JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 1, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.11.013

EDITORIAL COMMENT

The Core Value of Cost-Effectiveness Analyses*

Sanket S. Dhruva, MD,†‡ Harlan M. Krumholz, MD, SM†§

Over the past 4 years, transcatheter aortic valve replacement (TAVR) has transformed the cardiac care of patients in the United States with severe aortic stenosis (SAS). In September 2011, a balloon-expandable prosthesis (Sapien, Edwards Lifesciences, Irvine, California) received U.S. Food and Drug Administration (FDA) approval for the treatment of inoperable patients on the basis of a randomized trial showing improved 1-year mortality (50.7% vs. 30.7%) (1). This indication was extended in September 2012 to high-risk patients after another randomized trial showed similar 1-year mortality in patients receiving TAVR and surgical aortic valve replacement (SAVR)—24.2% and 26.8%, respectively (2). This device has been enhanced, leading to a most recent FDA approval in June 2015 of the third-generation balloon-expandable valve (3). In January 2014, the FDA also approved a self-expanding prosthesis (CoreValve, Medtronic, Dublin, Ireland) for TAVR on the basis of nonrandomized data in patients who were at prohibitive surgical risk (4).

The mortality and quality-of-life benefits of TAVR have led it to become a widely adopted therapy for patients with SAS who are at prohibitive and high surgical risk. Within the first 19 months post-approval, nearly 8,000 patients underwent TAVR (5). Estimates project >100,000 TAVR candidates in North America with >9,000 annual incident possible procedures (6). However, TAVR is an expensive technology, and treating all eligible North American patients with TAVR would cost >$7 billion (7). Given these potentially large expenses, cost-effectiveness analyses are important to put the procedure in perspective compared with alternative strategies. On the basis of randomized data, TAVR in high surgical-risk patients with the balloon-expandable valve was found to be cost-effective only via the iliofemoral, but not the transapical, route (8). In the overall population, the incremental cost-effectiveness ratio (ICER) was $76,877 per quality-adjusted life year (QALY) gained (8). There are no cost-effectiveness analyses of the self-expanding prosthesis, but its studies have enrolled a slightly different patient population.

SEE PAGE 29

In this issue of the *Journal*, Reynolds et al. (9) present a rigorous economic analysis using data from the U.S. CoreValve High Risk Study, which randomized 795 patients (mean age 83 years, 53% male) with SAS and New York Heart Association functional class II or greater heart failure symptoms at increased surgical risk to TAVR or SAVR (10). TAVR patients had lower 2-year mortality (11). Although both TAVR and SAVR improved disease-specific and generic health status at 1 month, only patients receiving iliofemoral TAVR had a significant health status benefit over SAVR (12). This relative improvement was not sustained at 6 or 12 months. A relative benefit isolated to iliofemoral patients is consistent with findings from high-risk patients treated with the balloon-expandable valve (13). This may be due to delayed recovery

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Robert Wood Johnson Foundation Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut; ‡Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut; and the §Section of Cardiovascular Medicine, Yale School of Medicine; Department of Health Policy and Management, Yale School of Public Health; and Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut. Dr. Krumholz is supported by grant U01 HL105270-05 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute; is the recipient of research agreements from Medtronic and Johnson & Johnson (Janssen), through Yale University, to develop methods of clinical trial data sharing; is the recipient of a grant from Medtronic in collaboration with the Food and Drug Administration, through Yale University, to develop methods and facilitate best practices for medical device surveillance; and chairs a cardiac scientific advisory board for United Healthcare. Dr. Dhruva has reported that he has no relationships relevant to the contents of this paper to disclose. Neil Moat, MBBS, served as Guest Editor for this paper.

because of a ministernotomy or minithoracotomy used for direct aortic entry.

The investigators found that the higher technology cost of the TAVR system ($32,000 commercially) accounted for the largest proportion of TAVR expenses. Shorter ICU and hospital lengths of stay offset much of that charge, so overall in-hospital TAVR costs were $11,260 more per patient over SAVR. At 12 months, TAVR cost $9,207 more than SAVR.

In the CoreValve High Risk study, data are likely only generalizable to the study cohort: SAS patients with New York Heart Association functional class II or greater heart failure symptoms at increased surgical risk (10). Of 995 screened patients, just 757 (76%) underwent attempted TAVR or SAVR. This randomized data must be supplemented by studies to ensure that trial efficacy is translated into real-world effectiveness—and safety (14). Furthermore, early results in the use of this technology may not be applicable to patients receiving TAVR later, because of improvements gained through experience and device iterations.

Conclusions from cost-effectiveness analyses depend on modeling and discount rates, and Reynolds et al. (9) integrated the self-expanding prosthesis' survival and quality-of-life data based on U.S. health care system conditions. They found an ICER of $55,090 for TAVR versus SAVR per QALY. Sensitivity analyses suggested that reducing TAVR in-hospital costs by about $1,650 would bring the ICER to <$50,000.

So, is this a good value? What level of cost-effectiveness is reasonable? Should we quibble about the $1,650 to meet this $50,000 threshold? Although the $50,000 bar has unclear origins, it is frequently—likely incorrectly—attributed to the U.S. Congress' mandate that dialysis be paid for by taxpayer-funded Medicare (15,16). Only in the past 2 decades has this threshold even been widely used, possibly because it is a convenient number (15,17). Cost-effectiveness depends more on the costs that a health care system is willing to bear. The World Health Organization suggests a benchmark of 3× the gross domestic product per capita as an upper threshold, which would be about $150,000 per QALY in the United States—significantly higher than the $50,000 bar (18). No matter the threshold, we have no precedent for denying payment of therapies that show benefit—even for supremely expensive treatments. Indeed, Medicare is prohibited from considering cost in nearly all of its coverage determinations (15).

More importantly, why do we care about cost-effectiveness thresholds? We do not ration explicitly such that a highly effective therapy is withheld from people whose lives could be saved. Moreover, we pay for many treatments with uncertain benefits: 22% of implantable cardioverter-defibrillator implantations are not evidence-based, and 13% of nonacute percutaneous coronary interventions are classified as inappropriate and 33% are classified as uncertain (19,20). Also, the >$100 million that was spent monthly on ezetimibe before any outcomes trials provided evidence of its clinical benefit indicates that our health care system can sometimes pour resources into uncertain therapies (21). Even with new treatments lacking outcomes data, we similarly seem immune to cost considerations: if only 5% of U.S. adults with elevated low-density lipoprotein cholesterol took the new PCSK9 inhibitors, annual insurance premiums would increase by $124 for each person in the pool (22). In these cases, the cost-effectiveness ratio cannot be calculated with any confidence because of the uncertainty about effectiveness.

Perhaps these calculations are best used for determining value and negotiating prices. Although there is little precedent for using these calculations for cost, many have called for payment based on value. To do so, we must foremost rely on rigorous clinical data to ensure that benefits outweigh risks and supplement them with observational data to provide bounds to the estimates.

If cost-effectiveness analyses are to be useful, then they must be timely and relevant to current clinical practice. Ideally, cost-effectiveness analyses would be available as close as possible to FDA approval. The cost-effectiveness analysis of the self-expandable valve was presented at the Transcatheter Cardiovascular Therapeutics conference (held in Washington, DC from September 13-17, 2014) about 8 months after FDA approval, and is now being published in the *Journal*. But there have already been important developments: The device was approved for valve-in-valve procedures in March 2015 and a new, recapturable self-expandable system was approved in June 2015 with a smaller sheath size that will likely allow for more iliofemoral TAVR. Thus, this technology has been evolving rapidly, and ideally, cost-effectiveness analyses would be updated simultaneously and also allow for comparison between the balloon-expandable and self-expanding TAVR systems.

In addition to technological advances, treatment paradigms for SAS are evolving from dependence on classic aortic stenosis symptoms. Recent guidelines give a Class IIa recommendation to AVR for patients with very severe aortic stenosis but no symptoms (23). A recent registry study published in the *Journal* suggests that even patients with SAS who are asymptomatic may benefit from AVR (24). And, although TAVR has FDA approval only in high- and prohibitive-risk patients, it is increasingly performed in Europe for

intermediate-risk patients while multiple trials in this patient population are ongoing (7). Additionally, SAVR outcomes have improved substantially over the past decade (25). All of these factors related to aortic valve disease, TAVR, and SAVR must be considered in future cost-effectiveness analyses.

At this time, the study by Reynolds et al. (9) makes an important contribution as the first cost-effectiveness analysis of the self-expanding prosthesis. We are already paying for this technology given the mortality and quality-of-life benefits of TAVR, and although we do not need to fixate on achieving the $50,000/QALY, we must monitor cost-effectiveness over time as science moves forward. These analyses are likely to become increasingly important as cost-consciousness takes a greater hold in health care, and as a society, we will achieve greater benefit if we can curb misuse and direct our resources toward beneficial interventions. In deciding what not to do based on cost, we should start where effectiveness is unproven.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Harlan M. Krumholz, Yale School of Medicine, 1 Church Street, Suite 200, New Haven, Connecticut 06510. E-mail: harlan.krumholz@yale.edu.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

3. U.S. Food and Drug Administration. FDA News Release: FDA approves SAPIEN 3 THV artificial heart valve - Third generation of valve contains design change to minimize leakage. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm451678.htm. Accessed November 3, 2015.

4. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–81.

5. Mack MJ, Brennan J, Brindis R, et al. Outcomes following transcatheter aortic valve replacement in the United States. JAMA 2013;310:2069–77.

6. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002–12.

7. Osnabrugge RL, Kappetein AP, Reynolds MR, Cohen DJ. Cost-effectiveness of transcatheter valvular interventions: economic challenges. EuroIntervention 2013;9 Suppl:S48–54.

8. Reynolds MR, Magnuson EA, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol 2012;60:2683–92.

9. Reynolds MR, Lei Y, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. J Am Coll Cardiol 2016;67:29–38.

10. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

11. Reardon MJ, Adams DH, Kleiman NS, et al. 2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol 2015;66:113–21.

12. Arnold SV, Reynolds MR, Wang K, et al. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk: results from the CoreValve US Pivotal Trial. J Am Coll Cardiol Intv 2015;8:1207–17.

13. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;60:548–58.

14. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. Circulation 2008;118:1294–303.

15. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoeconomics Outcomes Res 2008;8:165–78.

16. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.

17. Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. J Health Economics 1997;16:1–31.

18. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2304–22.

19. Al-Khatib SM, Hellkamp A, Curtis J, et al. Non–evidence-based ICD implantations in the United States. JAMA 2011;305:43–9.

20. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection, and appropriateness of percutaneous coronary intervention. JAMA 2015;314:2045–53.

21. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. N Engl J Med 2008;358:1819–28.

22. Schulman KA, Balu S, Reed SD. Specialty pharmaceuticals for hyperlipidemia—impact on insurance premiums. N Engl J Med 2015;373:1591–3.

23. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

24. Taniguchi T, Morimoto T, Shiomi H, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2015;66:2827–38.

25. Barreto-Filho JA, Wang Y, Dodson JA, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999–2011. JAMA 2013;310:2078–85.

KEY WORDS aortic stenosis, appropriate use, cost-benefit analysis, heart valve prosthesis, quality-adjusted life-years, transcatheter valve therapy