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European Journal of Cardio-thoracic Surgery 28 (2005) 838–844

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Importance of implant technique on risk of major paravalvular leak (PVL) after St. Jude mechanical heart valve replacement: a report from the Artificial Valve Endocarditis Reduction Trial (AVERT)☆

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Received 19 November 2004; received in revised form 2 September 2005; accepted 5 September 2005; Available online 7 November 2005

Abstract

Objective: To examine risk factors for major paravalvular leak (PVL) events after mechanical heart valve replacement. **Methods:** We analyzed outcome of 807 patients randomized into the Artificial Valve Endocarditis Reduction Trial (AVERT). The mean follow-up time was 30.6 months and 21 major PVL events were reported. Three additional major PVL events associated with endocarditis were excluded from analysis. All baseline medical history variables, as well as operative parameters (including use of pledgets and suture technique) were examined using Cox regression. **Results:** Major PVL was reported after 11 aortic, 9 mitral, and 1 double valve replacement. 6/404 (1.5%) patients with conventional valves experienced a major PVL event versus 15/403 (3.7%) in the Silzone group. 10/172 (5.8%) patients with valve suture technique without pledgets experienced a major PVL event versus 11/635 (1.7%) patients with pledgets. Final multivariable model showed that only suture technique without pledgets ($p = 0.005$) was an independent significant risk factor for major PVL events. Silzone cuff showed a strong trend ($p = 0.055$). **Conclusions:** Suture technique without pledgets is an independent significant risk factor for major PVL events. In this study, use of pledgets during valve replacement had a protective effect against subsequent paravalvular leak, supporting the use of buttress reinforcement for valve suture. The use of Silzone cuff, although not statistically significant, showed a strong trend as a risk factor.

Keywords: Valve surgery; Paravalvular leak; Prosthetic valve endocarditis; Risk factors

1. Introduction

Major paravalvular leak (PVL) after prosthetic heart valve replacement is a rare but serious complication. The occurrence of PVL due to prosthetic valve endocarditis (PVE) is a well-known phenomenon, which is also included in the diagnostic criteria of PVE [1]. However, PVL may occur also without definite signs of infection, and recent studies suggest that minor PVL is a rather common finding. When assessed by intraoperative transesophageal echocardiography, PVL has been reported in up to 18% of patients after aortic valve replacement (AVR) and 23% for mitral valve replacement (MVR) [2–4]. Minor PVL seems to have a benign prognosis with progression of regurgitation requiring reoperation in less than 1%, whereas major PVL leads almost always to reoperation. The prevalence and risk factors of major PVL have not been well characterized yet.

The Artificial Valve Endocarditis Reduction Trial (AVERT) was designed to evaluate the efficacy of the Silzone (St. Jude Medical, Minneapolis, MN) silver-coated sewing ring to reduce PVE, based on studies documenting the safety and efficacy of silver for antimicrobial protection. This randomized clinical trial, the protocol for which has been published previously [5], began recruitment of patients in July 1998. Reports of a higher incidence of explant due to PVL in the Silzone study arm led to suspension of patient enrollment in January 2000. Additionally, the manufacturer voluntarily recalled all the Silzone valves from the market. Initial results were published previously [6]. The AVERT continues to follow the 807 randomized patients.

☆ Presented at the joint 18th Annual Meeting of the European Association for Cardio-thoracic Surgery and the 12th Annual Meeting of the European Society of Thoracic Surgeons, Leipzig, Germany, September 12–15, 2004.

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doi:10.1016/j.ejcts.2005.09.014

The aim of the current analysis using the AVERT database was to examine risk factors for major PVL after mechanical heart valve replacement.

2. Material and methods

2.1. Study protocol

Details of the AVERT study design, sample size determination, and early clinical findings have been presented previously [5]. Briefly, the AVERT was designed to determine whether silver coating of prosthetic valve sewing rings reduce the risk of PVE. Patients requiring replacement of the aortic and/or mitral valve with a mechanical prosthesis were eligible to be randomized in two study arms: patients receiving a Silzone-coated prosthesis or a conventional cuffed St. Jude mechanical heart valve. Between July 1998 and January 2000, a total of 807 patients were randomized at 12 North American and 7 European centers. Baseline patient information and details of the operative procedures were collected at the time of surgery. Data were collected according to a uniform study protocol with consistent definitions at all sites. Data collection was monitored on a routine basis by independent study staff. Approximately 200 variables were reported during hospitalization. Further data were collected by the site coordinators annually by administration of a patient questionnaire assessing overall health status, medication use, and symptoms associated with possible adverse events. Suspected adverse events are by protocol reported to the AVERT Coordinating Center (University of Pittsburgh).

2.2. Event definition

A PVL event was collected per study protocol as a non-structural dysfunction event, defined as any abnormality resulting in stenosis or regurgitation at the study value that is not intrinsic to the valve itself. Furthermore, non-structural dysfunction refers to only those non-structural problems that result in dysfunction of a study valve exclusive of infection or thrombosis diagnosed by reoperation, autopsy, or clinical investigation [7]. According to the protocol "A paravalvular leak must be reported as major if it results in reoperation or reintervention for repair, or explant, or death. If reintervention is recommended but is refused by the patient, or cannot be performed due to comorbidity or other reasons, the paravalvular leak is still reportable as major". The paravalvular leak and hemolysis events as well as any other non-structural dysfunction events were collected during the follow-up period for AVERT cohort.

2.3. Patient population

There were 807 patients randomized into the AVERT study (403 Silzone and 404 conventional). Demographics, medical history, information about previous cardiovascular operations, operations performed, intraoperative characteristics, and detailed information about the operative procedure performed on the whole study cohort are given in Tables 1–5. As of July 15, 2005 we had a total of 3652 valve years of follow-up on these patients (1837 years and 1815 years for Silzone and conventional cuffed valves, respectively). A total of 24 reported PVLs met the definition of major as of July freeze database. Three major PVL events were preceded by confirmed endocarditis episodes and these cases were subsequently excluded from the analysis. In all analyses, we report the results based on these 21 major PVL events. Of these 21 cases, 15 (3.7%) were reported in Silzone and 6 (1.5%) in conventional cuffed valves.

Table 1
Demographics and medical history

	Patient cohort (n = 807)
Mean age (year)	61.3 ± 10.6
Male	58.9
Weight (kg)	77.8 ± 16.8
Height (cm)	168.3 ± 10.4
Body mass index (kg/m^2)	27.4 ± 5.0
NYHA functional class	
I	8.7
II	40.5
III	42.3
IV	7.9
Ejection fraction	
<35%	9.6
36–50%	20.1
>50%	70.3
Hypertension	46.6
Diabetes	14.3
Smoking (current/past)	39.2
Hypercholesterolemia	31.7
Renal failure	5.8
On dialysis	15.2
Angina pectoris	19.8
Coronary artery disease	33.2
Myocardial infarction	9.5
Cardiac arrhythmias	25.9
Syncope	7.4
TIA	2.9
Stroke, CVA, RIND	6.3
Carotid artery disease	4.2
Peripheral vascular disease	4.6
Non-cerebral embolism	1.5
Hemorrhage, bleeding	1.1
Pulmonary hypertension	24.7
Lung disease	10.9
Immunosuppressive therapy	1.1
Active/treated endocarditis	5.5
Endocarditis (inactive)	2.9

Numbers refer to percentages of patients with those characteristics or mean values and standard deviations. CVA, cerebrovascular accident; RIND, reversible ischemic neurological deficits; TIA, transient ischemic attack.

2.4. Statistical methods

To investigate the risk factors for major PVL events in the AVERT trial, all baseline medical history variables, as well as operative parameters (including use of pledgets and suture technique), and diseased valve etiology were examined using Cox regression methods. Patients without major PVL were censored at the earliest of the last contact date, date of death, or study valve explant date. All attributes with a trend ($p < 0.25$) of univariable association with PVL events were

Table 2
Previous cardiovascular operations

	Patient cohort (n = 807)
Previous cardiovascular surgery	
None	77.7
Aortic valve repair	0.5
Aortic valve replacement	2.4
Mitral valve repair	4.2
Mitral valve replacement	2.6
Any valve replacement	4.7
CABG	5.6
Balloon angioplasty	1.4
Permanent pacemaker	2.2
Carotid endarterectomy	1.5
Other surgery	7.3
Prior operations with CPB	
None	85.1
One	12.6
Two	2.0
More than two	0.3

Numbers refer to percentages of patients with those characteristics or mean values and standard deviations. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

considered for multivariable modeling. Forward stepwise regression ($p < 0.25$ entry criterion) was used to build the multivariable model, with Silzone forced in. The first-order interactions of Silzone with other factors were not tested due to small number of events. Statistical analyses were performed using SAS 8.02 (Statistical Analysis Software, SAS Institute, Cary, NC).

Table 3
Operations performed

	Patient cohort (n = 807)
Implant position	
Aortic (total number)	58.7 (474)
Mitral (total number)	32.0 (258)
Double (total number)	9.3 (75)
Type of approach	
Full sternotomy	96.5
Partial sternotomy	1.7
Lateral thoracotomy	0.1
Heart port	1.6
Converted to standard	15.4
Urgency of surgery	
Elective	90.3
Urgent	9.7
Concomitant surgical procedures	
None	58.2
Aortic valve repair	0.0
Mitral valve repair	1.5
Tricuspid valve repair	5.2
Any valve repair	6.7
CABG	26.2
Intra-aortic balloon	1.1
Aortic root enlargement	1.7
Repair VSD	0.4
Repair ASD	0.3
Other procedures	12.8

Numbers refer to percentages of patients with those characteristics or mean values and standard deviations. CABG, coronary artery bypass grafting; VSD, ventricular septal defect; ASD, atrial septal defect.

Table 4
Intraoperative characteristics

	Patient cohort (n = 807)
CPB time (min)	105.9 ± 55.1
Without concomitant procedures	86.7 ± 39.0
With concomitant procedures	132.6 ± 62.7
Aortic cross-clamp time (min)	76.1 ± 41.3
Without concomitant procedures	63.2 ± 30.3
With concomitant procedures	94.0 ± 47.4
Patient received antibiotics	97.9
Cuff dipped in antibiotics	6.8
Suture dipped in antibiotics	3.1
Pledgets dipped in antibiotics	0.3

Numbers refer to percentages of patients with those characteristics or mean values and standard deviations.

3. Results

Major PVL was reported after 11 aortic, 9 mitral, and 1 double valve replacement (Table 6). Concomitant procedures

Table 5
Valve characteristics by position

	Aortic	Mitral
Number of patients	549	333
Valve being replaced		
Native	96.5	93.7
Tissue	2.6	4.5
Mechanical	0.9	1.8
Valve dysfunction		
Insufficiency	22.3	50.8
Stenosis	46.7	10.8
Mixed	30.7	38.4
Valve disease etiology		
Degenerative myxomatous	52.6	37.2
Rheumatic	21.7	52.0
Infectious	4.9	7.2
Ischemic	1.3	7.2
Congenital	33.2	0.0
Other	5.1	0.0
Valve pathology		
Annular dilatation	4.4	10.8
Annular calcification	47.5	19.8
Leaflet perforation	3.8	3.0
Leaflet calcification	74.5	34.8
Leaflet thickening	47.7	54.1
Papillary muscle elongation/rupture	–	3.0
Commissural fusion	20.6	29.7
Chordal elongation/rupture	–	16.5
Chordal fusion/thickening	–	35.7
Other	16.6	25.5
Valve implanted		
SJM conventional	48.1	50.5
SJM Silzone	50.5	49.3
Other	1.5	0.2
Suture technique		
Simple interrupted	17.5	14.1
Continuous	12.0	5.1
Everted mattress	24.6	39.3
Non-everted mattress	49.7	45.4
Figure of eight	0.2	0.6
Other	0.2	3.0
Pledgets use	75.4	84.1

Table 6
Patients with major paravalvular leak[a]

No.	Age	Sex	Valve replaced	Valve type	Suture Technique	Pledgets	Urgency of surgery	Concomitant surgery[b]	Type of procedure	Days to explant	Days to repair
1	71	M	Mitral	Conventional	Non-everted mattress	Yes	Elective	–	Full sternotomy	–	1561
2	68	F	Mitral	Silzone	Everted mattress	Yes	Urgent	–	Full sternotomy	168	–
3	65	M	Aortic	Silzone	Non-everted mattress	Yes	Urgent	–	Full sternotomy	–	–
4	70	F	Aortic	Silzone	Non-everted mattress	Yes	Elective	–	Full sternotomy	1902	–
5	59	F	Mitral	Silzone	Continuous	No	Elective	TVR	Full sternotomy	77	–
6	46	M	Aortic	Conventional	Everted mattress	Yes	Elective	–	Full sternotomy	1407	–
7	67	M	Aortic	Silzone	Non-everted mattress	Yes	Elective	–	Full sternotomy	386	–
8	42	F	Mitral	Conventional	Simple interrupted	No	Elective	–	Heart port	101	–
9	58	M	Aortic	Conventional	Simple interrupted	No	Elective	CABG	Full sternotomy	342	205
10	58	F	Aortic	Silzone	Simple interrupted	No	Elective	–	Full sternotomy	1125	–
11	73	F	Mitral	Silzone	Simple interrupted	No	Elective	–	Full sternotomy	518	–
12	62	M	Aortic	Silzone	Simple interrupted	No	Elective	CABG	Full sternotomy	286	–
13	60	M	Mitral	Silzone	Everted mattress	Yes	Elective	CABG	Full sternotomy	646	–
14	52	M	Aortic	Conventional	Non-everted mattress	Yes	Elective	CABG	Full sternotomy	–	898
15	50	M	Aortic	Conventional	Continuous	No	Elective	–	Full sternotomy	–	43
16	44	M	Aortic	Silzone	Continuous	No	Elective	–	Full sternotomy	133	–
17	71	F	Mitral	Silzone	Everted mattress	Yes	Elective	–	Full sternotomy	112	–
18	65	M	Double	Silzone	Non-everted mattress	Yes	Elective	–	Full sternotomy	190	–
19	65	F	Mitral	Silzone	Non-everted mattress	Yes	Elective	–	Heart port	89	–
20	70	M	Aortic	Silzone	Simple interrupted	No	Elective	–	Full sternotomy	401	–
21	72	F	Mitral	Silzone	Continuous	No	Urgent	–	Full sternotomy	–	77

[a] Three patients with endocarditis not listed.
[b] Received coronary artery bypass grafting (CABG) or tricuspid valve repair (TVR).

were performed in 4/21, with tricuspid valve repair in one patient and coronary artery bypass grafting in three patients, respectively. 20/21 patients had replacement of the native valve at baseline operation, one patient had replacement of a mechanical prosthesis. During the follow-up period, 20/21 patients had reoperation due to major PVL, one patient died. Out of the 20 reoperated patients 4 had refixation and 16 had explant of the mechanical heart valve prosthesis with PVL.

Table 7 shows results of the final multivariable model and the major PVL rate for each predictor. Only suture technique without pledgets was an independent significant risk factor for major PVL events. In the whole AVERT study population, the majority of implanted valves (75.4% in aortic position and 84.1% in the mitral position, respectively) were sutured with pledget reinforcement using everted or non-everted mattress sutures (Table 5). However, a major PVL event occurred in 5.8% (10/172) of patients with no pledget use versus only 1.7% (11/635) of patients with pledget use (Table 7). Due to the low number of PVL events we could not detect any association between valve position and risk of a PVL event. 1/21 patients was randomized and operated during active endocarditis, none of the other patients with major PVL had a history of endocarditis at baseline. The majority of patients (19/21) were operated with a conventional surgical approach via full sternotomy. At two participating centers, a total of 13/807 patients randomized in AVERT were operated with minimal invasive approach using a heart port system. 2/13 had major PVL but the number of events was too small to test its effect on the occurrence of major PVL in an adequate statistical analysis. The use of Silzone-coated cuff was forced into the model and we observed that the effect of Silzone did not reach conventional significance ($p = 0.055$).

Table 7
Multivariable model and predictors for major PVL

Attribute	Hazard ratio	95% CI	p value[*]
Silzone valve versus conventional	2.5	(0.98, 6.52)	0.055
Use of pledget	0.3	(0.12, 0.69)	0.005

	Number of PVL events	Number of patients	Percentage
Conventional valve	6	404	1.5
Silzone valve	15	403	3.7
No pledget use	9	172	5.8
Pledget use	9	635	1.7

[*] Results of the multivariable model.

4. Discussion

Using the AVERT database, the present study identifies use of implant suture technique without pledget reinforcement as an independent risk factor for major PVL events. Previous AVERT interim analysis [6] that led to discontinuation of enrollment and voluntary withdrawal of the Silzone valve already reported a higher incidence of major PVL in patients who received a Silzone valve implant compared with a conventional cuffed mechanical heart valve. However, in this current analysis there was no strong evidence of the effect of Silzone on the risk of major PVL when other factors were taken into account. This study, however, includes data from a much longer follow-up period than previous results from the AVERT trial. The early observation of higher incidence of PVL among Silzone patients is not supported by statistical evidence in this analysis. Mechanisms responsible for the development of major PVL in patients with a Silzone valve have not been well defined. Contradictory findings in other

trials (small in sample size, non-randomized trials, or only single arm studies compared to AVERT) did not show higher rates of PVL in Silzone valves [8–12]. This conflicting situation has been reviewed previously [13,14]. It has been suggested that Silzone coating inhibits normal fibroblast growth into the prosthetic valve sewing cuff by possible direct toxic effects of silver to the surrounding tissue; this is supported by the findings of poor tissue ingrowth and loosening of sutures in explanted valves [6,15]. In contrast, a recently published echocardiographic analysis of the majority of patients randomized into AVERT [16], excluding patients having had major PVL with consecutive reoperation, did not show statistical significant differences in the prevalence or severity of PVL in the Silzone-coated valve compared with the conventional prosthetic valve. In addition, this echocardiographic analysis showed lower PVL rates (combined PVL rate of 8.7%) in the AVERT population than those previously reported in larger series [16]. The current analysis clearly identifies a strong trend in the total AVERT study cohort of the use of a Silzone valve as a risk factor for the development of major PVL, with hazard ratio 2.5 although it did not reach conventional significance (Table 7).

The interesting finding in this study seems to be the importance of implant technique on risk of major PVL events. Multivariable modeling showed a highly significant effect ($p = 0.005$) with higher PVL event rates in patients without pledget use at valve sutures. This protective effect against subsequent major PVL supports the use of buttress reinforcement for valve sutures in aortic and mitral position. A previous investigation [17] reported a similar result for mitral valve replacement. In combination with the other risk factor for major PVL event—the use of Silzone valves—it has been hypothesized that technique of valve implantation may have accounted for differences between the Cardiff Embolic Risk Factor Study (CERFS) and AVERT. CERFS investigators found significantly higher rates of thromboembolic events in patients with implanted Silzone valves, but no excess in PVL rates [12]. To date, AVERT follow-up [6] and also other studies [8,10,18] could not confirm these findings. Interpretation of conflicting findings in different clinical trials is difficult [13] and a certain limitation of CERFS seems to be that this is a non-randomized study and the patient numbers are relatively small compared to AVERT. Nevertheless, Ionescu and coworkers [12] raised the interesting idea that mattress sutures with pledget use force the sewing ring into much firmer contact with the surrounding tissue than continuous sutures do, even inducing a degree of pressure necrosis if sutures are overtightened. In addition, it would be possible that such a firmer initial fixation of the Silzone valve may enhance possible toxic effects to the surrounding tissue leading to a higher incidence of PVL rates. So far, our results do not support this hypothesis; mattress suture with pledget use had protective effects against major PVL events in our study cohort.

This study in fact did not find that Silzone was a significant independent predictor of major paravalvular leak in patients when they were followed for an extended period. This study included AVERT patients who were followed out to 5 years (90% of patients were followed) and the numbers of additional leaks since the original reports has been very low.

We did not find additional significant predictive factors in the AVERT database. In particular, valve position, history of endocarditis, and immunosuppressive therapy at the time of baseline valve surgery did not significantly elevate the risk for major PVL event. However, we did not have sufficient number of events to examine these effects in depth, and hence the lack of statistical evidence should be interpreted with caution. Theoretically, the use of minimal invasive procedures may also elevate the risk of major PVL events. In the AVERT database, numbers of valves implanted with heart port systems are too small for adequate statistical analysis. This database was also limited to patients who had St. Jude mechanical valves implanted and may not be generalizable to other types of artificial valves.

The present analysis is also limited, since other possible predicting factors for the occurrence of major PVL events are difficult to evaluate. Despite data regarding the valve disease etiology and description of the intraoperative findings of valve pathology (Table 5) collected in the AVERT database, one may not exclude other confounding factors like annular tissue condition when the valve is implanted, which is difficult to assess objectively. Other possible confounding factors seem to be surgery-related problems at the time of implant. In addition, the number of sutures used for valve implantation was not counted. Since the analysis was performed only in the 21 patients with major PVL events, current results may also not be extrapolated to the larger amount of patients who have minor to moderate PVL.

Acknowledgement

The Artificial Valve Endocarditis Reduction Trial is sponsored by St. Jude Medical.

References

[1] Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994;96:200–9.
[2] O'Rourke DJ, Palac RT, Malenka DJ, Marrin CAS, Arbuckle BE, Plehn JF. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. J Am Coll Cardiol 2001;38:163–6.
[3] Movsowitz HD, Shah SI, Ioli A, Kotler MN, Jacobs LE. Long-term follow-up of mitral periprosthetic regurgitation by transesophageal echocardiography. J Am Soc Echocardiogr 1994;7:488–92.
[4] Rallidis L, Moyssakis IE, Ikonidis I, Nihoyannopoulos P. Natural history of early aortic paraprosthetic regurgitation: a five-year follow-up. Am Heart J 1999;138:351–7.
[5] Schaff H, Carrel T, Steckelberg JM, Grunkemeier GL, Holubkov R, for the AVERT Investigators. Artificial valve endocarditis reduction trial (AVERT): protocol of a multicenter randomized trial. J Heart Valve Dis 1999;8:131–9.
[6] Schaff HV, Carrel TP, Jamieson WRE, Jones KW, Rufilanchas JJ, Cooley DA, Hetzer R, Stumpe F, Duveau D, Moseley P, van Boven WJ, Grunkemeier GL, Kennard ED, Holubkov R. Paravalvular leak and other events in Silzone-coated mechanical heart valves: a report from AVERT. Ann Thorac Surg 2002;73:785–92.
[7] Edmunds Jr LH, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1996;62:932–5.
[8] Stalenhoef JE, Mellema EC, Veeger NJ, Ebels T. Thrombogenicity and reoperation of the St. Jude Medical Silzone valve: a comparison with the conventional St. Jude Medical valve. J Heart Valve Dis 2003;12:635–9.
[9] Auer J, Berent R, Ng CK, Punzengruber C, Mayr H, Lassnig E, Schwarz C, Puschmann R, Hartl P, Ebner B. Early investigation of silver-coated Silzone heart valve prosthesis in 126 patients. J Heart Valve Dis 2001;10:717–23.

[10] Houel R, Kirsch M, Hillion ML, Loisance D. Silzone-coated St. Jude Medical valve: a save valve. J Heart Valve Dis 2001;10:724–7.
[11] Herijgers P, Herregods MC, Vandeplas A, Meyns B, Flameng W. Silzone coating and paravalvular leak: an independent, randomized study. J Heart Valve Dis 2001;10:712–6.
[12] Ionescu A, Payne N, Fraser AG, Giddings J, Grunkemeier GL, Butchart EG. Incidence of embolism and paravalvular leak after St. Jude Silzone valve implantation: experience from the Cardiff Embolic Risk Factor Study. Heart 2003;89:1055–61.
[13] Grunkemeier GL, YingXing W. The Silzone effect: how to reconcile contradictory reports? Eur J Cardiothorac Surg 2004;25:371–5.
[14] Bodnar E. The Silzone dilemma – what did we learn? J Heart Valve Dis 2000;9:170–3 [editorial].
[15] Tozzi P, Al-Darweesh A, Vogt P, Stumpe F. Silver-coated prosthetic heart valve: a double-bladed weapon. Eur J Cardiothorac Surg 2001;19:729–31.
[16] Davila-Roman V, Waggoner AD, Kennard ED, Holubkov R, Jamieson E, Englberger L, Carrel TP, Schaff HV. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT). Echocardiography study. J Am Coll Cardiol 2004;44:1467–72.
[17] Dhasmana JP, Blackstone EH, Kirklin JW, Kouchoukos NT. Factors associated with periprosthetic leakage following primary mitral valve replacement: with special consideration of suture technique. Ann Thorac Surg 1983;35:170–8.
[18] Horstkotte D, Bergemann R. The Gelia Study Group. Thrombogenicity of the St. Jude Medical prosthesis with and without Silzone-coated sewing cuffs. Ann Thorac Surg 2001;71:1065.

Appendix A. Conference discussion

Dr C. Yankah (*Berlin, Germany*): Did you have the opportunity to study histologically the sutures used for the Silzone valve implantation in order to exclude any chemical reactions which might have been initiated by the Silzone valve ring to cause suture disruption on and thus a paravalvular leak?

Dr Englberger: We did not have all the histological examinations of the explanted valves, but there are some anecdotal reports that the tissue surrounding a Silzone valve seems to be different than the tissue surrounding a conventional valve. But that is still hypothetical.

Your question gives me also the possibility to look at some limitations of the trial, because we cannot exclude confounders here. If we have intraoperative findings like a calcified annulus or weak tissue, that is difficult to explain or hard to collect in a study. Some other confounders like the surgeon itself cannot be ruled out in such a trial. There are still only hypothetical explanations about factors which cause this higher rate of paravalvular leak in Silzone patients, which was seen only in the AVERT database.

Editorial comment

How much can we do to reach the ideal valve prosthesis?

Since the introduction of the first prosthetic heart valve for orthotopic implantation, by Starr and Edwards in the early sixties, a countless number of devices have been created, marketed and used clinically. Many have not stood the test of time and some even constituted true clinical disasters with serious consequences for the patients. The most notorious was the problem of strut fracture of the initial models of the Björk–Shiley C–C valve, in the 1980s, which caused the death of many patients and obliged to elective reoperation for substitution of the prosthesis in many others, and resulted in a major legal battle and compensation to the patients which eventually led to the disappearance of the manufacturers.

A much more recent problem was that of the St. Jude Silzone valve (St. Jude Medical, Minneapolis, MN, USA). This prosthesis was a modification of the original St. Jude valve by inclusion of a silver-coated sewing ring aiming at reducing prosthetic valve endocarditis (PVE), based on studies which documented the safety and efficacy of silver for antimicrobial protection. But a significant incidence of early major paravalvular leak (PVL) events obliged withdrawal of the valve from the market.

In a paper published in this issue of the journal, Englberger et al. [1] proposed to examine the risk factors for major PVL events after heart valve replacement with the Silzone valve. To this end, the authors of this multi-institutional study analysed the late outcome of 807 patients randomised into the Artificial Valve Endocarditis Reduction Trial (AVERT). Twenty-one major PVL were reported (11 after aortic, 9 after mitral, and 1 after double valve replacement). Six of the 404 (1.5%) patients who received conventional valves experienced a major PVL event versus 15/403 (3.7%) in the Silzone group. The incidence was much higher (10/172; 5.8%) in patients with non-pledget valve suture technique versus that in the patient group with pledgeted sutures (11/635; 1.7%). The final multivariable model showed that only suture technique without pledgets was an independent significant risk factor for major PVL events, while the Silzone cuff "showed a strong trend" towards statistical significance. They thus conclude that the high incidence of unfavourable events associated with the Silzone valve was not associated exclusively to the modified sewing ring.

The AVERT clinical randomised trial was designed precisely to evaluate the efficacy of this prosthesis and began recruitment of patients in July 1998. Although the initial results of the trial were published in 2002 [2], reports of a higher incidence of PVL in the Silzone group led to suspension of patient enrolment in January 2000 and the manufacturer voluntarily recalled all the Silzone valves from the market. Hence, the current report may appear to be of a very limited interest. The results are fairly well known and the prosthesis no longer exists, although many patients still live with it, the vast majority without complications. Since the complication is easily diagnosed and could be successfully corrected in all but one of the reported cases, there was no indication for prophylactic prosthetic replacement. As anything that can be said about a valve that can no longer be used it is of only academic importance, this paper can, as one of the reviewers in the process of evaluation for consideration for publication put it, be accepted as "the last and final report on the AVERT trial".

Nonetheless, the AVERT investigators continue to follow the 807 randomised patients and their late findings may be of interest for the management of these patients. Because the number of events registered during the follow-up period was relatively small (only 20/21 patients had reoperation due to major PVL and one died), this should tranquilise the remaining patients. It is highly unlikely that the complication that led to