Implications of Contemporary Clinical Trials

The Placement of Aortic Transcatheter Valve (PARTNER) Trial
A Health Economic and Policy Perspective

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Major advances in medicine have the curious property of simultaneously being the cause of both great excitement and great anxiety. Clinicians embrace the power of science to reduce human suffering and prolong life in ways that their forbearers could hardly have imagined. Patients, knowing little of the enormous theoretical and practical challenges to be surmounted in producing real medical breakthroughs, have been conditioned by the media to expect dramatic headlines in each morning’s news reports as they sip their coffee. Healthcare payers and policy makers, reading those same reports, worry that consumers’ enthusiasm for high-tech solutions to the chronic health problems of modern society is fueling a destructive growth rate in medical spending.

Although cardiovascular medicine has no unique claim to technological innovation, the sheer number of patients affected with cardiovascular disease means that major technological advances addressing important clinical problems have measurable effects on the annual healthcare bill for the country. Over the last few decades, cardiovascular medicine has seen a series of remarkable, but expensive, therapeutic innovations evolve into guideline-endorsed standard care (eg, drug-eluting stents, implantable cardioverter-defibrillators, left ventricular assist devices). In each of these cases, the early dissemination phase of these technologies was marked by predictions that cardiovascular physicians, unable to restrain their enthusiasm for therapeutic novelty, would sink the national economy by adding billions of extra dollars to the already excessive annual healthcare bill. The apparent failure of such predictions to come true has left physicians increasingly inured to the voices of the Cassandras who make them.

Administrative inefficiency and overuse of tests and therapies partially explain why the United States spends more than any other country on health care (17% of the gross domestic product at last accounting) but not why the spending continues to grow every year. Of the factors that account for the majority of the annual rise in healthcare costs, scientific progress leading to technological innovation is most important.1 Simply put, the medical care of 2012 is not the same as care even several years ago; it is better, in some cases substantially so. In the history of medicine to date, better medical care almost always has cost more money.

The clinical outcome data from the 2 pivotal Placement of Aortic Transcatheter Valves (PARTNER) trials provide evidence that transcatheter aortic valve replacement (TAVR) is an important technological advancement likely to inspire both excitement and dread: an expensive breakthrough for inoperable aortic stenosis (AS) and a less invasive alternative to surgical AVR.2–5 What remains unclear is how best to apply the technology in clinical practice, mindful of both value and cost. The dissemination of percutaneous coronary intervention for chronic coronary artery disease was marked by a period when the technical ability to perform the procedure safely and successfully was more influential in treatment decisions than the expected benefits to the patient. On the other hand, the deployment of primary prevention implantable cardioverter-defibrillators, a therapy with a far stronger claim to a public health benefit and good value for the money, has fallen far short of initial predictions.6 Neither of these examples is a good policy model for rational dissemination of TAVR. Permitting widespread use before developing a good understanding of the clinical and economic value of a therapy is a reliable formula for producing much flat of the curve medicine: money spent for procedures on low-risk patients very unlikely to experience any benefit. However, significant underuse of a therapy that can save lives and reduce suffering is also not desirable. Mindful of the lessons from the past and from early TAVR adopters in Europe, the American College of Cardiology and the Society of Thoracic Surgeons (STS), together with the Centers for Medicare and Medicaid Services and the Food and Drug Administration, have agreed to a controlled dissemination plan that includes a mandatory registry to encourage rational evidence-based use (https://www.ncdr.com/TVT). Having detailed accurate data about how TAVR is being used is a critical first step, but having such data does not guarantee agreement on how to interpret and act on the findings.

The economic and policy implications of the 2 PARTNER trials pose substantially different issues. Therefore, we consider them separately, starting with the “inoperable” AS cohort (cohort B). Using parametric statistical modeling, Reynolds and colleagues7 estimated that for this population of elderly (mean age, 83 years), very symptomatic (93% New York Heart Association class III or IV) patients, TAVR...
extended survival from a life expectancy of 1.2 to 3.1 years, mostly by preventing heart failure–related and sudden deaths. Although the increment is significant in both a clinical and a statistical sense, the TAVR-treated patients still had a life expectancy less than half of what is expected from the US actuarial life tables (6.5–7.8 years). Although the cause of this very high residual mortality is not clear, the extensive comorbidity in this portion of the AS population may create a ceiling effect on any benefit from TAVR.

Patients facing severe illness, of course, usually want to have their survival extended when possible, but they are not indifferent to the quality of that survival. Combining quality-of-life (QOL) outcomes with survival provides a more informative picture of the health benefits of TAVR. A favorable outcome, defined as being alive at 1 year and having at least a 10-point increase over baseline in heart failure–related QOL as measured by the Kansas City Cardiomyopathy Questionnaire, was observed in 48% of the TAVR patients and 14% of the control patients. Excellent outcomes (alive at 1 year with at least a 20-point increase) were obtained in 38% of TAVR patients and 9% of control subjects. In terms more familiar to clinicians, an excellent outcome, defined as being alive at 1 year and in New York Heart Association class I, was seen in ~25% of the TAVR patients compared with essentially none of the conservatively treated patients. Interestingly, the PARTNER investigators did not identify any strong subgroup effects of different comorbidities in the QOL benefits of TAVR at 1 year. The STS risk score appeared to define a gradient of survival benefit for TAVR, with the highest-risk 25% (STS score ≥15) showing no survival benefit, but STS score did not affect QOL benefit.

Having defined the clinical benefits of TAVR in this population, we are now in a position to consider the cost of producing that benefit. Using trial data, Reynolds and colleagues estimated the cost of a TAVR procedure at $43,000, including a device cost of $35,400. Hospitalization for the procedure averaged 4 days in the intensive care unit and 6 non–intensive care unit days, with total costs of about $79,000 (including $5000 of physician fees). Eighty-four percent of the standard therapy patients in this trial underwent balloon aortic valvuloplasty. During the first year of follow-up, the TAVR patients had more days in skilled nursing and rehabilitation facilities (averaging $2500 per patient more than conservative care) but fewer cardiovascular hospitalizations (saving about $27,000 per TAVR patient). At 1 year, total costs for the TAVR patients averaged $52,000 per patient more than the conservatively treated patients. With the lifetime model extrapolations, TAVR added 1.6 years of life expectancy at a cost of about $80,000 (both discounted at 3%), which yielded an incremental cost-effectiveness ratio of $50,212 per life-year added. Factoring in the reduced QOL of the survivors (1-year utility weights, 0.72 for TAVR and 0.62 for standard therapy) yielded a cost per quality-adjusted life-year of $62,000. These results confirm that TAVR represents good value for the money, perhaps not a best buy but very respectable when measured against standard benchmarks in health economics.

In severe AS patients for whom surgical AVR is the current standard of care, evaluating the economics of TAVR is more challenging because the clinical outcomes have been framed in terms of noninferiority. In PARTNER A, although mortality was very similar out to 3 years (at which time it was ~50%), it was transiently higher in the surgical AVR group in the perioperative period compared with transfemoral TAVR. That early mortality difference equates to a 0.065–life-year advantage for TAVR (~24 extra days). At 1 year, TAVR had 2.1 per 100 more major strokes. Early major vascular complications were also higher in TAVR, whereas early major bleeding was higher in the surgical AVR group. Using our earlier definition of an excellent clinical outcome at 1 year indicates that ~35% of both groups were alive and had New York Heart Association class I symptoms. Using patient-reported QOL outcomes, ~60% of patients in both groups were alive and had a ≥20-point increase from baseline in their QOL score.

Index admission costs totaled about $72,000 for TAVR and $74,400 for AVR. Procedural costs for surgical AVR were about half those of TAVR, but cost parity was achieved because surgical AVR patients spent an additional 2.3 days in the intensive care unit and 4 more non–intensive care unit days in the hospital. Follow-up costs out to 1 year were also essentially the same (about $22,000). Thus, the 1-year cumulative cost for each therapy was around $100,000, with a statistically insignificant difference between the 2 therapies of about $2200 favoring TAVR. The major economic analysis question posed by the results of PARTNER A is whether to use the small, nonsignificant early differences favoring TAVR (0.065 more life-years and $2200 lower cost) to conclude that TAVR is the preferable strategy (“dominant” in the language of the health economist, meaning better health outcomes and lower costs). Alternatively, using 3-year survival, major complication data, and 1-year QOL data, along with the nonsignificance of the cost difference, one could conclude that the choice is a therapeutic and policy toss-up. Clinicians looking at the data would generally favor the therapeutic equivalence interpretation in which there is no best treatment and in which individual treatment decisions might be determined primarily by the patient’s preference to have a less invasive procedure or to avoid a novel therapy with a long-term durability that remains to be firmly established.

Just as early percutaneous coronary intervention technologies were substantially improved by several generations of innovations building on the basic technological concepts, we can expect that TAVR will continue to improve in ways that will make the procedure safer and possibly enhance the durability of the results. Although these developments are unlikely to affect the major health outcomes or economic attractiveness of TAVR for inoperable patients, they may lead to more surgical candidates choosing the catheter-based approach instead, as has happened with coronary revascularization. However, TAVR moving to a lower-risk population than PARTNER A may change even the small advantages it demonstrated. The 30-day mortality for AVR in PARTNER A was 6.5%. The operative mortality for AVR in the STS database is currently <3%. Operating on
lower-risk patients is also likely to involve shorter postoperative hospital stays and lower overall costs. The clinical and economic advantages of TAVR in such patients cannot be assumed and need to be empirically demonstrated.

Cost effectiveness is the first of 2 economic questions that must be considered for any expensive new medical treatment. The second is affordability: How much will the technology add to the total healthcare bill, and are there funds to pay for it? The substitution of TAVR for surgical AVR in patients already being referred for AVR is not likely to have much effect at current prices because the 2 therapies have very similar short- and long-term costs. However, some data suggest that only about half of the patients who have surgically eligible AS currently get an AVR, so it is possible that the availability of TAVR will result in significantly more patients receiving a procedure. Whether that, in turn, will ultimately reduce the number of very elderly patients with “inoperable” AS by intervening earlier is also unknown. What is even less clear is the expected budgetary impact of TAVR on patients currently receiving only palliative care. Population-based estimates suggest that there may be a million adults in the United States with clinically diagnosed AS, and about half of them may be patients ≥75 years of age with severe AS. If 100,000 patients end up getting an AS treatment because of the introduction of TAVR, at an incremental cost of about $80,000, the bill will total $8 billion. Even this may be an underestimate of the total financial impact of TAVR.

One effect of TAVR that does not show up in the PARTNER economic analyses has to do with the front-end cost of screening and referral. No data are available on the cost of such screening, but a full evaluation in these symptomatic elderly patients is likely to be done on an inpatient basis and to involve multiple days in the hospital, multiple diagnostic tests (eg, coronary angiography, pulmonary function tests, chest/abdomen/pelvis computed tomographic angiography), and multiple specialist consultations. Assuming that this evaluation reveals that 2 of every 3 referred patients are ineligible for TAVR, as in PARTNER, substantial additional costs related to TAVR are incurred without a clear increment in benefits. These considerations highlight the need for a full technology assessment of a novel therapy to look beyond the questions of economic efficiency and to assess all the changes created by that technology in the healthcare system.

An old adage holds that if you place a frog in a slowly heating pot of water, it will make no attempt to escape, but if you place it in boiling hot water, it will frantically try to escape. Although there have been many predictions over the last 50 years that various new technological medical innovations would surely set the waters of health care to boiling, the predictions have so far been wrong. However, there is little doubt that the metaphoric water is slowly getting hotter, and new technology is the most important source of the heat. TAVR is exciting because it offers an effective and less invasive option for treating severe AS that may make this therapy available to patients for whom so-called comfort care was previously the only option. Mindful of past criticisms regarding excessive use of expensive technology, the cardiovascular community, through its leadership in the American College of Cardiology and STS, has committed to making the clinical introduction of TAVR a model of responsible dissemination. If successful, this model will define a new health policy paradigm that encourages and rewards innovation while keeping the healthcare cost waters from boiling.

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References

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