

VENTRICULAR DYSFUNCTION AND THE RISK OF STROKE AFTER MYOCARDIAL INFARCTION

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ABSTRACT

Background In patients who have had a myocardial infarction, the long-term risk of stroke and its relation to the extent of left ventricular dysfunction have not been determined. We studied whether a reduced left ventricular ejection fraction is associated with an increased risk of stroke after myocardial infarction and whether other factors such as older age and therapy with anticoagulants, thrombolytic agents, or captopril affect long-term rates of stroke.

Methods We performed an observational analysis of prospectively collected data on 2231 patients who had left ventricular dysfunction after acute myocardial infarction who were enrolled in the Survival and Ventricular Enlargement trial. The mean follow-up was 42 months. Risk factors for stroke were assessed by both univariate and multivariate Cox proportional-hazards analysis.

Results Among these patients, 103 (4.6 percent) had fatal or nonfatal strokes during the study (rate of stroke per year of follow-up, 1.5 percent). The estimated five-year rate of stroke in all the patients was 8.1 percent. As compared with patients without stroke, patients with stroke were older (mean [\pm SD] age, 63 ± 9 years vs. 59 ± 11 years; $P<0.001$) and had lower ejection fractions (29 ± 7 percent vs. 31 ± 7 percent, $P=0.01$). Independent risk factors for stroke included a lower ejection fraction (for every decrease of 5 percentage points in the ejection fraction there was an 18 percent increase in the risk of stroke), older age, and the absence of aspirin or anticoagulant therapy. Patients with ejection fractions of ≤ 28 percent after myocardial infarction had a relative risk of stroke of 1.86, as compared with patients with ejection fractions of >35 percent ($P=0.01$). The use of thrombolytic agents and captopril had no significant effect on the risk of stroke.

Conclusions During the five years after myocardial infarction, patients have a substantial risk of stroke. A decreased ejection fraction and older age are both independent predictors of an increased risk of stroke. Anticoagulant therapy appears to have a protective effect against stroke after myocardial infarction. (N Engl J Med 1997;336:251-7.)

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CURRENT estimates of the incidence of stroke among patients with coronary artery disease are as low as 3.4 percent per 1000 patient-years of follow-up.¹ Stroke is also a known but infrequent early complication of myocardial infarction. In the two-week period after myocardial infarction, the reported incidence of stroke ranges between 0.7 percent and 4.7 percent.²⁻⁸ After myocardial infarction, focal areas of akinesia or dyskinesia (or both) in the left ventricle appear to increase the risk of mural thrombi.⁹⁻¹² Moreover, a greater extent of myocardial damage and greater left ventricular dysfunction after anterior myocardial infarction, as well as the detection of mural thrombi by echocardiography, have been shown to be risk factors for both peripheral thromboembolism and stroke in the period soon after the infarction.¹³⁻¹⁶ The rate of occurrence of mural thrombi and the early rate of stroke appear to be lower after inferior-wall myocardial infarction than after anterior infarction.^{17,18}

Although strokes are primarily an early complication of myocardial infarction, impaired left ventricular function after myocardial infarction may be an additional risk factor for subsequent stroke. Estimates of short-term rates of stroke after myocardial infarction (i.e., stroke within 30 days) range from 3.0 percent to 5.2 percent.^{7,19} In one study, the principal mechanism of stroke during this period was embolic cerebral infarction, as documented by computed tomographic (CT) scanning.¹⁹

The long-term cumulative risk of stroke and its relation to the extent of left ventricular dysfunction after myocardial infarction have not been determined. We used data from the Survival and Ventricular Enlargement (SAVE) trial²⁰ to study the relation between the left ventricular ejection fraction (LVEF) and the incidence of stroke in patients with left ventricular dysfunction but without symptomatic heart

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failure after myocardial infarction. In addition, we examined the effects of therapy with captopril, an agent known to reduce ventricular remodeling and enlargement after myocardial infarction, on the rate of stroke. The aims of the study were to examine the LVEF as a risk factor for stroke and to determine the effect of other factors, such as age and the use of anticoagulants, thrombolytic agents, or captopril, on long-term rates of stroke.

METHODS

The SAVE Trial

The SAVE trial was a prospective, randomized, placebo-controlled study of 2231 patients with myocardial infarction and left ventricular dysfunction (LVEF, ≤ 40 percent as measured by radionuclide ventriculography). From 3 to 16 days after myocardial infarction (mean, 11 days), patients were randomly assigned to receive therapy with the angiotensin-converting-enzyme inhibitor captopril or placebo. Patients with overt heart failure requiring vasodilator therapy were excluded. In patients with symptoms or signs of myocardial ischemia, cardiac catheterization was used to guide treatment. If coronary revascularization (angioplasty or coronary-artery bypass grafting) was considered necessary, it was performed before randomization. Other criteria for exclusion were contraindications to captopril therapy and coexisting medical disorders such as renal insufficiency (creatinine concentration, >2.5 mg per deciliter [$220 \mu\text{mol}$ per liter]), severe valvular disease, refractory hypertension, cancer, or other conditions considered likely to limit survival. The design and results of the SAVE trial have been reported previously.²⁰ All the patients provided informed consent.

Definitions

Stroke was a prospectively defined end point of this study. The definition included all strokes that occurred either as early complications of acute myocardial infarction (i.e., between the index myocardial infarction and randomization on day 3 through day 16 after infarction) or after random assignment to therapy with captopril or placebo.

Statistical Analysis

Univariate comparisons of characteristics between patients who had stroke and those who did not were performed with the chi-square test for categorical variables (sex, history of previous myocardial infarction, history of diabetes, history of hypertension, current smoking status, and location of myocardial infarction) and with the two-sample *t*-test for continuous variables (age and LVEF). The relation between LVEF and stroke was assessed by both univariate and multivariate Cox proportional-hazards analysis. The covariates included in the multivariate Cox regression analysis were age, use or nonuse of an anticoagulant agent (heparin or warfarin) after myocardial infarction, use or nonuse of aspirin after myocardial infarction, smoking status before randomization, presence or absence of hypertension, presence or absence of diabetes, presence or absence of a previous myocardial infarction, random assignment to captopril or placebo, presence or absence of atrial fibrillation or flutter as a complication of the index myocardial infarction, and use or nonuse of thrombolytic therapy at the time of the myocardial infarction.

The data on the use of anticoagulants (either warfarin or heparin) and aspirin that were included in the analyses were those obtained at the study visit just before the index admission to the hospital for stroke or before death from stroke; these variables were analyzed as time-dependent covariates in the multivariate Cox-model analysis. For patients who did not have stroke, the use of an anticoagulant or aspirin was determined at the last follow-up visit or at the final visit at the end of the SAVE study. No data

on the intensity of anticoagulation (i.e., the international normalized ratio) were prospectively collected in the SAVE data base. Kaplan-Meier estimates of the distribution of times from randomization to stroke were computed. Log-rank analysis was performed to compare the event curves for different groups. In all analyses, a *P* value of 0.05 or less was considered to indicate statistical significance.

RESULTS

Study Population

Patients enrolled in the SAVE trial were followed for an average (\pm SD) of 42 ± 10 months (range, 24 to 60). The average age was 59 years (range, 26 to 79); 82 percent of patients were male; 36 percent had had a previous myocardial infarction; 38 percent had a history of hypertension; and 22 percent had diabetes mellitus. Sixty percent of the patients were in Killip class 1 and 40 percent were in Killip class 2 or higher during the acute infarction. The mean LVEF was 31.0 ± 6.7 percent (measured 2 to 16 days after infarction by radionuclide ventriculography). Thirty-four percent of the patients received thrombolytic therapy. Two hundred twenty-seven (10 percent) of the patients had atrial fibrillation or atrial flutter for at least one hour as a complication of the index myocardial infarction.

Adjuvant medications (i.e., medications other than captopril) at the time of randomization were given at the discretion of the treating physicians and recorded in the case-report forms. Medications used at the time of randomization included beta-blockers (received by 35 percent of the patients), nitrates (52 percent), calcium-channel blockers (42 percent), aspirin (59 percent), other antiplatelet agents (14 percent), and anticoagulant drugs (heparin or warfarin, received by 28 percent).

Total Incidence of Stroke

Twelve (0.5 percent) of the 2231 patients in the SAVE trial had acute stroke as a complication of the index myocardial infarction, before randomization. After randomization, during the entire follow-up period, 91 additional patients (4.1 percent) had a fatal or nonfatal stroke. In 10 of these patients, the stroke was considered the proximate cause of death. The estimated five-year cumulative rate of stroke in all the patients was 8.1 percent. The normalized rate of stroke was 1.5 percent per patient-year of follow-up (Fig. 1). In 50 patients with documentation of stroke on CT scanning or magnetic resonance imaging (MRI), 48 (96 percent) had a stroke of ischemic origin and 2 (4 percent) had cerebral hemorrhage.

Risk Factors for Stroke

Univariate characteristics of patients with and without stroke are shown in Table 1. Independent risk factors for stroke determined by multivariate Cox proportional-hazards analysis (Table 2) included a reduced LVEF (there was an 18 percent increase in

the risk of stroke for every reduction of 5 percentage points in the LVEF at the time of randomization), older age, and nonuse of aspirin and anticoagulant agents at the clinic visit just before a clinically documented stroke (this was a time-dependent covariate). Random assignment to therapy with captopril and the use of thrombolytic agents to treat the index myocardial infarction did not decrease the risk of stroke during follow-up.

The presence of atrial fibrillation or flutter before randomization was not an independent long-term risk factor for stroke. Patients with atrial fibrillation or flutter before randomization had lower rates of use of aspirin (52 percent, vs. 59 percent in those without atrial fibrillation or flutter; $P=0.04$), beta-blockers (27 percent vs. 36 percent, $P=0.001$), and thrombolytic therapy (29 percent vs. 35 percent, $P=0.05$), but they had similar rates of use of anticoagulants.

LVEF as a Longitudinal Risk Factor for Stroke

To determine a threshold LVEF at which the rate of stroke was increased, the subjects were divided into three subgroups on the basis of the LVEF (≤ 28 percent [$n=724$], 29 to 35 percent [$n=817$], and >35 percent [$n=690$]). The characteristics of the patients in these subgroups are shown in Table 3. The total cumulative rate of stroke in each subgroup was as follows: 8.9 percent for patients with an LVEF of ≤ 28 percent; 7.8 percent for those with an LVEF of 29 to 35 percent; and 4.1 percent for those with an LVEF above 35 percent (Fig. 2). Univariate analysis demonstrated that patients in whom the LVEF was 28 percent or lower after myocardial infarction had a risk of stroke during the follow-up that was nearly twice as high as that among the other patients (relative risk, 1.86; 95 percent confidence interval, 1.15 to 3.04; chi-square = 6.27; $P=0.01$).

In the multivariate analysis, the protective effects of anticoagulant therapy in reducing the rate of stroke were evident in all three subgroups defined by LVEF: for an LVEF of ≤ 28 percent, the relative risk was 0.17 (95 percent confidence interval, 0.09 to 0.29; chi-square = 38.33; $P<0.001$); for an LVEF of 29 to 35 percent, the relative risk was 0.14 (95 percent confidence interval, 0.06 to 0.28; chi-square = 29.38; $P<0.001$); for an LVEF above 35 percent, the relative risk was 0.23 (95 percent confidence interval, 0.12 to 0.47; chi-square = 16.82; $P<0.001$). The beneficial effects of aspirin were observed both among the patients with the lowest LVEF values (LVEF, ≤ 28 percent; reduction in risk, 66 percent; chi-square = 11.63; $P<0.001$) and those with intermediate values (LVEF, 29 to 35 percent; reduction in risk, 59 percent; chi-square = 5.03; $P<0.03$). The effect of age on the risk of stroke did not differ significantly among the three LVEF groups, although there was a suggestion of a stronger effect

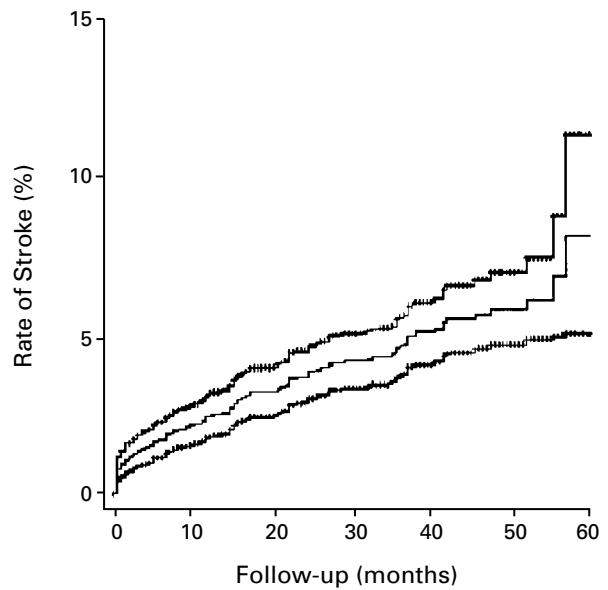


Figure 1. Kaplan-Meier Estimate of the Cumulative Rate of Stroke among 2231 Patients in the SAVE Trial.

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.

of age in the lowest-LVEF group. No other risk factors had a significant effect on the risk of stroke, after adjustment for the LVEF, in these multivariate analyses.

DISCUSSION

This study confirms the results of earlier investigations that suggested that the size of a myocardial infarction⁸ is associated with the subsequent risk of stroke and establishes that the LVEF (especially in patients with an LVEF of ≤ 28 percent) is the most powerful independent predictor of stroke in patients after myocardial infarction. Furthermore, for every absolute decrease of 5 percentage points in the LVEF, the risk of stroke increases by 18 percent. Finally, our results suggest that age and systemic anticoagulation or aspirin use are also independent factors that affect the long-term risk of stroke after myocardial infarction.

Many studies have examined heart size and decreased LVEF as risk factors for systemic embolic events after myocardial infarction. Segal et al.²¹ stratified patients according to the size of the heart on a chest roentgenogram and noted a trend toward more

TABLE 3. CHARACTERISTICS OF PATIENTS ACCORDING TO LVEF.*

CHARACTERISTIC	LVEF $\leq 28\%$ (N=724)	LVEF 29–35% (N=817)	LVEF $> 35\%$ (N=690)	P VALUE†
Age — yr	60 ± 10	59 ± 11	59 ± 11	0.006
LVEF — %	23 ± 4	32 ± 2	38 ± 2	<0.001
Male sex — no. (%)	617 (85.2)	667 (81.6)	557 (80.7)	NS
History of diabetes — no. (%)	179 (24.7)	176 (21.5)	137 (19.9)	NS
History of hypertension — no. (%)	265 (36.6)	316 (38.7)	256 (37.1)	NS
Current smoking at randomization — no. (%)	292 (40.3)	345 (42.2)	288 (41.7)	NS
Previous myocardial infarction — no. (%)	329 (45.4)	274 (33.5)	189 (27.4)	<0.001
Atrial fibrillation or flutter before randomization — no. (%)	89 (12.3)	73 (8.9)	65 (9.4)	0.07
Anticoagulant therapy at randomization — no. (%)	221 (30.5)	239 (29.3)	172 (24.9)	0.05
Aspirin use at randomization — no. (%)	374 (51.7)	494 (60.5)	442 (64.1)	<0.001
Location of myocardial infarction — no. (%)				<0.001
Anterior Q-wave	422 (58.3)	469 (57.4)	338 (49.0)	
Inferior Q-wave	79 (10.9)	139 (17.0)	176 (25.5)	
Anterior and inferior Q-wave	96 (13.3)	83 (10.2)	82 (11.9)	
Non-Q-wave	63 (8.7)	91 (11.1)	62 (9.0)	
Other	64 (8.8)	35 (4.3)	32 (4.6)	
Thrombolytic therapy — no. (%)	226 (31.2)	296 (36.2)	247 (35.8)	NS

*Plus-minus values are means ±SD.

†P values were calculated by one-way analysis of variance for age and LVEF and by the chi-square test for categorical variables. NS denotes not significant.

embolic events in the patients with the largest hearts. Tanne et al.²² also suggested that increased heart size on the chest roentgenogram was an independent risk factor for stroke after myocardial infarction. Kyrle et al.²³ used fractional shortening, determined echocardiographically, as an index of ventricular dysfunction and noted a similar trend toward more venous and arterial embolic events in patients with worse ventricular function. Finally, Dunkman et al.,²⁴ over a period of follow-up similar to that in this study, noted a trend toward a higher rate of all thromboembolic events (stroke and pulmonary and systemic embolism) among patients with reduced LVEF values.

During the early period after infarction, reported rates of stroke range between 0.5 percent and 2.5 percent.^{2,3,5-7} Consistent with these observations was the 0.5 percent rate of early stroke (before randomization — i.e., within 3 to 16 days after myocardial infarction) in the SAVE trial. Univariate analysis demonstrated that atrial arrhythmia as a complication of the index myocardial infarction increased the risk of stroke. However, multivariate analysis did not establish the importance of atrial dysrhythmia between myocardial infarction and the time of randomization as a long-term risk factor for stroke. It also appears from the univariate data that the use of thrombolytic therapy decreased the risk of early stroke. Again, multivariate analysis did not demonstrate the persistence of the early effects of thrombolytic therapy on the overall risk of stroke, suggesting that the beneficial effect of thrombolytic therapy is limited to the early postinfarction period. Therapy with captopril did not protect patients against strokes, suggesting that the preservation of left ventricular size alone²⁵ may not reduce the relative risk of stroke after myocardial infarction.

On the basis of longitudinal data on cumulative rates of stroke in the SAVE trial, in contrast to the previous reports, it appears that stroke rates continue to increase in a constant fashion even beyond the first six months after myocardial infarction. This analysis further demonstrates that patients with LVEF values of ≤ 28 percent appear to have the highest risk of such events. Specifically, although the rate of events is low in patients with left ventricular dysfunction (LVEF, ≤ 40 percent) and no symptoms of heart failure, especially as compared with the rate in patients with reduced left ventricular function and symptomatic heart failure, the risk over time is not negligible.

Given the persistent risk of stroke after myocardial infarction, the implications with respect to long-term anticoagulant therapy in these patients become more apparent. Anticoagulant therapy with either warfarin and heparin or aspirin appears to be associated with significant protection from stroke. These observations confirm the results of previous studies. In one study of 999 patients after acute myocardial infarction, the value of short-term warfarin therapy

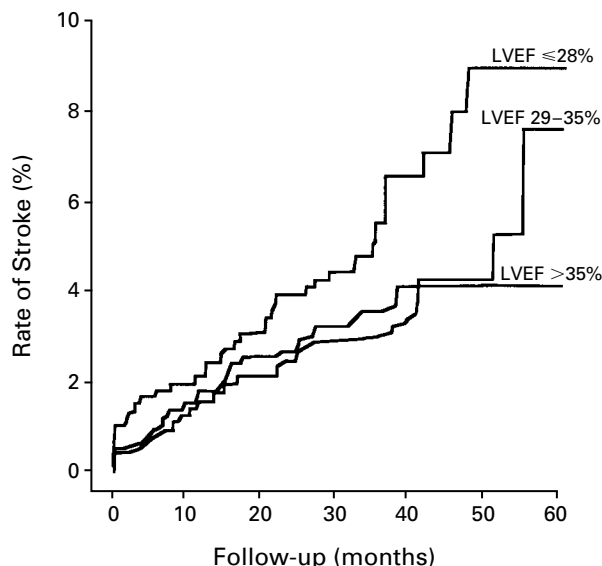


Figure 2. Cumulative Rate of Stroke in the SAVE Trial, According to the Left Ventricular Ejection Fraction (LVEF).

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.

(in the first 28 days) in reducing the risk of stroke was clear (rate of stroke, 0.8 percent, vs. 3.8 percent in the control group; $P<0.001$).²⁶ A similar but nonsignificant reduction in the rates of both stroke and thromboembolism in the period immediately following myocardial infarction was also observed in the Medical Research Council trial.²⁷ In contrast, beneficial effects on the rate of stroke were not observed in a study of therapy with heparin and phenindione during hospitalization after myocardial infarction.²⁸

The long-term benefit of anticoagulation after myocardial infarction in reducing the risk of stroke has also been demonstrated in both the Warfarin Re-Infarction Study (WARIS) (total stroke rate, 6.7 percent; reduction in the rate of total stroke with warfarin, 55 percent)²⁹ and the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) study (total stroke rate, 3.6 percent; reduction in the rate of total stroke with warfarin, 39 percent).³⁰ The reduction in risk with anticoagulation in our retrospective analysis of data from the SAVE trial (81 percent) was even greater

than the reductions in previous randomized trials. However, in neither the WARIS nor the ASPECT study was information on the LVEF available, nor was the reduction in the rate of stroke specifically analyzed in relation to the LVEF and other clinical variables. Our study suggests that the beneficial effects of anticoagulation on the rate of stroke after myocardial infarction is evident not only in patients with moderate-to-severe decreases in the LVEF but also in patients with relatively well preserved left ventricular function (LVEF, >35 percent).

The principal cause of stroke in the SAVE trial (responsible for 96 percent of the strokes) was ischemic infarction, documented by CT scanning or MRI. The higher rate of use of anticoagulant agents at the time of randomization among patients who subsequently had strokes did not appear to result in an increased incidence of hemorrhagic stroke. These observations underscore the important role of anticoagulant therapy in protecting patients from this complication of myocardial infarction. Because therapy with aspirin also reduced the risk of stroke (by 56 percent), it appears that therapy with one or both of these agents should be considered for patients with left ventricular dysfunction after myocardial infarction, especially for those with LVEF values of ≤ 28 percent.

The limitations of this study include the small number of events and the fact that therapy with aspirin and anticoagulant agents was not randomly assigned. Moreover, no data on the intensity of anticoagulation for patients receiving such therapy were prospectively collected. Therefore, it remains unclear what specific range of values for the international normalized ratio should be used to guide therapy in asymptomatic patients with reduced LVEF after myocardial infarction. Also, because of the nature of the data base, we were unable to differentiate retrospectively between the use of aspirin alone and the use of warfarin alone. Finally, the lack of follow-up data on the presence or absence of chronic atrial dysrhythmia did not permit us to evaluate the role of this known risk factor for stroke.

Our results establish the importance of a reduced LVEF as an independent risk factor for stroke after myocardial infarction. The relation between the magnitude of the reduction in the LVEF after myocardial infarction and the subsequent risk of stroke suggests yet another context in which to understand the potential role of long-term anticoagulation.^{31,32} Studies designed to determine whether aspirin alone offers as much protection as warfarin and to establish the optimal intensity of anticoagulation with warfarin are needed. Given the inclusion criteria with respect to LVEF in the SAVE trial, our observations cannot be extrapolated to patients with an LVEF greater than 40 percent after myocardial infarction or to patients with LVEF values of ≤ 40 percent and with other causes of heart failure, such as idiopathic

dilated cardiomyopathy,^{33,34} myocarditis, or valvular heart disease. These groups of patients also merit further study.

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