Cost-Effectiveness of a Conservative, Ischemia-Guided Management Strategy After Non–Q-Wave Myocardial Infarction

Results of a Randomized Trial

Paul G. Barnett, PhD; Shuo Chen, PhD; William E. Boden, MD; Bruce Chow, MS; Nathan R. Every, MD, MPH; Philip W. Lavori, PhD; Mark A. Hlatky, MD

Background—Use of coronary angiography after myocardial infarction has been controversial, with some physicians advocating routine use and others advocating selective use only after documentation of residual myocardial ischemia. The effects of these strategies on economic outcomes have not been established.

Methods and Results—We analyzed data from a randomized, controlled clinical trial conducted in 17 Department of Veterans Affairs hospitals that enrolled 876 clinically uncomplicated patients 24 to 72 hours after an acute non–Q-wave myocardial infarction. The routine invasive strategy included early coronary angiography with revascularization based on established guidelines. The conservative, ischemia-guided strategy included noninvasive testing with radionuclide ventriculography and exercise thallium scintigraphy, followed by coronary angiography in patients with objective evidence of myocardial ischemia. We measured the cost of hospitalization and outpatient visits and tests during follow-up and calculated the incremental cost-effectiveness ratio. The conservative, ischemia-guided strategy had lower costs than the routine invasive strategy, both during the initial hospitalization ($14,733 versus $19,256, \( P < 0.001 \)) and after a mean follow-up of 1.9 years ($39,707 versus $41,893, \( P = 0.04 \)). The hazard ratio for death was 0.72 (confidence limits, 0.51 to 1.01) in the conservative strategy. The conservative strategy had lower costs and better outcomes in 76% of 1000 bootstrap replications, and a cost-effectiveness ratio below $50,000 per year of life added in 96% of replications.

Conclusions—A conservative, ischemia-guided strategy of selective coronary angiography and revascularization for patients who develop objective evidence of recurrent ischemia is more cost-effective than a strategy of routine coronary angiography after uncomplicated non–Q-wave myocardial infarction. (Circulation. 2002;105:680-684.)

Key Words: cost-benefit analysis • myocardial infarction • angiography • tests

After initial stabilization and treatment of an acute myocardial infarction, clinicians must address the management of the patient’s underlying coronary artery disease. Two distinct approaches have emerged, termed invasive and conservative,1,2 invasive and noninvasive,3 or routine invasive and selective invasive. The routine invasive strategy uses early coronary angiography to guide additional management and often leads to coronary revascularization. The conservative, ischemia-guided strategy uses noninvasive functional testing to guide additional management, reserving coronary angiography for selected patients with evidence of ischemia on stress testing. These different clinical strategies have been compared in several recent randomized trials in patients with non–Q-wave myocardial infarction or non–ST-segment elevation acute coronary syndrome with mixed results.1–4
Methods

This was a prospectively designed substudy of the multicenter randomized Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial. The design" and main results of the VANQWISH study have been published. Briefly, eligible patients had symptoms and enzymatic evidence of an acute myocardial infarction but without development of new, abnormal Q-waves (ie, 0.04 seconds in duration in 2 contiguous leads) on serial ECGs over the first 48 to 72 hours. Patients with persistent or recurrent ischemia at rest or persistent heart failure were excluded, as were patients with other serious coexisting illness.

After providing written informed consent, patients were randomized to either a routine invasive or conservative, ischemia-guided strategy. Patients assigned to the routine invasive strategy underwent coronary angiography with coronary revascularization recommended according to previously established guidelines. Patients assigned to the conservative, ischemia-guided strategy underwent noninvasive testing, which consisted of radionuclide ventriculography as the initial test, followed by exercise thallium perfusion scintigraphy. Patients unable to exercise underwent intravenous dipyridamole thallium perfusion scintigraphy. Coronary angiography was recommended in the conservative, ischemia-guided strategy only if the patient had either postinfarction angina with new ischemic ECG changes or ST depression of at least 2 mm on exercise ECG or reversible defects in 2 or more coronary vascular territories on thallium scintigraphy.

Cost of Care

To measure utilization, we linked the VANQWISH database to the Veterans Affairs (VA) patient treatment file (for hospital stays) and the VA national patient care database (for outpatient visits). We used a microcosting method to translate the resource consumption profile documented in the case report form during the initial hospital stay into cost. We estimated the parameters of the cost function using data from the Myocardial Infarction Triage and Intervention (MITI) registry of 6060 patients with acute myocardial infarction from 19 Seattle-area hospitals during the period from 1988 to 1994. We applied VANQWISH exclusion criteria to the MITI data by excluding patients who had recurrent pain, congestive heart failure, resuscitation after cardiac arrest, or coronary artery bypass graft surgery within the last 3 months. We performed a linear regression of the MITI data, with the log of cost-adjusted charges as the dependent variable and the following independent variables: length of stay; use of cardiac catheterization, coronary angioplasty, and bypass surgery; death in the hospital; or admission after 1991. Hospital lengths of stay in VANQWISH were ~30% longer than the stays in the MITI registry. Because length of stay was a predictor of total cost in the MITI, a simple regression model would estimate VA costs to be substantially higher than those of private hospitals. Recent evidence suggests, however, that total cost of VA hospitalizations is not significantly different from that of non-VA providers. Therefore, we assumed that the cost for a patient with a given percentile of length of stay in the VA hospital would be the same as the cost for a patient with the same percentile of length of stay in an MITI hospital. The final regression model used the rank of length of stay as an independent variable, with a restricted cubic spline function that was a third degree polynomial with two knots. We applied the cost function developed in the MITI database to the estimate of the cost of initial VA stays after applying the smearing estimator for retransforming log costs to total costs.

The cost of hospital stays during follow-up was estimated using the national mean Medicare reimbursement rate for that diagnosis-related group. We assigned a hospital cost of $5362 per diagnosis-related group relative value weight, adjusted by $2050 for every day that the stay deviated from the VA mean length of stay for that diagnosis-related group. We estimated the cost of VA physician services by the average reimbursement provided for inpatient Medicare physician services in each diagnosis-related group, adjusted for length of stay.

We assigned outpatient visits to 1 of 12 categories and estimated per-visit cost as the VA national mean cost. We obtained the cost of contract care paid for by the VA from the fee basis file. When patients were hospitalized in non-VA hospitals, total charges were obtained and multiplied by the hospital specific cost-to-charge ratio.

Total medical costs per patient were measured as the sum of initial hospital costs and follow-up hospital and outpatient costs through the end of protocol follow-up (December 31, 1996). All costs were adjusted to 1997 dollars and discounted at 3% per year of follow-up, starting at the date of randomization. Total costs were compared using the Wilcoxon rank-sum method. The relationship between total costs and length of follow-up were displayed graphically using a modification of the method proposed by Ettione. All analyses were performed on an intention-to-treat basis.

Cost-effectiveness was estimated using the observed, within-trial experience. The difference in the total costs between the invasive and conservative strategies was divided by the difference in discounted life years of survival of these 2 groups. The precision of the cost-effectiveness estimate was assessed by the bootstrap method using 1000 resamplings of the patients assigned to either the invasive or conservative strategy.

Sensitivity Analysis

We tested whether study results would be affected by use of an alternative method of cost measurement on the basis of the VA Decision Support System. We obtained data from 4 VA hospitals on 1150 admissions for acute myocardial infarction from 1997 to 1998 and estimated the cost using the same regression techniques used with the MITI data.

The VA-based cost of subsequent hospital stays was estimated using a cost function based on the 1996 VA Cost Distribution Report. Cost was regressed on mean diagnosis-related group weight and deviation from the diagnosis-related group mean length of stay. The resulting regression coefficients were used to estimate VA inpatient cost.

To estimate lifetime cost-effectiveness ratios, we projected the remaining life expectancy of patients alive at the end of follow-up using the 1998 United States life tables. We projected future health-care costs for each patient on the basis of the costs incurred by the patients assigned to the conservative or invasive strategy after either 18 or 24 months of follow-up.

Results

Of 920 patients randomized in VANQWISH, 876 (95%) were enrolled in VA hospitals and included in the economic analysis. Of these patients, 435 were randomly assigned to the conservative strategy and 441 to the invasive strategy. At baseline, the randomized groups had similar clinical characteristics. Mean age was 61 years, 98% were male, 43% had a prior myocardial infarction, and 25% had diabetes.

Patients assigned to the invasive strategy were more likely to undergo coronary angiography, angioplasty, and bypass surgery during the initial hospitalization and had a longer initial hospital stay (Table 1). As a result of this more intensive use of resources, the cost of initial hospitalization was 31% higher in patients assigned to the invasive strategy than in patients assigned to the conservative strategy, $19 256 versus $14 733, P<0.001 (Table 2).

Over a mean follow-up of 23 months, subsequent use of medical care by patients assigned to the invasive strategy was slightly, but not significantly, lower than that of patients assigned to the conservative strategy (Table 1). Follow-up costs in the patients assigned to the invasive strategy were 9% lower than those assigned to the conservative strategy, but this difference was not significant (Table 2).
The higher initial cost of treatment in the patients assigned to the routine invasive strategy (by $4523) was only partially offset by lower follow-up costs (by $2338). The total cost during the trial, therefore, remained significantly higher in the patients assigned to the invasive strategy ($41 893 versus $39 707, *P*<.0001). The costs in later follow-up (Figure) remained lower in the patients assigned to the conservative, ischemia-guided strategy.

**Cost-Effectiveness**

As previously reported, the survival of patients assigned to the conservative strategy was significantly better than that of patients assigned to the invasive strategy through 1 year of follow-up, with a hazard ratio for death of 0.72 (confidence limits, 0.51 to 1.01). This translates to 1.86 life years of survival in the conservative management group versus 1.79 life years in the invasive group over the 2 years of observed follow-up.

We used the bootstrap method with 1000 random samples of patients to estimate the precision of the cost-effectiveness calculation. In 76.5% of samples, the conservative strategy had lower costs and better outcomes. In 12.9%, the conservative strategy had higher costs and better outcomes, with a cost-effectiveness ratio below the $50 000 threshold. In another 6.6% of replications, the conservative strategy had lower costs and worse outcomes but was preferred because the cost-effectiveness ratio for the invasive strategy was above the $50 000 threshold. Thus, in 96% of replications, the conservative strategy would be preferred at a cost-effectiveness threshold of $50 000 or less per year of life saved.

**Sensitivity Analysis**

The conservative strategy was cost-effective compared with any critical threshold between $25 000 and $100 000 per life year added. It remained cost-effective when a 5% discount rate was used instead of 3%.

Our findings were not sensitive to the cost-determination method. When we estimated costs based solely on VA sources, the cost of the initial stay in patients assigned to the invasive strategy ($18 293) was still greater than that of patients assigned to the conservative strategy ($13 474, *P*<.0001), as were the mean total costs over the entire study ($41 985 versus $39 531). Most importantly, cost-effectiveness results were unchanged, with conservative strategy more cost-effective in 96.1% of replications when judged against a critical cost-effectiveness threshold of $50 000 or less per year of life saved.

We also projected the future life expectancy and health-care costs of patients alive at the end of follow-up. The projected survival in the conservative management strategy (13.20 life years) remained higher than in the invasive strategy (12.31 life years). When future health-care costs

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**TABLE 1. Utilization of Health Services by Study Subjects Over a Mean Follow-Up Period of 23 Months**

<table>
<thead>
<tr>
<th>Service</th>
<th>Conservative Strategy (n=435)</th>
<th>Invasive Strategy (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hospital stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average days of stay</td>
<td>9.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Catheterization</td>
<td>23.4%</td>
<td>93.9%*</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>6.9%</td>
<td>18.8%*</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>7.1%</td>
<td>13.6%*</td>
</tr>
<tr>
<td>Subsequent short-term hospital stays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stays</td>
<td>1.85</td>
<td>1.80</td>
</tr>
<tr>
<td>Number of days of stay</td>
<td>14.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Subsequent revascularizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioplasty</td>
<td>5.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>11.7%</td>
<td>6.8%*</td>
</tr>
<tr>
<td>Rehabilitation, mental health, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-term care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stays</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of days of stay</td>
<td>5.77</td>
<td>7.89</td>
</tr>
<tr>
<td>VA outpatient care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of visits</td>
<td>64.4</td>
<td>62.7</td>
</tr>
<tr>
<td>Non-VA hospital stays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stays</td>
<td>0.08</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*P*<.01 by Wilcoxon rank-sum test.

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**TABLE 2. Average Costs Incurred by Study Subjects Over a Mean Follow-Up Period of 23 Months**

<table>
<thead>
<tr>
<th>Service</th>
<th>Conservative Strategy (n=435)</th>
<th>Invasive Strategy (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hospital stay</td>
<td>14 733</td>
<td>19 256*</td>
</tr>
<tr>
<td>Subsequent short-term hospital stays</td>
<td>15 377</td>
<td>13 780</td>
</tr>
<tr>
<td>Rehabilitation, mental health, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-term care</td>
<td>2030</td>
<td>2055</td>
</tr>
<tr>
<td>VA outpatient care</td>
<td>5978</td>
<td>5784</td>
</tr>
<tr>
<td>Non-VA hospital stays</td>
<td>1280</td>
<td>511</td>
</tr>
<tr>
<td>VA contract care</td>
<td>309</td>
<td>506</td>
</tr>
<tr>
<td>Subtotal, follow-up care</td>
<td>24 974</td>
<td>22 636</td>
</tr>
<tr>
<td>Total, initial stay and follow-up</td>
<td>39 707</td>
<td>41 893†</td>
</tr>
</tbody>
</table>

*P*<.001, †*P*<.037.
were projected on the basis of patterns observed after 18 months, the slightly lower late follow-up costs in the invasive group (by $94 per month) led to projected lifetime costs of $153 550 in the conservative group and $135 859 in the invasive group. The corresponding cost-effectiveness ratio was $19 952 per year of life saved for the conservative strategy. When future costs were projected on the basis of patterns observed after 24 months, however, the late follow-up costs in the conservative strategy were lower by $87 per month and led to projected lifetime costs of $132 348 in the conservative strategy and $139 003 in the invasive strategy. The corresponding cost-effectiveness of the conservative strategy was dominant, with lower costs and better survival than the invasive strategy.

**Discussion**

The principal finding of this randomized trial was that a conservative, ischemia-guided approach to coronary angiography with selective myocardial revascularization in patients with non–Q-wave myocardial infarction was more cost-effective than an invasive management strategy using routine coronary angiography. Over an average 2-year follow-up, cumulative medical costs were significantly lower in conservatively managed patients and clinical events were less frequent as well. These results suggest that coronary angiography and revascularization after non–Q-wave myocardial infarction are most cost-effective when limited to patients with objective evidence of spontaneous or stress-induced myocardial ischemia.

Characterization of the patient’s risk and selection of therapies to reduce that risk are major goals of management after early treatment of the myocardial infarction. Coronary angiography permits the identification of patients who would have increased survival after coronary revascularization, namely, those with left main or severe 3-vessel coronary artery disease, especially in the setting of reduced left ventricular function. Patients with severe coronary artery disease are also likely to have abnormal findings on stress testing, however, so an alternative approach to risk stratification relies on functional testing to document induced ischemia. There is no consensus on which approach yields better clinical outcomes, and, consequently, there are wide practice variations in the use of angiography across different geographic regions.

Clinical outcomes after invasive and conservative management have been examined in both observational and randomized studies. McClellan et al found substantial variation in use of coronary angiography after myocardial infarction among 205 021 Medicare patients in the United States, with no significant effect of invasive management on mortality after 1 to 4 years. The OASIS investigators examined 7987 patients in a large registry drawn from 6 countries with widely varying rates of coronary angiography but little difference in cardiovascular death over 6 months. The TIMI-IIIb trial randomized 1473 patients with acute coronary syndromes to an early invasive or early conservative strategy and found no significant difference in death and nonfatal myocardial infarction after 1 year of follow-up. VANQWISH found significantly better survival in the first year of follow-up among patients randomized to the conservative, ischemia-guided strategy. In contrast, FRISC-II and TACTICS-TIMI-18 have reported significantly lower rates of death and nonfatal myocardial infarction among patients randomized to an invasive treatment strategy. In both studies, however, the favorable effect of the invasive strategy was demonstrable primarily in those patients with non–ST-segment elevation acute coronary syndromes who had either elevated levels of troponin or ST depression on the admission ECG. Thus, VANQWISH, FRISC-II, and TACTICS-TIMI-18 are consistent in finding that the potential benefits of the invasive strategy do not extend to all patients. Consequently, there is a need for careful risk stratification and tailoring management to the patient’s level of risk.

**Economic Outcomes**

The effect of the routine invasive and conservative, ischemia-guided strategies on resource utilization, cost, and cost-effectiveness has not been clearly established. The more frequent early use of coronary revascularization procedures is an integral component of the invasive strategy, so the initial costs of this approach should be higher than those of the conservative strategy. However, the early cost advantage of the conservative strategy will be eroded to a greater or lesser extent by hospital readmissions for recurrent symptoms. In the present study, the late costs of conservatively treated patients reduced by roughly half but did not offset the higher initial costs of the invasive approach. Most other studies have not compared costs of the invasive versus conservative approach. In preliminary data from TACTICS-TIMI-18, initial hospital costs were 16% higher in the invasive strategy than in the conservative strategy ($14 660 versus $12 667), whereas the 6-month follow-up costs were 16% lower ($6063 versus $7203), yielding a total cost over 6 months that was 3% higher for the invasive strategy ($20 616 versus $19 987). This pattern of costs is similar to that in VANQWISH, with initially higher costs in the invasive group but with lower follow-up costs. The more favorable incremental cost of the invasive strategy in TACTICS-TIMI-18 reflects the smaller gap in initial costs (16% versus 31%) and a larger difference in follow-up costs (16% versus 9%). A full comparison of results must await final publication of the TACTICS-TIMI-18 economic study, but it is noteworthy that the initial costs of the invasive strategy in that study ($14 660) were actually lower than the costs of the conservative strategy in VANQWISH ($14 733), suggesting that their methods of cost accounting must differ considerably from ours. In the present study, the invasive strategy had higher total costs using 2 alternative methods to measure cost.

**Cost-Effectiveness**

With lower overall costs and improved clinical outcomes, the conservative, ischemia-guided approach to management in VANQWISH was a dominant strategy in cost-effectiveness terms. The bootstrap analysis suggests it is very unlikely (<4%) that the routine invasive strategy was really more cost-effective but missed as a result of a small sample size. The cost-effectiveness results in this study cannot be readily compared with the findings of other trials. No indi-
vidual trial has shown a significant difference in mortality, and pooling data from TIMI-3B,¹ VANQWISH,² FRISC-II,³ and TACTICS-TIMI-18⁴ shows a mortality rate at 6 months to 1 year of 4.2% (148 deaths) in patients assigned to the invasive strategy versus 4.1% (143 deaths) in patients assigned to the conservative strategy. Because VANQWISH found the invasive strategy to be more costly and its effect on mortality is uncertain, it seems unlikely that the invasive strategy would be judged cost-effective even on the basis of the results of the other available trials.

Our findings are also in general agreement with the cost-effectiveness model of Kuntz et al.²¹ who found that coronary angiography was highly cost-effective in patients with postinfarction angina and a strongly positive exercise test, criteria for angiography similar to those of our conservative, ischemia-guided management strategy. By contrast, their model found that angiography was not cost-effective in the absence of postinfarction angina or a positive exercise test.²¹ Although different in design, the model of Kuntz et al.²¹ agrees with our finding that a selective approach to coronary angiography after myocardial infarction is more cost-effective.

Limitations

The present study should be interpreted in light of several limitations. The economic analysis was based on the results of a single randomized trial and is generalizable to the extent that the findings of the parent trial can be generalized. VANQWISH results were consistent with most, but not all, previous studies in this area. Second, the cost data are limited to the trial follow-up period. Although the cost curves seem parallel out to 40 months, the possibility that long-term costs might differ between the groups cannot be excluded. However, lifetime cost projections suggest that the conservative strategy would remain cost-effective even under assumptions about late costs favorable to the invasive strategy. Finally, we used resource consumption profiles to assign costs, and although our findings were not sensitive to the method of cost allocation, it is possible that different results may have been observed if the study had been performed in a different set of hospitals.

In conclusion, this study suggests that a conservative, ischemia-guided management strategy after non-Q-wave myocardial infarction with selective use of coronary angiography and revascularization is both clinically effective and cost-effective in most patients with uncomplicated non-Q-wave myocardial infarction.

Acknowledgments

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References

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