary outcome cluster of death, nonfatal myocardial infarction, or nonfatal stroke.

Figure 2



Kaplan-Meier plot for the time to first hospitalization for any reason.

TABLE 1. Studies Involving the Use of Oral Anticoagulants for Patients With Left Ventricular Dysfunction

Study	N	% Ischemic Etiology	Intervention(s)/Target INR	Primary Outcomes	Results
Post-hoc analyses					
SOLVD*	6513	67.6 (warfarin) 80.6 (no warfarin)	Warfarin (n = 861) vs. no warfarin (n = 5652) No target INR identified	All-cause death, CV death, HF death, sudden death, fatal MI, noncardiac vascular deaths	All cause deaths (adjusted): HR, 0.76 (95% CI, 0.65–0.89; $P = 0.0006$) CV deaths (adjusted): HR, 0.72 (95% CI, 0.61–0.86; $P = 0.0002$) HF death (adjusted): HR, 0.77 (95% CI, 0.61–0.98; $P = 0.03$) Sudden death (adjusted): HR, 0.66 (95% CI, 0.47–0.91; $P = 0.01$) Fatal MI (adjusted): HR, 0.55 (95% CI, 0.34–0.90; $P = 0.02$) Noncardiac vascular deaths (adjusted): HR, 0.99 (95% CI, 0.53–1.64; $P = 1.00$)
V-HeFT	642 (V-HeFT I) 804 (V-HeFT II)	44.2 (V-HeFT I) 53.1 (V-HeFT II)	No treatment vs. anticoagulant only (warfarin) vs. antiplatelet only (aspirin, dipyridamole, or both) vs. anticoagulant + antiplatelet No target INR defined	Thromboembolic events	V-HeFT I: Thromboembolic event rate w/AC 2.9/100 patient years Thromboembolic event rate with no treatment was 2.7/100 patient years (P = NS) V-HeFT II: Thromboembolic event rate w/AC 4.9/100 patient years Thromboembolic event rate with no treatment 2.1/100 patient years ($P = 0.01$)
SAVE	2,231	Not stated No target INR defined	No treatment vs. anticoagulant only (heparin or warfarin) vs. aspirin vs. both AC or aspirin	Stroke	As LVEF decreases risk of stroke increases Rate of stroke: 8.9% for patients with LVEF ≤28% 7.8% for patients with LVEF 29–35% 4.1% for patients with LVEF >35%
Randomized controlled trials					
WASH	279	56 (warfarin) 63 (aspirin) 60 (no AC)	No AC vs. aspirin (300 mg) vs. warfarin Target INR of 2.5 (range, 2–3)	Death, MI, and stroke	Composite outcome (death, MI, stroke) No AC: 26% Aspirin: 32% Warfarin: 26%
WATCH	1587	67 (aspirin) 67 (clopidogrel) 70 (warfarin)	Aspirin (162 mg) vs. clopidogrel (75 mg) and warfarin Target INR of 2.5 to 3.0 (range, 2–3.5)	Death, MI, and stroke	Composite outcome (death, MI, stroke) ASA vs clopidogrel; 20.7% vs 21.6% ($P = 0.71$) ASA vs warfarin; 20.7% vs 19.6% ($P = 0.67$) Clopidogrel vs warfarin; 21.6% vs 19.6% ($P = 0.43$)
HELAS	197	58	First treatment arm for patients with CHF and a history of MI: ASA or warfarin Second treatment arm for patients with idiopathic DCM: warfarin or placebo Target INR of 2–3	Non-fatal stroke, MI, DVT or PE, re-hospitalization, exacerbation of heart failure and death	Number of events per 100 patient years Stroke: IHD/ASA: 2.1 IHD/warfarin: 2.4 DCM/placebo: 1.5 DCM/warfarin: 0 Embolic events were rare and accounted for 2.2 events per 100 patient years. There were no peripheral or pulmonary embolisms. Composite endpoint (non-fatal stroke, peripheral or pulmonary embolism, myocardial re-infarction, re-hospitalization, exacerbation of heart failure, or death from any cause IHD/ASA: 14.9 IHD/warfarin: 8.9 DCM/placebo: 14.8 DCM/warfarin: 8.9

*Results are presented for warfarin compared to no warfarin unless otherwise indicated; hazard/risk ratios (HR) <1 favor warfarin therapy.

CV indicates cardiovascular; HF, heart failure; MI, myocardial infarction; AC, anticoagulation; NS, not significant; LVEF, left ventricular ejection fraction; DVT, deep vein thrombosis; PE, pulmonary embolism; IHD, ischemic heart disease; ASA, aspirin; DCM, dilated cardiomyopathy; INR, international normalized ratio.

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
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Thromboembolism and Antithrombotic Therapy in Patients With Heart Failure in Sinus Rhythm : Current Status and Future Directions

Luca Bettari, Mona Fiuzat, Richard Becker, G. Michael Felker, Marco Metra and Christopher M. O'Connor

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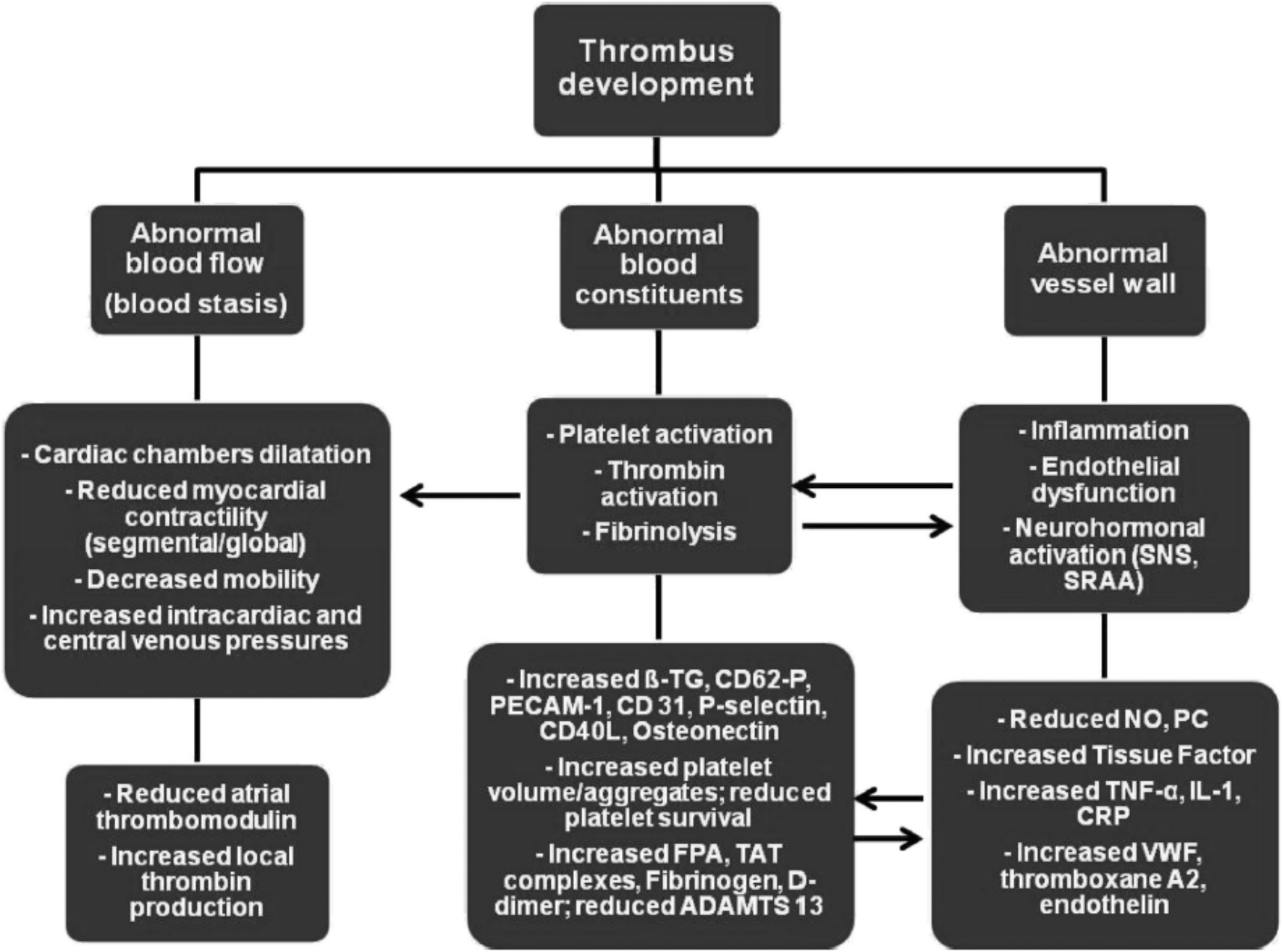
Table 1. VTE Incidence in HF RCTs

RCT	No. Patients	LVEF, %	AF, %	VTE, %/y	Anticoagulants-Antiplatelet Agents, %	Follow-Up, y	Considerations
SOLVD	6378	31	0	2.1	9–46	3.3	Higher VTE in women with lower LVEF No lower VTE with warfarin Lower VTE with aspirin
SAVE	2231	31	10	1.5	28–14	3.5	Higher VTE with lower LVEF and older age Lower VTE with warfarin or aspirin
V-HeFT I	642	30	16	2.7	19–13	2.3	Higher VTE with lower LVEF and peak $\dot{V}o_2$ No higher VTE with AF No lower VTE with warfarin Lower VTE with aspirin
V-HeFT II	804	29	15	2.1	21–27	2.6	Higher VTE with lower LVEF and peak $\dot{V}o_2$
SCD-HeFT	2114	25	9	3.4	28–59	3.8	No higher VTE with AF No lower VTE with warfarin or aspirin Higher VTE with lower LVEF and hypertension No lower VTE with warfarin

Data are provided as means. AF indicates atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SAVE, Survival and Ventricular Enlargement; SCD-HeFT, Sudden Cardiac Death-Heart Failure Trial; SOLVD, Studies of Left Ventricular Dysfunction; V-HeFT, Veterans Affairs Vasodilator-Congestive Heart Failure Trials; $\dot{V}o_2$, oxygen consumption; VTE, venous thromboembolism.


Thrombus development
Abnormal blood flow (blood stasis)
Abnormal blood constituents
Abnormal vessel wall
- Cardiac chambers dilatation
- Reduced myocardial contractility (segmental/global)
- Decreased mobility
- Increased intracardiac and central venous pressures
- Platelet activation
- Thrombin activation
- Fibrinolysis
- Inflammation
- Endothelial dysfunction
- Neurohormonal activation (SNS, SRAA)
- Reduced atrial thrombomodulin
- Increased local thrombin production
- Increased ß-TG, CD62-P, PECAM-1, CD 31, P-selectin, CD40L, Osteonectin
- Increased platelet volume/aggregates; reduced platelet survival
- Increased FPA, TAT complexes, Fibrinogen, D-dimer; reduced ADAMTS 13
- Reduced NO, PC
- Increased Tissue Factor
- Increased TNF-α, IL-1, CRP
- Increased VWF, thromboxane A2, endothelin

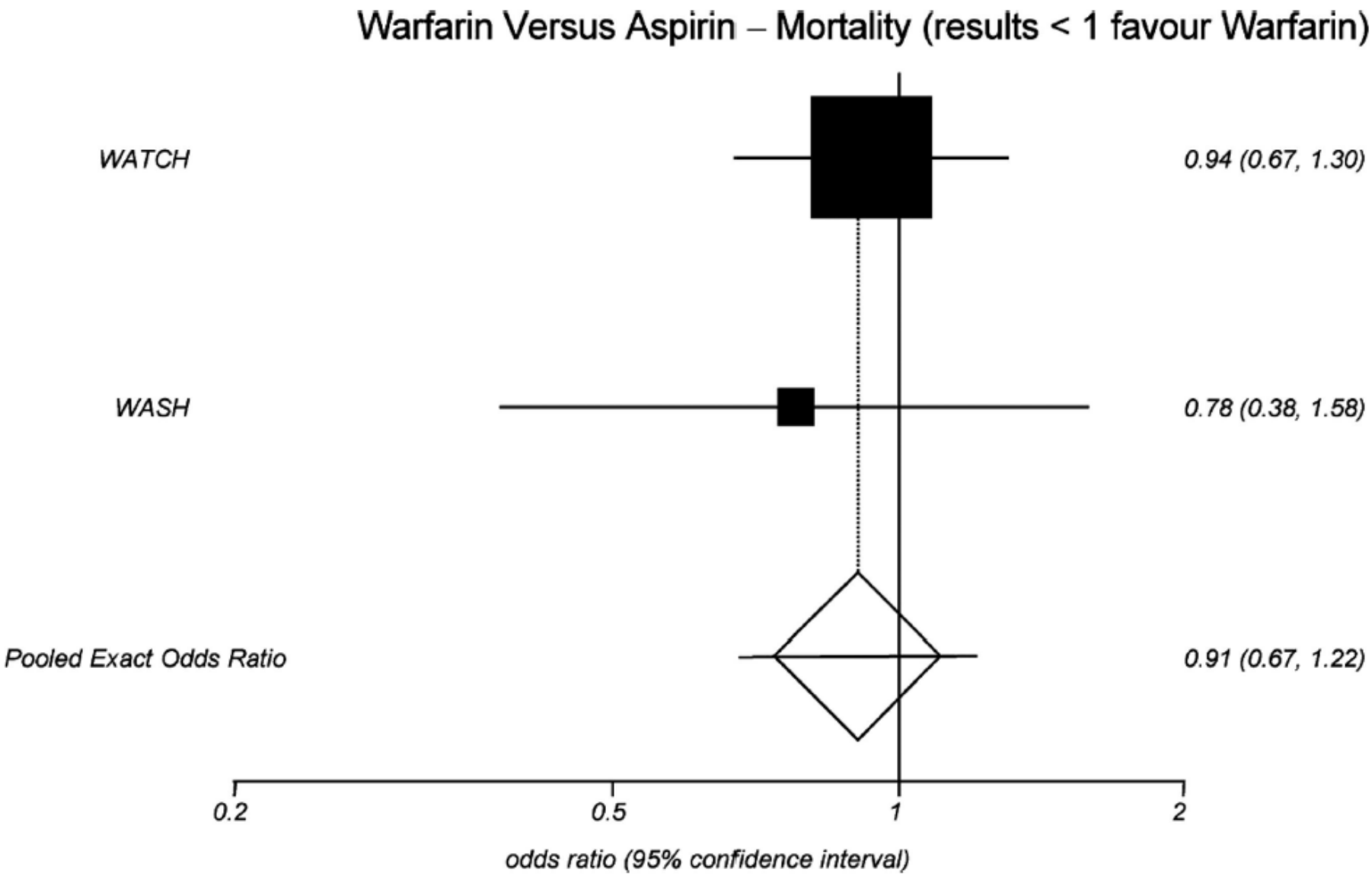
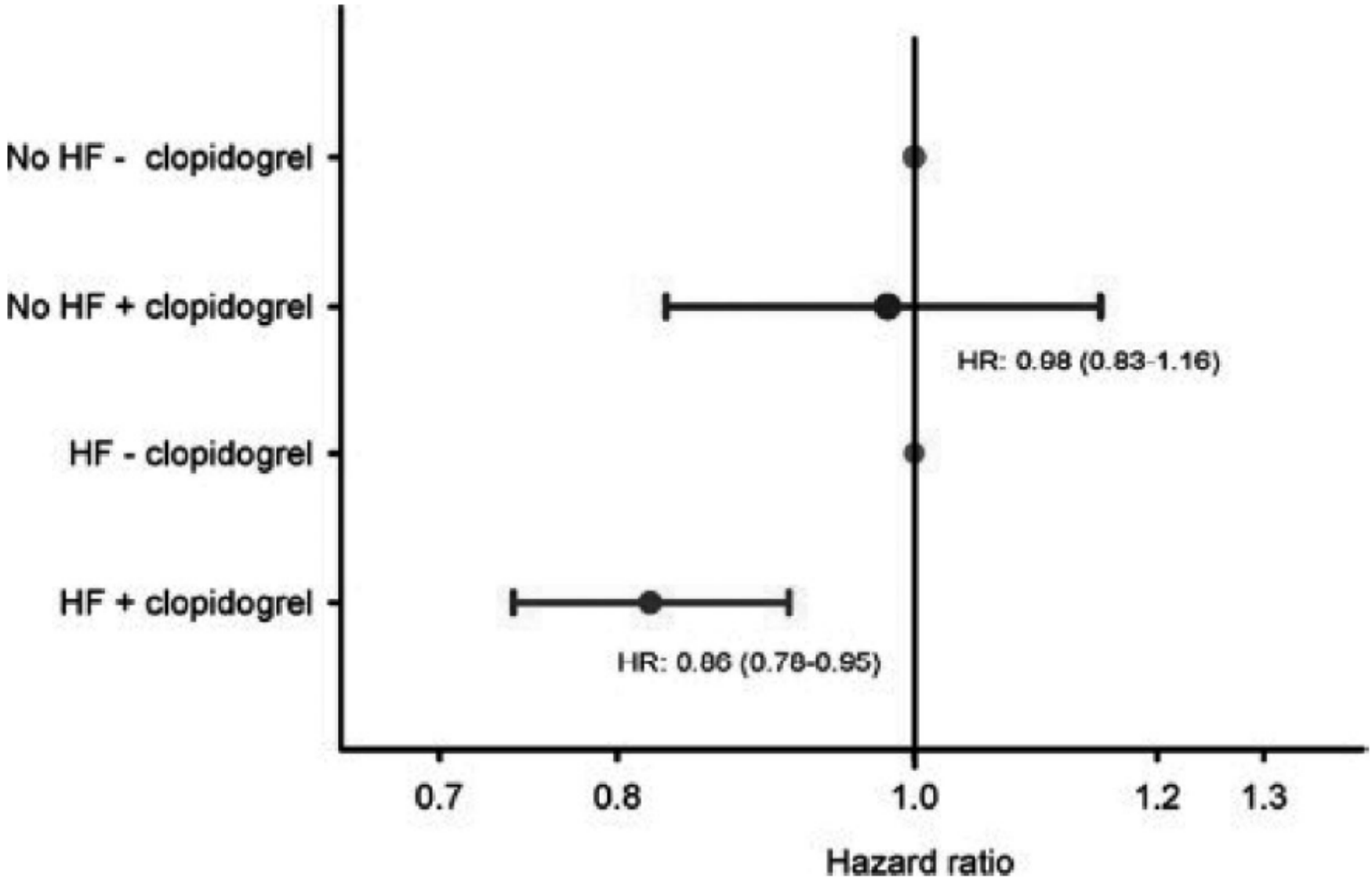

Warfarin Versus Aspirin – Mortality (results < 1 favour Warfarin)
WATCH
0.94 (0.67, 1.30)
WASH
0.78 (0.38, 1.58)
Pooled Exact Odds Ratio
0.91 (0.67, 1.22)
0.2
0.5
1
2
odds ratio (95% confidence interval)

Table 2. RCTs on Antiplatelet vs Anticoagulation Therapy in HF

RCT	No. Patients	Therapy	End Points	Results/Considerations
HELAS*	197	IHD: warfarin (INR, 2–3) vs aspirin (325 mg) DCM: warfarin (INR, 2.5) vs placebo	Death, stroke, re-MI Rehospitalization, PE, HF exacerbation	Trend toward benefit with warfarin in IHD
WASH*	279	Warfarin (INR, 2–3) vs aspirin (300 mg)	Death, MI, stroke	More HF hospitalization with aspirin More major bleeding with warfarin
WATCH*	1587	Warfarin (INR, 2–3) vs aspirin (162.5 mg)/clopidogrel (75 mg)	Death, MI, stroke	More HF hospitalization with aspirin More major bleeding with warfarin Fewer strokes with warfarin
WARCEF	2860 (target)	Warfarin (INR, 2.5–3) vs aspirin (325 mg)	Death, stroke	

DCM indicates dilated cardiomyopathy; HELAS, Heart Failure Long-term Antithrombotic Study; IHD, ischemic heart disease; INR, international normalized ratio; MI, myocardial infarction; PE, pulmonary embolism; WARCEF, Warfarin Aspirin Reduced Cardiac Ejection Fraction; WASH, Warfarin/Aspirin Study in Heart Failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure. Other abbreviations as in Table 1.

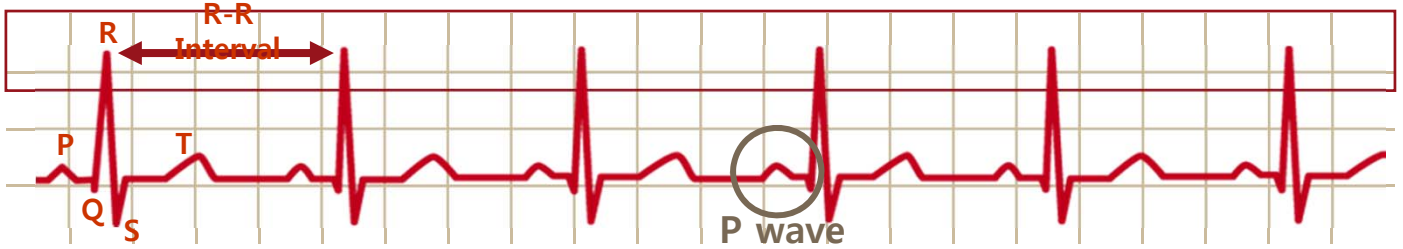
*No significant difference—underpowered.


No HF - clopidogrel
No HF + clopidogrel
HR: 0.98 (0.83-1.16)
HF - clopidogrel
HF + clopidogrel
HR: 0.86 (0.78-0.95)
0.7
0.8
1.0
1.2
1.3
Hazard ratio

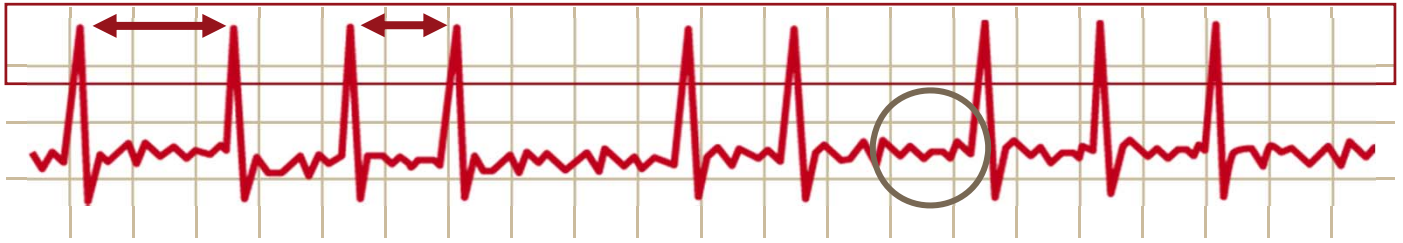
The Clinical Definition of Atrial Fibrillation

"**Atrial fibrillation (AF)** is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function"

Sinus Rhythm



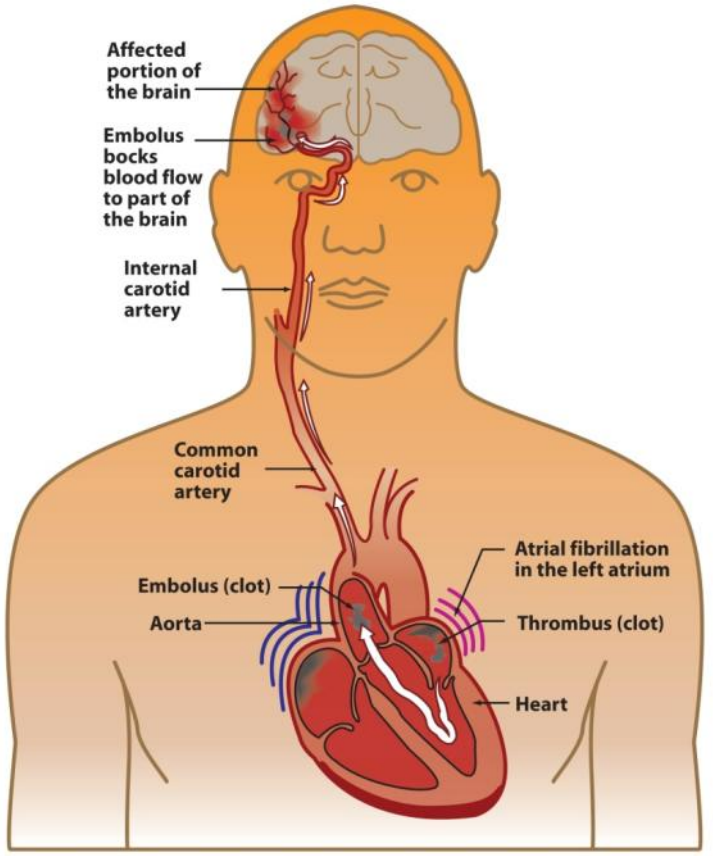
Atrial Fibrillation



ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906.

AF is an Independent Risk Factor for Stroke

- AF patients have a near 5-fold increased risk of stroke[1]
- 1 in every 6 strokes occurs in a patient with AF[2]
- Ischemic stroke associated with AF is typically more severe than stroke due to other etiologies[3]
- Stroke risk persists even in asymptomatic AF[4]



1. Wolf *et al. Stroke.* 1991;22:983-988.
2. Fuster V, *et al. Circulation.* 2006;114:e257-e354.
3. Dulli DA, *et al. Neuroepidemiology.* 2003;22:118-123.
4. Page RL, *et al. Ci*rculation. 2003;107:1141-1145.

Principles of Management

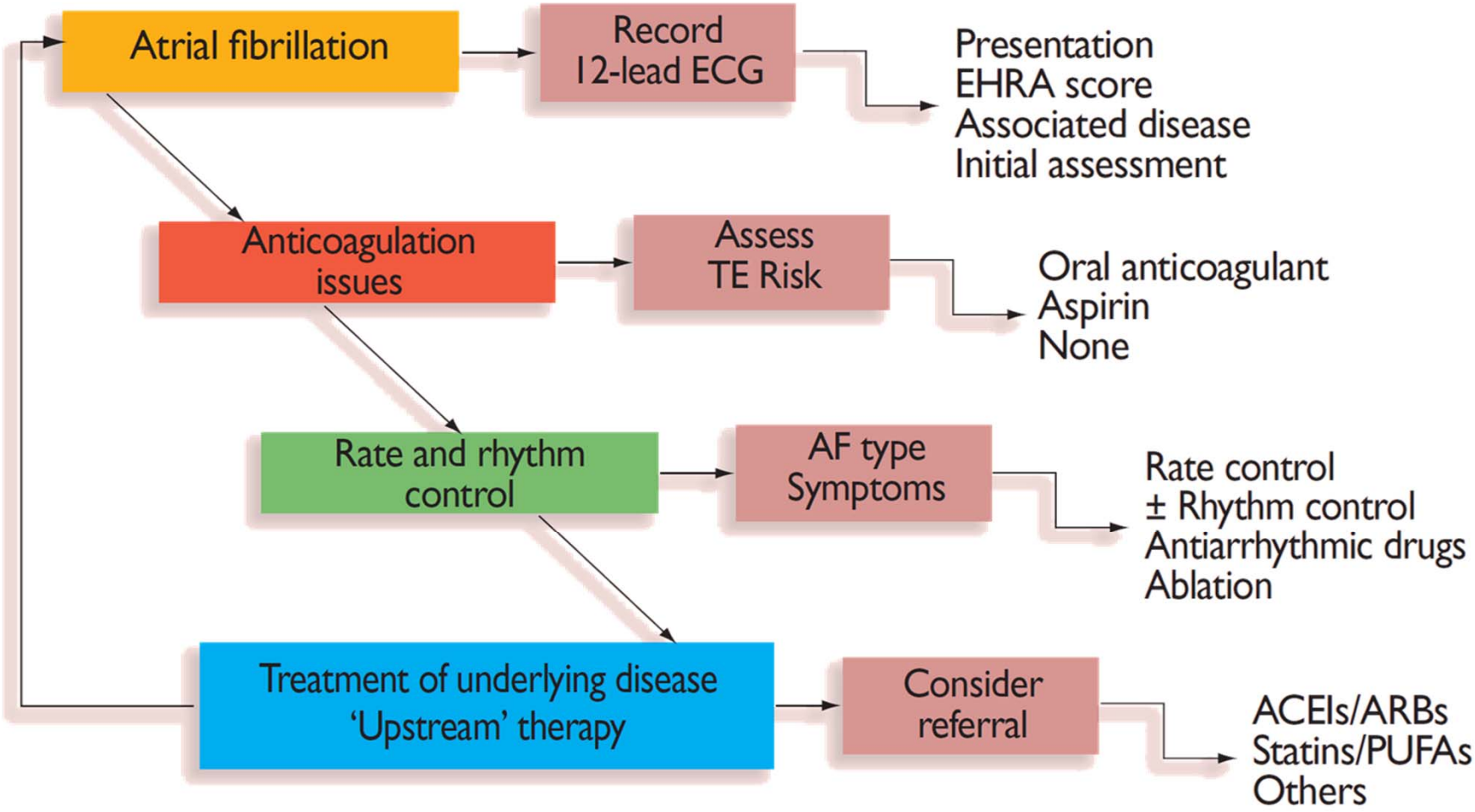


TABLE 9. Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ Index

$CHADS_2$ Risk Criteria	Score
Prior stroke or TIA	2
Age >75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N=1733)	Adjusted Stroke Rate (%/y)* (95% CI)	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. Data are from van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–43[153]; and Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70.[152]

AF indicates atrial fibrillation; $CHADS_2$, Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; and TIA, transient ischemic attack.

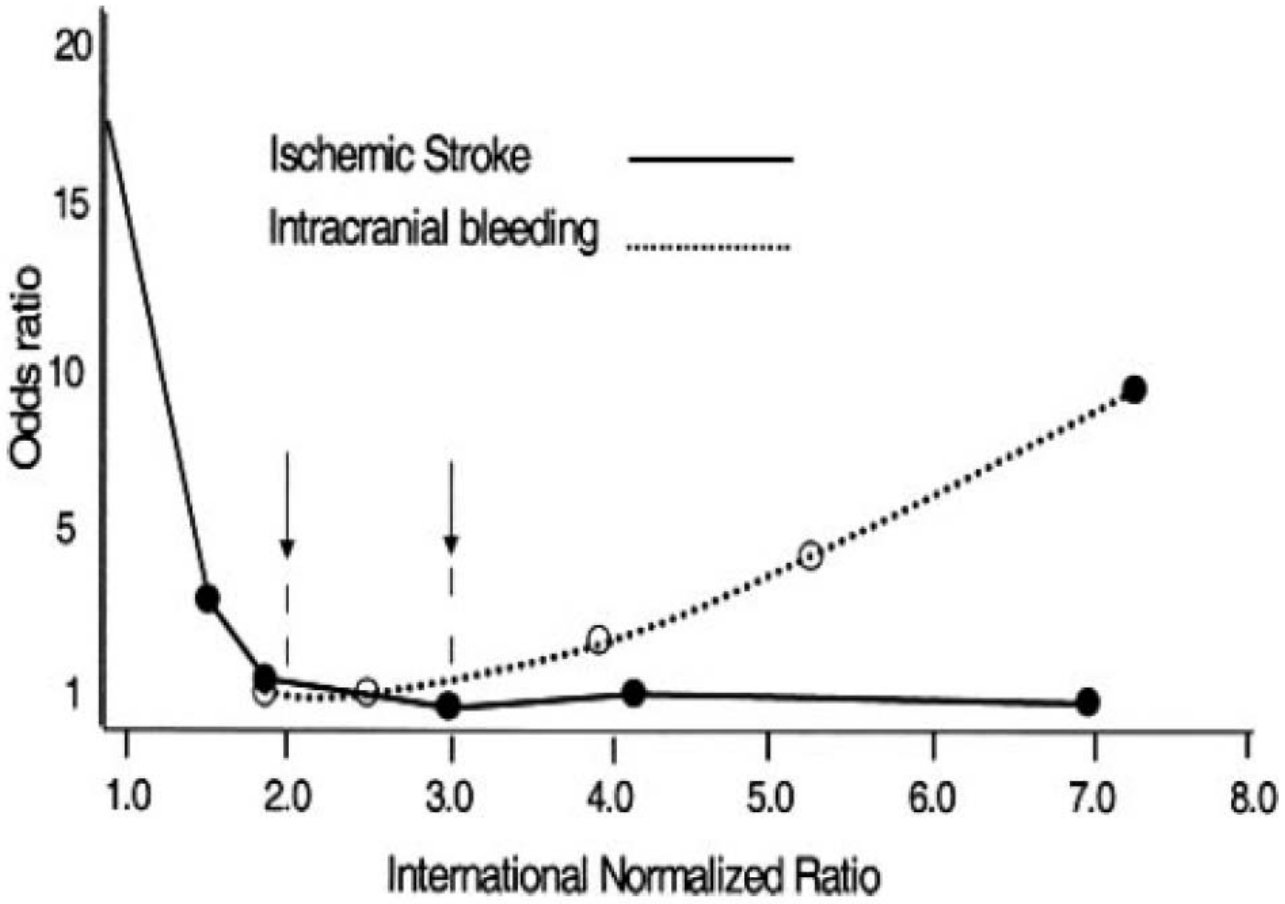


Figure 5. Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897–902.[166] Data from Odén A, Fahlén M, Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res* 2006;117:493–9.[167]

TABLE 10. Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

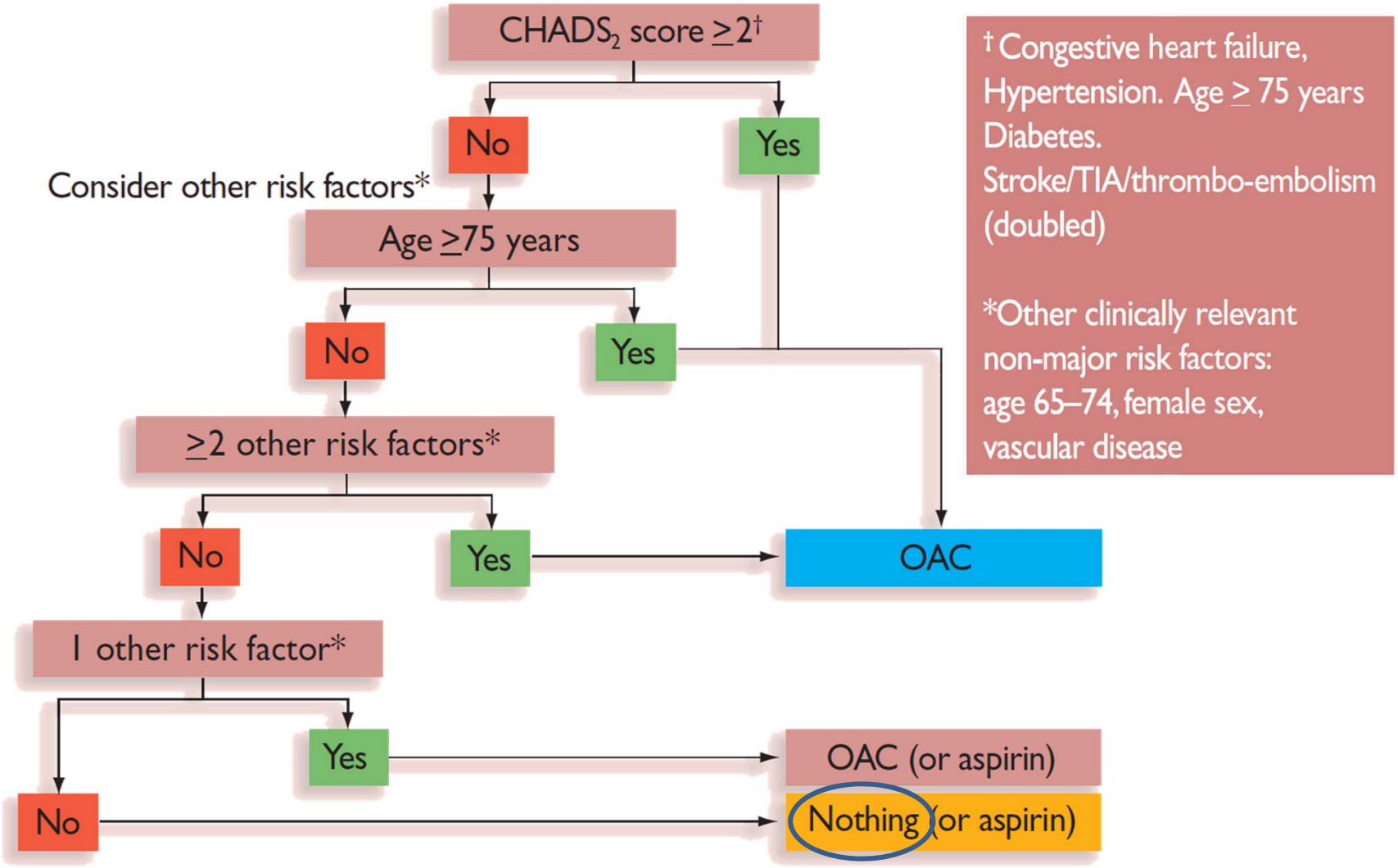
Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

*If mechanical valve, target international normalized ratio (INR) greater than 2.5.
INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

CHA_2DS_2-VASc Thromboembolic Risk Score



- **For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS2 score = 0), we suggest no therapy rather than antithrombotic therapy** (Grade 2B). **For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B).

—. American College of Chest Physician 2012

- **For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, CHADS2 score = 1), we recommend oral anticoagulation rather than no therapy** (Grade 1B). **We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B). **For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B).

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Selected OAC Recommendations

Recommendations	Class[a]	Level[b]
Antithrombotic therapy to prevent thrombo-embolism is recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications).	I	A
It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.	I	A
The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.	I	A
• For the patients with a $CHADS_2$ score of ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0–3.0 (target 2.5), unless contraindicated.		A
For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ scores 0–1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors[a].	I	A
In patients with no risk factors who are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin.	IIa	B
Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.	IIa	B

Table 3 Recommendation for combining anticoagulant with antiplatelet therapy

2011 Focused update recommendation	Comments
Class IIb 1. The addition of clopidogrel to aspirin (ASA) to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation.[10] *(Level of Evidence: B)*	New recommendation

Bleeding Risk – HAS-BLED Score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Improving Thromboprophylaxis Using Atrial Fibrillation Diagnostic Capabilities in Implantable Cardioverter-Defibrillators

The Multicentre Italian ANGELS of AF Project

Giuseppe Boriani, MD, PhD; Massimo Santini, MD; Maurizio Lunati, MD; Maurizio Gasparini, MD; Alessandro Proclemer, MD; Maurizio Landolina, MD; Luigi Padeletti, MD; Giovanni Luca Botto, MD; Alessandro Capucci, MD; Stefano Bianchi, MD; Mauro Biffi, MD; Renato Pietro Ricci, MD; Marco Vimercati, BS; Andrea Grammatico, PhD; Gregory Y.H. Lip, MD; on behalf of the Italian ClinicalService Project

Background—Atrial fibrillation (AF) is a well-established risk factor for stroke and thromboembolism and is a frequent comorbid arrhythmia in patients with implantable cardioverter-defibrillators (ICDs). The Anticoagulation Use Evaluation and Life Threatening Events Sentinels (ANGELS) of AF project was a medical care program aimed at supporting adherence to oral anticoagulation (OAC) guidelines for thromboprophylaxis through the use of ICD AF diagnostics.

Methods and Results—Fifty Italian cardiology clinics followed 3438 patients with ICDs. In a subgroup of 15 centers (the ANGELS of AF centers), cardiologists attending to follow-up visits were supplied with specific reports describing stroke risk factors and risk scores (American College of Chest Physicians and $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack]), AF occurrence and duration, and current antithrombotic therapy for patients with AF, especially those with a $CHADS_2$ score >0 and not on OAC therapy. The remaining centers represented a control group of patients as a comparison of OAC use. In the ANGELS of AF centers, 709 (36%) patients had AF described either in their clinical history (n=426 [22%]) or as new-onset AF (n=257 [14%]). Among 683 (96%) patients with CHADS2 score >0, 209 (30.6%) were not taking an OAC. Appropriate OAC therapy was prescribed in 10% (22/209) of patients after evaluation of ANGELS of AF reports. The percentage of patients on OAC therapy, as indicated by guidelines, increased during follow-up from 46.1% at baseline, to 69.4% at the stroke risk evaluation phase, to up to 72.6% at the end of the observation period. In control centers, corresponding figures were 46.9% at baseline and 56.8% at the end of the observation period ($P<0.001$ versus ANGELS of AF group).

Conclusions—The ANGELS of AF project demonstrates the possibility to improve OAC use in accordance with available guidelines for stroke risk reduction in AF by supplying attending physicians with reports about patients risk factors and AF information from continuous ICD monitoring.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01007474.

(*Circ Cardiovasc Qual Outcomes*. 2012;5:182-188.)

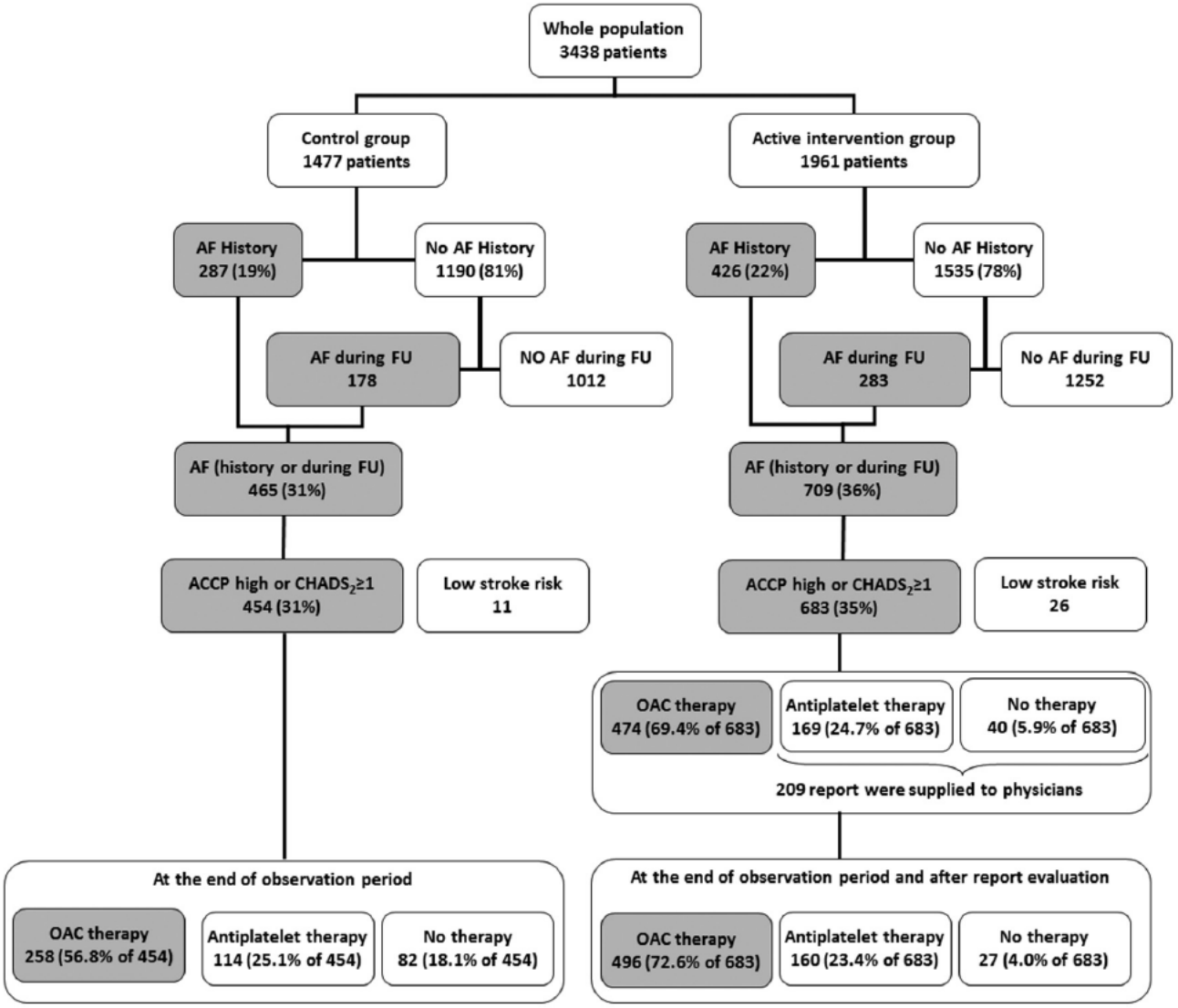


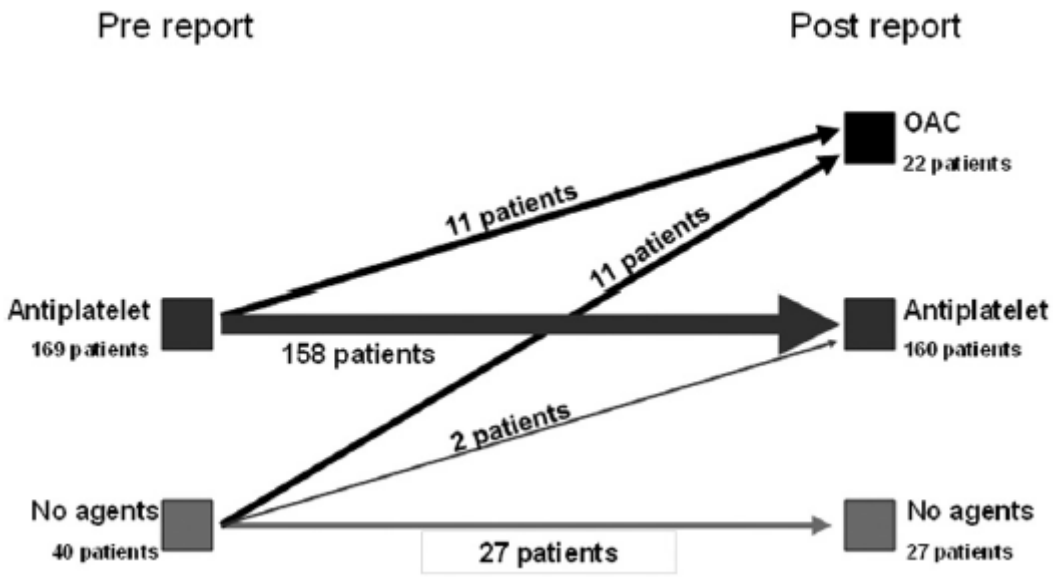
Figure 1. ANGELS (Anticoagulation Use Evaluation and Life Threatening Events Sentinels) of AF flowchart. ACCP indicates American College of Chest Physicians; AF, atrial fibrillation; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; FU, follow-up; OAC, oral anticoagulation.

Table 1. Baseline Patient Characteristics

Characteristics	Overall Population (n=3438)	Active Intervention Arm (n=1961)	Control Arm (n=1477)
Male sex	2802 (82)	1608 (82)	1194 (81)
Age, y	71±11	71±11	73±6
Comorbidities			
Heart failure	2790 (81)	1532 (78)	1258 (85)
Vascular disease	1814 (53)	1022 (52)	792 (54)
Hypertension	1571 (46)	809 (41)	762 (52)
Diabetes	735 (21.4)	389 (19.8)	346 (23.4)
Prior stroke/TIA	135 (4)	81 (4)	54 (4)
Atrial fibrillation	713 (21)	426 (22)	287 (19)
Drug therapies			
Anticoagulant therapy	1597 (46)	904 (46)	693 (47)
Acenocoumarol	364 (10)	202 (10)	162 (11)
Warfarin	1234 (36)	702 (36)	532 (36)
Antiplatelet therapy	789 (23)	477 (24)	312 (21)
Diuretics	3310 (96.3)	1891 (96.4)	1419 (96.1)
β-blockers	2797 (81)	1561 (80)	1236 (84)
ACE inhibitors	2747 (80)	1571 (80)	1176 (80)
Antiarrhythmic therapy	1648 (48)	935 (48)	713 (48)

Data are presented as n (%) or mean±SD.

TIA indicates transient ischemic attack; ACE, angiotensin-converting enzyme.


Pre report
Post report
OAC
22 patients
11 patients
11 patients
Antiplatelet
169 patients
158 patients
Antiplatelet
160 patients
2 patients
No agents
40 patients
No agents
27 patients
27 patients

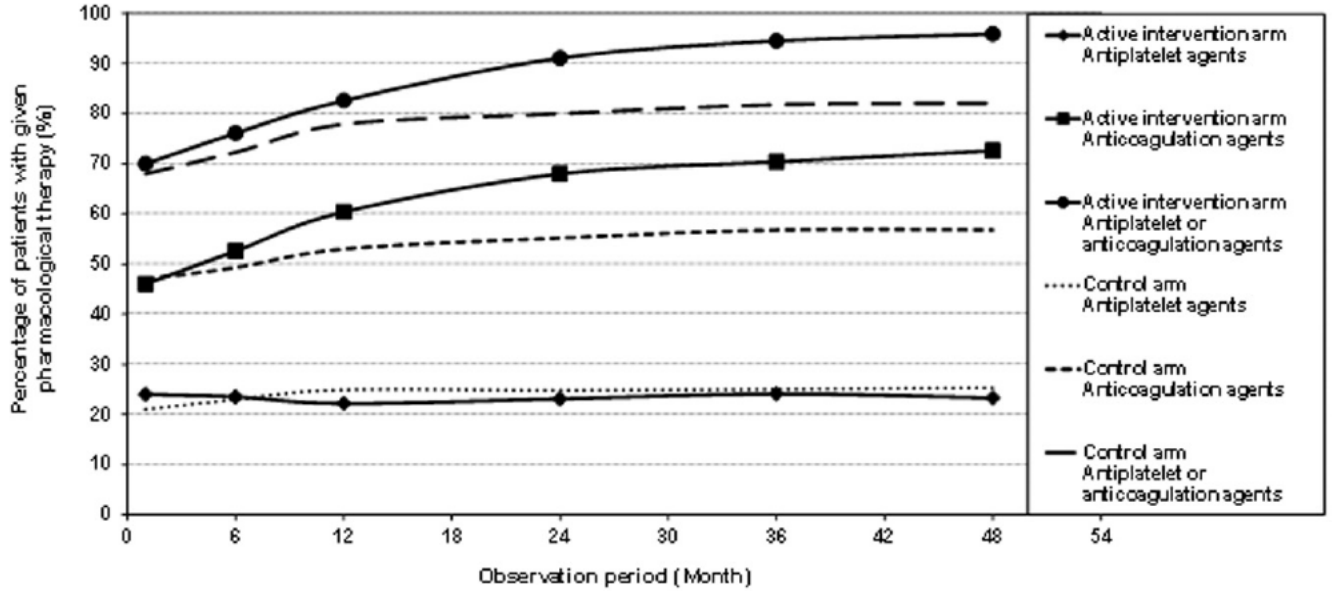

Percentage of patients with given pharmacological therapy (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
Observation period (Month)
Active intervention arm Antiplatelet agents
Active intervention arm Anticoagulation agents
Active intervention arm Antiplatelet or anticoagulation agents
Control arm Antiplatelet agents
Control arm Anticoagulation agents
Control arm Antiplatelet or anticoagulation agents

Table 2. Annual Rate of Stroke, TIA and Embolic Events as a Function of $CHADS_2$ in 1174 Patients With a History of AF or a New-Onset AF

$CHADS_2$	Patients	Antithrombotic Therapy	Total Follow-Up, y	Patients With Events	Annual Rate of Patients With Event, per 100 Patient-y
0	37		102	0	0
1	242	All	743	3	0.40
		OAC	369	1	0.27
		APA	185	1	0.54
		Null	189	1	0.53
2	436	All	1202	7	0.58
		OAC	565	1	0.18
		APA	347	3	0.86
		Null	290	3	1.03
3	329	All	838	8	0.95
		OAC	428	4	0.93
		APA	265	4	1.51
		Null	145	0	0
≥4	130	All	275	4	1.45
		OAC	137	3	2.19
		APA	84	0	0
		Null	54	1	1.86
All	1174	All	3160	22	0.70
All		OAC	1530	9	0.59
All		APA	907	8	0.88
All		Null	723	5	0.69

The number of patients for each antithrombotic therapy changed during the observation period because of changes in the administered drug and, thus, is not shown. The total follow-up period assigned to each antithrombotic therapy is calculated while taking into account the actual therapy taken by the patient and, therefore, the drug changes.

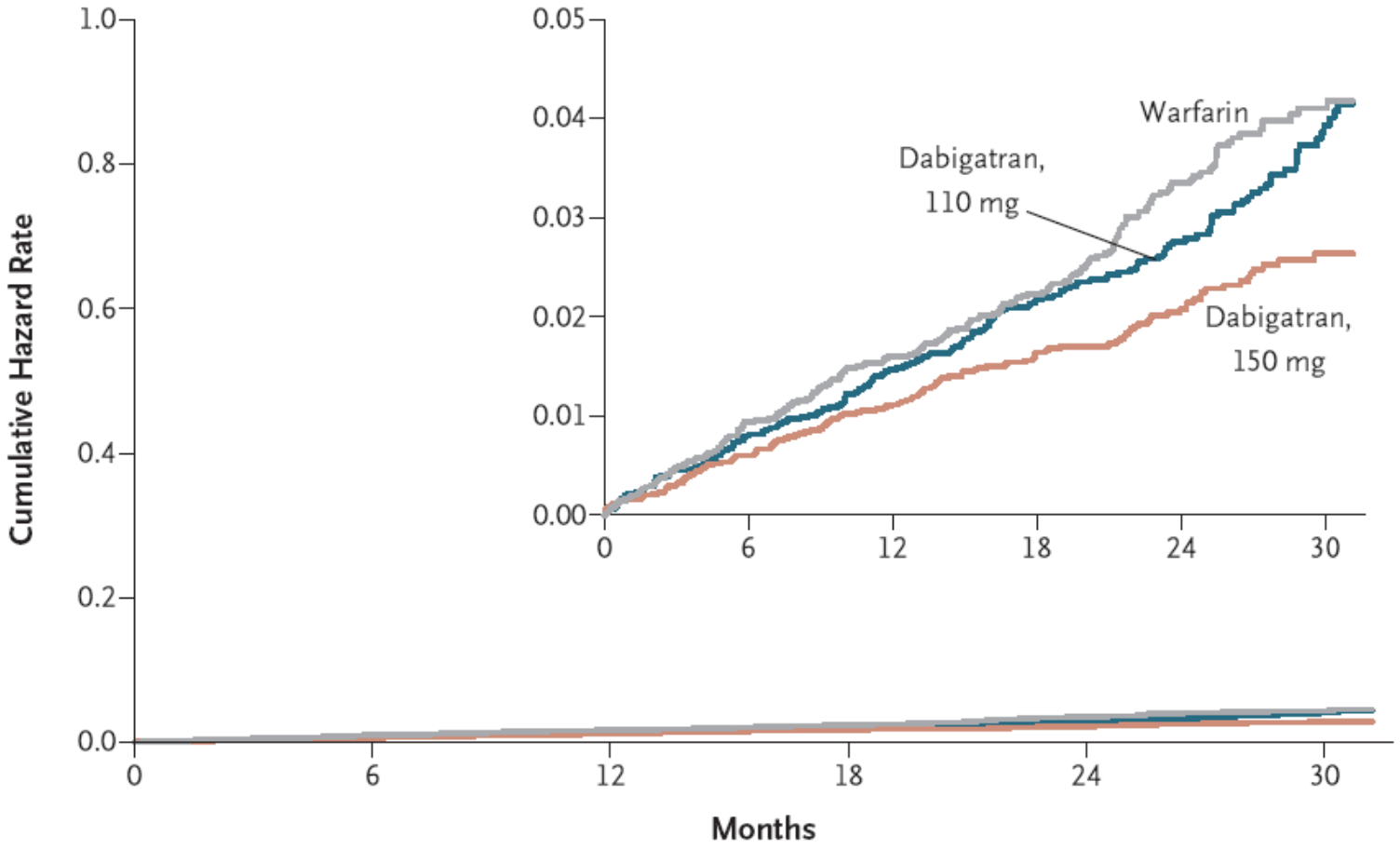
OAC indicates oral anticoagulation; APA, antiplatelet; Null, no antithrombotic therapy.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

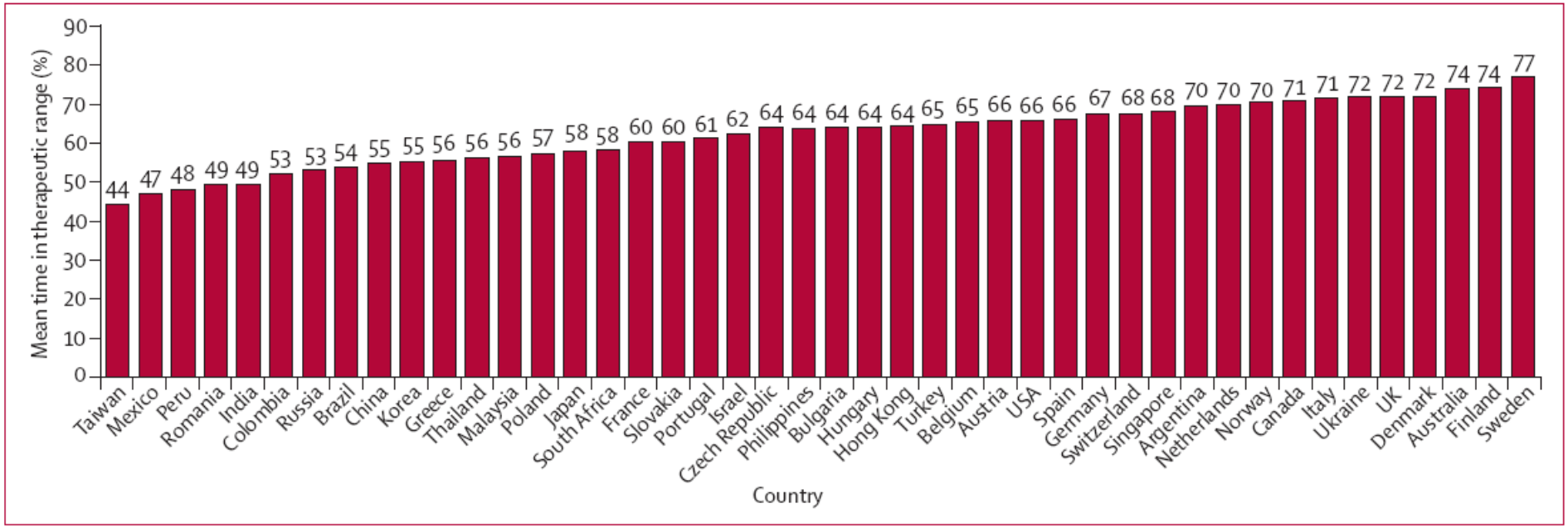
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY investigators

Lancet 2010; 376: 975–83

Country Distribution of Mean Time in Therapeutic Range in RE-LY trial



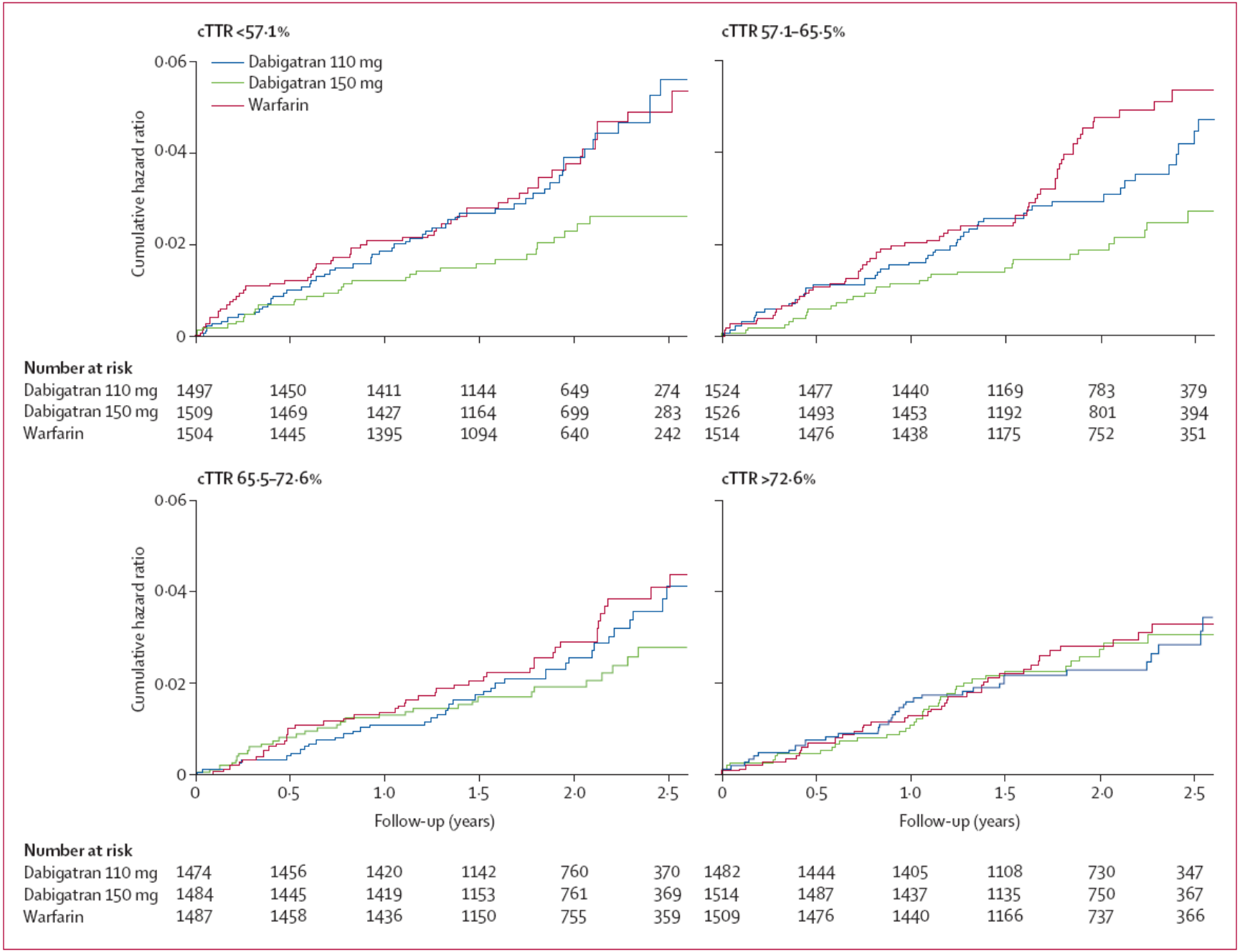


Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

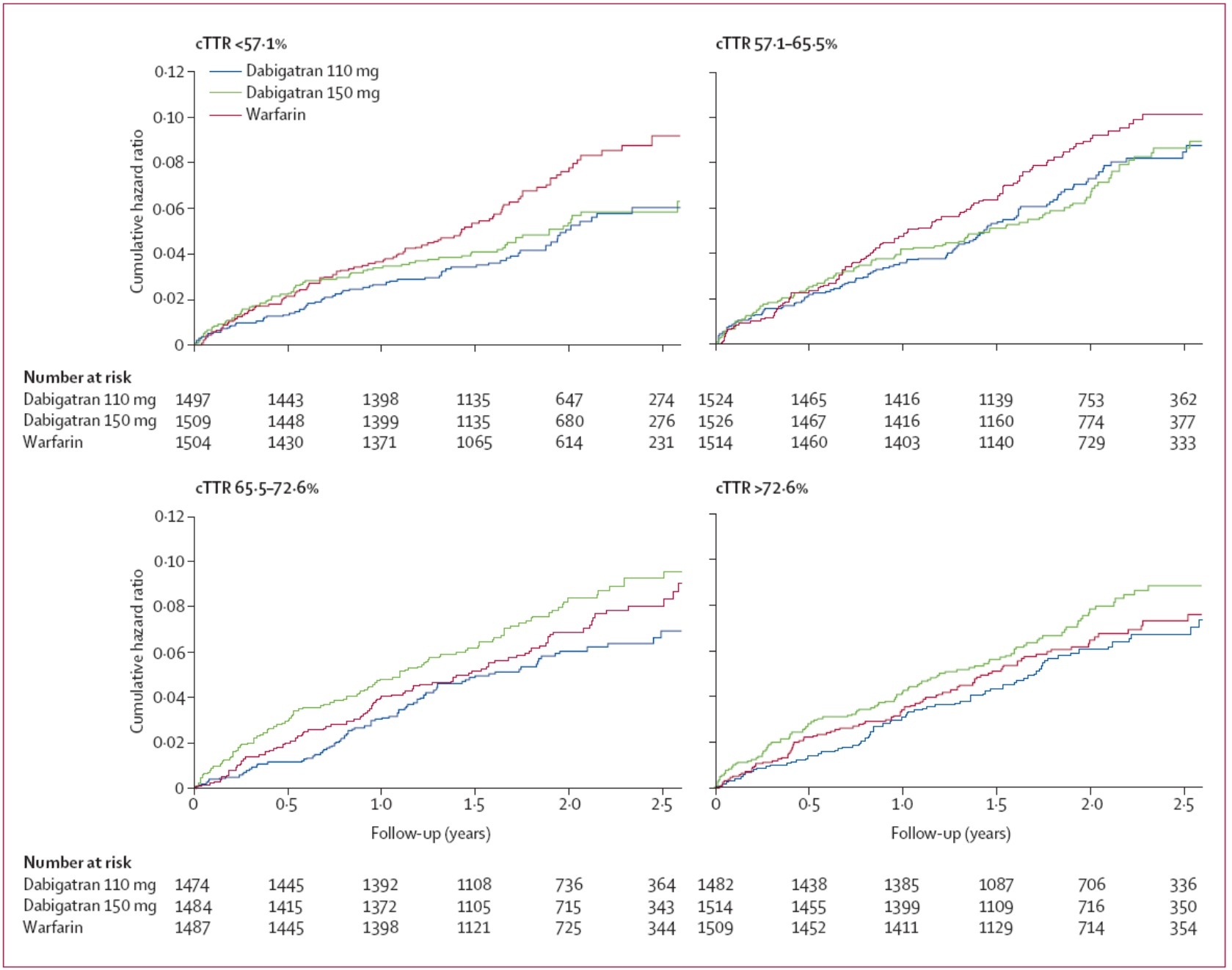


***Figure 3*: Time to major bleeding event in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

CLINICAL RESEARCH STUDY

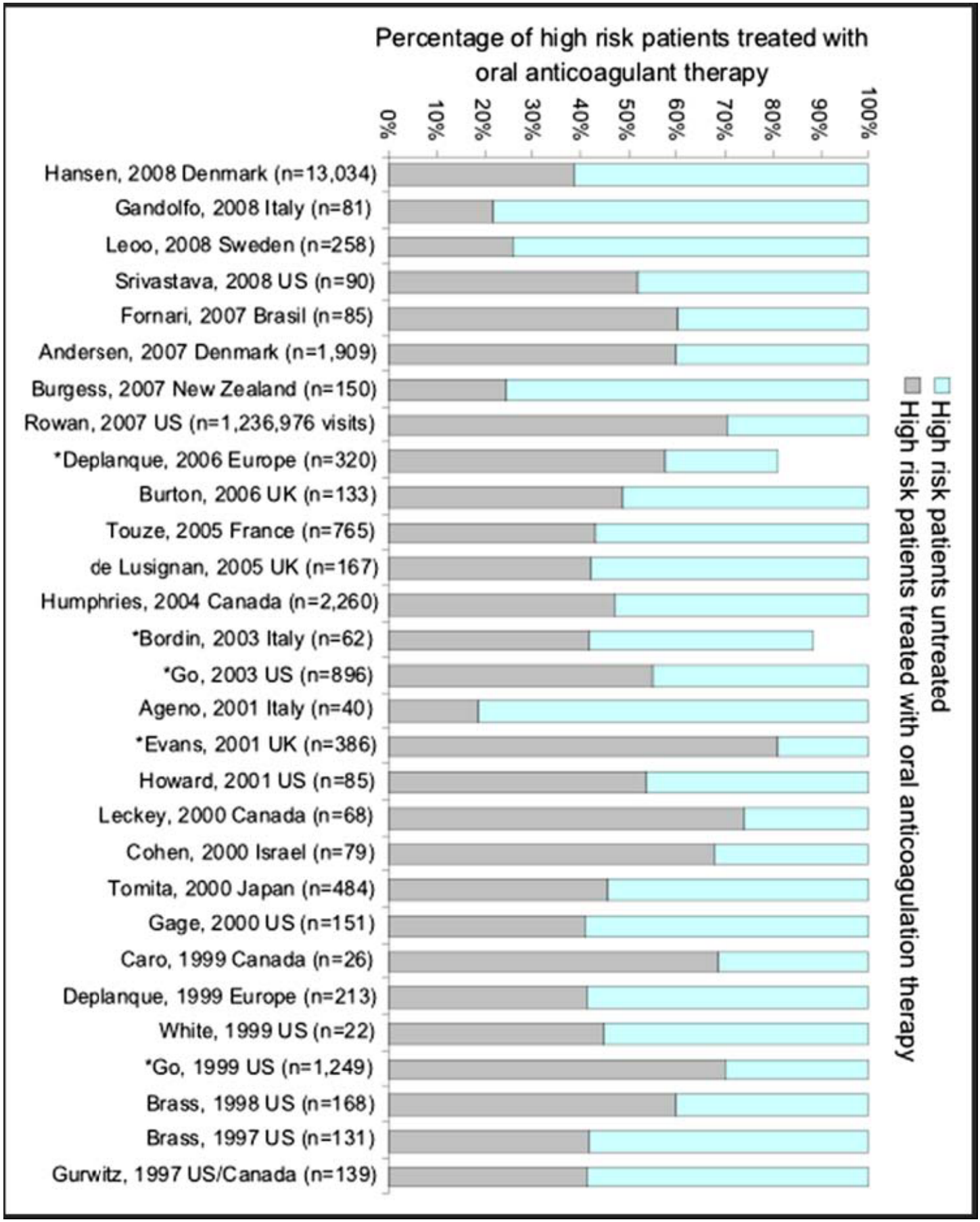
THE AMERICAN JOURNAL of MEDICINE®

Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review

Isla M. Ogilvie, PhD,[a] Nick Newton, PhD,[a] Sharon A. Welner, PhD,[a] Warren Cowell, MSc,[b] Gregory Y. H. Lip, MD[c]

[a]BioMedCom Consultants Inc., Montréal, Canada; [b]Global Health Economics and Reimbursement, Bayer HealthCare, Uxbridge, England; [c]Haemostasis Thrombosis & Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK.

The American Journal of Medicine (2010) 123, 638-645


Percentage of high risk patients treated with oral anticoagulant therapy
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Hansen, 2008 Denmark (n=13,034)
Gandolfo, 2008 Italy (n=81)
Leoo, 2008 Sweden (n=258)
Srivastava, 2008 US (n=90)
Fornari, 2007 Brasil (n=85)
Andersen, 2007 Denmark (n=1,909)
Burgess, 2007 New Zealand (n=150)
Rowan, 2007 US (n=1,236,976 visits)
*Deplanque, 2006 Europe (n=320)
Burton, 2006 UK (n=133)
Touze, 2005 France (n=765)
de Lusignan, 2005 UK (n=167)
Humphries, 2004 Canada (n=2,260)
*Bordin, 2003 Italy (n=62)
*Go, 2003 US (n=896)
Ageno, 2001 Italy (n=40)
*Evans, 2001 UK (n=386)
Howard, 2001 US (n=85)
Leckey, 2000 Canada (n=68)
Cohen, 2000 Israel (n=79)
Tomita, 2000 Japan (n=484)
Gage, 2000 US (n=151)
Caro, 1999 Canada (n=26)
Deplanque, 1999 Europe (n=213)
White, 1999 US (n=22)
*Go, 1999 US (n=1,249)
Brass, 1998 US (n=168)
Brass, 1997 US (n=131)
Gurwitz, 1997 US/Canada (n=139)
High risk patients untreated
High risk patients treated with oral anticoagulation therapy

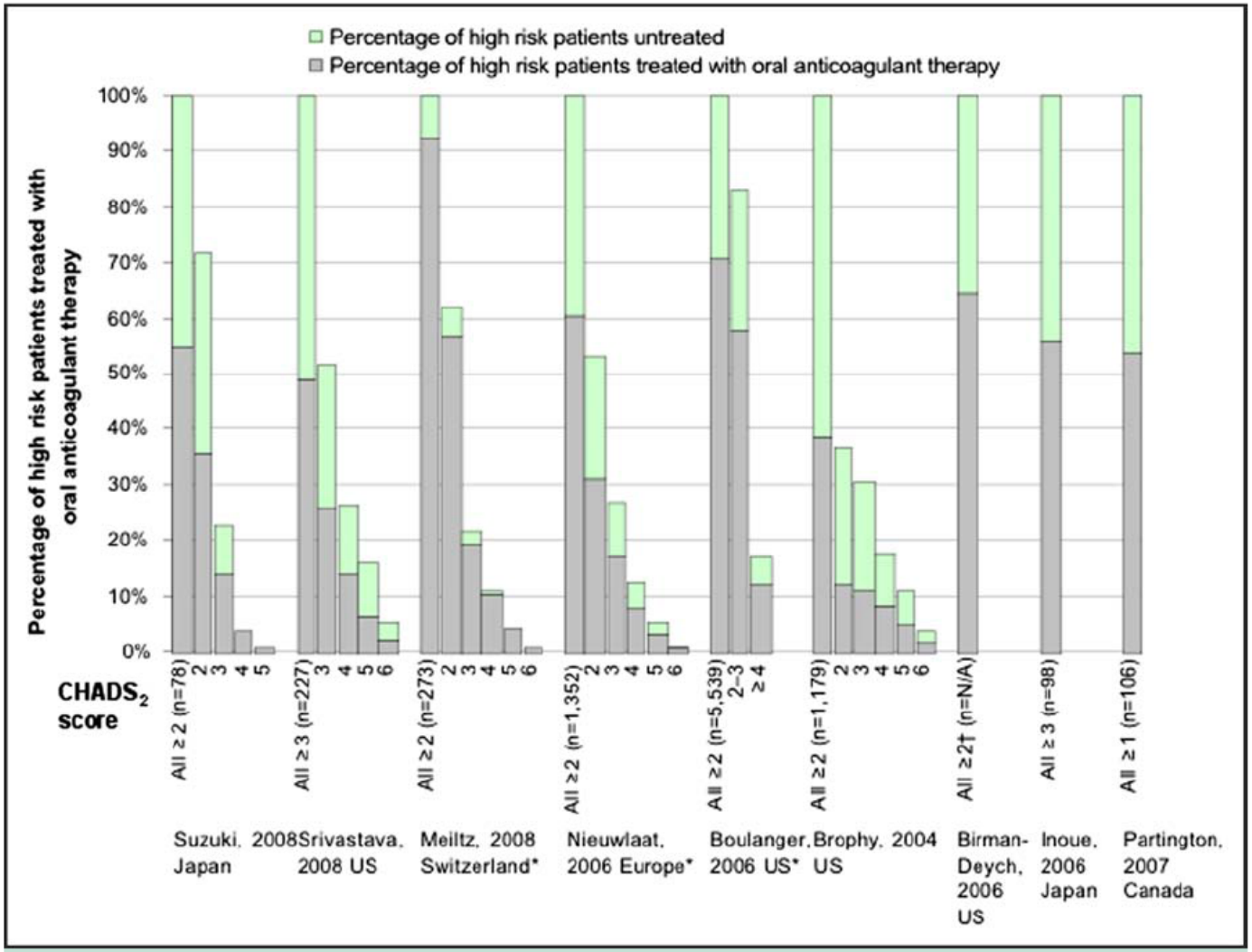


Figure 3 Patients with atrial fibrillation at high risk of stroke ($CHADS_2$ score): oral anticoagulant treatment levels as a proportion of patients eligible for therapy.

*Includes patients treated with both oral anticoagulation therapy and antiplatelet therapy.

†Patients defined as having a $CHADS_2$ score of >1 and a bleeding score of <2 (the n value for this population was not available).

$CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

n engl j med 364;9 nejm.806 org march 3, 2011

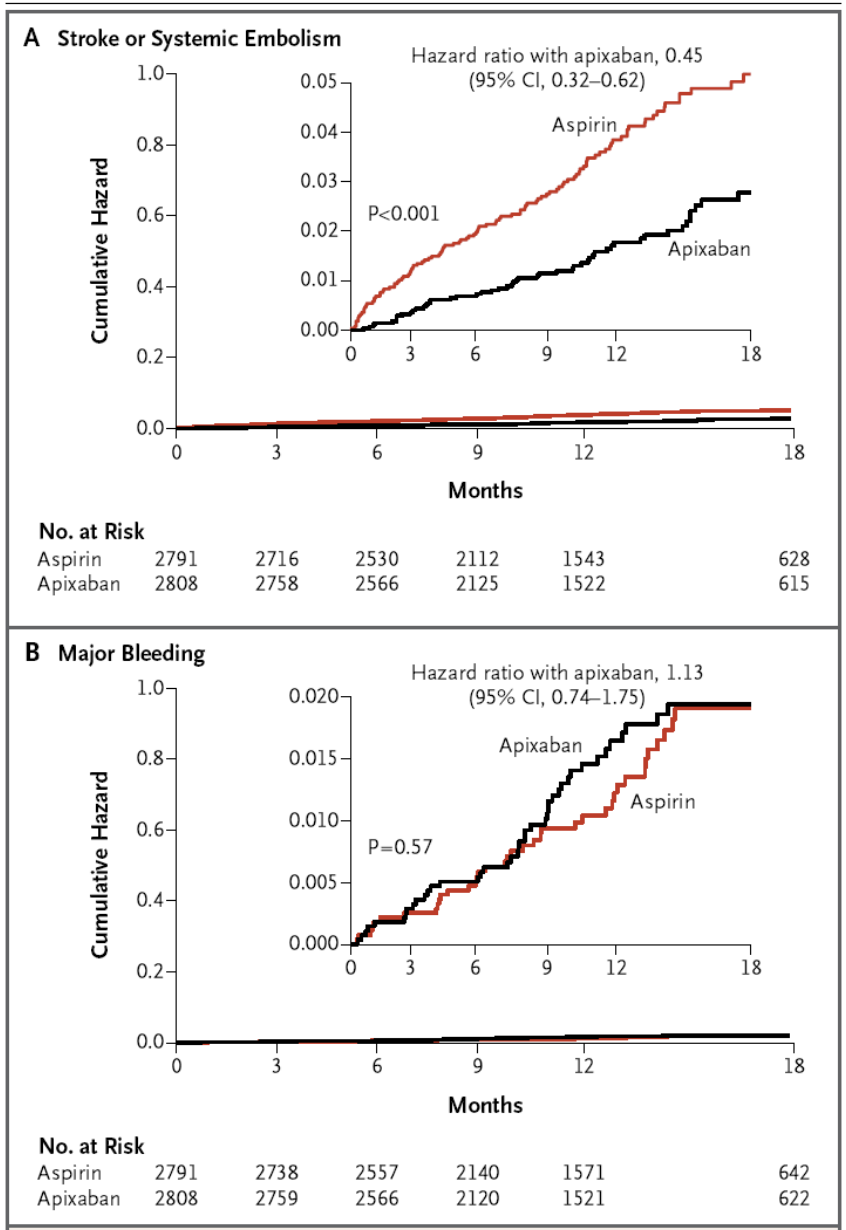


Figure 1. Cumulative Hazard Rates for the Primary Efficacy and Safety Outcomes, According to Treatment Group.

Panel A shows the cumulative hazard rates for the primary efficacy outcome (stroke or systemic embolism), and Panel B the rates for the primary safety outcome (major bleeding) in the apixaban and aspirin groups.

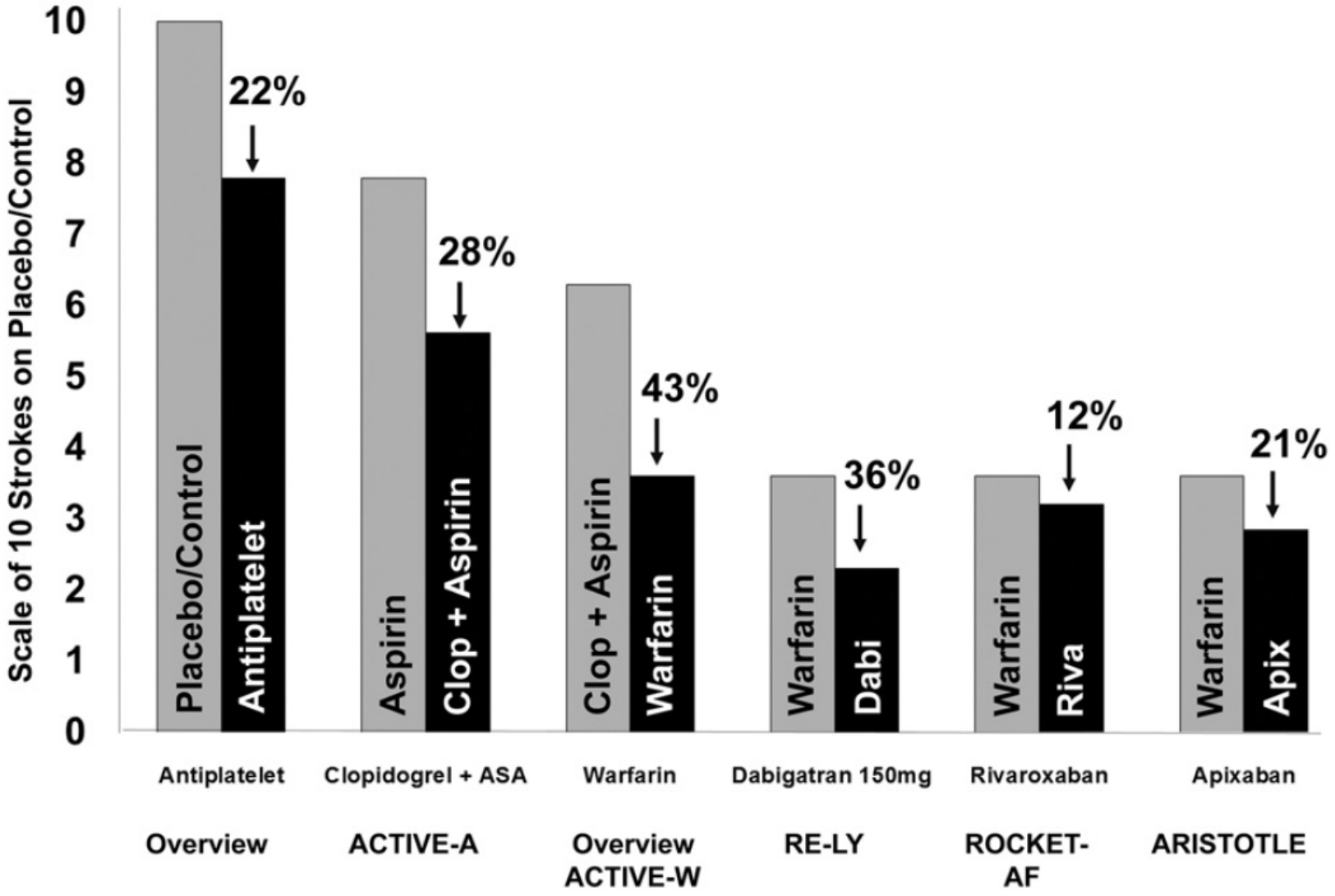

Scale of 10 Strokes on Placebo/Control
10
9
8
7
6
5
4
3
2
1
0
Placebo/Control
Antiplatelet
22%
Aspirin
Clop + Aspirin
28%
Clop + Aspirin
Warfarin
43%
Warfarin
Dabi
36%
Warfarin
Riva
12%
Warfarin
Apix
21%
Antiplatelet
Clopidogrel + ASA
Warfarin
Dabigatran 150mg
Rivaroxaban
Apixaban
Overview
ACTIVE-A
Overview
ACTIVE-W
RE-LY
ROCKET-
AF
ARISTOTLE

Table 1. Comparison of Pharmacological Characteristics of Warfarin and the New Oral Anticoagulants for Atrial Fibrillation

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Administration	Once a day	Twice a day	Once a day	Twice a day	Once a day
Target	Vitamin K–dependent factors	Factor II	Factor Xa	Factor Xa	Factor Xa
Time to peak effect	3–5 d	1 h	2.5–4 h	3 h	1–2 h
Dose	Variable	150 mg twice a day and 110 mg twice a day	20 mg every day (15 mg every day for renal impairment)	5 mg twice a day (2.5 mg twice a day for high risk)	30 mg every day and 60 mg every day (with adjustment for high exposure)
Half-life	40 h	12–14 h	7–11 h	12 h	9–11 h
Interactions	Multiple	Inhibitors of P-glycoprotein transporter*	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and prostaglandin transporter†
Renal clearance, %	0	80	35	25	40
Anticoagulation monitoring	Required	Not required	Not required	Not required	Not required
Antidote	Vitamin K	None	None	None	None

*Inhibitors of P-glycoprotein transporter include amiodarone (cautions with interaction) and verapamil.
†Inhibitors of CYP 3A4 and P-glycoprotein transporter include antifungals and protease inhibitors.

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

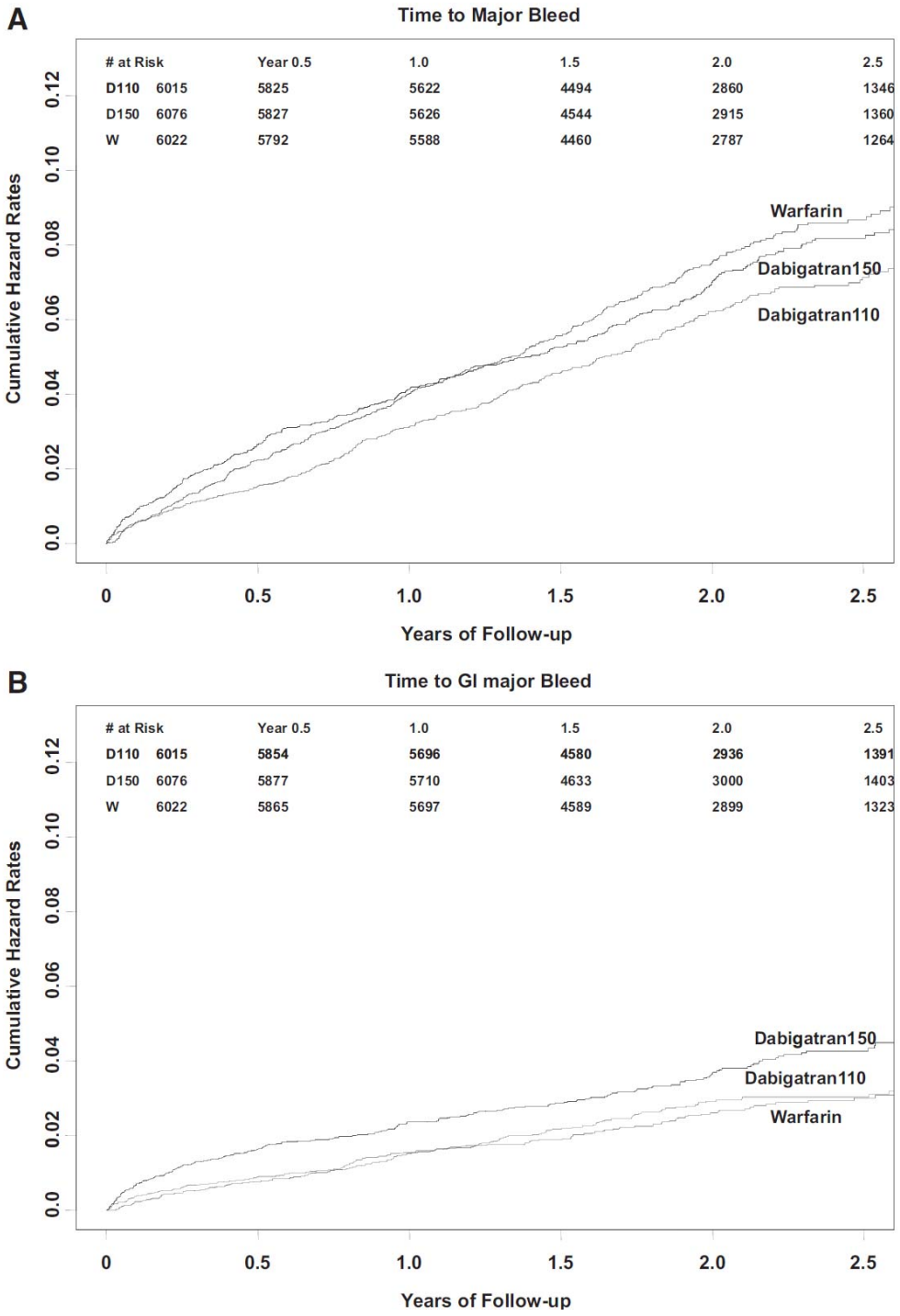
John W. Eikelboom, MBBS; Lars Wallentin, MD; Stuart J. Connolly, MD; Mike Ezekowitz, MD; Jeff S. Healey, MD; Jonas Oldgren, MD; Sean Yang, BComSc; Marco Alings, MD; Scott Kaatz, DO; Stefan H. Hohnloser, MD; Hans-Christoph Diener, MD; Maria Grazia Franzosi, PhD; Kurt Huber, MD; Paul Reilly, MD; Jeanne Varrone, MD; Salim Yusuf, MD

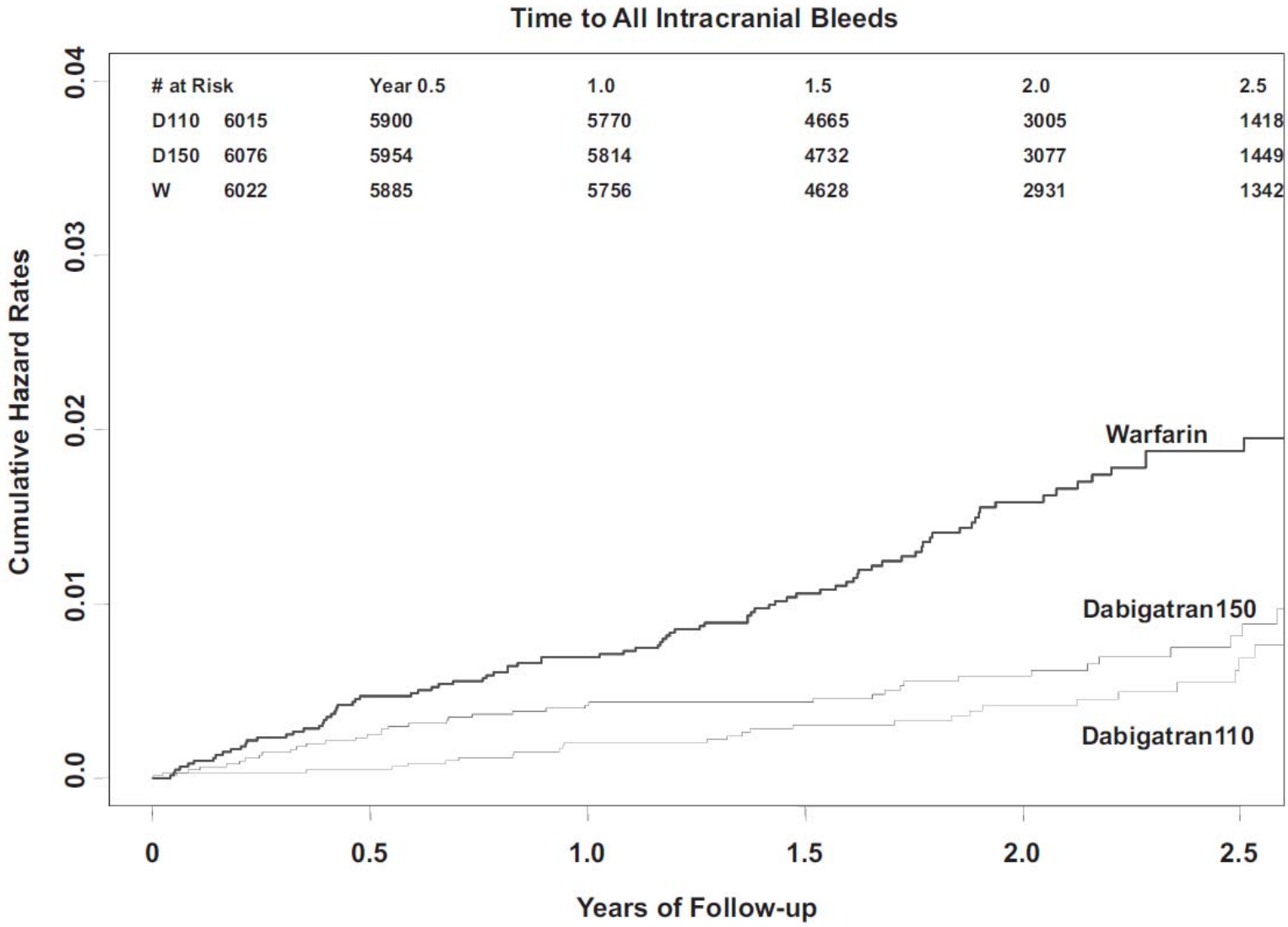
Background—Dabigatran 150 and 110 mg twice a day and warfarin are effective for stroke prevention in atrial fibrillation. The purpose of this study was to compare their risks of bleeding in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.

Methods and Results—The RE-LY trial randomized 18 113 patients to receive dabigatran 110 or 150 mg twice a day or warfarin dose adjusted to an international normalized ratio of 2.0 to 3.0 for a median follow-up of 2.0 years. Compared with warfarin, dabigatran 110 mg twice a day was associated with a lower risk of major bleeding (2.87% versus 3.57%; $P=0.002$), whereas dabigatran 150 mg twice a day was associated with a similar risk of major bleeding (3.31% versus 3.57%; $P=0.32$). There was a significant treatment-by-age interaction, such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; $P<0.001$) and a similar risk in those aged ≥75 years (4.43% versus 4.37%; $P=0.89$; P for interaction <0.001), whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; $P<0.001$) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; $P=0.07$; P for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.

Conclusions—In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00262600. (***Circulation*. 2011;123:2363-2372.**)


A
Time to Major Bleed
at Risk Year 0.5 1.0 1.5 2.0 2.5
D110 6015 5825 5622 4494 2860 1346
D150 6076 5827 5626 4544 2915 1360
W 6022 5792 5588 4460 2787 1264
Warfarin
Dabigatran150
Dabigatran110
Cumulative Hazard Rates
0.0 0.02 0.04 0.06 0.08 0.10 0.12
0 0.5 1.0 1.5 2.0 2.5
Years of Follow-up
B
Time to GI major Bleed
at Risk Year 0.5 1.0 1.5 2.0 2.5
D110 6015 5854 5696 4580 2936 1391
D150 6076 5877 5710 4633 3000 1403
W 6022 5865 5697 4589 2899 1323
Dabigatran150
Dabigatran110
Warfarin
Cumulative Hazard Rates
0.0 0.02 0.04 0.06 0.08 0.10 0.12
0 0.5 1.0 1.5 2.0 2.5
Years of Follow-up


Time to All Intracranial Bleeds
at Risk
Year 0.5
1.0
1.5
2.0
2.5
D110 6015
5900
5770
4665
3005
1418
D150 6076
5954
5814
4732
3077
1449
W 6022
5885
5756
4628
2931
1342
Warfarin
Dabigatran150
Dabigatran110
Cumulative Hazard Rates
0.0
0.01
0.02
0.03
0.04
0
0.5
1.0
1.5
2.0
2.5
Years of Follow-up

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subclinical Atrial Fibrillation and the Risk of Stroke

Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D., Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D., Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc., Christophe Bailleul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D., Ellison Themeles, M.Sc., Elizabeth S. Kaufman, M.D., and Stefan H. Hohnloser, M.D., for the ASSERT Investigators*

N Engl J Med 2012;366:120-9.

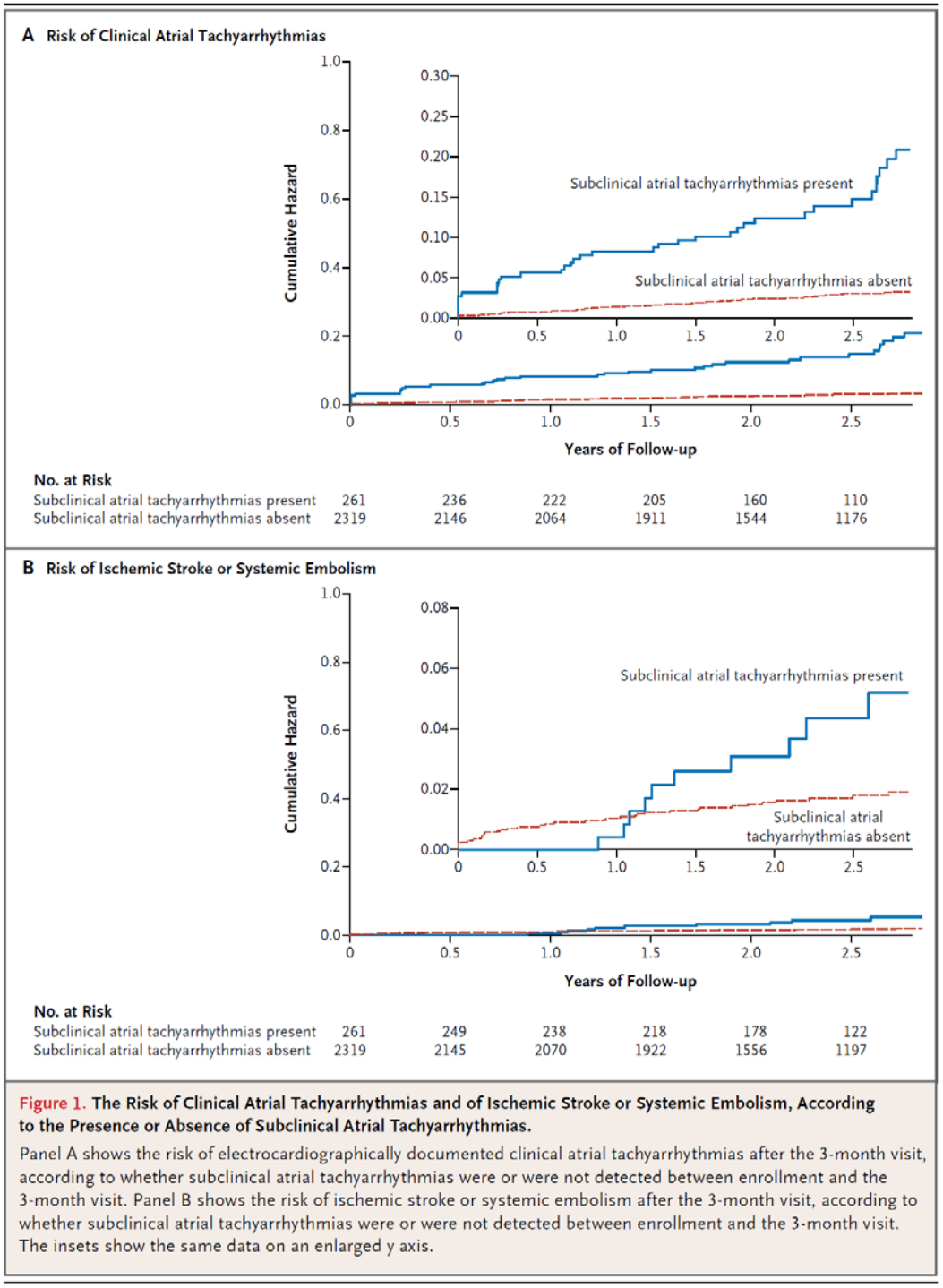


Figure 1. The Risk of Clinical Atrial Tachyarrhythmias and of Ischemic Stroke or Systemic Embolism, According to the Presence or Absence of Subclinical Atrial Tachyarrhythmias.

Panel A shows the risk of electrocardiographically documented clinical atrial tachyarrhythmias after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. Panel B shows the risk of ischemic stroke or systemic embolism after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. The insets show the same data on an enlarged y axis.

European Journal of Heart Failure (2012) **14**, 295–301
doi:10.1093/eurjhf/hfs005

Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project

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Received 24 October 2011; revision requested 1 December 2011; accepted 23 December 2011; online publish-ahead-of-print 30 January 2012

Aims Heart failure (HF) increases the risk of stroke and thrombo-embolism (TE) in non-valvular atrial fibrillation (NVAF), and is incorporated in stroke risk stratification scores. We aimed to establish the role of ejection fraction (EF) in risk prediction in patients with NVAF and HF.

Methods and results Patients with NVAF, history of HF, and measured EF were included in a retrospective analysis. Patients with HF and preserved ejection fraction (HFPEF) were defined as those with clinical HF and EF $\geq$ 50% in this study. Among 7156 patients with NVAF, 1276 (17.8%) patients with HF and measured EF were included. Of these, 747/1276 (58.5%) patients were on vitamin K antagonists. The stroke/TE event rate per 100 person-years was 1.05 [95% confidence interval (CI) 0.87–1.25]. Patients with HFPEF were more likely to be female ($P < 0.001$), older ($P < 0.001$), and hypertensive ($P < 0.001$), and less likely to have prior vascular disease ($P < 0.001$). There were no differences in rates of stroke ($P = 0.17$) and stroke/TE ($P = 0.11$) between patients with HFPEF and those with HF and reduced EF. There were no significant differences in rates of all-cause mortality when patients were stratified by EF. In multivariate analyses, only previous stroke (hazard ratio 2.36, 95% CI 1.45–3.86) and vascular disease (1.57, 1.07–2.30) increased the risk of stroke/TE amongst NVAF patients with HF, but EF <35% did not (0.75, 0.44–1.30).

Conclusion In NVAF patients with HF, there were no differences in rates of stroke, TE, or death between EF categories. Only previous stroke and vascular disease (and not decreased EF) independently increased risk of stroke/TE in multivariate analyses.

Keywords Heart failure • Atrial fibrillation • Ejection fraction • Stroke • Thrombo-embolism • Risk

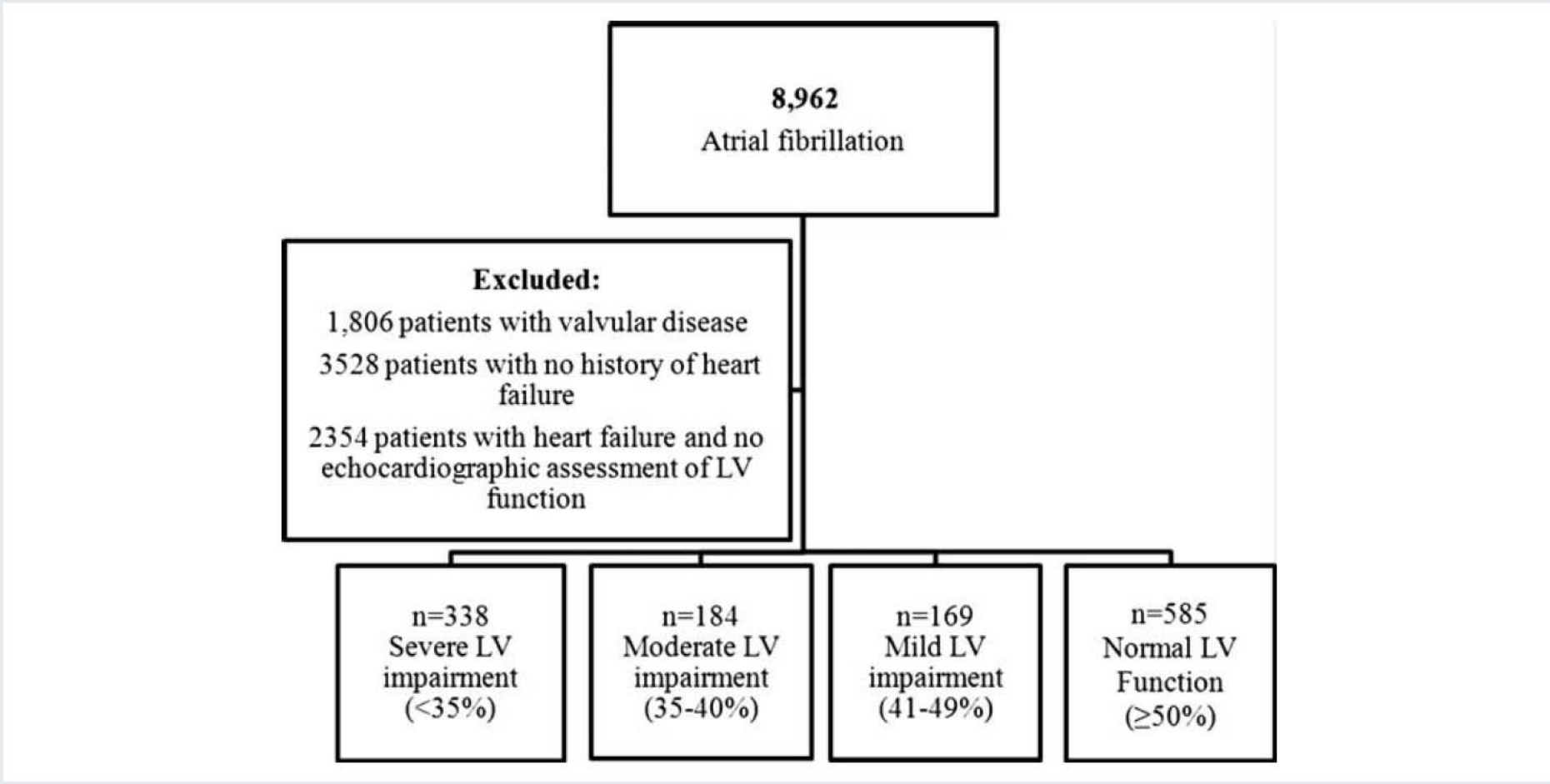

Figure 1 Study population in heart failure patients. LV, left ventricular.

Table 1 Characteristics of patients with heart failure by left ventricular ejection fraction

n (%)	HFREF (EF <50%), *n* = 691	HFPEF (EF ≥50%), *n* = 585	*P*-value	Age-adjusted *P*-value
Mean age (SD)	70.7 (12.0)	74.7 (12.5)	<0.001	–
Female sex	155 (22.4)	294 (50.3)	<0.001	<0.001
Type of AF			0.53	0.64
Paroxysmal	337 (48.8)	295 (50.4)		
Permanent	305 (44.1)	242 (41.4)		
Persistent	49 (7.1)	48 (8.2)		
Co-morbidities				
Hypertension	298 (43.1)	363 (62.1)	<0.001	<0.001
Diabetes	164 (23.7)	150 (25.6)	0.44	0.36
Previous stroke	45 (6.5)	40 (6.8)	0.82	0.97
Any vascular disease	365 (52.8)	205 (35.0)	<0.001	<0.001
Renal failure	116 (16.8)	90 (15.4)	0.54	0.83
Dyslipidaemia	157 (22.7)	153 (26.2)	0.17	0.08
Smoking	142 (20.5)	97 (16.6)	0.07	0.85
Pacemaker/ICD	204 (29.5)	111 (19.0)	<0.001	<0.001
Bleeding risk factors				
Previous bleeding	39 (5.6)	35 (6.0)	0.81	0.90
Labile INR	21 (3.0)	23 (3.9)	0.24	0.37
Antithrombotic agents				
Vitamin K antagonist	412 (59.6)	335 (61.4)	0.44	0.83
Antiplatelet	231 (33.4)	199 (37.3)	0.81	0.44
Any antithrombotic	529 (76.6)	458 (78.3)	0.33	0.51
Heart failure therapy				
ACEI/ARB	391 (56.6)	180 (38.1)	<0.001	<0.001
Beta-blocker	345 (49.9)	237 (50.1)	<0.001	<0.001
Digoxin	213 (30.8)	128 (27.1)	0.001	0.001
Diuretic	397 (57.5)	259 (54.8)	<0.001	<0.001
Antiarrhythmic agent	280 (40.5)	290 (49.6)	0.06	<0.001
Calcium channel blocker	40 (5.8)	54 (23.3)	0.11	0.07
$CHADS_2$				
Intermediate (score = 1)	198 (28.7)	88 (15.0)	<0.001	<0.001
High (score ≥2)	493 (71.3)	497 (85.0)		
CHA_2DS_2-VASc				
Intermediate (score = 1)	66 (9.6)	22 (3.8)	<0.001	<0.001
High (score ≥2)	625 (90.4)	563 (96.2)		
HAS-BLED				
Low (score = 0–2)	508 (73.5)	413 (70.6)	0.07	0.10
High (score ≥3)	183 (26.5)	172 (29.4)		

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; $CHADS_2$ (one point each for congestive heart failure, hypertension, age ≥75, and diabetes, and two points for previous stroke or thrombo-embolism); CHA_2DS_2-VASc (one point for congestive heart failure, hypertension, diabetes, vascular disease, age 65–74, and female sex, and two points for previous stroke or thrombo-embolism and age ≥75); HAS-BLED [Hypertension, Abnormal renal and/or liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years)]; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; ICD, implantable cardiac defibrillator; INR, international normalized ratio; SD, standard deviation.

Table 2 Event rates (95% confidence interval) per 100 person-years in patients with heart failure and measured ejection fraction

	HFREF (EF <50%)			HFPEF (EF ≥ 50%)	
	Events	Event rate	*P**	Events	Event rate
Stroke	46	0.67 (0.49–0.89)	0.17	51	0.87 (0.65–1.15)
Stroke/TE	65	0.94 (0.73–1.20)	0.11	68	1.16 (0.90–1.47)
Stroke/TE/death	175	2.53 (2.17–2.94)	0.85	151	2.58 (2.19–3.03)
Bleeding	78	1.13 (0.89–1.41)	0.06	88	1.50 (1.21–1.85)
All-cause death	139	2.01 (1.69–2.38)	0.43	107	1.83 (1.50–2.21)

HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; TE, thrombo-embolism.
*P-value for two-sided χ^2 test using Fisher's exact test using patients with normal ejection fraction (EF ≥50%) as the reference group.

Table 3 Hazard ratio (95% confidence interval) of stroke and thrombo-embolism in patients with heart failure and measured ejection fraction

	Univariate HR (95% CI)	Multivariate HR (95% CI)
Hypertension	1.14 (0.80–1.63)	0.91 (0.62–1.43)
Age ≥75	1.72 (1.10–2.70)	1.37 (0.85–2.20)
Diabetes	1.05 (0.70–1.57)	0.94 (0.62–1.34)
Previous stroke	2.56 (1.59–4.14)	2.36 (1.45–3.86)
Vascular disease	1.43 (1.01–2.03)	1.57 (1.07–2.30)
Age 65–74	1.15 (0.71–1.89)	1.06 (0.64–1.74)
Female sex	1.49 (1.05–2.13)	1.43 (0.96–2.13)
Ejection fraction <35%*	0.72 (0.45–1.15)	0.75 (0.44–1.30)
Ejection fraction 35–49%*	1.14 (0.77–1.71)	1.27 (0.83–1.93)
Ejection fraction†	1.04 (0.96–1.12)	1.05 (0.97–1.13)

CI, confidence interval; HR, hazard ratio.

*Hazard ratio calculated with the patients with normal ejection fraction, i.e. EF ≥50%, as the reference category

†Ejection fraction as a continuous variable with the hazard ratio representing the risk associated with a 1% drop in ejection fraction.

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Stroke aetiology and predictors of outcome in patients with heart failure and acute stroke: a 10-year follow-up study

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Aims The aim of this study was to investigate stroke aetiology and assess the predictors of early and late outcome in patients with heart failure (HF) and acute stroke.

Methods and results A total of 2904 patients, admitted between 1993 and 2010, were regularly followed up at months 1, 3, and 6, and yearly thereafter up to 10 years. There were 283 (9.7%) stroke patients with HF; atrial fibrillation (AF) was present in 144 (50.9%) of them. Stroke aetiology in patients with HF and AF was mainly cardioembolism (82%) regardless of HF aetiology. In contrast, in the 139 non-AF patients with HF, the stroke mechanism was associated with the aetiology of HF: valvular heart disease and dilated cardiomyopathy were related to cardioembolism in 60% and 66.7% of patients, respectively, whereas HF due to coronary artery disease or hypertension was associated with atherosclerotic and lacunar stroke in 40.8% and 61.5%, respectively. In the overall population, HF was an independent predictor of 10-year mortality [hazard ratio = 1.54, 95% confidence interval (CI) 1.29–1.83; $P < 0.001$]. Probability of 10-year survival was 19.4% (95% CI 14.5–23.5) for HF patients and 44.1% (95% CI 41.4–46.8) for non-HF patients ($P < 0.0001$). Ten-year mortality in HF patients was associated with functional class of HF, age, diabetes, stroke severity, and in-hospital aspirin use. The presence of AF in HF stroke patients did not influence 10-year survival and composite cardiovascular events ($P = 0.429$ and $P = 0.406$, respectively).

Conclusions In patients with HF, stroke aetiology is influenced by the presence of AF and the underlying cause of HF. Early and late stroke outcome is associated with HF severity but not with the presence of AF.

Keywords Heart failure • Stroke • Mortality • Atrial fibrillation

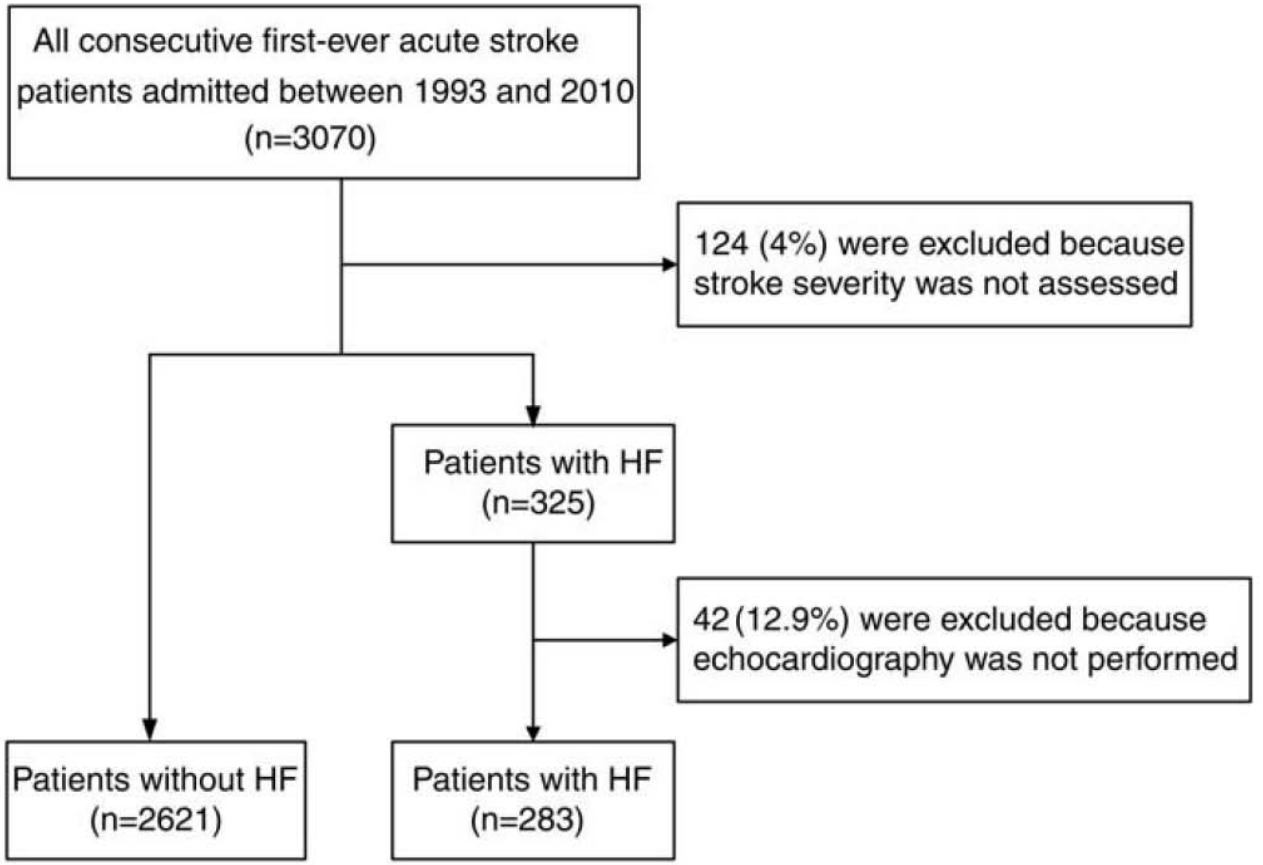

Figure 1 Flow diagram of the study. HF, heart failure.

Table 1 Demographics, risk factors, clinical characteristics, and stroke subtypes of 2904 acute stroke patients with/without heart failure

Variable	All patients (n = 2904)	Without heart failure (n = 2621)	With heart failure (n = 283)	P-value
Mean age (years)	69.8 (12.1)	69.7 (12.1)	70.4 (11.9)	0.358
Sex (male)	1805 (62.2)	1615 (61.6)	190 (67.1)	0.071
Hypertension	2021 (69.6)	1835 (70.0)	186 (65.7)	0.153
Diabetes mellitus	728 (25.1)	640 (24.4)	88 (31.1)	0.017
Dyslipidaemia	930 (32.0)	848 (32.4)	82 (29.0)	0.255
Cigarette smoking	912 (31.4)	818 (31.2)	94 (33.2)	0.501
Coronary artery disease	544 (18.7)	404 (15.4)	140 (49.5)	<0.001
Valvular heart disease	141 (4.9)	85 (3.2)	56 (19.8)	<0.001
Atrial fibrillation	930 (32.0)	725 (27.7)	144 (50.9)	<0.001
Neurological severity (NIHSS score)	10.0 (9.0)	9.9 (9.1)	10.69 (8.4)	0.168
Ejection fraction[a] (%)	61.4 (13.8)	65.2 (8.3)	41.8 (11.9)	<0.001
Stroke subtypes				
Large artery atherosclerotic	476 (16.4)	437 (16.7)	39 (13.8)	0.237
Cardioembolic	886 (30.5)	703 (26.8)	183 (64.7)	<0.001
Lacunar	555 (19.1)	539 (20.6)	16 (5.7)	<0.001
Systemic hypoperfusion	23 (0.8)	6 (0.2)	17 (6.0)	<0.001
Miscellaneous causes	58 (2.0)	58 (2.2)	0	0.005
Undetermined aetiology	474 (16.3)	461 (17.6)	13 (4.6)	<0.001
Intracerebral haemorrhage	432 (14.9)	417 (15.9)	15 (5.3)	<0.001

Numbers in parentheses for nominal data indicate percentages and for continuous data the standard deviation. P-values are for comparison between patients with and without heart failure.

[a]Echocardiographic data were available in all patients with heart failure and in 1004 patients without heart failure.

NIHSS score, National Institutes of Health Stroke Scale.

Table 2 Aetiology of heart failure, NYHA functional status, and treatment among 283 acute stroke patients with heart failure and with/without atrial fibrillation

	Patients without heart failure ($n = 2621$)	Patients with heart failure ($n = 283$)	Heart failure with atrial fibrillation ($n = 144$)	Heart failure without atrial fibrillation ($n = 139$)	*P*-value[a]
Aetiology of heart failure					0.160
Coronary artery disease		136 (48.1)	60 (41.7)	76 (54.7)	
Valvular heart disease		48 (17.0)	28 (19.4)	20 (14.4)	
Dilated cardiomyopathy		66 (23.3)	36 (24.8)	30 (21.6)	
Hypertension		33 (11.7)	20 (13.9)	13 (9.4)	
Heart failure functional class					0.356
NYHA I		104 (36.7)	47 (32.6)	57 (41.0)	
NYHA II		95 (33.6)	48 (33.3)	47 (33.8)	
NYHA III		52 (18.4)	30 (20.8)	22 (15.8)	
NYHA IV		32 (11.3)	19 (13.2)	13 (9.4)	
Preserved left ventricular function (EF $\geq$40%)		167 (59.0)	94 (65.3)	73 (52.5)	0.030
Stroke in-hospital treatment					
Thrombolysis	51 (1.9)	6 (2.1)	4 (2.8)	2 (1.4)	0.684
Aspirin	1890 (72.1)	228 (80.6)	121 (84.0)	107 (77.0)	0.176
Heparin[b]	1263 (48.2)	193 (68.2)	111 (77.1)	82 (59.0)	0.001
Treatment at discharge[c]					
Antiplatelets	1368 (59.5)	117 (49.0)	40 (33.9)	77 (62.0)	$<$0.001
Warfarin	375 (16.3)	86 (36.0)	65 (55.1)	21 (17.4)	$<$0.001
Diuretics	589 (25.6)	146 (61.1)	76 (64.4)	70 (57.9)	0.353
Beta-blockers	395 (17.2)	57 (23.8)	32 (27.1)	25 (20.7)	0.288
ACE inhibitors/ARBs	669 (29.1)	119 (49.8)	50 (42.4)	69 (58)	0.028
Calcium channel blockers	527 (22.9)	65 (27.2)	27 (22.9)	28 (23.1)	0.998
Vasodilators	137 (6.0)	44 (18.4)	20 (16.90	24 (19.8)	0.618
Statins	401 (17.4)	34 (14.2)	15 (12.7)	19 (15.7)	0.580

Stroke in-hospital treatment and treatment at discharge are also presented for patients without heart failure.
Numbers in parentheses indicate percentages.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association.
[a]*P*-values for comparisons between heart patients with and without atrial fibrillation.
[b]Low dose heparin for deep venous thrombosis prophylaxis.
[c]Based on data from 2537 patients who were discharged alive (239 with heart failure).

Table 3 Association between stroke subtype and aetiology of HF in patients without HF, patients with HF and AF, and non-AF patients with HF

Stroke type	Patients without HF ($n = 2621$)	Patients with HF and AF ($n = 144$)	Non-AF patients with HF			
			Coronary artery diseases ($n = 76$)	Valvular diseases ($n = 20$)	Dilated myocardiopathy ($n = 30$)	Hypertension ($n = 13$)
Large artery atherosclerotic	437 (16.7)	12 (8.3)	31 (40.8)	1 (5.0)	2 (6.7)	2 (15.4)
Cardioembolic	703 (26.8)	118 (81.9)	24 (31.6)	12 (60.0)	20 (66.7)	1 (7.7)
Lacunar	539 (20.6)	3 (2.1)	4 (5.2)	1 (5.0)	2 (6.7)	8 (61.5)
Systemic hypoperfusion	6 (0.2)	4 (2.8)	6 (7.9)	3 (15.0)	4 (13.3)	0
Undetermined aetiology	461 (17.6)	3 (2.1)	6 (7.9)	2 (10.0)	1 (3.3)	0
Intracerebral haemorrhage	417 (15.9)	4 (5.3)	5 (6.6)	1 (5.0)	1 (3.3)	2 (15.4)

Numbers in parenthesis indicate percentages.
AF, atrial fibrillation; HF, heart failure.

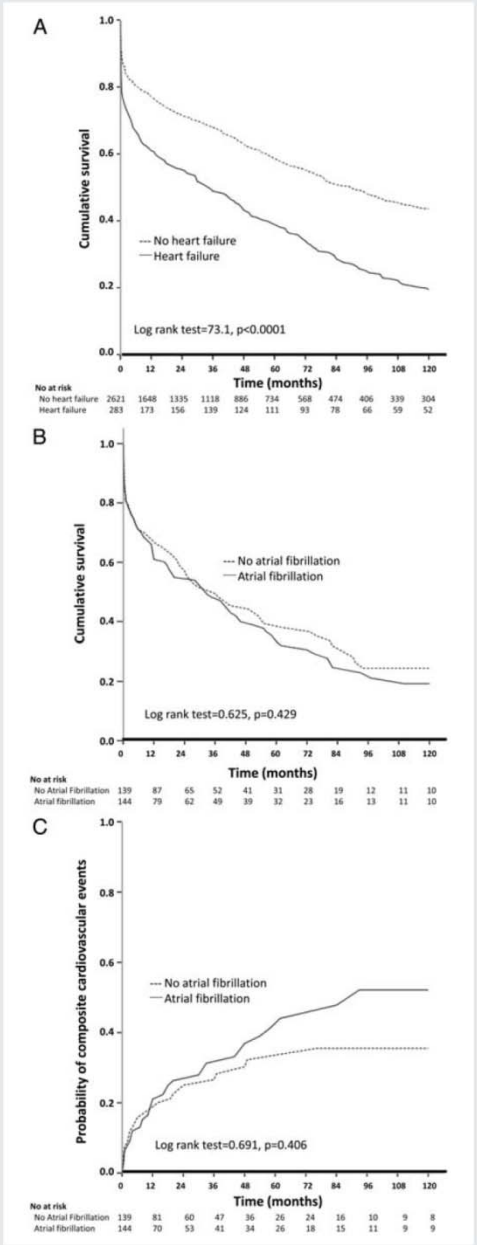

Figure 2 Kaplan–Meier curves. (*A*) Ten-year cumulative survival of first-ever stroke patients with/without heart failure. (*B*) Ten-year cumulative survival for first-ever stroke patients with heart failure and with/without atrial fibrillation. (*C*) Cumulative probability of composite cardiovascular events in stroke patients with heart failure and with/without atrial fibrillation.

Table 4 Multivariate Cox regression analyses determining the effect of various factors on 10-year mortality among 283 patients with heart failure and first-ever acute stroke

	Model A[a]	Model B[b]
Age (per 10 years increase)	1.35 (1.15–1.59)*	
Diabetes mellitus	1.50 (1.05–2.14)***	
Coronary artery disease		1.68 (1.12–2.52)***
Stroke severity (per 1-point increase in NIHSS score)	1.05 (1.03–1.08)*	
Heart failure functional class		
NYHA I	1.0	1.0
NYHA II	1.70 (1.05–2.75)***	1.68 (1.06–2.73)***
NYHA III	2.98 (1.68–5.26)*	2.90 (1.59–5.31)*
NYHA IV	2.91 (1.59–5.33)*	3.13 (1.77–5.52)*
Aspirin in hospital	0.66 (0.45–0.96)***	0.49 (0.31–0.76)*
Oral anticoagulant at discharge		0.55 (0.35–0.87)***
Statin at discharge		0.26 (0.08–0.62)**

Model A: adjusted for history of smoking, atrial fibrillation, stroke subtypes, aetiology of heart failure, ejection fraction, and in-hospital therapy.
Model B: recommended therapy at discharge added to Model A in 239 surviving patients.
Values are presented as hazard ratio (95% confidence intervals).
NIHSS score, National Institute of Health Stroke Scale score; NYHA, New York Heart Association.
*$P < 0.001$; **$P < 0.01$; ***$P < 0.05$.

Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

*GISSI-HF investigators**

Summary

Background Large observational studies, small prospective studies and post-hoc analyses of randomised clinical trials have suggested that statins could be beneficial in patients with chronic heart failure. However, previous studies have been methodologically weak. We investigated the efficacy and safety of the statin rosuvastatin in patients with heart failure.

Methods We undertook a randomised, double-blind, placebo-controlled trial in 326 cardiology and 31 internal medicine centres in Italy. We enrolled patients aged 18 years or older with chronic heart failure of New York Heart Association class II–IV, irrespective of cause and left ventricular ejection fraction, and randomly assigned them to rosuvastatin 10 mg daily (n=2285) or placebo (n=2289) by a concealed, computerised telephone randomisation system. Patients were followed up for a median of 3·9 years (IQR 3·0–4·4). Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00336336.

Findings We analysed all randomised patients. 657 (29%) patients died from any cause in the rosuvastatin group and 644 (28%) in the placebo group (adjusted hazard ratio [HR] 1·00 [95·5% CI 0·898–1·122], p=0·943). 1305 (57%) patients in the rosuvastatin group and 1283 (56%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 1·01 [99% CI 0·908–1·112], p=0·903). In both groups, gastrointestinal disorders were the most frequent adverse reaction (34 [1%] rosuvastatin group *vs* 44 [2%] placebo group).

Interpretation Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe.

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See Comment page 1195

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	Rosuvastatin (N=2285)	Placebo (N=2289)
Patients' characteristics		
Age (years)	68 (11)	68 (11)
Age >70 years	1002 (43·9%)	1012 (44·2%)
Women	543 (23·8%)	489 (21·4%)
Heart disease risk factors		
BMI (kg/m²)	27·1 (4·6)	27·1 (4·4)
SBP (mm Hg)	127 (18)	127 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	73 (14)	73 (13)
Current smoking	323 (14·1%)	321 (14·0%)
History of hypertension	1260 (55·1%)	1224 (53·5%)
NYHA class		
II	1398 (61·2%)	1462 (63·9%)
III	828 (36·2%)	771 (33·7%)
IV	59 (2·6%)	56 (2·4%)
LVEF (%)	33·4% (8·8)	33·1% (8·7)
LVEF >40%	236 (10·3%)	225 (9·8%)
Medical history		
Admission for HF in previous year	1189 (52·0%)	1131 (49·4%)
Previous AMI	727 (31·8%)	774 (33·8%)
Previous stroke	99 (4·3%)	109 (4·8%)
Diabetes	625 (27·4%)	571 (25·0%)
CABG	296 (13·0%)	319 (13·9%)
PCI	185 (8·1%)	192 (8·4%)
ICD	146 (6·4%)	155 (6·8%)
Pacemaker	300 (13·1%)	263 (11·5%)
History of atrial fibrillation	440 (19·3%)	477 (20·8%)
Peripheral vascular disease	184 (8·1%)	160 (7·0%)
COPD	538 (23·5%)	522 (22·8%)
Neoplasia	76 (3·3%)	91 (4·0%)
Heart failure cause		
Ischaemic	909 (39·8%)	919 (40·2%)
Dilatative	793 (34·7%)	783 (34·2%)
Hypertensive	409 (17·9%)	414 (18·1%)
Other cause	70 (3·1%)	65 (2·8%)
Non-detectable/unknown	104 (4·5%)	108 (4·7%)

(Continues in next column)

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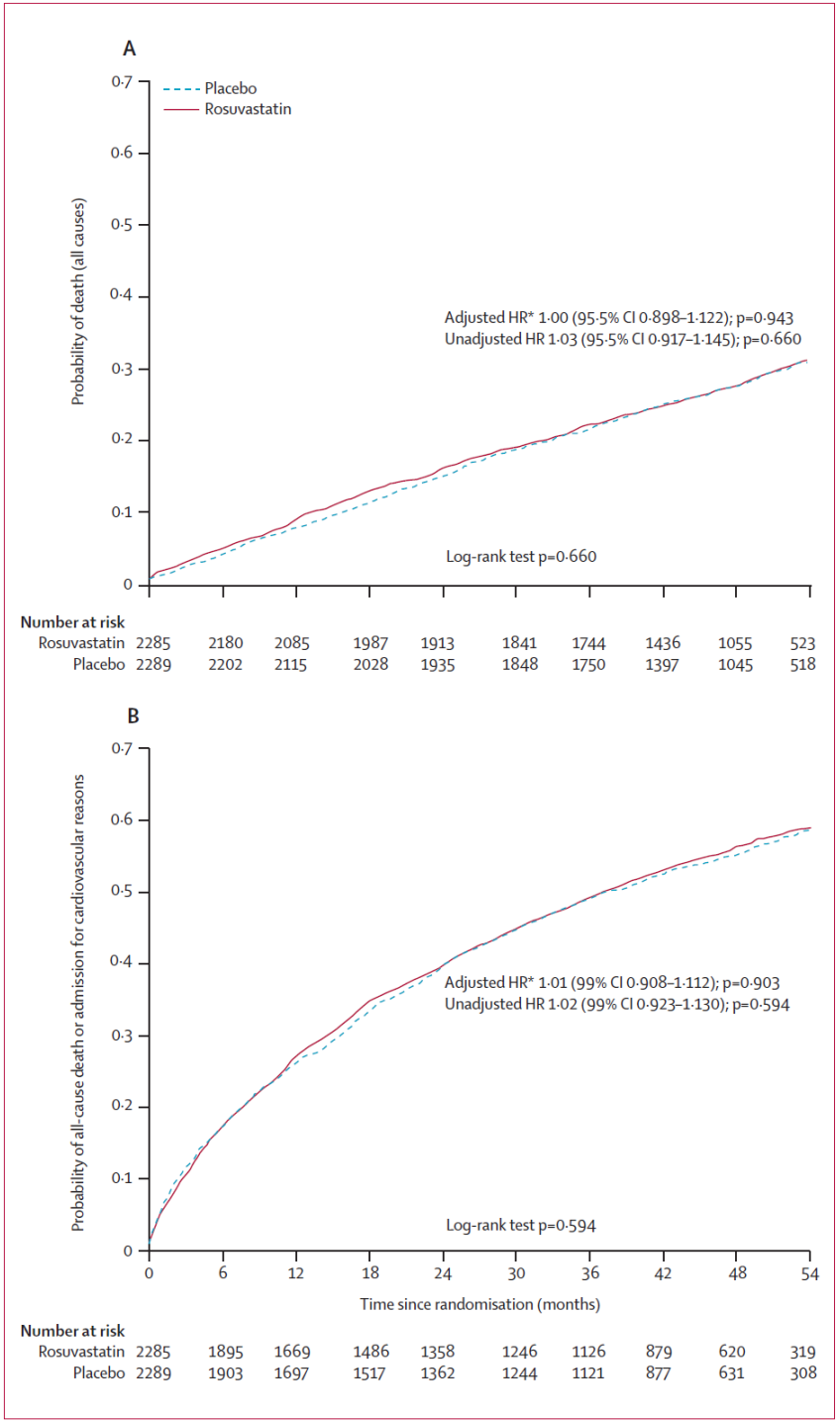
	Rosuvastatin (N=2285)	Placebo (N=2289)
Physical examinations		
Pulmonary rales	646 (28·3%)	614 (26·8%)
Third heart sound	576 (25·2%)	552 (24·1%)
Mitral insufficiency	1467 (64·2%)	1462 (63·9%)
Aortic stenosis	44 (1·9%)	49 (2·1%)
ECG findings		
QRS >120 ms*	794 (35·2%)	761 (33·6%)
Atrial fibrillation	430 (18·8%)	454 (19·8%)
Pathological Q waves	384 (16·8%)	439 (19·2%)
Left ventricular hypertrophy	492 (21·5%)	449 (19·6%)
Medical treatment		
ACE inhibitors	1766 (77·3%)	1784 (77·9%)
ARBs	442 (19·3%)	392 (17·1%)
ACE inhibitors/ARBs	2150 (94·1%)	2126 (92·9%)
β blockers	1433 (62·7%)	1420 (62·0%)
Spironolactone	890 (39·0%)	945 (41·3%)
Diuretic drugs	2057 (90·0%)	2061 (90·0%)
Digitalis	915 (40·0%)	915 (40·0%)
Oral anticoagulant drugs	681 (29·8%)	698 (30·5%)
Aspirin	1020 (44·6%)	1044 (45·6%)
Other antiplatelet agents	179 (7·8%)	188 (8·2%)
Nitrates	729 (31·9%)	761 (33·3%)
Calcium-channel blockers	230 (10·1%)	231 (10·1%)
Amiodarone	464 (20·3%)	421 (18·4%)

Data are mean (SD) or number (%). BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. LVEF=left ventricular ejection fraction. HF=heart failure. AMI=acute myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. ICD=implantable cardioverter defibrillator. COPD=chronic obstructive pulmonary disease. ACE=angiotensin-converting enzyme. ARBs=angiotensin receptor blockers. *Available for 4523 patients (2257 rosuvastatin, 2266 placebo).

Table 1: **Baseline characteristics of patients**


A
Placebo
Rosuvastatin
Probability of death (all causes)
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
Adjusted HR* 1·00 (95·5% CI 0·898–1·122); p=0·943
Unadjusted HR 1·03 (95·5% CI 0·917–1·145); p=0·660
Log-rank test p=0·660
Number at risk
Rosuvastatin 2285 2180 2085 1987 1913 1841 1744 1436 1055 523
Placebo 2289 2202 2115 2028 1935 1848 1750 1397 1045 518
B
Probability of all-cause death or admission for cardiovascular reasons
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
Adjusted HR* 1·01 (99% CI 0·908–1·112); p=0·903
Unadjusted HR 1·02 (99% CI 0·923–1·130); p=0·594
Log-rank test p=0·594
0 6 12 18 24 30 36 42 48 54
Time since randomisation (months)
Number at risk
Rosuvastatin 2285 1895 1669 1486 1358 1246 1126 879 620 319
Placebo 2289 1903 1697 1517 1362 1244 1121 877 631 308

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Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial

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Aims This ancillary analysis of the GISSI-HF database aims at assessing the effect of rosuvastatin on the occurrence of atrial fibrillation (AF) in patients with chronic heart failure (HF) who were not in AF at study entry.

Methods and results GISSI-HF was a double-blind, placebo-controlled trial testing n-3 PUFA and rosuvastatin vs. corresponding placebos in patients with chronic HF. Atrial fibrillation occurrence was defined as the presence of AF in the electrocardiogram (ECG) performed at each visit during the trial or AF as a cause of worsening HF or hospital admission or as an event during hospitalization. Among the 3690 patients (80.7%) without AF on their baseline ECG, 15.0% developed AF during a median follow-up period of 3.7 years, 258 randomized to rosuvastatin (13.9%) vs. 294 allocated to placebo (16.0%). Although the difference was not significant at unadjusted analysis ($P = 0.097$) and multivariable analysis adjusting for clinical variables ($P = 0.067$), it became significant after adjustment for clinical variables and laboratory examinations ($P = 0.039$), and for clinical variables, laboratory examinations, and background therapies ($P = 0.038$).

Conclusion This study shows that there is some evidence of a beneficial effect of rosuvastatin in terms of reduction of AF occurrence in patients with HF. Larger populations are needed to provide a definite answer to the question.
ClinicalTrials.gov Identifier: NCT00336336

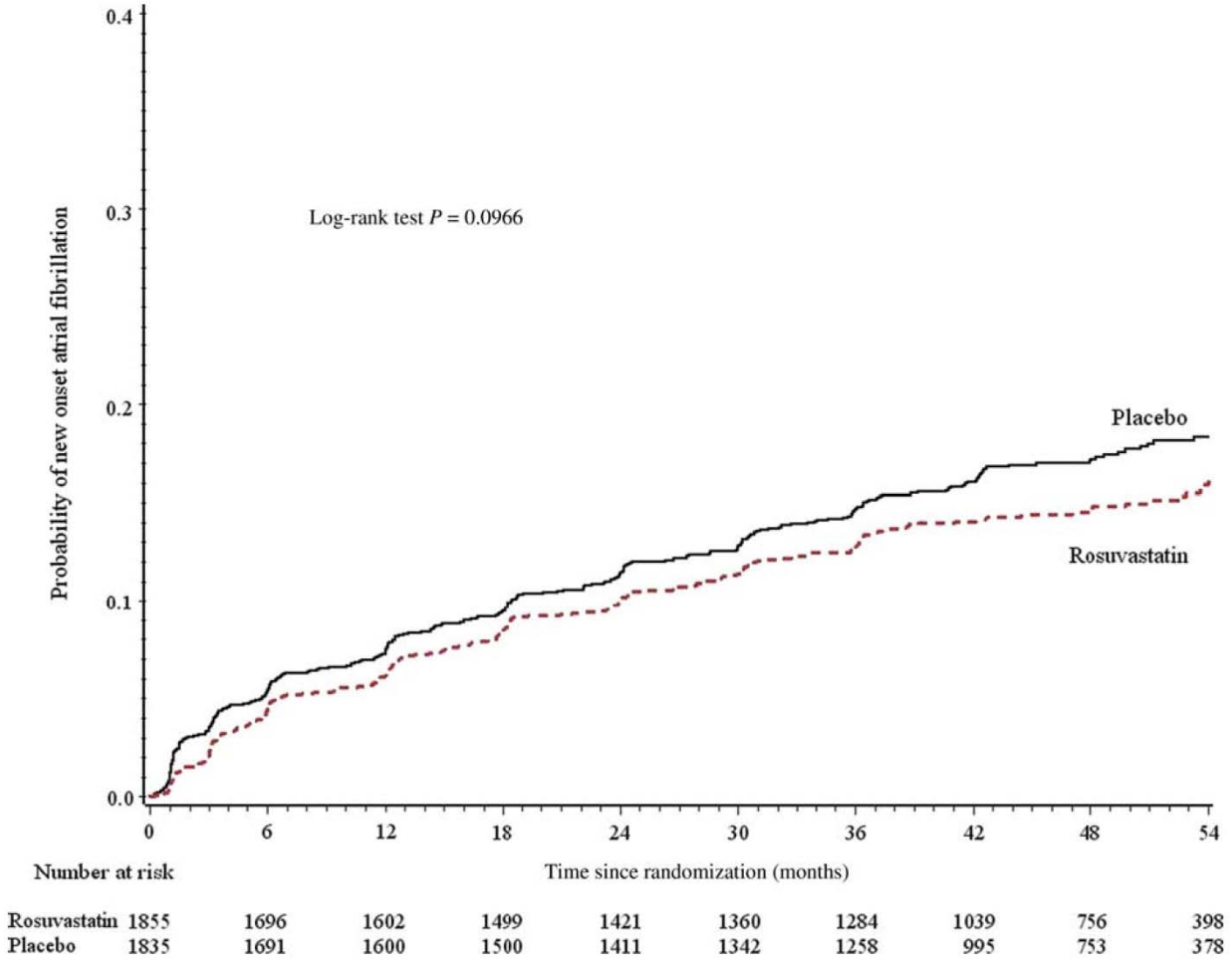
Keywords Atrial fibrillation • Heart failure • Rosuvastatin

Table 2 Baseline characteristics of patients developing atrial fibrillation during the course of GISSI-HF

	AF during study (n = 552)	No AF during study (n = 3138)	P-value
Patients' characteristics			
Age (years), mean ± SD	70 ± 10	66 ± 11	<0.0001[a]
Age >70 years, n (%)	286 (51.8)	1198 (38.2)	<0.0001[b]
Women, n (%)	110 (19.9)	713 (22.7)	0.15[b]
Risk factors			
BMI (kg/m^2), mean ± SD	27.3 ± 4.6	26.8 ± 4.4	0.01[a]
SBP (mmHg), mean ± SD	129 ± 19	126 ± 18	0.003[a]
Heart rate (b.p.m.), mean ± SD	70 ± 13	72 ± 13	0.03[a]
History of hypertension, n (%)	328 (59.4)	1640 (52.3)	0.002[b]
NYHA class III–IV, n (%)	217 (39.3)	1082 (34.5)	0.03[b]
LVEF (%), mean ± SD	33.8 ± 9.4	32.4 ± 8.0	0.002[a]
Medical history			
Admission for HF in previous year, n (%)	313 (56.7)	1456 (46.4)	<0.0001[b]
Previous AMI, n (%)	179 (32.4)	1127 (35.9)	0.11[b]
Previous stroke, n (%)	30 (5.4)	114 (3.6)	0.044[b]
Diabetes, n (%)	140 (25.4)	840 (26.8)	0.49[b]
CABG, n (%)	85 (15.4)	457 (14.6)	0.61[b]
PCI, n (%)	48 (8.7)	290 (9.2)	0.68[b]
ICD, n (%)	42 (7.6)	231 (7.4)	0.84[b]
Pacemaker, n (%)	96 (17.4)	398 (12.7)	0.003[b]
History of paroxysmal atrial fibrillation, n (%)	216 (39.1)	336 (10.7)	<0.0001[b]
Peripheral vascular disease, n (%)	38 (6.9)	230 (7.3)	0.71[b]
Chronic obstructive pulmonary disease, n (%)	160 (29.0)	655 (20.9)	<0.0001[b]
Neoplasia, n (%)	26 (4.7)	111 (3.5)	0.18[b]
Heart failure cause			
Ischemic aetiology, n (%)	227 (41.1)	1328 (42.3)	0.60[b]
Physical examinations			
Pulmonary rales, n (%)	154 (27.9)	796 (25.4)	0.21[b]
Third heart sound, n (%)	149 (27.0)	793 (25.3)	0.39[b]
Mitral insufficiency, n (%)	369 (66.9)	1945 (62.0)	0.03[b]
Aortic stenosis, n (%)	8 (1.5)	50 (1.6)	0.80[b]
ECG findings			
QRS ≥120 ms, n (%), available for 3653 patients	299 (54.4)	1552 (50.0)	0.06[b]
Left ventricular hypertrophy, n (%)	95 (17.2)	662 (21.1)	0.04[b]
Laboratory examinations			
Haemoglobin (g/dL), mean ± SD, available for 3666 patients	13.6 ± 1.6	13.7 ± 1.6	0.09[a]
White cell count (mm^3), mean ± SD, available for 3661 patients	7314 ± 2329	7328 ± 2061	0.89[a]
Fibrinogen (mg/dL), mean ± SD, available for 3375 patients	378 ± 114	364 ± 111	0.008[a]
Glycaemia (mg/dL), median (IQR), available for 3646 patients	102 (89–122)	103 (90–124)	0.23[c]
eGFR (ml/min/1.73 m^2), mean ± SD, available for 3671 patients	66.1 ± 22.5	70.8 ± 22.2	<0.0001[a]
Sodium (mEq/L), mean ± SD, available for 3666 patients	140 ± 4	140 ± 4	0.06[a]
Bilirubin (mg/dL), median (IQR), available for 3482 patients	0.74 (0.56–1.00)	0.70 (0.50–0.93)	0.002[c]
Lipid profile			
Total cholesterol (mg/dL), mean ± SD, available for 3658 patients	192 ± 42	197 ± 42	0.03[a]
LDL cholesterol (mg/dL), mean ± SD, available for 3306 patients	116 ± 38	121 ± 36	0.01[a]
HDL cholesterol (mg/dL), mean ± SD, available for 3552 patients	48 ± 14	48 ± 13	0.67[a]
Triglycerides (mg/dL), mean ± SD, available for 3643 patients	140 ± 76	148 ± 97	0.18[a]

Continued

Kaplan–Meier curves for time to new onset of AF



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Paul M Ridker, M.D.

ABSTRACT

BACKGROUND

Controversy persists regarding the extent of shared pathways between arterial and venous thrombosis and whether treatments of known efficacy for one disease process have consistent benefits for the other. Observational studies have yielded variable estimates of the effect of statin therapy on the risk of venous thromboembolism, and evidence from randomized trials is lacking.

METHODS

We randomly assigned 17,802 apparently healthy men and women with both low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to receive rosuvastatin, 20 mg per day, or placebo. We followed participants for the first occurrence of pulmonary embolism or deep-vein thrombosis and performed analyses of the data on an intention-to-treat basis.

RESULTS

During a median follow-up period of 1.9 years (maximum, 5.0), symptomatic venous thromboembolism occurred in 94 participants: 34 in the rosuvastatin group and 60 in the placebo group. The rates of venous thromboembolism were 0.18 and 0.32 event per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio with rosuvastatin, 0.57; 95% confidence interval [CI], 0.37 to 0.86; P=0.007); the corresponding rates for unprovoked venous thromboembolism (i.e., occurring in the absence of a known malignant condition, trauma, hospitalization, or surgery) were 0.10 and 0.17 (hazard ratio, 0.61; 95% CI, 0.35 to 1.09; P=0.09) and for provoked venous thromboembolism (i.e., occurring in patients with cancer or during or shortly after trauma, hospitalization, or surgery), 0.08 and 0.16 (hazard ratio, 0.52; 95% CI, 0.28 to 0.96; P=0.03). The rates of pulmonary embolism were 0.09 in the rosuvastatin group and 0.12 in the placebo group (hazard ratio, 0.77; 95% CI, 0.41 to 1.45; P=0.42), whereas the rates of deep-vein thrombosis only were 0.09 and 0.20, respectively (hazard ratio, 0.45; 95% CI, 0.25 to 0.79; P=0.004). Consistent effects were observed in all the subgroups examined. No significant differences were seen between treatment groups in the rates of bleeding episodes.

CONCLUSIONS

In this trial of apparently healthy persons, rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism. (ClinicalTrials.gov number, NCT00239681.)

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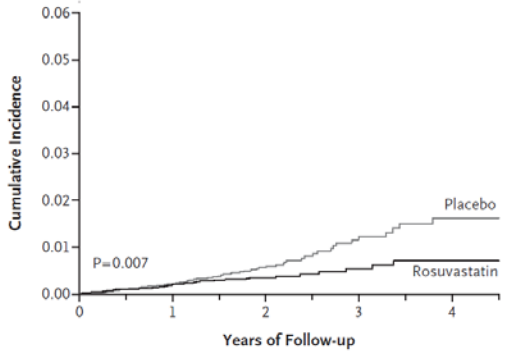
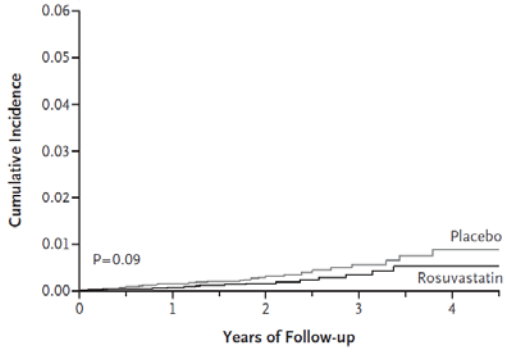
A Venous Thromboembolism



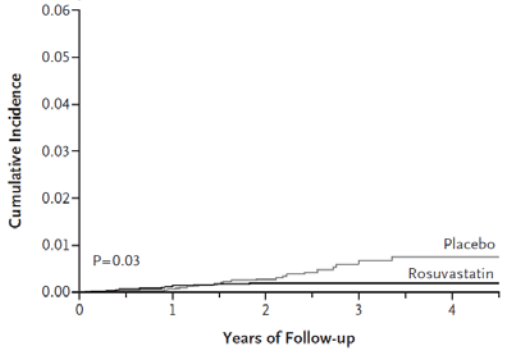
No. at Risk										
Rosuvastatin	8901	8648	8447	6575	3927	1986	1376	1003	548	161
Placebo	8901	8652	8417	6574	3943	2012	1381	993	556	182

B Unprovoked Venous Thromboembolism



No. at Risk										
Rosuvastatin	8901	8648	8447	6575	3927	1986	1376	1003	548	161
Placebo	8901	8652	8417	6574	3943	2012	1381	993	556	182

C Provoked Venous Thromboembolism



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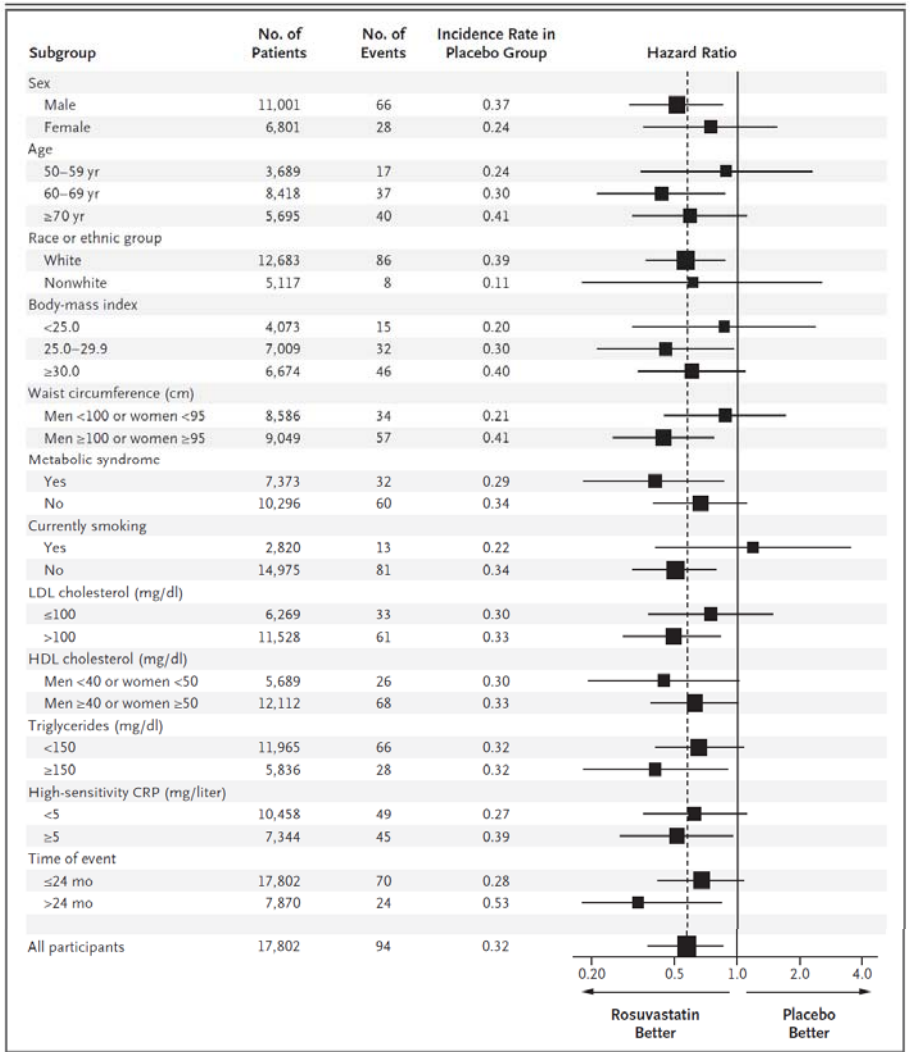

Figure 2. Effects of Rosuvastatin on the Risk of Venous Thromboembolism, According to Baseline Characteristics of the Study Participants.

Hazard ratios for the rosuvastatin group as compared with the placebo group are shown, with the size of each black square proportionate to the number of participants in the subgroup in whom venous thromboembolism developed; the horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates the overall hazard ratio for the entire trial cohort. The incidence rate in the placebo group is the number of events per 100 person-years of follow-up. Not shown are P values for tests of interaction between rosuvastatin and subgroup variables, each of which was nonsignificant (P>0.10). For each subgroup, the number of patients for whom data were available is shown. Data were missing for some participants in some subgroups. The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.[27] To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. The body-mass index is the weight in kilograms divided by the square of the height in meters. CRP denotes C-reactive protein, HDL high-density lipoprotein, and LDL low-density lipoprotein.

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ORIGINAL ARTICLE
Heart Failure

Effect of Atorvastatin vs. Rosuvastatin on Cardiac Sympathetic Nerve Activity in Non-Diabetic Patients With Dilated Cardiomyopathy

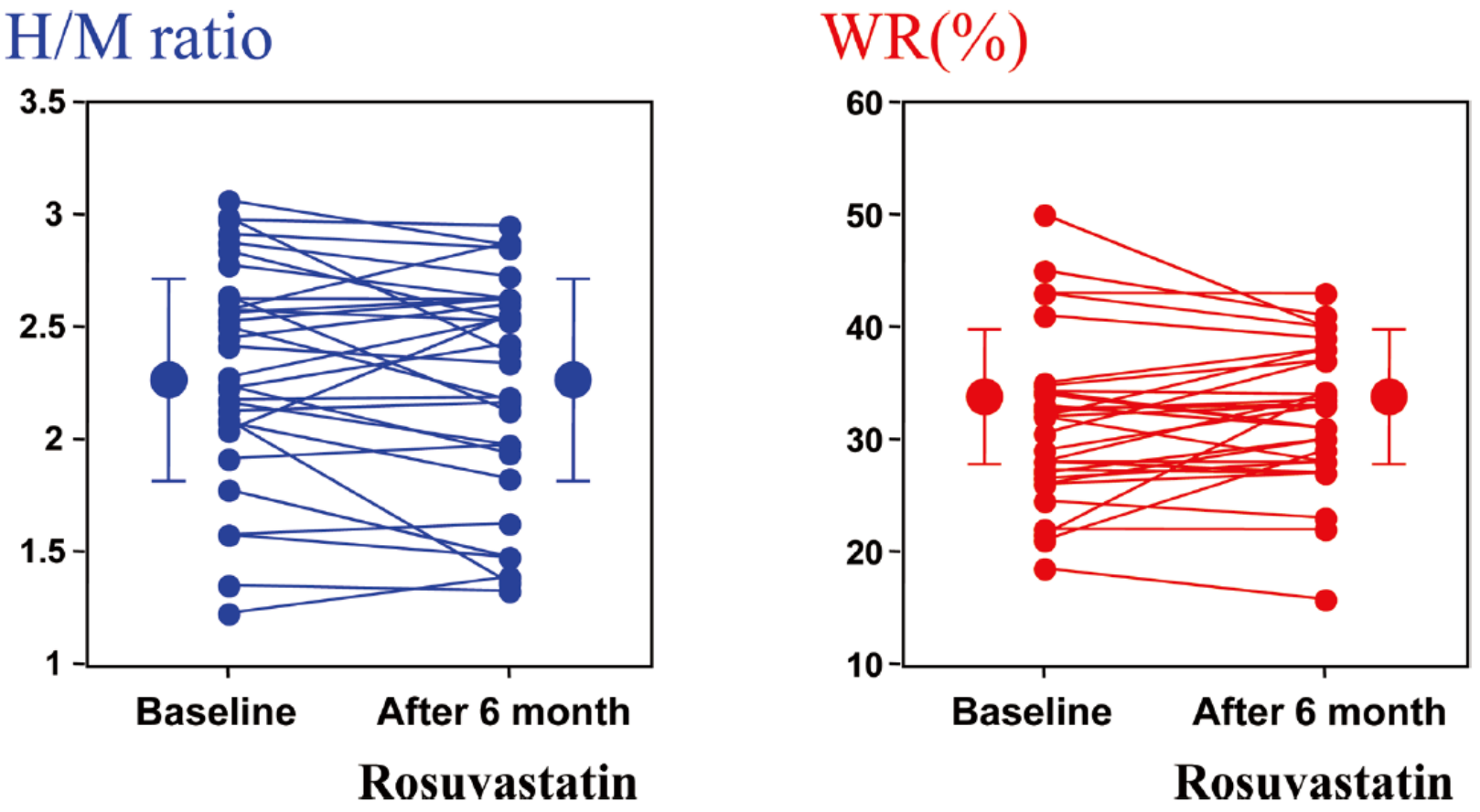
Takayoshi Tsutamoto, MD; Hiroshi Sakai, MD; Kunihiro Ibe; Masayuki Yamaji, MD; Chiho Kawahara, MD; Ichiro Nakae, MD; Masanori Fujii, MD; Takashi Yamamoto, MD; Minoru Horie, MD

Background: Effects of statin therapy on cardiac sympathetic nerve activity in patients with chronic heart failure (CHF) have not previously been evaluated.

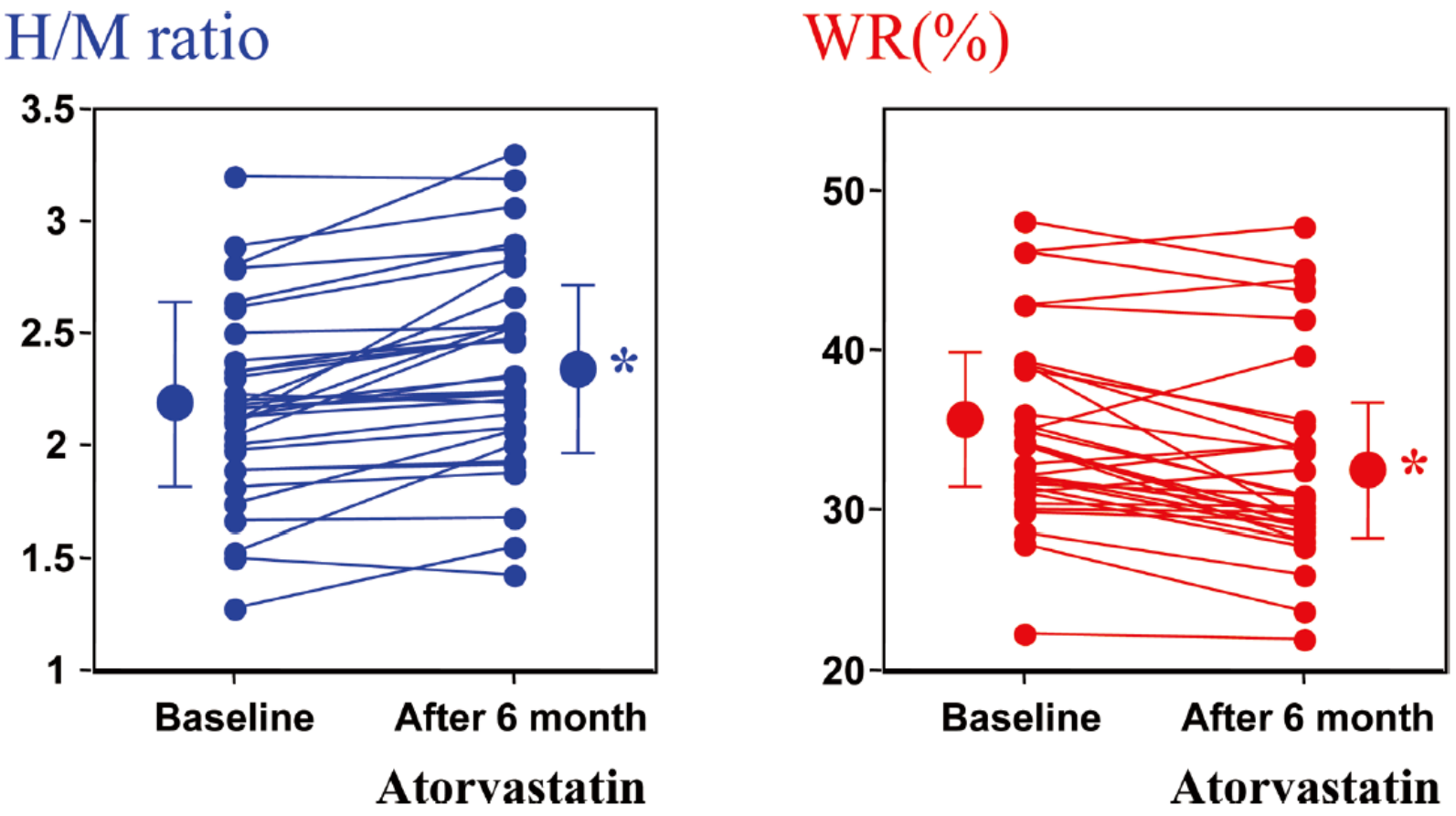
Methods and Results: To compare the effects of lipophilic atorvastatin and hydrophilic rosuvastatin on cardiac sympathetic nerve activity in CHF patients with dilated cardiomyopathy (DCM), 63 stable outpatients with DCM, who were already receiving standard therapy for CHF, were randomized to atorvastatin (n=32) or rosuvastatin (n=31). We evaluated cardiac sympathetic nerve activity by cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, hemodynamic parameters and neurohumoral factors before and after 6 months of treatment. There were no differences in the baseline characteristics of the 2 groups. In the rosuvastatin group, there were no changes in MIBG parameters, left ventricular ejection fraction or plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) after 6 months of treatment. In contrast, the atorvastatin group showed a significant increase in the delayed heart/mediastinum count ratio (2.18±0.4 vs. 2.36±0.4, P<0.0001), and the washout rate was significantly decreased (34.8±5.7 vs. 32.6±6.3%, P=0.0001) after 6 months of treatment compared with the baseline values. The plasma NT-proBNP level was also significantly decreased (729±858 vs. 558±747 pg/ml, P=0.0139).

Conclusions: Lipophilic atorvastatin but not hydrophilic rosuvastatin improves cardiac sympathetic nerve activity in CHF patients with DCM. (*Circ J* 2011; **75:** 2160–2166)

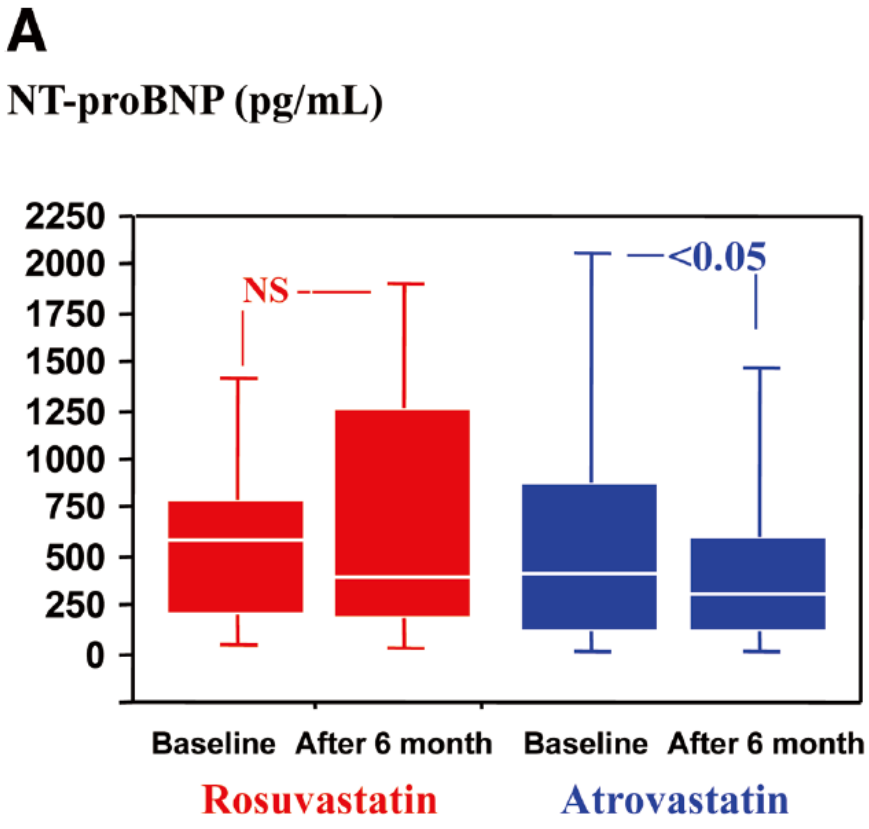
Comparisons of cardiac 123I-MIBG scintigraphic parameters before and after 6 months of treatment with rosuvastatin



Comparisons of cardiac 123I-MIBG scintigraphic parameters before and after 6 months of treatment with atorvastatin



Comparison of pNT-proBNP and LVEF before and after 6 months of treatment with either rosuvastatin or atorvastatin.



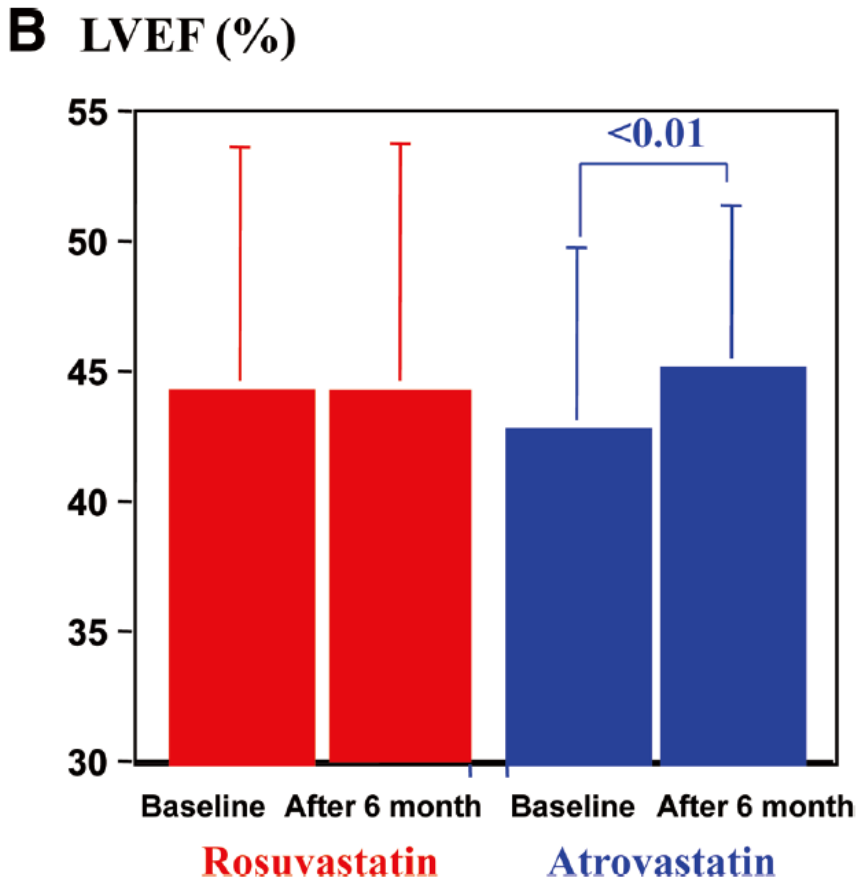


Table 3. Guidelines for Antithrombotic Therapy in HF

Society	Recommendations	Evidence
ACC/AHA, 2009	Anticoagulants in patients with HF and paroxysmal or persistent AF or previous VTE	I-A
	Antiplatelet agents for MI and death prevention in patients with HF and CAD	I-B
	Anticoagulants in patients with underlying disorders that may be associated with increased VTE risk (eg, amyloidosis) and in patients with familial DCM and history of VTE in first-degree relatives	IIb-B
ESC, 2008	Anticoagulants for patients with >1 moderate risk factor (age ≥75 years, hypertension, LVEF ≤35%, diabetes mellitus)	I-A
	Aspirin or vitamin K antagonist for primary VTE prevention in patients of HF with AF without additional risk factors	I-A

ACC/AHA indicates American College of Cardiology/American Heart Association; CAD, coronary artery disease; ESC, European Society of Cardiology. Other abbreviations as in Tables 1 and 2.

Summary

- **CHF with AF treat with warfarin**
- **CHF with sinus rhythm, usage of warfarin is still debate**
- **Lipophilic statins such as atorvastatin, simvastatin can use in CHF**
- **PUFA can be useful in CHF**

감사합니다.