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Editorial to Accompany Reynolds et al: The Core Value of Cost-Effectiveness Analyses

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Over the past 4 years, transcatheter aortic valve replacement (TAVR) has transformed the cardiac care of patients in the US with severe aortic stenosis who previously had few treatment options. In September 2011, a balloon-expandable prosthesis (SAPIEN®, Edwards Lifesciences) received 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 most recently to the June 2015 FDA approval of the third-generation SAPIEN 3 valve. (3) In January 2014, the FDA also approved a self-expanding prosthesis (CoreValve®, Medtronic) for TAVR on the basis of non-randomized data in patients at prohibitive surgical risk. (4)

TAVR's mortality and quality of life benefits have led it to become a widely adopted therapy for patients with severe aortic stenosis at prohibitive and high surgical risk. Within the first 19 months post-approval, nearly 8,000 patients underwent TAVR with the SAPIEN valve. (5) Estimates project over 100,000 TAVR candidates in North America with over 9,000 annual incident possible procedures. (6) However, TAVR is an expensive new technology and treating all eligible North American patients with TAVR would cost more than $7 billion. (7) Given these large possible expenses, cost-effectiveness analyses are important to put the procedure in perspective compared with alternative strategies. Based on randomized trial data, TAVR with the SAPIEN valve in high surgical risk patients 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

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prosthesis, but it is one of only 2 FDA-approved therapies for TAVR and its studies have enrolled a slightly different patient population.

In this issue of *JACC*, Reynolds et al. (9) present a rigorous economic analysis using data from the U.S. CoreValve® High Risk Study. This study randomized 795 patients (mean age 83, 53% male) with severe aortic stenosis and New York Heart Association (NHYA) Class II or greater heart failure symptoms at increased surgical risk to TAVR or SAVR. TAVR patients had lower 2-year mortality (22.2% versus 28.6% in SAVR group, $p<0.05$). (10) While 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. (11) This relative improvement was not sustained at 6 or 12 months. A benefit isolated to iliofemoral patients is consistent with findings from high-risk patients treated with the balloon-expandable valve. (12) This may be due to delayed recovery 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® study, data are likely only generalizable to the study cohort: severe aortic stenosis patients with NYHA Class II or greater heart failure symptoms at increased SAVR risk. (13) Of 995 screened patients, just 752 (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) Further, trial results early in the use of this innovative 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 integrated the self-expanding prosthesis' survival and quality of life data based on healthcare system conditions in the US. 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? The $50,000 bar has unclear origins, although it is widely – although 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 healthcare 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 US – significantly more 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. That 22% of implantable cardioverter-defibrillator implantations are not evidence-based, 12% of percutaneous coronary interventions are inappropriate and 38% uncertain, and more than $100 million was spent monthly on ezetimibe before any outcomes trials indicates that our healthcare system can sometimes pour resources in ineffective therapies. (19–21) Even with new treatments lacking outcomes data, we similarly seem immune to cost considerations: If only 5% of adults in the US with elevated LDL 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 pricing. 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 it 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 the time of FDA approval. The CoreValve® was approved in January 2014 and the cost-effectiveness analysis was presented at the Transcatheter Cardiovascular Therapeutics conference about 8 months later, and is now being published in this issue of *JACC*. But there have already been important developments: The device was approved for valve-in-valve procedures in March 2015 and a new, recapturable CoreValve® 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 innovations, treatment paradigms for severe aortic stenosis 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 *JACC* suggests that even patients with severe aortic stenosis who are asymptomatic may benefit from AVR. (24) And while TAVR has FDA approval in the US 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. makes an important contribution as the first cost-effectiveness analysis of the self-expanding prosthesis. We are already paying for this technology given TAVR's mortality and quality of life benefits and do not need to fixate on achieving the $50,000/QALY, but we must monitor cost-effectiveness over time as science

moves forward. These analyses are likely to become increasingly important as cost-consciousness takes greater hold in healthcare and, as a society, we will achieve greater benefit if we can curb misuse and direct our resources towards beneficial interventions. But in deciding what not to do based on cost, we should start where effectiveness is unproven.

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