Is TAVR Ready for the Global Aging Population?

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ABSTRACT

The emergence of the global pandemic of chronic diseases necessitates critical assessment of interventions that can be targeted at both the individual and population levels. Among cardiovascular diseases, the increasing prevalence of valvular heart diseases such as aortic stenosis parallels the rising burden of atherosclerotic cardiovascular diseases. As an alternative to surgical aortic valve replacement, technological innovation has allowed development of minimally invasive transcatheter aortic valve replacement (TAVR). This review examines whether TAVR can be applicable in low-resource regions across the world. Although revolutionary, TAVR is currently complex and requires a "Heart Team" approach for optimized patient care. We propose the emergence of telemedicine networks, newer valve designs that allow implementation of minimal approaches, and the use of minimal numbers of specialists for adapting TAVR to settings where surgical backup is not available. With efforts to reduce resource utilization, these alternate strategies have the potential to affect implementation of TAVR globally.

Aortic stenosis (AS) is the most common form of valvular heart disease in the elderly and is characterized by thickening, calcification, and restricted leaflet motion-causing obstruction to the blood flowing across the valve [1]. Many patients with AS do not experience noticeable symptoms until late stages of the disease. However, the onset of symptoms in AS is associated with high morbidity and mortality and necessitates timely referral for surgical aortic valve replacement (SAVR). As an alternative to SAVR, technological innovation has allowed development of minimally invasive transcatheter aortic valve replacement (TAVR) techniques that are particularly useful for patients who have comorbidities that increase risks for SAVR [2,3]. The growth of experience with TAVR procedures and development of smaller caliber catheters and better valve designs is now allowing TAVR to be performed also in lower risk patients [4,5]. The potential for TAVR has generated enthusiasm in Western medical communities; unfortunately there is inadequate information on how this technological revolution can be adapted in low-resource regions globally.

In this state-of-the-art review, we examine whether TAVR is ready for worldwide implementation, particularly with the challenges surrounding development of surgical programs in low-resource settings. The discussion is divided into 3 sections: we first discuss the epidemiology of AS and highlight the current recommended approaches for SAVR and TAVR; second, we list the challenges in adapting Western standards to the rest of the world; and third, we propose key strategies that may be helpful in successful future implementation of SAVR and TAVR programs.

GLOBAL BURDEN OF VALVULAR HEART DISEASE

The increasing prevalence of AS parallels the rising burden of atherosclerotic cardiovascular disease (CVD) in the aging population of the developing world [6]. In 2013, approximately 17 million deaths from CVD occurred globally with nearly 80% of the deaths occurring in low- and middle-income countries [7–9]. The rate of the CVD increase globally has yet to reach its peak and will be modified by prevalent diseases such as human immunodeficiency virus (HIV). For example, in many nations in Africa, as the treatment for HIV becomes more effective, the prevalence of CVD in surviving populations may rise steeply [10].

Although, because the aging population is expected to increase the burden of both atherosclerotic and degenerative disorders such as AS, the true prevalence of degenerative valve disease is not known in the developing world. An Indian study of 136,098 patients undergoing echocardiographic assessment found AS in 13,289 cases (7.3%) with 65% being degenerative in etiology [11]. A Chinese study found a 23% prevalence of degenerative valvular heart disease in patients ages 45 to 65 years, which increased to 65% in those older than 65 [12]. According to the United Nations, there are approximately 102 and 119 million people in India and China over the age of 60 and 65 years, respectively [13]. As the prevalence of AS increases with each decade, from 2% under 65 to over 13% after 75 years [7,14], it can be easily projected that diseases such as AS, which require longer periods of care and therefore incurred costs, may create a health care crisis with the potential to overwhelm the limited health care systems [8]. Diseases such as AS are likely to contribute in a major way to the annual global death rate from CVD, which will exceed 23 million annually by 2030 [14], and to costs, which are projected to exceed 47 trillion dollars [15].

SAVR VERSUS TAVR: CURRENT TRENDS

With the onset of symptoms, 75% of patients with AS die within 3 years in the absence of SAVR [16]. However, the

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outcomes of SAVR are dependent on presence of comorbidities [17,18]. A significant proportion (34%) of the patient's pool for SAVR may be deemed to have prohibitive risks and may be left untreated. The TAVR procedure was initially introduced to take care of these patients with prohibitive risks. The procedure is minimally invasive, using small incision sites for transfemoral, transaortic, subclavian, or transapical approaches [19]. The number of TAVR procedures has significantly increased since the US Food and Drug Administration approved them in 2012 [20]. Although TAVR was developed initially to meet the needs of the patients who were denied for SAVR [21], subsequent evolution in technology and clinical trials have shown that TAVR is also a safe and efficacious option for patients considered to have high and intermediate risk of complications for SAVR [22]. The outcomes for patients undergoing TAVR procedures have demonstrated excellent outcomes for patients in all risk categories [23] with survivals comparable to that of SAVR [24]. Currently, trials are also underway for low-risk AS populations.

TAVR PROJECTIONS

By 2014 TAVR was performed in 50 countries, in over 720 centers, and since 2007 over 100,000 TAVR procedures have been performed [25]. In 2015, approximately 71,000 TAVR procedures had been performed that year, and by 2025, globally, 289,000 TAVR procedures will be conducted annually [22]. TAVR continues to grow in the West [26]; however, no specific projections have been made for TAVR in low-resource regions.

THE HEART TEAM APPROACH

TAVR programs have seen remarkably positive patient outcomes, and an important component of the success has been credited to the development of the "Heart Team" approach. The Heart Team is a multidisciplinary team of physicians and specialists brought together for each procedure [25]. The diverse Heart Team brings together their understanding of disease progression, procedural complications, and outcomes to select the most suitable patients for a TAVR procedure; this has been identified as the defining factor in the high rates of positive outcomes for TAVR procedures [27,28]. The assessment of patients eligible for TAVR requires a multidisciplinary-physician review to overcome the comorbidities that come with the patient pool (an elderly population); about 27% of patients are rejected for a TAVR procedure, and 2 of the most common reasons for rejection include patient frailty or dementia [29].

The Heart Team compiles various diagnostic tests and determines the best option (TAVR, SAVR, or balloon aortic valvuloplasty) [30]. Criteria are based on risk scores, echocardiographic parameters, concomitant valvular heart disease and coronary disease, comorbid conditions, and frailty [31]. Overall, the success of the Heart Team requires substantial clinical and administrative resources to support the outcomes of a TAVR program [28].

When a TAVR program is first established, most referrals to the program are from general cardiologists [29]. As the amount of data required to make decisions about patients increases, the role of coordinated care becomes critical and the Heart Team approach must be upheld in order to continue the demonstrated success of TAVR [32,33]. The Heart Team takes into consideration noncardiac mortality and morbidity, the incorporation of a broad understanding of possible outcomes is vital because when complications from TAVR occur they can be sudden, dramatic, and life threatening [34].

In a German study, 1.2% of the subjects' experienced catastrophic complication during a TAVR operation, resulting in emergency conversion to open heart surgery. Furthermore, the study found that the increased time to convert between the cardiac catheterization laboratory and the operating room resulted in 67% increase in the 30-day mortality rate. The study suggests that the 30-day mortality rate can be reduced by 35% to 50% when using the Heart Team approach, as well as, implementing a hybrid operating room, this being a regular operating room combined with a cardiac catheterization laboratory [35].

COST CONSIDERATIONS

When comparing the cost of TAVR to SAVR, the cost of the SAVR is less expensive with the estimated cost of the surgical valve being one-sixth that of a TAVR valve [36]. In a complex procedure such as an AVR, however, the cost is just 1 of the factors that need to be considered.

For patients eligible for Medicare or Medicaid, the cost of a TAVR procedure in the United States is primarily covered by insurance; however, for those who do not fit the criteria for the procedure but elect to have the intervention preformed, the costs range from $80,000 to $200,000, with an average cost of $164,238 [37]. In the United States, the cost of the valve alone is an approximately $30,000, and TAVR procedures have been described as "money losers." In 2012, Medicare was reimbursing on average $51,000; however, teaching hospitals received higher reimbursement than community hospitals did [38]. A 2016 study comparing the minimally invasive TAVR to open heart surgery of SAVR showed that TAVR had a $55,090 gain per quality-adjusted life-year, and for SAVR, it was more than $10,000 less at $43,114 per quality-adjusted life-year gained [39]. An American College of Cardiology study points to the fact that both SAVR and TAVR receive the same insurance reimbursement (approximately $42,000); however, for TAVR the direct hospital cost ($50,662) and device costs ($35,132) were much higher compared with SAVR's hospital cost ($34,240) and device cost ($6,836). The study shows that the overall difference in the procedure contribution margins were $16,372 (TAVR's margin was −$7,432 and SAVR margin was $8,934). With these calculations, TAVR

TABLE 1. Factors influencing global uptake of transcatheter aortic valve replacements

	Known Features	Unknown Features
Global aging	• 2% >65 yrs • 13% <75 yrs	Will poor nutrition, alcohol, tobacco, and other environmental factors accelerate AS
Aging specific to developing world	• India: 102 million >65 yrs • China: 119 million >65 yrs	Lack of population studies on burden of AS in developing world population
Timing of intervention in AS	• Onset of symptoms is associated with poor prognosis	Technical skills and resources needed for appropriate diagnosis and referral
Heart Team for TAVR	• Multidisciplinary team improves patient selection and TAVR outcomes	Lack of trained clinical specialist hinders assessment and procedural capacity
Cost of TAVR	• Increased cost compared to surgical AVR	Cost keeps TAVR out of reach for majority of population
Follow-up	• Post-procedure assessment for diagnosis valve degeneration or valve thrombosis	The impact of post-TAVR outcomes when resources for follow-up are not in place

AS, aortic stenosis; AVR, aortic valve replacement; TAVR, transcatheter aortic valve replacement.

procedures lose money whereas SAVR shows a gain [40]. Comparing TAVR patients with SAVR patients, those who undergo SAVR are required to remain in a hospital for longer post-operative care for 4.4 days, whereas patients who undergo TAVR can be discharged within 1 to 3 days. Reducing TAVR post-operative care is key to reducing health care costs.

Discharge of patients following a TAVR procedure shows the greatest potential for affecting the cost of the procedure; in Canada, significant effort has been geared to identifying a standard approach to having patients discharged after 1 day, typically patients are being released after 2 or 3 days [41,42]. In a French study, a single patient was discharged on the day of the TAVR procedure, this patient was considered to be low risk and was 65 years old, and the procedure had no complications [43]. What this case study indicates is that a TAVR procedure requires a personalized approach for each patient, and when low-risk patients are approved for TAVR that a reduced post-operative care period can be possible and the cost of overall care will be reduced.

CHALLENGES FOR TAVR AND SAVR IN LOW-RESOURCE SETTINGS

In the poorest nations, the vast majority of people needing surgery never receive surgery; it is estimated that only 3.5% of needs are met [44]. Developing countries account for 70% of the global population, but only 26% of the total amount of surgical procedures that are preformed; compounding the issue is the fact that these regions account for 80% of all deaths from surgically treatable conditions [45]. For those who have access to surgery in developing countries, the death rate attributed to major surgery is between 5% and 10%, with approximately 1 million patients dying during or right after surgery each year [46].

A region's access to health care and medical interventions can be defined by a myriad of factors including social values, economic interests, and political processes. These are not single events but rather continuous processes with activities and actors that change over time, all regions land somewhere on a gradient or classification scheme [47]. Factors affecting where a country is situated on the gradient can be explored to determine whether introducing a new medical intervention such as TAVR would be feasible (Table 1). In this regard, the World Health Organization has developed the Mortality Stratum—a scale that has been recommended for developing strategies for cardiovascular disease prevention. Potentially a scale like this could be used for the implementation of cardiac interventions such as TAVR. The Mortality Stratum classifies regions into 5 statuses: A, very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; and E, high child mortality and very high adult mortality [48]. Conceivably an intervention such as TAVR may be more suited for C regions because such regions have successfully implemented efforts to bring down child mortality, but adult mortality due to noncommunicable disease requires focus. The barriers for introduction of TAVR and adaptation of new technology in such regions, however, require further in-depth considerations.

The following section examines a list of questions that are relevant for implementation of SAVR and TAVR in low-resource settings:

Can low-resource regions meet the potential rise in patients eligible for TAVR?

Simply having the tools to preform TAVR does not guarantee the highest level of patient outcomes [49] (Figure 1).

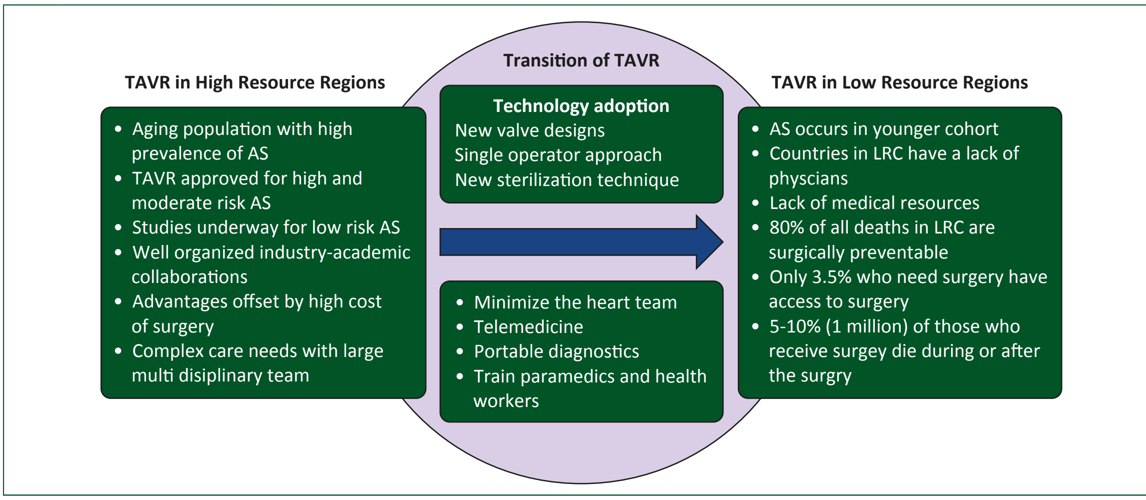

FIGURE 1. Adaption of transcatheter aortic valve replacement (TAVR) to combat the growing prevalence of aortic stenosis (AS) in low-resource regions of the world.

According to the Lancet Commission on the state of surgery, globally there has been either a regression and/or stagnation of safe surgery in low-resource settings. Furthermore, the report states that the incidence of cancer, road traffic injuries, CVD, and metabolic disease are projected to increase significantly and will place greater burden on health systems in these low- and middle-income regions. The report estimates that 9 of 10 people in low-resource settings who need surgery do not have access to surgery, and the few who receive surgery face catastrophic health expenditures due to the cost of the surgery [50]. The complexity of conducting surgery, even a minimally invasive procedure such as TAVR in low- and middle-income countries or low-resource settings could be described as insurmountable when taking into account all the shortfalls found in these settings, including a lack of surgeons, poor clinic standards, and overall view of surgery as unimportant [51]. However, the use of the term insurmountable is a false notion. It is true that there are challenges such as a lack of data affecting policy makers' ability to determine the real need of patients [52], and even more so, there are issues related to access to material, infrastructure, and physicians trained for specialized surgeries such as those found in cardiac valve programs, but these issues are certainly not insurmountable [53,54].

In addition to physician shortages, the issues surrounding access to surgery in low-resource settings include system development, capacity building, locally driven care, public health challenges and solutions, and ethics [55]. Even if there were fully staffed facilities, there is a lack of actual operating rooms that can function as surgical units and of basic needs such as portable water, electricity, blood banks, diagnostic equipment, or the proper maintenance of the equipment [45]. In hospitals with autoclave sterilizers, it can be difficult to maintain or repair the vital equipment, and this increases the risk associated with infections and undermines entire surgical programs [56]. Indeed, the occurrence of infections is 9× greater in low-resource settings [57]. The above-mentioned barriers to achieving safe and efficacious surgery in the global setting are increasing post-discharge complications [58].

Can the "Heart Team" approach be used in low-resource settings?

Heart Teams comprise a number of specialists including interventional cardiologists, imaging cardiologists, cardiothoracic surgeons, cardiac anesthetists, and general physicians, who come together to optimize patient selection, procedural planning, and post-operative care [59]. The shortfall of trained health workers is at the core of the global health care crisis, and when coupled with the projected rise in chronic disease in an aging population [60], the challenge of meeting surgical capacity is further increased. In resource-limited regions of the world, the global physician and specialist shortage may pose difficulties in recruiting members for the development of a Heart Team. Shortages are not just felt in low-resource countries; within the next 10 years, one-third of physicians in the United States are set to retire, and there will be a shortage of 15,000 cardiologists [15]. Statistics such as these are further complicated when you add that currently, in the United States, 30% of working cardiologists are foreign-trained, placing a strain on the developing countries that see their cardiologists emigrating [15,61]. The issue of "brain drain," trained physicians immigrating to other countries, further adds to the burden that regions such as Africa face. It is estimated that Africa only has 2% of the world's trained physicians but bears 25% of the global burden of disease [62]. One condition that persists in developing regions, but certainly is also an issue in developed nations of the West, is the allocation of medical specialist [63,64], specifically being that most physicians

TABLE 2. Strategies for improving uptake of transcatheter aortic valve replacements in resource-limited setting

Strategies	Description
Technology adoption	Telemedicine and portable ultrasound: • Increasing accessibility • Remote consulting for early diagnosis • Possibilities for Training and feedback • Referral and follow-up network
Minimalist TAVR	Reduces the resources needed for TAVR • Conscious sedation instead of general anesthesia • Using cardiac catheterization lab with onsite surgical rooms instead of using primary operating rooms
Minimalist Heart Team	• Following trends in European countries in using less personnel (standby surgeon) • Use of conscious sedation by cardiologist (standby anesthesiologist) • Reducing the need for imager (standby imager), having primary interventionist getting trained in imaging

TAVR, transcatheter aortic valve replacement.

are found in urban centers. Barriers to attracting medical staff to less urban areas can include a lack of infrastructure and opportunities for growth [65]. The ability for a patient to travel to larger urban centers can be an obstacle for people who are already facing financial difficulty [66—68].

STRATEGIES FOR OVERCOMING THE GLOBAL CHALLENGES

From examining the preceding questions, simply stating that surgical capacity is not meeting the global need is too simplistic; the core of the issue is found when attempting to define the barriers to accessing surgeries [69]. In the developing world, surgery has lacked focus largely due to the demand that infectious disease places on health systems and, therefore, the training of surgeons has not been a priority [58]. Surgery has the perception of being an expensive undertaking; however, some percutaneous interventions, such as for CVD, are highly effective. Overall, interventions have the greatest value for a health system when they reduce the greatest burden of disease, when reductions are found, these interventions can be considered cost effective [70]. Here we posit solutions to the challenges expressed in the aforesaid sections (Table 2).

Technology can improve physician access

Technology has the potential to have the greatest impact in low-resource settings [71]. What is emerging is increased access to portable diagnostic equipment, with the potential to allow medical staff (both those who are fully trained physicians and those who function as physicians) to better identify disease and work within their capabilities to try to prevent the acceleration of the disease and reduce the burden that late-stage diagnosis can place on a health care system [72,73].

Portable ultrasound can open the door for easier access to local workforce training in diagnosis and interventions [74—76], and this will increase the ability to screen and identify treatable subclinical diseases that were going undiagnosed [77]. Portable machines will allow for targeted screening for patients identified as high risk [78—80]. With an increased ability to have medically trained non-physicians begin to identify subclinical disease, there will be facilitation in the collection of data. Large portions of the developing world are unable to provide data on CVD; in Sub-Saharan Africa (89.8%), the Middle East and Northern Africa (48.1%), South Asia (24.2%), and East Asia and the Pacific (21.1%), and in large developing countries such as China, the lack of data available varies greatly between rural and urban areas [6]. With an increased availability of data, there will be a more comprehensive understanding of the global burden of CVD and the specific need for TAVR.

The field of portable diagnostics falls into the much broader context referred to as telemedicine, which refers to use of telecommunication to diagnosis and treat patients [81]. The use of telemedicine has a history beginning over 40 years ago, but as technology and interconnectedness has grown via wireless connection and now specifically smartphones [82], the ability for the physicians to be with the patient but separated geographically has begun to change the capability of medicine. Telemedicine could be the key to overcoming the very challenging aspect of TAVR patient selection in low-resource settings. As was already mentioned, there are many specialties involved in patient assessment (cardiology, neurology, pulmonology, etc.), and for this reason it can be challenging to ensure smaller communities would have access to the specialists, but with telemedicine the specialist will virtually come to the patient.

Telemedicine has the potential to change the training of a physician, by allowing students to remain in their communities, and with the use of video conferencing, they can view not just a lecture but also live patient assessments and surgeries [83]. Following the training, this same technology will allow for the newly trained doctor (nurse or medical personnel) to have skilled professionals from anywhere in the world oversee their procedure, providing real-time assistance during surgical and other medical procedures [84]. Although, careful attention must be paid to medical licensing and what legally a physician can do (when crossing boundaries from their area of licensing) will become a topic of great concern for many [85].

Studies of telemedicine within various chronic disease groups indicate that telemedicine allows for care to be more personalized, and the patients perceive an increase in their ability to control their disease [86]. In a study of Spain and multiple African countries, it was found that telemedicine creates an environment for effective diagnosis and treatment, and over a 3- to 5-year period proved to be cost-saving compared with traditional face-to-face care [87]. Some new developments in technology have the potential to strengthen patient assessments, including the use of gaming systems such as Wii Fit, that are connected to Bluetooth wireless networks, allowing for customizable rehabilitation exercise, this collected data can be transmitted quickly and effortlessly to the physician [88]. This could work well for post-operative recovery and monitoring of a TAVR patient. Devises such as the Wii Fit, or wearable sensors, allow for daily monitoring and progress tracking [89–91], this would allow for vital data to be transmitted and would provide a better understanding of patient post-procedural progress compared with the standard 30-day, 6- and 12-month single-visit follow-ups.

Minimalist approach to TAVR

As the patient pool eligible for TAVR expands beyond high-risk or inoperable to intermediate- and low-risk patients, there will need to be a refinement of the procedure to reduce the overall costs of the intervention. As the methods for TAVR begin to be refined and efficiencies are developed, TAVR programs can find ways to reduce the resources needed for the procedure. Approaches to minimalist TAVR include preforming conscious sedation rather than placing the patient under general anesthesia [92,93], and using transthoracic echocardiography to guide the implantation of the valve [94]. In addition, a mature TAVR team can perform the procedure in a cardiac catheterization lab with transfemoral access rather than an operating room [95,96], as well as, reducing length of stay following the procedure [42,97]. These changes to the traditional approaches of the TAVR procedure reduce patient time and the overall cost of health services [98–100].

In particular, the use of conscious sedation can reduce the length of time the patient needs to be sedated. Registry data suggest that the 30-day outcomes are advantageous compared with those of general anesthesia. In addition, the length of post-operative stay and in-hospital mortality rates are reduced [101].

Minimizing the Heart Team

It can be argued that the greatest burden to implementing TAVR, besides the cost of the valve, is the robust nature of the Heart Team, with its many specialists. Some research and investigation has been focused on limiting the number of those who are required to be present during the patient selection and procedure [102]. In India, efforts are focused on reducing the use of general anesthesia during some interventions; in these cases, conscious sedation is applied to the patient by general cardiologists, thereby reducing the need for an anesthesiologist to be present [103]. A German study found that there was no statistical difference in the rate of in-hospital mortality when there was no surgical backup. The only difference between procedures with a cardiac surgeon presence and without was that in the procedures without a surgeon, there were higher rates of new permanent pacemaker implantations [104]. When comparing having surgical backup to no surgical backup during catheterization procedures, it has been demonstrated that patients who underwent percutaneous coronary intervention at hospitals without cardiac surgeons onsite were noninferior [105,106].

The future of TAVR performed in the United States will begin to look more like TAVR in Europe, that being without a cardiovascular surgeon and limited to no guidance during the procedure by echocardiographic imagers, although this would be assessed case by case [107]. The ability for the TAVR procedure to be adapted will be a key to successfully rolling out TAVR in low-resource settings. In these settings, implementing a surgical program will require a broad approach that is flexible enough to be operational regardless of the specifics of the setting [108].

SUMMARY

When technology and medicine come together in the way they have with the development of TAVR, it can shift the global burden of disease. Currently, due to a lack of resources and capacity, TAVR is only penetrating the burden of CVD in the developed world. TAVR, when performed in optimal conditions has proven to increase the life expectancy and quality of life for those with valvular heart disease associated with serve AS. When focusing on the potential to reduce the burden of disease, with efforts to streamline or reduce the resources needed for TAVR, there is a potential to affect the developing world with even greater outcomes than are currently being demonstrated in the developed world.

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