

MARKERS OF MYOCARDIAL DAMAGE AND INFLAMMATION IN RELATION TO LONG-TERM MORTALITY IN UNSTABLE CORONARY ARTERY DISEASE

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ABSTRACT

Background In patients with unstable coronary artery disease, there is a relation between the short-term risk of death and blood levels of troponin T (a marker of myocardial damage) and C-reactive protein and fibrinogen (markers of inflammation). Using information obtained during an extension of the follow-up period in the Fragmin during Instability in Coronary Artery Disease trial, we evaluated the usefulness of troponin T, C-reactive protein, and fibrinogen levels and other indicators of risk as predictors of the long-term risk of death from cardiac causes.

Methods Levels of C-reactive protein and fibrinogen at enrollment and the maximal level of troponin T during the first 24 hours after enrollment were analyzed in 917 patients included in a clinical trial of low-molecular-weight heparin in unstable coronary artery disease. The patients were followed for a mean of 37.0 months (range, 1.6 to 50.6).

Results During follow-up, 1.2 percent of the 173 patients with maximal blood troponin T levels of less than 0.06 μg per liter died of cardiac causes, as compared with 8.7 percent of the 367 patients with levels of 0.06 to 0.59 μg per liter and 15.4 percent of the 377 patients with levels of at least 0.60 μg per liter ($P=0.007$ and $P=0.001$, respectively). The rates of death from cardiac causes were 5.7 percent among the 314 patients with blood C-reactive protein levels of less than 2 mg per liter, 7.8 percent among the 294 with levels of 2 to 10 mg per liter, and 16.5 percent among the 309 with levels of more than 10 mg per liter ($P=0.29$ and $P=0.001$, respectively). The rates of death from cardiac causes were 5.4 percent among the 314 patients with blood fibrinogen levels of less than 3.4 g per liter, 12.0 percent among the 300 with levels of 3.4 to 3.9 g per liter, and 12.9 percent among the 303 with levels of at least 4.0 g per liter ($P=0.004$ and $P=0.69$, respectively). In a multivariate analysis, levels of troponin T and C-reactive protein were independent predictors of the risk of death from cardiac causes.

Conclusions In unstable coronary artery disease, elevated levels of troponin T and C-reactive protein are strongly related to the long-term risk of death from cardiac causes. These markers are independent risk factors, and their effects are additive with respect to each other and other clinical indicators of risk. (N Engl J Med 2000;343:1139-47.)

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THERE are numerous studies showing that elevated blood levels of troponin T or I are associated with an increased risk of cardiac events after an episode of unstable coronary artery disease.¹⁻⁵ In addition, elevated levels of markers of inflammation in the blood, such as the acute-phase proteins, C-reactive protein, and fibrinogen, are associated with an increased risk of cardiac events in patients who have had an episode of unstable coronary artery disease as well as in apparently healthy persons.⁶⁻⁹ However, very limited information is available concerning the levels of troponins, C-reactive protein, and fibrinogen and the long-term mortality rate in patients with unstable coronary artery disease. We extended the follow-up period in the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, from five months to a mean of three years, and we evaluated and compared the usefulness of troponin T, C-reactive protein, and fibrinogen levels and other indicators of risk, including findings on the standard 12-lead electrocardiogram, as predictors of the long-term risk of death from cardiac causes.

METHODS**Study Design**

The study was part of a prospective, randomized, multicenter trial (FRISC) of low-molecular-weight heparin (dalteparin sodium) in 1506 patients with unstable coronary artery disease.¹⁰ The study was begun in April 1992. In 15 of the 23 participating hospitals, the protocol included a special blood-sampling schedule, and all 917 patients with complete data on troponin T, C-reactive protein, and fibrinogen levels were evaluated in the extended study.

The original inclusion criteria were a history of unstable angina or chest pain suggestive of acute myocardial infarction and onset of chest pain within 72 hours before enrollment in conjunction with electrocardiographic signs of ischemia in the form of ST-segment depression, T-wave inversion, or both. The exclusion criteria were mainly related to conditions associated with an increased risk of bleeding. The patients were randomly assigned to receive dalteparin sodium or placebo subcutaneously twice daily for five to seven days and then once daily for another five weeks. Coronary angiography and revascularization were recommended for patients who had refractory or incapacitating angina despite medical treatment and for those with signs of severe ischemia during exercise testing. All therapeutic decisions were made without knowledge of the patient's troponin T, C-reactive protein, or fibrinogen levels.

All patients provided witnessed informed consent, and the study was approved by the ethics committees of all participating university hospitals and by the Swedish Medical Products Agency.¹⁰

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Blood Sampling and Laboratory Methods

Venous blood samples were obtained at enrollment and after 12 and 24 hours. Blood was collected in tubes containing EDTA and centrifuged, and plasma was frozen in aliquots and stored at -70°C for subsequent analysis at the core laboratory in Uppsala, Sweden. The troponin T level was determined at each time point by the Enzygum-Test system (Boehringer Mannheim). Levels of C-reactive protein and fibrinogen were determined in the initial sample by turbidimetry (Hitachi model 717, Boehringer Mannheim) and rate nephelometry (Beckman Instruments), respectively. Details of the analytic procedures have been described elsewhere.^{2,9} Standard 12-lead electrocardiograms were obtained on admission and sent to a central site for evaluation.²

Evaluation of End Points

All patients were monitored during hospitalization and thereafter by outpatient visits at six weeks and at five to six months. During this period an independent end-points committee evaluated all deaths. Thereafter, until the end of follow-up on December 31, 1996, information about deaths and the causes of death was obtained from the Swedish National Cause of Death Register. This register records information on the deaths of all Swedish residents. The register contains the date and the cause of death as stated by the patient's physician, autopsy records, or both. In the current, extended study, we defined all deaths in which the underlying cause was considered to be cardiac according to the *International Classification of Diseases, 9th Revision* as death from cardiac causes.

Statistical Analysis

Since there was no significant difference in mortality in the original study between patients in the placebo group and patients in the dalteparin group at the end of randomized treatment or after five months of follow-up,¹⁰ the two groups were merged into one cohort in all statistical analyses for the current study. Differences in proportions were evaluated by the chi-square test. The Mann-Whitney test was used to test the equality of distributions in independent groups. In all survival analyses, the end point was death from cardiac causes, and data on patients who died of other causes were censored at the time of death. The cumulative survival curves in relation to troponin T, C-reactive protein, and fibrinogen levels were determined according to the Kaplan-Meier method, with the use of log-rank tests (for pairwise comparisons and analyses of trend) for statistical assessment. On the basis of previous reports of the FRISC trial,^{2,9} we evaluated the following cutoff levels: less than 2, 2 to 10, and more than 10 mg of C-reactive protein per liter; less than 3.4, 3.4 to 3.9, and 4.0 g or more of fibrinogen per liter; and less than 0.06, 0.06 to 0.59, and 0.60 μg or more of troponin T per liter. We also evaluated a cutoff value of 2.80 μg per liter for troponin T, since this value has been suggested to indicate a left ventricular ejection fraction of less than 0.40.¹¹

We used Cox regression analysis to calculate the unadjusted and adjusted relative risk ratios and 95 percent confidence intervals for death from cardiac causes after two years and for the total follow-up period in relation to troponin T, C-reactive protein, and fibrinogen levels. To identify independent predictors of death from cardiac causes, we used multivariate Cox regression analyses with forward, stepwise selection in three models. All clinical variables associated with death from cardiac causes in the univariate analysis that had a P value of 0.05 or less, as well as sex, body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and smoking status were included in the first model. The index diagnosis and the troponin T level were added to the second model, and C-reactive protein and fibrinogen levels were added to the third model. Variables included in the different models fulfilled the proportional-hazards assumption, since the results of tests of these variables for nonproportional hazards were not significant. Variables with a P value of less than 0.05 were entered in the model, and variables with a P value of more than 0.10 were removed. The hazard ratio and the 95 percent confidence interval were calculated as appropriate.

For all statistical analyses, a P value of less than 0.05 was considered to indicate a significant difference. All calculations were performed with SPSS software (version 9.0, Statistical Package for the Social Sciences).

RESULTS

Base-Line Characteristics

The median age of the study population was relatively old (70 years), half had a history of stable angina, and almost one third had had a previous myocardial infarction. Approximately 46 percent had had angina at rest in the week preceding the episode of chest pain, and 58 percent had chest pain on admission to the hospital. The median time from the onset of the episode of chest pain to admission was 5 hours, and the median time from the onset of chest pain to enrollment was 24 hours. The index event was unstable angina in 61 percent of patients and myocardial infarction in 39 percent. The electrocardiogram showed both ST-segment depression and T-wave inversion in 45 percent of the patients, ST-segment depression alone in 16 percent, T-wave inversion alone in 38 percent, and abnormal Q waves in 18 percent.

Clinical Outcome

The mean duration of follow-up was 37.0 months (range, 1.6 to 50.6). After one month 16 of the 917 patients (1.7 percent) had died, after one year 61 (6.7 percent) had died, and after two years 87 (9.5 percent) had died; during the entire follow-up period 124 patients (13.5 percent) died. All 16 patients who died within one month after the index event died of cardiac causes, but thereafter this proportion decreased: at one year 54 of the 61 deaths (89 percent) were due to cardiac causes, at two years 70 of 87 deaths (80 percent) were due to cardiac causes, and during the active follow-up period, 92 of the 124 deaths (74 percent) were due to cardiac causes.

Clinical Variables and Electrocardiographic Findings

As compared with those who survived, patients who died of cardiac causes during follow-up were older and more frequently had a history of stroke, congestive heart failure, hypertension, diabetes mellitus, stable angina, or previous myocardial infarction (Table 1). A larger percentage also used cardiac medications before admission and had ST-segment depression or abnormal Q waves on the admission electrocardiogram and a diagnosis of acute myocardial infarction as the index event (Table 1).

Troponin T Levels

The median maximal troponin T level during the first 24 hours after enrollment was significantly higher in patients who died of cardiac causes during follow-up than in those who survived (1.1 vs. 0.28 μg per liter, $P < 0.001$), but there was no significant difference in the levels between survivors and those who died of noncardiac causes. Kaplan-Meier analysis showed an increased probability of death from cardiac causes

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY POPULATION AT BASE LINE, ACCORDING TO WHETHER THEY SURVIVED THE FOLLOW-UP PERIOD OR DIED OF CARDIAC OR NONCARDIAC CAUSES.*

CHARACTERISTIC	SURVIVAL (N=793)	DEATH FROM CARDIAC CAUSES (N=92)	P VALUE†	DEATH FROM NONCARDIAC CAUSES (N=32)	P VALUE‡
Male sex (%)	64.4	71.7	0.16	68.8	0.62
Age (yr)			<0.001		<0.001
Median	69	74		77	
25th and 75th percentiles	62, 75	69, 77		71, 82	
History of congestive heart failure (%)	6.3	19.6	<0.001	25.0	<0.001
Previous stroke (%)	3.3	8.7	<0.05	6.3	0.36
Hypertension (%)	31.0	42.4	<0.05	46.9	<0.10
Diabetes mellitus (%)	10.0	29.3	<0.001	21.9	<0.05
Current smoker (%)	18.7	17.4	0.77	12.5	0.38
Stable angina >2 mo before enrollment (%)	47.3	68.5	<0.001	62.5	<0.10
Previous myocardial infarction (%)	25.5	44.6	<0.001	46.9	<0.01
Angina at rest in week preceding enrollment (%)	45.3	47.8	0.64	46.9	0.86
Ongoing chest pain at admission (%)	58.4	57.6	0.89	53.1	0.55
Time from onset of chest pain to admission (hr)			0.40		0.73
Median	5.3	5.8		5.5	
25th and 75th percentiles	3, 11	3, 12		2, 12	
Time from onset of chest pain to enrollment (hr)			0.43		0.68
Median	23.5	25.0		21	
25th and 75th percentiles	14, 33	14, 39		17, 37	
Cardiac medications at admission (%)					
Aspirin	32.4	41.3	<0.10	50.0	<0.05
≥2 Antianginal drugs§	23.3	43.5	<0.001	34.4	0.15
≥1 Drug for congestive heart failure¶	25.7	46.7	<0.001	50.0	<0.01
Electrocardiographic findings at admission (%)					
Pathologic Q waves	16.9	25.0	0.05	25.0	0.23
ST-segment depression	58.1	82.6	<0.001	68.8	0.23
Index event (%)					
Acute myocardial infarction	36.4	59.3	<0.001	40.6	0.63
Unstable angina	63.6	40.7	<0.001	59.4	0.63

*NS denotes not significant.

†P values are for the comparison of survivors with those who died of cardiac causes.

‡P values are for the comparison of survivors with those who died of noncardiac causes.

§Antianginal drugs included beta-blockers, calcium-channel inhibitors, and long-acting nitroglycerin.

¶Drugs for congestive heart failure included diuretics, angiotensin-converting-enzyme inhibitors, and digoxin.

during follow-up with increasing levels of troponin T (Fig. 1A). This association remained significant (log-rank test for trend, $P < 0.01$) when the analysis was restricted to death from cardiac causes that occurred after the first six months. The rates of death from cardiac causes and unadjusted and adjusted relative risks of death from cardiac causes at two years and for the entire follow-up period are presented in Table 2 according to the troponin T levels. Of the 132 patients (14.4 percent) who had had a maximal troponin T level of at least $2.8 \mu\text{g}$ per liter, 27 (20.5 percent) died of cardiac causes during follow-up, as compared with 65 of the remaining 785 patients (8.3 percent) ($P < 0.001$ by the log-rank test).

C-Reactive Protein and Fibrinogen Levels

The median C-reactive protein level and the median fibrinogen level were both significantly higher at

enrollment among patients who died of cardiac causes during follow-up than among those who survived (13 vs. 5 mg per liter, $P < 0.001$, and 3.9 vs. 3.6 g per liter, $P < 0.01$, respectively). The median fibrinogen level at enrollment was also higher among patients who died of noncardiac causes than among those who survived (3.9 vs. 3.6 g per liter, $P < 0.05$), whereas there was no corresponding significant difference in C-reactive protein levels.

The Kaplan–Meier analysis showed that patients with the highest levels of C-reactive protein at enrollment (more than 10 mg per liter) had a significantly higher probability of death from cardiac causes during the entire follow-up period than did patients with levels of 2 to 10 mg per liter or those with levels of less than 2 mg per liter (Fig. 1B). The mortality curves were similar in the two groups with lower levels. The probability of death from cardiac causes was higher

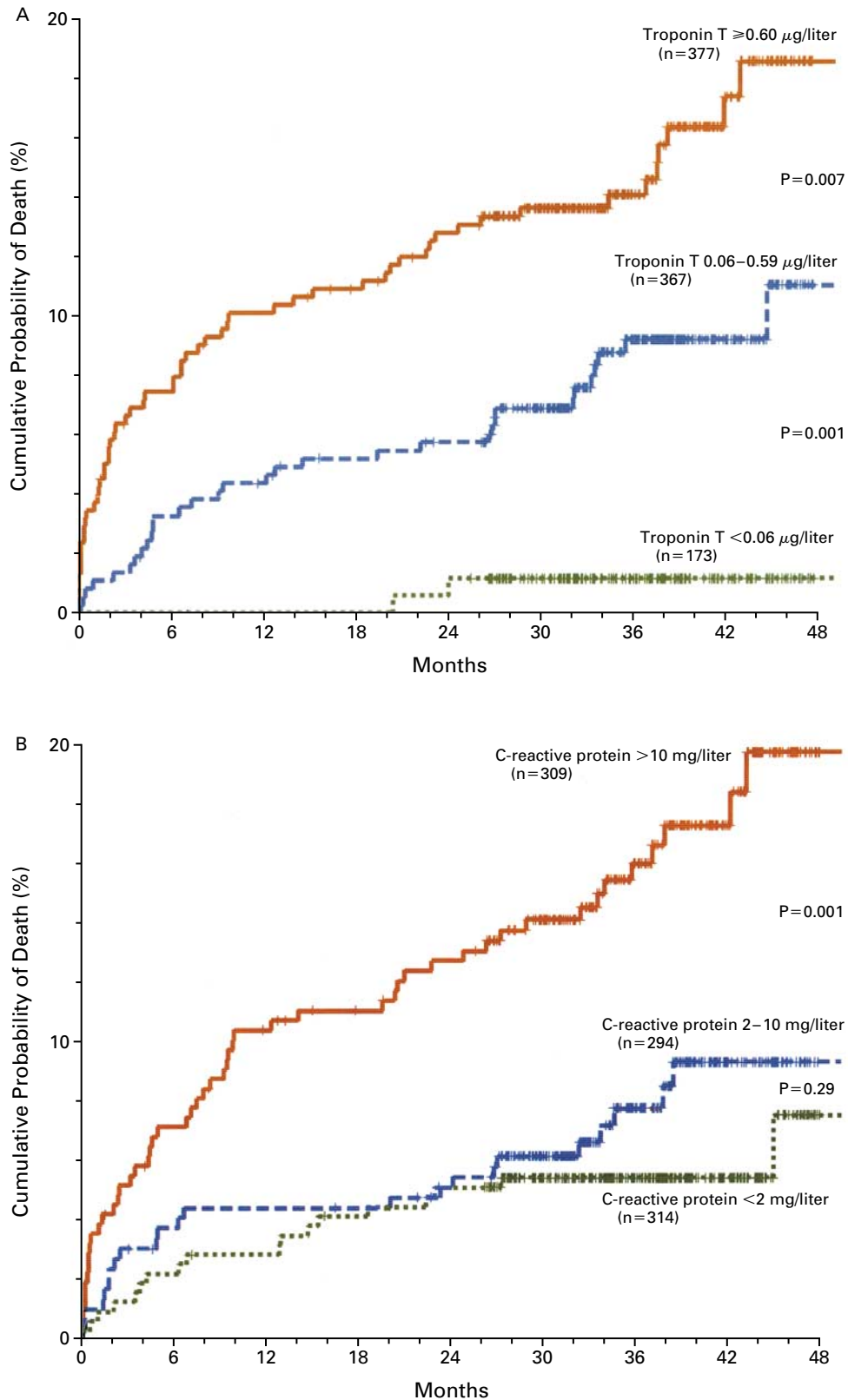


Figure 1. Cumulative Probability of Death from Cardiac Causes in Relation to Maximal Troponin T Levels during the First 24 Hours after Enrollment (Panel A) and to C-Reactive Protein Levels (Panel B) and Fibrinogen Levels (Panel C, Facing Page) at Enrollment. The number of patients in each group at the beginning of the study is given in parentheses. Tick marks indicate censored patients.

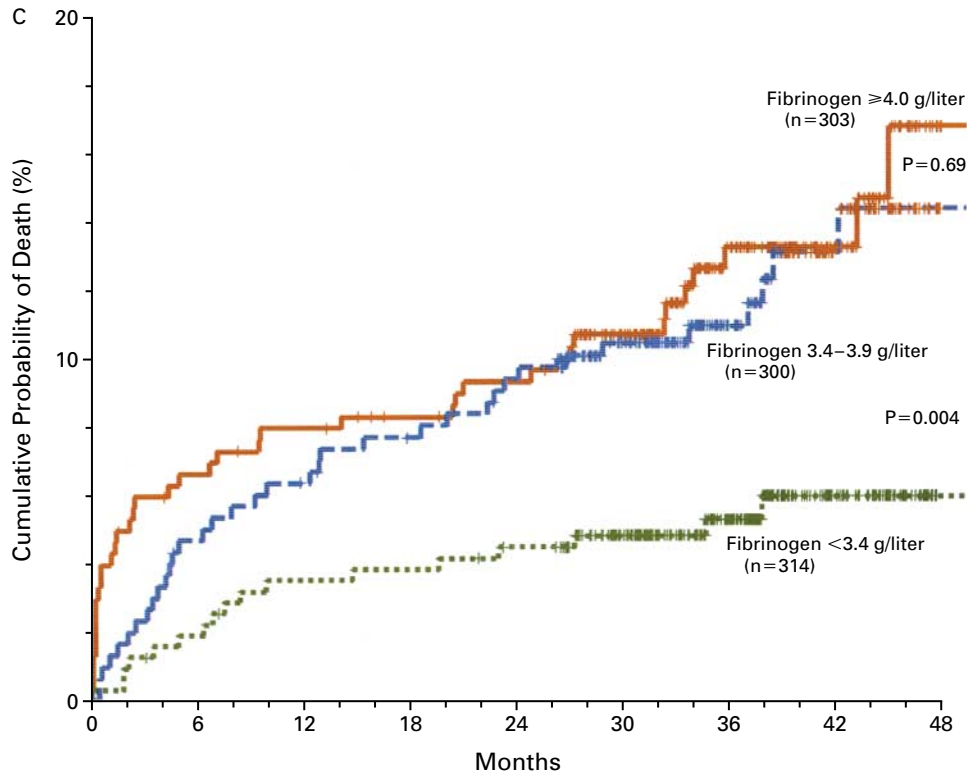


TABLE 2. RATES AND UNADJUSTED AND ADJUSTED RELATIVE RISKS OF DEATH FROM CARDIAC CAUSES AT TWO YEARS AND FOR THE ENTIRE FOLLOW-UP PERIOD IN RELATION TO MAXIMAL TROPONIN T LEVELS DURING THE FIRST 24 HOURS AFTER ENROLLMENT AND TO C-REACTIVE PROTEIN AND FIBRINOGEN LEVELS AT ENROLLMENT.*

VARIABLE	No. OF PATIENTS	AT TWO YEARS			ENTIRE FOLLOW-UP PERIOD		
		DEATH FROM CARDIAC CAUSES	RELATIVE RISK (95% CI)	ADJUSTED RELATIVE RISK (95% CI)†	DEATH FROM CARDIAC CAUSES	RELATIVE RISK (95% CI)	ADJUSTED RELATIVE RISK (95% CI)†
		%			%		
Troponin T ($\mu\text{g/liter}$)							
<0.06	173	0.6	1.0		1.2	1.0	
0.06–0.59	367	5.7	10.1 (1.4–75.4)	8.9 (1.2–66.1)	8.7	7.8 (1.87–32.4)	6.8 (1.6–28.2)
≥ 0.60	377	12.7	23.7 (3.3–171.4)	19.0 (2.6–138.1)	15.4	14.5 (3.55–59.4)	11.3 (2.7–46.4)
C-reactive protein (mg/liter)							
<2	314	5.1	1.0		5.7	1.0	
2–10	294	5.1	1.0 (0.5–2.05)	0.95 (0.5–1.9)	7.8	1.4 (0.8–2.6)	1.3 (0.7–2.4)
>10	309	12.6	2.6 (1.5–4.7)	2.3 (1.3–4.1)	16.5	3.1 (1.8–5.2)	2.6 (1.5–4.5)
Fibrinogen (g/liter)							
<3.4	314	4.5	1.0		5.4	1.0	
3.4–3.9	300	9.3	2.1 (1.1–4.1)	2.2 (1.1–4.1)	12.0	2.3 (1.3–4.1)	2.3 (1.3–4.1)
≥ 4.0	303	9.2	2.2 (1.1–4.1)	2.1 (1.1–4.0)	12.9	2.5 (1.4–4.5)	2.3 (1.3–4.1)

*CI denotes confidence interval.

†Adjusted relative risks were adjusted for age, sex, body-mass index, and smoking status.

throughout follow-up for patients with the highest fibrinogen levels (at least 4.0 g per liter) than for those with the lowest levels (less than 3.4 g per liter) (Fig. 1C). During the first few months, patients with intermediate levels of fibrinogen (3.4 to 3.9 g per liter) had a probability of death from cardiac causes that was similar to that in the group with the lowest levels, but thereafter the risk gradually approached that in the group with the highest levels. The rates of death from cardiac causes and unadjusted and adjusted relative risks of death from cardiac causes at two years and for the total follow-up period are shown in Table 2 according to the levels of C-reactive protein and fibrinogen at enrollment.

Multivariate Analyses

Multivariate analysis of the relation among clinical data, findings on the electrocardiogram obtained at admission, and the risk of death from cardiac causes (model 1) showed that five variables were significant: older age, male sex, the presence of diabetes, a history of congestive heart failure, and the presence of ST-segment depression at admission. In model 2, increasing troponin T levels, but not the index diagnosis (unstable angina or acute myocardial infarction), were independently associated with the prognosis, as were a number of other clinical variables and the presence of ST-segment depression at admission. Finally, in model 3, in which the C-reactive protein level and the fibrinogen level at enrollment were added to the other variables, increasing C-reactive protein levels together with increasing troponin T levels, the presence of diabetes, a history of congestive heart failure, older age, use of two or more antianginal drugs at admission, and the presence of ST-segment depression at admission were independent predictors of death from cardiac causes.

The hazard ratios and the 95 percent confidence intervals for the independent prognostic variables in models 1, 2, and 3 are given in Table 3. The two-year rates of death from cardiac causes according to the troponin T and C-reactive protein levels and the presence or absence of ST-segment depression at admission are shown in Figure 2. When the multivariate analysis in model 3 was restricted to patients with the index diagnosis of unstable angina, five variables remained independent predictors of the risk of death from cardiac causes: older age, the presence of diabetes, the presence of ST-segment depression at admission, troponin T levels of at least 0.06 μg per liter, and C-reactive protein levels of more than 10 mg per liter.

DISCUSSION

As expected from the results of previous studies of acute coronary syndromes,¹²⁻¹⁴ we found that several base-line variables, including the electrocardiographic findings, were important predictors of the risk of death from cardiac causes. In the multivariate analysis, in-

creasing age, a history of congestive heart failure, diabetes, and the presence of ST-segment depression at study entry remained independent predictors of a higher risk of death from cardiac causes. Our study probably underestimates the prognostic value of ST-segment depression, since the prognostic information can be further refined if the degree of depression is taken into consideration¹³ or if the ST segment is continuously monitored.^{15,16}

An elevation in the blood levels of the cardiac isoform of troponin T is a specific marker for myocardial damage¹⁷ and is more sensitive than the conventionally used levels of creatine kinase or its MB isoenzyme.¹⁸ Previous studies have found an increased short-term risk of death from cardiac causes with increasing levels of troponin T or I.^{2,3} We found that this risk continues to increase for at least three to four years after an episode of unstable coronary artery disease. Our most striking finding was the very low rate of death from cardiac causes among patients with maximal troponin T levels of less than 0.06 μg per liter: 1.2 percent (2 of 173 patients) after a mean follow-up of three years. In contrast, 15.4 percent (58 of 377 patients) of those with maximal troponin T levels of at least 0.60 μg per liter died of cardiac causes during the same time. This finding is only partly in accordance with the results of Stubbs and colleagues, who followed 183 patients with unstable angina for a median of three years and found a similar rate of death from cardiac causes in the "troponin T-positive" group (19 percent) but a much higher rate in the "troponin T-negative" group (12 percent).⁵ However, they used a cutoff level of 0.2 μg of troponin T per liter, which is much higher than our cutoff level of 0.06 μg per liter. Taken together, these results indicate that in order to identify a group that is truly at low risk of death from cardiac causes, any detectable myocardial damage must be taken into account.

The troponin T level yielded strong prognostic information, even after adjustment for other prognostic variables such as clinical history and electrocardiographic findings. Previous studies have shown that the combination of electrocardiographic findings and the troponin T level is useful in determining the short-term risk of acute myocardial infarction or death.^{2,19} We found that this combination also provides complementary prognostic information regarding the long-term risk of death from cardiac causes.

Why are the troponin levels such strong prognostic factors? Emerging data suggest that patients with even a minor elevation in troponin levels, as compared with those having little or no elevation, have a larger number of visible coronary thrombi, complex lesions, and impaired flow in the affected coronary artery, according to the grading system of the Thrombolysis in Myocardial Infarction study^{20,21} as well as evidence of greater activation of the coagulation system.²² Therefore, the risk of cardiac events is already increased in

TABLE 3. INDEPENDENT PREDICTORS OF DEATH FROM CARDIAC CAUSES AFTER A MEAN FOLLOW-UP OF 37.0 MONTHS IN THREE COX REGRESSION MODELS.*

VARIABLE	MODEL 1	MODEL 2	MODEL 3
	hazard ratio (95% CI)		
Age (for each 10 yr of age)	1.9 (1.4–2.5)	1.7 (1.3–2.3)	1.6 (1.2–2.2)
Diabetes			
No	1.0	1.0	1.0
Yes	2.8 (1.8–4.4)	2.6 (1.6–4.2)	2.3 (1.4–3.6)
History of congestive heart failure			
No	1.0	1.0	1.0
Yes	1.8 (1.04–3.1)	1.8 (1.01–3.0)	1.8 (1.02–3.0)
Sex			
Male	1.0		
Female	0.6 (0.38–0.95)	NS	NS
No. of antianginal drugs at admission			
0 or 1		1.0	1.0
≥2	NS	1.7 (1.1–2.7)	1.8 (1.2–2.8)
Current smoker			
No		1.0	
Yes	NS	1.8 (1.01–3.2)	NS
ST-segment depression at admission			
No	1.0	1.0	1.0
Yes	2.3 (1.3–3.9)	1.9 (1.1–3.4)	1.9 (1.1–3.3)
Troponin T (μg per liter)			
<0.06	—	1.0	1.0
0.06–0.59	—	6.1 (1.5–25.6)	6.4 (1.5–26.9)
≥0.60	—	12.1 (3.0–49.9)	10.8 (2.6–44.6)
C-reactive protein (mg per liter)			
<2	—	—	1.0
2–10	—	—	1.1 (0.60–2.1)
>10	—	—	2.3 (1.3–4.0)

*Model 1 included age; sex; body-mass index; smoking status; presence or absence of hypertension, previous acute myocardial infarction, history of congestive heart failure, diabetes, a history of stable angina, and previous stroke; number of antianginal drugs the patient was taking at the time of admission; the number of drugs for congestive heart failure the patient was taking at the time of admission (0 or ≥1); and the presence or absence of ST-segment depression and Q-wave abnormalities on the electrocardiogram at admission. Model 2 included all the variables in model 1 as well as the index diagnosis (unstable angina or acute myocardial infarction) and the troponin T levels during the first 24 hours after enrollment. Model 3 included all the variables in model 2 as well as C-reactive protein and fibrinogen levels at enrollment. CI denotes confidence interval, and NS not significant.

patients with any elevation of troponin T, as shown in our study and some previous studies.^{2,3} Also in accordance with this concept is the finding that the beneficial effects of antithrombotic and antiplatelet therapy seem confined to patients with an elevation in troponin T levels.^{23,24} However, in patients with a more pronounced elevation of troponin T, there is already sufficient myocardial necrosis to reduce left ventricular systolic function. A troponin T level of at least 2.8 μg per liter has been shown to identify patients with a left ventricular ejection fraction of less than 0.40.¹¹ In our study this subgroup constituted 14.4 percent of the population and had a clearly increased long-term risk of death, in accordance with the well-known adverse influence on prognosis of depressed left ventricular function.²⁵ Thus, our findings suggest that both these mechanisms are important in explaining the prognostic value of troponin T levels.

Inflammatory processes are involved in the initiation of unstable coronary artery disease because they

destabilize the atherosclerotic plaque and enhance the formation of thrombus.^{26,27} C-reactive protein is a sensitive acute-phase protein whose levels increase in response to inflammation, infection, and tissue damage.²⁸ Some authors have suggested that C-reactive protein might not only mirror an underlying inflammatory process, but also directly interact with atherosclerotic vessels by activating the complement system, thereby promoting inflammation and thrombosis.²⁹ Fibrinogen is also an acute-phase protein whose levels increase in response to inflammation. Fibrinogen has a key role in the coagulation cascade and in platelet aggregation and is a determinant of plasma viscosity.³⁰

Myocardial necrosis induces an acute-phase reaction and may account for some of the elevation in C-reactive protein and fibrinogen levels that we found. However, as previously reported,⁹ the correlations between troponin T and fibrinogen levels as well as between troponin T and C-reactive protein levels were weak ($r=0.14$ and $r=0.29$, respectively). The increased risk

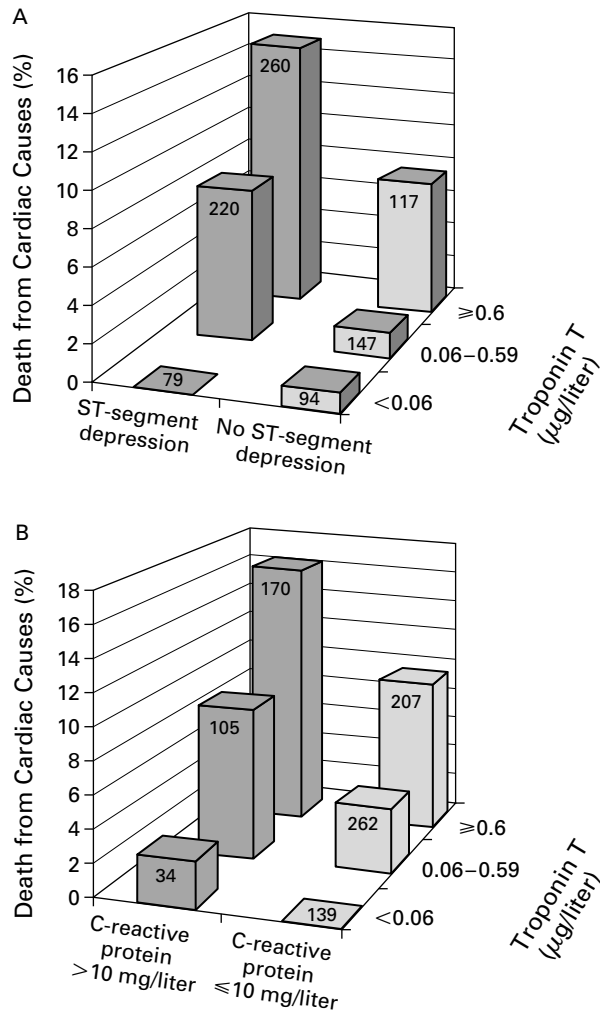


Figure 2. Incidence of Death from Cardiac Causes at Two Years, According to the Presence or Absence of ST-Segment Depression on the Admission Electrocardiogram and the Maximal Troponin T Levels during the First 24 Hours after Enrollment (Panel A) and to the C-Reactive Protein Levels and the Maximal Troponin T Levels (Panel B).

The numbers of patients in each group are shown on the bars.

associated with elevated C-reactive protein was seen at all levels of troponin T (Fig. 2B). Furthermore, it remained significant even when the multivariate analysis was restricted to patients with an index diagnosis of unstable angina. Although several studies have shown an increased short-term risk of new cardiac events in patients with elevated levels of C-reactive protein or fibrinogen,^{9,31,32} previous studies have not evaluated the long-term prognostic value of these markers in unstable coronary artery disease. We found that the difference in mortality between those with and those without even a moderate elevation of C-reactive protein or fibrinogen at the time of the index event continued to increase for several years.

Several factors may influence the levels of C-reactive protein and fibrinogen and thereby act as confounders.^{33,34} However, in our study there were no major changes in the relative risk of death from cardiac causes that was associated with C-reactive protein or fibrinogen levels after adjustment for age, smoking status, body-mass index, and sex (Table 2). Biasucci et al. have shown that C-reactive protein remains elevated for at least three months after the index event in a large proportion of patients with unstable angina.³⁵ Therefore, the prognostic value of elevated inflammatory markers in many patients with unstable coronary artery disease may be related mainly to a chronic low-grade inflammation. Although our finding that the combination of a marker of inflammation (C-reactive protein) and a marker of myocardial damage (troponin T) was a powerful predictor of death from cardiac causes, this finding has not been replicated in any previous studies.³⁶⁻³⁸ The reasons for this difference are not known.

The main limitation of our study is that we did not systematically investigate left ventricular function. Left ventricular function has been the single most important predictor of the risk of death in most studies of patients with acute coronary syndromes.²⁵ However, there are indications that the prognostic value of the troponin T level and that of left ventricular function are additive.³⁹

Our use of the Swedish National Cause of Death Register, which is based on death certificates, entails some risk of misclassification of the cause of death. However, the validity of death certificates in Sweden has been found to be fairly good, especially with respect to death from ischemic heart disease.⁴⁰

Our findings support the concept that an active inflammatory condition is a cause of instability in coronary artery disease. The use of biochemical markers of these conditions in addition to findings on admission electrocardiograms and other information obtained from the clinical history substantially improves the early stratification of long-term risk. Better risk stratification, in turn, will improve the ability of physicians to tailor the treatment in individual patients with unstable coronary artery disease.

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