

# Further Experience with the “No-React” Bioprosthesis in Patients with Active Infective Endocarditis: 11-Year Single Center Results in 402 Patients

Michele Musci<sup>1</sup> Aref Amiri<sup>1</sup> Henryk Siniawski<sup>1</sup> Julia Stein<sup>1</sup> Yuguo Weng<sup>1</sup> Roland Hetzer<sup>1</sup>

<sup>1</sup>Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany

Address for correspondence Michele Musci, MD, PhD, Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Augustenburger Platz 1, 13353 Berlin, Germany (e-mail: musci@dhzb.de).

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## Abstract

**Objectives** We investigated early, midterm, and long-term results following valve replacement with the “No-React” bioprosthesis in patients with active infective endocarditis (AIE). **Patients and Methods** Between February 2000 and February 2011, a total of 402 patients (median 61 years, 17 to 91 years) received “No-React” bioprostheses due to single valve AIE in 315 (aortic valve replacement  $n = 158$ , aortic conduit  $n = 30$ , mitral valve replacement  $n = 116$ , tricuspid valve replacement  $n = 11$ ) and double valve AIE in 87 cases. Prosthetic AIE was found in 105 patients (26.1%). Mean follow-up was  $2.8 \pm 3.2$  years (1 month to 11.4 years) with 1,124 patient years, completed in 97.1%. This retrospective study analyzes both prospectively updated data ( $n = 255$ ) and patients recently operated upon ( $n = 147$ ).

**Results** There was a highly significant difference in the survival between patients operated on urgently and patients operated on in an emergency (30-day, 1-, 5-, and 10-year survival were  $80.9 \pm 2.3\%$ ,  $63.8 \pm 2.9\%$ ,  $48.3 \pm 3.3\%$ , and  $39.7 \pm 4.1\%$  vs.  $61.3 \pm 4.5\%$ ,  $45.0 \pm 4.7\%$ ,  $33.1 \pm 4.6\%$ , and  $14.0 \pm 5.1\%$ , respectively,  $p < 0.001$ ), due to native versus prosthetic AIE ( $p = 0.032$ ), single versus double valve replacement ( $p = 0.005$ ), and with or without abscess formation ( $p < 0.001$ ). Thirty-day, 1-, 5-, and 10-year freedom from reoperation due to recurrent endocarditis were 100%,  $95.1 \pm 1.4\%$ ,  $86.4 \pm 2.6\%$ , and  $82.1 \pm 3.6\%$  and due to structural valve deterioration (SVD) were 100%, 100%,  $98.9 \pm 0.8\%$ , and  $91.4 \pm 4.0\%$ , respectively. There was no difference in prosthesis durability between the older ( $> 60$  years) and the younger patients.

**Conclusions** Our experience in the use of “No-React” bioprostheses in patients with native and prosthetic AIE shows satisfactory early, midterm, and long-term results, in particular low rates of reoperation due to recurrent endocarditis and SVD. Because these prostheses are readily available and their implantation straightforward, we strongly recommend their use in patients with AIE. Patients’ survival differed significantly depending on their surgical urgency. Early mortality was independently predicted by septic shock, abscess formation, and number of implanted valves besides age per 10 years.

## Keywords

- ▶ infective endocarditis
- ▶ surgery
- ▶ bioprosthesis

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## Introduction

Despite improvements in medical therapy, the proportion of approximately one-third of endocarditis patients requiring surgery due to failed medical therapy has remained unchanged over the past few decades.<sup>1,2</sup>

These developments reflect our experience of continuing high numbers of patients who have to be operated on for active infective endocarditis (AIE) each year at our institution. Between May 1986 and February 2011, a total of 1,629 AIE patients were operated on at the Deutsches Herzzentrum Berlin, 71.5% ( $n = 1,164$ ) for native valve endocarditis (NVE) and 28.5% ( $n = 465$ ) for prosthetic valve endocarditis (PVE). In the literature, there is a controversial discussion on whether to implant mechanical or biological prostheses in patients with severe AIE; however, the few studies that compare both types of valve are limited in terms of the numbers of patients, and the study populations are mostly not comparable with each other.<sup>3–5</sup>

In 2000, we introduced No-React valves (formerly called Shelhigh SuperStentless valves, made today by BioIntegral Surgical, Inc., Ontario, Canada) in our endocarditis program, because of their several characteristics. The most important was that these bioprostheses do not contain fabric material on their surface and that the No-React anticalcification process causes the tissue to become totally biocompatible sounded promising (→ Fig. 1a, b).<sup>6</sup> Indeed, preliminary results in 2003 and 2004 showed that No-React valves resist infection as well as homografts and they were found to have good hemodynamic characteristics.<sup>7,8</sup> In 2008, we reported our results with a larger cohort of 255 patients and the early and midterm results confirmed our expectations.<sup>9</sup>

In this study, we have reviewed 402 AIE patients in whom No-React bioprosthesis was implanted between February 2000 and February 2011. This retrospective study analyzes both prospectively updated data ( $n = 255$ )<sup>10</sup> and patients recently operated upon ( $n = 147$ ).

The aim of this study was to investigate the outcome after surgical therapy in these AIE patients. The study has an

advantage that is the effects of different valve types on the outcome after an endocarditis operation are excluded.

One main objective was to analyze the outcome of these very sick patients in relation to clinically important issues: the survival in relation to the type of endocarditis; to the preoperative clinical situation of the patient; and to important surgical criteria such as surgical urgency, valve position, abscess formation, and the necessity to perform single or double valve replacement.

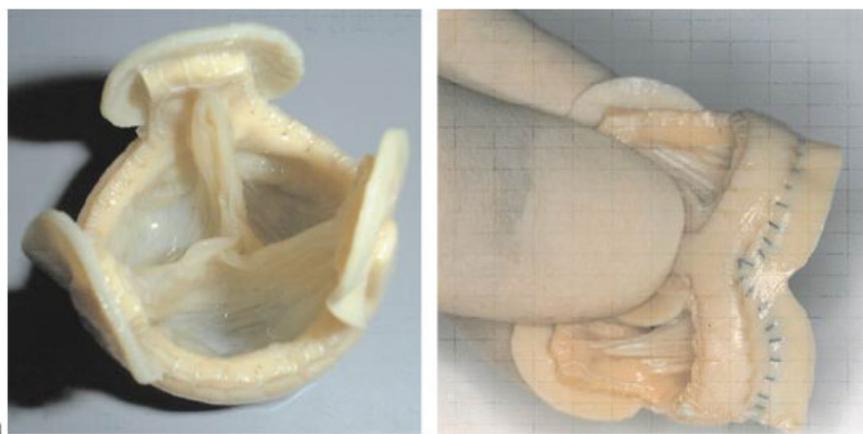
In addition, this study was performed to analyze the reoperation rate due to reinfection or structural valve deterioration (SVD) of the implanted prostheses in regard to our previous findings, in a larger group of patients and over a longer period.<sup>8,9</sup> To improve patients' survival, another goal of this study was to compare clinical differences between early survivors and nonsurvivors ( $\leq 30$  days) and to identify independent risk factors for early mortality by the application of univariate and multivariate analysis.

## Patients and Methods

### Patient Population

→ Table 1 gives an overview of the patient population.

Between February 2000 and February 2011, 402 patients with AIE (289 men, 113 women, median age 61 years) received implantation of a No-React valve bioprosthesis. In 297 (73.9%) patients, NVE was present and in 105 (26.1%) patients, PVE was present. A large proportion of patients were referred to our department in a condition of cardiac decompensation: 98 (24.4%) patients were intubated, 60 (14.9%) had protracted septic shock, and 107 (26.6%) required high doses of catecholamines. The operation was performed electively in 27 (6.7%), urgently in 256 (63.7%), and as an emergency procedure in 119 (29.6%) patients. Staphylococci (38.3%) and Streptococci (27.6%) were the most common microorganisms found in the blood cultures, with a high percentage of *Staphylococcus aureus* (26.4%).



**Fig. 1** (a) The No-React semistented bioprosthesis (formerly called Shelhigh SuperStentless) is a composite trileaflet valve, which is covered with pericardium and has no stent and therefore an optimal opening area. (b) As the framework is flexible, it is possible to implant the stent-free valve in aortic position by placing one suture at the regular base of the annulus and an additional suture at the struts. The super-flexible stent can be easily compressed.

**Table 1** Patient population

Period	2/2000–2/2011
Patients with AIE	<i>n</i> = 402
Men	<i>n</i> = 289 (71.9%)
Women	<i>n</i> = 113 (28.1%)
Age	
Median	61 years
Range	17–91 years
Subgroup by age	
> 65 years	<i>n</i> = 146 (36.3%)
50–65 years	<i>n</i> = 148 (36.8%)
40–49 years	<i>n</i> = 48 (11.9%)
17–39 years	<i>n</i> = 60 (15.0%)
Endocarditis	
Native AIE	<i>n</i> = 297 (73.9%)
Prosthetic AIE	<i>n</i> = 105 (26.1%)
Preoperative status	
Intubation	<i>n</i> = 98 (24.4%)
Septic shock	<i>n</i> = 60 (14.9%)
High-dose catecholamines	<i>n</i> = 107 (26.6%)
Operation	
Elective	<i>n</i> = 27 (6.7%)
Urgent	<i>n</i> = 256 (63.7%)
Emergency	<i>n</i> = 119 (29.6%)
Blood microorganisms	
Staphylococci	<i>n</i> = 48 (11.9%)
<i>S. aureus</i>	<i>n</i> = 106 (26.4%)
Streptococci	<i>n</i> = 85 (21.1%)
<i>Viridans streptococci</i>	<i>n</i> = 26 (6.5%)
Enterococcus species	<i>n</i> = 43 (10.6%)
Culture negative	<i>n</i> = 54 (13.4%)
Others	<i>n</i> = 16 (4.0%)
Unknown	<i>n</i> = 24 (6.0%)
Indication for surgery	No. of patients
Progressive heart failure	323 (80.4%)
+ Recurrent septic embolisms	119 (29.7%)
+ Vegetations	242 (60.2%)
+ Therapy-resistant septic infections	124 (30.9%)
Abscess formation	177 (44.1%)
Aortic	115 (28.7%)
Mitral	52 (13.0%)
Aortic + mitral	10 (2.5%)
Therapy-resistant septic infection	141 (35.2%)
Recurrent septic embolism	156 (38.9%)
Concomitant CABG	58 (14.4%)

Abbreviations: AIE, active infective endocarditis; CABG, coronary artery bypass grafting.

Follow-up was completed in 97.1%, with 12 patients lost to follow-up, by telephone contact with the patient, by analyzing standardized mail questionnaires sent to the patients, by consulting the population registry, and by contacting peripheral hospitals. The mean follow-up time was  $2.8 \pm 3.2$  years (range, 1 month to 11.4 years), with 1,124 patient years.

The study population of 402 patients represents 24.7% of all patients operated on at our institution due to AIE between May 1986 and February 2011 (*n* = 1,629) and 38.3% of all

patients operated on for endocarditis in the study period between February 2000 and February 2011 (*n* = 1,050).

It has to be mentioned that this study analyzes previously reported patients (*n* = 255)<sup>9</sup> in a longer follow-up as well as new ones (*n* = 147).

### Indications for Surgery and Operations Performed

► **Table 1** gives an overview of operative indications during the acute phase of AIE. In general, patients developed several indications for surgery during antibiotic treatment for AIE. The majority had to be operated on due to progressive heart failure in combination with recurrent septic embolisms, vegetations, or therapy-resistant infections. A total of 177 patients (44.1%) developed abscess in the aortic and mitral valve.

► **Table 2** gives an overview of the number of No-React bioprostheses implanted and their position.

In the 402 patients, 419 operations were performed: 315 (78.4%) patients received single valve and 87 (21.6%) patients received double valve replacement. Fifty-eight (14.4%) patients underwent a concomitant coronary artery bypass graft operation.

The operation was defined as an urgent procedure when performed within 3 days after admission and as an emergency procedure when performed on the day of admission or within 24 hours.

### Definition of Active Infective Endocarditis

AIE was defined on the basis of vegetations or abscess shown in the echocardiogram and accompanied by positive blood cultures or intraoperatively harvested valve cultures, on the basis of clinical evidence of persistent sepsis or recurrent septic embolism, or on the basis of the intraoperative diagnosis.

**Table 2** Numbers of No-React bioprostheses implanted and their position

Valve type	Native AIE	Prosthetic AIE	Sum
<b>Single valve implantation</b>	232	83	315
Aortic valve	120	38	158
Aortic conduit	3	27	30
Mitral valve	99	17	116
Tricuspid valve	10	1	11
<b>Double valve implantation</b>	65	22	87
Aortic and mitral valve	38	11	49
Aortic conduit and mitral valve	1	2	3
Left- and right-sided implantation	8	–	8
Others	18	9	27

Abbreviation: AIE, active infective endocarditis.

### The No-React Semistented Bioprostheses

The No-React semistented bioprosthesis (formerly called Shelhigh SuperStentless) and the BioMitral valve are made entirely of biological material and are composite valves consisting of three individual porcine semilunar cusps, available in the sizes 21 to 29 mm for aortic valves and 27 to 31 mm for mitral valves. They are made from noncoronary cusps taken from three glutaraldehyde-fixed aortic valves that are congruent to each other and sewn together with cardiovascular sutures. The resulting composite trileaflet valve, which is covered with pericardium, has a very flexible stent and therefore an optimal opening area (►Fig. 1a). It is also free from mechanical parts and foreign material at the surface and this is favorable for implantation in patients with endocarditis. The aortic valve has a very flexible ring situated between the valve tissue and the pericardial coat. The addition of three so-called struts gives the ring the character of a "skeleton," which simplifies the implantation process. As the framework is flexible, it is possible to implant the stent-free valve in aortic position by placing one suture at the regular base of the annulus and an additional suture at the flanges on the top of every strut. The super-flexible stent can be easily compressed (►Fig. 1b). This allows the valve to keep a continuous symmetric position with perfect coaptation of the cusps. The xenograft, which is coated with heparin, is conserved in glutaraldehyde at very low pressure (< 4 mm Hg) and detoxified. This process is basically an in-house rinsing process. One of the solutions used is a heparin solution that helps to bind the free glutaraldehyde toxic molecule. Once the rinsing is completed, under totally aseptic conditions, glutaraldehyde cannot be extracted from the valve, causing the tissue to become totally biocompatible. This biomodification process eliminates residual glutaraldehyde and ensures stable and permanent cross-linking of the valve tissue. This process is found to be an excellent anti-calcification treatment. It is designed to reduce the reaction of the adjacent tissue and to limit valve calcification and tissue destruction in the long term.<sup>6</sup>

### Statistical Analysis

SPSS for Windows version 18.01 (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis. Qualitative data are presented as number (*n*) and percent. For quantitative data, mean ± standard error was calculated. Analysis of survival and freedom from endpoints was performed according to Kaplan–Meier estimation. Comparisons of survival in different patient groups were performed using weighted log-rank tests.

A logistic regression model was applied to investigate possible risk factors for early mortality (≤ 30 days). A univariable approach with all possible risk factors was evaluated and a multivariable logistic regression with all combinations of relevant risk factors was analyzed. The best model was chosen according to Akaike's information criterion. Survivors and nonsurvivors were compared by Pearson's  $\chi^2$  test or Student's *t*-test as appropriate.

A value of  $p < 0.05$  was considered statistically significant.

## Results

### Overall Survival, Survival in Relation to Surgical Urgency and Type of Endocarditis

►Fig. 2a shows the survival curves for the whole study population ( $n = 402$ ) with a 30-day, 1-, 5-, and 10-year survival of  $75.1 \pm 2.2\%$ ,  $58.3 \pm 2.5\%$ ,  $43.8 \pm 2.7\%$ , and  $31.3 \pm 3.5\%$ , respectively. The comparison of the survival in relation to surgical urgency shows a highly significant difference between the patients operated on electively ( $n = 27$ , 6.7%) or urgently ( $n = 256$ , 63.7%) and those operated on in an emergency ( $n = 119$ , 29.6%) ( $p < 0.001$ ). Analysis of the survival curve shows a particularly clear difference between the two groups in the first 30 days.

There were 14 (3.5%) intraoperative deaths, 9 due to septic multiorgan failure and 5 due to myocardial failure. Main causes of the 101 (25.2%) early deaths (≤ 30 days) were septic multiorgan failure in 67 (16.7%), myocardial failure in 20 (5.0%), cerebral disorders in 9 (2.2%), hemorrhagic shock in 3 (0.7%) cases, and pulmonary failure in 1 (0.2%) case.

Analysis of the survival in relation to the type of endocarditis (►Fig. 2b) found a significant difference between NVE patients and those with PVE ( $p = 0.032$ ).

### Survival in Relation to Valve Position and Comparison of Single versus Double Valve Replacement

►Fig. 2c shows the survival curves showing the relationship with valve position and the comparison between single and double valve replacement in patients with left-sided AIE.

There was no significant difference between the survival rates of patients after aortic valve replacement (AVR) or mitral valve replacement (MVR) ( $p = 0.632$ ).

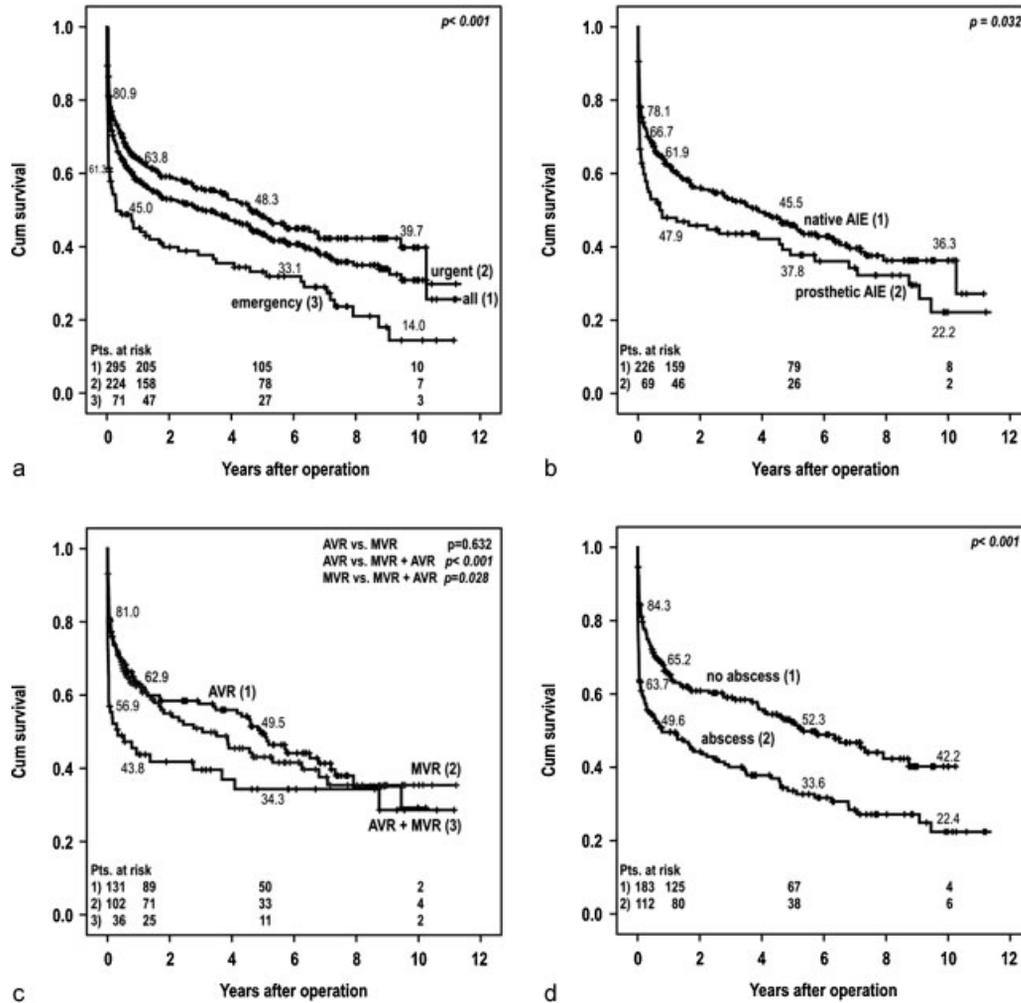
Compared with patients with single valve replacement, those with double valve replacement (AVR and MVR) had a significantly worse survival. Comparison of the survival curves of single versus double valve replacement showed a significantly better survival after AVR ( $p = 0.001$ ) and after MVR alone ( $p = 0.028$ ) (►Fig. 2c), but the low number of patients at risk in the double valve replacement group has to be taken into consideration. A particularly clear difference is seen between the two groups in the first 30 days and in the period of between 1 month and 1 year.

### Survival in Relation to Abscess Formation

►Fig. 2d shows the survival curves in relation to abscess formation.

Of the study population of 402 patients, a large number of patients, 177 (44.1%), developed abscess formation. Of these, 115 (28.7%) showed isolated abscess of the aortic valve, 52 (13.0%) of the mitral valve, and 10 (2.5%) abscess formation on both valves (►Table 1).

Comparing the groups with and without abscess, the figures for better survival in patients without abscess were highly significant ( $p < 0.001$ ).



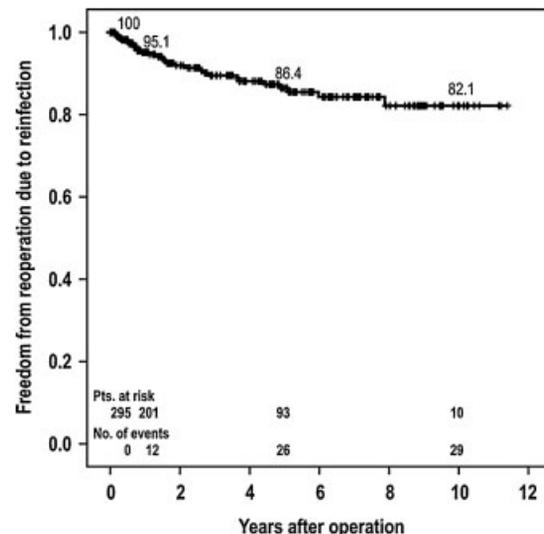
**Fig. 2** (a) Survival curves for the whole study population and comparison of the survival in relation to surgical urgency. (b) Survival in relation to type of endocarditis. (c) Survival in relation to valve position and comparison of single versus double valve replacement. (d) Survival in relation to abscess formation. AIE, active infective endocarditis; AVR, aortic valve replacement; MVR, mitral valve replacement. Note: Numbers depicted are the 30-day, 1-, 5-, and 10-year values.

### Reoperation Due to Reinfection or SVD after No-React Implantation

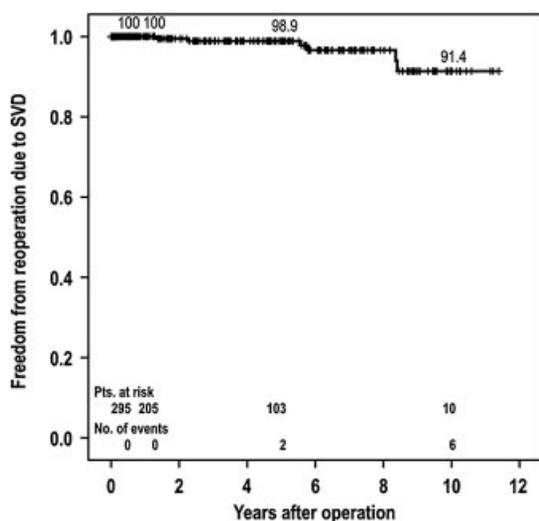
A total of 29 out of 402 patients (7.2%) had to be reoperated upon for reinfection following No-React implantation (12 after AVR, 10 after MVR, and 7 after double valve replacement). In these patients, there were 2 (0.49%) early reinfections (< 60 days) at the 41st and 59th postoperative day with the same microorganism, 10 (2.48%) late reinfections up to 1 year postoperatively (73 to 329 days, median 190 days), and 17 (4.22%) very late reinfections up to 8 years postoperatively (408 to 2,877 days, median 937 days) resulting in a 30-day, 1-, 5-, and 10-year freedom from reoperation due to reinfection of 100%,  $95.1 \pm 1.4\%$ ,  $86.4 \pm 2.6\%$ , and  $82.1 \pm 3.6\%$ , respectively ( $\rightarrow$  Fig. 3).

Six patients, two after AVR and four after MVR, had to be operated on due to SVD at a median postoperative time of 5.7 years (range, 1.3 to 8.4 years), resulting in a 30-day, 1-, 5-, and 10-year freedom from reoperation due to SVD of 100%, 100%,  $98.9 \pm 0.8\%$ , and  $91.4 \pm 4.0\%$  ( $\rightarrow$  Fig. 4).

There was no difference in prosthesis durability between the older (> 60 years) and younger patients.



**Fig. 3** Freedom from reoperation due to reinfection. Note: Numbers depicted are the 30-day, 1-, 5-, and 10-year values.



**Fig. 4** Freedom from reoperation due to structural valve deterioration (SVD). Note: Numbers depicted are the 30-day, 1-, 5-, and 10-year values.

Preliminary early ( $\leq 60$  days) and midterm ( $325 \pm 251$  days) echocardiography study of 45 consecutive AVR patients showed good hemodynamic parameters. The calculated instantaneous (maximal Doppler) gradient and mean pressure gradient through aortic implants were  $24 (\pm 8.4)$  and  $15 (\pm 4.6)$  mm Hg. Mean effective orifice area was  $1.62 \pm 0.4$  cm<sup>2</sup>.

#### Clinical Differences between Early Survivors and Nonsurvivors ( $\leq 30$ Days)

► **Table 3** gives clinical differences between early survivors and nonsurvivors ( $\leq 30$  days) after No-React implantation.

Comparing the two groups, the following statistically significant clinical differences were found: early nonsurvivors more often underwent emergency operation ( $p < 0.001$ ), more often showed abscess formation in aortic ( $p = 0.003$ ) and mitral valve position ( $p < 0.001$ ) intraoperatively, and had to be operated on more often due to PVE ( $p = 0.012$ ).

Preoperatively more nonsurvivors were on artificial ventilation ( $p \leq 0.0001$ ); they developed more septic shock ( $p \leq 0.0001$ ), were more often on high-dose catecholamines ( $p \leq 0.0001$ ), had more renal insufficiency ( $p = 0.024$ ), and showed more infection with *Staphylococcus* species ( $p = 0.012$ ).

Gender ( $p = 0.136$ ), preoperative cerebral ( $p = 0.882$ ) or spleen embolization ( $p = 0.107$ ), preoperative diabetes mellitus ( $p = 0.060$ ), and infection with *S. aureus* ( $p = 0.315$ ) and *Streptococcus* species ( $p = 0.117$ ) were nonsignificant variables in the comparison.

#### Risk Factors for Early Mortality in Univariable and Multivariable Analysis

► **Table 4** gives the risk factors for early mortality in the univariate logistic regression analysis with odds ratio (OR), 95% confidence interval (CI), and  $p$ -values.

On univariable statistical analysis, 15 statistically significant risk factors for early mortality were found, with the following 6 variables showing the highest OR: preoperative necessity of reanimation (OR 6.99), preoperative development of septic shock (OR 4.24), preoperative high doses of catecholamines (OR 4.51), preoperative necessity of ventilation (OR 3.17), abscess formation (OR 3.10), and preoperative development of cardiogenic shock (OR 2.89).

On multivariable analysis, septic shock (OR 4.01, CI 2.40 to 6.71,  $p < 0.001$ ), abscess formation (OR 2.34, CI 1.40 to 3.86,  $p < 0.001$ ), number of valves implanted (OR 2.26, CI 1.28 to 3.98,  $p = 0.005$ ), and age per 10 years (OR 1.31, CI 1.10 to 1.55,  $p = 0.002$ ) were found to be independent risk factors for early mortality.

## Discussion

The present study shows that the extent of AIE in the patient population has not changed since the previous publication of our early and midterm results<sup>9</sup> and confirms our previous results, showing that the survival of patients differs significantly depending on the surgical urgency. This analysis of the data for 402 patients operated upon for AIE with range of follow-up of up to 11 years still shows that most patients are referred too late for surgery. They are on artificial ventilation or in septic shock or on a high dose of catecholamines. Combining all those patients, approximately 66% of the total cohort of patients come to surgery practically in terminal condition and 80.4% of the patients are in progressive heart failure. Only 17 patients (6.7%) were considered totally elective with no abscess formation, and were also considered to have early and optimal diagnosis, with surgery giving them the best possible results. The largest cohort of patients (256 patients, 63.7%) was operated on urgently, and 119 patients (29.6%) were operated on in an emergency. Despite high operative mortality and morbidity, the long-term survival was satisfactory considering how sick the patients were prior to surgery and the complexity of the operative procedures, similar to published data from Toronto and Stanford University.<sup>4,10</sup>

This is clearly demonstrated and shown in the survival curve, where after the first 30 days the lines for urgent and emergency operation run parallel. In addition, survival in patients after double valve replacement (aortic and mitral) was significantly worse than with single valve replacement. Although, currently, complicated AIE has become a so-called surgical disease, ethical, logistical, and financial issues create major challenges to the performance of large, randomized, controlled studies to compare outcomes in AIE patients treated with surgery versus medical therapy.<sup>11</sup>

In the literature, there is only one recently published study from two medical centers in Seoul, South Korea. This prospective, randomized trial enrolled over a period of 5 years 76 patients with infective endocarditis who were candidates for both early surgery ( $n = 37$ ) and conventional treatment ( $n = 39$ ), concluding that early surgery, as compared with conventional treatment, significantly reduced the composite

**Table 3** Differences between early survivors and nonsurvivors ( $\leq 30$  days) after No-React implantation

Variables	Survivors (n = 293)	Nonsurvivors (n = 103)	p-Value
Gender			
Male	216 (76.1%)	68 (23.9%)	0.136
Female	77 (68.8%)	35 (31.2%)	
Endocarditis			
Native endocarditis	225 (77.3%)	66 (22.7%)	<b>0.012</b>
Prosthetic endocarditis	68 (64.8%)	37 (35.2%)	
Priority of operation			
Urgent operation	224 (80.0%)	56 (20.0%)	< <b>0.001</b>
Emergency operation	69 (59.5%)	47 (40.5%)	
Number of valves implanted			
One	239 (77.1%)	71 (22.9%)	<b>0.007</b>
Two	54 (62.8%)	32 (37.2%)	
Aortic valve abscess formation			
No	214 (78.4%)	59 (21.6%)	<b>0.003</b>
Yes	79 (64.2%)	44 (35.8%)	
Mitral valve abscess formation			
No	259 (77.3%)	76 (22.7%)	< <b>0.001</b>
Yes	34 (55.7%)	27 (44.3%)	
Preop. ventilation			
No	239 (79.9%)	60 (20.1%)	< <b>0.0001</b>
Yes	54 (55.7%)	43 (44.3%)	
Preop. septic shock			
No	216 (84.0%)	41 (16.0%)	< <b>0.0001</b>
Yes	77 (55.4%)	62 (44.6%)	
Preop. catecholamines			
No	239 (82.4%)	51 (17.6%)	< <b>0.0001</b>
Yes	54 (50.9%)	52 (49.1%)	
Preop. renal insufficiency			
No	177 (78.3%)	49 (21.7%)	<b>0.024</b>
Yes	116 (68.2%)	54 (31.8%)	
Preop. diabetes mellitus			
No	229 (76.3%)	71 (23.7%)	0.060
Yes	64 (66.8%)	32 (33.3%)	
Preop. cerebral embolization			
No	224 (74.2%)	78 (25.8%)	0.882
Yes	69 (73.4%)	25 (26.6%)	
Preop. spleen embolization			
no	249 (72.6%)	94 (27.4%)	0.107
yes	44 (83.0%)	9 (17.0%)	
<i>Staphylococcus</i> species infection			
No	197 (78.2%)	55 (21.8%)	<b>0.012</b>
Yes	96 (66.7%)	48 (33.3%)	
<i>Staphylococcus aureus</i> infection			
No	225 (75.3%)	74 (24.7%)	0.315
Yes	68 (70.1%)	29 (29.9%)	
<i>Streptococcus</i> species infection			
No	207 (71.9%)	81 (28.1%)	0.117
Yes	86 (79.6%)	22 (20.4%)	

Note: Bold p-values are statistically significant.

endpoint of death from any cause or embolic events by effectively reducing the risk of systemic embolism among patients with infective endocarditis and large vegetations.<sup>12</sup>

Therefore, present practice guidelines, which recommend surgery in cases of heart failure or high risk of heart failure,

high embolic risk, and uncontrolled infection, are largely based on the results of observational series and expert opinion.<sup>13</sup> Our results are consistent with those of published studies showing the benefit of surgical therapy.<sup>8,9,14–17</sup> A recent large multicenter study—which adjusted the results for

**Table 4** Risk factors for early mortality ( $\leq 30$  days) in the univariable logistic regression analysis after No-React implantation

Risk factors	Odds ratio	95% CI	p-Value
Preop. reanimation	6.99	2.08–22.9	< 0.001
Preop. septic shock	4.24	2.64–6.81	< 0.001
Preop. catecholamines	4.51	2.76–7.34	< 0.001
Preop. ventilation	3.17	1.94–5.18	< 0.001
Abscess formation	3.10	1.94–4.95	< 0.001
Cardiogenic shock	2.89	1.46–5.71	0.002
Emergency operation	2.73	1.70–4.37	< 0.001
Mitral valve abscess formation	2.71	1.54–4.77	< 0.001
Aortic-ventricular dehiscence	2.19	1.25–3.84	0.006
Aortic valve abscess formation	2.02	1.26–3.23	0.003
Number of implanted valves (two vs. one)	2.00	1.20–3.23	0.007
Prosthetic vs. native endocarditis	1.86	1.14–3.01	0.013
<i>Staphylococcus</i> species	1.79	1.13–1.34	0.012
Preop. renal insufficiency	1.68	1.07–2.64	0.024
Age	0.98	0.97–1.0	0.045
Preop. diabetes mellitus	1.61	0.98–2.66	0.062
Gender (male vs. female)	1.44	0.89–2.34	0.137
<i>Staphylococcus aureus</i>	1.30	0.78–2.16	0.316
Preop. cerebral embolization	1.04	0.62–1.76	0.882
<i>Streptococcus</i> species	0.65	0.38–1.12	0.117
Preop. spleen embolization	0.54	0.26–1.15	0.112

Abbreviations: CI, confidence interval; vs., versus; preop., preoperative; intraop., intraoperative.

Note: Bold p-values are statistically significant.

most important biases, namely, treatment selection, survivorship, and hidden biases—confirmed the beneficial effect of early surgery on in-hospital mortality for NVE.<sup>18</sup> This study confirms our results, which are also supported by the analysis of the 30-day mortality. In our study, early nonsurvivors (< 30 days) as compared with early survivors were not only more often operated on in an emergency but preoperatively they also showed clinical signs of cardiac decompensation: preoperatively nonsurvivors were significantly more often on ventilation, required more high-dose catecholamines, and had more renal insufficiency. In addition, early nonsurvivors developed more septic shock and intraoperatively showed significantly more abscess formation as a sign of deterioration of the endocarditis. In this study, we could demonstrate with the use of multivariable analysis that early mortality was independently predicted by septic shock, abscess formation, and number of implanted valves besides age per 10 years. For the risk stratification and survival in our study, it has to be taken into consideration that our hospital is a referral surgical center receiving patients who have already been treated medically elsewhere and that we had no input regarding the medical management. They were referred for surgery only after medical therapy failed. In summary, our results suggest that early outcome can be improved if patients are

operated upon before they deteriorate, developing heart failure or septic shock, and we believe that better outcome could have been achieved if patients had been referred earlier for surgery. Recent international guidelines confirm the trend of early surgery in the management of complicated AIE as an extension of surgical indications, especially at the early stage of the disease.<sup>13</sup>

Our study confirms previous reports that documented the association of periannular abscess complications with increased mortality and the need for surgery in almost all patients. In our study, abscess formation, which was found in 44% of the patients, not only was associated with significantly decreased survival but also showed an association with early mortality in the univariable analysis (OR 3.10, 95% CI 1.94 to 4.95). These results accord with the data published by the investigators of the International Collaboration on Endocarditis Merged Database, a cohort from seven sites in five countries. They showed that, among 311 patients who had definite aortic valve AIE, 67 (22%) patients had periannular abscess. These patients were more likely to undergo surgery (84% vs. 36%,  $p < 0.001$ ), and their in-hospital mortality rate was higher (19% vs. 11%,  $p < 0.09$ ). In this study, periannular abscess formation showed a nonsignificant trend toward an increased risk of death (OR 1.9, 95% CI 0.9 to 3.8) but failed to

be an independent risk factor in multivariate analysis, in which *S. aureus* infection was independently associated with increased risk of death.<sup>19</sup> Our data show that No-React bioprostheses offer very good early, midterm, and long-term clinical results in patients with AIE. The reinfection rate in this study was found to be very low, even though many patients showed periannular abscess formation. With the No-React valves, out of 29 reoperations that had been done at 11 years due to recurrence of endocarditis, we have seen only two early (< 60 days) reinfections (0.49%) due to the same microorganism and 10 (2.48%) late reinfections up to 1 year postoperatively. In addition, in the long-term follow-up, we found 4.22% of patients ( $n = 17$ ) who had to be reoperated upon due to late reinfection, resulting in a 30-day, 1-, 5-, and 10-year freedom from reoperation due to reinfection of 100%,  $95.1 \pm 1.4\%$ ,  $86.4 \pm 2.6\%$ , and  $82.1 \pm 3.6\%$ , respectively. These data compare very well to the published results achieved at our institution in the treatment of severe, destructive AIE with cryopreserved homografts<sup>3</sup> and demonstrate that No-React bioprostheses show a high resistance to infection.

The reason for the resistance is not fully understood, but the presence of monolayer endothelium, positive for factor VIII immunoassay, found on the cusp surface of explanted valves<sup>20</sup> and on blood contacting surfaces has been suggested as a potential explanation.<sup>21</sup> It is noteworthy that it takes 6 weeks for endothelialization to occur; therefore, we believe that strict anticoagulation and antibacterial treatment must be maintained for at least 4 to 6 weeks postoperatively. At present in our institution, we are analyzing all explants and a separate study will be published on this subject.

We believe our lower risk of reinfection was due both to our surgical principles and to the use of No-React bioprostheses.

However, it has to be mentioned that the best type of prosthesis for implantation in patients with native and prosthetic AIE is a matter of controversial discussion in the literature. The few studies that compare mechanical and biological prostheses are limited in terms of the numbers of patients, and the study populations are mostly not comparable with each other.<sup>4,5,22</sup> SVD is one of the most frequent causes of valve-related reoperation after allograft AVR, and therefore there is a considerable life-time risk of reoperation, especially in young patients.<sup>23</sup> Previous experimental animal studies have shown that No-React tissue causes no foreign body reaction, leading to a resistance to calcification and degeneration.<sup>6</sup> In our study, at 5 and 10 years postoperatively, freedom from reoperation due to SVD was found to be very high at 98.9 and 91.4%. Additionally, it has to be mentioned that, although 63.7% of the patients were younger than 65 years and 26.9% were younger than 50 years with the youngest being 17 years old, we found no differences in SVD in any age group. The absence of clinical evidence for degenerative changes of No-React bioprostheses seen in our study may be explained by the manufacturing process used. Thus, the recognition that glutaraldehyde and formaldehyde are prerequisites for lim-

iting calcification and the importance of preservation of cross-linked collagen for the durability of biological tissue was fundamental to develop the method used in the No-React bioprostheses. In this process, heparin is used to lock the glutaraldehyde residue, so that glutaraldehyde leaching is abolished and its potential immunological reactivity is prevented, hence keeping all the advantages of glutaraldehyde but abolishing its side effects.<sup>6</sup> However, in our follow-up, the numbers of patients at risk are still low at 10 years, so that the question of whether No-React bioprostheses are resistant to degeneration has to be further explored at 15 and 20 years follow-up.

A recent report has warned of the possibility that the No-React valved conduit may undergo degeneration,<sup>24</sup> but such a phenomenon was not observed in our study population. Our results confirm the data of a 10-year follow-up study by Galiñanes et al<sup>20</sup> where no calcification of No-React bioconduits was found, while approximately one-third of their patients were younger than 65 years.

Another recently published study by Kaya et al from Nieuwegein, the Netherlands, retrospectively evaluated their results with the Shelhigh biological conduit model NR-2000C (Shelhigh, Inc., Milburn, New Jersey, United States) implanted in 175 patients (mean age of 71.1 years) who underwent aortic root replacement from November 1998 through December 2007. Their indication for surgery was aneurysmal disease of the aorta in 120 (68.6%) patients, aortic valve endocarditis in 20 (11.4%), acute type A aortic dissection in 11 (6.3%), and others in 24 (13.7%) patients. Their results showed that six (4.0%) patients required reoperation, either for endocarditis of the bioconduit ( $n = 5$ ) or for false aneurysm ( $n = 1$ ). Endocarditis of the bioconduit was reported in 11 (7.3%) patients, of whom 6 were treated nonoperatively and 5 required reoperation. The authors concluded that their midterm results of the implantation of the Shelhigh biological valved conduit are worrisome and that their relatively high incidence of endocarditis of the Shelhigh BioConduit has forced them to look for other alternatives.<sup>25</sup>

However, in their final recommendation the authors did not explain the finding that 20 endocarditis patients receiving the conduit had no reinfection, while a number of patients operated on for reasons other than endocarditis were infected.

In our study, 33 out of 402 patients (8.2%) received bioconduits mainly for severe prosthetic AIE (29 cases). None of those patients in our study population developed recurrent endocarditis leading to reoperation. We believe our lower risk of reinfection was due both to our surgical principles and to the use of No-React bioprostheses.

It has been our surgical strategy to treat active infective aortic root endocarditis by radical excision of all infected tissue, drainage and exclusion of myocardial abscesses from the blood stream, the repair with homologous material of any cardiac defects caused by infection, and the reconstruction of the aortic root with either by a cryopreserved aortic homograft or by using a bioconduit avoiding fabric material in the infected field.<sup>3,26</sup>

## Study Limitations

The present study is retrospective and nonrandomized, using prospectively updated data. Clinical endpoints such as exercise capacity and functional tests could not be assessed. There is a natural bias in the clinical assessment of the patient groups. Despite these limitations, the present study represents a unique attempt to collect and analyze a single-center experience in the surgical treatment of AIE with the use of the No-React bioprostheses over a period of 11 years in a large group of patients.

## Conclusions

Our experience in the use of “No-React” bioprostheses in patients with native and prosthetic AIE shows satisfactory early, midterm, and long-term results, in particular low rates of reoperation due to recurrent endocarditis and SVD.

Because these prostheses are readily available and their implantation straightforward, we strongly recommend their use in patients with AIE.

Patients' survival differed significantly depending on their surgical urgency.

Early mortality was independently predicted by septic shock, abscess formation, and number of implanted valves besides age per 10 years.

In summary, our results suggest that early outcome can be improved if patients are operated upon before their condition deteriorates into heart failure or septic shock and we believe that better outcome could have been achieved if patients had been referred earlier for surgery.

### Note

This study was presented at a lecture held at the 41st Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery, Freiburg, February 13, 2012.

### Conflict of Interest

There is no financial relationship with any corporate sponsor that might relate in any way to the subject presented.

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