外科手術リスクの低い患者に対するTAVRは外科手術と同様に優れている(Abstracts 19-LB-19883 and 19-LB-19835)

大いに期待されていたトライアルは、全てのリスク群に対し TAVR は外科手術と同等あるいは優れていることを示した

Highly anticipated trials show TAVR equal to or better than surgery across all risk groups

American College of Cardiology's 68th Annual Scientific Session で取り上げられた 2 つのスタディの結果、経カテーテル大動脈弁置換術（TAVR）が外科手術リスクの低い大動脈弁狭窄症患者に拡大された。1 つ目のスタディでは、後遺症を伴う脳卒中または総死亡を合計した発現率が、TAVR を施行された低リスク患者において 5.3% であったのに対し、外科的大動脈弁置換術（SAVR）では 6.7% であった。もう 1 つのスタディ PARTNER-3 では、TAVR は 1 年後の一次エンドポイントである死亡、脳卒中および再入院を 46% と、有意に減少させた。このスタディ結果は同時に *New England Journal of Medicine* に掲載された。

Full Text

Results from two studies featured at the American College of Cardiology's 68th Annual Scientific Session open transcatheter aortic valve replacement (TAVR) up to patients with aortic stenosis at low surgical risk. Both trials were simultaneously published online in the *New England Journal of Medicine* at the time of presentation. Currently, TAVR is used for treatment of severe aortic valve stenosis in patients at intermediate and high risk for complications associated with surgery. Results from these trials open the use of TAVR in low risk patients to a class I guideline indication on par with surgery.

In one trial, comparing self-expanding transcatheter aortic valve replacement (TAVR) to standard open-heart surgery for valve replacement—this time in patients with severe aortic stenosis who are considered low surgical risk—found no difference in the combined rate of disabling stroke or death from any cause at two years. These events occurred in 5.3 percent of TAVR patients and 6.7 percent of patients undergoing traditional surgery.

TAVR, which involves threading a replacement valve through a catheter in the groin or chest, is at least as safe and effective as surgery in these patients; these results echo what was found in an earlier trial of intermediate risk patients, researchers said.

"We now have a minimally invasive procedure that is as good as or better than surgery, while at the same time allowing most patients to be out of the hospital within a few days and be back to their normal activities within a week, and that's pretty important," said Michael J. Reardon, MD, professor and Allison Family Distinguished Chair of Cardiovascular Research at Houston Methodist Hospital and the study's senior author.

This randomized, prospective study included 1,468 patients with severe, symptomatic aortic stenosis from 86 centers in Australia, Canada, France, Japan, the Netherlands, New Zealand and the United States who were deemed to be at low risk of surgery. Low risk was defined as a predicted 30-day mortality of 3 percent or less for 30 days post-surgery and was based on a combination of clinical judgment from the local heart team and an independent screening committee.

A total of 725 patients received TAVR with one of three types of self-expanding devices and 678 patients underwent surgical aortic valve replacement (SAVR) with bioprosthetic surgical valves. The TAVR arm of the trial started with first- and second-generation valves (3.6 percent received CoreValve and 74.1 percent Evolut R); the new third generation Evolut Pro valve was introduced late in the trial and was implanted in 22.3 percent of patients enrolled.

Both groups were well-matched in terms of baseline characteristics such as hypertension, coronary disease and lung disease. Unlike earlier intermediate- and high-risk trials that included a 50-50 split of men and women, this trial was two-thirds men and one-third women. Reardon said this might be because women tend to be smaller, require smaller surgical valves at surgery and are deemed at higher surgical risk.

At 30 days, TAVR was statistically superior to SAVR in terms of the combined rate of all-cause mortality or disabling stroke (0.8 vs. 2.6 percent). Taken by itself, death at one month was not statistically different between the groups, but there were fewer for TAVR; deaths occurred in 1.3 percent of surgical patients and 0.5 percent of TAVR patients, which Reardon said is clinically meaningful. TAVR patients also had significantly better quality of life and hemodynamics at 30 days, which are important factors, especially in younger, more active patients.

"TAVR beat surgery at 30 days for mortality or disabling stroke, quality of life and time in the hospital. In other words, you're more likely to be alive without a disabling stroke, get out of the hospital sooner—in half the time—and have a better quality of life one month after getting a new valve," Reardon said, adding that hospital stays were twice as long for patients undergoing surgery than they were for TAVR, 6.2 days vs 2.6 days on average. "The mean age of patients in this study was 74, so while this is still not a young group of patients, many of them are very active and whether it be in their professional or social lives, getting back to full range of daily activities is very important to them."

By 12 months, TAVR was still superior to open heart surgery for major stroke, occurring in 0.8 percent of TAVR patients and 2.4 percent of surgical patients. TAVR had lower rates of all-cause mortality (2.4 vs 3 percent), but it was not statistically significant. Hospitalization for heart failure occurred in 3.2 percent of TAVR patients and 6.5 percent of surgical patients at one year.

"At one year, patients with TAVR were more likely than surgery patients to be alive, without a disabling stroke and without a hospital admission for heart failure," Reardon said.

Quality of life assessments were done using the Kansas City Cardiomyopathy Questionnaire (KCCQ), allowing patients to report their functional ability and wellness. This was performed at baseline, one and six months, and yearly thereafter. For the KCCQ, a five-point increase is considered a small improvement in quality of life, 10 points is moderate, and 20 points is large. Patients receiving TAVR reported significantly better quality of life, 20 vs. 9.1 at one month post-procedure. By one year, both TAVR and surgery had similar improvements in quality of life, 22.2 and 20.9, respectively.

Based on an analysis of echocardiograms, Reardon said there was some indication that the TAVR valve worked better; TAVR had a better orifice (2.2 cm2 vs 2.0 cm2) and lower mean gradients than surgery at all time points in the trial. Similar to earlier studies, TAVR has more pacemakers and more moderate to severe paravalvular leak. The TAVR group also had major vascular injury, including dissection, cardiac perforation or access site injury. There were more cases of atrial fibrillation, transfusions and acute kidney injury in the surgery arm.

"We've now looked at a broad risk spectrum of patients—those at high, intermediate and low surgical risk—and these series of trials have shown that TAVR is better than or as good as surgery in terms of disabling strokes and deaths from all causes. When we look at secondary outcomes of quality of life and functional recovery, these seem to favor TAVR at this point," Reardon said. "Given this data, it now seems reasonable to consider moving TAVR in low risk patients to a class I guideline indication on par with surgery for patients with severe aortic stenosis."

Reardon said this and PARTNER 3 are probably the final trials that will randomize TAVR against surgery given the positive outcomes and patient preference for less invasive therapy. His team plans to follow patients for 10 years, which should yield important long-term data about TAVR compared with surgically implanted valves, as well as the valves themselves. They will also do a cost-effectiveness analysis.

A key study limitation is the relatively short follow up time. Because patients with bicuspid aortic valves and those with anatomic incompatibility for TAVR valves were excluded, as were patients needing other major cardiac surgical procedures such as mitral valve repair, researchers cannot say how these patients might fare.

The study received funding from Medtronic.

In a second trial among patients with severe, symptomatic aortic stenosis who were at low surgical risk, transcatheter aortic valve replacement (TAVR) using the SAPIEN 3 valve compared with conventional surgery significantly reduced the primary endpoint of death, stroke and re-hospitalizations by 46 percent at one year, according to data from the latest PARTNER trial presented at the American College of Cardiology's 68th Annual Scientific Session. In addition, the rates of death from any cause, stroke and repeat hospitalizations independently favored TAVR at 30 days and at one year, researchers said.

Unlike open surgery, TAVR involves threading a replacement valve through a catheter in the groin. TAVR is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe aortic valve stenosis in patients at intermediate and high risk for complications associated with surgery.

PARTNER 3 is the fifth randomized trial of the PARTNER series of studies, which collectively includes over 9,000 patients with severe aortic stenosis, a problem that occurs when the valve in the heart's main artery doesn't open fully, forcing the heart to work harder to pump blood. The earliest trials evaluated TAVR in the "sickest" patients—many of whom cannot be treated with surgery—with subsequent research moving down the spectrum of risk. This study was performed in patients at low surgical risk, which comprise the majority of patients who are candidates for surgery to have their aortic valve replaced.

"This is a landmark study because it involves 80 percent of the people who are currently being treated with surgery for aortic stenosis. Our hope was that TAVR would be non-inferior or comparable to surgery, and we were surprised to find an almost 50 percent reduction in the primary endpoint, from 15.1 percent in the surgical group to 8.5 percent with TAVR," said Martin B. Leon, MD, director of the Center for Interventional Vascular Therapy at New York-Presbyterian/Columbia University Irving Medical Center, professor of medicine at Columbia University Vagelos College of Physicians and Surgeons and lead author of the study. "This is beyond anything we could have expected, mostly because surgery is so good in treating aortic stenosis in these low risk patients."

PARTNER 3 included 1,000 patients with severe aortic stenosis at 71 centers in the U.S. and several other countries with over 95 percent of patients enrolled at U.S. sites. Participants were carefully screened to be low risk for either TAVR or surgery and were randomly assigned to receive the SAPIEN 3 TAVR valve, the newest generation technology, or surgical valve replacement. Compared with the earlier PARTNER trials with intermediate- and high-risk surgical patients, this low-risk group was younger (73 years on average), had fewer co-morbid conditions and had fewer symptoms. There were also more men than women enrolled (67.5 percent vs. 32.5 percent, respectively).

The primary endpoint was the combined rate of all-cause death, any stroke and re-hospitalizations (those related to the valve, the procedure or heart failure) at one year after the procedure.

"Taken by themselves, each component of the primary endpoint also favored TAVR, which is confirmatory evidence of the outcome," Leon said.

A total of 16 patients died during follow up. Of these, 11 were in the surgery group and five were in the TAVR group, so the one-year mortality rate was 1 percent for TAVR and 2.5 percent for surgery. Twenty patients suffered a stroke, 14 of which occurred in the surgery group (3.1 percent) and six in TAVR (1.2 percent). Patients in the surgical group were also more likely to go back to the hospital compared with those in the TAVR group (11 percent and 7.3 percent, respectively).

Several secondary endpoints were also analyzed. The length of hospital stay was reduced from seven to three days with TAVR. Patients in the TAVR group also had more rapid 30-day functional recovery based on six-minute walk tests and other self-reported quality of life measures.

"Surgery eventually catches up to TAVR in terms of functional recovery and quality of life, but it takes several months," Leon said. "TAVR is a less invasive procedure, so we expect an earlier return to normal daily activities compared with surgery. There has also been an evolution of TAVR technology, increased operator experience and enhanced procedural techniques, all of which combine to lower complications after TAVR especially in the lowest risk patients."

Post-operative or new onset atrial fibrillation was found in almost 40 percent of the surgical patients compared with only 5 percent of those receiving TAVR. Major vascular complications were similar between the groups, as was the need for new permanent pacemakers (4 percent after surgery vs 6.5 percent after TAVR). However, Leon said that the incidence of new left bundle block was higher with TAVR, which may be a predictor of needing a new pacemaker in future. Moderate or severe paravalvular leaks, leaks around the valve, were similar in the two groups.

"The results of this trial in low risk patients indicates that the choice of TAVR versus surgery for severe aortic stenosis should be independent of surgical risk profile assessments," Leon said. "The combined rate of death and disabling stroke at one year was only 1 percent with TAVR, which was an unexpectedly favorable outcome. Based on these findings, the choice of TAVR versus surgery should be a shared decision-making process that respects patient preferences and considers some of the knowledge gaps, especially in treating young patients."

There are two major limitations to the PARTNER 3 trial. First, the data are limited to one-year follow-up and longer-term follow-up is needed to be certain that the transcatheter valves are as durable as surgical valves. The patients in this trial will be followed for 10 years. Second, certain patients were excluded in this study, such as patients with bicuspid aortic valve disease and those with poor anatomy such that the valve couldn't be threaded through the femoral artery in the groin.

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