Timing of Intervention in Asymptomatic Aortic Stenosis

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The decision to perform an intervention for asymptomatic severe aortic stenosis (AS) requires careful weighing of the risks of early intervention against those of watchful observation, and the optimal timing of intervention remains controversial. With improvements in surgical and postoperative care, long-term survival after surgical aortic valve (AV) replacement (AVR) is excellent in low-risk patients, and the emergence of transcatheter AVR may change the thresholds for early preemptive intervention, although a durability issue has to be resolved. A watchful observation strategy also has a risk of sudden death, irreversible myocardial damage, and increase in operative risk while waiting for symptoms to develop. We have been waiting for a prospective randomized trial to solve the intense debate between early AVR and watchful observation, and the RECOVERY (Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis) trial provides the evidence to support early AVR for asymptomatic severe AS. Risk assessment with severity of AS and staging classification may help to facilitate the identification of patients who may benefit from early intervention. Based on the results of the RECOVERY trial, early surgical AVR is reasonable for asymptomatic patients with very severe AS (aortic jet velocity ≥4.5 m/s) and low surgical risk. Further evidence is required to extend the indications of surgical AVR and to consider transcatheter AVR in asymptomatic patients with severe AS.

Key Words: Aortic stenosis; Aortic valve replacement; Early surgery; Trials

Aortic stenosis (AS) is the most common valvular disease leading to intervention in developed countries, with a growing prevalence due to the aging of populations. Aortic valve replacement (AVR) is the only effective therapy for severe symptomatic AS, and despite the absence of data from randomized clinical trials, current guidelines recommend AVR in symptomatic patients with severe AS because of their dismal natural history. Although one-third to one-half of patients with severe AS are asymptomatic at the time of diagnosis, the decision to perform intervention in asymptomatic patient requires careful weighing of the risks of early AVR against those of watchful observation, and optimal timing of intervention for these patients remains controversial. The 2 sets of consensus guidelines for the performance of early surgery on the basis of severity of AS differ, reflecting the controversy. According to the 2014 AHA/ACC guidelines, it is reasonable to consider elective AVR in asymptomatic patients with very severe AS (aortic velocity ≥5.0 m/s) rather than waiting for symptom onset, whereas the 2017 ESC guidelines recommend watchful waiting in asymptomatic patients without very severe AS (aortic velocity >5.5 m/s), because early surgery is unlikely to be beneficial. However, the evidence base for these recommendations is insufficient and the time has come for a prospective randomized trial to address the question of whether early AVR is preferable to a strategy in which AVR is deferred until symptoms develop and the first randomized trial comparing early surgical AVR with conventional treatment in asymptomatic patients with severe AS, recently demonstrated that early AVR significantly reduced the primary endpoint of operative death or cardiovascular death among asymptomatic patients with very severe AS. The aims of this review are to discuss the benefits and risks of early intervention and to identify optimal timing of intervention in asymptomatic patients with severe AS.

Risks of Early Intervention

Surgical AVR is reasonable in asymptomatic AS patients at higher risk of death or the imminent need for AVR during follow-up, but operative death and the annual risk of AV prosthesis-related complications are the major risks of early AVR. Improvements in surgical and postoperative care have led to lower operative mortality rates; the median operative mortality rate for AVR was 2.2% according to the STS Adult Cardiac Surgery Database 2019. The risk of operative death must be lower for asymptomatic patients and low-risk patients with severe AS, and the operative mortality rate of early surgical AVR was 0–1.4% in previous observational studies regarding asymptomatic severe AS, and 1.1–1.3% in recent trials comparing surgical vs. transcatheter AVR in low-risk patients. Stroke has also been reported as a major perioperative complication, and the 30-day incidence of stroke was 2.4% and 3.4% after surgical AVR, respectively, in 2 recent trials in low-risk patients.
Abnormal Aortic Valve With Reduced Systolic Opening

No AS symptoms

AS Stage C
(Vmax ≥4 m/s)

- LVEF <50%
- Other cardiac surgery
- ETT with ↓BP or ↓ex.capacity

Vmax ≥5 m/s

OR

- BNP >3x normal

OR

- Rapid disease progression

Low surgical risk

SAVR or TAVI (1)

SAVR (2a)

SAVR (2b)

AS Stage B
(Vmax 3.3-9 m/s)

- Other cardiac surgery

↓LVEF to <60% on 3 serial studies

Figure 1. Timing of intervention for asymptomatic AS: 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. AS, aortic stenosis; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BP, blood pressure; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; and Vmax, maximum velocity. Adapted from Otto CM, et al.\textsuperscript{2}

In addition to perioperative risk, early surgical AVR is associated with long-term risks of infective endocarditis, structural deterioration of the bioprosthesis, and anticoagulation-related complications with mechanical prostheses. Among 1,099 propensity score-matched patient pairs aged 50–69 years who had undergone AVR in Sweden during 1997–2013,\textsuperscript{18} 5.8% in the mechanical valve group had strokes during a maximum follow-up of 16 years; 9.6% in the mechanical valve group and 4.9% in the bioprosthetic valve group had major bleeding events (hazard ratio (HR) 0.49; 95% confidence interval (CI) 0.34–0.70, P<0.001), and 2.2% in the mechanical valve group and 5.2% in the bioprosthetic valve group underwent AV reoperation (HR 2.36; 95% CI 1.42–3.94, P=0.001) during follow-up.\textsuperscript{18} The respective 15-year cumulative incidence of stroke, major bleeding, and reoperation was 8.6%, 13.0%, and 6.9% in the mechanical prosthesis group and 7.7%, 6.6%, and 12.1% in the bioprosthesis group in a similar study done in New York State; there was no significant difference in the incidence of stroke, but patients with a bioprosthesis had a greater likelihood of reoperation but lower likelihood of major bleeding.\textsuperscript{19} Transcatheter aortic valve-in-valve implantation has become an attractive alternative to reoperation in patients with...
failed aortic bioprosthetic valves. Actuarial 15-year survival was 60.6% in the bioprosthesis group compared with 62.1% in the mechanical prosthesis group (HR 0.97; 95% CI 0.83–1.14). With improvements in surgical and postoperative care, long-term survival after surgical AVR is excellent, with survival after isolated AVR in elderly, low-risk patients matching that of an age- and sex-matched general population.

With improvements in devices, patient selection, and procedural outcomes, transcatheter AV implantation (TAVI) has become a safe and effective procedure for treatment of severe symptomatic AS in all adults regardless of estimated surgical risk, and both surgical and transcatheter AVR are effective approaches in adults aged 65–80 years. In recent trials that enrolled low-risk patients, TAVI was noninferior or superior to surgery in the rate of death or stroke, and the emergence of TAVI as a less invasive alternative with a lower procedural risk may change the thresholds for early preemptive AVR in asymptomatic patients. TAVI has the advantages of causing less pain and allowing for more rapid recovery, but the long-term durability issue of bioprosthetic TAVI valves has to be resolved before recommending TAVI to asymptomatic patients with a longer life expectancy. To date, durability of TAVI valves has compared favorably with that of surgically implanted bioprosthetic valves up to 5 years, but these data reflect observations made in older patients and may not be applicable to younger or asymptomatic patients. Considering the much higher perioperative mortality after surgical replacement of failed TAVI prostheses, redo-TAVI might be an effective option for patients with valve dysfunction after TAVI. Because of concerns about the long-term durability of TAVI valves and lack of outcome data on TAVI for asymptomatic AS, current guidelines recommend surgical AVR in preference to TAVI in asymptomatic patients.

Given that the risks related to AVR have been decreasing in contemporary practice with improvements in AV prostheses, procedural techniques and postprocedural care, early intervention could be a preferred management option if the risks of watchful observation are greater than those of early AVR.

**Benefits of Early Intervention**

In patients with asymptomatic severe AS, it appeared relatively safe to delay surgery until symptoms developed following a watchful waiting strategy. However, this conservative treatment strategy has the risk of sudden death, denial or late reporting of symptoms, irreversible myocardial damage, and increase in operative risk while waiting for symptoms to develop. and patients’ survival was worse than that of age- and sex-matched populations in previous observational studies, implying unmet needs for a more effective treatment option. According to the 2020 ACC/AHA guidelines, the risk of sudden death is <1% per year in initially asymptomatic patients with severe AS when patients are followed prospectively and if patients promptly report symptom onset, but the annual risk of sudden death tends to increase during progression of AS while waiting for development of symptoms. The risk of sudden death may persist after surgery if AVR is performed later in the presence of irreversible myocardial damage, and prevention of sudden death would be the most important benefit of early AVR. In addition to the risk of sudden death, the overall risk of AVR may also increase while surgery is deferred until symptoms develops. Performance of urgent surgery on an unstable patient with acute decompensation carries much greater operative risk than early elective surgery. Because performance of AVR in the presence of left ventricular (LV) myocardial damage is associated with a higher long-term risk, cardiovascular events occur more frequently after later surgery than earlier surgery.

There has been an increasing need for direct comparison of watchful observation and early intervention to objectively evaluate the risks and benefits of early AVR. Recent observational studies showed that early AVR had favorable outcomes in all-cause death compared with conventional
The RECOVERY trial was designed to compare long-term clinical outcomes of early surgical AVR with those of a conventional treatment strategy based on current guidelines in asymptomatic patients with very severe AS. According to the 1998 ACC/AHA guidelines and a traditional definition of severe AS, very severe AS was defined as an AV area of \( \leq 0.75 \) cm\(^2\) with either a peak aortic jet velocity of \( \geq 4.5 \) m/s or a mean transaortic gradient of \( \geq 50 \) mmHg. Of 1,031 patients with very severe AS, each patient was specifically questioned about the presence of any symptoms during ordinary physical activity, and 758 patients (74%) with symptoms were excluded; 273 asymptomatic patients were assessed for eligibility, 128 of whom were excluded. Because the presence of exertional symptoms is a clear indication for AVR, only patients who were entirely asymptomatic were enrolled and exercise testing was performed on all the patients with vague, nonspecific symptoms. Of the 145 patients who underwent randomization, 73 were assigned to the early surgery group and 72 to the conservative treatment group. The mean age of the patients was 64 years, and 49% were men. The most common cause of AS was a bicuspid AV (61%), and the mean peak aortic jet velocity was 5.1 m/s, and the mean AV area was 0.63 cm\(^2\).

There were no operative deaths in the early surgery group and among the 53 patients (74%) who later underwent AVR in the conservative management group. During a median follow-up of 6.2 years, 1 patient in the early surgery group and 72 to the conservative treatment group. The mean age of the patients was 64 years, and 49% were men. The most common cause of AS was a bicuspid AV (61%), and the mean peak aortic jet velocity was 5.1 m/s, and the mean AV area was 0.63 cm\(^2\). There were no operative deaths in the early surgery group and among the 55 patients (74%) who later underwent AVR in the conservative management group. During a median follow-up of 6.2 years, 1 patient in the early surgery group and 11 patients in the conservative treatment group died from cardiovascular causes (HR, 0.09; P=0.003). In the conservative treatment group, sudden cardiac death occurred in 5 patients who had not developed symptoms and did not undergo AVR and in 1 patient who underwent later AVR due to development of symptoms during follow-up. The number needed to prevent 1 cardiovascular death within 4 years was 20 patients. The cumulative incidence of the primary endpoint (operative or cardiovascular death) was 1.4% at both 4 and 8 years in the early surgery group as compared with 5.7% at 4 years and 25.5% at 8 years in

Taniguchi et al compared initial surgical vs. conservative strategies using data from CURRENT AS (Contemporary Outcomes After Surgery and Medical Treatment in Patients with Severe Aortic Stenosis). The 5-year cumulative incidence of all-cause death was significantly lower in patients undergoing initial AVR (15%) compared with those who were managed conservatively (26%) in 291 propensity score-matched pairs (HR 0.60; 95% CI 0.40–0.88, P=0.009). Lee et al recently reported a lower all-cause death risk with early surgery (HR 0.52; 95% CI 0.32–0.84, P=0.008) than conventional treatment in 93 propensity score-matched pairs. However, the decision of whether to undergo early surgery was left to the discretion of the attending physician and not randomized, and deaths occurring among those who refused surgery after development of symptoms in the conventional treatment group were counted in the analysis. Baseline differences between the treatment groups, treatment-selection bias, unmeasured confounders and incomplete adherence to the watchful observation strategy might have seriously affected outcomes of the conventional treatment group and only a randomized clinical trial can reduce the limitations inherent to observational studies.

Review of Randomized Clinical Trials for Timing of Intervention

Because it is hard to make asymptomatic patients feel better, preemptive AVR can be justified only when there is clear evidence that early AVR improves long-term outcomes compared with conventional treatment in asymptomatic severe AS. We have been waiting for a prospective randomized trial to solve the intense debate between early AVR and watchful observation, and the RECOVERY (Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis) trial provides evidence to support early preemptive AVR for asymptomatic severe AS.
the conservative management group (Figure 3A). A total of 5 deaths (6.8%) from any cause occurred in the early surgery group and 15 (20.8%) in the conservative management group (HR, 0.33; P=0.03). The number needed to save 1 life within 4 years was 16 patients. The cumulative incidence of death from any cause was also lower in the early surgery group than in the conservative management group (10.2% vs. 31.8% at 8 years) (Figure 3B). The RECOVERY trial, the first randomized trial comparing early surgery with conventional treatment in asymptomatic patients with severe AS, demonstrated that early surgery significantly reduced the rates of cardiovascular death and death from any cause.

Further evidence from a randomized clinical trial is required to apply Level of Evidence A to early intervention for asymptomatic severe AS. Ongoing clinical trials with completion estimated in the near future are AVATAR (Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) and EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis) trial.

AVATAR is a randomized, event-driven trial that was launched in 2015 at 8 centers in 7 European countries. The study’s purpose is to compare clinical outcomes of early surgical AVR to conventional treatment in asymptomatic patients with severe AS with normal LV ejection fraction (EF) and low to intermediate surgical risk. The primary endpoint is all-cause death and major adverse cardiac events, including acute myocardial infarction, stroke, and unplanned hospitalization for heart failure. The assumptions for this event-driven trial include that enrollment duration is assumed to be 24 months, the incidence of the primary endpoint would be 9% in the control group vs. 3.5% in the AVR group during a 36-month follow-up period and 156 subjects in each group; a total of 312 subjects are required. Although inclusion of soft outcomes such as heart failure events in the primary endpoint may be considered a limitation, the advantages of the AVATAR trial are the broader scope of trial patients (peak aortic velocity >4 m/s) and performance of exercise testing to prove asymptomatic status before enrollment. The EARLY TAVR trial is a randomized trial of Edwards Sapien 3 TAVI vs. active surveillance, enrolling a total of 1,109 patients. Patients included in this trial must be ≥65 years of age, asymptomatic, and diagnosed with severe AS. Major exclusion criteria include bicuspid AV, STS score >10%, LVEF <50%, and unsuitability for transfemoral TAVI. Before enrollment, most patients will undergo an exercise test to confirm their asymptomatic status. The primary endpoint is a composite of all-cause death, stroke, and unplanned cardiovascular hospitalization at 2 years. Because the study population in the RECOVERY trial is quite different from the populations enrolled in the previous TAVI trials, the findings of RECOVERY cannot be directly applied to early TAVI, and we will have to wait for the results of the EARLY TAVR trial for consideration of TAVI in asymptomatic patients with severe AS.

**Conditions Favoring Early Intervention**

Identification of the risk factors for AS that predict clinical outcome affects the timing and indications of AVR for asymptomatic AS patients and risk assessment is expected to facilitate the identification of patients who may benefit from early intervention among asymptomatic patients with severe AS.

**LV Systolic Dysfunction**

In patients with a low LVEF and severe AS, survival is better in those who undergo AVR than in those treated medically. Thus, AVR is indicated in asymptomatic patients with severe AS and LVEF <50% according to the current guidelines. LV systolic dysfunction occurs as a result of excessive afterload and is expected to reverse following AVR, but reduced LVEF does not improve in some patients and adversely influences survival. Persistent systolic dysfunction appears related to the development of irreversible myocardial fibrosis, and a cutoff for an abnormal LVEF is unclear in patients with AS. In a multicenter registry, asymptomatic AS patients with LVEF <60% have increased risks of all-cause and cardiovascular death. In the CURRENT AS registry, survival in patient with severe AS was impaired when LVEF was <60%. Further studies are needed on whether asymptomatic patients with severe AS and LVEF <60% or mid-wall fibrosis on cardiac magnetic resonance can benefit from early AVR.

**Very Severe AS**

Traditionally, severe AS was defined as an AV area ≤0.75 cm², a peak aortic jet velocity ≥4.5 m/s, or a mean transaortic gradient ≥50 mmHg, but this definition had a limitation in sensitivity for the diagnosis of severe AS. Since 2006, the definition of severe AS has been revised as an AV area ≤1.0 cm², a peak aortic jet velocity ≥4.0 m/s, or a mean transaortic gradient ≥40 mmHg to include all patients with symptoms or at risk of developing symptoms. However, there are many patients who fit this arbitrary definition but do not manifest significant alterations in circulation, and the outcomes of patients with an AV area between 0.8 and 1.0 cm² are highly variable. For these reasons, severe AS was defined as an AV area <0.8 cm² in the landmark randomized trials of TAVI for inoperable or high-risk patients. Prospective clinical studies demonstrate that disease progression occurs in nearly all patients with severe asymptomatic AS, and the traditional definition of severe AS was used to define very severe AS in the RECOVERY trial. Eventually, most patients in the conservative management group required AVR during follow-up, suggesting that AVR is almost unavoidable in asymptomatic patients with an AV area ≤0.75 cm².

The risk-benefit ratio may be shifted toward benefit for early surgery in the RECOVERY trial that enrolled patients with very severe AS, because the risk of waiting increases according to the severity of AS. However, long-term survival in the conservative management group in the RECOVERY trial was better than that reported previously. The rate of all-cause death at 4 years was 9.7% in the conservative management group (mean age, 63 years; mean aortic jet velocity, 5.0 m/s), and it was lower than the 13% reported in Rosenhek et al’s study, including 128 asymptomatic patients (mean age, 60 years; mean aortic jet velocity, 5.0 m/s), which provided a rationale for watchful observation strategy recommended in current guidelines. Although the same watchful observation strategy was followed in both studies, there were 3 deaths (2.3%) from refusal of surgery and 4 perioperative deaths (3.1%) in the earlier study, whereas all patients in the conservative management group in the RECOVERY trial underwent AVR once they developed symptoms and there were no operative
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