VASANT B. PATEL, MD
Department of Cardiology, Cleveland Clinic

DAVID J. MOLITERNO, MD
Department of Cardiology, Cleveland Clinic

THE VETERANS AFFAIRS NON–Q-WAVE INFARCTION STRATEGIES IN HOSPITAL (VANQWISH) STUDY

Invasive vs conservative management of non–Q-wave myocardial infarction

ABSTRACT

In the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, most patients with non–Q-wave myocardial infarction (MI) fared no better with early invasive management (ie, diagnostic angiography within 2 to 3 days, followed by revascularization if indicated) than with a more conservative approach (ie, radionuclide ventriculography and thallium stress testing as initial diagnostic tests). These results should not be construed to diminish the value of early diagnostic angiography, which in patients with non–Q-wave MI provides essential information for determining the need, timing, and method of revascularization. Until more information is available that incorporates contemporary practices and outcomes in patients with non–Q-wave MI, early coronary angiography should remain an acceptable method of risk stratification and should be followed by appropriate medical therapy or revascularization.

In spite of these data, angiography still has an important early role in non–Q-wave MI

IN AN ACUTE myocardial infarction (MI), most physicians in the United States would prefer to send the patient to the catheterization laboratory early if they have access to one, even if the patient has a non–Q-wave MI—ie, one that does not extend through the full thickness of the myocardium. In our opinion, we should continue to do so, even though official guidelines no longer endorse early angiography for patients with non–Q-wave MI, and two recent studies[1,2] seem to cast doubt on this practice.

On first blush, the results of the recently completed VANQWISH (Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital) trial[1] look unfavorable for the early, invasive approach in non–Q-wave MI. Patients who were randomly assigned to go to the catheterization laboratory early (1 to 4 days after enrollment) actually had a trend toward a slightly lower survival rate than those who underwent radionuclide ventriculography and thallium stress testing first, and angiography only if indicated. We should interpret these findings with caution, however. In patients with non–Q-wave MI, angiography quickly provides information essential for determining whether a revascularization procedure is needed, how quickly, and by what method.

EVOLUTION OF THE CONTROVERSY OVER INVASIVE VS CONSERVATIVE MANAGEMENT

Early invasive management endorsed

Non–Q-wave (nontransmural or subendocardial) MIs account for more than half of all MIs. Yet optimal management remains unclear. The 1987 guidelines from the American College of Cardiology and the American Heart Association recommended that all patients with non–Q-wave MIs undergo coronary angiography,[3] though no large-scale, prospective study had tested this approach.

The TIMI-IIIB trial casts doubt on invasive management

In 1994, the TIMI (Thrombolysis in Myocardial Infarction)-IIIB trial,[2] the first sizable clinical trial to test management strategies for non–Q-wave MI, cast doubt on this policy. In this prospective trial, 1,473 patients were randomized to receive either fibrinolysis

or placebo, then separately randomized to undergo either early invasive therapy (early angiography and revascularization) or conservative therapy.

Surprisingly, patients did no better with fibrinolysis than with placebo, and those receiving fibrinolysis had a higher rate of recurrent MIs. In addition, the early invasive approach did not confer an overall benefit: an endpoint event (death, MI, or refractory angina) occurred within 42 days in 16.2% of patients in the early invasive therapy group vs 18.1% of those in the conservative therapy group, but the difference was not statistically significant. Subsequently, the 1996 ACC/AHA guidelines no longer endorsed routine coronary angiography in patients with non–Q-wave MI.[4]

Reasons for the persistence of early invasive management

Nevertheless, most physicians in the United States (but not in Canada or Europe) still favor resorting to angiography early in a non–Q-wave MI.[5] Some reasons why the early invasive strategy is still common:

- Many physicians believe that early invasive management is better, based on the assumption that minimizing the ischemic burden by revascularization will improve short-term and long-term outcome.
- Patients expect aggressive management (a "quick fix").
- We have more catheterization laboratories in this country than in Europe or Canada, and the conservative approach used there may be due to necessity rather than choice.
- Subgroup analysis and later follow-up data from the TIMI-IIIB study showed that some patients clearly benefit from an early invasive approach.[6]

VANQWISH STUDY DESIGN

Addressing this controversy, investigators at 15 Veterans Affairs medical centers undertook the VANQWISH study.

Inclusion criteria

To be included, patients had to have an evolving acute MI and meet all of these criteria:

- No ST segment elevation
- A creatine kinase MB isoenzyme level more than 1.5 times the upper limit of normal for the hospital
- No new Q waves or R waves on serial electrocardiograms
- No persistent or recurrent ischemia at rest while receiving medical therapy
- No severe heart failure.

Treatment

Patients were randomly assigned to either early invasive management or conservative management.

Early invasive management consisted of coronary angiography as the initial diagnostic test, followed by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), as indicated by the TIMI-IIIB management guidelines.

Conservative management consisted of radionuclide ventriculography to assess left ventricular function as the initial diagnostic test, followed by a symptom-limited thallium treadmill exercise test. However, conservatively managed patients also underwent coronary angiography if they had any of the following:

- Recurrent postinfarction angina with ischemic ECG changes
- ST segment depression of at least 2 mm on ECG at peak exercise
- Redistribution defects in two or more different vascular regions on thallium scintigraphy, or one redistribution defect with increased uptake of thallium by the lung.

After patients in the conservative management group underwent angiography, investigators at each study site decided whether to perform revascularization of the culprit stenosis alone, to perform complete revascularization, or to continue medical therapy alone.

Guidelines no longer endorse routine angiography in non–Q-wave MI

Endpoints

The primary endpoint was death or nonfatal MI. These were tallied at hospital discharge, at 1 month after discharge, and at 1 year after discharge. Follow-up visits were at 1 month after discharge and at 3-month intervals thereafter until termination of the trial.

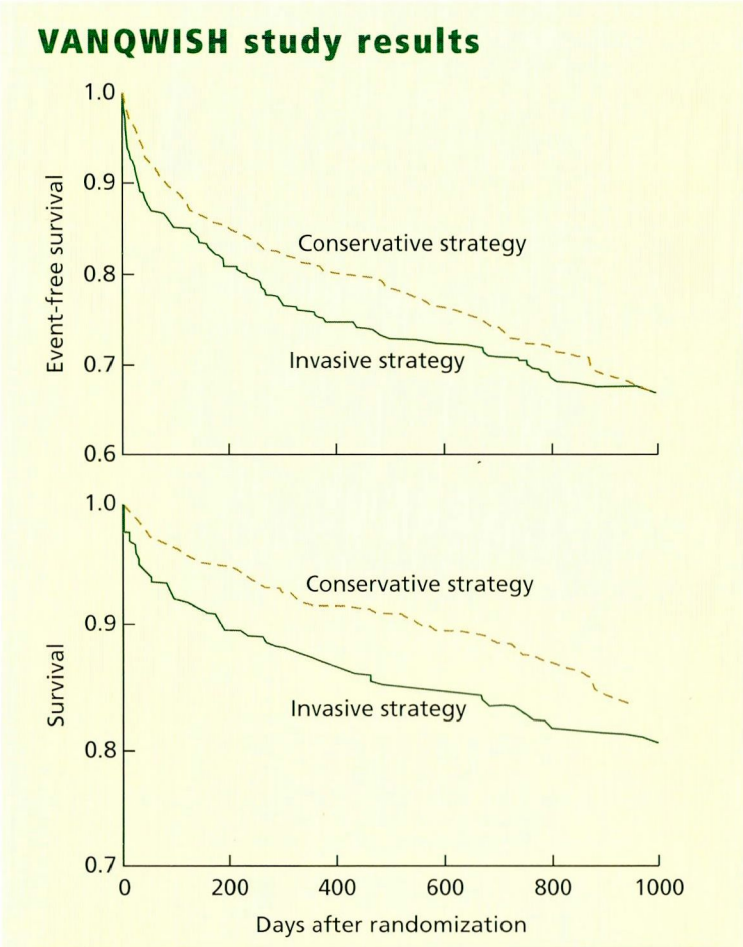

FIGURE 1. (Top) Kaplan-Meier analysis of the probability of event-free survival according to strategy group during 12 to 33 months of follow-up. Events included in the analysis were death and nonfatal myocardial infarction. (Bottom) Probability of survival. Analysis included death from any cause.

VANQWISH STUDY RESULTS

In all, 920 patients were enrolled, 462 in the early invasive management group and 458 in the conservative management group. The mean age was 62 years. More than 97% were men.

Revascularization. Ninety-six percent of the patients in the early invasive management group underwent coronary angiography after randomization, as did 48% of the patients in the conservative management group. However, only 204 (44%) of the early invasive management group underwent PTCA or CABG, as did 33% in the conservative management group had multivessel disease.

The prevalence of multivessel coronary artery disease was high: 74% of patients in the early invasive management group and 80% of patients in the conservative management group.

Cardiac events. At an average follow-up of 23 months, 152 cardiac events (80 deaths and 72 nonfatal MIs) had occurred in 138 patients assigned to early invasive management, and 139 cardiac events (59 deaths and 80 nonfatal MIs) in 123 patients assigned to conservative management. The rate of nonfatal MI or death was higher in the early invasive management group than in the conservative management group at hospital discharge (36 vs 15 events, $P = .004$), at 1 month after discharge (48 vs 26 events, $P = .012$), and at 1 year after discharge (111 vs 85 events, $P = .05$). However, the cumulative mortality rate from all causes did not differ significantly between the two groups at long-term follow-up (FIGURE 1).

The higher early mortality rates in the early invasive management group were predominantly due to a remarkably greater number of deaths in patients undergoing CABG—11 (11.6%) of 95 patients in the early invasive strategy group, vs 3 (3.4%) of 87 patients in the conservative strategy group.

Of importance, no patients died in the early invasive management group who underwent PTCA. Among the patients who underwent PTCA, CABG, or both, the 1-year mortality rate was greater in the early invasive management group than in the conservative management group (10% vs 9%). However, the survival curves had converged by late follow-up.

In addition, patients in the early invasive strategy group had a longer hospital stay (median stay 9.5 days vs 8.2 days for the conservative strategy group, $P=.02$). (The TIMI-IIIB trial reported the opposite.)

The researchers concluded that most patients with non–Q-wave MI do not benefit from routine, early invasive management consisting of coronary angiography and revascularization, and that conservative management is safe and effective.[1]

KEY QUESTIONS UNRESOLVED

Despite these attempts to better define the optimal approach in patients with non–Q-wave MI,[1,2] the issue remains unresolved. The debate continues for several important reasons.

Some subgroups in TIMI-IIIB did benefit from early, invasive management

A closer look at the outcomes at 1 year from the TIMI-IIIB trial[6] revealed that specific groups of patients with non–Q-wave MI did in fact benefit from early invasive management: women, persons age 65 or older, and those with ST segment depression or elevated troponin T or creatine kinase levels at presentation (FIGURE 2).[6] A reduction in death or MI was also observed at 42 days in elderly patients managed aggressively.[2]

These patient subgroups previously have been shown to be at particular risk for subsequent ischemic events, as age, left ventricular dysfunction, and dynamic ST segment changes are additional predictors of worse outcome in acute MI.

In contrast, in the VANQWISH trial, no subgroup appeared to benefit from the early invasive approach. However, only 3% of the VANQWISH patients were women—one of the subgroups that might benefit.

CABG patients in VANQWISH had a very high mortality rate

In the VANQWISH trial, patients with multivessel coronary artery disease were appropriately assigned to undergo CABG. However, the early mortality rate of 11.6% in patients undergoing CABG in the invasive-strategy group was unacceptably high—four times higher than the 3.2% early mortality rate reported from the combined results of previous CABG trials.[7] The mortality rate was of special concern when we consider that high-risk patients with recurrent or persistent ischemia or severe heart failure had been excluded.

Deaths in CABG patients account for most of the early adverse cardiac events in the VANQWISH trial. Most deaths occurred within 30 days of CABG, but the study report did not supply any details. Moreover, many patients from the conservative-strategy group required coronary angiography (48%) and revascularization (33%) during or shortly after the index hospitalization, indicating a high crossover rate. In these patients, the surgical mortality was lower and the number of deaths due to percutaneous revascularizations was higher than in the invasive-strategy group. This finding is disturbing since the baseline demographics of the conservative-treatment and early invasive-treatment groups were similar, and since most revascularizations were done within 30 days of randomization.

With this in mind, and since the survival curves in VANQWISH converge at the end of the follow-up period (1,000 days), the data are insufficient to conclude that long-term survival is improved with initially conservative management.

Survival was higher with conservative management

The VANQWISH trial did not use IIb/IIIa inhibitors or stents

Several large-scale randomized, placebo-controlled trials[8–10] showed that the use of platelet glycoprotein IIb/IIIa inhibitors markedly reduces mortality and myocardial infarctions among patients with non–Q-wave MI and those undergoing a percutaneous intervention. The EPIC trial[8] demonstrated that, in fact, the patients who appear to derive the greatest benefit from glycoprotein IIb/IIIa inhibitors are those with acute coronary syndromes who are undergoing coronary angioplasty.[8]

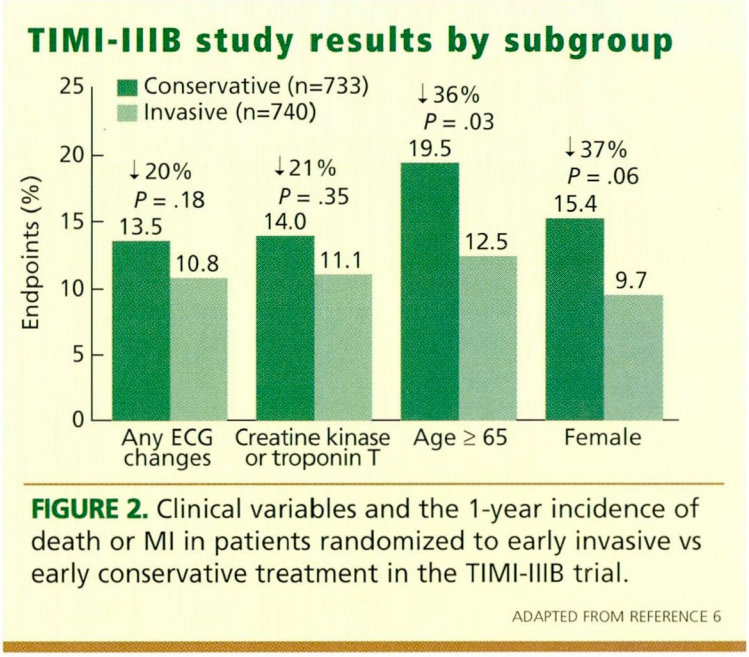

FIGURE 2. Clinical variables and the 1-year incidence of death or MI in patients randomized to early invasive vs early conservative treatment in the TIMI-IIIB trial.

ADAPTED FROM REFERENCE 6

Additionally, coronary stents are now used in at least 60% of percutaneous revascularization procedures in the United States.[11] The combined use of glycoprotein IIb/IIIa inhibitors and coronary stents appears to significantly reduce death, MI, and the need for urgent revascularization as evidenced in the EPISTENT trial.[9]

The VANQWISH trial was performed without the use of coronary stents or glycoprotein IIb/IIIa inhibitors. Thus, patients undergoing CABG or PTCA in contemporary practice have far better outcomes than those observed in the VANQWISH trial.

AREAS FOR FURTHER INVESTIGATION

To further investigate the contribution of IIb/IIIa inhibitors and an early invasive vs conservative approach in the setting of severe unstable angina or non–Q-wave MI, a multicenter, randomized, open-label trial named TACTICS-TIMI 18 is underway. In this trial, approximately 1,720 patients will receive aspirin, heparin, and tirofiban (a glycoprotein IIb/IIIa inhibitor) and will be randomized to either a conservative approach or to catheterization with revascularization (when indicated) within 48 hours. The primary endpoint will be the combined incidence of death, myocardial infarction, and rehospitalization.[10]

More than 60% of PTCA patients now get stents

Further investigation is needed to determine the optimal role of angiography and revascularization in patients with non–Q-wave MI, especially given the benefit of empiric glycoprotein IIb/IIIa inhibitors in patients with unstable angina pectoris not undergoing percutaneous revascularization.[12]

The results of the VANQWISH trial are of concern and intriguing and should be interpreted with caution in limiting the use of angiography in patients with non–Q-wave MI. Early coronary angiography is a common practice in the United States, and one must differentiate between early angiography and early revascularization, since diagnostic angiography in this setting clearly and quickly provides important prognostic and diagnostic information used to determine the need, timing, and method of revascularization.

REFERENCES

1. **Boden WE, O'Rourke RA, Crawford MH, et al.** Outcomes in patients with acute non–Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998; 338:1785–1792.
2. **The TIMI IIIB Investigators.** Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non–Q-wave myocardial infarction: results of the TIMI IIIB Trial: Thrombolysis in Myocardial Ischemia. Circulation 1994; 89:1545–1556.
3. Guidelines for coronary angiography: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Angiography). J Am Coll Cardiol 1987; 10:935–950.
4. **Ryan TJ, Anderson JL, Antman EM, et al.** ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996; 28:1328–1428.
5. **Yusuf S, Flather M, Pogue J, et al.** Variations in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation in six countries. Results from the OASIS (Organization to Assess Strategies for Ischemic Syndromes) registry. Lancet 1998 (in press).
6. **Anderson HV, Cannon CP, Stone PH, et al.** One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non–Q-wave myocardial infarction. J Am Coll Cardiol 1995; 26(7):1643–1650.
7. **Yusuf S, Zucker D, Peduzzi P, et al.** Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Surgery Trialists Collaboration. Lancet 1994; 344:563–570.
8. **Lincoff AM, Califf RM, Anderson KM, et al.** Evidence for prevention of death and myocardial infarction with platelets membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1997; 30:149–156.
9. **The EPISTENT Investigators.** Randomised placebo-controlled and balloon-angioplasty controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. Lancet 1998; 352:87–92.
10. **Cannon CP, Weintraub WS, Demopoulos LA, et al.** Invasive versus conservative strategies in unstable angina and non–Q-wave myocardial infarction following treatment with tirofiban: Rationale and study design of the international TACTICS-TIMI 18 trial. Am J Cardiol 1998; 82(6):731–736.
11. **Malone AP.** Salomon Smith Barney equity research: medical supplies & technology, April 3, 1998-Company Analysis. Guidant Corporation.
12. **The CAPTURE investigators.** Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349:1429–1435.

ADDRESS: *David J. Moliterno, MD, Department of Cardiology, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*