EDITORIAL COMMENT

Is ST Segment Elevation Non–Q-Wave Myocardial Infarction After Thrombolytic Therapy a New Clinical Entity That Requires an Invasive Management Strategy?*

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The Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial compared a strategy of early diagnostic coronary angiography (followed by revascularization, if necessary) to a conservative ischemia-guided approach (for spontaneous or inducible ischemia) in 920 patients with acute non–Q-wave myocardial infarction (NQMI) (1). In 1998, the investigators reported that patients assigned to the invasive diagnostic strategy did not benefit from routine, early cardiac catheterization and concluded that a conservative, ischemia-guided initial approach is both safe and effective in acute NQMI (2). VANQWISH did not exclude patients who presented with ST segment elevation, as long as the patients did not develop new Q-waves during admission. Thus, 272, or ~30% of the patients, had ST segment elevation on the randomization electrocardiogram (ECG); 97 patients received thrombolytic therapy and 18 patients without ST segment elevation received thrombolytic therapy.

In this issue of the Journal, Wexler et al. (3) present the VANQWISH results, comparing the clinical characteristics and outcomes after randomization in the 115 patients who developed NQMI after thrombolytic therapy with the data of the remaining 805 patients who did not receive thrombolytic therapy. The results of the two cohorts show that the overall event rates (death or recurrent MI) are comparable in the conservative and invasive strategy groups, regardless of whether thrombolytic therapy was given. The data indicate that patients with ST segment elevation MI who receive thrombolytic therapy tend to have less extensive coronary disease and better residual left ventricular function compared with patients with non-ST segment elevation MI. The 30% incidence of NQMI in patients with an acute coronary syndrome who present with ST segment elevation and receive thrombolytic therapy in VANQWISH is similar to the 29% and 24% incidence observed in the Thrombolysis In Myocardial Infarction (TIMI II) trial and the Danish trial in Acute Myocardial Infarction (DANAMI) of patients with an initial index MI treated with intravenous thrombolytic therapy (4,5).

A major finding in this report is contained in the patient subgroup that presented with ST segment elevation, received thrombolytic therapy and evolved a NQMI, one of the prespecified subgroups for analysis in VANQWISH. The data indicate that 19 (33%) of 58 patients randomized to the invasive strategy died or had a recurrent nonfatal MI, as compared with 11 (19%) of 57 patients randomized to the conservative strategy (p = 0.152). After an average 23-month follow-up, more deaths occurred in the invasive group than in the conservative group (11 vs. 2), a difference that could not be explained by periprocedural mortality rates. Of the 11 deaths in the invasive strategy, two occurred before angiography and four were noncardiac. Both deaths in the conservative group were noncardiac.

How can the VANQWISH results be applied to most patients with ST segment elevation MI who evolve a NQMI in current clinical practice? To respond to this question, we need to examine the hypothesis that the VANQWISH investigators studied. What is the role of coronary angiography as an initial diagnostic strategy in the management of stabilized patients who present with ST segment elevation and evolve a NQMI? In VANQWISH, patients were randomized an average of three to seven days after the onset of MI (after discharge from the coronary care unit). Patients with ST segment elevation MI who were hemodynamically unstable, those who had recurrent ischemia refractory to medical therapy and those who had coronary revascularization within the previous three months were excluded (1). Thus, the highest risk patients with ST segment elevation MI were not enrolled in the study. Coronary revascularization was recommended (percutaneous transluminal coronary angioplasty [PTCA] for single-vessel, and coronary artery bypass graft [CABG] surgery for multivessel disease), using the best clinical judgment of the treating physician; less than half of the patients in both strategy groups received coronary revascularization. Thus, the invasive strategy in VANQWISH did not test routine, immediate prophylactic coronary revascularization for patients with ST segment elevation MI who received thrombolytic therapy and developed an NQMI after symptom onset. The TIMI II results addressed the potential benefit of earlier diagnostic catheterization and revascularization in patients with ST segment elevation NQMI who received thrombolytic therapy. Aguirre et al. (4) reported that 767 patients had an NQMI after treatment with intravenous thrombolytic therapy in TIMI II. All patients in TIMI II received intravenous thrombolytic therapy with recombinant tissue–type plasminogen activator (rt-PA). The proto-
col required patients <76 years old with ischemic cardiac pain >30 min and ST segment elevation ≥1 mm in two or more contiguous ECG leads who presented within 4 h of symptom onset. The invasive strategy in TIMI II consisted of coronary angiography and PTCA, if feasible, within 1.5 to 2 days after rt-PA, earlier than the 3 to 7 days as in the overall VANQWISH study. In the invasive strategy group in TIMI II, 73% of patients with ST segment elevation NQMI underwent early protocol revascularization (within 21 days), greater than the 47% of patients in VANQWISH who had a revascularization procedure performed either during the index hospital admission or during follow-up. In patients randomized to the conservative strategy, coronary angiography was performed in 18% of the VANQWISH patients during the index hospital admission and 43% of the patients with ST segment elevation NQMI in TIMI II. Interestingly, revascularization was performed in 28% of patients in VANQWISH and 25% in TIMI II. In TIMI II, the one-year mortality rate was 3.4% for ST segment elevation NQMI, remarkably similar to the 3.5% observed in VANQWISH after a slightly longer follow-up. In the Aguirre report, which was a retrospective analysis of the TIMI II data, reinfarction and mortality rates were similar, regardless of whether the patient was assigned to the invasive or conservative postlytic management strategy. Thus, the VANQWISH and TIMI II results are consistent and indicate that early (one to two years) mortality rates are low in clinically stable patients with ST segment elevation NQMI who receive thrombolytic therapy and a conservative management approach, with cardiac catheterization reserved for spontaneous or inducible ischemic events. The TIMI IIIb trial, which also used thrombolytic therapy and tested an invasive versus conservative strategy in patients presenting with an acute coronary syndrome, does not contain a sufficient number of patients to answer the question of the optimal revascularization strategy for patients with ST segment elevation NQMI, because only 10%, or 143, of the TIMI III patients presented with ST segment elevation and only 32% of patients ultimately developed NQMI (6).

One might ask whether the coronary revascularization approach, as applied in the VANQWISH ST segment elevation NQMI group, is current. Did the procedures, as used, have sufficient long-lasting benefits? The study was conducted before the widespread use of glycoprotein IIb/IIIa receptor blockers, which have been shown not only to improve myocardial perfusion in the early phase of ST segment elevation MI, but also to reduce the incidence of MI and periprocedural MI (an event known to increase short- and long-term mortality rates) in patients with an acute coronary syndrome (7–9). Coronary stents for percutaneous coronary intervention (PCI) procedures were not widely available when VANQWISH patients were enrolled. Stents may have the potential to provide a more long-lasting revascularization by reducing the rate of restenosis, compared with standard PTCA (10). The question of whether glycoprotein IIb/IIIa receptor blockers and coronary stenting influence an invasive versus conservative management strategy in acute coronary syndromes (unstable angina and NQMI) is currently being addressed by the ongoing Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive vs. Conservative Strategy (TACTICS–TIMI 18 trial. This study compares an invasive strategy (within 4 to 48 h) of early coronary angiography and revascularization using Tirofiban and coronary stents, when feasible, to a more conservative strategy that reserves coronary angiography and revascularization for patients who do not meet at least one of six prespecified criteria (11). The study does not address patients with ST segment elevation NQMI who receive thrombolytic therapy, because patients with persistent ST segment elevation are excluded.

The excellent clinical outcome observed in VANQWISH with the conservative approach applies to men who present with ST segment elevation MI, receive thrombolytic therapy, evolve a NQMI, are treated medically, are clinically stable after several days and are subsequently risk-stratified using noninvasive testing. This patient subgroup is a large segment of patients with MI admitted to the hospital each year. Cardiac catheterization facilities are not available at all hospitals, and patients who are clinically stable are often managed locally and transferred to larger institutions only if they develop complications or have major inducible ischemia. Patients in VANQWISH were enrolled before the era of aggressive lipid-lowering therapy, which has been shown to decrease myocardial ischemic events and routine early use of angiotensin-converting enzyme inhibitors for even mild degrees of left ventricular function after MI (12). The impact of aggressive lipid-lowering therapy in patients with an acute coronary syndrome is currently being addressed in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial, which tests the incremental benefit of 80 mg of atorvastatin on coronary event rates over an average four-month follow-up, and in the Antiplatelet and Statin Therapy in Acute Coronary Syndromes trial (A to Z trial), which uses high dose simvastatin (13). The Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation trial, which compares PCI plus intensive medical therapy to intensive medical therapy alone may also provide answers to the role of PCI in patients with acute coronary syndrome who receive aggressive lipid-lowering therapy, if the subset with uncomplicated MI or unstable angina responsive to medical therapy is sufficiently large (14). It is possible that the long-term outcome of medically treated patients similar to those enrolled in VANQWISH may be even better this decade with the more widespread use of aggressive high dose lipid-lowering therapy if shown to be beneficial.

A major contribution of the VANQWISH and TIMI II conservative approach to current therapeutic strategy for stable ST segment elevation NQMI is the demonstration that predischarge noninvasive testing is a remarkably efficient tool in identifying patients with inducible myocardial
ischemia who could potentially benefit from coronary revascularization. VANQWISH recommended an initial radionuclide ventriculogram to assess left ventricular function. Coronary angiography with or without myocardial revascularization was then recommended only if the following clinical criteria were met: recurrent postinfarction angina with ischemic ST segment shift $\geq 0.1$ mV or T-wave inversion in two or more contiguous leads; exercise-induced ST segment depression $\geq 0.2$ mV during peak exercise; and “high risk” thallium pattern redistribution defects in two or more different vascular regions, or one redistribution defect with an increased lung to heart ratio of thallium uptake (which occurred in 20% of the ST segment elevation NQMI group) (3). The TIMI II approach used supine exercise radionuclide ventriculography. Because both VANQWISH and TIMI II report no significant survival or recurrent MI benefit to routinely sending every patient with ST segment elevation NQMI to the cardiac catheterization laboratory, one would think that noninvasive testing would be a preferred approach to risk stratify stable patients with ST segment elevation NQMI (15). This is not the case in many medical centers. In a recent study, Dakik and Verani (16) reported a much lower utilization rate for radionuclide stress testing than for coronary angiography ($\sim 10\%$ vs. $77\%$) in patients with an acute coronary syndrome, even though revascularization guided by nuclear stress test results was associated with a lower mortality rate than that found without nuclear testing. The DANAMI trial of patients with an initial acute MI (24% NQMI) treated with thrombolytic therapy also showed that when inducible myocardial ischemia is present after an infarction (using symptom-limited bicycle ergometry), coronary events can be significantly reduced by coronary revascularization (5). Clearly, current evidence suggests that routine predischarge risk stratification using clinical and noninvasive testing should be part of the management strategy for all clinically stable patients who evolve a NQMI after thrombolytic therapy.

Patients who present with prolonged ST segment elevation and chest pain $\geq 20$ to $30$ min develop an MI with abnormal creatine kinase, MB fraction (CK-MB) elevation in $\geq 90\%$ of cases. When there are no contraindications, this patient group represents a class I indication for emergent treatment with either thrombolytic therapy or direct PTCA, according to the 1999 update to the American College of Cardiology/American Heart Association MI guidelines (17). Thus, treatment is instituted promptly before the clinician can determine whether the ECG evolution of the infarction will ultimately be Q wave or NQMI. Is it critical to know what type of MI will ultimately evolve? The pathophysiology of the disease process (unstable plaque) leading to the MI event is similar. Phibbs et al. (18) argue that the distinction between Q wave and NQMI is not useful, because the concept of Q wave and NQMI as a clinical entity is linked to the concept that Q wave MI represents transmural necrosis and NQMI represents subendocardial necrosis. Pathologic studies, however, have consistently demonstrated that about half of all subendocardial infarcts are accompanied by Q waves, and half of transmural infarcts are not. Furthermore, regardless of whether the MI is Q wave or NQMI, the postinfarct history in the modern era is similar. Indeed, prospective, randomized trials comparing conservative to invasive management of NQMI, such as VANQWISH, have not shown a survival benefit in favor of invasive management. It is well recognized that there is a large continuum of clinical presentations with Q wave and NQMI, and that early and late prognosis is related more to the degree of preexisting left ventricular dysfunction and acutely necrotic myocardium, extent of coronary artery disease, propensity to lethal cardiac arrhythmias and rapidity of cardioprotective measures than whether or not the patient develops a Q-wave or NQMI. Thus, early detection of high risk patients with ST segment elevation MI both in the acute and subacute phase (as in VANQWISH) is a critical component of early treatment, not only to reduce infarct size, but also to select those in whom a revascularization procedure would improve the long-term prognosis.

The new definition of MI recommended by the Joint Committee of the European and American Colleges of Cardiology is any degree of myocardial necrosis caused by myocardial ischemia and detected using a sensitive and specific preferred biomarker, such as cardiac troponin, to be labeled an MI (19). Thus, patients with an acute coronary syndrome who were previously ruled out for MI but who were ruled in for unstable angina because they were CK-MB negative but cardiac troponin positive (so-called high risk patients with unstable angina) should now be labeled as having had an MI according to the new definitions.

Conversion of patients with unstable angina who are CK-MB negative and cardiac troponin positive—a sizeable clinical patient subset—to NQMI will result in a larger number of patients with MI being classified as NQMI. The prognosis of the new NQMI category (old NQMI and newly defined NQMI) will be more favorable than the old NQMI category because the prognosis of patients who are CK-MB negative and troponin positive is more favorable than the prognosis of patients who are CK-MB positive and troponin positive. The new definition will have an impact on the design of acute coronary syndrome clinical trials that combine the patient subsets of unstable angina and NQMI (because most of the adverse survival prognosis in patients with unstable angina is contained in the CK-MB negative and cardiac troponin positive group of patients who will now be categorized as NQMI). This will result in more patients with NQMI who require an early decision regarding the need for coronary angiography in the clinical setting. The new VANQWISH results presented by Wexler et al. (3) are timely and provide the clinician with important noninvasive therapeutic approaches for stabilized patients with ST segment elevation NQMI that identify which patients may potentially benefit from an invasive interventional management strategy.
REFERENCES


