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Stress Test Criteria Used in the Conservative Arm of the FRISC-II Trial Underdetects Surgical Coronary Artery Disease When Applied to Patients in the VANQWISH Trial

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OBJECTIVES We sought to determine whether the stringent stress test criteria for crossover to cardiac catheterization in the conservative arm of the Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II) trial subjected this strategy to a disadvantage by failing to identify patients with surgical coronary artery disease (CAD).

BACKGROUND In FRISC-II, an invasive strategy provided superior outcomes compared with a conservative strategy for patients with acute coronary syndromes. However, compared with the stress test criteria for crossover to catheterization in the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, the FRISC-II criteria were more restrictive and did not use nuclear imaging or pharmacologic stress testing.

METHODS We analyzed the conservative arm of VANQWISH to identify the prevalence of surgical CAD in those patients who met the VANQWISH, but not FRISC-II, criteria for catheterization.

RESULTS Of 385 VANQWISH patients, 90 (23%) met the FRISC-II criteria for catheterization. Another 98 patients (25%) met only VANQWISH stress test criteria (60 patients by exercise and 38 by pharmacologic nuclear stress testing). Among subjects who underwent predischarge angiography, those meeting only VANQWISH stress test criteria had a high prevalence of surgical CAD (51%), comparable to patients who met FRISC-II criteria (54%, $p = 0.805$).

CONCLUSIONS The overly stringent risk stratification protocol for conservative-arm patients in FRISC-II could have failed to identify almost as many patients with surgical CAD as it identified. A lower threshold for catheterization in the FRISC-II conservative patients might have improved their outcomes and therefore diminished the putative benefit of an invasive strategy. (J Am Coll Cardiol 2002;39:1601–7) © 2002 by the American College of Cardiology Foundation

The Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II) trial (1,2) showed significantly fewer deaths or nonfatal myocardial infarctions (MIs) at one year for those patients receiving early cardiac catheterization (invasive strategy), compared with those who underwent medical stabilization followed by stress testing to identify high-risk candidates for cardiac catheterization (conservative strategy). This outcome differed from the findings of the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial (3), which showed fewer deaths or nonfatal MIs for patients with non–Q-wave MI randomized to a conservative strategy versus an invasive strategy at 12 months, and no significant difference in strategies by an average of 23 months. The favorable outcomes of the invasive strategy in FRISC-II have been attributed to a distinct advantage of an invasive approach, especially in the era of stents, glycoprotein IIb/IIIa inhibitors and low molecular weight heparin. However, the one-year mortality benefit of the invasive strategy in the FRISC-II trial has not yet been substantiated by any other trial, including the recent Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction-18 (TACTICS-TIMI-18) trial (4), which, to date, has reported only a six-month advantage of an invasive strategy for cardiovascular outcomes, but not specifically for mortality. These discrepancies, together with the relatively low rates of crossover to early cardiac catheterization in the conservative arm of FRISC-II (10% by 7 days) (1,2) compared with VANQWISH (23% by discharge, which occurred by 8.2 days on average) (3) and TACTICS-TIMI-18 (51% by discharge) (4), raise the possibility that the rigorous stress test criteria used in FRISC-II compro-

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Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/American Heart Association
CABG	= coronary artery bypass graft surgery
CAD	= coronary artery disease
D-MPI	= dipyridamole myocardial perfusion imaging
ECG	= electrocardiographic/ electrocardiogram
EST	= exercise stress test/exercise stress testing
FRISC-II	= Fast Revascularization During Instability in Coronary Artery Disease
METs	= metabolic equivalents
MI	= myocardial infarction
TACTICS-TIMI-18	= Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction-18
VANQWISH	= Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital

mised sensitivity in identifying high-risk patients in the conservative strategy who would have benefited from cardiac catheterization.

It is essential to understand how a conservative strategy is defined in any trial. A strategy that is too conservative might put patients at a disadvantage, not because the invasive approach is superior, but because the conservative strategy is suboptimal. The conservative arm in both FRISC-II and VANQWISH allowed for crossover to cardiac catheterization in patients with refractory postinfarction angina with electrocardiographic (ECG) changes (postinfarction angina). However, the stress test criteria for crossover to cardiac catheterization in the conservative arm of FRISC-II were more strict compared with the criteria in VANQWISH and TACTICS-TIMI-18. In FRISC-II, exercise stress test (EST) criteria required ≥3 mm ST-segment depression (2). Furthermore, nuclear imaging and pharmacologic stress testing were not used. Therefore, the conservative strategy of FRISC-II may have been disadvantaged by its failure to identify a large number of patients with surgical coronary artery disease (CAD), thus exaggerating the purported benefit of the FRISC-II invasive strategy.

The primary aim of this study was to determine the prevalence of surgical CAD among VANQWISH patients who met VANQWISH stress test criteria for crossover to cardiac catheterization but who would not have met FRISC-II criteria.

METHODS

Study source. Only patients in the VANQWISH trial were used in these analyses. In VANQWISH, 920 patients admitted with non–Q-wave MI were randomized to one of two management strategies: an invasive arm, in which patients underwent coronary angiography before discharge, or a conservative arm, in which patients were selected to receive cardiac catheterization based on their failure to be stabilized medically or a subsequent high-risk stress test result. Details of the study protocol have been published previously (3).

Stress test data. Patients in the conservative arm of VANQWISH who were stabilized medically underwent a predischarge, symptom-limited treadmill EST using the standard Bruce protocol with planar thallium scintigraphy, or thallium scintigraphy with single photon emission computed tomography. Patients unable to exercise to a level of five metabolic equivalents (METs) received intravenous dipyridamole with perfusion scintigraphy. There were two EST criteria for patients to crossover to cardiac catheterization: 1) ST-segment depression of ≥2 mm on an ECG recorded during peak exercise or 2) redistribution defects in two or more vascular regions on thallium scintigraphy, or one redistribution defect with increased thallium uptake by the lung (high-risk nuclear perfusion abnormalities).

For patients in the conservative arm of FRISC-II who were stabilized medically, the stress testing criteria varied from those for VANQWISH (2). Patients in FRISC-II underwent predischarge bicycle stress testing and crossed over to cardiac catheterization only for one or more of the following four criteria: 1) ST-segment depression ≥3 mm; 2) limiting chest pain associated with decrease in blood pressure or a low maximum work load (<90 W in men or <70 W in women); 3) ST-segment elevation in leads without pre-existing Q-waves; or 4) T-wave inversion on stress testing.

Study population. We identified patients in the conservative arm of the VANQWISH trial on the basis of whether they would have qualified for crossover to cardiac catheterization by postinfarction angina or FRISC-II EST criteria (FRISC-II-Criteria patients), versus only VANQWISH EST criteria (VANQWISH-EST-Criteria patients) (Fig. 1). Thus the VANQWISH-EST-Criteria group included patients who did not have postinfarction angina but who had ≥2 and <3 mm ST-segment depression alone or <2 mm ST-segment depression with high-risk nuclear perfusion abnormalities. Patients with a history of coronary artery bypass graft surgery (CABG) before enrollment were excluded because of the difficulty in classifying the indication for repeat CABG in these patients and because they were excluded from FRISC-II.

Patients who underwent dipyridamole myocardial perfusion imaging (D-MPI) and had high-risk nuclear perfusion abnormalities were analyzed separately (High-Risk D-MPI patients), as it is not known if these patients would have been able to perform adequately on a bicycle stress test or what the results of the test might have been.

The FRISC-II-Criteria group included those with postinfarction angina or at least one of the FRISC-II stress

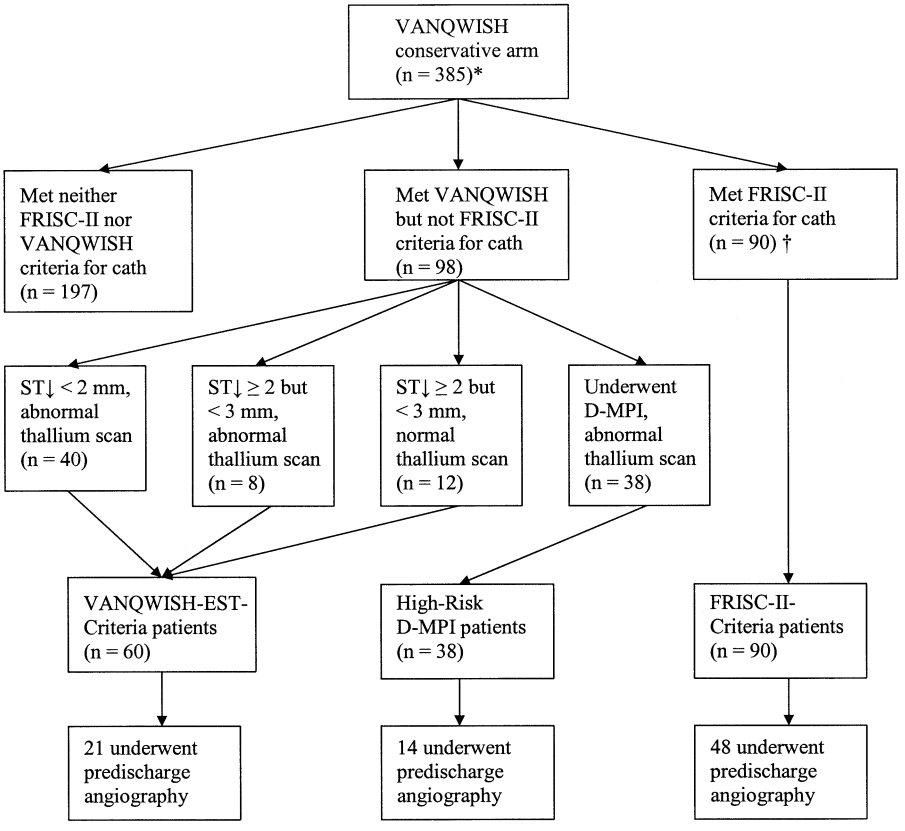

Figure 1. Study design. *There were 458 patients in the conservative arm of VANQWISH; 73 with prior coronary artery bypass graft surgery were excluded from our study. †Eighty-seven of these patients also met VANQWISH criteria for cath; three did not (two patients had ST-segment elevation on exercise stress testing, and one experienced angina at low workload). Cath = cardiac catheterization; D-MPI = dipyridamole myocardial perfusion imaging; FRISC-II = Fast Revascularization During Instability in Coronary Artery Disease trial; ST ↓ = ST-segment depression; VANQWISH = Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital trial.

test criteria for coronary angiography. Patients who developed T-wave inversions during EST were not identified in the VANQWISH database, and therefore could not be included in the FRISC-II-Criteria group. A decrease in blood pressure with EST was not quantified in the FRISC-II study. In our analysis we used a systolic blood pressure <90 mm Hg during peak exercise or a systolic blood pressure during peak exercise that dropped by ≥10 mm Hg compared with the systolic blood pressure during a warm-up phase, as defined in VANQWISH (3). In FRISC-II, patients who achieved <90 W (70 W for women) during bicycle EST and who had angina qualified for cardiac catheterization. Because patients in the VANQWISH trial underwent treadmill EST in which exercise capacity was measured in METs, the thresholds for low workload in watts were converted to METs (5).

Outcomes. The primary outcome was the number of patients from each comparison group who had surgical CAD, defined as a Class I indication for CABG by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for CABG (6). We chose surgical CAD as the primary end point, as patients with this finding would be the most likely to benefit from revascularization. Additional outcomes analyzed were clinical events (all-cause death [death], cardiac death, nonfatal MI and a composite end point of death or nonfatal MI). Analysis of angiography results was performed only for patients who underwent catheterization before discharge, to avoid the potential bias of including later catheterization results obtained because of progression of CAD or new acute coronary events.

Statistical analysis. Continuous variables were compared with *t* tests, and categorical variables with chi-square (two-sided) and Fisher's exact (two-tailed), as appropriate. Odds ratios were derived for all comparisons and exact confidence intervals were used when required. Because the goal of the study was to compare angiographic characteristics by stress test results in a group of patients without other clinical indications for catheterization (regardless of other markers of coronary disease) and because of the limited number of primary outcome events, we limited our analyses to univariate comparisons. We used STATCALC (EpiInfo, Centers for Disease Control and Prevention, Atlanta, Georgia) and SPSS version 10.0 (SPSS, Inc., Chicago, Illinois) to perform the statistical analyses.

RESULTS

Patients. Out of 458 conservative-arm patients in VANQWISH, 73 were excluded on the basis of prior CABG,

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Table 1. Baseline Clinical Characteristics of the VANQWISH Patients in the Conservative Arm Who Qualified for Cardiac Catheterization According to Comparison Group*†

Characteristic	FRISC-II-Criteria (n = 90)	VANQWISH-EST-Criteria (n = 60)	High-Risk D-MPI (n = 38)
Clinical characteristics (no. [%], except where noted otherwise)			
Age (yrs)	61 ± 10‡	58 ± 10§	66 ± 10‡§
Male	85 (94)	60 (100)	37 (97)
Smoking			
Never smoked	15 (17)	7 (12)	5 (13)
Prior smoker	38 (42)	17 (28)	16 (42)
Current smoker	37 (41)	36 (60)	17 (45)
Family history of CAD	35 (39)	26 (43)§	9 (24)§
Hypertension	47 (52)	26 (43)§	25 (66)§
High cholesterol level	13 (14)	6 (10)	7 (18)
Diabetes mellitus	24 (27)‡	8 (13)§	17 (45)‡§
Prior MI	34 (38)	19 (32)	19 (50)
Cardiac disease other than CAD	7 (8)	7 (12)	6 (16)
Peripheral vascular disease	17 (19)	7 (12)	10 (26)
Neurologic disorder	9 (10)	6 (10)	8 (21)
Angina in 3 wk before randomization	45 (50)	26 (43)	17 (45)
PCI >3 months before randomization	10 (11)	2 (3)	3 (8)
Baseline ejection fraction (%)	49 ± 13	49 ± 13	46 ± 14
Medications 1 wk before randomization			
Nitrates	23 (26)	13 (22)	14 (37)
Beta-blocker	14 (16)‡	11 (18)	13 (34)‡
Calcium channel blocker	29 (32)	14 (23)	13 (34)
Aspirin	34 (38)	20 (33)	18 (47)
Lipid-lowering drug	9 (10)	3 (5)	5 (13)
ACE inhibitor	15 (17)‡	12 (20)	13 (34)‡
Diuretics	12 (13)‡	9 (15)	11 (29)‡
Digitalis	7 (8)	7 (12)	2 (5)

*Plus-minus values are means ± SD. †$p > 0.05$ for all baseline characteristics comparing VANQWISH-EST-Criteria patients to FRISC-II-Criteria patients. ‡$p < 0.05$ comparing High-Risk D-MPI patients to FRISC-II-Criteria patients. §$p < 0.05$ comparing High-Risk D-MPI patients to VANQWISH-EST-Criteria patients.

ACE = angiotensin converting enzyme; CAD = coronary artery disease; D-MPI = dipyridamole myocardial perfusion imaging; MI = myocardial infarction; PCI = percutaneous coronary intervention.

leaving 385 patients. Of the 385 patients, 222 (58%) in the conservative group of VANQWISH underwent predischarge EST, and 125 (32%) underwent D-MPI. The distribution of the number of patients meeting each criterion for crossover to cardiac catheterization are given in Figure 1. Sixty of 385 patients (16%) met VANQWISH EST criteria for cardiac catheterization: 20 by exercise ECG findings with or without nuclear perfusion criteria, and 40 by nuclear perfusion criteria alone. Of these 60 patients, 21 actually received predischarge coronary angiography. An additional 38 patients (10%) qualified for cardiac catheterization by high-risk D-MPI, of whom 14 received predischarge coronary angiography. Ninety patients (23%) met FRISC-II criteria: 70 with postinfarction angina and 20 with abnormal stress test results. Of these 90 FRISC-II-Criteria patients, 48 received predischarge coronary angiography.

As noted in Figure 1, not all patients who met VANQWISH EST criteria actually underwent coronary angiography before discharge. Although not all the reasons for this are clear, patients who were referred for predischarge cardiac catheterization were more likely to have a family history of CAD (62% vs. 33%, $p = 0.033$) and a lower ejection fraction (42 ± 12% vs. 53 ± 11%, $p = 0.001$). Similarly, not all subjects meeting FRISC-II criteria received angiography. However, there were no significant differences in baseline clinical characteristics between the patients in this group who did and did not undergo predischarge angiography.

Baseline characteristics are shown for each of the three comparison groups (Table 1). There were no significant differences between FRISC-II-Criteria patients and VANQWISH-EST-Criteria patients. High-Risk D-MPI patients were older and were more likely to have diabetes than patients in the other two groups ($p < 0.05$ for these comparisons).

Coronary angiography results. Coronary angiographic results and the primary outcome (Class I indication for CABG) are shown in Table 2. Patients in the VANQWISH-EST-Criteria group demonstrated a high prevalence of surgical CAD (12 of 21 patients, or 57%), as did High-Risk D-MPI patients (6 of 14 patients, or 43%). Both of these outcomes were similar to the prevalence of surgical CAD in VANQWISH patients meeting the FRISC-II criteria (26 of 48 patients, or 54%, Table 2, $p > 0.4$). When the analysis was repeated for only those 10 FRISC-II-Criteria patients who met FRISC-II stress test criteria (excluding the 38

Table 2. Coronary Angiography Results of Patients Who Underwent Angiography Before Discharge

Characteristic	FRISC-II-Criteria	VANQWISH-EST-Criteria	High-Risk D-MPI
Number of patients	90	60	38
Number of patients undergoing angiography before discharge	48	21	14
Angiography findings—no. (%)*			
No significant CAD	1 (2)	1 (5)	0 (0)
Single-vessel disease	12 (25)	5 (24)	4 (29)
Two-vessel disease	9 (19)	4 (19)	4 (29)
Three-vessel disease	20 (42)	9 (43)	4 (29)
Left main disease (± one-to-three vessel CAD)	5 (10)	2 (10)	2 (14)
Class I indication for CABG by class—no. (%)†‡	26 (54)	12 (57)	6 (43)
CABG before discharge—no. (%)§	19 (40)	4 (19)	3 (21)

*One patient from the FRISC-II-Criteria group is missing angiography results. †FRISC-II-Criteria patients versus VANQWISH-EST-Criteria patients: p = 0.819; Odds ratio (95% confidence intervals) = 0.89 (0.28 to 2.81). ‡FRISC-II-Criteria patients versus High-Risk D-MPI patients: p=0.456. Odds ratio (95% confidence intervals) = 1.58 (0.41 to 6.17). §p values ≥0.095 for all comparisons for patients who underwent CABG before discharge.

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; D-MPI = dipyridamole myocardial perfusion imaging.

patients with postinfarction angina), 8 (80%) had surgical CAD (p values for all comparisons ≥0.1). Of the 12 patients meeting VANQWISH EST criteria who had surgical CAD, 5 met VANQWISH ECG criteria of ≥2 mm ST-segment depression (with or without abnormal nuclear perfusion imaging), and 7 had only high-risk nuclear findings (with <2 mm ST-segment depression on EST).

Revascularization. We sought to determine whether the less stringent stress test criteria in VANQWISH translated not only to identifying more patients with surgical CAD, but also to a comparable surgical revascularization rate of these patients. The FRISC-II-Criteria patients had the highest rate of predischarge CABG among the three groups, although none of the differences were statistically significant (all p values >0.095; Table 2). Repeat analysis including only FRISC-II-Criteria patients with abnormal EST results (without postinfarction angina) also showed no statistically significant differences (all p values >0.1)

Clinical events at 12 months. Patients in the FRISC-II-Criteria group had the highest overall one-year event rates (Table 3). These event rates in the FRISC-II Criteria patients were higher for all outcomes when compared with the rates in patients meeting the VANQWISH EST criteria and were statistically significant for nonfatal MI (p = 0.001) and combined events (p < 0.001).

The all-cause mortality rate of the FRISC-II-Criteria patients was less than that of patients with high-risk D-MPI, although this was not statistically significant (p = 0.14). On the other hand, FRISC-II-Criteria patients had a higher nonfatal MI rate (p = 0.008). There was no significant difference in overall event rate between these two groups (p = 0.165).

Among FRISC-II-Criteria patients, the majority of combined events (27 of 30) occurred in patients with postinfarction angina; only 3 of 30 events occurred in patients with abnormal stress test results.

DISCUSSION

Study results and significance. Our findings demonstrate that a substantial number of patients in VANQWISH who did not meet FRISC-II criteria for undergoing cardiac catheterization, but who met the VANQWISH EST criteria, had surgical CAD. Similarly, those with high-risk D-MPI had a high prevalence of surgical CAD. This raises the possibility that the strict ECG stress test criteria and the lack of pharmacologic stress testing or nuclear imaging in FRISC-II resulted in an overly low-sensitivity risk stratification tool, which might have partly accounted for the superior outcomes of the invasive strategy in FRISC-II.

Although the FRISC-II criteria were not as sensitive in identifying the anatomical presence of surgical CAD in VANQWISH patients, the criteria did identify, as expected, the patients at the highest risk of the combined end point of death or nonfatal MI. This is not surprising, given that the most clinically high-risk patients (postinfarction angina) were included in this group. However, when these patients were excluded, there were no differences in clinical event rates between FRISC-II-Criteria patients (with only abnormal EST results) and either VANQWISH-EST-Criteria patients or High-Risk D-MPI patients, although the number of subjects was very small. Thus, the FRISC-II EST criteria may have failed to identify both a large proportion of patients with surgical CAD and a significant number with subsequent adverse events.

Degree of ST-segment depression during EST. Twelve of the 21 (57%) patients in VANQWISH with <3 mm

Table 3. Clinical Outcomes of the Comparison Groups at 12 Months After Randomization

Clinical Outcome No. (%)	FRISC-II-Criteria (n = 90)	VANQWISH-EST-Criteria (n = 60)	High-Risk D-MPI (n = 38)	Met None of the Cardiac Catheterization Criteria (n = 197)
Death	8 (9)	2 (3)	7 (18)	11 (6)
Cardiac death	5 (6)	1 (2)	4 (11)	4 (2)
Nonfatal MI	23 (26)	3 (5)	2 (5)	17 (9)
Combined events	30 (33)	4 (7)	8 (21)	23 (12)

See text for p values.

D-MPI = dipyridamole myocardial perfusion imaging; MI = myocardial infarction.

ST-segment depression who qualified for crossover to cardiac catheterization by the VANQWISH EST criteria were found to have surgical CAD. The use of less stringent ECG criteria is in accord with current guidelines from the ACC/AHA, which state that ST-segment depression ≥1 mm during EST is a valid predictor of adverse outcome in the postinfarction population (7). Prior studies have demonstrated that ≥1 mm ST-segment depression on stress testing after an acute coronary event is more sensitive for detecting three-vessel or left main CAD or for predicting subsequent cardiac events, compared with ≥2 mm or ≥3 mm ST-segment depression (8,9).

Incremental benefit of radionuclide imaging. In our analysis, more than half of the VANQWISH-EST-Criteria patients with a Class I indication for CABG (7 of 12) were patients with <2 mm ST-segment depression but an abnormal thallium scan, thus supporting the important role of radionuclide imaging in the prognostication of postinfarction survivors. The incremental benefit of nuclear scintigraphy over exercise ECG alone in detecting multivessel CAD and predicting cardiac events (particularly for patients with resting ECG abnormalities) has been previously demonstrated (10,11).

Prognostic utility of pharmacologic stress testing. We found that 32% of patients in the conservative group of VANQWISH required pharmacologic stress testing. This is consistent with other estimates indicating that approximately 30% of the postinfarction population are unable to perform an exercise stress test (12). Numerous studies have shown these patients to be at higher risk for cardiac events, justifying further risk stratification with pharmacologic stress testing (11,12). In VANQWISH, although patients with a high-risk D-MPI had a lower rate of nonfatal MI, they had a non-significantly higher mortality rate and a comparably high combined end point rate compared with the FRISC-II-Criteria patients. The results that exercise testing would yield in this group of patients are unknown, but it is reasonable to postulate that many of them would not be able to exercise sufficiently to identify inducible ischemia.

Comparison with the TACTICS-TIMI-18 trial. In the TACTICS-TIMI-18 trial (4), 2,220 patients with non-ST-segment elevation MI or unstable angina were randomized to invasive and conservative strategies. Stress test criteria for crossover to cardiac catheterization in the conservative arm included ≥2 mm ST-segment depression on EST (≥1 mm if associated with angina), as well as radionuclide or echocardiographic imaging and pharmacologic stress testing in appropriate patients. Fifty-one percent of the conservative arm patients underwent in-hospital coronary angiography, a much larger percentage than in both FRISC-II (10% by seven days) (1,2) and VANQWISH (23% by discharge) (3). Despite this, the study demonstrated a benefit of an invasive strategy. However, this benefit was predominantly in the high-risk patient subgroups and primarily for the outcome of MI. This latter finding is important because tirofiban was administered in 94% of the interventional procedures in the invasive arm, but only 59% of the procedures in the conservative arm. There was no significant mortality difference detected at six months between the two strategies in this study, although the study was not powered to detect a mortality difference, and longer-term follow-up is not yet available.

Study limitations. Because of its small sample size, our study may have failed to identify small but significant differences for surgical CAD among comparison groups. Nonetheless, we have established that a large number of the VANQWISH conservative-arm patients with surgical CAD would not have been identified had FRISC-II criteria been used, regardless of whether this difference was statistically significant. The clinical outcome comparisons are also limited by the sample size and inability to perform multivariable adjustment.

T-wave inversions on exercise ECG was a criterion for angiography in FRISC-II (2), but this variable was not recorded in the VANQWISH trial. Hence, the number of patients not meeting the FRISC-II stress test criteria may have been overestimated. However, we found no studies that support that T-wave inversions on exercise ECG, a nonspecific finding (7,8), is useful in the risk stratification of patients following acute coronary syndromes.

Our analysis of coronary anatomy includes only 35 of 98 (36%) of the patients who met the VANQWISH criteria or D-MPI criteria for crossover to cardiac catheterization, and 48 of 90 (53%) of the patients meeting FRISC-II criteria; the remaining patients did not receive cardiac catheterization despite qualifying. Potential reasons for this include perceived differences in comorbid conditions among patients or differences in patient and physician preference, although such reasons were not documented in VANQWISH. Therefore, we could not assess the true sensitivity and specificity of the VANQWISH criteria for identifying significant CAD. However, even if none of the patients excluded had surgical disease, the prevalence of surgical disease would still be relatively high in both VANQWISH-EST-Criteria patients (12 of 60, or 20%) and High-Risk D-MPI patients (6 of 38, or 16%).

Because not all patients underwent cardiac catheterization, it is also possible that referral bias skewed our results. However, there were no differences with respect to clinical characteristics between those who did and did not undergo catheterization in the FRISC-II group, and the only differences in the VANQWISH-EST-Criteria patients who underwent predischarge cardiac catheterization were a higher prevalence of family history of CAD and a lower ejection fraction. It is possible that these differences increased the degree of coronary disease in the group who underwent catheterization.

Despite the adoption of more sensitive risk stratification techniques in VANQWISH, the one-year death or nonfatal MI rate in the conservative arm of VANQWISH (18.6%) (3) was higher than in FRISC-II (14.1%) (1). Although this

observation does not support our hypothesis, extreme caution must be used in comparing results across trials. This discrepancy more likely reflects other differences between the VANQWISH and FRISC-II trials, such as the patient populations (VANQWISH patients had a higher clinical risk profile), adjuvant therapies (use of glycoprotein IIb/IIIa inhibitors and low molecular weight heparin in FRISC-II) and a higher complication rate of revascularization in VANQWISH.

Based on the results of TACTICS-TIMI-18, it could be argued that an invasive approach is superior and that risk stratification by stress testing is not needed. However, this has been clearly demonstrated only in higher-risk patients. Centers that prefer risk stratification for low-risk patients or that lack facilities to support a routine invasive strategy for patients who are not clearly high-risk (13) should use a risk stratification protocol similar to that of VANQWISH or TACTICS-TIMI-18, which includes radionuclide imaging, pharmacologic testing and more sensitive stress ECG criteria for ischemia, as advocated by ACC/AHA guidelines (10).

Conclusions. Our results of coronary angiographic findings in VANQWISH suggest that the more restrictive stress test criteria used in FRISC-II may have failed to identify a substantial number of patients with surgical CAD who might have benefited from early cardiac catheterization and revascularization. Our study supports the need for appropriate risk-stratification techniques should physicians choose to perform provocative testing in subgroups at low risk based on clinical characteristics or among patients who are not clearly high-risk and who present to medical centers without on-site catheterization facilities.

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