

Percutaneous Implantation of the CoreValve Self-Expanding Valve Prosthesis in High-Risk Patients With Aortic Valve Disease The Siegburg First-in-Man Study

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Background—The morbidity and mortality of surgical aortic valve replacement are increased in elderly patients with multiple high-risk comorbid conditions. Therefore, a prospective, single-center, nonrandomized study was performed in high-risk patients with aortic valve disease to evaluate the feasibility and safety of percutaneous implantation of a novel self-expanding aortic valve bioprosthesis (CoreValve).

Methods and Results—Symptomatic high-risk patients with an aortic valve area $<1 \text{ cm}^2$ were considered for enrollment. CoreValve implantation was performed under general anesthesia with extracorporeal support using the retrograde approach. Clinical follow-up and transthoracic echocardiography were performed after the procedure and at days 15 and 30 after device implantation to evaluate short-term patient and device outcomes. A total of 25 patients with symptomatic aortic valve stenosis (mean gradient before implantation, $44.2 \pm 10.8 \text{ mm Hg}$) and multiple comorbidities (median logistic EuroScore, 11.0%) were enrolled. Device success and procedural success were achieved in 22 (88%) and 21 (84%) patients, respectively. Successful device implantation resulted in a marked reduction in the aortic valve gradients (mean gradient after implantation, $12.4 \pm 3.0 \text{ mm Hg}$; $P < 0.0001$). The mean aortic regurgitation grade was unchanged. Major in-hospital cardiovascular and cerebral events occurred in 8 patients (32%), including mortality in 5 patients (20%). Among 18 patients with device success surviving to discharge, no adverse events occurred within 30 days after leaving the hospital.

Conclusions—Percutaneous implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic stenosis with or without aortic regurgitation is feasible and, when successful, results in marked hemodynamic and clinical improvement. (*Circulation*. 2006;114:1616-1624.)

Key Words: aorta ■ stenosis ■ valves ■ valvuloplasty ■ stents

Open heart surgery with mechanical or bioprosthetic valve replacement is the current reference standard therapeutic approach for severe aortic valve disease, offering symptomatic relief and improving long-term survival in most patients. However, the aortic stenosis in the Western population is primarily degenerative, and patients are typically elderly with multiple comorbid conditions that increase surgical risk and perioperative morbidity. In high-risk patients with baseline features such as left ventricular failure, concomitant coronary artery disease, prior bypass graft surgery, chronic obstructive pulmonary disease, and/or advanced age, operative mortality of up to 50% has been reported.¹⁻³ Moreover, surgery often is not performed in high-risk patients. In the Euro Heart Survey, up to 33% of patients in NYHA functional class III/IV with a single diseased valve

were declined for surgery because of associated comorbid conditions and short life expectancy.⁴ Therefore, less invasive techniques for treatment of high-risk patients are needed.

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Percutaneous treatment of aortic valve disease with implantation of a stent-based valve prosthesis has been evaluated in animal models over the past decade.⁵⁻¹⁰ In 2002, Cribier et al¹¹ performed the first human implantation of a balloon-expandable aortic valve prosthesis (percutaneous valve therapy) in a patient with aortic valve stenosis considered inoperable because of severe comorbidities. Initial reports with this new percutaneous valve have been promising,¹²⁻¹⁵ and recent results with a more flexible catheter delivered retrograde across the aortic valve have been favor-

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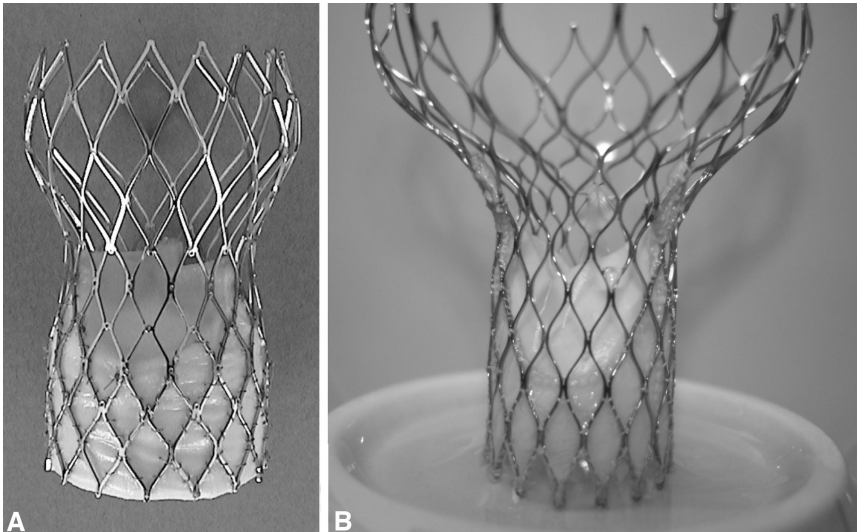


Figure 1. The CoreValve bioprosthesis. A, First generation; B, second generation.

able. The restriction of percutaneous valve therapy candidates to end-stage inoperable patients has clouded interpretation of the feasibility and safety of this procedure, however.

A self-expanding aortic valve prosthesis intended for retrograde delivery across the aortic valve has been developed (CoreValve, Paris, France). The stent design may simplify the implantation procedure, reduce paravalvular leaks, and facilitate treatment of aortic insufficiency and stenosis. After evaluation in animal models,^{16,17} this device was subsequently successfully implanted in a human being,¹⁸ and its use was expanded. In the present study, we report the immediate and 30-day follow-up results from the Siegburg first-in-man investigation in 25 consecutive patients treated with the self-expanding CoreValve aortic valve prosthesis.

Methods

Study Design

A prospective, nonrandomized, single-center registry study was performed at the Heart Center Siegburg (Siegburg, Germany) to evaluate the feasibility and safety of implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic valve disease (stenosis and/or regurgitation) using a retrograde percutaneous transvascular approach. The study was approved by the local medical ethics committee, and all patients and their closest relatives signed informed, written consent. There was an independent data safety monitoring board/clinical endpoint adjudication committee that adjudicated all adverse events and clinical results. This first-in-man study did not include a core angiographic or echocardiographic laboratory.

Patient Population

Inclusion criteria required all of the following: (1) native aortic valve stenosis with an aortic valve area <1 cm² and/or aortic valve regurgitation $\geq 3+$ by echocardiographic measure, (2) echocardiographic aortic valve annulus diameter ≥ 20 mm and ≤ 23 mm, (3) diameter of the ascending aorta 3 cm above the annulus of ≤ 30 mm, and (4) contraindication to surgery because of concomitant comorbid conditions assessed and agreed to by both an independent cardiologist and a cardiovascular surgeon. Exclusion criteria included hypersensitivity or contraindication to any study medication; sepsis or active endocarditis; excessive femoral, iliac, or aortic atherosclerosis, calcification, or tortuosity; aortic aneurysm; bleeding diathesis; or coagulopathy. Preintervention morphological patient screening included transthoracic and transesophageal echocardiography, ca-

rotid and arteriovenous duplex ultrasonography, computed tomography angiography, optional cardiac magnetic resonance imaging, and invasive cardiac evaluation with coronary arteriography and left ventriculography. The baseline risk of the patient population was estimated by the logistic EuroScore.¹ Risk criteria included cirrhosis of the liver, pulmonary hypertension or recurrent pulmonary emboli, pulmonary or right ventricular insufficiency, previous cardiac surgery, history of radiotherapy to the mediastinum, or severe connective tissue disease.

Device Description and Procedure

The CoreValve aortic valve prosthesis consists of a trileaflet bioprosthetic pericardial tissue valve that is mounted and sutured in a self-expanding nitinol stent (Figure 1). The inner diameter of the valve is 21 mm. The prosthetic frame (stent) is manufactured by laser cutting of a nitinol metal tube with length of 50 mm. The lower portion of the prosthesis has high radial force to expand and exclude the calcified leaflets and to avoid recoil; the middle portion carries the valve and is constrained to avoid the coronary arteries; and the upper portion is flared to fixate the stent in the ascending aorta and to provide longitudinal stability. First- and second-generation devices (Figure 1A and 1B) were used in the present study in patients 1 through 10 and 11 through 25, respectively. The first-generation device used bovine pericardial tissue and was constrained within a 24F delivery sheath. The second-generation device incorporated a porcine pericardial tissue valve within a 21F sheath, the reduced profile allowing access through smaller-diameter vascular beds. This device is also characterized by a broader upper segment for more secure fixation in the ascending aorta, allowing inclusion of patients with an ascending aorta diameter up to 45 mm.

Vascular access was obtained by standard surgical cut down of the common iliac artery in 9 patients, subclavian artery in 3 patients, and common femoral artery in 13 patients (second-generation device only). The procedure was performed with the patient under general anesthesia with transesophageal echocardiographic guidance and with extracorporeal percutaneous femoro-femoral bypass. Balloon valvuloplasty was performed before device placement, after which a 0.035-in Amplatz superstiff guidewire was placed in the left ventricle over which the device was passed. A snare was required to advance the first-generation device over the aortic arch; a snare was unnecessary with the lower-profile, more flexible second-generation device. Extracorporeal circulatory support was activated just before device placement across the native valve position and terminated several minutes later immediately after withdrawal of the delivery catheter and confirmation of adequate valve function. As shown in Figure 2, correct positioning of the device was confirmed by transesophageal echocardiography, after which the outer sheath was retracted, allowing deployment of the self-expanding prosthesis.

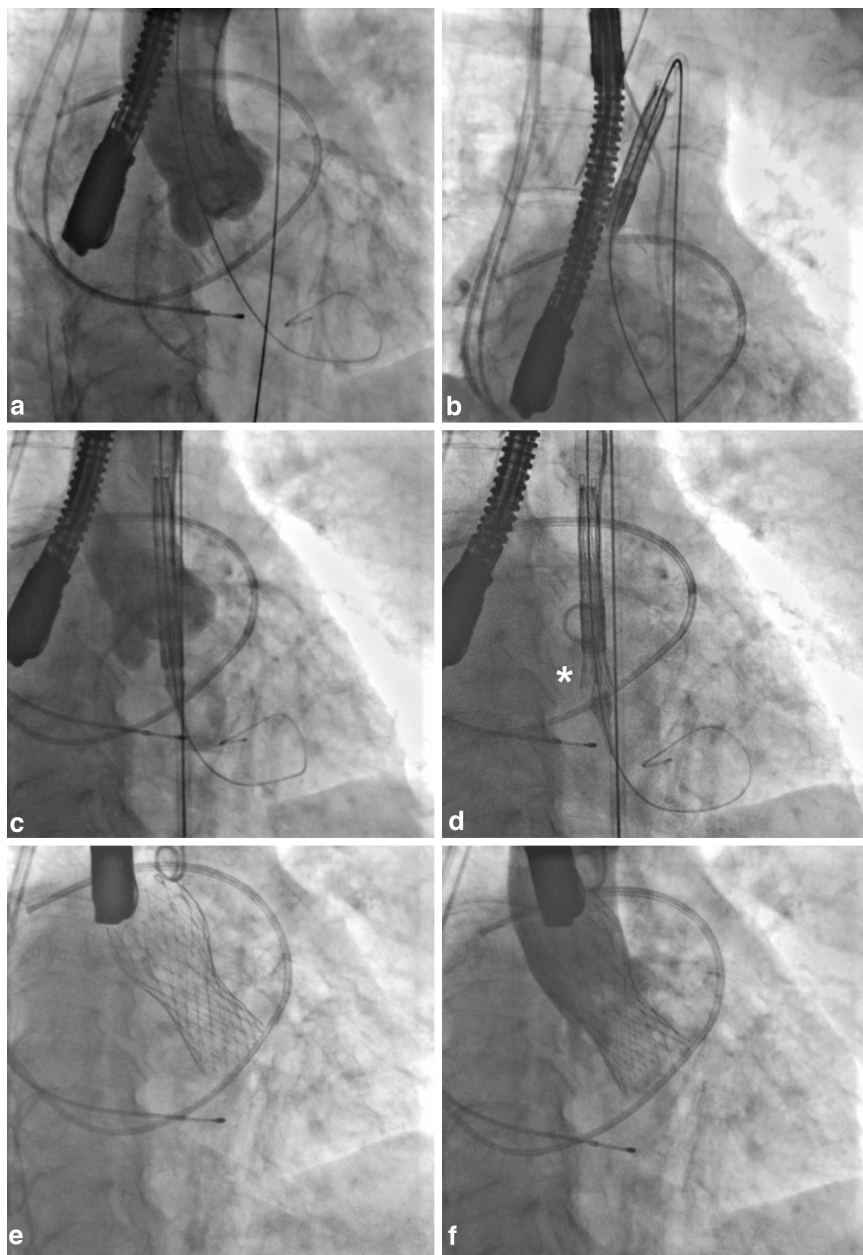


Figure 2. Case example. a, Baseline supra-aortic angiogram. b, Advancement of the first-generation prosthesis over the aortic arch. c, The device is positioned across the native valve, with the correct position confirmed by transesophageal echocardiography. d, Pullback of the outer sheath and deployment of the self-expanding prosthesis (*). e, Fully expanded valve prosthesis. f, Final aortogram demonstrates no evidence of aortic regurgitation.

Clinical, hemodynamic, and echocardiographic outcomes were assessed serially during the procedure. Aortography and transesophageal echocardiography were performed at baseline and after valve placement to assess paravalvular regurgitation. Angiography also was performed after valve deployment to ensure coronary and/or bypass graft patency. After the procedure, the patients were transferred to the intensive care unit, and general anesthesia was discontinued.

Clinical follow-up and transthoracic echocardiography were performed after the procedure, at hospital discharge, and at 15 and 30 days after device implantation. Ongoing follow-up is being performed to 4 years after the procedure.

Antiplatelet and Antithrombotic Medication

Aspirin (100 mg/d) was begun before the procedure and continued indefinitely. Prescription of clopidogrel varied in 3 distinct phases. In phase 1 (patients 1 through 3), a 300-mg loading dose of clopidogrel was given before the procedure. After major bleeding developed in 2 of these patients, the loading dose of clopidogrel was suspended in phase 2 (patients 4 through 7). As described below, after persistent

thrombocytopenia developed in phase 2 patients, the clopidogrel load was reinstated in phase 3 (patients 8 through 25). All patients were treated with clopidogrel 75 mg/d indefinitely. During the intervention, the patient received weight-adjusted intravenous heparin to achieve an activated clotting time of 300 to 350 seconds for the duration of the procedure.

Definitions and Statistical Analysis

Clinical events were adjudicated by an independent Clinical Events Committee. Device success was defined as stable device placement and function as assessed by angiography and echocardiography. Acute procedural success was defined as device success with no periprocedural major adverse cardiovascular and cerebral events (MACCEs) in the first 48 hours after device implantation. MACCEs consisted of death from any cause, major arrhythmia, myocardial infarction (creatinine kinase-MB >2 times the upper limit of normal), cardiac tamponade, stroke (as assessed by routine neurological assessment before and after the procedure and before hospital discharge), urgent or emergent conversion to surgery or balloon valvuloplasty, emergent percutaneous coronary intervention, cardio-

TABLE 1. Baseline Patient Characteristics*

Female gender	20 (80.0)
Age, y, mean±SD	80.3±5.4
Hypertension	16 (64.0)
Diabetes mellitus	9 (36.0)
Peripheral vascular disease	3 (12.0)
Coronary artery disease	12 (48.0)
Congestive heart failure	6 (30.0)
Prior myocardial infarction	4 (16.0)
Prior stroke	0 (0.0)
Prior bypass graft surgery	4 (20.0)
Prior percutaneous coronary intervention	4 (20.0)
NYHA class	
I	0 (0.0)
II	1 (4.0)
III	23 (92.0)
IV	2 (8.0)
Left ventricular ejection fraction, %, mean±SD	54.2±15.9
Mean additive EuroScore, mean±SD	9.0±2.3
Median logistic EuroScore, % (IQR)	10.97 (19.90–9.20)
Indication	
Aortic stenosis only	20 (80.0)
Aortic regurgitation only	0 (0.0)
Combined aortic stenosis and regurgitation	5 (25.0)
Peak pressure gradient, mm Hg, mean±SD	69.3±13.9
Mean pressure gradient, mm Hg, mean±SD	44.2±10.8
Aortic valve area, cm ² , mean±SD	0.72±0.13

Values are n (%), unless otherwise indicated. IQR indicates interquartile range.

*n=25 using intention-to-treat principle.

genic shock, endocarditis, or aortic dissection. Major bleeding was defined as hemorrhage requiring surgery and/or ≥3 U blood transfusion.

Categorical variables are presented as frequencies and were compared by χ^2 or Fisher exact test. Continuous variables are presented as mean±SD and were compared by use of a 2-tailed unpaired Student *t* test. Values of *P*<0.05 were considered statistically significant.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population

Between February 2005 and November 2005, 25 symptomatic patients (5 men, 20 women; mean age, 80 years; range, 68 to 94 years) were enrolled in the study. Baseline patient characteristics are listed in Table 1. All patients had severe symptomatic aortic valve stenosis with a peak transvalvular aortic pressure gradient of 69.3±13.9 mm Hg (range, 34 to 139 mm Hg). The preprocedural mean calculated aortic valve area was 0.72±0.13 cm². In 17 patients (68%), aortic regurgitation also was present (1+ in 11 patients, 2+ in 6 patients). The median calculated logistic EuroScore of the study population was 11.0% (interquartile range, 9.2% to 19.9%), and 96% of patients were in NYHA functional class III or IV.

TABLE 2. Procedural Data and In-Hospital MACCEs

		Post Hoc Stratification		
		Phase 1 (n=3)	Phase 2 (n=4)	Phase 3 (n=18)
Device success	22 (88.0)	3 (100)	3 (75.0)	16 (88.9)
Immediate procedural success	21 (84.0)	2 (66.7)	3 (75.0)	16 (88.9)
In-hospital MACCEs	8 (32.0)	1 (33.3)	3 (75.0)	4 (22.2)
Death	5 (20.0)	1 (33.3)	2 (50.0)	2 (11.1)
Major arrhythmia	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac tamponade	1 (4.0)	1 (33.3)	0 (0)	0 (0)
Stroke	1 (4.0)	0 (0)	0 (0)	1 (5.5)
Conversion to surgery	2 (8.0)	0 (0)	1 (25.0)	1 (5.5)
Conversion to valvuloplasty	1 (4.0)	0 (0)	0 (0)	1 (5.5)
Emergent PCI	0 (0)	0 (0)	0 (0)	0 (0)
Endocarditis	0 (0)	0 (0)	0 (0)	0 (0)
Aortic dissection	0 (0)	0 (0)	0 (0)	0 (0)
Major bleeding	6 (24.0)	3 (100.0)	1 (25.0)	2 (11.1)

Values are n (%); total number of patients=25. PCI indicates percutaneous coronary intervention.

Acute Device and Procedural Success

Acute device success was achieved in 22 (88.0%) of 25 enrolled patients (Table 2). In 2 patients (patients 5 and 11), the prosthesis was not deployed deeply enough within the native valve (ie, prosthetic valve level above the native valve level), resulting in significant paravalvular leakage (grades 4+ and 2+). In these 2 cases, although the prosthesis was not completely anchored in the native valve area, the upper part of the prosthesis, which is positioned in the ascending aorta, provided stable fixation of the device without migration or embolization. Urgent open heart surgery was performed with device retrieval and successful implantation of a conventional mechanical valve prosthesis. Both patients remained event free during the 30-day follow-up period. In 1 patient (patient 18; logistic EuroScore, 62.7%), the device could not cross the heavily calcified native valve despite successful predilatation with a 23-mm valvuloplasty balloon. Given the inoperable status of the patient, it was elected to accept the balloon valvuloplasty result because the peak pressure gradient had decreased from 85 mm Hg at baseline to 38 mm Hg after the procedure. The patient died suddenly 12 hours after the procedure, however, as a result of acute heart failure without evidence of aortic regurgitation, dissection, or tamponade. One additional patient died on the second postprocedural day after successful device implantation as a result of delayed pericardial tamponade secondary to a small, initially asymptomatic wire perforation of the left ventricle. Thus, acute procedural success was achieved in 21 of 25 patients (84%).

Acute Hemodynamic Valve Performance

As seen in Table 3 and Figure 3 (left), among the 21 patients with acute procedural success, the aortic peak and mean pressure gradients were markedly reduced immediately after CoreValve insertion. As seen in Table 3 and Figure 3 (right), the degree of aortic regurgitation immediately after valve

TABLE 3. Postprocedure Hemodynamic Valve Performance in Patients With Immediate Procedural Success

	Before Implantation (n=21)	After Implantation (n=21)	At 30-day Follow-Up (n=18*)
Peak pressure gradient, mm Hg, mean±SD	69.90±22.96	21.31±5.05	22.10±3.61
Mean pressure gradient, mm Hg, mean±SD	44.24±10.79	12.38±3.03	11.82±3.42
AR			
4+	0 (0)	0 (0)	0 (0)
3+	0 (0)	0 (0)	0 (0)
2+	4 (19.0)	4 (19.0)	1 (5.6)
1+	10 (47.6)	7 (33.3)	8 (44.4)
0	7 (33.3)	10 (47.6)	9 (50.0)
AR improved vs baseline	...	9 (42.9)	8 (44.4)
AR unchanged vs baseline	...	7 (33.3)	6 (33.3)
AR declined vs baseline†	...	5 (23.8)	4 (22.2)

Values are n(%), unless otherwise indicated.

*Only patients with acute procedural success surviving to discharge are included.

†Aortic regurgitation (AR) declined from baseline to after the procedure in 2 patients by 1 grade (0 to 1+ and 1+ to 2+) and in 3 patients from 0 to 2+. Among the 4 patients with 2+ postprocedural AR, the AR grade decreased to 1+ in 3 patients at 30 days.

implantation was improved or unchanged in 16 patients (76.2%) and worsened in 5 patients (by 1 grade in 2 patients, by 2 grades in 3 patients). The mean aortic regurgitation grade was 0.86±0.73 at baseline and 0.71±0.78 immediately after the procedure (*P*=NS).

In-Hospital MACCEs

In-hospital MACCEs occurred in 8 (32%) of 25 patients, including the 4 periprocedural adverse events described above (Table 2). Three additional patients died on postprocedural days 9, 13, and 15 as a result of progressive hemodynamic failure despite intact valve function (1 patient), disseminated intravascular coagulation as described below (1 patient), and noncardiac sepsis with multiorgan failure (1 patient). Thus, the in-hospital mortality rate was 20% (5 of 25 patients). There were no episodes of valve migration or thrombosis. No patient developed myocardial ischemia. One patient experienced a minor stroke on day 11 after the procedure. Major bleeding occurred in 5 of 10 patients (50%)

treated with the first-generation device and in 1 of 15 patients (6.7%) treated with the lower-profile second-generation device.

Clopidogrel Use and Thrombocytopenia

All patients developed thrombocytopenia between days 1 and 6, an expected complication of the use of extracorporeal circulation. In the first 2 patients with procedural success (phase 1), the thrombocytopenia was transient and mild (Figure 4A). In all 3 phase 2 patients with procedural success, in whom the preprocedural loading dose of clopidogrel had been omitted to reduce access site bleeding, postprocedure thrombocytopenia was severe and prolonged (Figure 4B), with fatal disseminated intravascular coagulation developing in 1 patient. After temporary suspension of the protocol, the clopidogrel loading dose was reinstated to block platelet activation and consumption. With resumption of the 300-mg clopidogrel loading dose, postprocedure thrombocytopenia

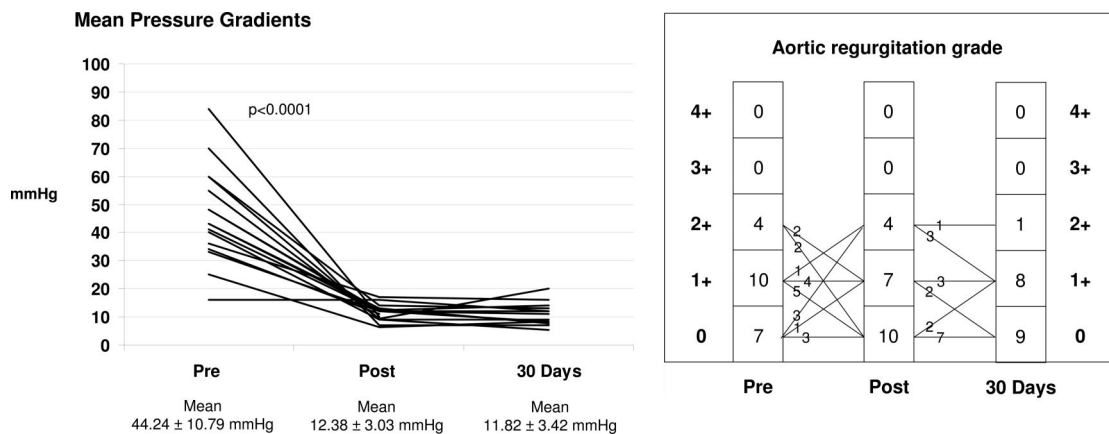


Figure 3. Mean pressure gradients (left) and aortic regurgitation grade (right) at baseline, immediately after CoreValve bioprosthesis placement, and at the 30-day follow-up in patients with acute procedural success.

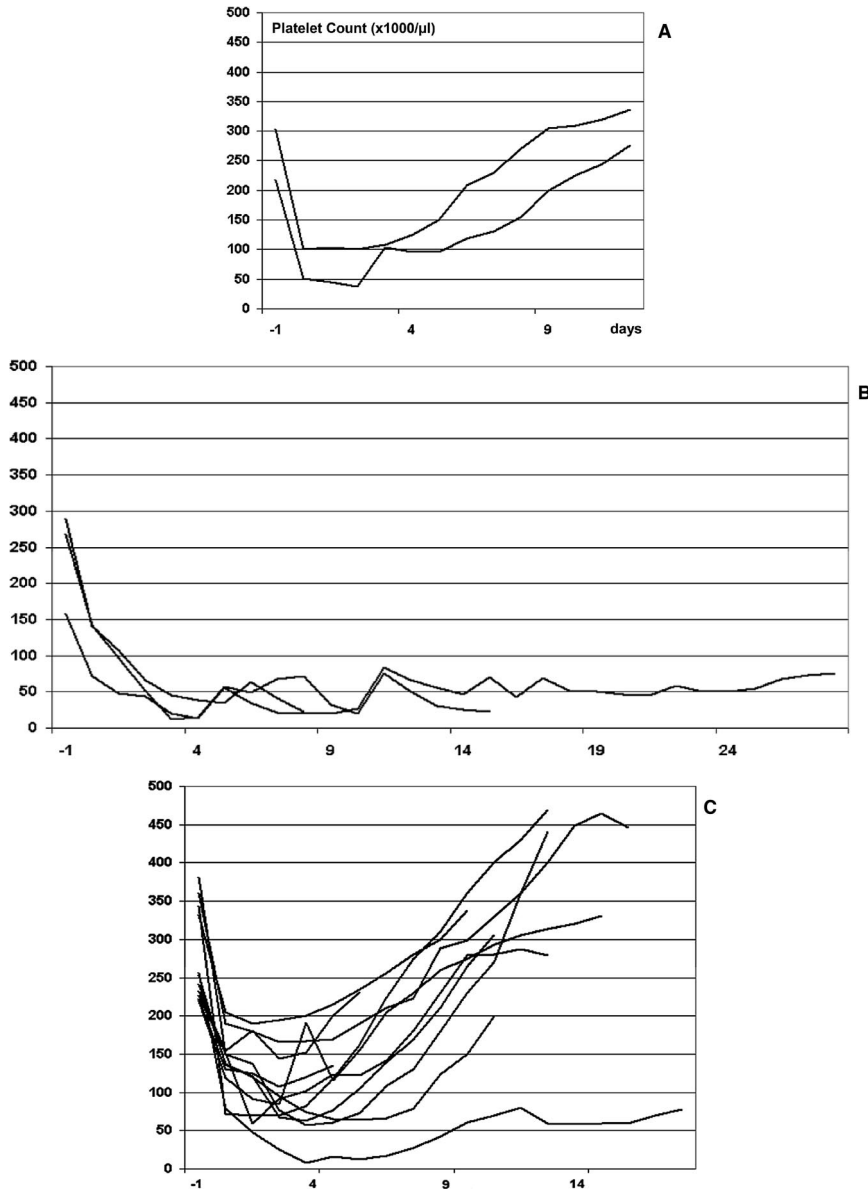


Figure 4. Daily platelet count measures in 16 individual patients with acute procedural success. A, Phase 1 (n=2); B, phase 2 (n=3); C, phase 3 (n=11).

was again mild and transient in all except 1 of the 18 phase 3 patients with procedural success (Figure 4C).

Postdischarge Follow-Up

None of the 18 patients in whom the device was successfully implanted and who survived to discharge had an adverse event within the 30-day follow-up after leaving the hospital. Repeat echocardiographic follow-up at day 30 confirmed stable fixation of the device with similar hemodynamic performance compared with the immediate postimplant evaluation. The peak pressure gradient was 22.1 ± 3.6 mm Hg at the 30-day follow-up compared with 21.3 ± 5.0 mm Hg immediately after the procedure ($P=0.30$), and the mean pressure gradient was 11.8 ± 3.4 mm Hg at 30 days compared with 12.4 ± 3.0 mm Hg after the procedure ($P=0.83$) (Figure 3, left). Aortic insufficiency at 30 days was absent in 9 patients (50.0%), grade 1+ in 8 patients (44.4%), and grade 2+ in 1 patient; no patient had grade 3+ or 4+ aortic insufficiency at 30 days (Table 3 and Figure 3, right).

As shown in Table 3 and Figure 3 (right), the degree of aortic regurgitation was reduced or unchanged at 30 days compared with baseline in 14 of the 18 patients (77.8%). Among 18 patients with device success surviving to discharge, no adverse events occurred within 30 days after leaving the hospital, valve function remained stable, and clinical status improved in all patients from NYHA class III (n=17) and II (n=1) at baseline to class II (n=12) or I (n=6) at the 30-day follow-up.

To date, 180- and 365-day follow-ups are available in 7 and 2 patients, respectively. One patient was rehospitalized for left ventricular failure without valve deterioration. The other 8 patients are alive and clinically unchanged, with stable valve function.

Discussion

The present study demonstrates the feasibility of percutaneous retrograde implantation of the self-expanding CoreValve

bioprosthesis for treatment of aortic valve stenosis with or without aortic regurgitation in patients with high-risk features for surgery. The CoreValve was successfully implanted without periprocedural events in 17 of 25 patients (68%), resulting in immediate marked hemodynamic improvement, with sustained valve performance for 30 days. The reduction in afterload achieved translated into symptomatic relief, with a reduction in NYHA class by 1 to 2 grades in all patients. An important point is that after successful device deployment, there were no cases of valve migration, destabilization, or thrombosis; myocardial ischemia from coronary obstruction; or stroke.

The self-expanding design of the CoreValve prosthesis offers several potential advantages over a balloon-expandable device. First and most important, a self-expanding percutaneous aortic valve may minimize the occurrence of paravalvular leaks and permit treatment of patients with aortic regurgitation. In contrast to the experience with a balloon-expandable percutaneous aortic valve,^{12,14,15} only 1 patient developed severe (3+ to 4+) aortic regurgitation after CoreValve placement, and in most cases, the degree of aortic insufficiency present at baseline was reduced after the procedure. By 30 days, the frequency of mild aortic regurgitation present immediately after implant was further reduced, likely attributable to further valve expansion and/or tissue in-growth. Second, by avoiding balloon trauma to the valve leaflets, the self-expanding design may theoretically prolong valve durability. Longer-term follow-up in a greater number of patients is required to confirm the validity of these hypotheses. Third, the self-expanding upper segment of the valve provides secure fixation in the ascending aorta, and no cases of valve migration or dislodgement were seen after device deployment.

Several important lessons are apparent from this first-in-man single-center study that should improve future results with this device. First, although the patient population was at high risk for surgical mortality, the periprocedural mortality in the present series was considerable (5 of 25 patients, 20%). However, the device and procedural technique evolved during the course of this investigation. Two patients died of procedure-related events (1 from wire perforation of the left ventricle, 1 after inability of the prosthesis to cross a heavily calcified valve). Such occurrences may become less common with device and technique iterations. Specifically, the lower-profile, more flexible second-generation device results in fewer major bleeding events, vascular complications, and aortic trauma during transvascular passage, which should reduce MACCEs. An 18F device has now entered clinical trials and should enhance the safety of the procedure.

A third patient who was not pretreated with clopidogrel died of disseminated intravascular coagulation resulting from platelet consumption, and severe thrombocytopenia of prolonged duration developed in 2 other patients not receiving a thienopyridine before the implant. Extracorporeal circulatory support was used in this early-phase experience to provide hemodynamic control during transaortic device passage and positioning, which frequently results in thrombocytopenia.^{19–21}

However, the occurrence of thrombocytopenia after extracorporeal bypass is not usually severe or prolonged, and the valve implant may be contributing to the development of thrombocytopenia by activating platelets (although hemolysis has not been seen). In this regard, the routine use of clopidogrel loading before establishment of extracorporeal bypass appears to mitigate platelet activation and consumption. As the device and technique evolve, it is likely that this procedure will be done without general anesthesia or cardiopulmonary support, which should further reduce thrombocytopenia, other bypass circuit-related complications, and vascular compromise.

A second lesson from this early-phase study is that precise positioning of the device remains challenging and was responsible for half of the procedural failures. In this regard, the role of transesophageal echocardiography to guide placement continues to evolve, and markers are being added to the device to facilitate accurate positioning. Reducing friction between the sheath and device will also minimize valve movement during sheath retraction. In the absence of circulatory support, rapid ventricular pacing may be used to decrease forward ejection force. However, as seen in the present study, a distinct learning curve is present, and in phase 3, an 89% procedural success rate was achieved, which should continue to increase. It is important to note that there were no deaths directly attributable to failure of the prosthesis, and the near-term serial measures of valve function were stable and clinical outcomes were robust, demonstrating the potential of this device as procedural success rates continue to improve.

Third, the retrograde approach used in the CoreValve procedure offers the advantages of relative procedural simplicity and avoidance of mitral valve support structures during implantation. The sheathed nature of the CoreValve isolates edges of the stent frame that might otherwise engage and dislodge atherosclerotic plaque during passage through the aorta. Nonetheless, tracking of the relatively long and high-profile stent valve apparatus can be difficult in small-diameter or noncompliant atherosclerotic aortas (although the reduced caliber and improved flexibility of the second-generation device has helped noticeably in this regard, eliminating the requirement for a snare to facilitate advancement). Retrograde crossing of heavily calcified aortic valves may occasionally be problematic, despite adequate predilatation, as seen in 1 case in the present series. Future studies should identify anatomic characteristics likely to impede retrograde device tracking and placement, whereas ongoing device iterations (including the 18F design) will improve device passage through the circulation and valve crossing.

Finally, the current device configuration limited its use to patients with a relatively small valve annulus and narrow ascending aorta. As a result, mostly women qualified for this early-stage investigation. Next-generation devices will include larger-caliber designs to allow treatment of a broader cross section of the patient population with degenerative aortic stenosis.

Study Limitations

Several important limitations of this study should be acknowledged. First, the present study describes the short-term results after CoreValve implantation; although the clinical stability seen in 9 patients followed up thus far to 6 to 12 months is encouraging, assessment of the long-term durability of this prosthesis will require at least 5 years of follow-up. Second, before this study, 4 patients were treated with the first-generation device in India and South America under different protocols and with less favorable results. The present investigation was performed at a single experienced center; a multicenter study is required to more fully understand the generalizability of the present results. Such studies are currently underway with the second-generation device. Third, the results of this study apply only to the patient population enrolled (high-risk patients with aortic stenosis and multiple comorbid conditions). Additional studies are required to determine the suitability of this device for patients who are otherwise good candidates for surgical aortic valve replacement and those with predominant aortic regurgitation. Fourth, the mid section of the nitinol frame necessarily covers the coronary ostia. Although myocardial ischemia was not present in any patient and coronary angiography was performed easily in all patients with successful device deployment, a larger experience is required to determine whether angiography or angioplasty is ever impeded. Finally, as discussed, whether the prosthesis itself contributes to the development of thrombocytopenia (in addition to the bypass circuit) is unknown and is the subject of ongoing experimental and clinical research. The truest test in this regard will be whether thrombocytopenia develops after CoreValve device placement without extracorporeal support. Further investigation also is required to clarify the optimal antiplatelet and antithrombotic regimen to support implantation of the CoreValve prosthesis. Pending such studies, it is strongly recommended that a 300-mg loading dose of clopidogrel be administered at least 12 hours before the procedure and that the platelet count be closely monitored after the procedure until returning toward normal.

Conclusions

The present early-stage experience has shown that percutaneous implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic stenosis with or without aortic regurgitation is feasible and, when successful, results in marked hemodynamic and clinical improvement with follow-up through 30 days. If ongoing multicenter studies with the improved second-generation device demonstrate a high procedural success rate with acceptably low morbidity and mortality, percutaneous aortic valve replacement with the CoreValve prosthesis may represent an important therapeutic alternative for high-risk patients with degenerative aortic valve disease who are poor operative candidates.

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Disclosures

Drs Laborde and Stone own options in CoreValve, SA. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The morbidity and mortality of surgical aortic valve replacement are increased in elderly patients with multiple high-risk comorbid conditions. Therefore, less invasive techniques are needed. This article describes the results of a prospective, single-center, nonrandomized study to evaluate the feasibility and safety of percutaneous implantation of a novel self-expanding aortic valve bioprosthesis (CoreValve) in high-risk patients with aortic valve disease. Procedural success was achieved in 84% of patients. Successful device implantation resulted in a marked reduction in the peak and mean aortic valve gradients. The in-hospital mortality was 20%. Among patients with device success surviving to discharge, however, no adverse events occurred within 30 days after leaving the hospital, valve function remained stable, and clinical status improved in all patients. Given this early experience, we believe that percutaneous implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic stenosis with or without aortic regurgitation is feasible and, when successful, results in marked hemodynamic and clinical improvement.