Valve-in-Valve Implantation of Medtronic CoreValve Prosthesis in Patients with Failing Bioprosthetic Aortic Valves

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Background—Transcatheter aortic valve implantation (TAVI) using the Medtronic CoreValve (MCV) system might represent an alternative to conventional redo surgery in older high-risk patients with a failing aortic valve bioprosthesis.

Methods and Results—Symptomatic patients with failing aortic valve bioprosthesis, aged ≥65 years with a logistic EuroSCORE ≥10% were considered for treatment. Local anesthesia was used to retrogradely implant the MCV system into the failing bioprosthetic valve. Clinical events were recorded and a transthoracic echocardiography was performed to evaluate the impact of MCV on hemodynamics after transcatheter aortic valve implantation. A total of 27 patients (aged 74.8±8 years, logistic EuroSCORE of 31±17%) were treated. In those with AS and AS and AR (n=25), the mean gradient declined from 42±16 mm Hg before to 18±8 mm Hg after MCV implantation (P<0.001), in those with AR the level declined by 2. There was no intraprocedural death and no procedural myocardial infarction. On the basis of the definitions of the Valvular Academic Research Consortium, the rate of major stroke was 7.4%, of life-threatening bleeding 7.4%, of kidney failure stage III 7.4%, and of major access site complication 11.1%, respectively. Within 30 days after the procedure, 2 patients died; 1 from stroke and 1 from cardiac failure (30-day mortality: 7.4%).

Conclusions—These results suggest that transfemoral MCV implantation into a wide range of degenerated aortic bioprosthetic valves—irrespective of the failure mode—is feasible, safe, and improves hemodynamics in older patients with higher risk for conventional aortic valve redo surgery. (Circ Cardiovasc Interv. 2012;00:00-00.)

Key Words: aortic valve implantation ■ aortic valve ■ bioprosthesis, valve-in-valve ■ valve replacement

Conventional surgical valve replacement requiring sternotomy, extracorporeal circulation, and cardiopulmonary cardiopulmonary arrest represents the therapy of choice known to improve symptoms and most importantly survival in significant aortic valve disease. Bioprosthetic valves are currently preferred over mechanical valves even in patients <70 years because they do not require long-term anticoagulant therapy, which is associated with bleeding events. However, the major drawback of bioprosthetic valves is their deterioration and failure over time, requiring redo surgery. The morbidity and mortality risk of aortic reoperation is not negligible, especially in older patients with several comorbidities.

Recently, treatment of severe aortic stenosis, using the Medtronic CoreValve (MCV) and the Edwards SAPIEN THV has been shown to be feasible, safe, and associated with an improvement in hemodynamics in older patients considered inoperable. Given the less-invasive nature of transcatheter aortic valve implantation—as compared with conventional redo surgery—transcatheter aortic valve implantation seems to be a suitable option, particularly to treat patients with a degenerated failed bioprosthetic heart valve. However, the transapical access, which requires full sedation, mechanical ventilation, and is certainly more invasive as compared with the transfemoral approach, was applied in the majority of procedures on the failing aortic valve bioprosthesis. The transfemoral implantation of the MCV prosthesis or the Edwards SAPIEN XT tissue heart valve represents a less-invasive alternative to treat failing aortic bioprosthesis because the procedure can be carried out with the patient breathing spontaneously under conscientious sedation. Despite the fact that >15000 patients with severe aortic stenosis have received the self-expandable MCV prosthesis until now, the experience regarding the valve-in-valve implantation for failed bioprosthesis, especially stenotic bioprosthetic valves,
is limited so far and longer-term follow-up data are rare. Here, we describe the largest experience of retrograde, transarterial valve-in-valve implantation—carried out by the same core team of physicians—for treatment of failed aortic bioprosthetic valves using the MCV system. In addition, we are reporting all end points according to Valvular Academic Research Consortium (VARC) and provide follow-up data with regard to clinical events and valve function for up to 3.5 years postprocedurally.

Methods

Patient Cohort

This article aimed to evaluate safety and feasibility as well as short- and longer-term changes in hemodynamics after MCV implantation in older patients with failed aortic valve bioprosthesis, who were considered to have a higher risk for conventional aortic valve redo surgery by the local heart team consisting of at least a cardiologist and a cardiac surgeon.

Patient Selection

Consecutive, symptomatic patients with a failing aortic valve bioprosthesis because of stenosis, regurgitation, or a combination of both, an inner diameter of the previously implanted aortic valve bioprosthesis between 18.5 and 27 mm, an ascending aorta diameter ≤55 mm above the sinotubular junction, and access vessels of at least 6 mm were included.

Follow-Up

At 10 days, patients underwent echocardiography to assess the final result of the MCV implantation into the failed bioprosthesis. In addition, patients were encouraged to return to the outpatient clinic for follow-up echos at 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years follow-up, respectively, to determine MCV performance and durability in valve-in-valve position.

Procedure

The MCV prosthesis (18F) was used for treatment as described previously. The following parameters were analyzed according to the VARC definitions: device and procedural success, all-cause mortality, peri-procedural myocardial infarction, spontaneous myocardial infarction, stroke, life-threatening bleeding, kidney failure, and access side complications, respectively.

Medication

During the intervention, weight-adjusted intravenous heparin was given to adapt the activated clotting time to 250 to 350 seconds, and clopidogrel preloading (300 mg) was recommended.

Definitions and Statistical Analysis

Events, procedural and device success were analyzed based on the VARC definitions. Mean value±SD was calculated for all continuous variables. Counts and percentages were calculated for categorical variables. Categorical variables were tested applying the χ², for continuous variables a paired t test or ANOVA followed by the Tukey test was used. A P value of <0.05 was considered statistically significant. Kaplan–Meier curves were generated to express patient’s survival postprocedur-ure. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the article.

Results

Baseline Characteristics

A total number of 27 patients were treated. The primary mode of failure is depicted in online-only Data Supplemental Figure I, whereas the baseline characteristics of the population are listed in Table 1. The additive EuroSCORE of the entire population was 11.8±2.5 points, corresponding to a predicted risk of mortality of 31.3±16.5 % (logistic EuroSCORE, range 10.1%–75.0%), and the Society of Thoracic Surgeons score ranged from 3.0 to 30.9 (online-only Data Supplemental Table I). In those patients with a logistic EuroSCORE <20%, 2 were unwilling to undergo conventional reoperation, 2 had morbid obesity with a body mass index >35 kg/m², which significantly affected patient’s mobility, and 2 were frail.

Procedural Results

The time between conventional aortic valve replacement and valve-in-valve implantation was 67±46 months. At the time of initial surgery, patients had received different types of conventional xenografts (Table 2 and online-only Data Supplemental Table II). Six of these valves were stentless (22%), and the remaining 21 stented (78%) (online-only Data supplemental Figure II).

The procedural characteristics are reported in online-only Data supplemental Table III. The MCV was finally deployed in the appropriate position in all patients (100%). However, in 1 patient, the MCV was ejected into the ascending aorta during systole. The catheter opened up further during retrieval and the outflow proportion of the frame expanded. The MCV was deployed at the level of the abdominal aorta and a second MCV was correctly implanted into the failed aortic valve bioprosthesis. Final angio confirmed an adequate perfusion of all major branches supplying blood to the intestine and...
abdominal organs. Nevertheless, a few hours later a surge in lactate levels was noted, accompanied by abdominal pain indicating malperfusion of an abdominal vessel. The embolized MCV was removed surgically and the patient recovered.

In 1 patient presenting with a failed aortic aspirate prosthesis, a clear landing zone for the MCV could not be identified because of a lack of calcification and the absence of a metal ring. This resulted in a deep implantation of the MCV with significant AR. A second MCV was implanted a little higher without complications.

Two patients died within 24 hours after the procedure, 1 because of a major stroke. In the second patient, the valve-in-valve procedure was uncomplicated but the patient complained about shortness of breath on the way to the ICU. There was no evidence of valve dysfunction, pericardial effusion, or myocardial ischemia. However, the patient’s situation quickly deteriorated, with the need of inotropic support, intubation, mechanical ventilation, and finally cardiopulmonary resuscitation, and resulted in death. The autopsy confirmed correct position of the MCV within the failed bioprosthesis, despite asymmetric expansion of the MCV inflow proportion. (Figure 1) There was no evidence of MCV migration, MCV dysfunction, paravalvular leak, or coronary obstruction. Therefore, the underlying cause of cardiac death remains unknown.

**Intraprocedural Hemodynamic Results**

In patients with AS or AS and AR (n=25) as the primary mode of bioprosthetic failure, peak gradient assessed invasively declined by 83% from 58±21 mm Hg at baseline to 12±8 mm Hg after MCV implantation, whereas aortic mean gradient decreased by 83% from 42±15 to 10±8 mm Hg (online-only Data Supplemental Figure III).

**Clinical Follow-Up at 30 Days Based on the VARC Definitions**

**At 30 Days**

Follow-up was complete in all patients (100%) at 30 days. Except the 2 deaths on day 1, no further events occurred within 1 month, resulting in a 30-day mortality of 7.4%. (online-only Data Supplemental Table IV and V, Figure II). Two patients (7.4%) had a major stroke. One of these patients died as described above, the other one had modified ranking score of 2 at 30 days’ follow-up. The VARC related end points

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**Table 2. Valve Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Failed Valve Type</th>
<th>Failure Mode</th>
<th>Valve Size, (mm)</th>
<th>Inner Diameter, (mm)</th>
<th>Implanted Valve Size (mm)</th>
<th>Baseline Mean Gradient (mm Hg)</th>
<th>Final Mean Gradient (mm Hg)</th>
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<tbody>
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<td>Sorin mitroflow S &amp; R</td>
<td>S &amp; R</td>
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<td>21</td>
<td>26</td>
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<td>2</td>
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<td>S &amp; R</td>
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<td>22.6</td>
<td>26</td>
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<td>23</td>
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<td>23</td>
<td>20.8</td>
<td>26</td>
<td>56</td>
<td>29</td>
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</table>

S indicates aortic stenosis; R, aortic regurgitation; SJM, St. Jude Medical; CE, Carpenter-Edwards.
by transfemoral implantation of MCV, irrespective of the failure mode (AS, AR, or AS&AR) and the type of bioprosthetic valve (stented or stentless).

Figure 2. Relative frequency in the occurrence of the different safety endpoints according to the valvular academic research consortium (VARC) definition at 30 days: All-cause mortality, periprocedural myocardial infarction (MI), major stroke, life-threatening bleeding, kidney failure stage III, major access site complications. Please note, the percentage value for the combined endpoint occurrence is lower than the sum of percentages values for the endpoints mentioned in rows 1 to 6 because some of the patients experienced more than one complication (eg, a patient might have had a stroke and died). RIFLE indicates Risk, Injury, Failure, Loss, ESRD (end stage renal disease).

Discussion

Three major findings emerge from this assessment of the treatment of a wide range of failed aortic valve bioprosthesis by transfemoral MCV implantation in elderly patients with high risk for conventional redo surgery:

1. Failure of bioprosthetic valves may be safely corrected by transfemoral implantation of MCV, irrespective of the failure mode (AS, AR, or AS&AR) and the type of bioprosthetic valve (stented or stentless).

2. Valve-in-valve implantation can be performed completely percutaneously under conscientious sedation. The procedure, if always carried out by the same team of experienced transcatheter valve operators, has a low mortality.

Echocardiography

The transthoracic echocardiographic measurements are reported in Table 4. In those patients with AS and AR or AS as the mode of bioprosthetic valve failure, aortic mean gradient declined from 42±16 mm Hg before the procedure to 18±8 mm Hg at 10 days, whereas aortic valve orifice area increased by 100% from 0.8±0.3 to 1.6±0.2 cm², respectively (online-only Data Supplemental Figure IV, Table IV). In those with AR and AR & AS, the level of AR as determined by transthoracic echocardiography declined by 1 (interquartile range 1) ($P<0.05$, online-only Data Supplemental Figure V).

Long-Term Follow-Up

The hemodynamic improvement after valve-in-valve procedure led to a remarkable clinical benefit, which was clearly demonstrated by the reduction in NYHA class. (Decline in NYHA class from 3 (interquartile range 1) at baseline to 1 (interquartile range 1) at the 6-month follow-up, $P<0.05$; Figure 3) There was no further death between the 1-month and 6-month follow-up. None of the patients was readmitted to the hospital because of structural or nonstructural valve dysfunction. Two patients died from cardiac failure: 1 at 219 days, and 1 at 901 days after valve-in-valve procedure. The survival rates at 6 months and 1-year follow-up were 92% and 88%, respectively. At long-term follow-up (mean follow-up time of 421±198 days), the surviving patients were clinically stable, with no signs of late valve migration, nonstructural or structural valve dysfunction (Figure 4, Table 4).

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1. Failure of bioprosthetic valves may be safely corrected by transfemoral implantation of MCV, irrespective of the failure mode (AS, AR, or AS&AR) and the type of bioprosthetic valve (stented or stentless).

2. Valve-in-valve implantation can be performed completely percutaneously under conscientious sedation. The procedure, if always carried out by the same team of experienced transcatheter valve operators, has a low mortality.
3. Valve-in-valve implantation results in marked, instantaneous improvement in hemodynamics, which remains evident at long-term follow-up.

Feasibility, Device Success, and Safety

All patients, in whom an MCV implantation into a failed bioprosthetic aortic valve was attempted, left the operating room with a functionally competent MCV in the correct anatomical position. None of the procedures were converted into conventional aortic valve replacement because of technical difficulties with the MCV nor was the heart-lung machine required. All the procedures were carried out in local anesthesia without mechanical ventilation, which facilitates postinterventional neurological recovery and eliminated ventilator-associated complications, which might considerably affect patients with underlying pulmonary disease. Therefore, we would consider all the procedures successful. However, with the application of the recently published V ARC definitions it can be seen that device success was not achieved in 11 of 27 patients (44%). The data are in agreement with 2 recently published multicenter registries, in which patients with a failing aortic valve bioprosthesis were treated by the transapical or transfemoral approach using the Edwards SAPIEN or the MCV, respectively. In these registries, 44% of the invasively characterized patients were discharged with a mean gradient >20 mm Hg, which would not be consistent with device success according to the V ARC definition. On the basis of previous studies and our own experience, the residual gradient of the MCV itself is almost negligible. Hence, it is likely that the residual gradient after valve-in-valve implantation is primarily the result of a prosthesis patient mismatch at the time of initial surgery rather than because of the MCV itself. Therefore, in some patients a conventional reoperation involving annular enlargement should be considered if a severe mismatch between the patient and the failed aortic valve bioprosthesis seems likely. However, the higher risk of the conventional reoperation for a

Table 3. Failure of Device Success According to VARC at 30 Days

<table>
<thead>
<tr>
<th>Bioprosthetic Valve Failure Mode</th>
<th>Implantation Failure</th>
<th>Malposition</th>
<th>Valve area &lt;1.2cm²</th>
<th>Mean Gradient &gt;20 mm Hg, vmax &gt;3.0m/s</th>
<th>Moderate or Severe AR After MCV</th>
<th>Second MCV Implantation</th>
<th>Failure of Device Success</th>
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</thead>
<tbody>
<tr>
<td>AS and AR (n=19) %</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>AS (n=6) %</td>
<td>0</td>
<td>5.3</td>
<td>10.5</td>
<td>21.0</td>
<td>10.5</td>
<td>5.3</td>
<td>36.8</td>
</tr>
<tr>
<td>AR (n=2) %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total (n=27) %</td>
<td>0</td>
<td>3.7</td>
<td>7.4</td>
<td>32.0</td>
<td>7.4</td>
<td>3.7</td>
<td>44.4</td>
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AS indicates aortic stenosis; AR, aortic regurgitation; MCV, Medtronic Core Valve.

Table 4. Transthoracic Echo Parameters

<table>
<thead>
<tr>
<th>Mode of Failure</th>
<th>Parameter</th>
<th>Preprocedure n=27</th>
<th>10 days n=23</th>
<th>Long-Term Follow-up n=23</th>
<th>ANOVA P</th>
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<tr>
<td>AS and AR</td>
<td>P max (mm Hg)</td>
<td>68.2±28.1</td>
<td>29.4±12.0*</td>
<td>28.8±12.7*</td>
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<td>n=19</td>
<td>P mean (mm Hg)</td>
<td>42.0±17.9</td>
<td>16.8±7.8*</td>
<td>16.1±7.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.7±0.3</td>
<td>1.6±0.2*</td>
<td>1.6±0.5*</td>
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<td>&lt;0.001</td>
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<td>AR (grade, 0/1/2/3/4)</td>
<td>0/10/6/2/1</td>
<td>5/12/2/0/0</td>
<td>7/11/1/0/0</td>
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<td>&lt;0.001</td>
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<tr>
<td>AS</td>
<td>P max (mm Hg)</td>
<td>71.8±14.6</td>
<td>38.0±14.0</td>
<td>27.0±15.2*</td>
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<td>n=6</td>
<td>P mean (mm Hg)</td>
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<td>21.8±10.6</td>
<td>14.5±8.2</td>
<td>n.s.</td>
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<tr>
<td>Aortic valve area (cm²)</td>
<td>0.6±0.2</td>
<td>1.5±0.2</td>
<td>1.7±0.6**</td>
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<td>&lt;0.05</td>
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<tr>
<td>AS and AR, and AS</td>
<td>P max (mm Hg)</td>
<td>69.0±25.3</td>
<td>30.8±12.4*</td>
<td>28.4±12.9*</td>
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<td>n=25</td>
<td>P mean (mm Hg)</td>
<td>42.5±15.8</td>
<td>17.7±8.3*</td>
<td>15.7±7.1*</td>
<td>&lt;0.001</td>
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<tr>
<td>Aortic valve area (cm²)</td>
<td>0.8±0.3</td>
<td>1.6±0.2*</td>
<td>1.7±0.6*</td>
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<td>&lt;0.001</td>
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AS indicates aortic stenosis; AR, aortic regurgitation. Long-term follow-up, a mean follow-up time of 421±198 days; n.s., nonsignificant.

*P<0.001 vs. preprocedure (results of the Tukey post hoc test).

**P<0.05 vs pre procedure (result of the Tukey post hoc test).
better hemodynamic outcome has to be balanced against the potentially lower risk of the valve-in-valve procedure with the acceptance of an inferior hemodynamic result. All our patients experienced an improvement in symptoms, even those with a mean gradient >20 mm Hg, suggesting that the valve-in-valve procedure resulted in a clinical benefit. Moreover, one has to keep in mind that, given the multiple comorbidities, it seems unlikely that all these patients are completely free of symptoms at follow-up. However, future randomized trials are necessary to address this issue.

The average age of the failed surgical valves was only 5.5 years, which is considerably shorter than reported in the literature. The reasons for this discrepancy remain largely unknown. Because our institutions are tertiary centers, it is tempting to speculate that lower-risk patients with a failing aortic valve bioprosthesis were conventionally reoperated in other centers, and only the complex cases, in which an early degeneration of the bioprosthesis occurred because of comorbidities or anatomical factors, were referred to us. However, further studies involving a larger patient population are required to address these issues.

With regard to the VARC combined safety end point, 6 of 27 patients had an event at 30 days. However, kidney function recovered at least partially in those with kidney failure stage III after the intervention, all the major access site complications could be fixed with stents, covered stents, or surgical repair, and all bleeding issues were resolved as well. Therefore, the deterioration of patient’s health caused by these complications was only transient in nature.

The incidence of death and major stroke was 11.1% and compares favorably with recent results from randomized transcatheter aortic valve implantation trials and valve-in-valve registries. Two patients were dead at 1 month, resulting in a 30-day mortality of 7.4% in our cohort. This was in agreement with the prediction based on the Society of Thoracic Surgeons score but certainly lower than the anticipated mortality according to the EuroSCORE. In 2 recent articles, the 30-day mortality was found to be 17% and 12%, respectively, and therefore slightly higher as compared with our report. However, the registry published by Eggebrecht et al. evaluated data from a mixed cohort of 47 patients with failing aortic bioprosthetic valves that were treated transfemorally or transapically by the MCV or the Edwards SAPIEN valve at 9 different clinical sites. The authors rightfully acknowledge the impact of individual operator learning curves in each center on the outcome of the patient. In addition, differences in the access route (transapical versus transfemoral), the sedation (general versus local anesthesia), the valve types used (MCV versus Edwards SAPIEN), and the patient population (prevalent AR versus prevalent AS as the primary cause of bioprosthetic valve failure) might have affected the results, and consequently the mortality at 30 days in a different way.

Notably, the occurrence of events according to the VARC definition dropped from 4 in the first half of patients (event rate 31%) to 2 in the second half of patients (event rate 14%) in our population. Moreover, there was no case of death or major stroke in the second half of the treated cohort (event rate 0%) as compared with 2 cases during the first half (event rate 14%). This strongly supports the notion that a growing experience of the operators directly translates into a net clinical benefit for the patient.

Impact of Transcatheter Valve Design on Hemodynamic and Procedural Outcome

We left 3 patients with a moderate AR grade 2 at follow-up. The AR was the consequence of leaks between the failing aortic bioprosthetic valve and the native annulus. Because all these patients were considered high risk for conventional reoperation, the decision was made to follow up the patients clinically. There was no sign of hemolysis, left ventricular enlargement, decline of left ventricular function or clinical deterioration, which is consistent with the hypothesis that the ventricles were well adapted to this level of volume overload. All other patients just had traces of AR, also primarily because of old paravalvular leaks between the failing bioprosthetic valve and the native annulus. One might argue that the balloon-expandable Edwards SAPIEN valve could provide a better sealing of residual leaks. However, even the Edwards SAPIEN valve would not be able to resolve the issue of paravalvular leaks outside of the surgically implanted bioprosthetic valve and
there was no evidence of incomplete expansion of the MCV within the annulus of the failing bioprosthetic valve leading to high-grade AR. Conversely, it was suggested that the supra-anular position of the MCV would result in larger effective orifice areas and lower transvalvular gradients after valve-in-valve procedure. Nevertheless, our own clinical experience using the Edwards SAPIEN and the MCV prosthesis does not support the hypothesis of different hemodynamic outcomes after the valve-in-valve procedure. Therefore, further studies are necessary to evaluate whether the impact of residual AR in the abovementioned cohort is as deleterious as in patients with native aortic valve stenosis treated with transcatheter aortic valve implantation and whether differences regarding the hemodynamic outcome exist depending on the type of transcatheter valve that was used for the valve-in-valve procedure.

**Valve Positioning and Selection**

Given that the distal 8 mm of the MCV frame are covered with pericardium to reduce paravalvular leaks, the MCV should not be implanted deeper than that. However, because of the resistance of the suturing ring and the wedge-shaped opening of the MCV, the MCV has the tendency to slide down into the left ventricle until the narrowest portion of the MCV is exactly at the level of the suturing ring of the failed bioprosthetic valve. Such an implantation would result in significant AR because the constraint part of the MCV is not covered with pericardium. We discovered that a high position of the MCV (=2 mm below the radiopaque suturing ring), fast ventricular pacing (rate of 160/min resulting in a small stroke volume), and constant push on the LV guide wire ensures correct MCV placement within the failed aortic valve bioprosthesis.

Nevertheless, one has also to take into account that the suturing ring of the failed bioprosthesis might act like a launching pad in case of high MCV positioning resulting in valve embolization. Edwards SAPIEN valve embolization as a complication of transfemoral valve-in-valve procedure was already described by Webb et al. The ease of use of transapical Edwards SAPIEN valve implantation, especially the well-controlled release, into failed bioprosthesis in aortic and mitral valve position is in agreement with our own results.

However, it is still a matter of discussion, which access and which valve work best for valve-in-valve procedures. The transfemoral procedures (using the MCV or the Edwards SAPIEN valve) seem to be more challenging in comparison with the transapical ones (using the Edwards SAPIEN valve) because movements of the transcatheter valve are much more difficult to correct. Nevertheless, the MCV can be released very slowly which makes fine-tuning of the position during valve-in-valve implantation possible. In addition, a MCV retrieval is possible in case of valve embolization into the ascending aorta or an expected embolization, as long as the MCV is still connected to the delivery system. Independent of the system that is used, patients, especially those with a poor lung function, benefit from the less-invasive transfemoral procedure, which does not require intubation and mechanical ventilation.

On the one hand, an extreme mismatch between the inner stent diameter of the failing bioprosthetic valve and the transcatheter valve represents a demanding situation, especially in some MCV cases, in which it is hard to prevent a downward motion of the MCV into the ventricle. This movement is also dependent on the type of failing bioprosthetic valve. On the other hand, using a MCV seem to be advantageous in cases, in which the distance between the failing bioprosthetic valve and the coronaries is very small, because the constraint part of the MCV will ensure an adequate perfusion of the coronaries. Using an Edwards SAPIEN valve might carry the risk of a coronary occlusion in the abovementioned patients. Nevertheless, there are no data available that would support the primary use of one of the transcatheter valves eg, as a function of the failure mode of the bioprosthetic valve or the native anatomy. Therefore, randomized studies are necessary to elucidate the ideal access and transcatheter valve for valve-in-valve procedure.

**Clinical and Echocardiographic Follow-Up**

As compared with previous reports, this study has several unique feature: (1) it is the valve-in-valve study with the longest clinical and echocardiography follow-up. The early hemodynamic improvement after valve-in-valve procedure was long lasting in the absence of structural or nonstructural valve deterioration. (2) It is the first valve-in-valve report, in which clinical end points and valve performance were analyzed according to the VARC definitions. (3) All the patients were treated completely percutaneously in local anesthesia, using the transfemoral approach. (4) All patients received the MCV for bioprosthetic valve failure. (5) The procedure was always carried out by the same team of experienced operators.

All the patients, who were discharged from the hospital after the valve-in-valve procedure, were characterized by an improvement in symptoms as documented by a decline in the NYHA class. At a mean follow-up of 42±198 days, 23 of 27 patients were alive, which is consistent with a 1-year survival rate of >85%. This is considerably higher as compared with a survival rate of <60% at 1 year as reported by Eggebrecht et al. The higher mortality in the latter study seemed to be primarily driven by patients who received a transapical Edwards SAPIEN valve for treatment of bioprosthetic valve failure. The higher invasiveness of the transapical approach, which requires a mini-thoracotomy, general anesthesia, intubation, and mechanical ventilation might have delayed the recovery, and hence caused mortality-relevant complications. Nevertheless, Eggebrecht et al describe a drop in complication rates in the second half of their cohort, underlining that a higher operator experience translates into a net clinical benefit for the patients.

**Risk of Conduction Abnormalities**

The self-expanding nature of the nitinol frame in conjunction with a deep implantation has been used to explain the high rates of conduction abnormalities requiring permanent pacemaker implantation after treatment of native aortic valve disease with the MCV. However, in our current series only 1 of 27 patients (3.7 %) developed third-degree heart block with the need of permanent pacing. The low rate of heart block might be explained by the fact that the high position of the MCV within the failed bioprosthesis, the fibrotic tissue surrounding the stentless bioprosthetic valves, and the rigid ring of the stented bioprosthetic valves precluding a full expansion of the inflow proportion of the MCV, protects the conduction
system in the LVOT from MCV induced mechanical stress. Nevertheless, in previous reports the rate of new pacemaker implantation after treatment of a failing bioprosthetic valve by MCV varied between 12% and 33%, and is, therefore, considerably higher than in our experience. However, further studies are necessary to fully understand the pathophysiology of conduction disturbances after MCV in aortic valve disease.

Conclusion

Transfemoral treatment of a broad range of failed bioprosthetic aortic valves with MCV prosthesis is feasible, safe, and results in marked improvement in hemodynamics in selected high-risk patients. However, smaller transcatheter valves matching more closely the inner diameter of the different bioprosthetic valves are needed to extend the range of bioprosthesis suitable for valve-in-valve therapy.

Disclosures

Dr. Linke is a consultant to Medtronic. Dr. Möbius-Winkel is a consultant to Boston Scientific.

References


Valve-in-Valve Implantation of Medtronic CoreValve Prosthesis in Patients with Failing Bioprosthetic Aortic Valves
Axel Linke, Felix Woitek, Marc W. Merx, Conrad Schiefer, Sven Möbius-Winkler, David Holzhey, Ardawan Rastan, Jörg Ender, Thomas Walther, Malte Kelm, Friedrich W. Mohr and Gerhard Schuler

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Data Supplement (unedited) at:
http://circinterventions.ahajournals.org/content/suppl/2012/10/10/CIRCINTERVENTIONS.112.972331.DC1
SUPPLEMENTAL MATERIAL

Supplemental Methods

Patient Cohort

This paper aimed to evaluate safety and feasibility as well as short- and longer-term changes in hemodynamics following Medtronic CoreValve implantation in older patients with failed aortic valve bioprosthesis, who had a higher risk for conventional aortic valve redo surgery. Using a retrograde approach, all MCV implants were performed due to clinical reasons under local compassionate release protocols after the patients had provided written informed consent. Patients were considered to have a higher risk if they were older than 65 years, had a logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) >10 or co-morbidities like porcelain aorta, prior chest radiation, prior cardiac surgery with open bypass grafts, severe pulmonary disease or liver cirrhosis, respectively. All patients considered for TAVI were discusses in the heart team consisting at least of a cardiologist and a cardiac surgeon. The decision to treat patients with TAVI was based on consensus papers pending agreement of the local heart team. At both institutions (University of Düsseldorf and Leipzig Heart Center), all patients were always treated by the same team of experienced operators.

Patient Selection

Consecutive, symptomatic patients with a failing aortic valve bioprosthesis due to stenosis, regurgitation or a combination of both, an inner diameter of the previously implanted aortic valve bioprosthesis between 18.5 and 27 mm, an ascending aorta diameter ≤ 45 mm above the sinotubular junction and access vessels of at least 6 mm were included.
Patients with known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, nitinol, any sepsis including active endocarditis, mitral or tricuspid valve regurgitation > grade II, peripheral arterial disease with either femoral, iliac or aortic vascular conditions (e.g. stenosis) that would make it impossible to insert the prosthesis into the access artery or to advance the prosthesis to the failing aortic valve were excluded. All patients underwent coronary angiography and angiography of the access vessels.

Follow-up
At 10 days, patients underwent echocardiography to assess the final result of the MCV implantation into the failed bioprosthesis. In addition, patients were encouraged to return to the outpatient clinic for follow-up echos at 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years follow-up, respectively to determine MCV performance and durability in valve-in-valve position.

Procedure
The Medtronic CoreValve prosthesis (18 F) was used for treatment. The nominal external diameter of the MCV (26 or 29 mm) matched or exceeded the reported inner diameter of the failed aortic valve prosthesis. Selection of the size of the MCV was based on transoesophageal measurements of the inner diameter of the failing bioprosthesis and the respective information provided by the manufacturer of the bioprosthesis.

An 18-french Cook sheath was introduced into the left or right common femoral artery applying a percutaneous approach. The failing aortic valve bioprosthesis was passed and a 0.038-in Amplatz-2 superstiff wire was positioned into the ventricle. Under rapid ventricular pacing balloon valvuloplasty was performed in patients with
bioprosthetic valve stenosis but not in those with predominant regurgitation followed by MCV implantation. In some cases, fast ventricular pacing at a rate of 140 to 160 beats/min was applied to stabilize the MCV during release. In case of significant paravalvular leakage (AR grade II) due to incomplete frame expansion, postdilatation was attempted. Since all of our procedures were performed in local anaesthesia with spontaneously breathing patients, we used fluoroscopy to guide positioning and deployment of the valve. Angiography as well as hemodynamic measurement of the left ventricular end-diastolic pressure and diastolic aortic pressure before and immediately after valve-in-valve implantation were applied to assess the level of aortic regurgitation intraprocedurally. The access artery was closed using the Prostar™ system (Abbott, Illinois, IL, USA).

The following parameters were analyzed according to the Valvular Academic Research Consortium (VARC) definitions: device and procedural success, all cause mortality, periprocedural myocardial infarction, spontaneous myocardial infarction, stroke, life threatening bleeding, kidney failure, and access side complications, respectively. Additionally, the gradient across the MCV and the degree of aortic regurgitation as determined by transthoracic echocardiography were analyzed before and after MCV implantation into the failed aortic valve bioprosthesis.

Medication

During the intervention, weight-adjusted intravenous heparin was given to adapt the activated clotting time to 250 to 350 seconds. On the day of the procedure, patients received 300 mg clopidogrel as a loading dose and were treated with 75 mg clopidogrel once a day for 6 months thereafter. Patients with an indication for oral anticoagulation received warfarin in addition. All other patients were treated with aspirin (100 mg daily) in combination with clopidogrel.
Definitions and Statistical Analysis

Events, procedural and device success were analyzed based on the VARC definitions.\textsuperscript{3}

Mean value±standard deviation was calculated for all continuous variables. Counts and percentages were calculated for categorical variables. The significance of change across time points were assessed by a paired t-test (for the invasive hemodynamics) or a one-way repeated measures ANOVA followed by the Tukey post-hoc test (echocardiographic parameters, e.g. peak and mean gradient, valve orifice area). A within-patient correlation structure between any pair of time points was assumed for repeated measures. Categorical variables were tested applying the Chi-Square. A p value of less than 0.05 was considered statistically significant. Kaplan-Meier curves were generated to express patient’s survival post procedure.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the manuscript.
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Supplemental Table 2: Valve characteristics

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<td>Number (Percent) or Mean±SD</td>
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<td>Procedure time (min)</td>
<td>56±27</td>
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<tr>
<td>Fluoroscopy time (min)</td>
<td>15.4±13.6</td>
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<td>Contrast medium (mL)</td>
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<td>Predilatation (n)</td>
<td>21 (78 %)</td>
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<td>Postdilatation for incomplete MCV expansion (n)</td>
<td>2 (7 %)</td>
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<td>Successful MCV implantation (n)</td>
<td>27 (100 %)</td>
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<td>Second valve used (n)</td>
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<td>Conversion to surgery (n)</td>
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<td>HLM time (min)</td>
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<td>Myocardial infarction (n)</td>
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### Supplemental Table 4: VARC Combined safety endpoint at 30 days

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<th>Failure Mode</th>
<th>All Cause Mortality</th>
<th>Peri-Procedural MI</th>
<th>Major Stroke</th>
<th>Life-threatening Bleeding</th>
<th>Kidney Failure Stage 3</th>
<th>Major Access Site Complication</th>
<th>Event Occurrence</th>
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### Supplemental Table 5: Valvular Academic Research Consortium (VARC) Safety Endpoint at 30 days

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<th>Patient</th>
<th>All Cause Mortality</th>
<th>Per-Procedure MI</th>
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<th>Life Threatening Bleeding</th>
<th>Kidney Failure Stage 3</th>
<th>Access Major Event</th>
<th>Total Occurrence</th>
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<tr>
<td>Sum</td>
<td>2 (7.4%)</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>2 (7.4%)</td>
<td>2 (7.4%)</td>
<td>3 (11.1%)</td>
<td>6 (22.2%)</td>
</tr>
</tbody>
</table>
Patients with failing bioprosthetic valve
N=27

Mode of Failure

AS
n=6 (22%)

AS&AR
n=19 (70%)

AR
n=2 (8%)

CV 26
n=4 (67%)

CV 29
n=2 (33%)

CV 26
n=15 (79%)

CV 29
n=4 (21%)

CV 26
n=2 (100%)

Patients with failing bioprosthetic valve
N=27

Mode of Failure

AS
n=6 (22%)

AS&AR
n=19 (70%)

AR
n=2 (8%)

CV 26
n=4 (67%)

CV 29
n=2 (33%)

CV 26
n=15 (79%)

CV 29
n=4 (21%)

CV 26
n=2 (100%)

Supplemental Figure 1
Supplemental Figure 3

Aortic Valve Gradient [mmHg]

Baseline Post Procedure

*** p<0.001 vs. baseline

- peak gradient
- mean gradient
Supplemental Figure 4

Aortic Valve Gradient [mmHg]

Baseline at 10 days post procedure at long-term follow-up

*** p<0.001 vs. baseline

peak gradient
mean gradient
Supplemental Figure 5

before TAVI

at 10-days post procedure

at Long-term Follow-up

IV
III
II
I
0

IV
III
II
I
0

Patients with leading AS
Patients with AS & AR
Patients with leading AR
Figure Legends Online Supplement

Supplemental Figure 1:

Patient Flow Chart

Distribution of patients with regard to the mode of bioprosthetic valve failure and the size of the implanted Medtronic CoreValve Prosthesis (CV); AS: Aortic stenosis, AR: Aortic regurgitation

Supplemental Figure 2:

Radiography of failed aortic valve bioprosthesis before and after MCV implantation

A1) St. Jude Medical Epic (St. Jude Medical Inc., St. Paul, MN, USA) before MCV implantation; A2) after MCV implantation

B1) Carpentier Edwards Perimount (Edwards Lifesciences, Irvine, CA, USA) before MCV implantation; B2) after MCV implantation

C1) Sorin Mitroflow (Sorin, Arvada, CO, USA) before MCV implantation; C2) after MCV implantation

D1) Medtronic Mosaic (Medtronic Inc., Minneapolis, MN, USA) before MCV implantation; D2) after MCV implantation

E1) Carpentier Edwards Baxter (Edwards Lifesciences, Irvine, CA, USA) before MCV implantation; E2) after MCV implantation

F1) Medtronic Hancock II (Medtronic Inc., Minneapolis, MN, USA) before MCV implantation; F2) after MCV implantation

G1) AorTech Aortic Aspire (AorTech International plc, Weybridge, Australia) before MCV implantation; G2) after MCV implantation

H1) ATS 3F Aortic (Medtronic Inc., Minneapolis, MN, USA) before MCV implantation; H2) after MCV implantation
I1) St. Jude Medical Toronto (St. Jude Medical Inc., St. Paul, MN, USA) before MCV implantation; I2) after MCV implantation
J1) Shelhigh Superstentless (Shelhigh Inc., Union, NJ, USA) before MCV implantation; J2) after MCV implantation

Supplemental Figure 3:

**Peak and mean aortic gradient (invasive hemodynamics)**

Peak and mean gradient (determined invasively) across the failing bioprosthetic aortic valve in patients with AS and AS&AR before and after Medtronic CoreValve implantation (MCV), *** p<0.001 vs. baseline.

Supplemental Figure 4:

**Peak and mean aortic gradient (Echo)**

Peak and mean gradient (determined by Echo) across the failing bioprosthetic aortic valve in patients with AS and AS&AR before (baseline), at 10 and at long-term follow-up (421±198 days) after Medtronic CoreValve implantation, *** p<0.001 vs. baseline.

Supplemental Figure 5:

**Individual changes in the level of aortic regurgitation (Echo):**

The level of AR in before (baseline), at 10 days and at long-term follow-up (421±198 days) after MCV implantation as determined by Echo is depicted for each patient.
AR 0: aortic regurgitation grade 0; AR 1: aortic regurgitation grade 1; AR 2: aortic regurgitation grade 2; AR 3: aortic regurgitation grade 3; AR 4: aortic regurgitation grade 4.

However, the deformation of the inflow proportion does not affect MCV function since the MCV is located and functions supraannularly.
Supplemental References

