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Predictors of Nonfatal Reinfarction in Survivors of Myocardial Infarction After Thrombolysis

Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) Data Base

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Objectives. **This study was designed to reassess the prediction of recurrent nonfatal myocardial infarction in patients recovering from acute myocardial infarction after thrombolysis.**

Background. **Recurrent nonfatal myocardial infarction is a strong and independent predictor of subsequent mortality. Current knowledge of risk factors for nonfatal reinfarction is still largely based on data gathered before the advent of thrombolysis. Thus, this prospective study was planned to identify harbingers of nonfatal reinfarction in the postinfarction patients of the multicenter Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial.**

Methods. **Predictors of nonfatal reinfarction at 6 months were analyzed by multivariate technique (Cox model) in 8,907 GISSI-2 survivors of myocardial infarction with clinical follow-up, relying on a set of prespecified variables reflecting residual ischemia, left ventricular failure or dysfunction, complex ventricular arrhythmias, comorbidity as well as demographic and historical factors.**

Results. **The postdischarge to 6-month incidence rate of nonfatal reinfarction was 2.5%. Independent predictors of nonfatal reinfarction were cardiac ineligibility for exercise test (relative risk 2.97, 95% confidence interval [CI] 1.98 to 4.45), previous myocardial infarction (relative risk 1.70, 95% CI 1.22 to 2.36) and angina at follow-up (relative risk 1.50, 95% CI 1.10 to 2.04). On further multivariate analysis, performed in 6,580 patients with both echocardiographic and electrocardiographic monitoring data available, a history of angina emerged as an additional risk predictor (relative risk 1.58, 95% CI 1.10 to 2.25).**

Conclusions. **The 6-month incidence of nonfatal reinfarction is rather low in survivors of myocardial infarction after thrombolysis. Cardiac ineligibility for exercise testing and a history of coronary artery disease are risk predictors. Recurrent nonfatal infarction is not predictable by qualitative variables reflecting residual ischemia, except by postdischarge angina. Prediction of nonfatal reinfarction appears less accurate than prediction of mortality, as almost 50% of reinfarctions occur in patients without any of the identified risk factors.**

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Nonfatal reinfarction after an index acute myocardial infarction is a strong independent predictor of subsequent mortality (1–3). Thus, continuing investigation of risk factors for recurrent nonfatal myocardial infarction appears important for the improvement of management policies in survivors of myocardial infarction. Most studies examining the prognostic factors for nonfatal reinfarction (1,4–8) were carried out before the widespread application of thrombolysis. Therefore, within the framework of the large GISSI-2 data base (9), a specific study was planned to reassess the prediction of nonfatal reinfarction in patients recovering from acute myocardial infarction after thrombolysis. This report describes the results of the prospective analysis of the risk factors for recurrent nonfatal myocardial infarction in the postinfarction patients of the multicenter GISSI-2 trial (10,11).

Methods

Study patients. The 8,907 hospital survivors considered in this report had been enrolled in the GISSI-2 study, a factorial, randomized open trial designed to compare the benefits and risks of two thrombolytic agents, streptokinase and alteplase, in patients with acute myocardial infarction. The patients were also randomized to receive subcutaneous heparin or usual therapy. Exclusion criteria, the method of randomization,

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procedures for the administration of trial medications as well as guidelines for the recommended treatments have been reported elsewhere (10).

Patients were eligible for enrollment in the GISSI-2 study 1) if they had chest pain accompanied by ST segment elevation ≥1 mm in any limb lead of the electrocardiogram (ECG) or ≥2 mm in any precordial lead, or both; 2) if they had been admitted to the coronary care unit within 6 h of the onset of symptoms; and 3) if they had no clear contraindication to the fibrinolytic treatments or to heparin.

The patients included in this data base study were those in whom a diagnosis of definite acute myocardial infarction was validated at a central coordinating center on the basis of two of the following three criteria: 1) prolonged ischemic chest pain; 2) new appearance of abnormal Q waves with evolutionary ST and T wave changes on serial tracings; 3) enzymatic evidence, as indicated by an elevation of total serum creatine kinase to twice the upper limit of normal values.

Data collection. Before randomization a set of demographic and historical variables was collected prospectively for each patient. In addition, individual information on the clinical course, major clinical events, other treatments during hospital admission and at discharge and laboratory examinations was collected on a single form. Data on postdischarge clinical events, cardiovascular medications and revascularization procedures were reported on a follow-up form. These forms, together with three ECGs taken at set intervals (at entry, after 4 h and at hospital discharge) were sent to the coordinating center for review of the completeness and consistency of data and for central computer analysis of the ECG. The ECGs obtained in patients with early spontaneous postinfarction angina or reinfarction were also reviewed in the coordinating center.

Electrocardiography and special tests. Standard 12-lead ECGs were read centrally by four cardiologists and categorized according to the site and type of infarct. For the purpose of this study, infarct site was classified as inferior in the presence of either or both 1) pathologic Q waves in leads II, III and aVF or 2) an R/S wave ratio ≥1 in leads V_1 and V_2. The broad category of anterior infarct site included anterior location (pathologic Q waves in leads V_1 to V_4), lateral location (pathologic Q waves in isolated leads I and aVL or isolated leads V_5 and V_6) and anteroinferior location (concomitant signs of anterior and inferior infarction without a history of previous infarction). The development of new Q waves, 0.03 s in duration, was taken as evidence of a Q wave infarction, and the presence of serial ST-T wave changes in the absence of new Q waves in the predischarge ECG was judged to indicate a non-Q wave infarction. Patients with R/S ≥1 in leads V_1 to V_2 were assigned to the Q wave group.

Two-dimensional echocardiography was performed to assess segmental left ventricular systolic function just before the patients were discharged from the hospital (~2 weeks after the onset of infarction). Ejection fraction was calculated from left ventricular two-dimensional tomograms by either the area-length method or modified Simpson's rule (12). The segmental left ventricular performance pattern was evaluated to generate an infarct size index expressed as the percent of akinetic or dyskinetic segments. This functional index indirectly reflects left ventricular function as it is dependent on the degree of overall myocardial damage caused by ischemia or infarction. For wall motion analysis from standard two-dimensional tomograms (parasternal, apical and subcostal views), the left ventricular wall was divided into 11 segments according to the model originally proposed by Edwards et al. (13) as modified to consider the apex as a single segment (14).

An echocardiographic examination was not available for 17.8% of the patients, mostly because of poor echogenicity or logistic reasons. A determination of ejection fraction was available in 28.4% of the patients. A symptom-limited exercise stress test was performed, whenever possible, within 30 days from randomization according to standards and guidelines for exercise testing provided by an Italian ad hoc committee (15). Approximately 36% of patients were excluded from stress testing on clinical grounds. In 85% of the patients, 24-h Holter ambulatory ECG monitoring was performed shortly before hospital discharge; the other 15% did not have a Holter recording for logistic or technical reasons. Premature ventricular complexes were categorized according to mean frequency per hour and presence of repetitive forms (couplets, runs or ventricular tachycardia).

Quality control. Quality control of special tests (i.e., 24-h Holter ECG recordings, exercise stress ECGs and tape recordings of echocardiographic examinations) was ensured at the coordinating center by random check of a selected sample of ~10% of all examinations performed by each laboratory. All checking was performed by a staff of experienced cardiologists who had no knowledge of study treatments. Quality control was meant to verify the correct assignment of patients according to the presence or absence of prespecified risk variables. The highly satisfactory results of this quality control have been reported elsewhere (9).

Risk variables. For the purpose of this data bank study, an ad hoc committee developed written, a priori hypotheses concerning risk factors for recurrent nonfatal myocardial infarction, relying on review of published studies and consensus among the members of the committee. The variables analyzed included data from the history, ECG, hospital and postdischarge course and special tests. The following historical and demographic variables were selected: advanced age (>70 years), female gender, history of angina (>1 month in duration before the index infarction), history of previous myocardial infarction, history of treated hypertension, insulin-dependent diabetes mellitus and history of cigarette smoking.

Some variables related to the hospital course. *Early left ventricular failure* was defined as Killip class >II on admission or the new appearance of symptoms and signs of left ventricular failure within day 4 after entry into the coronary care unit. *Late left ventricular failure* was defined as the first appearance or persistence of symptoms and signs of left ventricular failure after day 4 of the hospital stay. For the diagnosis of left ventricular failure at least two of the following signs or

symptoms were required: 1) bibasilar pulmonary rales, 2) a third heart sound, 3) dyspnea, 4) radiographic evidence of pulmonary congestion. *Early spontaneous postinfarction angina* was defined as the occurrence of typical ischemic chest pain manifesting at rest or on minimal exercise during the hospital stay ≥24 h after randomization; transient ST segment depression or elevation ≥1 mm, or inversion or pseudonormalization of the T wave during the episode of chest pain was also required for this diagnosis.

The occurrence of angina pectoris after hospital discharge was recorded on the 6-month follow-up data form, and episodes were classified as effort, spontaneous or mixed angina. The first notation of angina at follow-up (antedating the prognostic end point) was analyzed in the present study.

From special tests the following variables were generated. *Recovery phase left ventricular dysfunction* was defined as an echocardiographic left ventricular ejection fraction <0.40 or, whenever an ejection fraction determination was not available, the presence of >36% akinetic or dyskinetic myocardial segments; the latter indicator of left ventricular dysfunction was selected assuming that its adverse impact on survival was roughly similar to that of an ejection fraction <0.40 (9). The presence of *complex ventricular arrhythmias* during 24-h ECG monitoring was defined as frequent (≥10/h) premature ventricular beats or couplets, or both, runs or ventricular tachycardia. The development of angina during exercise or the appearance of ST segment depression >1 mm 0.08 s after the J point, as determined by the clinic physician, was taken as evidence of *a positive exercise test* (i.e., effort residual ischemia). *Exclusion from exercise stress testing* for both cardiac and noncardiac clinical reasons was selected as an additional exercise test–related variable in view of previous studies (16) that consistently showed the process of being excluded for clinical reasons from exercise testing to identify a high risk group of postinfarction patients. *Inferior site of infarct* was the only candidate variable derived from the ECG. Type of infarction (non-Q wave vs. Q wave) was excluded from this analysis because the subset of patients with a non-Q wave infarct included in this data base (i.e., those presenting with ST segment elevation) did not have an excess of nonfatal reinfarction in comparison with that of the Q wave group at preliminary screening of relevant risk determinants (the incidence rate of nonfatal reinfarction was, respectively, 2.6% vs. 2.5%).

Follow-up. The participating clinical centers were asked to monitor their patients after hospital discharge for clinically relevant events occurring in the 1st 6 months from admission to the trial. Recurrent myocardial infarction was defined according to the same criteria as the index infarction; this diagnosis had to be validated at the coordinating center. The prespecified end point of this study—recurrent nonfatal myocardial infarction—was defined as survival of reinfarction by 30 days. Patients with a first reinfarction during follow-up were considered to have reached an end point and, among them, subsequent reinfarctions were not analyzed.

Statistical analysis. All patients were included in the study regardless of missing data. Those for whom information concerning one of the candidate variables was missing were grouped in a separate category. Accordingly, for every factor a dummy variable was created whose value was 1 for missing information and 0 otherwise. The association of each variable with nonfatal reinfarction was assessed first by calculating the crude odds ratio and the 95% confidence intervals. All variables were then included in a Cox regression model (17) (Statistical Analysis System 6.07, PHREG procedure; SAS Institute Inc.) to control simultaneously for potential confounding factors. A model including the same variables, but restricted to the 6,580 patients for whom both the echocardiographic indicator and 24-h Holter monitoring data were available, was then fitted to better control the role of these variables as a confounding factor. The 183 patients (2.1%) who died during the study period and did not experience a nonfatal reinfarction were considered censored at the time of death. Likewise, additional univariate and multivariate analyses were performed to evaluate the importance of selected variables for the prognostic end point, any recurrent (nonfatal plus clinically reported fatal) infarction.

Results

Altogether, 10,407 patients were discharged from the hospital with a diagnosis of definite acute myocardial infarction (Fig. 1). Follow-up information concerning reinfarction status was unavailable for 1,500 patients (14.4%). Of these patients, 188 had been lost to follow-up. Among 1,170 hospital survivors without clinical follow-up, and thus analyzed by coordinating center with regard to their vital status, a 6-month death rate of 5.9% was observed. For 142 additional patients, traced by clinical centers, reinfarction status could not be ascertained mostly because of early sudden deaths (107 events). Overall, patients without information on reinfarction status exhibited a higher mortality risk than those making up the study group. The baseline characteristics of the 8,907 patients included in this analysis are reported in Table 1.

Recurrent infarction. Among the 8,907 hospital survivors with complete follow-up data (85.6% of the total) a first recurrence was observed in 260 patients by 6 months (a 2.9% rate). In 38 patients a fatal outcome was observed within 30 days of the new infarction (fatal reinfarctions). Of these patients, 32 (84%) died within 1 week of the reinfarction. Overall, 222 patients experienced a nonfatal reinfarction by 6 months (a 2.5% rate). This 2.5% rate appears lower than that found in the corresponding GISSI-1 cohort allocated to streptokinase therapy (2.9%, p = NS) but higher than that observed in the similar cohort assigned to usual treatment (1.9%, $p < 0.05$). Notably, the two patient groups had a comparable prevalence of a history of previous infarction (13.7% for GISSI-2 patients and 14.7% for GISSI-1 patients).

Time course of nonfatal reinfarction. Excluding the 1st 30 days after hospital discharge in which a peak of incidence (nearly 33% of all recurrences) was seen, nonfatal reinfarctions occurred at a rather stable rate during follow-up.

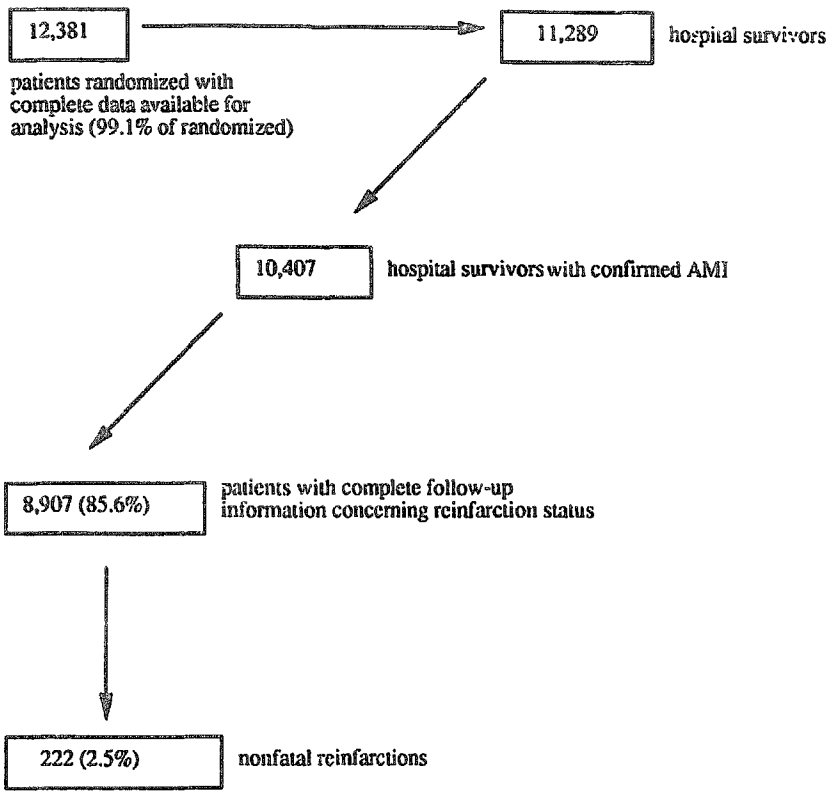

Figure 1. GISSI-2 data base flowchart. AMI = acute myocardial infarction; nonfatal reinfarctions = survival for >30 days after new infarction occurring ≤6 months after the initial infarction.

Medications and revascularization procedures during hospital admission and follow-up. The cardiovascular treatment regimen and the incidence of revascularization procedures are reported in Table 2. At the time of hospital discharge, nearly 75% of patients were taking aspirin (altogether slightly >80% were taking antiplatelet drugs), 25% were taking beta-adrenergic blocking agents and nearly 33% were taking calcium channel antagonists. The corresponding values at 6-month follow-up were somewhat lower for aspirin, slightly lower for beta-blockers and higher for calcium antagonists. Overall, these figures compared with the lower values observed in the corresponding cohorts of the GISSI-1 trial indicate an increase in the use of antiplatelet agents (82.4% vs. 47.1%, $p < 0.001$ at hospital discharge and 75.5% vs. 45.2%, $p < 0.001$ at 6-month follow-up) and beta-blockers (25.3% vs. 9.9%, $p < 0.001$ at hospital discharge and 24.7% vs. 11.3%, $p < 0.001$ at 6-month follow-up). Patients who underwent percutaneous transluminal coronary angioplasty or coronary artery bypass surgery after the index event comprised only 7% of the study group. As expected, higher incidence rates of revascularization procedures were seen in patients with residual ischemia. Cumulative rates of 19.4% and 14.5%, respectively, were observed among patients with early postinfarction angina (in-hospital rates 2.1% for coronary angioplasty and 1.5% for coronary bypass surgery; postdischarge rates by 6 months 4.0% for angioplasty and 11.8% for bypass surgery) and with a

Table 1. Baseline Characteristics of 8,907 Patients in the GISSI-2 Data Base

Female (%)	18.2
Mean age (yr)	61.0
Previous myocardial infarction (%)	13.7
Anterior Q wave myocardial infarction (%)	32.7
Non-Q wave myocardial infarction (%)	15.6
History (%)	
Hypertension	35.4
Angina pectoris (>1 mo)	20.7
Diabetes mellitus	14.1
Mean time from onset of pain to study entry (h)	2.5

Table 2. Medications and Revascularization Procedures at Hospital Discharge and at 6-Month Follow-Up of 8,907 Hospital Survivors

	At Discharge (%)	At 6 Months (%)
Medication		
Beta-blocking agents	25.3	24.7
Antiarrhythmic agents	10.4	10.0
Calcium channel antagonists	35.5	41.3
Digitalis	8.6	10.7
Diuretic drugs	18.8	18.9
Angiotensin-converting enzyme inhibitors	10.0	13.3
Antiplatelet agents		
Aspirin	76.7	63.8
Other	5.7	13.7
Revascularization procedure		
Coronary angioplasty	0.6	1.9*
Coronary bypass surgery	0.4	4.1*

*Incidence rates observed after hospital discharge.

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Table 3. Ranked Independent Predictors of Nonfatal Reinfarction Among 8,907 Hospital Survivors (Cox model)

Variable	Relative Risk	95% CI
Ineligibility (cardiac) for exercise test*	2.97	1.98–4.45
Previous myocardial infarction	1.70	1.22–2.36
Angina at follow-up	1.50	1.10–2.04

*A negative exercise test was the reference category. CI = confidence interval.

Table 4. Ranked Independent Predictors of Nonfatal Reinfarction Among 6,580 Hospital Survivors With Echocardiographic and Holter Monitoring Data Available (Cox model)

	Relative Risk	95% CI
Ineligibility (cardiac) for exercise test*	2.32	1.41–3.82
Previous myocardial infarction	1.78	1.20–2.64
History of angina	1.58	1.10–2.25
Angina at follow-up	1.47	1.01–2.15

*A negative exercise test was the reference category. CI = confidence interval.

positive exercise test (in-hospital rates 1.1% for angioplasty and 0.8% for bypass surgery; postdischarge rates by 6 months 4.5% for angioplasty and 8.1% for bypass surgery).

Univariate analysis. Of the 16 selected variables, only 5 were univariately predictive of recurrent nonfatal myocardial infarction, that is exclusion from exercise testing for cardiac reasons (odds ratio 4.74, 95% confidence interval [CI] 2.99 to 7.53), a history of previous myocardial infarction (odds ratio 2.71, 95% CI 1.84 to 4.00), angina at follow-up (odds ratio 2.11, 95% CI 1.48 to 3.00), history of angina (odds ratio 1.81, 95% CI 1.30 to 2.52) and history of treated hypertension (odds ratio 1.38, 95% CI 1.02 to 1.86).

Of 1,500 patients with postdischarge angina, 41% were classified as having effort angina, 33% as having spontaneous angina and 22% as having mixed angina. For 55 patients (4%) detailed classification was missing. A nonsignificant trend toward a greater incidence of nonfatal reinfarction was observed in patients with mixed or spontaneous angina than in those with effort angina (4.8% vs. 2.9%, p = NS).

Multivariate analysis. On multivariate analysis, performed according to the Cox model (17), three variables were retained as independent predictors of nonfatal reinfarction: the exclusion from the exercise test for cardiac reasons, previous myocardial infarction and angina at follow-up (Table 3). A complex indicator such as the process of being excluded from the exercise test for cardiac reasons turned out to be the most potent risk predictor. Conversely, noncardiac ineligibility for exercise test was not a predictive factor. A trend toward an increased risk of nonfatal reinfarction was observed for a history of angina (relative risk 1.30, 95% CI 0.96 to 1.75).

Notably, indicators of residual myocardial ischemia, such as early postinfarction angina and a positive exercise test, did not appear to be risk determinants. A similar conclusion applies to other variables (demographic [age >70 years, female gender], historical [history of treated hypertension, history of diabetes mellitus and history of cigarette smoking] and ECG [inferior location of infarct and presence of complex ventricular arrhythmias on Holter monitoring]) as well as to indicators of the extent of myocardial damage after infarction (early and late left ventricular failure, recovery phase left ventricular dysfunction).

Further analysis in patients with echocardiographic and 24-h Holter monitoring data available. To further investigate factors actually associated with increased risk of nonfatal reinfarction a separate multivariate analysis was performed on the subgroup of 6,580 patients with both echocardiographic and Holter monitoring data available, in which 154 recurrences were observed (2.3% incidence rate).

Univariate analysis. In this subgroup the same factors as in the previous analysis were risk predictors with the sole exception of a history of treated hypertension. With respect to eligibility for exercise testing, significant ($p < 0.01$) imbalances in all the selected variables were observed between patients who were excluded from exercise testing for cardiac reasons and those who were tested. Indeed, the excluded patients not only had a greater prevalence of female gender and advanced age but also had a more complicated previous history and clinical course after the index infarction. This more serious risk profile was also evidenced by the greater prevalence among these patients of digitalis, diuretic and antiarrhythmic therapy, as well as the lesser frequency of beta-blocker therapy, at hospital discharge.

Multivariate analysis On multivariate analysis the three factors (cardiac ineligibility for exercise testing, previous infarction and postdischarge angina) that were originally found to be significantly correlated with nonfatal reinfarction were still retained as independent risk indicators (Table 4). In addition, a history of angina emerged as a risk predictor, ranking third behind ineligibility (cardiac) for exercise stress testing and a history of previous infarction. Conversely, early postinfarction angina and a positive exercise test were not related to recurrent nonfatal infarction.

Low risk patients. Factors predictive of outcome allowed the identification of a subset of patients (2,915 [33%] of 8,907) with a 4.3% 6-month rate of nonfatal reinfarction (124 events [56% of the total]), whereas a 1.6% recurrence rate was observed among patients without any risk factor. However, 44% of the overall number of events occurred in this low risk group. Moreover, aside from an empiric variable such as cardiac ineligibility for exercise testing, 54% of events occurred in this group. Roughly similar estimates were seen in the subgroup of 6,580 patients with echocardiographic and Holter ECG monitoring data available. In this latter subgroup, patients with two of four predictors of nonfatal reinfarction (10.5% of the total) had a 5.8% recurrence rate. However, in this 690 patient subset, only 40 (26%) of 154 end point events were observed.

Recurrent nonfatal or fatal infarction as end point. When the end point was taken to be any recurrent myocardial

infarction (nonfatal or clinically reported fatal recurrences), the conclusions of this study were quite similar.

Discussion

Rate of recurrent nonfatal myocardial infarction. An ~5% to 10% incidence rate of recurrent nonfatal infarction in the year after hospital discharge has been reported (1,2,8,18–20) in survivors of myocardial infarction. The lower estimate of this range implies a 6-month rate slightly >3% (8), a figure that appears comparable to the relatively low rate of 2.5% observed in the present study. This GISSI-2 reinfarction rate, midway between the percentages found in the corresponding cohorts of the GISSI-1 trial, most likely represents the net result of two contrasting factors: 1) a recent history of early thrombolytic treatment with its attendant higher risk of reinfarction (21), and 2) increasing use of beta-blockers and antiplatelet agents (22,23). A case can be made that this low nonfatal reinfarction rate has been influenced to some extent by exclusion from the analysis of a subset of patients without information on reinfarction, who exhibited a poorer survival rate and thus were likely to be at a higher risk of reinfarction. Another explanation for the observed low event rate might relate to the lower incidence of multivessel disease seen among patients included in thrombolytic trials in comparison with historical control subjects (24).

Predictors of recurrent nonfatal infarction. In the past there have been difficulties in developing models for predicting recurrent myocardial infarction (4,5). Even in more recent major studies (1,6–8,25,26), involving >400 patients, discrepancies and inconsistencies are apparent, with only a few variables (i.e., history of previous angina or diabetes and continued cigarette smoking) identified as independent risk factors for recurrent infarction in at least two investigations (27). Thus, the results of the present study should be discussed in the light of this background information.

In the GISSI-2 patients studied here, cardiac ineligibility for exercise testing emerged as the most powerful predictor of nonfatal reinfarction. This finding parallels the already reported strong association with all-cause mortality (9) and reinforces the concept that cardiac ineligibility for exercise testing identifies a high risk group of postinfarction patients (1,16,18).

In keeping with the results of a major data base study (8), two variables reflecting a history of coronary artery disease before the index infarction were independent predictors of nonfatal reinfarction (Tables 3 and 4). This observation might reflect the reported greater likelihood of multivessel coronary artery disease or more severe residual stenosis of the infarct-related artery after thrombolytic therapy, or both, among patients with a history of either previous infarction or previous angina (28,29). However, in addition to the role played by the extent of coronary disease and the severity of residual stenosis, more specifically these findings appear to indicate a greater incidence in these patients of active coronary lesions with a particular propensity to generate unstable plaques and thereby trigger new coronary events (30). On the basis of these findings, broader indications for coronary angiography and a lower threshold for recommending angioplasty or bypass surgery appear appropriate in patients with a history of previous infarction or angina pectoris preceding the index infarction, especially in the presence of other markers of risk (9,29,31).

The occurrence of angina pectoris after hospital discharge was of prognostic value with respect to a nonfatal reinfarction. This finding is in line with those of one other large study, although the association found in the present study does not appear as strong as previously indicated (8). Moreover, caution is needed in interpreting the clinical relevance of these data because angina at follow-up, representing true prodromal syndrome and thus in close pathogenetic linkage with the cascade of events ultimately leading to the new infarction, could not be reliably identified and excluded from the analysis.

Variables not predictive of recurrences. Qualitative markers of residual ischemia, such as early postinfarction angina and a positive exercise test (i.e., effort ischemia), were not predictors of the prognostic end point. These findings, which are consistent with those previously reported concerning all-cause mortality (9), might have been influenced by the greater incidence rates of revascularization procedures observed in patients with residual ischemia. However, additional factors must be taken into account to explain these data. Previous studies (1,8) examining recurrent infarction as a separate end point have reached conflicting conclusions as to the predictive role of early postinfarction angina. This disagreement most likely reflects the variability in the characteristics of the patients studied and suggests that the clinical entity of early postinfarction angina includes various patient subsets at widely different levels of risk for recurrent coronary events. Should this assumption be correct, it would be all the more important in future investigations to search for harbingers of reinfarction relying on new (and perhaps semiquantitative) indicators of recurrent ischemia instead of a simple clinical and ECG variable such as early postinfarction angina.

That effort ischemia was not of prognostic value may also be explained by the observed low event rate, a factor known to lower the positive predictive value of an abnormal stress test. This inability of a positive exercise test to predict nonfatal reinfarction is consistent with the majority of available studies (1,7,25,26,32–37). It is also not surprising because an important proportion of myocardial infarctions are known to be caused by the sudden development of severe coronary obstruction or occlusion from preexisting mildly stenotic atherosclerotic plaques, rather than gradual progression of severe arterial narrowings, whose ischemic potential can be exposed by noninvasive evaluation (24,38,39). Moreover, even the correlation between angiographic severity of the residual coronary artery stenosis after thrombolysis or other morphologic characteristics and the risk of subsequent reinfarction has been questioned (26,40,41). Nonetheless, the findings of this study do not exclude the possibility that an indicator of severe exercise-induced ischemia may predict an increased risk of nonfatal reinfarction (42).

The lack of an association between some historical variables reflecting conventional risk factors for myocardial infarction (i.e., history of treated hypertension, insulin-dependent diabetes and history of cigarette smoking) and nonfatal recurrences of infarction may be explained by the relatively short follow-up period of this study. It is worth recalling that similar findings were reported by some but not all previous studies (1,6–8,26,43–45) of recurrent infarction in which either nonfatal reinfarction alone or a fatal plus nonfatal recurrence was taken to be the end point. It must be also underscored that the variable used in this data base to examine cigarette smoking relates to smoking status evaluated only at hospital admission and, in contrast to other studies (6,26), no subsequent information was obtained.

Not surprisingly (27), indicators of left ventricular dysfunction as well as demographic (age and gender) and ECG variables (infarct site and complex ventricular arrhythmias on Holter monitoring) were not of prognostic relevance. Data concerning infarct type confirm the results of other major investigations (3,8,46–48).

Study limitations. The results of the present study relate to a group of low risk postinfarction patients (2.1% death rate at 6 months). Thus, they may not apply to different patient groups with higher event rates or higher rates of revascularization procedures.

Conclusions. Overall, accumulating evidence from this and other studies carried out before and after the advent of thrombolytic therapy (1,7,8,25) indicates that risk factors for recurrent nonfatal infarction are different from those known to be related to reduced survival. Moreover, the observation that in this data base study almost one in two such reinfarctions occurred in patients without any of the identified risk factors confirms that also among patients who have received thrombolytic therapy, prediction of nonfatal reinfarction is even less accurate than prediction of fatal outcome (8). This disappointing realization, further reinforced by the negative or at best contradictory findings of studies examining the predictive value of angiographic variables (7,25,26,40,41), underlines the limitations of present knowledge of factors that promote and determine the initiation and timing of coronary thrombosis and acute myocardial infarction (49,50). It is hoped that the prospective assessment of new biologic markers of risk (51–55) in future studies may make the prediction of recurrent nonfatal infarction a more fruitful endeavor.

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