The New England
Journal of Medicine

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VOLUME 338 JUNE 18, 1998 NUMBER 25

OUTCOMES IN PATIENTS WITH ACUTE NON–Q-WAVE MYOCARDIAL INFARCTION RANDOMLY ASSIGNED TO AN INVASIVE AS COMPARED WITH A CONSERVATIVE MANAGEMENT STRATEGY

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ABSTRACT

Background Non–Q-wave myocardial infarction is usually managed according to an "invasive" strategy (i.e., one of routine coronary angiography followed by myocardial revascularization).

Methods We randomly assigned 920 patients to either "invasive" management (462 patients) or "conservative" management, defined as medical therapy and noninvasive testing, with subsequent invasive management if indicated by the development of spontaneous or inducible ischemia (458 patients), within 72 hours of the onset of a non–Q-wave infarction. Death or nonfatal infarction made up the combined primary end point.

Results During an average follow-up of 23 months, 152 events (80 deaths and 72 nonfatal infarctions) occurred in 138 patients who had been randomly assigned to the invasive strategy, and 139 events (59 deaths and 80 nonfatal infarctions) in 123 patients assigned to the conservative strategy (P=0.35). Patients assigned to the invasive strategy had worse clinical outcomes during the first year of follow-up. The number of patients with one of the components of the primary end point (death or nonfatal myocardial infarction) and the number who died were significantly higher in the invasive-strategy group at hospital discharge (36 vs. 15 patients, P=0.004, for the primary end point; 21 vs. 6, P=0.007, for death), at one month (48 vs. 26, P=0.012; 23 vs. 9, P=0.021), and at one year (111 vs. 85, P=0.05; 58 vs. 36, P=0.025). Overall mortality during follow-up did not differ significantly between patients assigned to the conservative-strategy group and those assigned to the invasive-strategy group (hazard ratio, 0.72; 95 percent confidence interval, 0.51 to 1.01).

Conclusions Most patients with non–Q-wave myocardial infarction do not benefit from routine, early invasive management consisting of coronary angiography and revascularization. A conservative, ischemia-guided initial approach is both safe and effective. (N Engl J Med 1998;338:1785-92.)

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MORE than half of all acute myocardial infarctions in the United States each year are classified as non–Q-wave myocardial infarctions, and this proportion is rising.[1-3] Nevertheless, the clinical course and prognosis of this type of myocardial infarction and the best approach to management remain controversial.[4-7] Since patients with non–Q-wave infarction reportedly have higher rates of both early and late ischemic complications (reinfarction and postinfarction angina), presumably because of the presence of viable but jeopardized myocardium within the perfusion zone of the infarct-related artery,[5,7-16] their treatment has become increasingly aggressive.

Although the 1987 American College of Cardiology–American Heart Association guidelines for coronary arteriography[17] recommended routine coronary angiography for all patients after non–Q-wave infarction, newer guidelines no longer endorse this approach to treatment.[18,19] Nevertheless, early invasive management is still widely practiced. Furthermore, several recent studies of patients with acute coronary syndromes have shown either no effect or

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*The study sites, investigators, and study personnel participating in the VANQWISH Trial are listed in the Appendix.

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an adverse effect when routine coronary angiography is followed by early myocardial revascularization.[20-23] Thus, despite the paucity of supporting data, many physicians assume that an "invasive" strategy (one characterized by routine coronary angiography followed by revascularization, if feasible) is superior to a "conservative" strategy (consisting of medical therapy, noninvasive testing, and subsequent invasive procedures if indicated by the development of spontaneous or inducible ischemia — i.e., an ischemia-guided approach) in terms of improving clinical outcomes.

To test this hypothesis, we initiated a multicenter, randomized, controlled trial to compare an invasive with a conservative strategy in patients with acute non–Q-wave myocardial infarction; the combined primary end point was death from any cause or recurrent nonfatal infarction during a minimum of 12 months of follow-up.

METHODS

Study Organization

The Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial began enrollment on April 14, 1993, after the institutional review boards at 15 participating centers had approved the protocol. Two study sites were dropped within six months because of poor enrollment, and an additional two sites were added later. Thus, 15 sites completed the study. This report includes data from all 17 sites. A data-monitoring board independently reviewed the interim results at regular intervals.

Selection of Patients

Details of the trial design have been published elsewhere.[24] Eligible patients had to have evolving acute myocardial infarction, a level of creatine kinase MB (CK-MB) isoenzymes that was more than 1.5 times the upper limit of normal for the hospital, and no new abnormal Q waves (or R waves) on serial electrocardiograms. Patients were excluded if they had serious coexisting conditions, ischemic complications that placed them at very high risk while in the coronary care unit (persistent or recurrent ischemia at rest despite intensive medical therapy or severe heart failure that persisted despite treatment with intravenous diuretics, vasodilators, or both). These were conditions that were deemed to pose clinical or ethical problems for the inclusion of patients in a randomized trial.[24]

The electrocardiographic analysis followed the Atlanta code,[25] with serial tracings obtained at multiple times after the onset of infarction. At least one electrocardiogram was obtained 48 hours after admission in order to rule out the late development of Q waves.[26] Electrocardiographically, the study patients had neither new, abnormal Q waves (i.e., Q waves lasting 0.04 second in two contiguous leads within a group of leads) nor R waves (more than 0.04 second in lead V_1 and an R:S ratio greater than 1 in lead V_2); we have previously demonstrated that these criteria reliably exclude evolving posterior infarction.[26,27]

Randomization Procedure

The study patients gave informed, written consent and were randomly assigned to a study group within 24 to 72 hours after the onset of symptoms according to the adaptive-allocation procedure,[28] which maximized the probability of balance between the treatment groups within the medical centers and with respect to each of five variables used for stratification: age, previous myocardial infarction, use of thrombolytic therapy, anterior location of the infarct, and ST-segment depression on the electrocardiogram obtained at entry.

Testing and Treatment

Patients assigned to the early invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Thereafter, the management guidelines of the Thrombolysis in Myocardial Infarction trial (TIMI IIIB) for revascularization were followed.[20] In patients with clinically significant single-vessel coronary artery disease, balloon angioplasty or, rarely, directional atherectomy was considered, whereas bypass surgery was recommended for patients with multivessel disease. In contrast to the TIMI IIIB guidelines, however, our protocol did not require early myocardial revascularization; investigators at each study site were allowed to decide whether to perform only revascularization of a culprit stenosis, perform complete revascularization, or continue medical therapy.

Patients assigned to the early conservative strategy underwent radionuclide ventriculography to assess left ventricular function as the initial noninvasive test; this was followed before discharge by a symptom-limited treadmill exercise test (according to the standard Bruce protocol) with planar thallium scintigraphy or thallium scintigraphy with single-photon-emission computed tomography. Patients who were unable to exercise to a level of at least 5 metabolic equivalents (MET) received intravenous dipyridamole (0.56 mg per kilogram of body weight) and then underwent perfusion scintigraphy.

Coronary angiography with or without revascularization was performed in patients randomly assigned to the conservative strategy only if one or more of the following three criteria were met: the patient had recurrent postinfarction angina with ischemic electrocardiographic changes; the patient had ST-segment depression of at least 2 mm on an electrocardiogram recorded during peak exercise; or there were redistribution defects in two or more different vascular regions on thallium scintigraphy, or one redistribution defect with increased uptake of thallium by the lung. Investigators at the study site decided whether to perform myocardial revascularization in patients who had objective evidence of ischemia.

Patients in both groups received enteric-coated aspirin (325 mg per day) and long-acting diltiazem (Cardizem, Hoechst Marion Roussel, Kansas City, Mo.; 180 to 300 mg per day), on the basis of the reported benefit of this combination for secondary prevention.[5,7,29-32] In addition, patients could receive any other standard medical therapy during hospitalization, including nitroglycerin, angiotensin-converting–enzyme inhibitors, beta-blockers, dose-adjusted intravenous heparin, and if clinically indicated, thrombolytic therapy.[24]

Follow-up

Enrollment ended on December 31, 1995. Patients were seen one month after discharge and at three-month intervals thereafter until the trial ended on December 31, 1996.

End Points

The primary end point of the trial was death or nonfatal myocardial infarction. An independent, three-member end-points committee, whose members were unaware of the treatment assignments, reviewed and adjudicated all suspected primary end points. We also analyzed overall mortality and major procedural complications after coronary angiography or myocardial revascularization.

Statistical Analysis

Sample size was calculated for an equivalence study on the basis of binomial proportions.[33] Our null hypothesis was that 20 percent of each group would reach a primary end point during 12 months of follow-up,[30,34] and we postulated that the null hypothesis of equivalence would be rejected if the difference between the groups exceeded 7.5 percent, with a two-sided significance level of 0.05 and 80 percent power.[24] The study chairman and executive committee were masked with respect to the results through-

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out the trial. Formal interim analyses for efficacy were conducted by the data-monitoring board, using accepted methods.[24,35,36]

Continuous data are presented as means ±SD. Odds ratios and 95 percent confidence intervals were used to compare the strategies with respect to major clinical outcomes. Survival curves were used to characterize the timing of the primary end point during follow-up, according to the method of Kaplan and Meier.[37] The Cox proportional-hazards regression model[38] was used to adjust for covariates in the analysis of the interaction between the strategy assignment and the five prespecified covariates. All tests of significance were two-tailed, and the strategies were compared according to the intention-to-treat principle.

RESULTS

Characteristics of the Study Population

Among 2738 patients with non–Q-wave myocardial infarction confirmed by measurement of CK-MB isoenzymes who were identified at screening, 920 patients (34 percent) were randomly assigned to treatment groups: 462 to the invasive-strategy group and 458 to the conservative-strategy group. A total of 247 patients (9 percent) were excluded because of very-high-risk ischemic complications during the first 48 hours after the onset of infarction.[24] The base-line characteristics of the subjects are shown in Table 1. Ninety-seven percent of the study population were men. Eight percent of the patients were older than 75 years, and 40 percent were older than 65. Vital status at one year was verified for 913 patients (the other 7 patients were assumed to be alive after searches of death registries had negative results); follow-up at one year was more than 99 percent complete.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS RANDOMLY ASSIGNED TO THE INVASIVE AND CONSERVATIVE STRATEGIES.*

CHARACTERISTIC	INVASIVE STRATEGY (N=462)	CONSERVATIVE STRATEGY (N=458)
Age — yr	62±10	61±10
Sex — no. (%)		
Male	448 (97.0)	448 (97.8)
Female	14 (3.0)	10 (2.2)
Risk factors — no. (%)		
Ever smoked	391 (84.6)	396 (86.5)
Current smoker	189 (40.9)	210 (45.9)
Family history of CAD	175 (37.9)	168 (36.7)
Hypertension	262 (56.7)	236 (51.5)
High cholesterol level	80 (17.3)	77 (16.8)
Insulin-dependent diabetes	115 (24.9)	125 (27.3)
Prior myocardial infarction	199 (43.1)	197 (43.0)
Coexisting illness — no. (%)		
Cardiac disease other than CAD	54 (11.7)	44 (9.6)
Peripheral vascular disease	84 (18.2)	82 (17.9)
Neurologic disorder	53 (11.5)	54 (11.8)
Medications during wk before randomization — no. (%)		
Nitrates	140 (30.3)	144 (31.4)
Beta-blocker	100 (21.6)	103 (22.5)
Calcium antagonist	167 (36.1)	163 (35.6)
Aspirin	213 (46.1)	206 (45.0)
Warfarin	24 (5.2)	26 (5.7)
Lipid-lowering drug	60 (13.0)	56 (12.2)
ACE inhibitor	97 (21.0)	101 (22.1)
Angina in 3 wk before randomization — no. (%)†		
Before myocardial infarction	195 (42.2)	214 (46.7)
Canadian class I or II	147 (31.8)	158 (34.5)
Canadian class III or IV	48 (10.4)	54 (11.8)
Procedure >3 mo before randomization — no. (%)		
PTCA	40 (8.7)	44 (9.6)
CABG	88 (19.0)	68 (14.8)
Electrocardiographic location of myocardial infarction — no. (%)		
Anterior	204 (44.2)	188 (41.0)
Lateral	250 (54.1)	254 (55.5)
Inferior	166 (35.9)	172 (37.6)
Posterior	55 (11.9)	64 (14.0)
Base-line ejection fraction — %	53±15	50±14

*Plus–minus values are means ±SD. CAD denotes coronary artery disease, ACE angiotensin-converting enzyme, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass graft surgery.

†Canadian class refers to the classification system of the Canadian Cardiovascular Society.

End-Point Analyses

A total of 152 cardiac events (80 deaths and 72 nonfatal infarctions) occurred in 138 patients in the invasive-strategy group, as did 139 cardiac events (59 deaths and 80 nonfatal infarctions) in 123 patients in the conservative-strategy group (P=0.35) during an average of 23 months of follow-up (range, 12 to 44). As shown in Figure 1, the cumulative rates of death or nonfatal infarction in the groups did not differ significantly during long-term follow-up (hazard ratio for the conservative-strategy group as compared with the invasive-strategy group, 0.87; 95 percent confidence interval, 0.68 to 1.10), although there were striking differences between the groups in early clinical outcomes (i.e., clinical outcomes in the first 12 months). The frequency of death or nonfatal myocardial infarction was higher in the invasive-strategy group than in the conservative-strategy group before hospital discharge (36 vs. 15 events, P=0.004), at one month (48 vs. 26 events, P=0.012), and at one year (111 vs. 85 events, P=0.05). The same was true for the rate of death (21 vs. 6 deaths, P=0.007; 23 vs. 9, P=0.21; and 58 vs. 36, P=0.025, respectively).

During long-term follow-up, cumulative mortality from all causes did not differ significantly between the patients assigned to the conservative strategy and those assigned to the invasive strategy (hazard ratio, 0.72; 95 percent confidence interval, 0.51 to 1.01) (Fig. 2). Even among the 805 patients who did not receive thrombolytic therapy, there were more deaths in the invasive-strategy group (69 deaths) than in the conservative-strategy group (58). There were no significant differences between the groups in the incidence of nonfatal myocardial infarction during follow-up. Finally, there was remarkable consistency among the study sites; patients in the invasive-strategy group fared worse than those in

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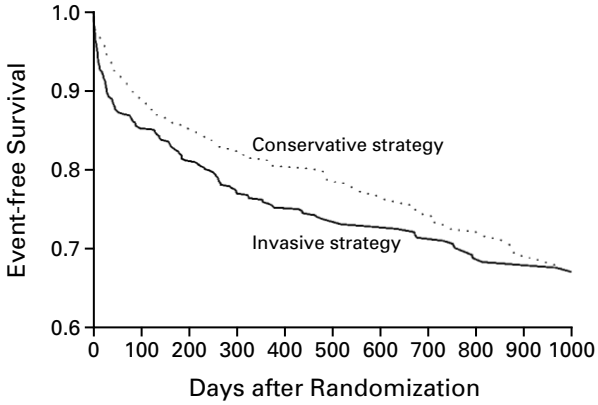

Figure 1. Kaplan–Meier Analysis of the Probability of Event-free Survival According to Strategy Group during 12 to 44 Months of Follow-up.

The events included in this analysis were death and nonfatal myocardial infarction (which together made up the primary end point). The Cox proportional-hazards ratio for the conservative as compared with the invasive strategy was 0.87 (95 percent confidence interval, 0.68 to 1.10).

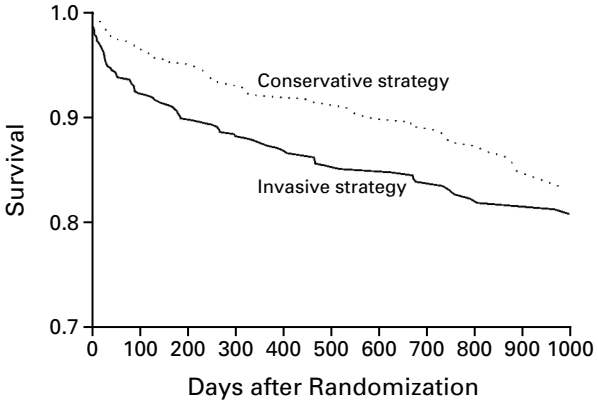

Figure 2. Kaplan-Meier Analysis of the Probability of Survival According to Strategy Group during 12 to 44 Months of Follow-up.

Death from any cause was included in this analysis. The Cox proportional-hazards ratio for the conservative as compared with the invasive strategy was 0.72 (95 percent confidence interval, 0.51 to 1.01).

the conservative-strategy group at 11 of 15 centers (73 percent).

Clinical Outcomes According to Treatment Strategy and Myocardial Revascularization

The clinical outcomes of all 920 patients are summarized in Table 2. Among the 462 patients assigned to the invasive strategy, 442 (96 percent) underwent coronary angiography (435 before hospital discharge and 439 by 30 days after the onset of symptoms). Among the 458 patients in the conservative-strategy group, only 24 percent (110 patients) underwent coronary angiography before discharge, and 29 percent (133 patients) by 30 days. Of the 110 patients who underwent catheterization before discharge, 45 percent had recurrent angina with ischemic electrocardiographic changes, 20 percent had ST-segment deviation of at least 2 mm during exercise testing, and 47 percent had one or more reversible perfusion defects during thallium scintigraphy.

The prevalence of multivessel coronary artery disease was high; 74 percent of patients in the invasive-strategy group and 80 percent of those in the conservative-strategy group had substantial left-main-stem stenosis, reduction of 50 percent or more of the luminal diameter in two or more major epicardial coronary arteries, or both.

A total of 204 patients (44 percent) underwent myocardial revascularization in the invasive-strategy group (95 had coronary-artery bypass graft surgery [CABG], 98 underwent percutaneous transluminal coronary angioplasty [PTCA], and 11 had both procedures), as did 152 (33 percent) in the conservative-strategy group (87 underwent CABG, 55 PTCA, and 10 both procedures) (Tables 2 and 3). Revascularization was performed earlier after randomization and within a narrower interval in the invasive-strategy group. Mortality 30 days after PTCA was 0 (0 of 98 patients) in the invasive-strategy group and 3.6 percent (2 of 55) in the conservative-strategy group — for a composite rate of 1.3 percent (Table 3). The 30-day death rate among patients who underwent only CABG was 7.7 percent (14 of 182 patients); 11 deaths occurred in the invasive-strategy group and 3 in the conservative-strategy group. Among the 21 patients who underwent both CABG and PTCA, only one death (4.8 percent) occurred (in a patient assigned to the conservative strategy). Overall, the death rate 30 days after revascularization was 4.8 percent (17 of 356 patients).

Of the 236 patients assigned to the conservative strategy who did not undergo angiography (52 percent), only 1.3 percent had had a nonfatal infarction or died by 30 days, and 11 percent by 1 year. The mortality was only 1 percent at 30 days and 6 percent at 1 year. Finally, the duration of hospitalization was significantly longer in the invasive-strategy group than in the conservative-strategy group (9.5 vs. 8.2 days, $P=0.024$).

Therapy with Drugs and Devices

At hospital discharge (a mean of 8.8 days after the onset of symptoms), 89 percent of patients were receiving aspirin, 52 percent a beta-blocker, and 55 percent a calcium-channel antagonist (diltiazem in 42 percent and another drug in 13 percent). There were no significant differences between the groups in use of medications. Certain newer treatment methods emerged during the course of the trial and were ap-

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TABLE 2. CLINICAL OUTCOMES OF PATIENTS WHO UNDERWENT CORONARY ANGIOGRAPHY WITH REVASCULARIZATION, CORONARY ANGIOGRAPHY WITHOUT REVASCULARIZATION, OR NO CORONARY ANGIOGRAPHY.*

PROCEDURE AND OUTCOME	INVASIVE STRATEGY (N=462)	CONSERVATIVE STRATEGY (N=458)
Coronary angiography		
No. of patients (%)	442 (96)	222 (48)
Time from randomization to angiography — days		
Median	2	14
Interquartile range	1–4	6–106
Angiography before discharge†		
No. of patients	431	106
Findings		
Ejection fraction — %	53±15	52±16
Single-vessel CAD — no. (%)	91 (21)	20 (19)
Two-vessel CAD — no. (%)	110 (26)	20 (19)
Three-vessel CAD — no. (%)	171 (40)	51 (48)
Left main disease with or without one-to-three-vessel CAD — no. (%)	36 (8)	14 (13)
<50% Stenosis — no. (%)	23 (5)	1 (1)
Revascularization		
No. of patients (%)	204 (44)	152 (33)
Time from randomization to revascularization — days		
Median	8	24.5
Interquartile range	5–18	11–19
Events 30 days after revascularization — no. (%)‡		
Death or nonfatal MI	22 (11)	14 (9)
Death	11 (5)	6 (4)
Events 1 yr after revascularization — no. (%)‡		
Death or nonfatal MI	37 (18)	23 (15)
Death	21 (10)	13 (9)
No revascularization		
No. of patients (%)	238 (52)	70 (15)
Events 30 days after angiography— no. (%)§		
Death or nonfatal MI	18 (8)	6 (9)
Death	12 (5)	2 (3)
Events 1 yr after angiography — no. (%)§		
Death or nonfatal MI	56 (24)	16 (23)
Death	31 (13)	9 (13)
No coronary angiography		
No. of patients (%)	20 (4)	236 (52)
Events 30 days after randomization — no. (%)¶		
Death or nonfatal MI	5 (25)	3 (1)
Death	5 (25)	2 (1)
Events 1 yr after randomization — no. (%)¶		
Death or nonfatal MI	9 (45)	26 (11)
Death	9 (45)	15 (6)

*CAD denotes coronary artery disease, and MI myocardial infarction. Plus–minus values are means ±SD.

†Four reports on angiography before discharge were missing for each strategy group.

‡Percentages shown are of patients who underwent revascularization.

§Percentages shown are of patients who underwent angiography but not revascularization.

¶Percentages shown are of patients who did not undergo angiography.

TABLE 3. MORTALITY 30 DAYS AFTER REVASCULARIZATION IN THE TWO TREATMENT-STRATEGY GROUPS.*

PROCEDURE AND TIME OF DEATH	INVASIVE STRATEGY	CONSERVATIVE STRATEGY	TOTAL
PTCA			
No. of patients	98	55	153
	number of deaths (percent)		
During PTCA	0	0	0
Same day as PTCA	0	2 (3.6)	2 (1.3)
≤7 days after PTCA	0	0	0
8–30 days after PTCA	0	0	0
Subtotal	0	2 (3.6)	2 (1.3)
CABG			
No. of patients	95	87	182
	number of deaths (percent)		
During CABG	0	0	0
Same day as CABG	2 (2.1)	0	2 (1.1)
≤7 days after CABG	3 (3.2)	2 (2.3)	5 (2.7)
8–30 days after CABG	6 (6.3)	1 (1.1)	7 (3.8)
Subtotal	11 (11.6)	3 (3.4)	14 (7.7)
PTCA and CABG			
No. of patients	11	10	21
	number of deaths (percent)		
During revascularization	0	0	0
Same day as revascularization	0	0	0
≤7 days after revascularization	0	0	0
8–30 days after revascularization	0	1 (10.0)	1 (4.8)
Subtotal	0	1 (10.0)	1 (4.8)
All patients			
No. of patients	204	152	356
Deaths — no. (%)	11 (5.4)	6 (3.9)	17 (4.8)

*PTCA denotes percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass graft surgery.

proved for clinical use after enrollment began; among them were stenting (in mid-1994) and platelet glycoprotein IIb/IIIa receptor antagonists (in 1995). Ticlopidine was not used routinely after PTCA.

Interaction Analysis

The lengths of time to death and to a cardiac event (death or nonfatal myocardial infarction) were compared for each of the five prespecified variables used in stratification in order to determine whether the main results were consistent among subgroups (Fig. 3). For death, there was moderately strong statistical evidence of benefit in the conservative-strategy group for 4 of 10 subgroups (patients who underwent thrombolysis, those with no prior infarction, those with no ST-segment depression, and those who were 60 or older). In no subgroup was the invasive strategy associated with a better outcome. For the combined primary end point, neither strategy conferred a statistically reliable advantage in any subgroup.

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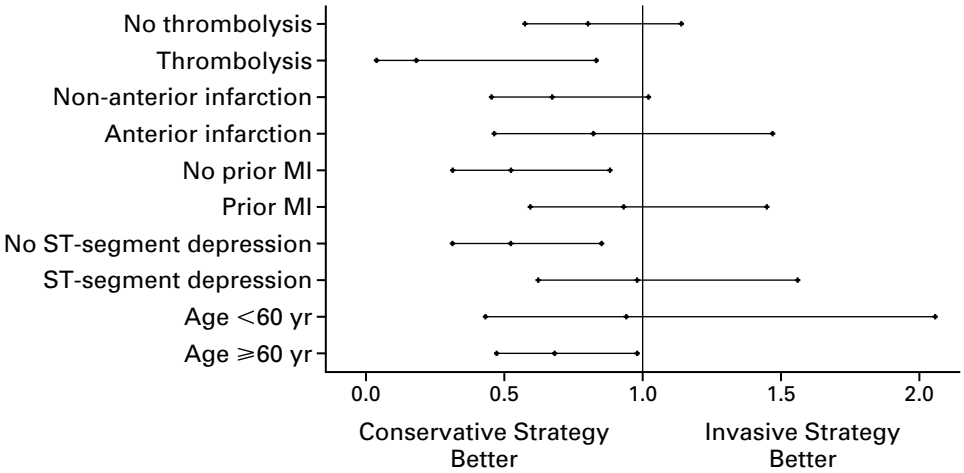

Figure 3. Hazard Ratios for Death in the Two Strategy Groups with Stratification According to Five Prespecified Variables. We conducted this interaction analysis for time to death in subgroups, using the Cox proportional-hazards model, in order to determine whether the main results were consistent among subgroups. Hazard ratios are shown with 95 percent confidence intervals. Hazard ratios that are less than 1.0 with confidence intervals that do not cross the unity boundary favor conservative management, and ratios above 1.0 favor invasive management. MI denotes myocardial infarction.

DISCUSSION

In this large, prospective, randomized trial of management of non–Q-wave myocardial infarction, we observed a substantial 28 percent rate of cardiac events during follow-up of 12 to 44 months, but no early or late clinical benefit with routine invasive management. Although the cumulative rate of death or recurrent infarction did not differ significantly between the two study groups, the rates of death or nonfatal myocardial infarction and of death were significantly higher during the first year of follow-up among patients randomly assigned to the invasive strategy. Both at hospital discharge and at 30 days, the rate of cardiac events and deaths among patients in the invasive-strategy group was increased by a factor of two to three, as compared with the rate in the conservative-strategy group. Moreover, overall mortality was significantly lower throughout the entire first year after infarction among patients assigned to the conservative strategy. The mortality curves for each strategy tended to converge by the end of follow-up (Fig. 2), a pattern that is not surprising in a population of patients with non–Q-wave myocardial infarction who were followed for up to 44 months.

For clinical and ethical reasons, we excluded a subgroup of patients with very-high-risk ischemic complications for whom an early invasive approach was clinically warranted; only 9 percent of all eligible patients with non–Q-wave infarction had such complications, however. Instead, our main goal was to assess the role of routine, early invasive management in the remaining patients with non–Q-wave infarction, more than 90 percent of the total, who were clinically stable at the time of transfer from the coronary care unit.

No subgroup of patients with non–Q-wave infarction appeared to benefit from an early invasive approach to treatment. Patients with anterior infarction, ST-segment depression on the electrocardiogram at entry, a reduced ejection fraction, or a previous infarction did not fare better with routine invasive management than with conservative treatment. Exclusion of the 115 patients who received early thrombolytic therapy did not change our overall findings.

Two other studies are relevant to our findings. In TIMI IIIB, there were no significant differences in the rates of death or recurrent infarction at six weeks among 1473 patients with acute coronary syndromes or in the subgroup of 476 patients with non–Q-wave infarction who were randomly assigned to an invasive strategy (18 events) or to a conservative strategy (22 events).[20] In TIMI IIIB, 64 percent of patients in the conservative-strategy group underwent coronary angiography within 6 weeks of randomization (90 percent of them within 10 days). In the current VANQWISH Trial, only 29 percent of patients in the conservative-strategy group subsequently underwent catheterization because they had objective signs of ischemia within 30 days.

The findings of the Danish Multicenter Randomized Study of Invasive versus Conservative Treatment in Patients with Inducible Ischemia after Thrombolysis in Acute Myocardial Infarction (DANAMI)[39] are indirectly related to our findings in the VANQWISH Trial. In DANAMI, only patients with first infarc-

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tions treated initially with thrombolytic therapy were included; 25 percent were classified as having non–Q-wave infarctions.[39] In VANQWISH, the median lengths of time from randomization to coronary angiography and revascularization in the invasive-therapy group were 2 days and 8 days, respectively, whereas in DANAMI this interval ranged from 2 to 10 weeks. The incidence of subsequent reinfarction and unstable angina was lower among patients in DANAMI who were assigned to the invasive strategy, but there was no significant difference in mortality.[39] The combined rate of death or reinfarction in DANAMI during a median follow-up of 2.4 years was 12 percent, whereas in the VANQWISH Trial it was 28 percent. Thus, as compared with the patient groups in both TIMI IIIB[20] and DANAMI,[39] our patients were at higher risk.[24] There was no clear benefit to routine early invasive management in terms of reducing mortality in any of the trials.

In the VANQWISH Trial, the 30-day death rate after CABG (7.7 percent) occurred in patients at moderately high risk among whom the event rate probably reflects the severity of their illness. Our findings are consistent with other reports that emphasize the fact that preoperative variables that identify patients as being at high risk (such as recent infarction) are associated with higher short-term mortality after CABG.[40-43] A recent study of 5517 patients who underwent CABG in 1993 showed that in-hospital mortality was highest among patients who underwent surgery within seven days of myocardial infarction (13 percent); who had previously undergone CABG (11 percent); who had peripheral or cerebral vascular disease (9 percent); who were 65 years of age or older (4 percent); or who had diabetes (3 percent).[40] These characteristics were common among our patients with non–Q-wave infarction.[24]

Several implications of our findings are noteworthy. First, the very low 30-day death rate after PTCA (1.3 percent) — even without stenting — was virtually identical to that observed at 30 days with conservative ischemia-guided management and no coronary angiography (1 percent) (Table 2). Second, early conservative management did not imply only watchful waiting; it embodied medical therapy, careful noninvasive testing, and coronary angiography, with or without myocardial revascularization, as indicated when ischemia recurred. Third, we found no evidence that using a routine strategy of early invasive treatment resulted in more expeditious management or shorter hospitalizations. Finally, routine coronary angiography in otherwise stable patients often leads to unnecessary revascularization procedures such as PTCA, the rate of which rose almost 6000 percent between 1980 and 1992.[44]

Our study has limitations. First, the study was not designed to compare myocardial revascularization with intensive medical therapy in survivors of acute non–Q-wave myocardial infarction. Considering the low rate of cardiac events among patients treated with conservative management, it seems unlikely that more aggressive intervention would have resulted in a different outcome. Nevertheless, clinical outcomes in the invasive-strategy group could have been different if a larger percentage of patients had undergone revascularization. Second, the very low percentage of female patients enrolled limits the generalizability of the overall findings to women. Third, the VANQWISH Trial was conducted before coronary stents or platelet glycoprotein IIb/IIIa receptor antagonists were widely available. Although it is possible that clinical outcomes might have been different in the invasive-strategy group if we had used stents, novel antiplatelet agents, or both, the long-term effects of such therapies in this population remain uncertain.

In summary, in this predominantly male population of moderate-to-high-risk patients with non–Q-wave myocardial infarction, we found no evidence that clinical outcomes were improved by a routine strategy of early invasive treatment; in fact, we observed substantial risk overall with this approach during the first year after infarction. By contrast, patients who were treated initially according to a conservative strategy had significantly lower mortality at hospital discharge, at one month, and at one year. These findings indicate that most patients with non–Q-wave myocardial infarction are not likely to benefit from routine early invasive treatment. A conservative initial strategy based on an ischemia-guided approach to management after infarction is both safe and effective.

Supported by a research grant from the Department of Veterans Affairs Cooperative Studies Program and by an unrestricted research grant from Hoechst Marion Roussel.

APPENDIX

The following persons and institutions participated in the VANQWISH Trial: S*tudy Chairman's Office (Syracuse, N.Y.):* W. Boden (chairman), H. Dai and D. Joyce (project coordinators), and P. Crawford (program assistant); *Veterans Affairs Medical Centers:* Albuquerque — M. Crawford, M. Holland, K. Wagoner; Cincinnati — L. Wexler, V. Thomas; Fresno, Calif. — P. Deedwania, E. Carbajal, R. Kanefield; Gainesville, Fla. — C. Pepine, J. Green, Jr., M. Limacher, E. Handberg-Thurmond, N. Davis; Hines, Ill. — M. Hwang, S. Lemoine; Houston — A. Blaustein, C. Rowe; Lexington, Ky. — C. Chasen, P. Frazier; Little Rock, Ark. — M. Murphy, J. Doherty, E. Smith, III, J. Calkins, Jr., A. Bierle; Loma Linda, Calif. — D. Ferry, A. Jacobson, G. Frivold, K. Okubo; Nashville — R. Smith, S. Levine, R. Bruce; Palo Alto, Calif. — J. Giacomini, C. Stepp; Richmond, Va. — R. Jesse, A. Minisi, C. Murphy; San Antonio, Tex. — R. O'Rourke, A. Jain, C. Patterson; San Diego, Calif. — A. Maisel; Seattle — K. Lehmann, J. Caldwell, S. Ferris; St. Louis — H. Stratmann, L. Younis, L. Conwill; Tampa, Fla. — R. Zoble, G. Cintron, J. Sullebarger, J. Umberger; *Cooperative Studies Program Coordinating Center (Palo Alto, Calif.):* P. Lavori (chief); D. Bloch, B. Chow, M. Iwane, R. Thomas, A. Busette, L. Sheridan, R. Yezzi, S. Jones, J. King, K. Small; *Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (Albuquerque, N.M.):* C. Haakenson, M. Miller, L. Guidarelli, L. Vasquez, F. Chacon, C. Tripp, G. Garcia, J. Price; *Cooperative Studies Program Central Office:* P. Huang, Washington, D.C., and J. Gold, Boston; *Planning Committee:* J. Abrams, University of New Mexico, Albuquerque; T. Bigger, Columbia University, New York; P. Carson, Georgetown University, Washington, D.C.; R. Kleiger, Jewish

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