

An Ischemia-Guided Approach for Risk Stratification in Patients with Acute Coronary Syndromes

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The optimal management approach for patients with non-ST-segment elevation acute coronary syndromes continues to be an issue of debate. An ischemia-guided strategy appears to be effective as an alternative to either a very conservative "wait-and-see" approach or a very aggressive routine revascularization approach. The need for another approach is supported by the lack of conclusive evidence-based results favoring an early routine invasive treatment strategy. In the Thrombolysis in Myocardial Infarction (TIMI) IIIB trial, there were no differences in the incidence of death or myocardial infarction (MI) between patients treated with an early invasive approach and those treated with a conservative approach to treatment. Significantly worse outcomes were shown in patients assigned to an early invasive strategy in the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial at 1-year follow-up (111 clinical events in the invasive group vs 85 in the conservative group; $p = 0.05$). Registry information, including that from the Organization to Assess Strategies for Ischemic Syndromes (OASIS), which included approximately 8,000 patients with unstable angina or suspected MI, has even suggested an excess hazard with a routine invasive approach. Patients with non-ST-segment elevation MI observed in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO)-IIB and Platelet IIb/IIIa in

Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials also fared better with an ischemia-guided strategy. Even the recent FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial investigators had to be very selective relative to eliminating high-risk patients in the first week and treating with intense anti-ischemic therapy and 5–7 days of low-molecular-weight heparin therapy to show an advantage for assigned revascularization. A careful clinical evaluation with attention to early risk stratification is essential in the ischemia-guided approach. The Braunwald classification for unstable angina helps identify independent clinical predictors of a poor outcome; high risk is clearly associated with Braunwald class III and type C. Electrocardiographic and biochemical markers for myocardial necrosis (cardiac troponin T or I) are important tools for assessing the presence and degree of ischemia and associated risk for adverse outcome. Noninvasive evaluation of left ventricular ejection fraction is essential for identifying those at high risk due to impaired contractile function. When these conventional markers do not provide conclusive information, noninvasive stress testing is most helpful to further identify those at highest risk for revascularization. ©2000 by Excerpta Medica, Inc.

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An ischemia-guided strategy represents a rational initial approach to treatment for most patients with acute coronary syndromes and is supported by the paucity of compelling data on benefit from routine early application of invasive strategies in evidence-based medicine. Ischemia may be manifest as chest pain, electrocardiographic changes, left ventricular dysfunction, or biochemical markers of ischemia-related myocardial injury. Data from randomized clinical trials, including the Thrombolysis in Myocardial Infarction (TIMI) IIIB^{1,2} and the Veterans Af-

fairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trials,^{3,4} do not clearly support routine use of an early invasive strategy compared with a more conservative strategy to prevent death or myocardial infarction (MI) in acute coronary syndromes.

Furthermore, information from large registries in several countries, including the Organization to Assess Strategies for Ischemic Syndromes (OASIS) Registry,⁵ suggests an excess hazard associated with the routine invasive approach. Administrative data on trends in risk found in the US Medicare database,⁶ as well as some trials in both the United States and Canada, also support a more conservative position. Comparisons of treatment strategies in these 2 countries suggest similar outcomes in patients with acute coronary syndromes, despite the much less frequent use of interventional procedures in Canada compared with the United States.⁷ In addition, the pathophysiology of a patient with an acute ischemic syndrome is extraordinarily complex and not simply a local problem.^{8–10} Risk stratification, based upon clinical and ischemia-related data, helps identify most of the pa-

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The treatment approach presented herein was developed in an educational debate format designed to explore possible strategies for management of acute coronary syndromes. The text represents a defense of 1 of 5 propositions, but not necessarily the author's personal recommendation or endorsement of this particular treatment strategy.

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tients who are at high risk for an adverse outcome and are likely to benefit from revascularization.

INVASIVE VERSUS CONSERVATIVE STRATEGIES

Selected-delayed invasive strategy: Selective use of an invasive treatment strategy after 5–7 days of aggressive medical anti-ischemic therapy and pretreatment with low-molecular-weight heparin in low- to intermediate-risk patients with acute coronary syndromes was tested in the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial.¹¹ The results of this trial suggest that an early invasive approach may be a preferred strategy for most patients with unstable coronary artery disease who have electrocardiographic signs of ischemia or raised biochemical markers of myocardial damage. In FRISC II, a multicenter study, 2,457 patients (median age, 66 years; 70% men) were randomly assigned to 1 of 4 treatment groups: (1) invasive treatment and dalteparin, (2) invasive treatment and placebo, (3) noninvasive treatment and dalteparin, or (4) noninvasive treatment and placebo, within 72 hours of starting an antithrombin (either open-label dalteparin or unfractionated heparin). Revascularization was done within the first 10 days in 71% of the invasive group and 9% of the noninvasive group and within the first year in 78% and 43%, respectively. After 1 year, the composite of death or MI occurred in 127 (10.4%) versus 174 (14.1%) patients (risk ratio, 0.74; 95% confidence interval, 0.60–0.92; $p = 0.005$). One drawback of the treatment course outlined in FRISC-II is that patients must be treated with low-molecular-weight heparin for a median of 6 days in the hospital. In addition to this delay, their plan selectively excluded elderly and other high-risk patients.

Invasive versus conservative strategies: A clear advantage has not been shown for the routine use of an early invasive treatment strategy in patients with non-Q-wave MI or unstable angina in clinical trials, such as TIMI IIIB^{1,2} and VANQWISH.³ The TIMI IIIB trial was the first study to directly compare outcomes of invasive versus conservative management in patients with unstable angina or non-Q-wave MI. In TIMI IIIB, 1,473 patients were randomly assigned to (1) therapy with either tissue-type plasminogen activator (tPA) or placebo and also to an early invasive management strategy with coronary arteriography at 18 or 48 hours, followed by revascularization if appropriate; or (2) to an early conservative strategy with arteriography and revascularization if initial therapy failed to prevent recurrent ischemia. The primary outcome for the tPA–placebo comparison (death, MI, or failure of initial therapy at 6 weeks) occurred in 54.2% of the tPA-treated patients and 55.5% of the placebo-treated patients ($p = \text{NS}$). The response parameter for the comparison of the 2 strategies (death, MI, or an unsatisfactory symptom-limited exercise stress test at 6 weeks) occurred in 18.1% of patients assigned to the early conservative strategy and 16.2% of patients assigned to the early invasive strategy ($p = \text{NS}$).² At 1 year, there were no differences in the incidence of

death or MI between patients randomly assigned to the early invasive and conservative strategies. As shown in Table 1, there were also no differences in event rates in patients categorized as having non-Q-wave MI or unstable angina.²

In the VANQWISH study³ high-risk patients with non-Q-wave MI by creatine kinase–myocardial band criteria did not benefit from an early invasive strategy. In VANQWISH, 920 patients were randomly assigned to an invasive approach (462 patients), using routine coronary angiography followed by revascularization, or a conservative approach (458 patients), consisting of medical therapy and noninvasive testing, with subsequent invasive management if indicated by development of ischemia within 72 hours of a non-Q-wave MI. The primary outcome was death or nonfatal reinfarction. In the average follow-up of 23 months, there were 152 events in 138 patients who had been assigned to the invasive strategy and 139 events in 123 patients assigned to the conservative strategy ($p = 0.35$). At 1-year follow-up, the investigators found significantly worse outcomes in patients assigned to the invasive strategy (111 vs 85 events; $p = 0.05$). Comparisons of outcomes of death or MI for the invasive versus conservative strategies for both the TIMI IIIB and VANQWISH trials are shown in Figure 1.

The OASIS Registry⁵ of approximately 8,000 patients with unstable angina or suspected MI provided a unique perspective into regional differences in treatment approaches. Patients were recruited from 95 hospitals in 6 countries, with plans to follow all patients for 24 months. The frequency and timing of invasive procedures (angiography, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting) were examined along with outcomes.

At 6-month follow-up, there were no significant differences in the rate of death or MI related to the use of invasive procedures or revascularization. This cohort had an overall event rate of 4.7% (range, 3.7–5.6%) at 7 days and 11% (range, 9–12%) at 6 months. The rate of stroke was significantly higher in the groups who underwent the invasive procedures, however, and the rates of subsequent angina or late readmissions were significantly lower. Thus, the benefit of lower rehospitalization and less frequent angina is offset by the higher risk of stroke in these patients.

Similarly, data analyses from the Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes (GUSTO) IIIB and Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials favored the ischemia-guided strategy.¹² Patients with a non-ST-segment elevation acute coronary syndrome who were treated with an ischemia-guided approach during the initial hospitalization had improved outcomes over patients who were treated with a conservative ischemia-guided strategy. The adjusted odds ratio for death or MI comparing the invasive versus the conservative strategy showed a 6-fold increase in death or

TABLE 1 Cumulative Event Rates at 1 Year in Thrombolysis in Myocardial Infarction (TIMI) IIIB Patients With Non-Q-Wave Myocardial Infarction (MI) and Unstable Angina*			
	Early Invasive Strategy (n = 484)	Early Conservative Strategy (n = 509)	p Value
Patients with evolving MI			
Death	5.2	6.3	0.59
Death or MI	11.1	14.0	0.35
Patients with unstable angina			
Death	3.6	3.6	0.98
Death or MI	10.7	11.5	0.74

*Data presented are number of patients (n) or percent estimated event rates by Kaplan-Meier method; p values from the log-rank statistic. Modified from *J Am Coll Cardiol*.²

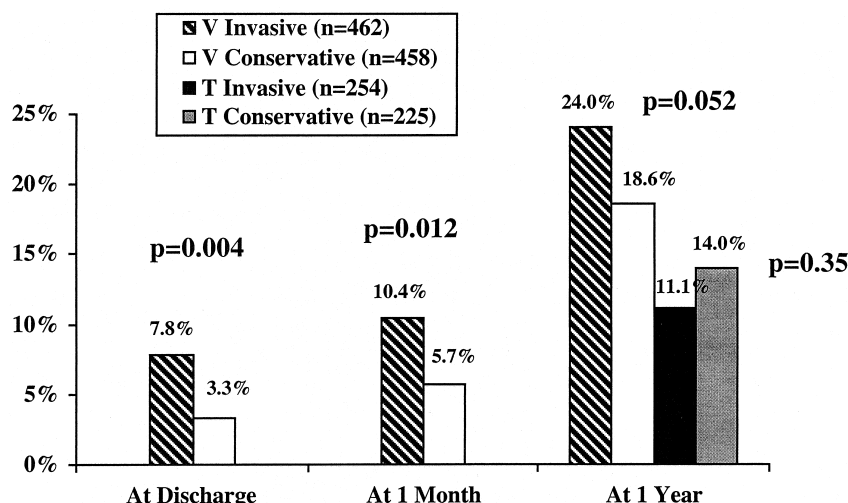


FIGURE 1. Comparison of outcomes (death or myocardial infarction [MI]) in non-Q-wave MI in the Thrombolysis in Myocardial Infarction (TIMI) IIIB and Veterans Affairs in Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trials. For each trial, the rates of death or MI for the invasive versus the conservative strategies are generally equivalent. T = TIMI IIIB; V = VANQWISH. (Data are from *J Am Coll Cardiol*² and *N Engl J Med*.³)

MI with the invasive strategy at 30 days and an almost 2-fold increase at 6 months.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

In a routine, aggressive approach to treatment of the non-ST-segment acute coronary syndromes by use of angiography followed by percutaneous intervention, an important fact is often missed (i.e., that the finding of a single culprit lesion is actually the unusual case). In the original report of the pathology of acute coronary syndromes, Davies and Thomas⁸ identified an average of 1.5 coronary artery clots per patient dying from an acute coronary syndrome. As they pointed out, these were often in different coronary territories. There is general agreement that gross pathology conducted in a remote period underestimates the true number of clots present in life so these data likely underrepresent the true number of complex lesions present in these cases. Thus, focus on only the

most “recent-appearing” or most “stenosed” lesion is unlikely to address the complex lesions elsewhere. Goldstein et al^{8a} found multiple complex lesions at angiography in about 40% of acute MI cases.

Data from the core angiographic laboratory in the VANQWISH trial (University of Florida, Gainesville, FL) revealed that complex plaque was visualized in 274 of 337 patients (81%) assigned to an invasive strategy.^{3,13} There were 1.5 complex lesions per patient and, thus, multiple complex plaques in different coronary territories. Again, based on intracoronary ultrasound studies, angiography markedly underestimates the number of and amount of complex plaques. Despite these findings, simple single-vessel angioplasty is still very common in an acute invasive strategy.

Another aspect of the complex pathophysiology of acute coronary syndromes is the evolving field that implicates inflammation, infection, sympathetic surges, changes in blood pressure, and activation of

TABLE 2 Braunwald Classification of Unstable Angina

Severity	Clinical Setting		
	A (Extracardiac Condition)	B (Primary)	C (Post MI, <2 wk)
Class I: New onset, severe or accelerated, no rest pain	IA	IB	IC
Class II: Rest angina, ≤ 1 mo but $>$ past 48 hr	IIA	IIB	IIC
Class III: Rest angina, past ≤ 48 hr	IIIA	IIIB	IIIC

MI = myocardial infarction.
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TABLE 3 Independent Predictors of 6 Month Outcomes in 282 Unstable Angina Patients

Independent Predictors*	Rate Ratio	95% CI
Death		
Age >70 yr	14.5	3.5–61
Male sex	3.7	0.9–14.8
Hypertension	3.5	1.0–12
Class C (post MI <2 wk)	8.0	2.2–28
Maximal antianginal therapy	3.2	1.0–10.4
Death or MI		
Age >70 yr	2.1	1.1–4.1
Class C	2.1	1.0–4.6
Death, MI, or intervention		
Male sex	2.7	1.8–4.1
Class III	3.0	2.1–4.3
Class C	1.6	1.0–2.4
Electrocardiographic changes present	1.8	1.2–2.8
Maximal (IV) antianginal therapy	2.1	1.5–3.1

CI = confidence intervals; IV = intravenous; MI = myocardial infarction.
*Definitions of classification categories as in Table 2.
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platelet aggregation and the coagulation cascade.^{9,10,14,15} This leads to the notion that a “pan-coronary” or even a “pan-arterial” process may be responsible for this syndrome. To this end, the microvasculature is often ignored although microvessels likely play a fundamental role in atherogenesis, the nutrition and disruption of plaque, and the collateral development necessary to perfuse ischemic myocardium faced with acute plaque disruption.¹⁶

Data from multiple studies, including the TIMI III registry¹⁷ and the GUSTO I trial,¹⁸ suggest that at least 10–15% of patients with acute coronary syndromes, documented by electrocardiographic changes on admission, have no severe or complex lesions on coronary angiography but have slow TIMI flow. This finding indicates coronary resistance vessel dysfunction. How a routine invasive strategy will affect these patients is unknown.

RISK STRATIFICATION FOR AN ISCHEMIA-GUIDED APPROACH

The essential first step in the ischemia-guided approach for patients with acute coronary syndromes is a rapid but careful clinical evaluation. This assessment should include documentation of age, gender, history of recent MI, diabetes, time interval from the onset of

angina or ischemia, blood pressure measurements, cardiac troponin levels, history of mitral insufficiency or congestive heart failure, continuous electrocardiographic findings and, when the patient is not high risk, early stress test results. A strong recommendation is made for evaluation of left ventricular function in all patients in the new American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of patients with unstable angina.¹⁹

Braunwald classification for unstable angina: The Braunwald classification for unstable angina has been well validated, as well as other demographic factors, to identify several independent predictors of the outcome of death, death or MI, and death or revascularization as being significant (Tables 2 and 3).^{20,21} Age >70 years is associated with a 14-fold increase in risk for death; other risk factors include male gender, hypertension, and Braunwald class C (development of angina within 2 weeks of a documented MI). The latter carries an 8-times incremental risk. The outcome of death, MI, or intervention is also influenced by Braunwald class III (rest angina within 48 hours), as well as the preceding class C. These findings may help identify patients who are suited to selective use of an early invasive strategy.

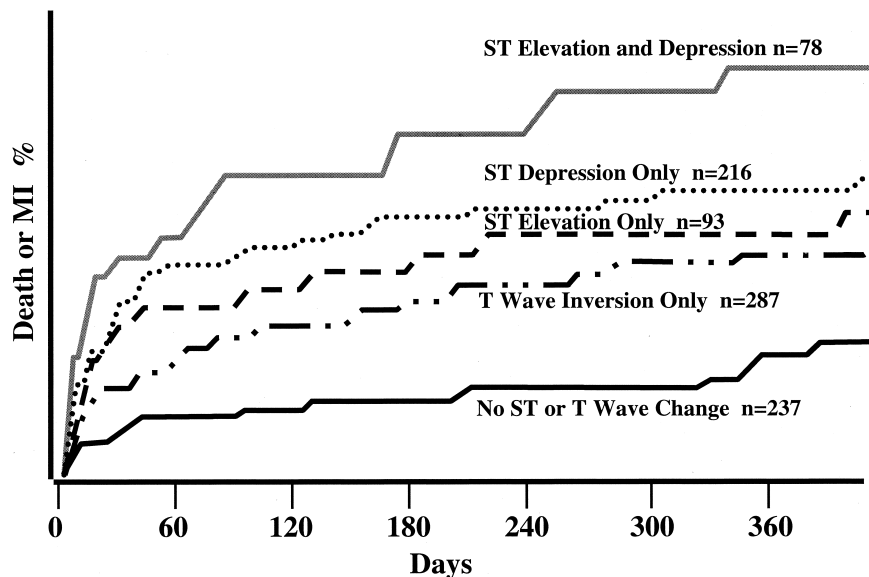


FIGURE 2. Life table of cumulative risk and time of myocardial infarction (MI) or death during 1 year of follow-up with regard to different types of ST-T-segment changes in the electrocardiogram at rest. ST-elevation + depression = combined ST elevation and ST depression; ST-depression only = ST depression without ST elevation; ST-elevation only = ST elevation without ST depression; T-inversion isolated = T-wave inversion without ST-segment change; No ST-T change = normal electrocardiogram. (Reprinted with permission from *J Intern Med.*²²)

Electrocardiographic findings	Incidence (%) of Death or MI		
	Patients (n)	6 Weeks	1 Year
LBBB	127	6.6	22.9
ST deviation ≥ 1 mm	202	3.6	11.0
Isolated T-wave changes	310	3.7	6.8
No electrocardiographic changes	777	3.7	8.2

LBBB = left bundle branch block; MI = myocardial infarction. Modified from *J Am Coll Cardiol.*²³

Admission electrocardiogram: The admitting electrocardiogram is of considerable importance in evaluating patients with acute coronary syndromes. No electrocardiographic changes are associated with a relatively good outcome provided that the tests are negative for cardiac troponin (T or I). More than half the patients reported from studies with non-ST-segment acute ischemic syndromes do not have electrocardiographic changes on admission. Various changes in the electrocardiogram are associated with increasing risks. Nyman et al²² conducted a study to determine the importance of electrocardiography in risk stratification for patients admitted to the hospital for suspected unstable coronary disease. Electrocardiograms were studied in 911 men with suspected unstable angina or non-Q-wave MI; the subjects were followed for 12 months. Clinical outcomes included cardiac death, MI, and severe (class III or IV) angina. Compared with patients with a normal electrocardio-

gram who had an 8% 1-year risk of MI or death, the risk of death or MI with isolated negative T waves was 14% ($p < 0.05$), ST elevation 16% ($p < 0.05$), ST depression 18% ($p < 0.01$), and the combination of ST elevation and ST depression 26% ($p < 0.001$; Figure 2). ST depression was the only finding related to future severe angina. The risk of cardiac events was comparably elevated in patients with an anterior or inferior site of electrocardiographic changes.

The utility of the admission electrocardiogram for risk stratification was also supported by data from the TIMI-III prospective registry ancillary electrocardiographic study published by Cannon et al.²³ Of 1,416 enrolled patients with unstable angina and non-Q-wave MI, new ST-segment deviation ≥ 1 mm was present in 14.3%, isolated T wave inversion in 21.9%, and left bundle branch block in 9.0%. As illustrated in Table 4, the presence of left bundle branch block, as well as the detection of ≥ 1 mm of ST-segment shift,

portended an increased risk for adverse outcomes at 1 year. No electrocardiographic changes and isolated T-wave changes were not predictive of a poor outcome, but it must be noted that cardiac troponin concentrations were not measured. One interesting feature of the study was that the subset of patients who had ≥ 0.5 mm but < 1.0 mm of ST-segment shift actually had a frequency of death or MI at 1 year that was almost equivalent to that of patients who had 1 mm of ST-segment change. This subset was included in the “no electrocardiographic changes” now in the table. Thus, any detectable ST-segment shift on the initial electrocardiogram portends some increased risk for an adverse outcome.

Continuous electrocardiographic monitoring: A feature of risk stratification relative to cardiac ischemia that has received little attention in the United States is that of continuous electrocardiographic monitoring. Episodes of ST-segment shifts can be prognostically important, however, as shown in a substudy from the c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) trial.²⁴ In the substudy, a vector-derived 12-lead electrocardiogram was obtained from 3 recorded ambulatory electrocardiographic leads in 332 acute coronary syndrome patients during a 5-day period. Monitoring was done from the start of glycoprotein IIb/IIIa receptor blocker treatment through 6 hours after coronary intervention. Ischemic episodes were documented in 31 (18%) of 169 abciximab-assigned patients and 37 (23%) of 163 placebo-assigned patients. There were ≥ 2 ST episodes in 5% abciximab-assigned patients versus 14% placebo-assigned patients ($p < 0.01$). Any episode of ST-segment shift within the 5 days predicted an increased relative risk for death or MI: 3.2 for death and 4.1 for MI. Abciximab significantly reduced the total ischemic burden ($p < 0.02$). Almost all of the benefit from this glycoprotein IIb/IIIa receptor blocker resided in a subset of patients who had ST-segment shifts on the vector-derived electrocardiogram.

Serum markers: The traditional serum marker indicative of cardiac necrosis in patients with acute coronary syndromes is the creatine kinase–myocardial band isoenzyme. Recent recommendations from the National Academy of Clinical Biochemistry standards of laboratory practice for the use of cardiac markers in coronary artery disease indicate that measurement of cardiac troponin (T or I) is the new standard for detecting ischemia-related myocardial cell damage.²⁵ An adverse prognosis has been associated with both creatine kinase–myocardial band and troponin T elevations in patients with unstable angina as well as non-ST-segment elevation MI. The presence of cardiac troponin T or I in a blood sample obtained at admission conveys considerable prognostic importance. Cardiac troponins are not detectable in the blood of healthy persons, are highly specific for myocardial tissue, and show a greater proportional increase about the upper limit of the reference interval in patients with confirmed MI.²⁶ After myocardial necrosis, troponin T or I can remain elevated for 7–10 days.²⁷

In 2 reports that examined troponin I status in patients with acute coronary syndromes, the risk for adverse outcome was elevated 2- to 3-fold if the troponin I was elevated, regardless of when the troponin I was elevated in terms of the duration of the event.^{26,28} In a multicenter study by Antman et al,²⁶ blood specimens were analyzed for troponin I in 1,404 symptomatic patients. For 573 patients with cardiac troponin I levels ≥ 0.4 ng/mL, the mortality rate at 42 days was significantly higher (21 deaths, 3.7%) than that for patients with troponin I levels < 0.4 ng/mL (8 deaths, 1.0%; $p < 0.001$; Figure 3). After adjustment for baseline factors that were independently predictive of mortality, there was a significant increase in the risk ratio for death with each 1 ng/mL increase in the troponin I level.

In another multicenter study conducted by Galvani et al,²⁸ which involved 91 patients with unstable angina, clinical outcomes comparing patients with and without elevations of troponin I were significantly different during 30 days of follow-up. For patients with troponin I > 3.1 ng/mL, the rate of death or nonfatal MI was 27.3%, compared with 5.8% for those without elevations ($p = 0.02$). At 1 year, 68% of patients with elevated troponin I levels were free of cardiac events, compared with 90% of those without elevations ($p = 0.01$). Similar associations have been reported for cardiac troponin T, and because there is only 1 commercial assay kit for troponin T (in contrast to troponin I), the variability is very low. Thus, elevations of cardiac troponins T or I are very important prognostic indicators in patients with an acute coronary syndrome.

Angiographic data and troponin levels: Elevated troponin T levels can be observed in about one-third of patients with unstable angina pectoris. Angiographic data and troponin T status were examined in a recent report from the CAPTURE trial.²⁹ In 853 patients, angiographic data at baseline and 18–24 hours after treatment were assessed for TIMI flow, lesion severity, and visibility of thrombus. Complex lesion characteristics and visible thrombus at baseline were significantly linked to troponin T increases. Abciximab reduced thrombus, increased TIMI flow, and reduced cardiac events in troponin-T–positive patients only. In using multivariate analysis, the CAPTURE investigators identified the troponin-T status, but not angiographic findings, as a significant independent predictor of both adverse outcome and benefit of treatment with glycoprotein IIb/IIIa blockers. They concluded that the troponin-T status was a more sensitive marker for underlying pathology, as well as for identifying patients most likely to benefit from treatment. These data have prompted Hamm and Braunwald³⁰ to recommend that cardiac troponin status be used to guide therapy with the glycoprotein IIb/IIIa platelet receptor blockers and low-molecular-weight heparins. This recommendation is based on the observations suggesting that platelet activation, inflammation, and other factors are central in the ischemia-related myo-

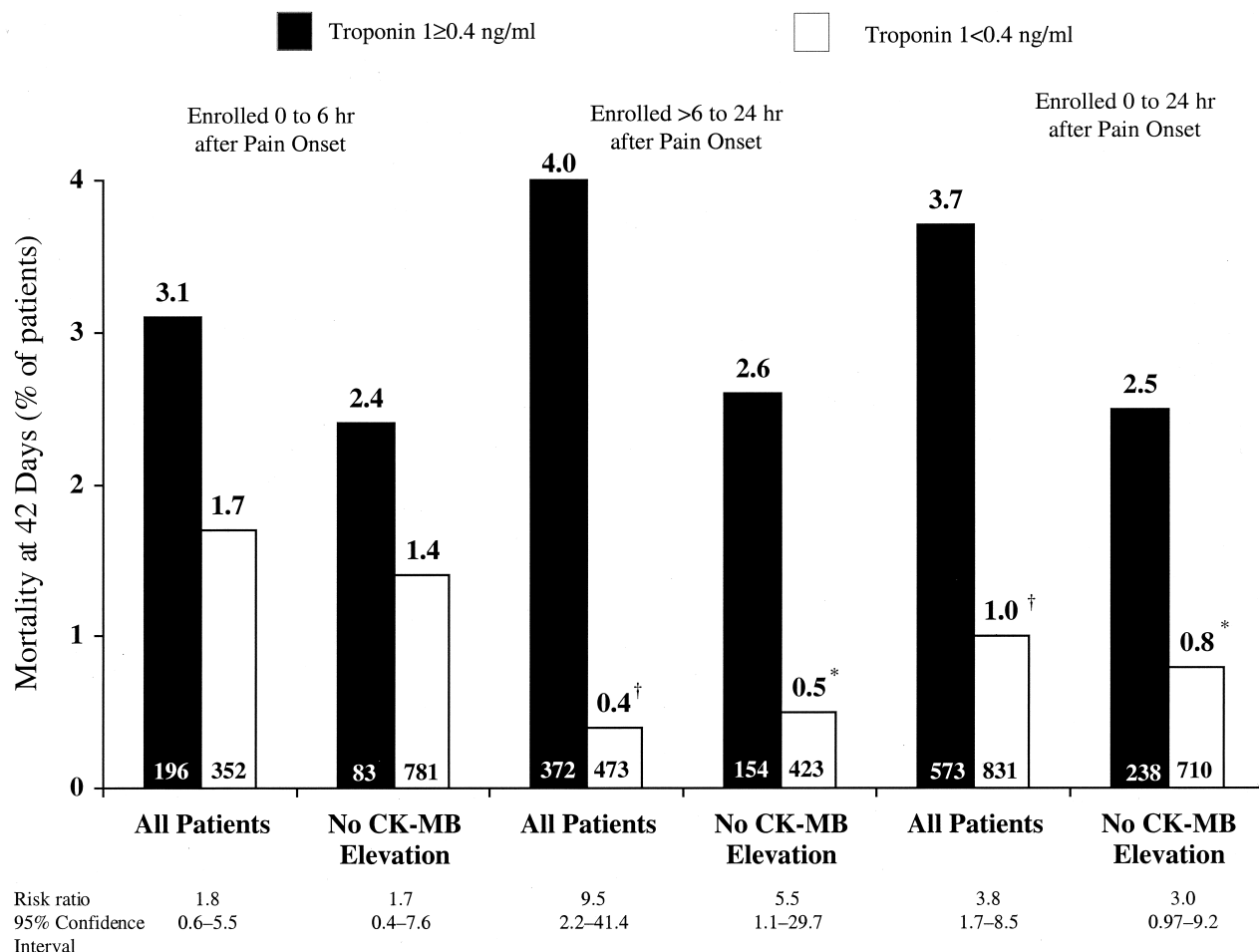


FIGURE 3. From a multicenter study, mortality rates at 42 days according to the time from onset of pain to study enrollment and the baseline cardiac troponin I levels. Mortality rates (without adjustment for baseline characteristics) are shown for study patients according to the time from the onset of chest pain to enrollment. For each subgroup, the findings are shown for all patients and for those in whom no elevation of creatine kinase–myocardial band (CK–MB) isoenzyme was found at the enrolling center. Numbers at the bottom of each bar represent numbers of patients in each category; numbers above the bars are percentages. For each comparison, the mortality rate was higher in the patients with cardiac troponin I levels of ≥ 4 ng/mL. Risk ratios and 95% confidence intervals for mortality are shown at the bottom of the figure for the group with cardiac troponin I levels of > 4 ng/mL compared with the group with lower levels. * $p < 0.05$; [†] $p < 0.001$. (Reprinted with permission from *N Engl J Med*.²⁶ Copyright© 1996 Massachusetts Medical Society. All rights reserved.

cellular dysfunction seen in higher-risk patients with non–ST-segment elevation acute coronary syndrome.

Noninvasive stress testing: For patients who have none of the ischemia-related high-risk markers discussed previously, or changes on electrocardiographic recordings, stress testing is appropriate. Conventional exercise testing is still viable for many of the patients who present with a suspected acute ischemic syndrome. If these patients perform poorly on the exercise stress test, e.g., if they cannot achieve stage II of the Bruce protocol or develop hypertension or ST-segment shifts (> 1 mm), they are considered high-risk for an adverse outcome. For patients who cannot exercise or have electrocardiograms that are insensitive for an ischemia-related change, a stress perfusion test is acceptable, though much more costly.^{31–33} Recently, wall-motion abnormalities seen with echocardiographic stress testing have been reported as

strongly predictive of adverse outcome, and the test is less costly than a perfusion test.³⁴ Regardless of which ischemia-related abnormalities are used, these tests have the ability to help predict risk of death, nonfatal MI, or recurrent angina for up to several years.

RECOMMENDATIONS FOR TREATMENT

In the ischemia-guided management for an acute ischemic syndrome, all patients should be given aspirin, excluding those who are hypersensitive; clopidogrel is recommended for the latter group. A low-molecular-weight heparin such as enoxaparin, as underscored in the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE)³⁵ and TIMI 11B³⁶ trials, is also recommended, with administration of a 2–3-day regimen for in-hospital patients. Patients with evidence of isch-

emia or a recent MI should be given a β -blocker unless it is contraindicated. Based on the Heart Outcomes Prevention Evaluation (HOPE) trial³⁷ data, almost all patients with vascular disease who are >55 years of age should be receiving an angiotensin-converting enzyme inhibitor for long-term prophylaxis. A broad range of patients could benefit from angiotensin-converting enzyme inhibitors, including those with diabetes, a history of MI, and those with renal failure, left ventricular dysfunction, or hypertension as well as those without these comorbid conditions. Statin therapy should be part of the regimen for patients with a low-density lipoprotein (LDL) concentration >100 mg/dL, particularly those who have had a prior revascularization procedure. Modification of lifestyle and attention to other preventable risk factors are essential for secondary prevention.

The ongoing search for high-risk patients who are suitable candidates for a more aggressive approach to treatment is mandatory. High risk is clearly associated with Braunwald class III, which is angina at rest within the preceding 48 hours, and Braunwald type C, which is development of angina within 2 weeks after an MI. Other high-risk indicators include angina associated with new or worsening mitral regurgitation, an S₃ or rales, hypertension or pulmonary edema, ST-segment deviations or left bundle branch block, or elevated cardiac troponin levels.

In patients with recurrent signs or symptoms of ischemia, a previous revascularization procedure, or other high-risk features of an acute coronary syndrome such as positive cardiac troponin I or T, the anti-ischemic medical regimen should be re-examined with particular attention to optimizing β -blocker and nitrate dosing and the possible addition of a rate-slowing calcium antagonist such as verapamil or diltiazem. Dihydropyridines should be used with caution and only in patients receiving full doses of β -blockers. The antithrombotic, antiplatelet regimen should be optimized with a low-molecular-weight heparin, and a glycoprotein IIb/IIIa receptor blocker should be strongly considered. For these patients, angiography with early revascularization, if possible, is clearly in order.

Relative to the strategy outlined above, an optimal anti-ischemic regimen is absolutely essential if the risk for adverse outcome is to be minimized. This should include a potent antithrombotic and antiplatelet regimen for at least 2–3 days, ongoing risk stratification based upon the clinical findings, with cardiac troponin, stress testing and left ventricular function assessments to quantify the risk of adverse outcome, and, finally, a program for secondary prevention.

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