

Cost and Cost-effectiveness of an Early Invasive vs Conservative Strategy for the Treatment of Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

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PATIENTS PRESENTING WITH UNstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) account for approximately 1.4 million US hospital admissions annually in the United States and 2 million to 2.5 million worldwide.^{1,2} Two recent reports have presented economic results from trials comparing invasive and conservative management strategies, however the results of these trials may not apply to current US practice. The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial took place prior to the routine use

For editorial comment see p 1905.

Context In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-Thrombolysis in Myocardial Infarction (TIMI) 18 trial, patients with either unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI) treated with the platelet glycoprotein (Gp IIb/IIIa) inhibitor tirofiban had a significantly reduced rate of major cardiac events at 6 months with an early invasive vs a conservative strategy.

Objective To examine total 6-month costs and long-term cost-effectiveness of an invasive vs a conservative strategy.

Design Randomized controlled trial including a priori economic end points.

Setting Hospitalization for UA/NSTEMI with 6-month follow-up period.

Patients A total of 2220 patients with UA/NSTEMI; economic data from 1722 patients at US-non-VA hospitals.

Intervention Early invasive strategy with routine catheterization and revascularization as appropriate vs a conservative strategy with catheterization performed only for recurrent ischemia or a positive stress test.

Main Outcome Measure Total 6-month costs and incremental cost-effectiveness ratio.

Results The average initial hospitalization costs among those in the invasive strategy group were \$15 714 vs \$14 047 among those in the conservative strategy group, a difference of \$1667 (95% confidence interval [CI], \$387-3091). The in-hospital costs were offset significantly at the 6-month follow-up, with an average cost in the invasive group of \$6098 vs \$7180 in the conservative group, a difference of \$1082 (95% CI, -\$2051 to \$76). The average total costs at 6 months, including productivity costs, for the invasive group was \$21 813 vs \$21 227 for the conservative group, a \$586 difference (95% CI, -\$1087 to \$2486). The average 6-month costs excluding productivity costs in the invasive group was \$19 780 vs \$19 111 in the conservative group, a difference of \$670, 95% CI; (-\$1035 to \$2321). Estimated cost per year of life gained for the invasive strategy, based on projected life expectancy, was \$12 739 for the base case, and ranged from \$8371 to \$25 769, based on model assumptions.

Conclusions In patients with UA/NSTEMI treated with the Gp IIb/IIIa inhibitor tirofiban, the clinical benefit of an early invasive strategy was achieved with a small increase in cost, yielding favorable projected estimates of cost per year of life gained. These results support the broader use of an early invasive strategy in these patients.

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of^{3,4} platelet glycoprotein (Gp) inhibition and coronary stenting, and the clinical results differ qualitatively from those of more contemporary trials. The Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trial,^{5,6} carried out more recently in Scandinavia, might not generalize in a straightforward manner to the United States.

In contrast to previous trials,^{3,5,7,8} the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-Thrombolysis in Myocardial Infarction (TIMI) 18 trial compared an early invasive strategy to a conservative strategy using the current practice of Gp IIb/IIIa inhibition and coronary stenting. Clinical results demonstrated that an early invasive strategy was superior to a more conservative approach in reducing major cardiac events at 6 months.⁹ This article presents primary results of the economic study from TACTICS-TIMI 18.

METHODS

Study Design

The methods^{10,11} and major clinical findings^{9,12} of TACTICS-TIMI 18 have been reported previously. In brief, 2220 patients with either unstable angina or NSTEMI were treated with aspirin, heparin, and the Gp IIb/IIIa inhibitor tirofiban (FIGURE 1). They were then randomized to an early invasive strategy

that included catheterization within 4 to 48 hours of randomization and revascularization as appropriate, or to a more conservative strategy that included catheterization performed only because of recurrent ischemia or a positive stress test. Patients were followed up for 6 months. The primary economic end point was total 6-month costs for all patients recruited at US–non-Veterans Affairs (VA) hospitals (n=1722). If one strategy proved to be both more effective and more costly than the other, an evaluation of cost-effectiveness would be performed. Direct costs associated with hospitalizations, emergency department visits, outpatient visits and procedures, nursing home and rehabilitation stays, and cardiac medications were considered. Costs resulting from lost productivity were also included.

Sources of Cost Data

Inpatient and emergency department charges were obtained from the UB92, Medicare’s uniform formulation of the itemized hospital bill, which is generated for patients treated at most non-federal hospitals. Charges were reduced to costs using the Medicare whole hospital cost/charge ratio obtained from the hospital’s annual Medicare Cost Report.¹³ Physician costs were estimated as a percentage of hospital costs according to diagnosis related grouping (DRG) and corresponding Medicare physician

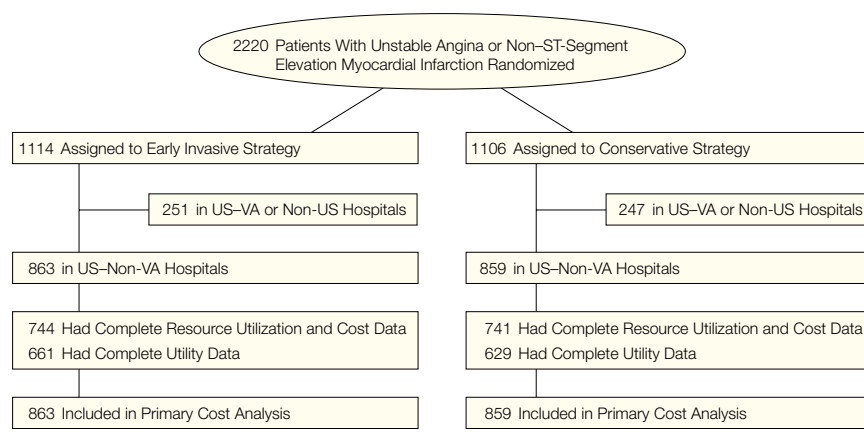
cost to hospital cost percentages.¹⁴ Costs of outpatient visits and procedures were estimated using the Medicare Fee Schedule relative-value unit (RVU) rates for Current Procedural Terminology codes in 1999 and the 1999 conversion factor of \$34.7315 per RVU. Costs of inpatient rehabilitation and skilled nursing facility stays were estimated using Medicare reimbursement rates. Tirofiban costs were calculated according to the number of 250 mL bags used at a cost of \$389.18 per bag. Cardiac-related medication use was converted to cost using Red Book¹⁵ average wholesale prices. Productivity costs were estimated from self-reported employment classification into 1 of 4 categories: professional, clerical or sales, skilled, unskilled, and full-time or part-time status, workdays missed, and work-effectiveness (0%-100%). This data was collected at baseline and at 30 days and 6 months after baseline. Average annual wages were obtained separately for men and women for 6 age categories,¹⁶ from which lost productivity costs were estimated based on changes in employment status and effectiveness, and workdays missed. Patient preferences for different health states or utilities were obtained using the Health Utilities Index (HUI)¹⁷ at baseline, 30 days, and 6 months. All costs were adjusted to year 2000 values using the medical care portion of the consumer price index.

Statistical Analysis

The clinical end points for patients in the economic study were analyzed using logistic regression adjusting for prior aspirin and age of 65 years.⁹ Differences in mean costs between treatment arms (invasive minus conservative) were compared on an intention-to-treat basis. Because the data were not normally distributed, the bootstrap method¹⁸ was used to obtain confidence intervals (CIs) using S-Plus software.¹⁹ Initial hospitalization length-of-stay and the number of rehospitalizations were compared using the Wilcoxon rank-sum test.

Quality-adjusted life-years (QALYs) for the in-trial period were obtained by multiplying survival in life-years by util-

Figure 1. Study Flow Chart



ity within 3 time periods (weeks 0-2, 2-12, 12-26), and summing the results. Life-years, utility, and QALYs were compared using the *t* test.

Cost-effectiveness

In-trial cost effectiveness was measured as cost per death or myocardial infarction (MI) prevented, with CIs obtained using the Fieller method.²⁰ Bootstrap methods (5000 replicates of original sample sizes) were used to examine the distribution of the cost-effectiveness ratio across different regions of the cost-effectiveness plane. Cost per year of life gained was estimated based on in-trial estimates of incremental costs and event (death or MI) rates, and life expectancy estimates derived from 2 sources: the Framingham Heart Study²¹ and more contemporary data from the Platelet glycoprotein IIB/IIIA in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial combined with data from the Duke Cardiovascular Disease Database.²²

Forty-year follow-up data from the Framingham Heart Study provides life expectancy estimates for subpopulations with a history of coronary heart disease and acute MI according to sex and 4 age categories.²¹ In order to evaluate long-term cost-effectiveness of the invasive strategy, these life expectancy estimates were applied to patients in TACTICS-TIMI 18 who survived 6 months with and without a nonfatal MI.

The PURSUIT trial enrolled patients from 1995-1997 with acute coronary syndromes.²² The US PURSUIT cohort, for which estimates of the impact of a nonfatal MI on life expectancy were derived using data from the Duke database, was similar to that of TACTICS-TIMI 18 cohort. Patients in this cohort had a mean age of 62 years, 65% were men; 34% had a history of a prior MI and 27% had diabetes. Life expectancy for those patients in the PURSUIT trial who survived 6 months without a nonfatal MI was estimated to be 16 years; the prevention of a nonfatal MI was estimated to yield on average one eighth the savings in life-years achieved by prevent-

ing early death (ie, 14-year life expectancy for patients with a nonfatal MI).²³ In a second set of analyses these estimates were applied to patients in TACTICS-TIMI 18. Details regarding the derivation of the life expectancy projections based on both the Framingham and PURSUIT/DUKE estimates are available upon request.

Eight cost-effectiveness ratios were estimated for both Framingham and PURSUIT/Duke projections of life expectancy. These differed by inclusion or exclusion of productivity costs, use of the overall TACTICS-TIMI 18 population, or the US-non-VA subgroup as the basis for clinical outcomes (death or MI), and consideration of nonsignificant statistical differences in survival at 6 months in the derivation of the life-expectancy estimates. The base case analysis used the overall TACTICS-TIMI 18 population projected life expectancy estimates from Framingham, and included productivity costs and observed survival differences. A 3% discount rate was applied to the life-expectancy differences; sensitivity analyses increased the discount rate to 5%.

Missing Data

Initial hospitalization costs were obtained from UB92s for 1597 (93%) patients. Complete resource use and cost data pertaining to the 6-month follow-up period were available for 1485 patients (86%). Patients missing cost data were equally distributed between the 2 groups during both the initial hospitalization and the follow-up period. Since patients with available cost data may be a biased sample of the total TACTICS-TIMI 18 US-non-VA patient population, resource-based regression models were used to impute missing initial hospitalization ($R^2=0.75$) and follow-up costs ($R^2=0.78$). (R^2 represents the proportion of variability in costs explained by the model.) For 128 patients, including 26 patients (15 invasive, 11 conservative) who dropped out or were lost to follow-up prior to the 6-month follow-up, as well as patients who had missing follow-up resource utilization ($n=88$), regression imputa-

tion was used to estimate follow-up costs on the basis of initial hospitalization costs and patient baseline characteristics ($R^2=0.05$ for patients completely missing follow-up resource utilization; $R^2=0.31$ for patients known to have undergone revascularization during follow-up). Twenty-five percent of patients had incomplete utility data at one or more points, which was imputed using multiple imputation,²⁴ implemented in SAS.²⁵ The primary cost comparison is based on the total overall economic cohort, including patients with imputed costs.

RESULTS

Clinical results for the US-non-VA patients (TABLE 1) were similar to those for the overall trial population.⁹ The estimated risk reduction associated with the invasive strategy for both primary and secondary end points was greater for the economic study population than for the overall patient population. Baseline characteristics of the patients included in the economic analysis were well matched between treatment arms (TABLE 2) and were representative of the overall trial population.⁹

Initial Hospitalization Costs

The average cost of the initial hospitalization was significantly higher for the invasive arm than the conservative arm (\$15 714 vs \$14 047) for the overall US-non-VA population, representing a difference of \$1667 with a 95% CI (\$387-\$3091). This difference tended to increase with age, diabetes, presence of a positive troponin assay result, and ST-segment changes (FIGURE 2). Adjustment for baseline covariates using linear regression did not significantly alter the cost difference. The average cost of the initial hospitalization for patients with UB92-derived (unimputed) initial hospitalization cost data was similar to that for the overall population (TABLE 3). By design, the duration of tirofiban use was longer for the conservative arm and thus the associated costs were higher. Of the US-non-VA patients in the conservative arm, 49% underwent catheterization and 33% underwent revasculariza-

Table 1. Cardiac Events at 6 Months*

| Variable | No. (%) | | | | Early Invasive vs Early Conservative | | | |
|-----------------------|-------------------------|-------------------------------|-------------------------|-------------------------------|--------------------------------------|------------------|---------------------|------------------|
| | Early Invasive | | Early Conservative | | All Patients | | US–Non-VA Hospitals | |
| | All Patients (n = 1114) | US–Non-VA Hospitals (n = 863) | All Patients (n = 1106) | US–Non-VA Hospitals (n = 859) | OR (95% CI) | P Value | OR (95% CI) | P Value |
| | Primary end point† | 177 (15.9) | 130 (15.1) | 215 (19.4) | 175 (20.4) | 0.78 (0.62-0.97) | .03 | 0.69 (0.54-0.89) |
| Death or MI | 81 (7.3) | 58 (6.7) | 105 (9.5) | 86 (10.0) | 0.74 (0.54-1.00) | .05 | 0.65 (0.46-0.91) | .01 |
| Death | 37 (3.3) | 27 (3.1) | 39 (3.5) | 29 (3.4) | 0.93 (0.58-1.47) | .74 | 0.92 (0.54-1.58) | .77 |
| MI | 53 (4.8) | 33 (3.8) | 76 (6.9) | 64 (7.5) | 0.67 (0.46-0.96) | .03 | 0.49 (0.32-0.76) | .001 |
| Rehospitalization ACS | 123 (11.0) | 91 (10.5) | 152 (13.7) | 125 (14.6) | 0.78 (0.60-1.00) | .05 | 0.69 (0.52-0.92) | .013 |

*VA indicates Veterans Affairs; OR, odds ratio; CI, confidence interval. Data in the Early Invasive columns are printed with permission from Cannon et al.⁹

†Death, myocardial infarction (MI), or rehospitalization for acute coronary syndromes (ACS) at 6 months.

Table 2. Baseline Characteristics of Study Participants*

| | Early Invasive (n = 863) | Early Conservative (n = 859) |
|---------------------------------|--------------------------|------------------------------|
| Age, mean (SD), y | 63 (12) | 63 (12) |
| Age ≥65 y | 382 (44) | 379 (44) |
| Women | 329 (38) | 319 (37) |
| White | 667 (77) | 689 (80) |
| Prior MI | 334 (39) | 328 (38) |
| Prior aspirin use | 560 (65) | 545 (63) |
| Diabetes | 246 (29) | 244 (28) |
| ST-segment changes | 311 (36) | 314 (37) |
| MI without ST-segment elevation | 345 (40) | 340 (40) |
| Troponin T >0.01, ng/mL† | 387 (55) | 377 (54) |

*Data are presented as number (percentage) unless otherwise indicated. MI indicates myocardial infarction.

†Troponin T was measured on a subset of patients (1402 US–non-Veterans Affairs patients: 704 in the invasive group; 698 in the conservative group).

tion (23% percutaneous coronary intervention [PCI], 10% coronary artery bypass graft [CABG] surgery) during the initial hospitalization. Of patients in the invasive arm, 97% underwent catheterization and 55% underwent revascularization (40% PCI, 15% CABG) during the initial hospitalization. These results and analogous results for the subsequent, postdischarge follow-up period were similar to those for the overall trial population.⁷ The median length of stay was significantly lower for the invasive arm in the US or non-VA population (3.9 days vs 4.3 days, $P < .001$).

Six-Month Follow-up Costs

More than half of the early difference in costs was offset by significantly lower 6-month follow-up costs in the in-

sive arm (\$6098 vs \$7180; difference –\$1082). Results for patients with unimputed follow-up costs were similar, with a significant difference of –\$1155. Table 3 presents follow-up costs according to category of resource use. Lower rehospitalization costs for the invasive arm account for most of the difference in follow-up costs. There was a trend toward a higher average number of rehospitalizations per patient in the conservative group (0.41 vs 0.35, $P = .07$).

Cumulative Six-Month Costs: The Primary Economic End Point. For the overall US–non-VA patient population, average total costs for the 6-month study period, including productivity costs, were \$21 813 for the invasive arm and \$21 227 for the conservative arm; the difference of \$586 had a 95% CI (–\$1087 to \$2486). Average total costs, excluding productivity costs, were \$19 780 and \$19 111 (the difference of \$670 has a 95% CI, –\$1035 to \$2321). No significant difference in total costs was found overall or for any subgroups except for patients with diabetes, for whom costs were significantly higher for the invasive arm (Figure 2). For patients with complete (unimputed) total 6-month cost data, the total cost difference was slightly smaller than for the overall US–non-VA population (\$436, 95% CI; –\$1429 to \$1279). FIGURE 3 illustrates how the difference in cumulative costs between groups for the overall US–non-VA population, including productivity costs, decreased over time following discharge from the initial

hospitalization. Treatment strategy was not a significant predictor of total 6-month costs after adjusting for baseline covariates.

Life-years, Utility, Quality Adjusted Life-years: In-Trial Analysis

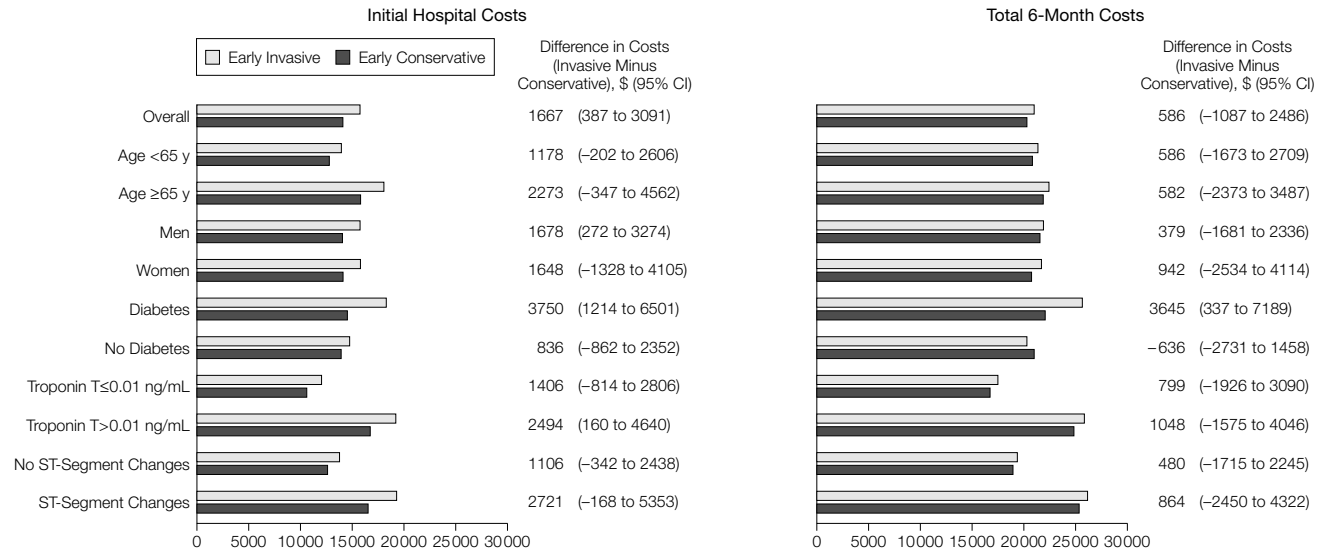
While there were fewer cardiovascular events for patients in the invasive strategy group, 6-month death rates were comparable (Table 1) and thus average life-years were similar (0.486 invasive vs 0.488 conservative, $P = .75$). Health status utility data was complete for 1290 patients (75%) and was imputed for at least one time point for the remaining 432 (25%). Average utility at baseline (0.642, invasive vs 0.631, conservative; $P = .51$) and both 30 days (0.715 vs 0.708, $P = .64$) and 6 months (0.718 vs 0.733, $P = .33$) was similar. With very little difference between groups in both utility and life-years, QALYs were also similar (0.354 vs 0.35, $P = .83$). This difference in QALYs translates into less than 9 hours over a 6-month time horizon.

Cost-effectiveness: In-Trial Analysis

With QALYs greater on average for the conservative strategy and associated costs less, an in-trial cost utility analysis rendered the invasive arm dominated by the conservative arm at 6 months.

The short time horizon, for such an analysis, however, limits its relevance for policy setting. Although life-years and QALYs at 6 months were similar, there was a significant difference

Figure 2. Initial Hospitalization and Total 6-Month Costs



Mean initial hospitalization costs by treatment arm for US–non-Veterans Affairs patients and within subgroups defined by primary stratification variables. Mean total 6-month costs by treatment arm for US–non-VA patients and within subgroups defined by primary stratification variables. CI indicates confidence interval.

between groups in the combined end point of death or MI. The estimated cost per death or MI prevented for the invasive strategy was \$17758, 95% CI (dominant, \$107535), with 26% of the bootstrap distribution falling in the dominant quadrant of the cost-effectiveness plane (lower costs and greater effectiveness; TABLE 4).

Lifetime Cost-effectiveness Analysis

Results of long-term cost-effectiveness analyses, which apply life expectancy estimates from Framingham to patients in TACTICS-TIMI 18 who were alive at 6 months, along with analogous results based on PURSUIT/Duke data, are presented in TABLE 5. For the overall trial population, estimated cost per year of life gained with the invasive strategy ranged from \$8371 to \$25769, depending on underlying assumptions. For the base case model, the undiscounted difference in life expectancy favored the invasive strategy by 0.068 years (25 days) using Framingham estimates and 0.070 years (26 days) using PURSUIT/Duke estimates, yielding cost-effectiveness ratios of \$12739 and \$13022, respectively, after applying an annual dis-

Table 3. Mean Initial Hospitalization 6-Month Follow-up and Total 6-Month Cases

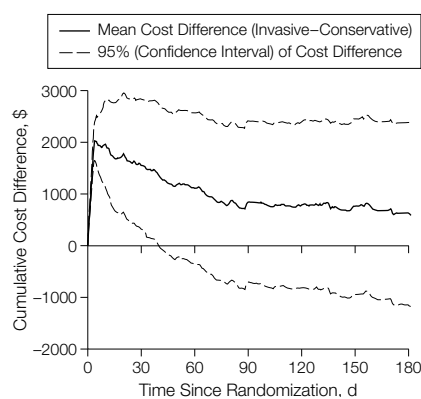
| Variable* | Invasive | Conservative | Cost Difference (95% CI) |
|--|----------|--------------|--------------------------|
| Initial hospitalization costs | | | |
| No. of US–non-VA patients | 863 | 859 | |
| Total costs, \$ | 15 714 | 14 047 | 1667 (387 to 3091) |
| No. of patients with complete (unimputed) cost data | | | |
| Hospital, \$ | 11 288 | 9619 | 1669 (579 to 2730) |
| Professional, \$ | 3372 | 3047 | 325 (3 to 609) |
| Tirofiban, \$ | 889 | 1059 | -170 (-219 to -129) |
| Total, \$ | 15 549 | 13 725 | 1824 (433 to 3162) |
| 6-Month follow-up cost data after discharge | | | |
| No. of US–non-VA patients | 863 | 859 | |
| Total 6-month follow-up cost data, \$ | 6098 | 7180 | -1082 (-2051 to -76) |
| No. of patients with complete (unimputed) initial hospitalization and 6-month follow-up cost data | | | |
| Rehospitalization, \$ | 2910 | 3891 | -981 (-180 to -173) |
| Emergency department visits, \$ | 78 | 68 | 10 (-16 to 38) |
| Outpatient, \$ | 143 | 146 | -3 (-27 to 16) |
| Medications, \$ | 487 | 486 | 1 (-38 to 43) |
| Tirofiban, \$ | 12 | 27 | -15 (-31 to 1) |
| Other, \$† | 412 | 425 | -13 (-245 to 200) |
| Indirect (productivity), \$ | 2033 | 2187 | -155 (-833 to 433) |
| Total 6-month follow-up costs | 6075 | 7230 | -1155 (-2270 to -72) |
| Total 6-month costs, including initial hospitalization | | | |
| No. of US–non-VA patients | 863 | 859 | |
| Cost, \$ | 21 813 | 21 227 | 586 (-1087 to 2486) |
| No. of patients with complete cost data | | | |
| Cost, \$ | 21 528 | 21 091 | 436 (-1429 to 2279) |

*VA indicates Veterans Affairs.
†Includes nursing home, rehabilitation, or visiting nurse costs.

count rate of 3%. (Estimated gains in life expectancy for the invasive strategy would occur in the 13th year using Framingham data and in the 15th year using PURSUIT/Duke data). Discounting the life expectancy benefit annually by 5%, these cost effectiveness ratios would become \$16358 and \$17377, respectively.

Estimates of cost per year of life gained with the invasive strategy were consistently lower when based on Framing-

Figure 3. Difference in Cumulative Costs Over 6 Months



Difference in cumulative costs (invasive minus conservative) over 6 months including 95% confidence intervals (CIs) for the cost difference obtained from bootstrap resampling.

ham data vs PURSUIT/Duke data. Cost-effectiveness ratios were also lower when in-trial survival differences were incorporated into the life expectancy calculations, and when productivity costs were included, as these costs were higher for patients in the conservative arm. Based on the observed incremental cost differences and MI rates for the overall trial population, using \$50000 per year of life gained as a willingness-to-pay threshold and applying a discount rate of 3%, a decrease in life expectancy associated with a nonfatal MI of only 5.6% (6.5% with productivity costs excluded) would yield acceptable cost-effectiveness ratios for the invasive strategy. Alternatively, using the observed event rates and the estimated impact of a nonfatal MI on life expectancy from PURSUIT/Duke data, an increase in cost of the invasive strategy as high as \$2250 when in-trial survival differences are incorporated (\$1300 when the survival differences are not incorporated) would still have yielded acceptable cost-effectiveness ratios for the invasive strategy.

COMMENT

At 6 months, the invasive strategy was found to cost \$586 more on average

than the conservative strategy when productivity costs were included (and \$670 more with productivity costs excluded). It was also found to prevent 2 deaths and 20 nonfatal MIs per 1000 patients for the overall TACTICS-TIMI 18 population (and 3 deaths and 30 nonfatal MIs per 1000 patients, for the US–non-VA patient population), with an estimated cost per year of life gained ranging from \$8371 to \$25769, depending on the assumptions of the model. Although empirical utility data was unavailable for the long-term cost-effectiveness estimates, any reasonable quality adjustment made to these cost-effectiveness ratios (for example, inflating them by 15%) would have yielded favorable results (estimates of cost per year of life gained less than \$30000). Cost effectiveness of the invasive strategy for the treatment of UA/NSTEMI thus approaches that of CABG surgery for left main coronary disease²⁶ and is more favorable than that of tissue-plasminogen activator vs streptokinase in the treatment of acute MI.²⁷

A limitation of this study is that costs were only measured up to 6 months. As illustrated in Figure 2, the mean cost difference between treatment arms was relatively constant beyond 90 days,

Table 4. Cost-effectiveness of the Invasive Strategy in Terms of Cost per Death or Myocardial Infarction Averted*

| Subgroup (No. Treated Conservatively, No. Treated Invasively) | Productivity Costs Included | Cost-effectiveness Based on Trial Data | | | | |
|---|-----------------------------|--|---|---------------------------------------|-----------|------------|
| | | Δ Cost, \$ (Invasive – Conservative) | Δ Death or MI (Conservative – Invasive) | C/E Ratio, \$ per Death or MI Averted | % | |
| | | | | | Dominant† | Dominated‡ |
| Effectiveness Based on All Patients, Costs Based on US–Non-VA Patients | | | | | | |
| Overall sample (1106, 1114) | Yes | 586 | 0.023 | 25 478 | ... | ... |
| | No | 670 | 0.023 | 29 130 | ... | ... |
| ST-segment elevation change (418, 434) | Yes | 864 | 0.061 | 14 164 | ... | ... |
| | No | 1599 | 0.061 | 26 213 | ... | ... |
| Troponin T >0.01 (480, 506) | Yes | 1048 | 0.034 | 30 824 | ... | ... |
| | No | 1252 | 0.034 | 36 824 | ... | ... |
| Effectiveness and Costs Based on US–Non-VA Patients | | | | | | |
| Overall sample (859, 863) | Yes | 586 | 0.033 | 17 758 | 26 | 0.5 |
| | No | 670 | 0.033 | 20 303 | 22 | 0.6 |
| ST-segment elevation change (314, 311) | Yes | 864 | 0.069 | 12 522 | 31 | 0.2 |
| | No | 1599 | 0.069 | 23 173 | 18 | 0.3 |
| Troponin T >0.01 (377, 387) | Yes | 1048 | 0.042 | 24 952 | 24 | 3 |
| | No | 1252 | 0.042 | 29 810 | 18 | 3 |

*Δ indicates change; C/E, cost-effectiveness; MI, myocardial infarction; and ellipses, not estimable without patient-level cost data for all TACTICS-TIMI 18 patients.
 †Lower costs and more effective than the alternative.
 ‡Higher costs and less effective than the alternative.

which supports the assumption that the 6-month difference in cumulative costs of \$586 provides a reasonable estimate of the long-term incremental costs of the invasive strategy.

While 2 other trials have published economic results comparing an early invasive vs conservative approach to the treatment of UA/NSTEMI, TACTICS-TIMI 18 was the first trial to formally specify a priori a primary economic end point,¹¹ and to derive hospital costs directly from hospital billing information. The FRISC II trial enrolled 2457 patients in Scandinavia in 1996-1998.⁵ Average total 12-month costs were significantly higher in the invasive group (the difference roughly \$2235), and with an observed 3.7% difference in the rate of death or MI favoring the invasive arm, the estimated cost per death or MI avoided was \$60 393.⁶ In TACTICS-TIMI 18, a nonsignificant \$586 increase in total 6-month costs for the invasive strategy, yielded an estimated cost per death or MI avoided of \$17 792. Two factors may contribute to the difference in economic results between FRISC II and TACTICS-TIMI 18. In FRISC II,

average initial hospitalization length-of-stay was longer for the invasive strategy (12.0 vs 8.1 days) whereas in TACTICS-TIMI 18 average length of stay was shorter for the invasive strategy (5.4 vs 6.0 days). Additionally, the more stringent criteria used in the conservative strategy of FRISC II prior to undergoing cardiac catheterization resulted in a lower percentage of conservatively managed patients undergoing cardiac catheterization and subsequent revascularization.^{5,6,9}

The VANQWISH trial enrolled 920 patients in the US between 1993 and 1995, and its results reported a significantly higher mortality rate for the invasive strategy than the results of TACTICS-TIMI 18 and FRISC II.³ Costs for 876 VANQWISH patients enrolled from 17 Department of Veterans Affairs hospitals were significantly higher for the invasive strategy.⁴ These results may have limited applicability to current practice due to the now common use of Gp IIb/IIIa inhibition and coronary stenting.

The benefits of an invasive strategy can likely be achieved without expen-

diture for new catheterization facilities. Patients with UA/NSTEMI admitted to a community hospital without catheterization facilities can be stabilized medically and then transferred to a tertiary institution, precluding the need to build new catheterization facilities. Whether there is sufficient capacity at tertiary institutions is perhaps uncertain, though in the United States that likelihood is quite high.¹

Health care systems function with limited resources. Patients with UA/NSTEMI account for 1.4 million hospital admissions per year, at a 6-month cost of approximately \$30 billion in the United States alone; thus, cost-effectiveness must be carefully considered when developing treatment guidelines for this patient population.²⁸ The economic results reported herein suggest that the benefit of an early invasive strategy in reducing major cardiac events is achieved with a small increase in cost overall, yielding favorable cost-effectiveness ratios when the impact of the lower nonfatal MI rate is projected over the long term. These results reinforce the support provided by

Table 5. Long-term Cost-effectiveness Based on Estimates of Life Expectancy*

| Subgroup (No. Treated Conservatively, No. Treated Invasively) | Δ Cost, \$ (Invasive – Conservative)† | Framingham Heart Study | | | | PURSUIT Trial | | | |
|---|---------------------------------------|---|--------------------------------------|--|--------------------------------------|---|--------------------------------------|--|--------------------------------------|
| | | Using Observed Δ in TACTICS-TIMI 18 Mortality | | Assuming No Δ in TACTICS-TIMI 18 Mortality | | Using Observed Δ in TACTICS-TIMI 18 Mortality | | Assuming No Δ in TACTICS-TIMI 18 Mortality | |
| | | Δ in Life-Years‡ | C/E Ratio \$ per Year of Life Gained | Δ in Life-Years‡ | C/E Ratio \$ per Year of Life Gained | Δ in Life-Years‡ | C/E Ratio \$ per Year of Life Gained | Δ in Life-Years‡ | C/E Ratio \$ per Year of Life Gained |
| Effectiveness Based on All Patients, Costs Based on US–Non-VA Patients | | | | | | | | | |
| Overall sample (1106, 1114) | 586 | 0.046 | 12 739 | 0.036 | 16 278 | 0.045 | 13 022 | 0.026 | 22 538 |
| | 670 | 0.046 | 14 565 | 0.036 | 18 611 | 0.045 | 14 889 | 0.026 | 25 769 |
| ST-segment elevation change (418, 434) | 864 | 0.227 | 3806 | 0.089 | 9708 | 0.217 | 3982 | 0.057 | 15 158 |
| | 1599 | 0.227 | 7044 | 0.089 | 17 966 | 0.217 | 7369 | 0.057 | 28 053 |
| Troponin T >0.01 (480, 506) | 1048 | 0.103 | 10 175 | 0.056 | 18 714 | 0.079 | 13 266 | 0.038 | 27 579 |
| | 1252 | 0.103 | 12 155 | 0.056 | 22 357 | 0.079 | 15 848 | 0.038 | 32 947 |
| Effectiveness and Costs Based on US–Non-VA Patients | | | | | | | | | |
| Overall sample (859, 863) | 586 | 0.070 | 8371 | 0.058 | 10 103 | 0.063 | 9302 | 0.039 | 15 026 |
| | 670 | 0.070 | 9571 | 0.058 | 11 552 | 0.063 | 10 635 | 0.039 | 17 179 |
| ST-segment elevation change (314, 311) | 864 | 0.268 | 3224 | 0.115 | 7513 | 0.254 | 3402 | 0.065 | 13 292 |
| | 1599 | 0.268 | 5966 | 0.115 | 13 904 | 0.254 | 6295 | 0.065 | 24 600 |
| Troponin T >0.01 (377, 387) | 1048 | 0.122 | 8590 | 0.079 | 13 266 | 0.085 | 12 329 | 0.049 | 21 388 |
| | 1252 | 0.122 | 10 262 | 0.079 | 15 848 | 0.085 | 14 729 | 0.049 | 25 551 |

*Δ indicates change; C/E, cost-effectiveness; VA, Veterans Affairs; PURSUIT, Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression; TACTICS, Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy; and TIMI, Thrombolysis in Myocardial Infarction.

†The top line of each row includes productivity costs; the second line of each row does not include productivity costs.

‡Invasive minus conservative discounted 3% annually.

the clinical results of TACTICS-TIMI 18 for the broader use of an early invasive strategy using upstream Gp IIb/IIIa inhibition for the treatment of UA/NSTEMI.

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