JACC Vol. 31, No. 2
February 1998:312–20

Design and Baseline Characteristics of the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) Trial

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Objectives. **The Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) trial was designed to compare outcomes of patients with a non–Q wave myocardial infarction (NQMI) who were randomized prospectively to an early "invasive" strategy versus an early "conservative" strategy. The primary objective was to compare early and late outcomes between the two strategies using a combined trial end point (all-cause mortality or nonfatal infarction) during at least 1 year of follow-up.**

Background. **Because of the widely held view that survivors of NQMI are at high risk for subsequent cardiac events, management of these patients has become more aggressive during the last decade. There is a paucity of data from controlled trials to support such an approach, however.**

Methods. **Appropriate patients with a new NQMI were randomized to an early "invasive" strategy (routine coronary angiography followed by myocardial revascularization, if feasible) versus an early "conservative" strategy (noninvasive, predischarge stress testing with planar thallium scintigraphy and radionuclide ventriculography), where the use of coronary angiography and myocardial revascularization was guided by the development of ischemia (clinical course or results of noninvasive tests, or both).**

Results. **A total of 920 patients were randomized (mean follow-up 23 months, range 12 to 44). The mean patient age was 61 ± 10 years; 97% were male; 38% had ST segment depression at study entry; 30% had an anterior NQMI; 54% were hypertensive; 26% had diabetes requiring insulin; 43% were current smokers; 43% had a previous acute myocardial infarction; and 45% had antecedent angina within 3 weeks of the index NQMI.**

Conclusions. **Baseline characteristics were compatible with a moderate to high risk group of patients with an NQMI.**

(J Am Coll Cardiol 1998;31:312–20)

Approximately 50% of the 1.5 million patients in the United States who sustain an acute myocardial infarction (AMI) each year have non–Q wave myocardial infarction (NQMI) (1–3). The percentage of NQMIs has increased over the past two decades, probably due to a variety of factors (4,5). Because of the widespread use of both aspirin and thrombolytic agents in AMI, 40% to 45% of patients who present with acute ST segment elevation do *not* have electrocardiographic (ECG) Q waves after thrombolysis (6–9), thus contributing to the expanding pool of patients with NQMI.

Despite a more favorable early prognosis, long-term survival of patients with NQMI is similar to that of patients who have had a Q wave AMI (10,11). The higher rate of infarct extension and postinfarction ischemia after NQMI (10–14) resulted in a more aggressive approach to diagnosis and treatment. The 1987 American College of Cardiology/

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Manuscript received March 5, 1997; revised manuscript received September 29, 1997, accepted October 13, 1997.

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0735-1097/98/$19.00
PII S0735-1097(97)00486-5

Abbreviations and Acronyms

ACC/AHA	=	American College of Cardiology/American Heart Association
AMI	=	acute myocardial infarction
CK	=	creatine kinase
ECG	=	electrocardiogram, electrocardiographic
GUSTO IIa	=	Global Use of Strategies to Open Occluded Arteries
LDH	=	lactic dehydrogenase
NQMI	=	non–Q wave myocardial infarction
SGOT	=	serum glutamic oxaloacetic transaminase
TIMI	=	Thrombolysis in Myocardial Infarction
VANQWISH	=	Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital

American Heart Association (ACC/AHA) Joint Task Force Report on Guidelines for Coronary Arteriography recommended that NQMI (even in asymptomatic patients) constituted a class I ("definite") indication for diagnostic coronary angiography (15). This 10-year old recommendation, not derived from prospective, randomized trials, contrasted with the approach often applied after Q wave AMI, where only higher risk patients were recommended to undergo coronary angiography. Even though the recently published ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction (16) reclassified coronary angiography after NQMI as a class IIb indication (usefulness/efficacy is not established by evidence/opinion), an aggressive approach to early invasive management of NQMI has become firmly entrenched in clinical practice.

The utility of *routine* invasive testing in the management of survivors of AMI remains uncertain. Published findings in post-AMI patients with ST segment elevation (Thrombolysis in Myocardial Infarction-IIB trial [TIMI-IIB]) (17) or ST segment depression (TIMI-IIIB trial) (18) have suggested that the routine use of invasive testing followed by myocardial revascularization may result in unnecessary diagnostic and interventional procedures. Recently published data from Global Use of Strategies to Open Occluded Arteries (GUSTO) demonstrated no improvement in clinical outcomes in regions of the United States where angiography and angioplasty were performed more frequently (19). Moreover, it remains unproven whether these procedures improve quality of life (20).

We initiated a prospective, randomized trial at 15 Department of Veterans Affairs medical centers, from which 920 patients with NQMI were randomized to an early "invasive" versus an early "conservative" strategy. The primary objective was to compare early and late outcomes between the two randomized management strategies using a combined trial end point (all-cause mortality or nonfatal infarction) during 12 to 44 months of follow-up. Secondary objectives included analysis of risk stratification covariates and detailed cost-effectiveness comparisons, including functional status and quality of life assessments.

Methods

Ethics, approval process and written informed consent. This Department of Veterans Affairs Cooperative Study (CS no. 368), known as the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) trial, was approved by the Palo Alto Cooperative Studies Program Human Rights Committee and by the Cooperative Studies Evaluation Committee in 1991. Patient recruitment began on April 14, 1993. The protocol and consent form were approved by the Institutional Review Boards at each of the 15 Department of Veterans Affairs medical centers.

Objectives. The primary objective was to test the hypothesis that patients recovering from NQMI would have equivalent long-term clinical outcomes (all-cause mortality or recurrent nonfatal infarction), using either an early conservative or invasive diagnostic strategy. The invasive strategy consisted of routine diagnostic coronary angiography ("anatomic" risk assessment). The conservative strategy consisted of selective, specialized, noninvasive testing ("functional" risk assessment).

An important secondary objective was to establish clinical, demographic, ECG, laboratory and diagnostic risk factors for patients with NQMI at hospital discharge and during long-term follow-up. Other secondary objectives were to assess direct and indirect costs and other health care outcomes (functional status and quality of life).

Patient selection. Patients with suspected NQMI were screened for trial eligibility by study coordinators during hospital admission. Serial 12-lead ECGs and cardiac enzymes (creatine kinase [CK], lactic dehydrogenase [LDH] and serum glutamic oxaloacetic transaminase [SGOT]) and isoenzymes (CK-MB) were obtained on hospital entry and at regular intervals for 24 to 72 h. Patients were eligible to receive any therapy considered to be standard care during the early course of the hospital period. Inclusion and exclusion criteria are summarized in Table 1.

Electrocardiographic and enzymatic diagnosis. The ECG analysis was modeled after the Atlanta code in which serial tracings were obtained at multiple time points after NQMI symptom onset during the initial 24 to 72 h in the coronary care unit (4). At least one ECG was obtained 48 h after hospital admission to exclude the late development of Q waves, the vast majority of which (80%) occur within that period (21). Patients were excluded from the study if they had abnormal Q waves (i.e., 30 ms in duration in two leads within a given lead group) or R waves (i.e., 40 ms in lead V_1 and an R/S ratio of 1 in lead V_2) (22).

Acute ST segment displacement or T wave inversions were not prerequisites. Significant ST segment shifts were defined as the presence of 1 mm of ST segment elevation, depression or T wave inversion (or, in the presence of left ventricular hypertrophy, 2 mm of ST segment depression) in two leads within a given NQMI location.

Serial ECGs were interpreted by site investigators and forwarded to a core laboratory for subsequent analysis. For the purpose of stratifying patients between randomized strategy

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Age 18 years (no upper age limit for trial enrollment)
2. Clinical history compatible with AMI
3. Biochemical confirmation of myocardial necrosis, based on an abnormal rise of cardiac enzymes (CK, LDH, SGOT) or CK-MB activity above upper normal limit for the individual hospital laboratory
4. Absence of new ECG Q waves (0.04 s in duration; 0.1 mV in amplitude) or R waves (0.04 s in lead V_1; R/S ratio = 1 in lead V_2) in two or more leads within one of three lead groups (anterior = leads V_1 to V_4; inferior = leads II, III and aVF; lateral = leads I, aVL, V_5 and V_6)
5. Patient physically able to undergo invasive or noninvasive diagnostic testing
Exclusion Criteria
1. Unstable angina or angina refractory to intensive medical therapy during hospital period after NQMI
2. Persistent left bundle branch block
3. Congestive heart failure that does not clear with medical therapy
4. Cardiogenic shock
5. Ventricular fibrillation or symptomatic ventricular tachycardia > 48 h after index NQMI
6. Pericarditis
7. CABG or PTCA within 3 mo preceding randomization
8. Participation in another clinical research trial or use of an investigational drug within previous 30 days
9. Inability to undergo testing or to cooperate with protocol
10. Family/home circumstances that would preclude follow-up
11. Concomitant severe illness or comorbidity that might adversely affect follow-up during trial
12. Inability/unwillingness to provide informed, written consent

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; CK = creatine kinase; CK-MB = creatine kinase, MB isoenzyme; ECG = electrocardiographic; LDH = lactic dehydrogenase; NQMI = non–Q wave myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SGOT = serum glutamic oxaloacetic transaminase.

assignments, the designations of "anterior versus nonanterior" location and "ST segment depression versus no ST segment depression" were derived from the *entry* ECG, whereas data for coding *baseline* ECGs were derived from the tracing judged by the site investigator to be most representative of all serial tracings obtained within the initial 24 to 72 h of NQMI onset. Thus, certain discrepancies may be apparent between various ECG categories derived at the time of randomization (blocking variables) and at "study baseline" (24 to 72 h after index NQMI).

For patient qualification, one or more cardiac enzymes (total CK, LDH, SGOT) had to be 1.5 times the hospital's upper normal laboratory limit and/or two consecutive total CK and CK-MB determinations separated by 4 h had to exceed the upper normal limit.

Randomization procedure. Patients who met study entry criteria and gave written, informed consent were randomized, using the adaptive allocation (biased coin) procedure (23). This procedure maximized the probability that the number of patients allocated to each strategy was balanced within center and for each of the following five prognostic (stratifying) variables: age (<60 or ≥60 years), previous AMI (yes/no), use of thrombolytic agents (yes/no), AMI location by ECG (anterior/nonanterior) and entry ST segment depression (yes/no).

Experimental protocol. Randomization occurred typically within 1 to 3 days of NQMI onset, generally on transfer from the coronary care unit. Patients transferred from an outlying hospital center were randomized within 7 days of clinical and enzymatic NQMI onset. The protocol summarizing patient management is depicted in Figure 1. For patients assigned to the invasive strategy, early diagnostic coronary angiography was performed as the *initial* post-NQMI test, generally within 3 to 7 days after NQMI onset. Decisions to proceed with additional noninvasive testing or myocardial revascularization were left to the discretion of the investigators. TIMI-IIIB management guidelines for revascularization were followed (18): patients with significant single-vessel coronary artery disease were considered candidates for percutaneous transluminal coronary angioplasty or atherectomy, whereas coronary artery bypass graft surgery was recommended for multivessel disease. The decision to revascularize a "culprit" stenosis only, to perform a "complete" revascularization procedure or to continue medical therapy was left to the individual investigator's discretion. Whenever appropriate, all study patients received enteric-coated aspirin, 325 mg/day, and diltiazem (Cardizem CD), 180 to 300 mg/day, based on previously published data supporting this therapy as a secondary prevention in NQMI (24–26).

For patients randomized to the conservative strategy, a radionuclide ventriculogram to assess left ventricular function was performed as the first noninvasive test, generally 3 to 7 days after NQMI. Coronary angiography was not required if the ejection fraction was reduced. Before hospital discharge (6 to 9 days after NQMI), a *symptom-limited* (standard Bruce) treadmill exercise test was performed with planar or single-photon emission computed tomographic thallium scintigraphy. In patients who could not achieve 5 metabolic equivalents of exercise, an intravenous infusion of dipyridamole, 0.56 mg/kg, was administered, after which thallium scintigraphy was performed. To ensure quality and accuracy, each participating site was required to submit examples of thallium studies and to correctly interpret "unknowns" provided by the Nuclear Cardiology Laboratory (see Appendix) before initiation of the trial.

Coronary angiography with or without myocardial revascularization was performed in patients randomized to the conservative strategy only if one or more of the following criteria were satisfied: 1) *clinical criterion*—the patient developed recurrent post-NQMI angina associated with ischemic ECG changes; 2) *exercise ECG criterion*—the patient exhibited ≥2 mm of ST segment deviation during peak exercise; 3) *thallium scintigraphic criterion*—the patient displayed two or more redistribution defects or one redistribution defect plus increased lung uptake of thallium.

Decisions to perform myocardial revascularization in patients assigned to either strategy were made by the local site investigator, using the results of invasive or noninvasive tests, or both, performed at his or her institution. For patients

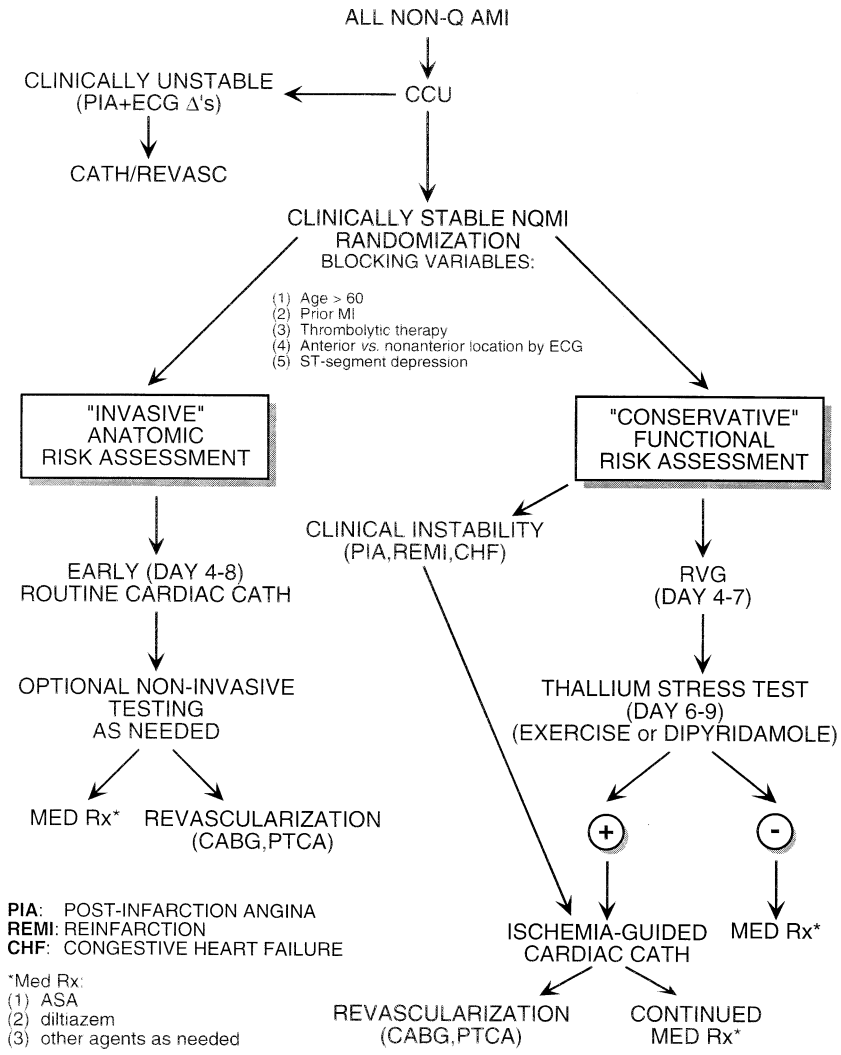

Figure 1. Trial design of VANQWISH. ASA = acetylsalicyclic acid (aspirin); CABG = coronary artery bypass graft surgery; CATH = catheterization; CCU = coronary care unit; MED Rx = medical drugs; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; REVASC = revascularization; RVG = radionuclide ventriculography; Δ's = changes.

assigned to the invasive arm in whom coronary angiographic findings were "equivocal" for significant stenosis, optional noninvasive testing could be obtained as needed. All coronary angiograms were forwarded subsequently to a core laboratory for subsequent blinded review and coding (see Appendix), but these centrally obtained interpretations were not used for local decision-making.

Patient intake and follow-up. Patient intake ended on December 31, 1995, after the enrollment of 920 patients, and the trial concluded on December 31, 1996. Study patients were seen at 1 month after hospital discharge and at 3-month intervals until trial termination. Patient follow-up ranged from 12 to 44 months (average 23). Electrocardiograms were obtained at 1, 3 and 12 months and annually until trial termination. Quality of life assessments and questionnaires were obtained at 1 and 12 months of follow-up and at the final visit.

End points. The primary end point of the trial was all-cause mortality or recurrent nonfatal AMI, whichever occurred first during a minimal 12-month follow-up period. Secondary end points included Kaplan-Meier estimates of cumulative event-free survival, hospital readmissions for unstable angina, need for myocardial revascularization, major procedural complications after coronary angiography or myocardial revascularization, quality of life assessments and resource utilization between the two strategies.

Statistical methodology. The trial was designed to evaluate whether the primary end point rates for the two strategy groups were equivalent during cumulative follow-up (12 to 44 months; mean 2.5 years). Sample size was calculated using the formula of Makuch and Simon (27) for an equivalence study design based on binomial proportions. The assumptions included an end point rate of 20% in each group during 12-month follow-up (28,29); a intergroup difference of 7.5% (the minimal group difference judged to be of clinical significance); a 5% two-sided significance level; and 80% power. The calculated sample size of 894 patients was inflated to the target of 922 patients (461 per group) to adjust for a projected 3% lost to follow-up rate during the first 12 months of follow-up.

Formal interim analyses for efficacy were conducted as requested by the Data Monitoring Board, using the method of

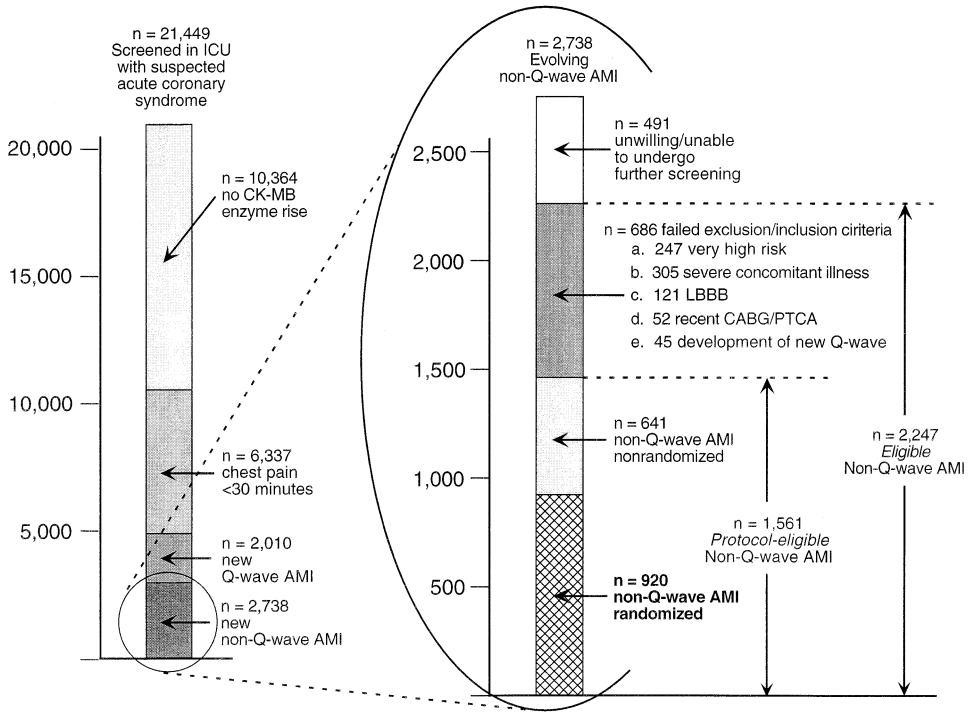

Figure 2. Randomization of patients to the VANQWISH trial. There were 1,561 protocol-eligible NQMI patients, 920 of whom were subsequently randomized (59%); among all eligible NQMI patients (n = 2,247), 41% were randomized, and among all (eligible plus ineligible) NQMI patients (n = 2,738), 34% were randomized. A total of 247 (9%) of all eligible NQMI patients were excluded for "very high risk" attributes (unstable angina after infarction, congestive heart failure that did not respond to medical therapy, cardiogenic shock or symptomatic ventricular arrhythmia). ICU = intensive care unit; LBBB = left bundle branch block; other abbreviations as in Fig. 1.

Lan and DeMets (30) with an O'Brien-Fleming type spending function (31), which adjusted for multiple looks at the data while preserving a near nominal overall significance level. Patients who did not adhere to the assigned strategy were included as randomized in analyses (i.e., by intention-to-treat).

Results

Figure 2 presents a summary of patient selection and randomization. A total of 21,449 patients with a suspected acute coronary syndrome was screened during 32.5 months of recruitment. Of these patients, 2,738 patients had evidence of evolving NQMI, 920 of whom (34%) were randomized. This high proportion of patients with NQMI who were randomized to the VANQWISH trial supports external generalizability of subsequent trial results.

The adaptive allocation randomization procedure resulted in balanced distribution of patients at each site according to the stratifying variables and protocol strategy. Baseline characteristics by stratifying variables are presented in Table 2.

Table 3 summarizes the baseline clinical characteristics for the entire study group. A high percentage of patients had smoked previously (86%), about half of whom (43%) were current smokers. Fifty-four percent were hypertensive, 26% had diabetes requiring insulin and 18% had peripheral vascular disease, but only 17% reported a history of hypercholesterolemia under treatment.

Of note, 43% of patients had a history of angina and 45% had antecedent angina within 3 weeks of NQMI. Of this group, 63% had at least Canadian Cardiovascular Society class II angina. These clinical characteristics are compatible with a moderate to high risk group of patients with NQMI.

Cardiac medications at hospital admission included aspirin (46%), calcium channel blockers (36%), nitrates (31%), beta-blockers (22%), diuretics (22%), angiotensin-converting enzyme inhibitors (22%), a lipid-lowering agent (13%), digitalis (9%) and warfarin (5%).

The randomization ECG demonstrated a spectrum of findings, as illustrated in Table 4. More than half of the patients (57%) *did not* have ST segment shifts (ST segment elevation or depression) on the qualifying tracing, and 21% had *no ECG changes at all*. Approximately 30% presented with ST segment elevation. T wave inversion was common (49%); left ventricular hypertrophy was uncommon (11%); and one-quarter of the patients had previous Q waves. The slight discrepancy in the reported rate of anterior AMI location between Tables 2

Table 2. Distribution by Randomization Variables*

	Invasive Strategy [no. (%) of pts]	Conservative Strategy [no. (%) of pts]
Age < 60 yr (n = 363)	180 (39.0%)	183 (40.0%)
ST seg depression on admitting ECG (n = 355)	182 (39.4%)	173 (37.8%)
Ant infarct location (n = 277)	136 (29.4%)	141 (30.8%)
Previous AMI (n = 396)	199 (43.1%)	197 (43.0%)
Received thrombolytic therapy (n = 115)	58 (12.6%)	57 (12.5%)

*p = NS for all comparisons. Ant = anterior; Pts = patients; seg = segment; other abbreviations as in Table 1.

Table 3. Baseline Characteristics of 919 Patients*†

	Invasive Strategy [no. (%) of pts]	Conservative Strategy [no. (%) of pts]
Gender		
Male (n = 895)	447 (97.0%)	448 (97.8%)
Female (n = 895)	14 (3.0%)	10 (2.2%)
Age (yr) (mean ± SD)		
61.8 ± 10.0	461 (50.2%)	
61.0 ± 10.5		458 (49.8%)
Race		
White (n = 683)	344 (74.6%)	339 (74.0%)
Black (n = 107)	57 (12.4%)	50 (10.9%)
Hispanic (n = 100)	45 (9.8%)	55 (12.0%)
Other (n = 29)	15 (3.3%)	14 (3.1%)
Risk factors for CAD		
Ever-smoked (n = 787)	391 (84.8%)	396 (86.5%)
Current smoker (n = 399)	189 (41.0%)	210 (45.9%)
Family history of CAD (n = 343)	175 (38.0%)	168 (36.7%)
Hypertension (n = 498)	262 (56.8%)	236 (51.5%)
Hypercholesterolemia (n = 157)	80 (17.4%)	77 (16.8%)
Diabetes (n = 240)	115 (25.0%)	125 (27.3%)
Procedures > 3 mo before admission		
PTCA (n = 84)	40 (8.7%)	44 (9.6%)
CABG (n = 156)	88 (19.1%)	68 (14.9%)
Angina in 3 wk before admission (n = 409)	195 (42.3%)	214 (46.7%)
Other medical conditions		
Nonischemic heart disease (n = 98)	54 (11.7%)	44 (9.6%)
Peripheral vascular disease (n = 166)	84 (18.2%)	82 (17.9%)

*One patient died before baseline information could be obtained. †p = NS for all comparisons. CAD = coronary artery disease; other abbreviations as in Tables 1 and 2.

Table 4. Characteristics of Randomization Electrocardiogram*

	Invasive Strategy [no. (%) of pts]	Conservative Strategy [no. (%) of pts]
Any ST seg changes (n = 397)	199 (43.3%)	198 (43.2%)
ST seg elevation (n = 272)	137 (29.8%)	135 (29.5%)
ST seg depression (n = 356)	177 (38.5%)	179 (39.1%)
T wave inversion (n = 448)	224 (48.7%)	224 (48.9%)
Preexisting Q waves (n = 225)	107 (23.3%)	118 (25.8%)
LVH (n = 104)	58 (12.6%)	46 (10.0%)
Infarct location†		
Anterior (n = 392)	204 (44.4%)	188 (41.1%)
Inferior (n = 504)	250 (54.4%)	254 (55.5%)
Lateral (n = 338)	166 (36.1%)	172 (37.6%)
Posterior (n = 119)	55 (12.0%)	64 (14.0%)
Any localized infarct (n = 728)	369 (80.2%)	359 (78.4%)

*p = NS for all comparisons. †Patients may have more than one infarct location. LVH = left ventricular hypertrophy; other abbreviations as in Tables 1 and 2.

and 5 was due to the occasional use of different ECGs for the randomization procedure ("entry" tracing) and the baseline tracing (most representative ECG for evolving NQMI).

Of the 272 (30%) of 920 patients who presented with ST segment elevation, 97 (36%) received thrombolytic therapy. A total of 115 patients (13%) received thrombolytic therapy. Some patients who had ST segment elevation did not meet accepted ECG criteria or had contraindications to thrombolytic therapy; 18 patients without ST segment elevation also received thrombolytic therapy.

Table 5 presents the characteristics of the patients according to their treatment with thrombolytic therapy. Patients who received thrombolytic therapy were slightly younger (58.6 vs. 61.8 years), were much more likely to be current smokers (62% vs. 41%) and were much less likely to have hypertension (36% vs. 57%) or diabetes (13% vs. 28%).

Discussion

Aggressive approach to post-NQMI evaluation. Postinfarction angina, reinfarction and increased late mortality are important ischemia-related complications of patients recovering from NQMI (10–14,20,29). Although both observational (32–38) and retrospective analyses (39–43) suggest that high and low risk subsets can be identified, that ischemia-related complications occur in 40% of survivors and that conservative management may be appropriate for most patients with NQMI, the overall diagnostic and therapeutic approach to these patients has become more aggressive during the last decade. This practice is based on the presumption that an

Table 5. Characteristics of 919 Patients by Treatment With Thrombolytic Therapy*

	Tx	No Tx	p Value (Tx vs. no Tx)
Age (yr) (mean ± SD)			0.0019
58.6 ± 9.6	115 (12.4%)		
61.8 ± 10.3		805 (87.6%)	
Risk factors for CAD			
Ever-smoked (n = 787)	100 (87.7%)	687 (85.4%)	NS
Current smoker (n = 399)	71 (62.3%)	328 (40.8%)	< 0.0001
Family history of CAD (n = 343)	46 (40.1%)	297 (36.9%)	NS
Hypertension (n = 498)	41 (38.0%)	457 (56.8%)	< 0.0001
Hypercholesterolemia (n = 157)	10 (8.8%)	147 (18.3%)	0.017
Diabetes (n = 240)	15 (13.2%)	225 (28.0%)	0.001
Procedures > 3 mo before admission			
PTCA (n = 84)	8 (7.0%)	76 (9.4%)	NS
CABG (n = 156)	15 (13.2%)	141 (17.5%)	NS
Angina in 3 wk before admission (n = 409)	42 (36.8%)	367 (45.6%)	NS
Other medical conditions			
Nonischemic heart disease (n = 98)	11 (9.7%)	87 (10.8%)	NS
Peripheral vascular disease (n = 166)	12 (10.5%)	154 (19.1%)	0.035

*One patient who received thrombolytic therapy died before baseline information could be obtained. †Treatment versus no treatment. Data are presented as number (%) of patients. Tx = treatment; other abbreviations as in Table 3.

invasive strategy of routine coronary angiography is superior to a conservative strategy of noninvasive stress testing with selective revascularization in patients who are at risk for developing adverse ischemic outcomes.

Previous NQMI trials. There are few prospective trials to guide clinical decision-making in the management of NQMI. The TIMI-IIIB trial (18) was the only published multicenter clinical trial to prospectively examine the impact of randomly assigned diagnostic and therapeutic strategies on short-term outcome in patients recovering from NQMI. The primary objective of the TIMI-IIIB trial was to assess 6-week outcomes in a large group of patients with unstable angina or NQMI, randomized to either an early invasive or early conservative strategy. Only 476 (32%) 1,473 patients had NQMI, 252 of whom were randomized to the early invasive strategy and 224 to the early conservative strategy. There were 18 deaths or recurrent nonfatal AMIs in the invasive strategy group and 22 in the conservative strategy groups at 6 weeks ($p = 0.30$) (18).

TIMI-IIIB was not powered to detect differences in management strategies in the subset of patients with NQMI. Moreover, among the 733 patients randomized to the early conservative strategy in TIMI-IIIB, 64% underwent diagnostic coronary angiography before day 42, and 90% underwent coronary angiography before hospital discharge (18). This high "crossover" rate and the short period of follow-up limit TIMI-IIIB's usefulness to provide clinically meaningful comparisons between the two strategies.

ST segment elevation versus ST segment depression and thrombolytic therapy. When our study was designed in 1992, it was not clear that the direction of ST segment deviation was associated with a different response to thrombolytic therapy. Not until the TIMI-IIIB trial was published in 1994 (18) did it become apparent that only patients presenting with ST segment elevation were benefited by thrombolytic therapy.

Furthermore, patients who received thrombolytic therapy in this study had different baseline cardiovascular risks. They were strikingly more likely to be current smokers and much less likely to have hypertension or diabetes. They also had a lower prevalence of peripheral vascular disease and known hypercholesterolemia and were slightly younger.

Patients may be more likely to present with ST segment elevation if they have plaque rupture without previous sufficient flow-limiting disease to stimulate the development of collateral channels. Multiple moderate lesions in major coronary arteries or branch vessels ("diffuse disease") are more likely to be present in patients who have multiple cardiac risk factors. Plaque rupture in these patients may jeopardize less myocardium, and thus patients may present with ST segment depression, T wave inversion or no ECG changes (i.e., with NQMI). Also, cigarette smoking decreases high density lipoprotein cholesterol, stimulates platelet aggregation, promotes vasoconstriction, increases myocardial oxygen demand, reduces oxygen supply by the presence of carboxyhemoglobin and increases fibrinogen levels (44–47). These factors are more likely to result in a "catastrophic event" in the case of plaque rupture among patients who present with ST segment elevation.

Finally, because we had no way of anticipating the nonhomogeneity of the thrombolytic and nonthrombolytic NQMI populations, it is fortuitous that this study is sufficiently powered for the major end points *without* inclusion of the 115 patients receiving thrombolytic therapy.

Rationale for this trial. Clearly, prospective, long-term trials utilizing risk stratification and comparative diagnostic approaches are needed to determine the optimal management strategy for survivors of non–Q wave AMI and to ascertain the cost-effectiveness of an invasive versus conservative management in terms of clinical outcomes, resource utilization and other health care outcomes.

The conduct of such a multicenter trial like VANQWISH within the Department of Veterans Affairs affords certain advantages and disadvantages. Because the veteran population is typically older and often sicker than other patient groups, the associated comorbidity might be expected to result in a higher risk for adverse outcomes. Moreover, the Department of Veterans Affairs health care system is less influenced by physician referral pressures and reimbursement practices in choosing postinfarction diagnostic or therapeutic procedures, thus minimizing the potential for a priori selection bias. However, the low percentage of women veterans limits generalizability of overall trial findings to female patients after NQMI.

Conclusions. The VANQWISH trial represents the largest, most comprehensive clinical comparison of long-term management strategies in patients recovering from NQMI. Data from this trial will hopefully clarify the optimal diagnostic and therapeutic approach to managing patients with this prevalent clinical disorder.

Appendix

Participating Investigators and Institutions for Cooperative Study 368 (VANQWISH Trial)

Study Chairman's Office (Boston). William E. Boden, *Study Chairman*; Hugh Dai, Diane M. Joyce, *Project Coordinators*; Patricia A. Crawford, Program Assistant.

Department of Veterans Affairs Medical Centers. *Albuquerque, New Mexico*: Michael Crawford, Matthew R. Holland, Karen Wagoner; *Cincinnati, Ohio*: Laura Wexler, Virginia Thomas; *Fresno, California*: Prakash C. Deedwania, Enrique Carbajal, Rebecca Kanefield; *Gainesville, Florida*: Carl J. Pepine, J. Russell Green, Jr., Marian Limacher, Eileen Handberg-Thurmond, Nancy Davis; *Chicago, Illinois*: Ming H. Hwang, Sandra Lemoine; *Houston, Texas*: Alvin S. Blaustein, Cynthia Rowe; *Lexington, Kentucky*: Craig A. Chasen, Penelope Frazier; *Little Rock, Arkansas*: Marvin L. Murphy, James E. Doherty, Eugene S. Smith III, Joe B. Calkins, Jr., Anita Bierle; *Loma Linda, California*: David D. Ferry, Alan Jacobson, Geir Frivold, Karen Okubo; *Nashville, Tennessee*: Raphael F. Smith, Stewart Levine, Randalyn Bruce; *Palo Alto, California*: John Giacomini, Carole Stepp; *Richmond, Virginia*: Robert Jesse, Anthony Minisi, Catherine Murphy; *San Antonio, Texas*: Robert A. O'Rourke, Avanindra Jain, Carolyn Patterson; *San Diego, California*: Alan Maisel; *Seattle, Washington*: Kenneth Lehmann, James Caldwell, Scott Ferris; *Saint Louis, Missouri*: Henry Stratmann, Liwa Younis, Linda Conwill; *Tampa, Florida*: Robert G. Zoble, Guillermo B. Cintron, J. Thompson Sullebarger, Julie Umberger.

Cooperative Studies Program Coordinating Center (Palo Alto, California). Philip W. Lavori, *Chief*; Dan Bloch, Bruce Chow, Marika K. Iwane, Ronald G.

Thomas, *Biostatisticians*; Andres Busette, Lenore Sheridan, Raymond Yezzi, *Statistical Assistants*; Sheila Jones, Juawanna King, *Research Assistants*; Kathleen Small, *Administrative Officer.*

Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (Albuquerque, New Mexico). Clair M. Haakenson, Michael J. Miller, *Clinical Research Pharmacists*; Loretta A. Guidarelli, *Study Coordinator*; Linda L. Vasquez, *Computer Assistant*; Frances Chacon, Cindy Tripp, Gloria Garcia, *Production Controllers*; Julie Price, *Research Assistant.*

End Points Committee. Christopher P. Cannon, *Chairman, Brigham and Women's Hospital, Boston, Massachusetts*; Kim A. Eagle, *University of Michigan Medical Center, Ann Arbor, Michigan*; Douglas W. Losordo, *St. Elizabeth's Hospital, Boston, Massachusetts.*

Data Monitoring Board. Bertram Pitt, *Chairman, University of Michigan Medical Center, Ann Arbor, Michigan*; Mark A. Moskowitz, *University Hospital, Boston, Massachusetts*; Arthur J. Moss, *University of Rochester Medical Center, Rochester, New York*; Robert F. DeBusk, *Stanford University School of Medicine/ Medical Center, Palo Alto, California*; Stanley P. Azen, *University of Southern California, Los Angeles, California*; Robert C. Schlant, *Emory University School of Medicine, Atlanta, Georgia*; Janet Wittes, *Statistics Collaborative, Inc., Washington, D.C.*

Core Laboratories. Robert E. Kleiger, *Electrocardiography Core Laboratory, Jewish Hospital/Washington University School of Medicine, St. Louis, Missouri*; Jeffrey A. Leppo, *Nuclear Cardiology Quality Assessment Laboratory, University of Massachusetts Medical Center, Worcester, Massachusetts*; Richard A. Kerensky, Carl J. Pepine, *Coronary Angiography Quality Assessment Laboratory, University of Florida, Gainesville, Florida.*

Quality Assurance. The *Study Chairman's Office* reviewed and approved all coronary angiography requests for patients who were randomized initially to the conservative strategy. The Study Chairman had no knowledge of the trial end points and clinical events during patient enrollment. The *Coordinating Center* centrally randomized patients and conducted internal data checks and external data checks with national data bases and conducted site visits. The *Nuclear Cardiology Core Laboratory* certified sites in the interpretation of nuclear studies by utilizing phantom studies of unknown radionuclide ventriculograms and planar thallium perfusion scintigrams. This laboratory reviewed a 20% random sample of all thallium studies. The *Coronary Angiography Core Laboratory* overread baseline coronary angiograms using standard Coronary Artery Surgery Study (CASS) coronary angiography guidelines. The *Electrocardiography Core Laboratory* overread all study ECGs and provided the End Points Committee with blinded review of relevant ECGs for suspected study end points. The *End Points Committee* adjudicated all suspected study end points, including cardiac etiology of deaths, nonfatal reinfarctions, ischemic cardiac events resulting in rehospitalization and procedure-related cardiac events. The *Data Monitoring Board* was an independent committee that reviewed semiannual interim reports of study data for safety and efficacy and the possible need for early trial termination. This board met annually in a joint meeting with the *Human Rights Committee*, which consisted of lay and clinical persons who ensured the safety and ethical treatment of patients through a review of study data, site visits and patient interviews.

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