Cardiac revascularization of the medically refractory elderly patient: it is TIME to pay the piper

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This editorial refers to "Cost-effectiveness of invasive versus medical management of elderly patients with chronic symptomatic coronary artery disease" by J. Claude et al. on page 2195

"...the value of our expectations always signifies something in the middle between the best we can hope for and the worst we can fear?..." Jacob Bernoulli

It is appropriate that the first "trial-based analysis demonstrating the cost-effectiveness of angioplasty relative to medical therapy" should come from Basel, Switzerland. Basel was home to the Bernoulli family, who made countless seminal contributions to quantitative thinking about risk versus benefit. Of all the Bernoulli contributions, none has had more influence than the concept of utility, the notion that the risk of an event must include not only its mathematical probability, but also some measure of the desire for, or aversion to, that event, that the individual risk-assessor experiences.

The English word 'risk' is derived from the Italian risicare, to choose or to dare. What patient group is better suited to take the concept of utility and provide evidence of its relevance to medical choices than the chronically ill, co-morbid elderly population? If there is one patient group that understands that even a modest likelihood of being left unable to care for oneself may be too high, or that there are medical outcomes worse than death (for example, disabling stroke), that patient group is the chronically ill, co-morbid elderly.

The Swiss TIME investigators have demonstrated both the clinical and cost effectiveness of revascularization versus optimal medical therapy, in stable patients, precisely because they chose to study patients who had:
- symptomatic ischaemia, which was medically refractory; and
- high risk, by virtue of age and co-morbidity.

I would like to offer four ideas for consideration, regarding the TIME trial generally, and its cost-effectiveness conclusions in particular.

Point one: Consider the potential clinical benefit before either the risk or cost

If there is little or no potential clinical benefit to the patient, almost any risk or cost, may be too high.

Unlike the designers of many trials of either coronary artery bypass grafting (CABG) surgery, or percutaneous coronary intervention (PCI), the TIME investigators did not begin their screening or enrolment process with patient coronary anatomy. Like the veterans affairs (VA) AWESOME investigators, the TIME trialists began with patients who had symptoms that were refractory to well-defined medical therapy. The importance of the initial focus on medically refractory symptoms and ischaemia is that it identifies patients who are likely to demonstrate clinical benefit from coronary revascularization. Under those circumstances, treating a coronary obstruction is likely to relieve ischaemia and symptoms.

When patients with coronary lesions, but minimal or no symptoms and/or no objective evidence of ischaemia, are enrolled into a revascularization trial, the potential means of demonstrating clinical benefit are limited to endpoints like survival. Survival trials require either very large sample sizes or a population with frequent endpoints (namely high risk). When potentially eligible patients are screened down to a low risk randomized cohort, as is the case with most trials, the failure to...
demonstrate a clinical benefit is as likely a function of inadequate power as it is a function of the treatment alternative not being beneficial. 

By the same token, if the patient is on little or no proven risk reducing medical therapy to begin with, detecting a benefit of revascularization may not be as clinically helpful, because the measured ‘benefit’ is relative to inadequate or sub-optimal therapy. After thousands of patients, randomized into concordant trials for each drug, we know that aspirin, statins, b-blockers, and angiotensin-converting-enzyme (ACE) inhibition drugs reduce adverse cardiac events, such as cardiovascular mortality, in patients with coronary disease. 

Use of these medications should be measured, and strongly encouraged in both arms of contemporary trials, as was the case in TIME.3–5

Point two: The emphasis on coronary anatomical features, to the exclusion of physiological function, in coronary revascularization is ‘outdated’

No sooner were nine trials of PCI with balloon only, versus CABG completed, than many authorities wanted to insist that they were all ‘outdated’ because stents were not part of the PCI methodology. Similarly, after five stent versus CABG trials were completed, they too were considered ‘outdated’ because drug-eluting stents were not part of the PCI methodology. Yet few people have argued that nearly all of these trials, and the five trials of the CABG versus medical therapy from the 1970s may be ‘outdated’ because of relatively little medical therapy in either arm. For example, given all of the survival data from medical trials, do we really ‘know’ that a patient with three major epicardial coronary arteries having >70% diameter narrowing, no reversible ischaemia, who receives CABG, even with an internal thoracic artery to his left anterior descending artery, will live longer than the same patient treated with aspirin, clopidogrel, and randomized clinical trial doses of statins, beta-blockers and ACE-inhibition?

Based largely upon the five CABG versus medical trials, the notion has continued for nearly three decades, that benefit from CABG is primarily a function of a number of coronary arteries with >70% lumenal narrowing. A vast literature of acute myocardial infarction in general, and cardiogenic shock or pulmonary oedema, in particular, support the contention that there are patients with single or double vessel coronary disease who derive life-saving benefit from revascularization.

The emphasis on anatomical features extends to individual lesion characteristics. Largely based upon the NHLBI lesion classification, many PCI trials have excluded every category of individual coronary anatomy deemed unfavourable for simple balloon angioplasty. These exclusions mean that these trial results may not apply to many of the patients who meet the low-risk clinical inclusion criteria of those trials.

The two inclusion criteria, which are a regular part of both CABG and PCI trials, are one or more major epicardial coronary branches with a >70% diameter stenosis and the left ventricular ejection fraction >0.35. Accordingly, Guidelines, based upon the published trials, provide their strongest recommendations about both the decision to revascularize, and then whether to do so by CABG or PCI, largely based upon the number of coronaries with a >70% stenosis, whether the left main is narrowed and provided the LVEF is >0.35. The TIME trialists have focussed our attention on patients who are likely to benefit from revascularization, regardless of whether they have single or triple vessel disease and regardless of whether their coronary anatomy is simple or complex.3–5

Point three: The epidemiology of our time emphasizes the importance of including elderly and co-morbid patients in revascularization trials, and the risks implicit in treating such patients

The average age is increasing throughout the world and the elderly are the fastest growing group. Additionally, with epidemics of obesity, diabetes and smoking, clinically significant co-morbidity is increasing at alarming rate. Most of the published trials of PCI, CABG, or both, have systematically excluded elderly patients (>70 or >75 or >80 years of age) who have either cerebrovascular, peripheral vascular, pulmonary, or renal co-morbidity; who are haemodynamically unstable, who have on-going myocardial infarction, who have severe left ventricular dysfunction (LVEF < 0.35); or who have unfavourable anatomic features for either CABG or PCI. This is a large proportion of the patients most of us are called upon to make decisions as to whether to revascularize, and if so, how to revascularize. The TIME trial, focusing as it does on people >75 years (who have been excluded from most trials of CABG or PCI), who have symptoms despite two or more anti-anginals, and who had on average two or more co-morbidities, is ‘real world’. The TIME in-hospital mortalities serve to emphasize the potential risks of this real world revascularization.

Point four: Much of the information in the figures of clinical effectiveness versus cost can be inferred from the early versus late costs and charges data

If one relieves enough medically refractory ischaemia sufficiently to relieve symptoms, which interfere with a patient’s lifestyle, one can reduce the subsequent numbers of clinic visits, re-hospitalizations and additional revascularizations. Clearly, the initial procedure must be performed with low mortality, MI and stroke rates, and low enough rates of restenosis, to justify the procedure, and recoup the cost of the procedure. These are among the reasons to save money by not doing PCI,
where it is not needed (minimal or no symptoms, easily controlled with tolerable medical management). Alternatively, as the TIME investigators point out in their comparison with RITA-2, saving money may not be a good reason to fail to use stents, including drug-eluting stents, and the adjunctive medications, which are supported by multiple concordant, randomized trials demonstrating reduced acute complications and/or restenosis, for the patients who clearly need revascularization.8,10

Given increasing age and co-morbidity, as well as increasing prevalence and survival rates of congestive heart failure, the numbers and proportions of patients like those enrolled in the TIME trial, that interventionists and surgeons will have to evaluate for revascularization, will be increasing.10 This landmark study has demonstrated benefits of revascularization, which for many patients, are worth both the risks and the costs.

References

2182 Editorial

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