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VIEWPOINTS

Cautious Optimism Regarding Early Transcatheter Aortic Valve Replacement

Omar M. Abdelfattah, MD; Amar Krishnaswamy, MD; Samir R. Kapadia, MD

Leonardo da Vinci provided his first drawing of the aortic valve 5 centuries ago, and by the following century Lazare Riviere first described pathologic aortic valve stenosis in the "Opera Medica Universa." Although it took another 300 years until Harken first implanted an aortic valve prosthetic in the proper anatomical position in 1966, there has been rapid evolution in aortic valve care during the past 5 decades. The remainder of the 20th century saw important improvements in surgical techniques and valve design, and the 21st century brought a revolution to this space with the first human transcatheter aortic valve replacement (TAVR) placed by Cribier in 2002. During the past 2 decades, there has been an unprecedented degree of technologic innovation in the field and randomized trial data confirming TAVR as a safe and effective treatment option for anatomically feasible patients with severe aortic stenosis (AS) across all surgical risk groups.

Without question, the roll out of TAVR has been methodical and data driven. Approval of the early-generation devices was provided only after randomized trials confirmed efficacy and safety in patients considered either inoperable or at high surgical risk.[1,2] Expansion of the therapeutic indication to include intermediate and low surgical risk patients followed after subsequent trials randomly assigned patients to either the surgical standard or TAVR and confirmed the safety and efficacy among these groups. Accordingly, TAVR treatment is now available in 715 US TAVR centers (as of August 2020). Although the focus of these trials has been the treatment of patients with symptomatic severe AS, we have begun to question whether there is a benefit to treating patients with AS at an earlier stage.

At the time of diagnosis, up to one-half of the patients with severe AS fit the definition of "asymptomatic." The idea that timely intervention can prevent irreversible damage to the heart (including left ventricle [LV] hypertrophy, left atrium [LA] enlargement, and eventual LV dysfunction) combined with the safety and minimally invasive nature of the procedure have raised the question of earlier intervention in the course of AS.[3] The treatment of asymptomatic severe AS is the focus of a number of randomized controlled trials. AVATAR (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) and RECOVERY (Randomized Comparison of Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis [NCT01161732]) were designed to understand whether early surgical intervention might be beneficial rather than ongoing monitoring.[3] In this regard, both trials have shown early surgical aortic valve replacement (SAVR) to be beneficial in terms of all-cause mortality and new-onset heart failure compared with conservative management.[3] However, the small number of included patients with variable follow-up limits the extension of these findings. Nevertheless, the findings are thought provoking, especially when one considers the less invasive option of TAVR. In this regard, the Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis (NCT03042104) study using the balloon-expandable SAPIEN-3 prosthetic (Edwards Lifesciences, Irvine,

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Correspondence to: Samir R. Kapadia, MD, Department of Cardiovascular Medicine, Heart, Vascular & Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, J2-3, Cleveland, OH 44195. Email: kapadis@ccf.org
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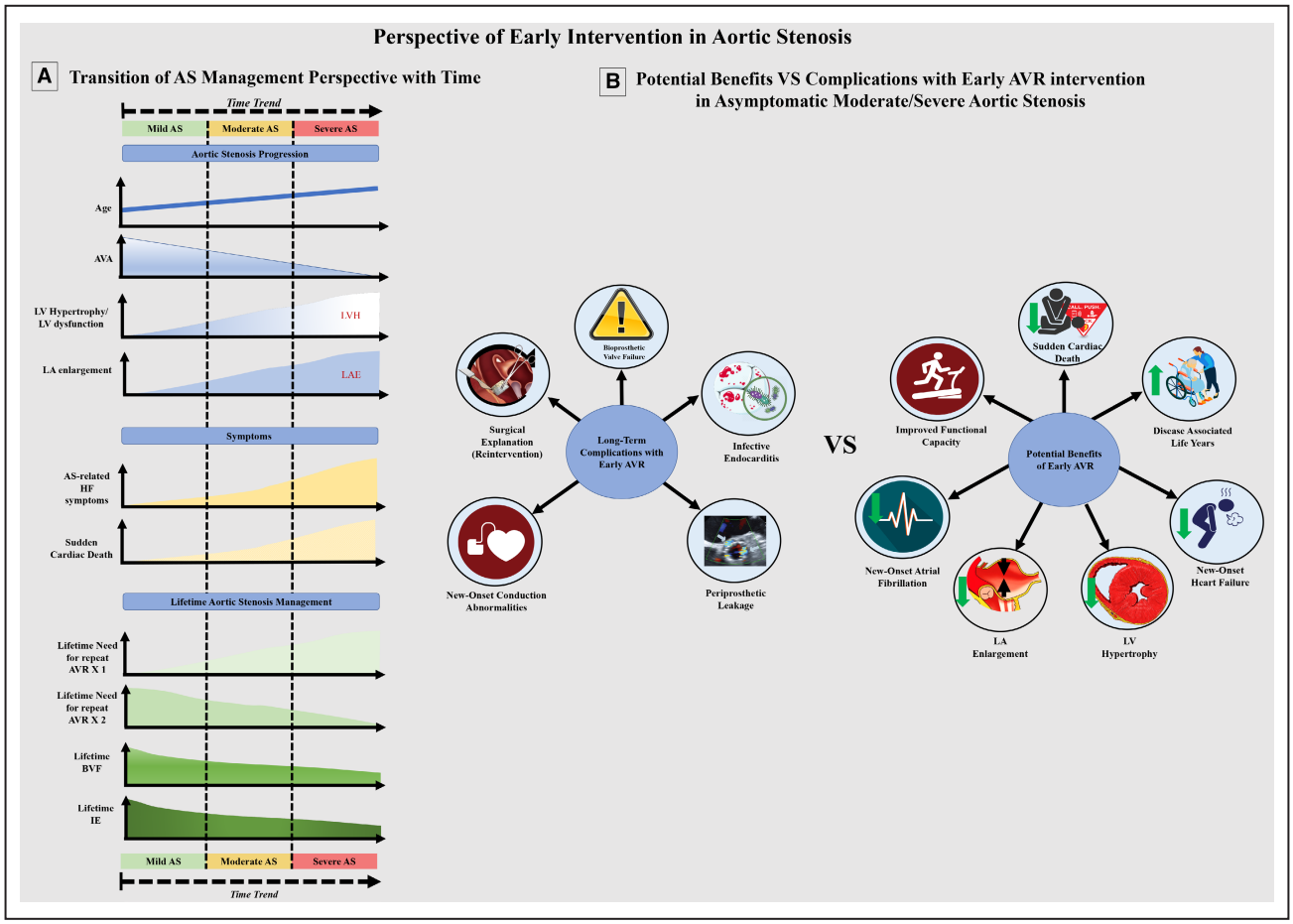

Figure. Perspective of early intervention in AS.
A, Transition in the AS management strategies across the spectrum of AS and the accompanying hemodynamic and procedural considerations as time progresses in a univariate nature. **B**, Risks and benefits associated with early intervention in asymptomatic moderate/severe AS. AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BVF, bioprosthetic valve failure; HF, heart failure; IE, infective endocarditis; LA, left atrium; LAE, left atrial enlargement; LV, left ventricle; and LVH, left ventricular hypertrophy.

CA), which has completed enrollment, may provide more insight into whether earlier percutaneous intervention would be beneficial compared with conservative management in asymptomatic severe AS.

Given the known trajectory and natural history of AS, even more thought provoking is the idea of treating AS at an earlier stage in the disease process. The timing of aortic valve replacement (AVR) is confounded by the fact that markers of transition from an asymptomatic or compensated state to symptomatic state remain unclear (and clinically may be missed). The recent VALVENOR (Suivi d'une Cohorte de Patients Présentant une Sténose Valvulaire Aortique en Région Nord-Pas-de-Calais) study showed that, compared with the general population, patients with symptomatic moderate AS experienced higher cardiovascular mortality compared with mild AS (although still less than that of patients with severe AS).[4] In this regard, the PROGRESS (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement [NCT04889872]) trial, TAVR-UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure: A Randomized Trial [NCT:02661451]), and the EXPAND TAVR II Pivotal Trial (NCT05149755) will assess TAVR versus clinical monitoring for patients with symptomatic moderate AS.

Although cautious optimism is warranted, unbridled enthusiasm in applying TAVR should be tempered, and it is important to acknowledge its limitations. Specifically, understanding the incidence and prevention of valve degeneration is an important area of research because replacing the native valve is not a permanent cure for the problem. Furthermore, as we treat younger patients, understanding the anatomic constraints imposed by the need for future TAVR-in-TAVR, as well as the durability of this procedure and limitations of the same, will be important. To date, the

scientific literature provides limited data on the incidence and management of TAVR valve failure.[5] We have begun to learn that a specific subset of patients with TAVR (eg, small annular diameter, supra-annular valves) may face challenges for a percutaneous re-intervention. Therefore, the solution of an early AVR to prevent the unwanted complications of AS has to be balanced with the complications that may arise with early valve replacement (Figure – Panels A and B). Typically, we aim for TAVR as the last treatment in older age groups (late 80s or 90s). Therefore, the sequence of AVR interventions may be 1 of the following 4 options if patients need 3 AVRs in their lifetime when considering younger patients: (1) TAVR-SAVR-TAVR, (2) SAVR-TAVR-TAVR, (3) TAVR-TAVR-TAVR, or (4) SAVR-SAVR-TAVR. There are no objective data at the current time for each of these strategies, making the decision for early intervention difficult, and clinical trials with short-term follow-up are unlikely to answer these questions. Furthermore, although the current literature on TAVR explant is limited to highly comorbid clinical situations and not easily applicable to future "elective" TAVR explant, it may stand to reason that such an operation would be more involved than a "fresh" AVR and especially in the setting of a tall, self-expanding prosthesis that extends to the ascending aorta.

Although TAVR provides amazing procedural safety and excellent mid-term outcomes, it would be pivotal how we balance these benefits and the possible short-term gains that may be evident from the aforementioned trials with the potentially serious long-term consequences with early intervention that remain unknown.

ARTICLE INFORMATION

Affiliations

Department of Internal Medicine, Morristown Medical Center, Atlantic Health System, Morristown, NJ (O.M.A.); and Department of Cardiovascular Medicine, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH (A.K., S.R.K.).

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