CORRESPONDENCE

Transcatheter Aortic-Valve Replacement

TO THE EDITOR: Leon and colleagues (April 28 issue)[1] report the results of the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A randomized trial. They indicate that 2-year rates of death from any cause or disabling stroke were similar among intermediate-risk patients with severe aortic stenosis who were randomly assigned to transcatheter aortic-valve replacement (TAVR) and those who were assigned to surgical aortic-valve replacement (SAVR). However, SAVR resulted in a higher rate of death or disabling stroke at 2 years than did transfemoral-access TAVR (20.4% vs. 16.8%, P=0.07).

As indicated in Table S6 in the Supplementary Appendix (available with the full text of the article at NEJM.org), this difference appears to be driven by higher 30-day rates of disabling stroke among patients who underwent SAVR than among patients who underwent transfemoral TAVR (4.2% vs. 2.3%, P=0.04). The 30-day rate of new atrial fibrillation, which was markedly higher among the 265 patients in the SAVR group than among the 90 patients in the overall TAVR cohort (28.3% vs. 9.1%, P<0.001) (Table S5 in the Supplementary Appendix of the article), might have affected the early greater hazard of stroke after surgery, and subsequently the greater cardiovascular mortality, as has been previously shown.[2]

It cannot be ruled out that inappropriate antithrombotic treatment might have influenced the 30-day rate of stroke, leading to a higher incidence of this end point within the SAVR group (in which the absolute number of patients with new atrial fibrillation was much higher than in the TAVR group). These observations suggest that analyses of the effect of postoperative treatment for atrial fibrillation on stroke and related mortality are warranted.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The results of the PARTNER 2 trial may lead to a widening of off-label indications for TAVR to include patients who opt for this procedure in order to avoid surgery. The suggestion of this possibility comes from what Leon et al. report as the "high frequency of unexpected withdrawals" in the surgical group of the trial. Before the widening of off-label indications for TAVR is considered to be reasonable, some

THIS WEEK'S LETTERS

unknowns associated with TAVR must be explored.

First, the long-term effect of postprocedural paravalvular aortic regurgitation (the rate of which was 26.2% in the trial) on valve durability and function is not known. To evaluate this effect, a longer follow-up period to assess linearized rates of complications (e.g., objective performance criteria for transcatheter valves) is required, similar to the process used for surgical valves.

A bigger unknown is the long-term effect of underreported "silent infarcts" on the brain. Studies have indicated that silent infarcts are more common in patients who have undergone TAVR[1] than in patients who have undergone SAVR[2] (84% vs. 54%). These infarcts have been linked to dementia and overt stroke.[3,4]

Finally, an effective strategy for treatment of concomitant mitral regurgitation and coronary artery disease (both of which are highly prevalent among patients with aortic stenosis) is required. Such a strategy is needed before indications for TAVR can be extended to patients who do not have a high risk of complications from SAVR.

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TO THE EDITOR: The use of either SAVR or TAVR in the treatment of intermediate-risk patients who have severe aortic stenosis has become controversial. In the recent PARTNER 2 trial, TAVR with a second-generation valve system was compared with an outdated SAVR strategy that is not even described in the study methods. It would have been more interesting if new and emerging surgical techniques with the use of a minimally invasive or sutureless approach had also been considered; this would have provided a comparison that is much more grounded in reality than the comparison presented.

In addition, the study population was not truly homogeneous, given that 14.5% of the patients in the SAVR group underwent associated bypass surgery and 3.9% of patients in the TAVR group required concomitant percutaneous coronary intervention. Furthermore, 9.1% of the patients in the SAVR group underwent additional procedures, including mitral-valve or tricuspid-valve repair, and severe intraoperative complications developed in 32 patients in the TAVR group.

Finally, the efficacy being equal, the least expensive treatment option should be preferred. It is well recognized that TAVR is associated with significantly higher costs than SAVR.[1]

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Dr. Santarpino reports receiving consulting fees from Sorin Group Italia; and Dr. Pfeiffer, consulting fees from LivaNova Group. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In reply to Tamburino and Capranzano: we agree that a major proportion of the end point of lower mortality plus stroke in the transfemoral TAVR cohort in the PARTNER 2 cohort A trial was due to fewer disabling strokes, possibly because of less frequent new-onset atrial fibrillation in the patients who were assigned to TAVR.[1] However, strokes alone do not account for the total reduction in mortality. The contribution of reduced rates of acute kidney injury and serious bleeding events (both of which have been associated with increased late mortality after TAVR) must also be considered. An investigation of both the association of atrial fibrillation with stroke and the effect of anticoagulation regimens on stroke in patients with atrial fibrillation is under way in the PARTNER 2 cohort A trial.

Samarendra mentions the greater frequency of withdrawals in patients who were randomly assigned to surgery than in those who were assigned to TAVR. This greater frequency, which was also seen in the PARTNER 1 cohort A trial, suggests a lack of equipoise with respect to patients and providers. We also agree that assessment of the durability of bioprosthetic valves will require at least 5 to 10 years of follow-up, although the 5-year echocardiographic results look encouraging.[2] Although the rate of total (of mild or greater severity) paravalvular aortic regurgitation in the PARTNER 2 cohort A trial was indeed 26.2%, moderate or severe paravalvular regurgitation was present in only 8.0% of patients, and mild paravalvular regurgitation was not associated with subsequent mortality. Finally, although neuroimaging studies suggest increased perfusion deficits with TAVR versus surgery, the size of the deficits was twice as large in the surgical patients.[3] We do not think that rates of clinical stroke were underreported, since careful neurologic assessments were performed in all patients.

In reply to Santarpino et al.: it is incorrect to label the surgical techniques in our trial as "outdated" and to imply that the surgical outcomes were therefore substandard. In the 57 surgical centers in the trial, the all-cause mortality at 30 days after surgery was 4.1% and the ratio of observed-to-expected mortality was 0.71, according to the Society of Thoracic Surgeons (STS) risk scores. The STS score equals the predicted mortality expressed as a percentage. Moreover, although specific surgical techniques were not mandated, 15% of the patients did receive minimally invasive aortic-valve replacement and there were no differences in outcomes; this is consistent with the surgical literature, which shows no differences in outcomes between patients who undergo surgery with a minimally invasive approach and those who do not. Short-term or long-term data on sutureless aortic valves are lacking, and none show clear benefits. An inpatient cost differential favors surgery because of the high cost of the transcatheter valve, but recently this differential has narrowed because of lower in-hospital costs associated with reduced lengths of stay in the intensive care unit and the hospital among patients undergoing TAVR.

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Since publication of their article, the authors report no further potential conflict of interest.

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Aliskiren, Enalapril, or Both in Heart Failure

TO THE EDITOR: McMurray et al. (April 21 issue)[1] report on the results of the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE). They found that in patients with heart failure, aliskiren combined with an angiotensin-converting–enzyme (ACE) inhibitor increased the risk of adverse events without any benefit. These results contrasted with those of previous studies showing that blockade with an ACE inhibitor and an angiotensin II receptor blocker (ARB) improved cardiovascular outcomes.[2,3]

McMurray et al. state that ATMOSPHERE is the only trial that used an evidence-based dose of an ACE inhibitor. However, it is conceivable that the combination of an ARB and an ACE inhibitor can provide an additional therapeutic effect, since these drugs increase levels of angiotensin-(1-7) (a heptapeptide component of the renin–angiotensin system), which antagonizes angiotensin II effects.[4] Although knowledge of the effects of angiotensin-(1-7) in patients with heart failure is still limited, experimental studies show cardioprotection.[4,5]

In addition, the distribution of use of beta-blockers and a mineralocorticoid-receptor antag-