Prediction is very difficult, especially if it’s about the future.

Neils Bohr

Life expectancy in the United States has steadily increased in the past century, from just <60 years in 1930, to just <70 years in 1960, and to just <80 years in 2010. Progress, however, has its price. The numbers of elderly and very elderly members of the population in the United States and other developed nations are increasing rapidly along with their age-related health problems. At the same time, healthcare spending has risen dramatically. As new medical treatments have become more expensive to discover and produce, and the incremental benefits those treatments provide have become smaller, there is a growing perception that the return on continued increases in healthcare spending may be diminishing.1

Into this milieu enters transcatheter aortic valve replacement (TAVR), a therapy that is currently revolutionizing the approach to managing aortic stenosis (AS)—a condition, mainly, of the elderly. Cohort B of the Placement of Aortic Transcatheter Valves (PARTNER) trial,2 along with a number of nonrandomized studies, has shown that TAVR can greatly improve health outcomes in the important minority of patients with severe AS who are felt to be at prohibitive risk for surgical intervention. In this setting, TAVR reduced all-cause mortality by absolute margins of 20% and 25% at 1 and 2 years, respectively, while substantially improving functional status and quality of life, compared with medical management.2–4

Although the clinical benefits of TAVR for the inoperable population are unquestionably large, so too are the financial costs, not only of the treatment itself but also for the ongoing medical care of patients who are, on average, octogenarians with complex medical problems. Consequently, payers in varied settings have needed to carefully examine the affordability and value of TAVR before supporting its widespread adoption.

The current issue of Circulation: Cardiovascular Quality and Outcomes presents an interesting new analysis performed by Simons et al5 on the cost-effectiveness of TAVR for inoperable patients. The authors constructed a Markov model to project the medical care costs, quality of life, and survival of patients with inoperable AS treated with TAVR compared with medical management during a lifetime horizon. Because the PARTNER trial remains the only study to have randomized patients between these interventions, the authors used a novel, sophisticated mathematical algorithm to simultaneously calibrate 16-key model inputs to the observed outcomes from the trial. The approach used is somewhat analogous to regression analysis in that it seeks to identify a simultaneous set of parameters that, when inserted into their disease simulation model, fit the observed data most closely. The authors’ resulting model predicts that TAVR will increase quality-adjusted life expectancy by 0.73 discounted quality adjusted life years (QALYs) (or 0.86 life years) and increase total healthcare expenditures by $85 500 per person, resulting in an incremental cost-effectiveness ratio of $116 500 per QALY gained (or $99 900 per life year gained).

This study contributes to a rapidly growing literature on the subject. Prior studies have reported incremental cost-effectiveness ratios ranging from £16 100 to £61 900 per QALY gained,6 with intermediate values reported in the US dollars,7 Canadian dollars,8,9 and Euros.10 Thus, the current study has reached a somewhat more pessimistic view of the cost-effectiveness of TAVR than a number of other independent analyses that were largely derived from the same data set.

It is clear that the appropriate estimation of cost-effectiveness in this setting requires extrapolations of both clinical and economic outcomes beyond the time horizon of the trial itself, which had a minimum of 12-month follow-up and a maximum of 2.5 years when initially published.7 Although different modeling techniques have replicated the in-trial results with reasonable precision, as with forecasting weather or economic markets, predictions on the future survival and costs of these patient groups have varied, along with the methods used to make them.

The approach used by Simons et al5 to predict survival involved piecewise exponential modeling, where the hazards for each group were temporally adjusted such that the model would replicate published survival results at different time points. It is not clear from the article exactly how the piecewise exponential modeling was executed. As previously reported,3 although the relative mortality hazard for TAVR versus medical therapy in PARTNER remained stable at =0.5 with longer follow-up, the absolute mortality rates decelerated between years 1 and 2. In the medical management group, 1-year mortality was 51%, but among those who survived the first
year, mortality in the second year was 35%. Likewise, TAVR group mortality in year 1 was 31% but in year 2 only 18%. Presumably the piecewise exponential methodology used by the authors involved projecting the lower underlying hazard seen during some later portion of the follow-up during the remainder of each group's lifetime. This approach replicated our own previously reported patient-level projections from the trial for the TAVR cohort (2.93 versus 2.78 life years, with 3% discounting), which were created conditional on 3-month survival and also assumed an exponential survival function, but produced substantially different results for the medical management group (2.01 versus 1.20 discounted life years), for which our survival models used the entirety of observed follow-up for calculating the future hazard.

There is no empirical method to determine which approach is most correct. It is certainly possible that the observed deceleration in the hazard for the medically managed patients in PARTNER is real. One could imagine, for example, that the medically managed population was heterogeneous in its underlying risk such that the sickest patients died earliest, and the remaining selected survivors constituted a lower risk group that would be expected to have better odds of survival going forward. However, the idea that a population of patients with symptomatic, severe, inoperable AS would enjoy a sustained plateau in their risk of death does not resonate with the well-known natural history of AS, which is marked by inexorable progression. Furthermore, the risk of death for the elderly in general is not static but tends to increase with time/aging. For example, the risk of death for the average American 83 to 84 years of age is 7.0%, but for 85 to 86 years of age it is 8.7%. Hence, the use of exponential survival models, which assume a constant hazard rate over time, may not have been optimal.

It is also important to understand that the medical management arm of PARTNER was not truly a natural history study of untreated AS. The control group patients were frequently treated with balloon valvuloplasty, which increased costs but may also have improved quality of life (at least transiently) and in some cases effectively served as a bridge to TAVR or AVR. In addition, within the first year of follow-up, 16 (8.9%) of the control group subjects underwent surgical AVR or TAVR outside their study centers, with lower 1-year mortality rates (33% and 0%, respectively) than observed for the cohort as a whole. Moreover, crossover to TAVR was permitted by protocol after all patients had completed 12 months of follow-up and was done in 20 of the 58 survivors who became eligible. Thus, the published intention-to-treat survival statistics beyond the first 12 months of the study incorporated the impact of these life-prolonging interventions in the control group population. If longer term survival projections were based mainly on survival during the second year of study follow-up, then those projections could be overly optimistic.

Aside from survival projections, the other major source of uncertainty in estimating the cost-effectiveness of TAVR for inoperable patients stems from the estimation of future medical care costs. These costs will naturally vary across health systems and, therefore, need to be derived using local data for each country-specific analysis. In our US, trial-based analysis, we projected future healthcare costs for each group on the basis of a detailed review of observed costs for all health problems during months 6 to 12 of follow-up. In contrast, the Simons group estimated total baseline healthcare spending unrelated to the treatment of AS on the basis of previously published estimates for patients aged ≥85 years. Additional costs for AS-related procedures, complications, and hospitalizations were added on top of this already high baseline. We arrived at an empirical estimate of $22,500 per patient in annual costs after TAVR, whereas the Simons group’s model started with baseline costs of closer to $30,000 per year.

These chronic healthcare costs—which are frequently ignored in cost-effectiveness analyses of other interventions—have a peculiar but predictable result on model results. Because the medical management group has a short life expectancy, high chronic medical care costs accumulate to a greater degree in the TAVR group, which has better survival. As a result, the higher the background medical costs, the lesser the cost-effective TAVR appears. This line of reasoning has uncomfortable implications entirely unrelated to TAVR or aortic valve disease: at some point, if background medical costs exceed societal willingness to pay, any life-extending medical intervention will fail to be a good value in health economic terms. As Simons et al conclude, the cost-effectiveness equation at some point becomes much more about the patients than about the technology.

What conclusions can we, therefore, reach about the cost-effectiveness of TAVR for inoperable patients? There is no question that TAVR improves both quality of life and survival in this population, and that it increases costs. In all likelihood, the true cost-effectiveness ratio, on the basis of PARTNER trial experience, is somewhere between $50,000 and $100,000 per QALY gained in the United States and somewhat lower outside the United States, where both the initial treatment cost and background medical care costs are lower. The health benefits of TAVR for these patients are thus obtained at neither exceptionally good nor exceptionally poor value.

We expect results to improve rather than worsen going forward. Although the single-minded focus of these analyses on the PARTNER trial is understandable, the valve system used in PARTNER was first generation, and the trial was the initial clinical experience with TAVR for most of the participating centers. Most of the procedures in cohort B of PARTNER were performed in 2008. Improved clinical outcomes from European registries and the continued access program of the PARTNER trial have already been reported. Health economic models should, therefore, be updated periodically to incorporate the changing clinical evidence base with regard to both costs and clinical outcomes.

It is also likely that the value of TAVR for inoperable patients is not uniform across patients. TAVR may be a much better value for patients who are inoperable for technical reasons rather than because of severe, complex comorbidity because the life expectancy gain in these relatively lower risk patients is greater. Researchers will need to continue trying to define patient groups for whom TAVR is truly futile to better inform patients who are considering the procedure and to facilitate the decision making of heart teams.

In summary, the article by Simons et al contributes to our continuously evolving understanding of the health economics of TAVR, particularly from a methodological perspective. We do not, however, consider it the final word.
Disclosures

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