

Incidence and Prognosis of Secondary Ventricular Fibrillation in Acute Myocardial Infarction

Evidence for a Protective Effect of Thrombolytic Therapy

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The multicenter randomized study of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico has provided the opportunity to analyze the impact of thrombolytic treatment on secondary ventricular fibrillation incidence in a large population of patients (11,712) with acute myocardial infarction. A reduction of about 20% in the frequency of secondary ventricular fibrillation was observed among patients allocated to thrombolytic treatment (streptokinase, 2.4% versus control, 2.9%; relative risk, 0.80; 95% confidence interval, 0.64–1.00). Streptokinase appeared to exert its protective effect specifically in patients treated within 3 hours of onset of symptoms (streptokinase, 2.6% versus control, 3.7%; relative risk, 0.71; 95% confidence interval, 0.53–0.95). This protection was essentially due to a reduced incidence of late ventricular fibrillation occurring after the first day of hospitalization. The 311 patients with secondary ventricular fibrillation represented an overall incidence of 2.7%. Such incidence was not related to infarct location or sex but was significantly more common in patients older than 65 years (3.3% versus 2.3% in younger patients). A significant excess of in-hospital deaths was found in patients with secondary ventricular fibrillation compared with those in the reference group (38% versus 24%; relative risk, 1.98; 95% confidence interval, 1.56–2.52). Conversely, secondary ventricular fibrillation was not a predictor of 1-year mortality for hospital survivors. Thrombolytic treatment with intravenous streptokinase affords protection against secondary ventricular fibrillation most probably by a limitation of infarct size. When the arrhythmia complicates the course of infarction, it is associated with an adverse short-term outcome, whereas the long-term prognosis is not influenced. (*Circulation* 1990;82:1279–1288)

Ventricular fibrillation complicating acute myocardial infarction has been classified as “primary” when it is independent of the severity of underlying myocardial damage and manifests itself as an acute electrical event.¹ Secondary ventricular fibrillation occurs in infarcts complicated by heart failure or shock and has invariably been reported to entail a serious short-term prognosis, particularly when occurring in association with pro-

nounced pump failure.^{1–3} Extensive muscle damage with resultant impairment of cardiac function rather than the arrhythmia per se is generally thought to be responsible for the poor prognosis.⁴ Although excess mortality associated with secondary ventricular fibrillation has been shown during the hospital phase of acute myocardial infarction in a few comparative studies,^{5–7} including a limited number of ventricular fibrillation events, the majority of available data stem largely from either observational series^{8–11} or studies lacking a well-matched reference group.^{12–14} Moreover, there is no uniform agreement regarding the long-term prognostic significance of cardiac arrest caused by secondary ventricular fibrillation.^{1,2,9,12,13,15}

Given the limited amount of information available in this field, we reassessed from the multicenter randomized study of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) the epidemiology of secondary ventricular

The Steering Committee of the GISSI consists of Fausto Rovelli (chairman), Claudio De Vita, Giorgio A. Feruglio, Antonio Lotto, Aldo Selvini (until his death in December 1989), and Gianni Tognoni. The complete list of doctors participating in the GISSI has been previously published (*Lancet* 1986;1:397–401).

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fibrillation complicating acute myocardial infarction and its influence on in-hospital and long-term survival, with attention also paid to the timing of arrhythmia occurrence during hospitalization. As the GISSI trial was designed to test the efficacy of intravenous streptokinase in a large population of patients with acute myocardial infarction,¹⁶ we also had a unique opportunity to analyze the impact of thrombolytic treatment on secondary ventricular fibrillation frequency.

Methods

The patients considered in this report are part of the GISSI trial population. Patients were eligible for randomization in GISSI if they had chest pain accompanied by ST segment elevation or depression of 1 mm or more in any limb lead of the electrocardiogram, of 2 mm or more in any precordial lead, or both, and if they were admitted to the coronary care unit within 12 hours of onset of symptoms. Exclusion criteria, the method of randomization, details on administration of streptokinase and on data collection related to hospital stay and follow-up visits, and statistical methods of data analysis have been previously reported.^{16,17} "Anterior" infarction was defined by the presence of electrocardiographic changes in leads I, aVL, and V₁ to V₆ on the standard 12-lead electrocardiogram, whereas "posterior" location was defined by changes in leads II, III, and aVF.

For this analysis, true posterior infarction defined by an R/S wave ratio in lead V₁ greater than 1.0 was included with posterior infarcts. Multiple site infarction was defined by the concomitant presence of electrocardiographic changes in anterior or lateral and posterior leads, whenever a history of previous infarct had been excluded. Ventricular fibrillation was recognized by the occurrence on the electrocardiogram of coarse and irregular oscillations without discernible QRS complexes or T waves. For the purpose of this study, "secondary ventricular fibrillation" was defined as ventricular fibrillation complicating acute myocardial infarction associated with any degree of clinical heart failure or shock. Hence, classification of patients higher than Killip class I was considered as a classification criterion. Only monitored episodes of ventricular fibrillation occurring during coronary care unit stay and requiring resuscitation were included in this analysis.

The inclusion of patients with moderate heart failure (Killip class II) is consistent with our previous definition of primary ventricular fibrillation.^{18,19} Indeed, it was felt that the presence of moderate signs of left ventricular dysfunction was enough to classify ventricular fibrillation as occurring in complicated myocardial infarction, to render untenable the concept of a primary electrical event. No recommendations were made about the criteria for antiarrhythmic drug treatment. Specifically, there was no uniform policy of prophylaxis with lidocaine hydrochloride in the coronary care units.

For the analysis of risk factors possibly associated with secondary ventricular fibrillation, the appropriate reference group of patients was selected as the cohort of all those patients with the same baseline characteristics defining the group of patients with secondary ventricular fibrillation but without ventricular fibrillation during coronary care unit stay.

Definition of Early Versus Late Secondary Ventricular Fibrillation

Time of hospital entry was chosen as the 0 time from which the occurrence of ventricular fibrillation during coronary care unit stay was examined.

Early secondary ventricular fibrillation was that manifested within the first day of hospitalization, and late secondary ventricular fibrillation was that manifested after this time.

Follow-up

Because computerized vital statistics are not available in the Italian health care system, information on whether patients were alive or dead had to be secured through the census offices of their towns of residence by prepaid return mail forms. Only overall, not cardiovascular versus noncardiovascular, mortality data could be collected and evaluated. The yield of this cumbersome procedure was nevertheless very high, with 98.7% complete follow-up being achieved. The participating coronary care units were asked to monitor their patients for clinically important cardiovascular and cerebrovascular events occurring in the first 6 months after hospital discharge. Not all were willing to do this, and such follow-up information is available for 81% of the total patients discharged alive from the participating coronary care units.

Statistical Methods

Statistical significance was analyzed by χ^2 tests. Odds ratios as estimators of relative risk²⁰ and their 95% confidence intervals²¹ were used when appropriate to quantify associations. Life-table survival curves were produced by the Kaplan-Meier method.²²

Results

Study Patients

Among the 11,712 patients randomized in the GISSI study, 311 (2.7%) fitted the definition of secondary ventricular fibrillation. Of these, 203 patients were in Killip class II, 52 were in Killip class III, and 56 were in Killip class IV. Experiencing a first infarct were 246 patients (79%) in the group of patients with ventricular fibrillation and 2,463 patients (80%) in the reference category. The location of infarct was anterior in 135 patients (43%) and posterior in 104 (33%); multiple site infarcts, those exhibiting ST depression, and those with an indeterminate location comprised the rest of the population. Secondary ventricular fibrillation occurred with equal incidence irrespective of the site of infarct (Table 1).

TABLE 1. Incidence of Secondary Ventricular Fibrillation According to Infarct Site, Age, and Sex

Variable	Incidence (case/total)	Relative risk (95% CI)
Infarct site		
Anterior	2.8 (135/4,878)	1
Posterior	2.6 (104/4,013)	0.93 (0.69–1.26)
Others	2.6 (72/2,755)	0.94 (0.66–1.34)
Age (yr)		
≤65	2.3 (174/7,608)	1
>65	3.3 (137/4,101)	1.48 (1.17–1.86)
Sex		
Male	2.7 (252/9,398)	1
Female	2.6 (59/2,313)	0.95 (0.71–1.27)

CI, confidence interval.

The older age groups were at increased risk of secondary ventricular fibrillation (Table 1) with an incidence of the arrhythmia of approximately 50% higher than in younger patients. No differences in the incidence of the arrhythmia were observed between the sexes (Table 1).

Influence of Thrombolytic Treatment on Secondary Ventricular Fibrillation Incidence

A reduction of approximately 20% in the frequency of ventricular fibrillation of borderline statistical significance was observed among patients allocated to thrombolytic treatment (streptokinase, 139 of 5,860, 2.4% versus control, 172 of 5,852, 2.9%; relative risk, 0.80; 95% confidence interval, 0.64–1.00) (Figure 1). A statistically significant protection was apparent, however, excluding from the analysis the subset of ventricular fibrillation events occurring in patients with cardiogenic shock (streptokinase, 111 of 5,860, 1.9% versus control, 144 of 5,852, 2.5%; relative risk, 0.76; 95% confidence interval, 0.60–0.98). More notably, when patients were stratified according to treatment delay, streptokinase appeared to exert its protective effect essentially in patients treated within 3 hours of onset of symptoms (Figure 1). The incidence of secondary ventricular fibrillation was not influenced by administration of the drug later

TABLE 2. Incidence of Secondary Ventricular Fibrillation in Patients Randomized Within 3 Hours of Onset of Symptoms According to Killip Class

Killip class	Streptokinase (n=3,016)	Control (n=3,078)	Relative risk (95% CI)
II	56	70	0.81 (0.57–1.16)
III	6	23	0.26 (0.11–0.61)
IV	16	20	0.82 (0.42–1.57)

CI, confidence interval.

in the course of evolving myocardial infarction. Additionally, classification of these early (≤3 hours) randomized patients by Killip class allowed the identification of patients in Killip class III as the subset most protected against ventricular fibrillation occurrence, with a trend of similar direction mainly apparent in patients with moderate heart failure (Killip II) (Table 2).

Interestingly, when time of occurrence of secondary ventricular fibrillation was analyzed, thrombolytic treatment did not reduce the incidence of early events (streptokinase, 112 of 5,860 versus 112 of 5,852; relative risk, 0.99; 95% confidence interval, 0.77–1.30) but halved the frequency of late ventricular fibrillation (streptokinase, 27 of 5,860 versus control, 60 of 5,852; relative risk, 0.45; 95% confidence interval, 0.29–0.70). Moreover, in the subgroup of early (≤3 hours) randomized patients, streptokinase treatment resulted in an even more pronounced protection against late secondary ventricular fibrillation (streptokinase, 9 of 3,016 versus control, 39 of 3,078; relative risk, 0.23; 95% confidence interval, 0.12–0.45).

Distribution of Lidocaine Administration in Coronary Care Unit According to Treatment (Streptokinase Versus Control)

Among patients classified in Killip classes II–IV, lidocaine was administered somewhat more often to those patients allocated to thrombolytic treatment (streptokinase, 601 of 1,669, 36% versus control, 537 of 1,720, 31%; relative risk, 1.24; 95% confidence interval, 1.07–1.43). No significant excess of lidocaine

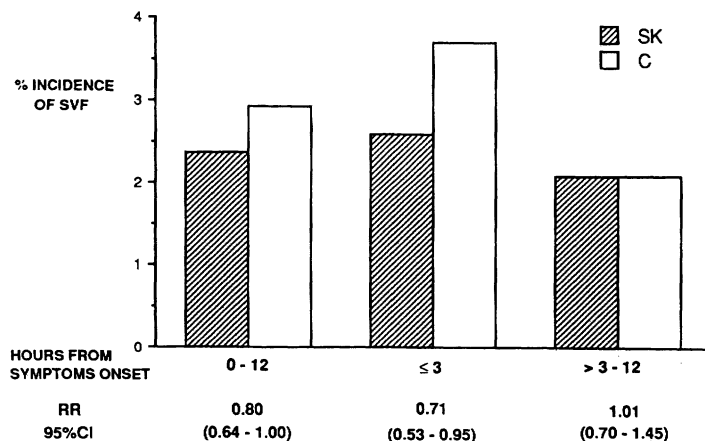


FIGURE 1. Bar graph of secondary ventricular fibrillation (SVF) incidence during coronary care unit stay for streptokinase (SK) and usual treatment (C) by time from onset of symptoms. The risk of ventricular fibrillation is significantly lower in early (≤3 hours) randomized patients allocated to thrombolytic treatment (SK, 78 of 3,016, 2.6% vs. C, 113 of 3,078, 3.7%), whereas no difference is apparent in patients randomized later (SK, 60 of 2,834, 2.1% vs. C, 58 of 2,761, 2.1%). Information concerning hours from onset of symptoms was available in 309 of 311 patients with SVF. RR, relative risk; CI, confidence interval.

TABLE 3. In-Hospital Mortality in Patients With and Without Secondary Ventricular Fibrillation According to Killip Class

Killip class	Mortality (deaths/total)	Relative risk (95% CI)*
II		
Without SVF	17.3 (428/2,469)	
With SVF	27.1 (55/203)	1.77 (1.28–2.45)
III		
Without SVF	35.3 (136/385)	
With SVF	48.1 (25/52)	1.70 (0.95–3.02)
IV		
Without SVF	71.9 (161/224)	
With SVF	67.9 (38/56)	0.83 (0.44–1.55)

CI, confidence interval.

*Relative risk for patients with secondary ventricular fibrillation (SVF) vs. those in the reference group.

administration, however, was found in the subgroup of patients randomized within 3 hours of onset of symptoms (streptokinase, 319 of 837, 38% versus control, 294 of 858, 34%; relative risk, 1.18; 95% confidence interval, 0.97–1.44).

In-Hospital Mortality Rate

Patients with acute myocardial infarction complicated by secondary ventricular fibrillation had a substantially worse short-term outcome than did those patients in the reference category. Indeed, a highly statistically significant excess of in-hospital mortality, up to twofold the relative risk, was found in the overall group of patients with arrhythmia (118 of 311, 38% versus 725 of 3,078, 24%; relative risk, 1.98; 95% confidence interval, 1.56–2.52). A similar finding is confirmed, excluding from the analysis patients with cardiogenic shock (80 of 255, 31% versus 564 of 2,854, 20%; relative risk, 1.86; 95% confidence interval, 1.41–2.45), whereas only a trend of the same direction is observed grouping together only patients with the most compromised hemodynamics, that is, those with pulmonary edema and cardiogenic shock (63 of 108, 58% versus 297 of 609, 49%; relative risk, 1.47; 95% confidence interval, 0.97–2.22). The reason for this minor discrepancy can be best appreciated stratifying patients by Killip

TABLE 4. In-Hospital Mortality According to Infarct Site in Patients With and Without Secondary Ventricular Fibrillation

Infarct site	Mortality (deaths/total)	Relative risk (95% CI)*
Anterior		
Without SVF	26.6 (407/1,534)	
With SVF	46.7 (63/135)	2.42 (1.70–3.45)
Posterior		
Without SVF	17.1 (141/824)	
With SVF	23.0 (24/104)	1.45 (0.85–2.49)
Other		
Without SVF	24.6 (177/720)	
With SVF	43 (31/72)	2.32 (1.40–3.85)

CI, confidence interval.

*Relative risk for patients with secondary ventricular fibrillation (SVF) vs. those in the reference group.

class. Indeed, the observed excess mortality associated with ventricular fibrillation occurrence was almost exclusively determined by the adverse outcome of patients classified in Killip classes II–III (Table 3). The negative prognostic significance of secondary ventricular fibrillation on in-hospital mortality was confirmed when patients were categorized in relation to their infarct sites, with the apparent exception of the posterior site (Table 4).

In-Hospital Nonfatal Clinical Events

No significant differences were noted in the incidence of left ventricular failure, angina, reinfarction, and pericarditis in the group of patients with secondary ventricular fibrillation and in the reference category. Pericarditis, however, was significantly more common in the subgroup of patients with ventricular fibrillation without cardiogenic shock in comparison with control patients (38 of 255, 15% versus 299 of 2,854, 10.5%; relative risk, 1.50; 95% confidence interval, 1.04–2.15).

Causes of In-Hospital Death

The frequency distribution of the causes of death in the group of patients with secondary ventricular fibrillation and in the reference cohort is provided in Figure 2, where as expected, a statistically significant

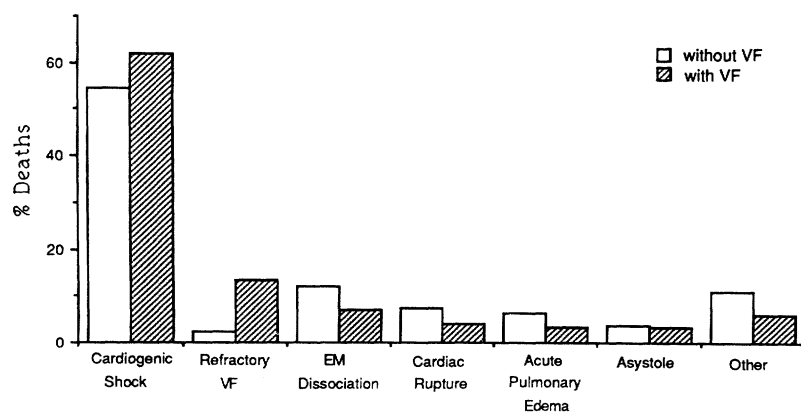


FIGURE 2. Bar graph showing causes of in-hospital death for patients with and without secondary ventricular fibrillation (VF). Cardiogenic shock was the most common cause of death in both groups of patients. Refractory VF was a significantly more common cause of death in patients with secondary VF. EM, electromechanical dissociation.

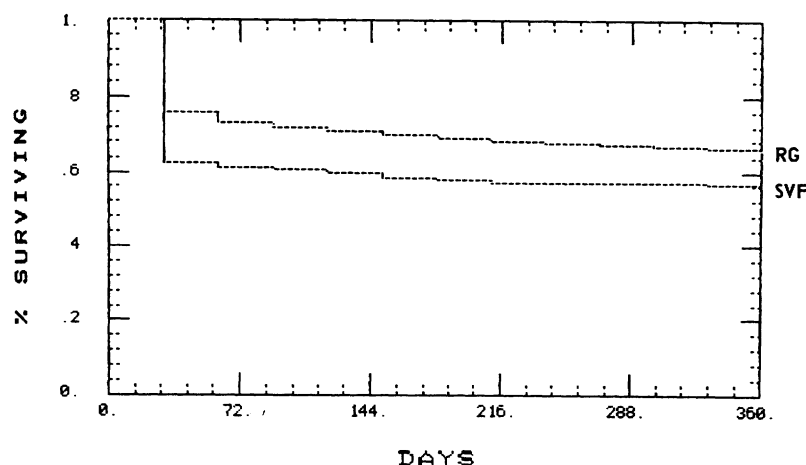


FIGURE 3. Graph showing cumulative 1-year survival in patients with and without secondary ventricular fibrillation (SVF). The 1-year survival is significantly lower in patients with SVF than in the reference group (RG). This is fully explained by deaths occurring during hospitalization. In fact, after the first month from the index infarct, the curves remain parallel.

excess of patients dying from refractory ventricular fibrillation is evident in the group of patients with secondary ventricular fibrillation (patients with ventricular fibrillation, 16 of 118, 13.6% versus patients without ventricular fibrillation, 18 of 725, 2.5%; relative risk, 6.16; 95% confidence interval, 3.28–11.55). Cardiogenic shock was the most common cause of death in patients with and without secondary ventricular fibrillation, with a trend toward greater exposure to the risk of dying from this complication in the group of patients with ventricular fibrillation (patients with myocardial infarction plus ventricular fibrillation, 73 of 118, 62% versus patients with myocardial infarction without ventricular fibrillation, 396 of 725, 54.6%; relative risk, 1.35; 95% confidence interval, 0.90–2.01).

One-Year Mortality Rate After Hospital Discharge

Survival data were available for all patients except for 34 of those in the reference group. For patients who survived the hospital phase of acute myocardial infarction, there was no difference in mortality rate between those who did and did not have secondary ventricular fibrillation (20 of 193, 10.4% versus 322 of 2,319, 13.9%; relative risk, 0.72; 95% confidence interval, 0.44–1.15), nor was there a statistically significant difference when allowance was made for the site of infarct (anterior site, 8 of 72, 11.1% versus 172 of 1,113, 15.5%; relative risk, 0.68; 95% confidence interval, 0.32–1.44; posterior site, 6 of 80, 7.5% versus 75 of 672, 11.2%; relative risk, 0.64; 95% confidence interval, 0.27–1.52). Stratification of patients by Killip class from II to IV confirmed the same finding. Indeed, patients with a history of secondary ventricular fibrillation showed a trend toward a decrease in the 1-year mortality rate compared with those without the index arrhythmia, but the difference was not statistically significant (Killip II, 13 of 148, 8.8% versus 251 of 2,015, 12.5%; $p=NS$; Killip III, 6 of 27, 22.2% versus 61 of 242, 25.2%; $p=NS$; Killip IV, 1 of 18, 5.6% versus 10 of 62, 16.1%; $p=NS$).

Distribution of Treatments at the Time of Hospital Discharge

Antiarrhythmic drugs and β -blockers were administered more often (33.3% versus 17.4% and 9.5%

versus 5.1%, respectively) and digitalis less often (29.1% versus 39%) at discharge in patients with secondary ventricular fibrillation. Despite this unbalanced distribution of treatment with antiarrhythmics and, to a lesser extent, β -blockers, no differences in 1-year mortality were observed among patients with secondary ventricular fibrillation regardless of whether they had been receiving either antiarrhythmic drugs or β -blockers at the time of discharge from the hospital. In contrast, higher mortality figures associated with digitalis administration at the time of hospital discharge were consistently found among both patients with ventricular fibrillation and those in the control group. Because of the purely descriptive and a posteriori nature of these findings, statistical calculations are not provided.

Clinical Events at 6-Month Follow-up

There were no differences in the incidence of clinical events (angina, congestive heart failure, reinfarction, and coronary artery bypass grafting) recorded at clinical follow-up at 6 months between patients with and patients without secondary ventricular fibrillation.

Cumulative 1-Year Survival Curves

The overall 1-year probability of death is significantly greater for patients with secondary ventricular fibrillation than for those without secondary ventricular fibrillation (Figure 3). The difference, however, is fully explained by excess mortality occurring during the hospital phase of acute myocardial infarction (the curves remain parallel after the end of the first month after admission). The same holds true when examining the curves of patients with anterior infarcts, whereas patients with secondary ventricular fibrillation complicating posterior infarcts do not exhibit reduced 1-year survival probabilities in comparison with control patients (Figure 4). Hence, the occurrence of a secondary ventricular fibrillation event does not predict long-term mortality.

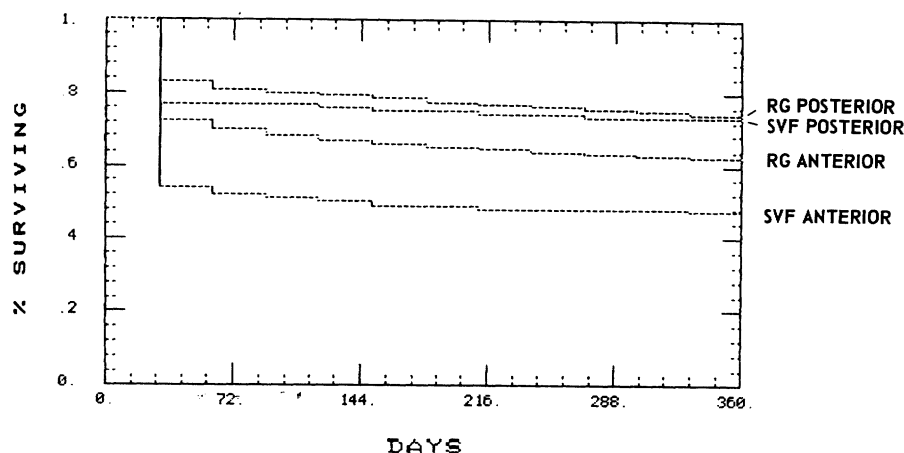


FIGURE 4. Graph showing cumulative 1-year survival in patients with and without secondary ventricular fibrillation (SVF) according to infarct site. The 1-year survival is significantly lower in patients with anterior site of infarct (Anterior) plus SVF than in the reference group (RG). The difference is fully explained by deaths occurring during hospitalization, as shown by the parallel curves seen after the first month from the index infarct. Among patients with posterior site of infarct (Posterior), those with SVF do not exhibit reduced 1-year survival probabilities in comparison with control patients.

In-Hospital and 1-Year Prognosis of Early Versus Late Secondary Ventricular Fibrillation

When time of occurrence of secondary ventricular fibrillation relative to in-hospital prognosis was examined (Table 5), patients with late ventricular fibrillation (after the first day of hospitalization) had a distinctly worse short-term survival rate than those with early ventricular fibrillation (57.5% versus 30.3%, $p < 0.0001$), although an episode of secondary ventricular fibrillation was associated with a reduced in-hospital survival rate irrespective of the timing of its occurrence. Patients with late ventricular fibrillation had a particularly poorer in-hospital outcome than did patients in whom the arrhythmia occurred early in the course of infarction, despite a similar proportion of individuals with moderate heart failure (Killip class II) at initial evaluation or with anterior site of infarct in both subgroups (66% versus 65% and 46% versus 42.4%, respectively). This worse prognosis is also consistent with the fact that patients with late secondary ventricular fibrillation experienced a significantly greater risk of developing overt left ventricular failure than did patients with early secondary ventricular fibrillation (36 of 87, 41.4% versus 44 of 224, 19.6%; relative risk, 2.89; 95% confidence interval, 1.70–4.90). Figures for pericarditis, reinfarction, and angina showed a consistent trend toward a more complicated in-hospital course among patients with late secondary ventricular fibrillation (pericarditis, 16 of 87, 18.4% versus 24 of 224, 10.7%; reinfarction, 4 of 87, 4.6% versus 2 of 224,

0.9%; angina, 16 of 87, 18.4% versus 28 of 224, 12.5%). None of these apparently obvious differences reached statistical significance possibly because of the low number of events.

After hospital discharge, the survival rate of patients with late secondary ventricular fibrillation was not significantly different from that of either patients with early secondary ventricular fibrillation or patients in the reference group (18.9% versus 8.3%, $p = \text{NS}$ and 18.9% versus 13.9%, $p = \text{NS}$, respectively), although there was a trend toward a higher mortality rate in the group of patients with late occurrence of the arrhythmia.

Discussion

Protective Effect of Streptokinase Against Secondary Ventricular Fibrillation

Trials of thrombolytic therapy in evolving myocardial infarction have consistently shown a trend toward a reduced incidence of ventricular fibrillation in actively treated patients.^{16,23–26} Moreover, a pooled analysis of the two largest trials (GISSI and ISIS-2) performed according to the Mantel-Haentzel-Peto method²⁷ demonstrates a statistically significant 13% reduction in the odds of developing ventricular fibrillation (relative risk, 0.87; 95% confidence interval, 0.79–0.96).

Because ventricular fibrillation after acute myocardial infarction may occur in completely different clinical circumstances, it is essential to ensure as precise a classification of the fibrillatory events as possible to clarify a complex interaction such as that between thrombolytic therapy and the risk of ventricular fibrillation. Unlike other trials, in the GISSI study, all ventricular fibrillation episodes have not been lumped together, irrespective of the underlying hemodynamics. This fact has made it possible to analyze the impact of streptokinase treatment on the frequency of both primary and secondary ventricular fibrillation. The present study represents a retrospective subgroup analysis of a large clinical trial that was designed to evaluate the effect of thrombolytic therapy in acute myocardial

TABLE 5. In-Hospital Mortality of Patients With (Early Vs. Late) and Without Secondary Ventricular Fibrillation

Patient	Mortality (deaths/total)	Relative risk (95% CI)
Without SVF	23.6 (725/3,078)	1
With early SVF	30.3 (68/224)	1.41 (1.05–1.90)
With late SVF	57.5 (50/87)	4.38 (2.94–6.54)

CI, confidence interval; SVF, secondary ventricular fibrillation.

infarction. Our data show that a worthwhile 29% reduction in the incidence of secondary ventricular fibrillation may be achieved in patients treated with streptokinase within 3 hours of onset of symptoms. Furthermore, it is also to be emphasized that this beneficial effect of thrombolytic treatment seems to be largely attributable to a markedly reduced incidence of late-onset ventricular fibrillation. Thus, these findings along with the observation that primary ventricular fibrillation frequency is unaffected by streptokinase treatment¹⁸ lend support to the concept that the protection exerted by thrombolytic agents against ventricular fibrillation occurrence applies only to those fibrillatory events that are by definition largely dependent on the severity of underlying myocardial damage. In this respect, timely reperfusion with resultant salvage of reversibly injured, ischemic myocardium and the subsequent limitation of left ventricular dysfunction^{28,29} is strongly suggested by our data as the most likely explanation for the observed reduction in the risk of secondary ventricular fibrillation. Subgroup analysis shows that this salutary effect of reperfusion therapy seems to be applicable to patients with left ventricular failure but not to individuals already in cardiogenic shock. This might indicate that in the latter case, the proportion of "stunned" myocardium contributing to the impairment of left ventricular function would be insignificant, as already evidenced by the clear absence of benefit on mortality.¹⁶ Furthermore, studies of intracoronary thrombolysis have also suggested that low rates of recanalization can be achieved in shock patients.^{30,31}

Although in a recent nonrandomized study³² a small number of patients treated with thrombolytic agents exhibited an improvement of the electrical stability of the heart to programmed extrastimulation and a reduced incidence of late malignant ventricular arrhythmias in comparison with individuals receiving routine care, it appears unlikely that a reperfusion-related reduction in cardiac instability prevented the occurrence of secondary ventricular fibrillation during the early phases of acute myocardial infarction. Had such a mechanism played an antifibrillatory role, its protective influence should have also resulted in a decreased incidence of the primary form of ventricular fibrillation. As previously mentioned, however, this was not the case in the GISSI trial,¹⁸ in which the incidence of primary ventricular fibrillation was not reduced even in patients receiving streptokinase within 1 hour of onset of symptoms.³³

Epidemiological Observations

The approximately 3% incidence of secondary ventricular fibrillation in the coronary care unit found in this study appears to be somewhat lower than that reported by most studies, which are usually in the range of 4–7%.^{5–8,10,13} Only in one study has a lower frequency, approximately 2%, so far been observed.³⁴ Apart from the previously discussed beneficial effect of reperfusion therapy on secondary ventricular fibrillation incidence, surely other factors

should be considered to explain this lower figure, namely, the more reliable estimate of the event obtainable in a large multicenter trial, the evolution over two decades of management strategy for acute myocardial infarction, the variable delay to coronary care unit admission, and possibly the exclusion from our analysis of ventricular fibrillation episodes occurring after coronary care unit discharge.

The incidence of secondary ventricular fibrillation in the coronary care unit does not appear to be related to infarct location or sex of the patient but appears to be significantly more common in patients older than 65, as previously suggested.³⁵ This is not surprising because the elderly patients with acute myocardial infarction are known to have a greater prevalence of adverse baseline factors, a greater likelihood of underlying left ventricular dysfunction, and multivessel coronary artery disease.^{36,37} Accordingly, in the GISSI trial, the elderly had an increased morbidity and mortality rate after acute myocardial infarction.³⁸

Effect of Secondary Ventricular Fibrillation on Short-term Survival

The negative prognostic implications of secondary ventricular fibrillation have been confirmed in the unusually large population of the GISSI trial, in which the overall mortality figures could be compared with those of a closely matched cohort. To date, the prognosis of myocardial infarction complicated by an episode of secondary ventricular fibrillation has commonly been determined without allowing for the clinical severity of infarction.^{8–12} Recently, the findings of two data bases have shown secondary ventricular fibrillation to be a negative predictor of short-term survival in patients with acute myocardial infarction.^{13,14} In the MILIS study, the probability of in-hospital death for secondary ventricular fibrillation patients was higher than for patients without the arrhythmia, even after having corrected for left ventricular ejection fraction.¹³ Our data are in agreement with those studies^{13,14} and the current view.^{1–4} Indeed, among GISSI patients, secondary ventricular fibrillation was associated with a risk of mortality that is double that of the reference group. This was so irrespective of the site of infarcts, with the apparent exception of the posterior site where numerical trends still paralleled the global results. Only among patients in cardiogenic shock at initial evaluation did short-term outcome appear to be uninfluenced by the occurrence of ventricular fibrillation, which could represent in such patients a preterminal arrhythmia in the setting of extensive irreversible destruction of left ventricular myocardium.

Although the possibility cannot be excluded that cardiac arrest in itself might have directly contributed in some way at least in some patients to the observed excess mortality,^{2,39} the bulk of evidence suggests secondary ventricular fibrillation as a marker of infarcts at higher risk for the fatal mechanical and electrical complications of extensive myocardial necrosis. This interpretation is also supported by the

positive relation found in our study between secondary ventricular fibrillation and pericarditis, a clinical marker of transmural infarction,^{40,41} which achieved statistical significance in the subgroup of patients classified in Killip classes II–III. Additionally, the tendency toward a greater risk of dying from cardiogenic shock, and possibly the significantly more common propensity to die from refractory ventricular fibrillation among secondary ventricular fibrillation patients, points in the same direction.

The mortality rate of 38% found in our study among patients whose infarction was complicated by secondary ventricular fibrillation appears to be lower than that reported by previous studies, that is, in the range of 50–85%.^{5–14} Apart from the limitations of previous studies that were frequently based on small noncontrolled series, two major factors may explain this difference in the estimated mortality rate of patients with secondary ventricular fibrillation. First, unlike some studies^{13,14} but in keeping with others,^{5,6,8,12,34} we have included in the analysis of secondary ventricular fibrillation those episodes of ventricular fibrillation occurring in infarcts with moderate heart failure (Killip class II). Second, epidemiological studies have consistently shown a decline in the in-hospital case fatality rates of patients with acute myocardial infarction over the past two decades,^{42–44} which reflects an improvement in both diagnostic and therapeutic strategies even in the years before thrombolysis.

Long-term Prognosis of Patients With Acute Myocardial Infarction Complicated by Secondary Ventricular Fibrillation

In keeping with MILIS data,¹³ the present study shows that the 1-year mortality rate of survivors of secondary ventricular fibrillation after hospital discharge is similar to that of patients with comparable infarcts, irrespective of the site of infarct and Killip class on admission. This finding implies that the arrhythmia per se does not alter survival probabilities in the posthospital phase of myocardial infarction, which are more likely to be dependent on the degree of myocardial damage or coronary disease rather than on a particularly high late susceptibility to ventricular fibrillation recurrence.^{45,46} Thus, our data may help clarify the conflicting conclusions reached by previous studies, which could never rely on an appropriate control population without ventricular fibrillation for direct comparison and were almost invariably flawed by the limited number of patients involved.^{9,12,15,47} The finding of an unbalanced distribution of treatment with antiarrhythmics between the groups of patients at hospital discharge is consistent with previous reports^{13,14} and may reflect the common empirical use of these drugs in patients with a recent episode of ventricular fibrillation. This excessive administration of antiarrhythmic agents, however, does not seem to have contributed to lowering the 1-year mortality rate of ventricular fibrillation patients, the survival

probabilities found among them being similar irrespective of whether they had been receiving these drugs at discharge from hospital. The last consideration may also be applied to β -blocker distribution between the groups. On the other hand, the lower exposure of patients with ventricular fibrillation to digitalis at discharge from hospital may reflect the empirical restraint in the use of the drug because of the fear of digitalis-associated proarrhythmic effects in survivors of acute myocardial infarction.^{48–50} The higher mortality rate seen among patients treated with digitalis is not surprising and most likely could be entirely explained by the more severe heart disease and the higher incidence of adverse risk factors usually found in such individuals.^{51,52}

Early Versus Late Secondary Ventricular Fibrillation

Two subsets of secondary ventricular fibrillation patients were identified when attention was paid to the timing of arrest after infarction. A significant increase in mortality rates was associated with late onset as opposed to early onset of ventricular fibrillation. This finding is consistent with previous observations^{13,53} and clearly reflects a more complicated in-hospital course of patients with infarcts with late secondary ventricular fibrillation, as evidenced by the significantly higher incidence of left ventricular failure and the overall trend toward greater risk of reinfarction, pericarditis, and early angina. This difference in survival between the two subsets of ventricular fibrillation patients was no longer apparent after hospital discharge, although a not statistically significant tendency toward higher mortality figures was seen in patients with late ventricular fibrillation.

Conclusions

Secondary ventricular fibrillation complicating acute myocardial infarction has generally been believed to represent a final electrophysiological derangement superimposed on extensive myocardial damage. This assumption has in turn led to the concept of inevitability, thereby diverting attention from its management and prophylaxis.¹ The fact that intravenous streptokinase when timely administered has proved effective in reducing the incidence of the arrhythmia, most probably by a limitation of infarct size, may shed new light on the beneficial effects of thrombolytic therapy. On the other hand, it seems reasonable to speculate that adjunctive measures such as “injury-delaying drugs” or free-radical scavengers⁵⁴ might further reduce the risk of secondary ventricular fibrillation and be clinically beneficial. Finally, although the high in-hospital morbidity and mortality rate of secondary ventricular fibrillation is confirmed by the present study, the arrhythmia per se does not seem to place hospital survivors at an extra risk of mortality.

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