Over the last decade, 2 basic approaches have evolved to guide the use of cardiac catheterization and coronary revascularization in patients with acute coronary syndrome (ACS). Both use risk stratification tools in an attempt to achieve the best outcome for patients. Where they differ is in the most efficient means to the goal. The “conservative” approach encompasses strategies built around the use of serial clinical evaluations and noninvasive stress tests to identify those high-risk patients who need referral to diagnostic catheterization. Several variants have been developed with associated early catheterization rates ranging from 10% (FRISC-II) to as high as 57% (TIMI-IIIB). The proponents of this approach cite the advantages of not exposing lower-risk patients to potential complications of invasive diagnostic procedures or to revascularization procedures without prognostic or symptomatic benefit (the so-called “oculovervascular reflex”). Because they use fewer expensive procedures, conservative approaches have also been regarded as more efficient economically, ie, lower cost. The “aggressive” approach is based on the belief that noninvasive methods are not sufficiently accurate to identify all patients with prognostically significant coronary lesions who require revascularization. Under the concept of “a stitch in time saves nine,” proponents of aggressive strategies have also argued that these may be more economically efficient due both to an efficient early risk stratification process that minimizes expensive hospital days occupied with “watchful waiting” and to a reduction in subsequent hospitalizations and procedures resulting from reactivated unreactivated disease. Aggressive strategies have typically used diagnostic cardiac catheterization in over 90% of ACS patients, most often between 4 and 48 hours after presentation.

Thus, both conservative and aggressive management strategies have claimed not only a more preferable risk:benefit ratio but also important economic advantages. Four major clinical trials have compared medical outcomes for these 2 strategies. Based on the first 3 of these, the 2000 ACC/AHA Guidelines for Unstable Angina gave both early invasive and early conservative strategies a Class I indication. In this issue of Circulation, the VANQWISH (Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital) trial becomes the first of these 4 to publish a careful economic analysis. Barnett and colleagues estimated costs for the 876 patients enrolled in 17 Veterans Administration Hospitals. Compared with the conservative strategy (which had a cardiac catheterization rate of 23%), the invasive strategy (cardiac catheterization rate 94%) had a longer hospital stay (by 0.6 hospital days) and a $4500 higher cost for the index hospitalization. Of course, VANQWISH patients were treated before (1993 to 1995) the routine use of glycoprotein IIb/IIIa inhibitors and coronary stents, both of which have increased at least the initial costs of percutaneous revascularization. Over the 23-month mean follow-up, the conservative arm patients spent an average of 1.3 extra days in the hospital and had fewer angioplasties than the invasive arm but significantly more (4.9 per 100 patients) bypass surgeries. Thus, follow-up care was less expensive for the invasive arm and narrowed the initial cost gap between the two arms by $2300, or about 50% of the initial difference. In 1000 bootstrap replications, patients in the conservative arm had better survival plus lower costs 76% of the time and better survival plus higher costs 24% of the time with an economically attractive cost-effectiveness ratio (<$50 000 per added life year) in an additional 20% of samples. Taken at face value, this new analysis of VANQWISH strongly argues that the conservative strategy is preferable on both clinical and economic grounds.

These results appear to be at odds with the recently published TACTICS-TIMI-18 trial. In this trial, 51% of the early conservative arm underwent diagnostic catheterization during the index hospital admission as contrasted with 97% of the early invasive arm. Patients in this trial had the benefit of several advances not available to the VANQWISH participants. By design, all study patients received tirofiban for 48 hours or until revascularization. Coronary stents were used in over 80% of percutaneous revascularization procedures. In addition, beta blockers and lipid lowering agents were used more frequently than in earlier trials. Comparison of the hard clinical endpoints at 6 months showed that the early invasive arm had 2 per 1000 fewer deaths and 20 per 1000 fewer nonfatal myocardial infarctions (MIs). In the preliminary economic analysis, costs for the early invasive arm were about $2000 higher than for the early conservative arm. In follow-up, the early invasive arm recouped about $1000, due to fewer hospitalizations and procedures, leaving a net incremental cost of about $1000 for the early invasive arm at
6 months. Quality of life was similar in the two arms at 6 months.7

Thus, VANQWISH and TACTICS-TIMI-18 found similar trends in costs: significantly higher initial hospitalization costs for early invasive therapy and a partial recoup of these costs in follow-up (about 50% in both trials). Although the net extra costs of the early invasive strategy were greater in VANQWISH than in TACTICS-TIMI-18, the more important difference is in death and nonfatal myocardial infarction rates. In TACTICS-TIMI-18, the invasive arm cost more money and provided a modest reduction in nonfatal MI. In VANQWISH, the invasive arm cost more money and had worse survival out to 1 year with no significant effect on MI rates. A pooled analysis of the 7070 patients enrolled in TIMI-IIIB, VANQWISH, FRISC-II, and TACTICS-TIMI-18 showed a nonsignificant 1 per 1000 difference in 6-month mortality.8 The VANQWISH investigators conclude from this that early invasive therapy would be unlikely to meet conventional criteria for economic attractiveness even if the pooled clinical trial data were used as the effectiveness measure in a cost-effectiveness analysis.

Critics of the VANQWISH results have often focused on the 11.6% mortality rate in the 95 invasive arm patients who had coronary bypass surgery as evidence that the trial results are not relevant to modern decision making. However, the 30-day mortality rate for revascularization overall was 5% in the invasive arm and 4% in the conservative arm, whereas the medically treated patients in the invasive arm had a 5% mortality rate compared with 1% in the conservative arm.3 Of the 3 per 100 extra deaths present in the invasive arm at 30 days, approximately 2 of those were in medically treated patients and 1 was in a revascularized patient. Therefore, the play of chance may provide a better explanation than excessive procedural deaths for the unexpectedly higher mortality rate for invasive therapy in VANQWISH.

However, the VANQWISH investigators do not make note of 2 important points. First, the cardiovascular clinical trials community has accepted the general concept that prevention of nonfatal myocardial infarction is a clinically important goal, even when no deaths are prevented. What remains contentious is how important it is relative to preventing death and whether preventing small infarctions (judged by levels of cardiac markers) is of similar value to preventing large infarctions. So spending money to prevent infarctions may be a good value even when there is no evident (short-term) effect on mortality or quality of life. In the PURSUIT cost-effectiveness analysis, where this issue was addressed explicitly, the prevention of a myocardial infarction was estimated to provide on average about 1/8 the savings in life years achieved by preventing early death.8 Although the adverse prognostic importance of elevations in cardiac markers has been well established, further work is needed to define the relationship between these events and reductions in life expectancy or quality of life, the two ultimate clinically relevant endpoints.

The other important caveat about the apparent lack of mortality benefits from early invasive therapy pertains to the small total number of patients enrolled in the 4 major clinical trials. With 7070 patients in the 4 ACS trials, statistical power to detect an absolute survival difference of at least 1% is only around 0.65. In other words, there is a 35% chance with the available data of missing a true 1% difference in 6-month survival rates. On the other hand, the available trial data do allow us to exclude a survival advantage for the invasive strategy of 2% or greater with a high confidence. Cost-effectiveness analysis in the GUSTO-I trial showed that t-PA, with a 1% absolute survival advantage over streptokinase, provided good value for its $2200 incremental cost.9 So it remains possible that the invasive strategy is economically attractive with an incremental cost of $1000 if it actually produces an improvement in life expectancy either directly or by preventing prognostically important myocardial infarctions.

Whereas myocardial infarction is the major nonfatal endpoint examined in clinical trials of invasive versus conservative management strategies, major bleeding often differentiates these strategies as well. In TACTICS-TIMI-18, the early invasive arm had 22 per 1000 more patients with a major bleed.4 Thus, extra bleeding balanced out, at least numerically, the nonfatal myocardial infarctions prevented in this trial. Growing acceptance of the importance of major bleeding has led one recent trial to incorporate it into the primary efficacy-safety endpoint.10

Given the residual uncertainties about the incremental medical benefits of an early invasive strategy in ACS patients, how are we to put our new economic insights to use? One important concept from economics is that of "diminishing marginal returns." The clinical analog is "flat of the curve" medicine.11 As we pay money to buy units of medical benefit, be they extra survivors or extra life-years or some other quantity, we start with those purchases that provide substantial clinical benefit for the dollar. After we run out of "best buys" to invest in, we may buy care that has a more modest return on investment. Eventually, we reach a point where we are paying money for very small increments of benefit that we judge are not adequate value for dollars spent (the "flat of the curve"). Providing early invasive care for the highest-risk subjects saves lives.1 However, providing routine catheterization for all makes it highly probable that some of the money spent this way will provide very little return on investment. In the invasive arm of VANQWISH, only 47% of patients who had a catheterization went on to have revascularization.3 In TACTICS-TIMI-18, 64% of invasive arm patients with a catheterization had revascularization.4 Furthermore, early invasive care produced only a 2% absolute increment in coronary bypass surgery in VANQWISH and a 7% absolute increment in TACTICS-TIMI-18. Clearly, current versions of early invasive therapy are inefficient at identifying patients for survival enhancing revascularization.

Two further complexities: first, the potential clinical benefits of an invasive strategy are not equivalent at all institutions. These benefits are highly dependent on the quality of coronary revascularization; operator and institutional experience are important determinants of this quality. For this reason, American Heart Association guidelines recommend that percutaneous coronary interventions be performed by operators with acceptable volume (≥75 per year) at high-volume centers (≥400 per year).12 Second, recent data from
FRISC-II have suggested that women may be harmed by an early invasive strategy, although this finding was not reproduced in TACTICS-TIMI-18.13

The economic analyses of major ACS trials also contain important messages for health care purchasers and insurers, many of whom are currently marketing new insurance products in which patients pay higher copayments to see physicians or undergo procedures at “higher cost” institutions. The categorization of institutions as costly or not is usually based on “units of service,” such as charges for procedures or typical admissions. The financial data from these trials demonstrate that long-term cost information is needed to understand the real economic implications of admission of a patient to one institution or another.

A recent, intriguing retrospective analysis of the TIMI-IIIIB trial data has shown that by using a simple clinical score (based on age, CK-MB, history of accelerated angina, and ST depression on the ECG), over half of the study population could be classified as low-risk; these patients demonstrated no benefit in prevention of death or MI out to 1 year from the early invasive strategy.14 In TACTICS-TIMI-18, the troponin positive subgroup, constituting about 60% of the total population, had a larger reduction in death or myocardial infarction with the early invasive strategy (odds ratio at 6 months 0.70, P=0.08) and smaller net incremental costs.4,7 Combining key clinical and ECG variables with markers such as troponin and C-reactive protein should provide a more powerful decision aid and is likely to improve the technical quality and cost effectiveness of management decisions. With proper validation, such tools should allow clinicians to provide the advantages of “early invasive” care to those who stand to benefit the most, while protecting lower-risk patients from unhelpful procedures and making more efficient use of our health care dollars.

References
Conservative Management of Acute Coronary Syndrome: Cheaper and Better for You?
Daniel B. Mark and Thomas H. Lee

Circulation. 2002;105:666-668
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/6/666

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/