Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement
The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial

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Background—The Nordic Aortic Valve Intervention (NOTION) trial was the first to randomize all-comers with severe native aortic valve stenosis to either transcatheter aortic valve replacement (TAVR) with the CoreValve self-expanding bioprosthesis or surgical aortic valve replacement (SAVR), including a lower-risk patient population than previous trials. This article reports 2-year clinical and echocardiographic outcomes from the NOTION trial.

Methods and Results—Two-hundred eighty patients from 3 centers in Denmark and Sweden were randomized to either TAVR (n=145) or SAVR (n=135) with follow-up planned for 5 years. There was no difference in all-cause mortality at 2 years between TAVR and SAVR (8.0% versus 9.8%, respectively; P=0.54) or cardiovascular mortality (6.5% versus 9.1%; P=0.40). The composite outcome of all-cause mortality, stroke, or myocardial infarction was also similar (15.8% versus 18.8%, P=0.43). Forward-flow hemodynamics were improved following both procedures, with effective orifice area significantly more improved after TAVR than SAVR (effective orifice area, 1.7 versus 1.4 cm² at 3 months). Mean valve gradients were similar after TAVR and SAVR. When patients were categorized according to Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) (<4% versus ≥4%), there was no statistically significant difference for TAVR and SAVR groups in the composite outcome for low-risk (14.7%, 95% confidence interval, 8.3–21.2 versus 16.8%; 95% confidence interval, 9.7–23.8; P=0.58) or intermediate-risk patients (21.1% versus 27.1%; P=0.59).

Conclusions—Two-year results from the NOTION trial demonstrate the continuing safety and effectiveness of TAVR in lower-risk patients. Longer-term data are needed to verify the durability of this procedure in this patient population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01057173.

Key Words: bioprosthesis □ hemodynamics □ myocardial infarction □ stroke □ transcatheter aortic valve replacement

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WHAT IS KNOWN

- Transcatheter aortic valve replacement has proven to be noninferior or even superior to surgical aortic valve replacement in patients with severe aortic stenosis, who are at intermediate or high surgical risk.
- The Nordic Aortic Valve Intervention (NOTION) trial indicated that these results also apply to patients at lower surgical risk; however, it is uncertain whether these findings apply at midterm follow-up.

WHAT THE STUDY ADDS

- At 2 years, the NOTION trial did not find a significant difference in the composite rate of death from any cause, stroke, or myocardial infarction between transcatheter aortic valve replacement and surgery.
- These results suggest that transcatheter aortic valve replacement is a reasonable option to surgical valve replacement.

reported in other randomized trials. The primary outcome was a composite rate of death from any cause, stroke, or myocardial infarction at 1 year; and although TAVR was not demonstrated to be statistically superior to SAVR for the primary outcome, the therapy was safe and effective in this lower-risk population. Furthermore, in a post hoc analysis TAVR was noninferior to SAVR on the primary outcome (P=0.01) using a noninferiority margin of 7.5%. Improvements in valve hemodynamics and functional class were sustained at 1 year post procedure. Presently, data on lower-risk patients are limited. The objective of the current analysis is to evaluate 2-year clinical and echocardiographic outcomes among lower-risk patients who underwent TAVR or SAVR in the NOTION trial.

Methods

Trial Design

The NOTION trial is an investigator-initiated, randomized, nonblinded, superiority trial conducted at 3 centers in Denmark and Sweden. The design of the trial has been described previously. Two-hundred eighty patients were randomly assigned to TAVR (n=145) or SAVR (n=135) with follow-up planned for 5 years.

The trial was conducted according to the principles of the Declaration of Helsinki, and the regional ethical review board at each site approved the protocol. All patients provided written informed consent. Data were collected and stored by the investigators and were fully monitored by an independent monitoring unit. The trial is registered at https://www.clinicaltrials.gov, identifier: NCT01057173. All authors vouch for the accuracy and completeness of the data and analyses, and confirm that the trial was conducted according to the protocol.

Procedures

Patients were randomized 1:1 to either TAVR or SAVR and stratified according to trial site, age (70–74 years or ≥75 years), and history.

Figure 1. Patient disposition to 2 years. ITT indicates intention-to-treat; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

All Enrolled
N=280

RANDOMIZATION

All Enrolled
N=280

Died prior to procedure
n=3

Died prior to procedure
n=1

Crossover
TAVR to SAVR
n=1

Crossover
SAVR to TAVR
n=1

Died
n=7

Died
n=6

Died
n=6

Died
n=5

Died
n=6

Died
n=6

Missed visits
n=2

Missed visits
n=5

Missed visits
n=6

Missed visits
n=6

Died
n=120

1 Year
n=113

Missed visits
n=2

Missed visits
n=5

Missed visits
n=6

Died
n=142

AT TAVR
n=145

AT SAVR
n=135

1 Year
n=133

Missed visits
n=2

Missed visits
n=5

Missed visits
n=6

2 Years
n=123

Missed visits
n=6

2 Years
n=113

Missed visits
n=6

Figure 1. Patient disposition to 2 years. ITT indicates intention-to-treat; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.
of coronary artery disease as previously described. All SAVR patients received a bioprosthesis with the specific type and size determined during the procedure. Patients randomized to TAVR received the CoreValve self-expanding bioprosthesis (Medtronic, Minneapolis, MN), predominantly via femoral artery access (96%) with some patients undergoing left transaxillary access (4%). All available CoreValve sizes (23, 26, 29, or 31 mm) were used. The procedure was performed under general or local anesthesia as previously described. All TA VR and SA VR patients received similar periprocedural prophylactic antibiotics and postoperative antiplatelet and anticoagulation regimens as previously described. All procedures were performed by senior cardiac surgeons and interventional cardiologists.

Follow-up assessments were performed before discharge and 1, 3, 12, and 24 months after the procedure and consisted of a physical examination, documentation of trial-specified outcomes and adverse events, New York Heart Association (NYHA) classification, blood sampling, and a 12-lead ECG. Transthoracic echocardiography was performed at baseline and 3, 12, and 24 months. Echocardiograms were evaluated by experienced cardiologists, and all clinical outcomes were confirmed by national electronic medical records. When a neurological event was suspected, an independent neurologist performed an evaluation, and cerebral imaging studies were performed.

Outcome Measures

The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction at 1 year after the procedure. Two-year outcomes reported here include the composite outcome as well as prespecified clinical outcomes, including all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, pacemaker implantation, and aortic valve reintervention. Hemodynamic outcomes include aortic valve effective orifice area, mean pressure gradient, and degree of total aortic valve regurgitation, as measured by echocardiography, reported out to 2 years. All outcomes were defined according to Valve Academic Research Consortium-2 definitions.

Statistical Analysis

For clinical outcomes, a time-to-event analysis was conducted using Kaplan–Meier estimates, and comparisons between the treatment groups were done using the log-rank test. The as-treated population, defined as patients in whom 1 of the 2 trial procedures was attempted, was used for all analyses. Event rates are given for the following postprocedural time windows: 0=0 to 29 days, 1 month=30 to 182 days, 6 months=183 to 364 days, 12 months=365 to 729 days, and 24 months=≥730 days.

Subgroup analyses of all-cause mortality at 2 years were conducted for several baseline characteristics. The Cox Proportional Hazard model was used to examine the interactions between treatment and each baseline characteristic. Categorical variables were compared using the Fisher exact test or the χ² test as appropriate. Continuous variables were presented as means±SD and compared with the use of the Student t test. Ordinal variables were compared using the Mantel–Haenszel test. All testing used a 2-sided α level of 0.05. P values were not adjusted for multiple comparisons. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Patients

Patients were enrolled from December 2009 through April 2013. Two-hundred eighty patients were eligible for the study. Four patients died before the procedure; therefore, aortic valve replacement was attempted in 276 patients, resulting in an as-treated population of 142 TAVR and 134 SAVR patients.

![Figure 2](http://circinterventions.ahajournals.org/)

Figure 2. Kaplan–Meier curves depicting (A) a composite rate of all-cause mortality, all stroke, and myocardial infarction (MI); (B) all-cause mortality; (C) composite rate of all-cause mortality, all stroke, and MI in transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients with Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) <4%; and (D) composite rate of all-cause mortality, stroke, and MI in TAVR and SAVR patients with STS-PROM ≥4%.
Patient characteristics have been described previously. Briefly, TAVR patients were slightly younger than the traditional TA VR patient (mean age, 79.1±4.8 years) and more commonly male (53.2%). The overall mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score was 3.0±1.7%, and the mean logEuroSCORE I was 8.6±4.8%. At 2 years post procedure, 94.6% of TA VR patients and 95.8% of SA VR patients had completed the follow-up.

All-Cause Mortality, Stroke, or Myocardial Infarction at 2 Years
The primary outcome measure, a composite of all-cause mortality, stroke, or myocardial infarction at 1 year, was not statistically different between TA VR and SA VR. After 2 years, TA VR and SA VR patients had a similar composite outcome (15.8% versus 18.8%; P=0.43; Figure 2). Rates of each individual component of the composite outcome were also not statistically different between the groups (Table 1). Between 1 and 2 years, 4 deaths occurred in the TAVR group and 3 in the SAVR group, but the overall mortality (8.0% versus 9.8%; P=0.54) as well as cardiovascular mortality (6.5% versus 9.1%; P=0.40) remained low at 2 years (Table 1). There were 2 additional strokes between 1 and 2 years of follow-up—1 in the TAVR group and 1 in the SAVR group—resulting in low 2-year stroke rates (3.6% versus 5.4%; P=0.46). Between 1 and 2 years, 2 additional TAVR patients experienced a myocardial infarction, resulting in a 2-year rate comparable with that of the SAVR group (5.1% versus 6.0%; P=0.69).

Secondary Clinical Outcomes at 2 Years
Additional secondary outcomes are presented in Table 1. Cumulative rates of new-onset or worsening atrial fibrillation...
remained significantly lower in the TAVR group compared with the SAVR group (22.7% versus 60.2%; P<0.001), whereas the pacemaker implantation rate remained higher in the TAVR group (41.3% versus 4.2%; P<0.001). Four new permanent pacemaker implantations occurred between 1 and 2 years in the TAVR group, all in patients who developed third-degree atrioventricular block. There were no aortic valve prosthesis reinterventions in either group.

**Functional Status**
Both patients in the TAVR and SAVR groups experienced significant improvements in NYHA functional class that were sustained over time (Figure 3). No patients were in NYHA class IV at 2 years. At 1 year, symptomatic dyspnea was more common in the TAVR group because of a higher number of patients in NYHA class II. However, at 2 years this difference was no longer present because more patients in the SAVR group changed from NYHA class I to II (Figure 3).

**Echocardiographic Outcomes**
Echocardiographic measurements are summarized in Figure 4. Aortic valve performance, as measured by mean aortic valve gradient and effective orifice area, improved after both TAVR and SAVR (Figure 4). Furthermore, effective orifice area significantly improved more after TAVR compared with SAVR at each time point (P<0.001), including at 2 years (Figure 4B). Improvements in mean valve gradient from baseline were not statistically different between TAVR and SAVR (Figure 4C). Total aortic regurgitation (AR) was higher in the TAVR group at each time point compared with SAVR, including at 2 years (moderate/severe AR, 15.4% versus 0.9%, P<0.001; Figure 5). These findings were comparable when using paired data at all follow-up time points (moderate/severe AR, 15.0% versus 1.0%, P<0.001). In addition, paired data showed that the percentage of patients with mild AR decreased from 61.9% at 3 months to 54.9% at 1 year and 38.9% at 2 years. Moderate AR did not change over time, but none/trace increased from 22.1% at 3 months to 29.2% at 1 year and to 46.0% at 2 years, suggesting improvements over time.

**Subgroup Analyses of Mortality**
Subgroup analyses of all-cause mortality at 2 years were performed to determine the relationship between several baseline characteristics and all-cause mortality at 2 years by the treatment group (Table 2). A statistically significant interaction was observed for medically treated hypertension but no other characteristics. A post hoc analysis of mortality stratified by...
permanently pacemaker implantation in TAVR patients revealed no significant difference in mortality between patients who received a pacemaker within 30 days after the procedure and those who did not (P log-rank=0.62). Furthermore, no significant difference in mortality at 2 years according to the degree of AR at 3 months was demonstrated for the TAVR group (Figure 6; P log-rank=0.57). Improvement in mild AR in the TAVR group was statistically significant at 2 years (P<0.001) but not at 1 year (P=0.17). Among patients with an STS-PROM <4%, the composite outcome of all-cause mortality, myocardial infarction, or stroke at 2 years was not significantly different between those who underwent TAVR and those who underwent SAVR (14.7% versus 16.8%; P=0.58; Figure 2). Similarly, there was no statistically significant difference in the composite outcome between TAVR and SAVR patients with an STS-PROM ≥4% (21.1% versus 27.1%; P=0.59; Figure 2).

### Discussion

The NOTION trial was the first randomized trial comparing TAVR and SAVR to include patients at lower surgical risk. The outcomes reported here demonstrate comparable safety and effectiveness of TAVR and SAVR in lower-risk patients at 2 years.

Randomized trials in high-risk patients have reported similar all-cause mortality rates for TAVR and SAVR after 2 years in patients treated with a balloon-expandable prosthesis (33.9% versus 35.0%, P=0.78) and better survival after TAVR (22.2% versus 28.6%, P<0.05) with the same self-expandable prosthesis as used in the current trial. In this analysis, the TAVR group had numerically lower-rates than the SAVR group for all outcomes, yet no statistically significant differences between the groups were observed. The subgroup analysis only demonstrated a nonintuitive statistically significant interaction between all-cause mortality at 2 years and medically treated hypertension. Intermediate-risk patients had a higher-rate of the composite outcome for both TAVR and SAVR compared with low-risk patients, but there was no significant difference between the treatment groups, supporting the efficacy and safety of TAVR in low-risk patients.

Prosthesis durability at 2 years remained consistent with 1-year data. At each time point, the TAVR group had significantly more improvement in effective orifice area compared with the SAVR group. AR continued to be higher in the TAVR group compared with the SAVR group, with unchanged rates of moderate/severe AR from 3 months to 2 years. This has also been demonstrated in other trials randomizing patients to TAVR or SAVR. The improvement in mild AR at 2 years is consistent with other data supporting an improvement in the severity of paravalvular regurgitation over time with a self-expandable bioprosthesis, presumably because of the ongoing remodeling at the interface of the bioprosthesis and native annulus, as well as neoendothelialization of the stented region of the bioprosthesis. Other secondary adverse outcomes remained low in both the groups with no significant differences between TAVR and SAVR, with the exception of the cumulative rate of atrial fibrillation that was higher in SAVR patients and permanent pacemaker implantation that was higher in TAVR patients. These outcomes were characteristics of the immediate postprocedural period and rarely late-onset events. At 2 years, no difference in NYHA class was present in the two. The higher pacemaker rate with TAVR is consistent with other studies using first-generation self-expanding technology TAVR prostheses.

The NOTION trial was designed in 2009 before the introduction of routine cardiac CT scan to measure the aortic annulus. As a consequence, echocardiography was used to determine the annulus diameter, which may have led to prosthetic undersizing in TAVR patients and thus a higher rate of AR. Although AR has been suggested as a predictor for increased mortality, this could not be demonstrated in the present trial. However, it is generally accepted that before introducing TAVR on a more routine basis into younger and lower-risk patients, the extent of paravalvular leakage needs.
New data are encouraging because annulus measurement by CT scan,19–22 optimization of the TA VR procedure, and improvements in prosthesis design have helped to mitigate paravalvular leakage24 as well as conduction abnormalities.

Subgroup analyses of all-cause mortality at 2 years were conducted for several baseline characteristics. However, the low number of deaths in either group allowed for the testing of only a small number of characteristics. Similar 2-year mortality between the groups was consistent across 6 clinical subgroups except for baseline medically treated hypertension. No differences in antihypertensive medications were found between the groups, making the significance of this finding uncertain.

Limitations
Since the NOTION trial was an all-comers trial, and all risk groups were included, the patient population was nonhomogeneous in operative risk. Moderate- and high-risk patients had higher, although not significantly higher, rates of adverse outcomes than low-risk patients. Because patients with significant concomitant coronary artery disease were excluded from the NOTION trial, outcomes in those patients cannot be extrapolated from this trial. The observed rate for the composite outcome in the TAVR group was higher than expected. The study is not powered to definitively demonstrate a potential significant difference between the 2 groups, and it is not powered for subgroup analysis. An independent echocardiographic core laboratory was not used, which may limit the conclusions that can be drawn from the AR findings. Finally, formal neurological assessments were not performed in all patients, so more subtle neurological symptoms may not have been captured.

Conclusions
The NOTION trial was the first to randomize all-comers and lower-risk patients to TAVR or SAVR. The 2-year results presented here demonstrate the continuing safety and effectiveness of the TAVR procedure in these patients, but with continued differences in AR, pacemaker implantation, and

Table 2. Univariate Subgroup Analysis for 2-Year Mortality

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients (%)*</th>
<th>Transcatheter</th>
<th>Surgical</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1/29 (4.2)</td>
<td>1/27 (3.8)</td>
<td>0.88 (0.05–14.04)</td>
<td>0.93</td>
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</tr>
<tr>
<td>≥75</td>
<td>10/113 (9.1)</td>
<td>12/107 (11.4)</td>
<td>0.77 (0.33–1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Male</td>
<td>6/76 (7.9)</td>
<td>7/70 (10.2)</td>
<td>0.76 (0.26–2.26)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>5/66 (8.2)</td>
<td>6/64 (9.5)</td>
<td>0.80 (0.24–2.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>10/117 (8.8)</td>
<td>12/117 (10.4)</td>
<td>0.81 (0.35–1.87)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>1/25 (4.0)</td>
<td>1/17 (5.9)</td>
<td>0.68 (0.04–10.92)</td>
<td></td>
<td></td>
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<tr>
<td>STS-PROM, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>≤4</td>
<td>7/118 (6.2)</td>
<td>8/108 (7.5)</td>
<td>0.78 (0.28–2.15)</td>
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<tr>
<td>≥4</td>
<td>4/24 (16.9)</td>
<td>5/26 (19.4)</td>
<td>0.85 (0.23–3.15)</td>
<td></td>
<td></td>
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<td>LVEF</td>
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<td></td>
<td></td>
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<tr>
<td>≤40%</td>
<td>1/9 (12.5)</td>
<td>0/10 (0.0)</td>
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<tr>
<td>&gt;40%</td>
<td>2/117 (1.7)</td>
<td>4/104 (3.9)</td>
<td>0.44 (0.08–2.40)</td>
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<td></td>
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<tr>
<td>Hypertension</td>
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<td></td>
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<tr>
<td>No</td>
<td>8/39 (21.3)</td>
<td>2/31 (6.5)</td>
<td>3.41 (0.72–16.08)</td>
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<tr>
<td>Yes</td>
<td>3/103 (3.0)</td>
<td>11/103 (10.9)</td>
<td>0.26 (0.07–0.92)</td>
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<td>Peripheral vascular disease</td>
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<td>10/136 (7.6)</td>
<td>13/125 (10.6)</td>
<td>0.68 (0.30–1.56)</td>
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<td>Yes</td>
<td>1/6 (16.7)</td>
<td>0/9 (0.0)</td>
<td>NA</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
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<td></td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>No</td>
<td>9/118 (7.9)</td>
<td>10/106 (9.6)</td>
<td>0.78 (0.32–1.93)</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>2/24 (8.7)</td>
<td>3/28 (10.9)</td>
<td>0.77 (0.13–4.60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

*Percentages are Kaplan–Meier rates.
TAVR vs SAVR 2-Year Outcomes

Figure 6. All-cause mortality among patients who received transcatheter aortic valve replacement according to degree of aortic regurgitation (none/trace, mild, and moderate/severe) measured at 3 months post procedure.

Disclosures
Dr Søndergaard is a proctor for Medtronic. Drs Franzen, P.S. Olsen, and Søndergaard have been involved in research contracts with Medtronic. Drs Franzen, P.S. Olsen, and Søndergaard have been involved in research contracts with St. Jude Medical. Drs Ihlemann, Clemmensen, and Søndergaard have received speakers fees from Edwards Lifesciences. Dr Ihlemann reports grants from Eli-Lilly, Daichii-Sankyo, AstraZeneca, Bayer, Boehringer-Ingelheim, Sanofi, Pfizer, and BMS. Dr Ihlemann reports speaking fees outside the submitted work. Dr Kjeldsen reports proctoring fees from Edwards Lifesciences. Dr Nissen reports grants from Danish Heart Foundation during the conduct of the study. Dr Franzen reports consulting fees from Edwards Lifesciences. Y. Chang is an employee of Medtronic. The other authors report no conflicts.

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References


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