

TAVR: Is The Glass Half Empty or Half Full? A Non-Interventional Cardiologist's View of a New Technology

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Transcatheter Aortic Valve Replacement (TAVR) is a new, disruptive technology that is currently being widely embraced and aggressively marketed. The technology has the potential to radically alter the conventional clinical approach to aortic stenosis, which affects ~1.5 million Americans, many of whom are elderly. Existing data suggest that the transcatheter strategy has advantages over a conventional surgical approach in the elderly, infirm patient population. However, TAVR remains associated with profound morbidity and mortality reflective of the underlying nature of the disease. Given this, it is important to temper enthusiasm for the technology with a realistic assessment of its impact on the natural progression of the disease, especially in the elderly and infirm population that is currently being targeted.

The commercial roll-out of the percutaneous aortic valve program (TAVR) in the US began in the Spring of 2012 and as of March 2013 more than 200 sites have been opened and more than 4500 procedures have been performed. (In Europe, the TAVR approach has been sanctioned since 2007, and nearly 40,000 percutaneous valves have been deployed.) The FDA allowed this technology to move forward in the US based on a carefully documented randomized trial experience but with a series of caveats, most notably: 1. that the sites identified must have substantial experience and expertise with complex cardiac interventions (on both the surgical and interventional cardiology fronts); 2. That patients selected for TAVR must have sufficient co-morbidities so as not to be conventional surgical candidates and 3. That comprehensive registry data has to be collected in order to document real world experience in the US with this new technology [1-3]. The appropriate concern was that if the technology was released in a haphazard fashion without careful attention to patient selection and quality control, then the outcomes would likely be sub-optimal and the health care costs would be high [4]. From all indications, these safeguards are in place and are currently buffering (if not completely tamping down) the high level of enthusiasm for the procedure throughout the interventional cardiology community.

Currently only one valve type is commercially available in the US (the Sapien Valve, made by Edwards Lifesciences) and it is anticipated that other manufacturers will shortly move their devices forward into the commercial market which should reduce device costs but may also compromise the safeguards that are currently in place. In addition, as additional randomized clinical trial data, most notably the Partners 2 trial, become available in a less restricted population of patients; it seems likely that the indications for percutaneous valve replacement will also be broadened.

Certainly the technological advances that led to the development of a percutaneous aortic valve are extraordinary and the release of this new, potentially paradigm shifting, and minimally invasive therapy is profoundly exciting. Aortic stenosis is a huge problem. There are approximately 1.5 million Americans with aortic stenosis of which 250,000 - 500,000 have severe and/or symptomatic disease [5]. These numbers will rise as the population ages. Despite this, only 85,000 surgical aortic valve replacements were done in the past year which speaks to a substantial unmet need that will potentially be filled by

this new technology. However, the history of new innovations in cardiology highlights the need for circumspection. With therapeutic interventions as diverse as PCI, dual chamber AICDs, and PFO closure, time has tempered much initial enthusiasm and our indications for the deployment of these technologies have undergone a gradual and nuanced revision. Coronary interventions for patients with angina except for select indications have not been shown to prolong life when contrasted with good medical therapy dual chamber AICDs (as opposed to single chamber devices) are probably deployed too frequently with the very real down-side of an increase in complication rate and closure devices (specifically for PFOs), while non-inferior to surgical options have not yet been shown to be clearly superior to medical therapy at preventing CVA [6-8]. Despite these cautionary outcome data, these interventions are commonly utilized today and it is unquestionably true that they continue to be beneficial and perhaps life-saving in individual circumstances. However, if the passage of time has taught us anything, it is that technological advances are not panaceas and also that patient selection is something that is not intuitive and ultimately requires a great deal of thought.

These caveats seem particularly important as we enter the TAVR era and it seems very appropriate to question whether TAVR "cures" aortic stenosis, whether it prolongs meaningful life in an elderly patient population and most critically how can we identify patients who will truly benefit from device utilization. Of course as the FDA approved indications expand and as device design improves (and these two things seem certain) we will have to repeatedly re-ask these same questions.

At the moment, the commercial utilization of the device is restricted to patients who have a prohibitively high STS (Society of Thoracic Surgeons) risk score or other perceived confounding co-morbidities that make them non-surgical candidates. The published experience in this group, both from a real-world European experience and also from carefully conducted clinical studies at experienced centers in the United States, suggests that overall and cardiac mortality is improved in this select patient population relative to non-surgical standard care [3]. However this benefit is at least partially counterbalanced by an increased risk of CVA. While these data certainly speak to feasibility, the actual morbidity and mortality data are still somewhat staggering. The "improved" mortality risk in the TAVR group in the US trial was still 43.3% at two years (versus 68% in the medical group) and the CVA risk was 13.8% (versus 5.5%). This translates into a greater than 50%

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risk of death or major morbidity at two years. In the group of TAVR patients that survived unscathed, there was a significant improvement in quality of life. The percentage of surviving patients who reported NYHA I-II symptoms two years following TAVR was ~80%, a considerable improvement from their pre-procedural status at which point only 5% were in these categories, and when patients were surveyed as to quality of life using a rigorous analytic tool, TAVR patients did better than a comparable standard care group [9,10]. However, ~40% of the standard therapy group reported NYHA class I-II status at two years again contrasted with only 5% at the time of randomization, and QOL improved in this group at 6 months and 1 year of follow-up (though not to the same degree as the TAVR group) so there was some value in non-TAVR therapy which included careful cardiology follow-up, medication adjustment and valvuloplasty in some patients. To summarize, at two years following TAVR in a cohort of patients deemed ineligible for AVR, ~45% were dead, ~14% had CVAs, and 20% of the survivors (or an additional 10-12% of the initially randomized patients) were NYHA III-IV. While these data have been used (correctly) to provide legitimacy for the interventional strategy, they also demonstrate that ~65% of patients who are deemed non-surgical candidates who undergo TAVR will either be dead or severely disabled two years after the procedure. This contrasts with ~85% who will be either dead or severely disabled at the same time point if a non-TAVR therapy is utilized. So clearly the results with TAVR are superior in terms of survival and quality of life, but one has to ask how much better an absolute risk of 65% versus 85% is? The odds in both circumstances are still solidly against meaningful functional recovery. A caveat that should be mentioned is that in general the European experience with TAVR shows slightly better survival than the US experience, perhaps reflecting the more complete learning curve (commercial roll-out in Europe was in 2007 and more than 40,000 procedures have been done) so there is some reason to believe that over time the outcome data in the US will improve.

Of course these discouraging data are reflective of the patient population being considered. Aortic stenosis is a very morbid disease, and this morbidity is reflective of the fact that the disease manifests in an elderly and frail population, it is associated with profound and risky valvular calcification, and it induces significant cardiac muscle dysfunction likely also confounded by an arrhythmogenic substrate [11]. These features are not easily navigated and they are certainly amplified if one selects a cohort of patients that by virtue of their comorbidities are the sickest of the sick. However, the current commercial roll-out of TAVR is limited to this specific high-risk patient population, which suggests that of the nearly 5000 patients who have received a percutaneous valve in the last 14 months, >3000 will be dead or will remain severely disabled by this time next year.

Given this, one could strongly argue that we need to do far better at patient selection even within this critically ill patient population and that identifying the subgroup of patients (probably ~35% of those currently undergoing TAVR) who will truly benefit by virtue not only of survival but also by significant improvement in their quality of life is critical. And we should not delude ourselves as we have with other novel mechanical therapies that TAVR is a true panacea. So an important question to ask is whether the published data provide some insight into who is most likely to benefit or, conversely, who is most likely to suffer dire consequences from TAVR. The literature does shed some light on these questions.

First, size matters: all published studies have shown that those with a low body mass index do poorly [1,12]. This association is likely multi-

factorial. Cachexia is a consequence of severe and long-standing aortic stenosis and is associated with poor nutritional status, limited cardiac reserve as well as with other intercurrent illnesses. In addition, from a purely mechanical standpoint, patients with small (and or diseased) femoral-iliac vasculature present access challenges as well as increased complexity during valve deployment. Vascular complications at the time of the procedure unquestionably herald poor long-term outcomes. These later issues may be surmounted with lower profile devices and more agile deployment equipment but this is by no means certain and the current literature strongly argues for circumspection in patients who are small and who have challenging vascular access. Paradoxically, women tend to do better with TAVR than with conventional aortic valve replacement; although whether this is due to worsened surgical outcomes or better TAVR outcomes is as yet uncertain [13]. Frailty, another element that can be prospectively identified and quantified, predicts a poor outcome [14]. This association clearly emerged from the randomized trial data and also from other "real-world" studies. However, while frailty is certainly acknowledged as an element in the TAVR evaluation process (especially when assessing the difficulty in recovery from surgical AVR), a formal and quantifiable assessment is not generally done and certainly there are no rigid standards that would preclude consideration of TAVR. Indeed, and despite the data suggesting that this predicts a poor outcome, anecdotal reports suggest that frailty is currently evoked as a reason to proceed down a minimally invasive therapeutic pathway rather than as a reason to avoid a procedure. Additional factors that predict poor outcomes include the presence of a porcelain aorta and intercurrent liver disease and of course procedural complications and persistent aortic insufficiency following valve deployment also predict a poor prognosis.

Ultimately, there has been a great deal of attention paid to improved survival in an elderly and infirm patient cohort following TAVR (relative to conventional treatment), but less information is available that would help predict which patients will experience an improvement in quality of life (although this is increasingly acknowledged). Indeed, the existing data includes multi-variant analysis that allows some prospective identification of who will do poorly following TAVR, but there are very limited data to allow prospective identification of who will do well and given that a minority of patients fall into this latter category, this seems like a missed opportunity. It does seem intuitive that patients who are relatively robust and without confounding comorbidities and who also have navigable vascular access and valves that are not disastrously and asymmetrically calcified will do better.

Recognizing that this is an opinion, and moreover that of a non-interventional cardiologist, it seems important to temper enthusiasm for the use of TAVR in the aged and infirm population that is currently being targeted. The presence of severe aortic stenosis in a patient deemed to be a poor surgical candidate does not seem to be a sufficiently compelling rationale to proceed with TAVR, especially given the fact that more than half of the patients will have an unhappy outcome within two years of the procedure. Of course, as more and more centers come on-line and more and more patients are made aware of the technology, introducing moderation will be challenging. Patients and families are eager for "cures", especially those that are presented as minimally invasive, but reducing the aortic valve gradient does not "cure" the complex multi-system impact of many years of aortic stenosis nor does it reverse the aging process in general. However, the reality is that medical centers are currently competing for TAVR patients and hospitals are marketing their procedural volumes in order to gain marketplace advantage. Interventionists are eager to perform these procedures in order to maintain their familiarity with

contemporary technologies and to ensure continued referrals to their practices. The further reality is that if patients are denied access at one center, it seems quite likely that they can and will go elsewhere, often in the same community. How this trend can be tempered is far from clear and the track-record in the device therapy realm in this regard is poor. An encouraging development is the creation of an STS-ACC transcatheter valve registry which is a novel partnership among the professional societies designed to serve as an objective, comprehensive and scientifically based resource to improve the quality of patient care and to monitor the safety and effectiveness of transcatheter valve therapies [15]. How this will actually work and whether the data generated will have meaningful impact on patient selection, outcomes, or reimbursement remains to be seen.

Inevitable and perhaps more encouraging is the likely expansion of the indications for TAVR to a more conventional patient population. As mentioned above, at the moment in the US, devices can only be used in patients who are deemed non-surgical candidates, except as part of a randomized clinical trial, such as Partners 2. When the results of these trials become available, it is likely that TAVR will become an option for many patients who are currently only being offered surgical replacement. The existing data suggest that TAVR is non-inferior to surgical AVR and indeed the liberalized use of TAVR has already become the standard of practice in many European countries. Given this, it is likely that more patients who are truly in need of valve replacement (and who either have reluctant surgeons or who are themselves reluctant to consider surgery) will have non-surgical options. Given the real gap between the number of patients with severe disease and the number of surgical AVRs being done, this will probably be an encouraging development. It's also possible that TAVR will be considered earlier in the natural history of the disease and whether this is a good or bad thing is unknowable. On the one hand, unpredictable sudden cardiac death is a complication of aortic stenosis and it is plausible that earlier interventions will reduce this. However, on the other hand, the durability of the percutaneous valves is uncertain and the risks of repeat procedures (either surgical or percutaneous) are unknown.

In summary, with the commercial roll-out of TAVR, we have clearly entered a new era in the treatment of valvular heart disease. This new therapeutic strategy represents an extraordinary advance but it will inevitably bring with it new challenges. As a profession, we would be well advised to proceed with caution, making sure that there are carefully crafted systems in place (such as the STS-ACC registry) to evaluate clinical outcomes in a scientific fashion at every step in the process. Without these, we risk disseminating the technology in an irrational and uncontrolled fashion. At the end of the day, it is our professional responsibility to decide how best to disseminate this new therapeutic strategy which will determine whether the TAVR glass is half-empty or half full.

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