Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 11, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.059

EDITORIAL COMMENT

Who Comes Off Best With Closed Chest?

Aortic Valve Replacement in Patients With High Surgical Risk*

Joachim Schofer, MD

Hamburg, Germany

Since its introduction, transcatheter aortic valve replacement (TAVR) has emerged as a new therapeutic option for patients with inoperable, severe aortic stenosis and as an alternative treatment modality to surgical aortic valve replacement (SAVR) in selected, high-risk patients (1,2). Because it is less invasive, this novel treatment is highly attractive to both physicians and patients. Not surprisingly, the use of TAVR has been increasing exponentially in Europe and North America. The available data on TAVR versus SAVR for patients at a higher surgical risk show similar outcomes for both groups (3). Therefore, to identify individuals who benefit more from 1 therapy or the other, a discriminating look at this heterogeneous group of high-risk, but still operable, patients is mandatory.

See pages 1090 and 1100

In this issue of the *Journal,* 2 substudies from the high-risk for surgery cohort (i.e., cohort A) of the PARTNER (Placement of Aortic Transcatheter Valve) trial focus on this important matter. The objective of the first study by Lindman et al. (4) was to determine clinical outcomes in patients with aortic stenosis after TAVR compared with SAVR by using a post-hoc analysis stratified according to diabetes status. In contrast to nondiabetic patients, among those with diabetes (42% of the total cohort), all-cause mortality at 1 year was significantly lower in the TAVR group compared with the SAVR group (18.0% vs. 27.4%). There was a significant interaction between diabetes and treatment group for 1-year all-cause mortality, and results were consistent among patients treated by using the transfemoral (TF) or transapical (TA) approach. Renal failure requiring dialysis >30 days occurred more often in the SAVR group (6.1% vs. 0%), but 1-year stroke rates were similar between groups (3.5% TAVR vs. 3.5% SAVR).

The authors (4) have to be congratulated for this first report on an improved outcome by transcatheter versus surgical therapy of severe aortic stenosis in diabetic high-risk patients. For SAVR, increased morbidity and mortality in diabetic patients compared with nondiabetic subjects have already been shown (5). Cardiac surgery and cardiopulmonary bypass can initiate a systemic inflammatory response syndrome (SIRS) that is associated with adverse outcome (6). Tissue ischemia–reperfusion injury seems to be the major cause for the release of various inflammatory mediators, and diabetic patients are more sensitive to the following oxidative stress and inflammation (7). Interestingly, SIRS has also been described in TAVR-treated patients and was associated with an unfavorable impact on survival (8). The number of ventricular pacing runs turned out to be an independent predictor for SIRS, supporting the hypothesis that tissue ischemia plays a key role. Although markers of inflammation were not systematically measured in the current study, white blood cell counts 24 h after the procedure tended to be lower in diabetic patients undergoing TAVR compared with those undergoing SAVR. This finding provides some support for the notion that SAVR may induce a greater amount of inflammation than TAVR in diabetic patients. The inflammation does not necessarily result in a higher cardiovascular mortality, but it may lead to increased noncardiac mortality, as found in the current study.

Based on these findings, is TAVR the preferable treatment in diabetic patients with high surgical risk? Although the work of Lindman et al. (4) is an important contribution to our understanding of patient selection for TAVR or SAVR, the definitive answer is still pending. The authors do not provide us with reliable information on diabetic medication (insulin and/or oral medications) or on the severity or duration of diabetes. In addition, data on glucose control in the study population are lacking and could be confounding. Moreover, the difference in mortality was no longer present after 2 years. This finding might be caused by patients' comorbidities, but it raises a question about the long-term effect of TAVR: does aortic regurgitation, which is more significant after TAVR, diminish the beneficial treatment effect over time? Finally, this was not a randomized trial, nor was it a pre-specified subgroup analysis; therefore, as the authors correctly state, these results should be considered hypothesis-generating and must be confirmed in future studies.

In the second study in this issue of the *Journal*, Généreux et al. (9) sought to identify the incidence, predictors, and prognostic impact of bleeding complications (BC) after SAVR compared with TAVR from the PARTNER I trial. Within 30 days of the procedure, SAVR compared with TF- and TA-TAVR was associated with significantly more major BC and an almost 3 times higher rate of transfusion. Independent predictors of major BC were major vascular complications and the use of intra-procedural hemodynamic support among TF-TAVR patients, procedural complications requiring conversion

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Medical Care Center, Hamburg University Cardiovascular Center, Hamburg, Germany. Prof. Schofer has reported that he has no relationships relevant to the contents of this paper to disclose.

to open surgery among TA-TAVR patients, and low baseline hemoglobin levels among SAVR patients. In accordance with previous studies, major BC were identified as a strong independent predictor of 1-year mortality among the full cohort (12). The surprising result of the current study, however, was that BC had a significant impact on prognosis after SAVR but not after TAVR.

The authors are to be complimented on this important analysis (9), which is currently the largest on this topic. Although other studies have already reported rates of bleeding after TAVR (10) or after TAVR compared with SAVR (11), the strength of the study by Généreux et al. (9) is the relative homogeneity of its patient population, the independent adjudication of events, and the direct comparison with a surgical cohort of similar risk. However, the study has several limitations. The PARTNER trial was performed by using first-generation devices (22- and 24-F introducer sheath diameter for TF and 29-F for TA), with operators and sites at the beginning of their learning curve. Considering the ongoing evolution toward lower-profile TAVR devices, even greater differences between TAVR and SAVR in rates of BC and transfusion are likely to be seen in the future.

The reason why major BC influence the prognosis after SAVR but not after TAVR is not completely understood (9). Specific causes of bleeding and reasons for transfusions were not systematically documented. However, the BC after surgery seemed to be more severe: among patients receiving transfusions, the proportion of patients receiving $\geq$4 transfusions was almost twice as high in the SAVR group compared with the TF-TAVR group. There is a close relationship between the severity of the initial bleeding event and the impact on survival. Accordingly, blood transfusion rate has been shown to be a predictor of inflammation and adverse outcome in cardiac surgery patients (13).

Although low baseline hemoglobin level was the only independent predictor for major BC after SAVR, the difference in hemoglobin between patients with and without major BC was only 0.6 g/dl (9). This difference is too small to be helpful in identifying patients at high risk for bleeding after surgery but seems to reflect a higher comorbidity of the patients who experience BC.

Although both studies (4,9) are important contributors to our understanding of suitable patient selection for TAVR or SAVR, further studies are needed before we can reliably determine the population for whom aortic valve replacement is done best with closed chest.

Reprint requests and correspondence: Prof. Joachim Schofer, Medical Care Center, Hamburg University Cardiovascular Center, Wördemanns Weg 25-27, Hamburg 22527, Germany. E-mail: schofer@herz-hh.de.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
3. Cao C, Ang SC, Indraratna P, et al. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Ann Cardiothorac Surg 2013;2:10–23.
4. Lindman BR, Pibarot P, Arnold SV, et al. Transcatheter versus surgical aortic valve replacement in patients with diabetes and severe aortic stenosis at high risk for surgery: an analysis of the PARTNER trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol 2014;63:1090–9.
5. Halkos ME, Kilgo P, Lattouf OM, et al. The effect of diabetes mellitus on in-hospital and long-term outcomes after heart valve operations. Ann Thorac Surg 2010;90:124–30.
6. Sablotzki A, Friedrich I, Mühling J, et al. The systemic inflammatory response syndrome following cardiac surgery: different expression of proinflammatory cytokines and procalcitonin in patients with and without multiorgan dysfunctions. Perfusion 2002;17:103–9.
7. Fransen E, Maessen J, Dentener M, et al. Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. Chest 1998;113:1290–5.
8. Sinning JM, Scheer AC, Adenauer V, et al. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012;33:1459–68.
9. Généreux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol 2014;63:1100–9.
10. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.
11. Tamburino C, Barbanti M, Capodanno D, et al. Comparison of complications and outcomes to one year of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis. Am J Cardiol 2012;109:1487–93.
12. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608–16.
13. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116:2544–52.

Key Words: aortic stenosis ■ bleeding ■ SAVR ■ TAVI ■ TAVR.