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One-year outcome following biologic or mechanical valve replacement for infective endocarditis

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Conflicts of interest

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Structured abstract

Background

Nearly half of patients require cardiac surgery during the acute phase of infective endocarditis (IE). We describe the characteristics of patients according to the type of valve replacement (mechanical or biological), and examine whether the type of prosthesis was associated with in-hospital and 1-year mortality.

Methods and Results

Among 5,591 patients included in the International Collaboration on Endocarditis Prospective Cohort Study, 1,467 patients with definite IE were operated on during the active phase and had a biological (37%) or mechanical (63%) valve replacement.

Patients who received bioprostheses were older (62 vs 54 years), more often had a history of cancer (9% vs 6%), and had moderate or severe renal disease (9% vs 4%); proportion of health care-associated IE was higher (26% vs 17%); intracardiac abscesses were more frequent (30% vs 23%). In-hospital and 1-year death rates were higher in the bioprosthesis group, 20.5% vs 14.0% (p=0.0009) and 25.3% vs 16.6% (p<.0001), respectively.

In multivariable analysis, mechanical prostheses were less commonly implanted in older patients (odds ratio: 0.64 for every 10 years), and in patients with a history of cancer (0.72), but were more commonly implanted in mitral position (1.60).

Bioprosthesis was independently associated with 1-year mortality (hazard ratio: 1.298).

Conclusions

Patients with IE who receive a biologic valve replacement have significant differences in clinical characteristics compared to patients who receive a mechanical prosthesis. Biologic valve replacement is independently associated with a higher in-hospital and 1-year mortality, a result which is possibly related to patient characteristics rather than valve dysfunction.

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INTRODUCTION

Despite improvements in diagnosis, antibiotic treatment and surgery, infective endocarditis (IE) remains a serious disease, with 50% of patients requiring cardiac surgery during the acute phase of IE and a 20% in-hospital mortality.[1-3] Cardiac surgery for IE typically involves valve replacement with a mechanical or xenograft biologic prosthesis, although valve repair and homograft replacements may be used. The main advantage of mechanical prostheses is their longevity, but they require lifelong treatment with anticoagulants and the subsequent bleeding risks. Bioprostheses do not require long-term anticoagulation, but have a shorter durability, particularly in the mitral position. In its 2009 guidelines on IE, the European Society of Cardiology did not favour any specific valve substitute but recommended a tailored approach for each individual patient and clinical situation.[4] The American College of Cardiology and the American Heart Association Valvular Disease Guidelines have stated that in general, a mechanical prosthesis is reasonable in patients under 65 years of age, while a bioprosthesis is favored in patients 65 years of age or older for both the aortic and the mitral positions, but do not provide specific recommendations for surgery in IE.[5]

There are limited data to support the choice of either type of prosthesis in IE.[6] The characteristics of patients receiving biological or mechanical prosthesis and the association between type of valve prosthesis and outcome are not clearly defined. Thus, the objectives of this observational study were to describe the characteristics of patients according to the type of prosthesis and to examine the relationship between prosthesis type and 1-year mortality.

METHODS

International Collaboration on Endocarditis - Prospective Cohort Study

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Data from the International Collaboration on Endocarditis - Prospective Cohort Study (ICE-PCS) were used for this study. Methods of this prospective, multicenter, international registry of IE have been previously reported.[7, 8] Between January 2000 and December 2006, 5,668 patients from 64 centres in 28 countries were enrolled. The ICE-PCS database is maintained at the Duke Clinical Research Institute, which serves as the coordinating centre for ICE studies, with institutional review board approval from Duke University School of Medicine. All patients from sites meeting criteria for participation were included in ICE-PCS. Sites had to meet the following criteria: (1) minimum enrolment of 12 cases per year in a centre with access to cardiac surgery; (2) patient identification procedures in place to ensure consecutive enrolment and to minimize ascertainment bias; (3) high-quality data, including query resolution; and (4) institutional review board and/or ethics committee approval or waiver based on local standards.

Patient Selection, Data Collection and Outcomes

Patients were identified prospectively and consecutively enrolled in ICE-PCS if they met criteria for possible or definite IE based on modified Duke criteria.[9] Only the first episode of IE recorded for an individual patient was used in the analysis. Patients with definite IE who underwent valve surgery during the active phase of IE and who had biological or mechanical valve replacement were included. Exclusion criteria were: age <18 years old; intravenous drug user; patients treated with valve repair rather than replacement or who received a homograft or an autograft; patients receiving both a mechanical prosthesis and a bioprosthesis and patients whose 1-year survival data were missing.

A standard case report form was used at all sites to collect data. The case report form included 275 variables and was developed by ICE according to standard definitions.[7] Data were collected during the index hospitalization and then entered at the coordinating centre or by site investigators using an Internet-based data entry system. Clinical characteristics

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including demographics, comorbid conditions, pre-existing valvular conditions, details regarding the current episode of IE (including source of acquisition,[10, 11] microbiology and echocardiography findings, complications, management, and outcome) were collected. All sites were queried to obtain 1-year outcome data for survival, with use of national death indices, medical records, or patient contact, as available.

Statistical analysis

The outcomes of interest in this study were in-hospital and 1-year mortality. Data are presented as means (standard deviations) for continuous variables and as frequencies (percentages) for categorical variables. Simple comparisons were made with the Wilcoxon rank-sum test or the Chi-square test as appropriate.

A generalized estimating equation method was used to determine factors that predicted implantation of a biological or a mechanical prosthesis. Variables found to have an association with the outcome of interest ($p<0.05$) on univariable analysis were considered for the final model in a backwards stepwise fashion. The final parameter estimates were converted to odds ratios (OR) with corresponding 95% confidence intervals (CI).

A proportional hazards regression model was used to determine if prosthesis type was associated with 1-year mortality. Variables that differed significantly ($p<0.05$) between the two prosthesis groups in univariable analysis and clinically sound variables were considered for the final model. Survival times were censored at 1 year or date of last contact. Risk estimates are presented as hazard ratios and 95% CI. Survival curves were produced by plotting the estimated survival distribution obtained from the proportional hazards regression model, stratified by type of prosthesis. Influence of age was studied both per ten-year intervals and with a cutoff of 65 years according to the ACC-AHA valvular disease guidelines.

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All tests were 2-sided, and statistical significance was determined at the 0.05 level. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

There were 5,668 patients with definite and possible IE enrolled in the ICE-PCS. Based on pre-specified inclusion and exclusion criteria for this study, 1,467 patients, including 917 (63%) who received mechanical prostheses only and 550 (37%) who received bioprostheses only, were included in this study (Figure 1).

The clinical characteristics of patients receiving biologic or mechanical prostheses are presented in Table 1. Compared to patients who received mechanical prostheses, those who received bioprostheses were older (61.6 SD 15.2 vs 53.6 SD 15.2 years; p<.0001), more often had a history of cancer (9% vs 6%; p=0.009) and moderate or severe renal disease (9% vs 4%; p<0.001). A higher proportion of bioprostheses were used in North and South America whereas in other regions of the world, mechanical prostheses were more frequently implanted. There were a higher proportion of health care-associated IE cases in the bioprosthesis group (26% vs 17%; p<.0001). For aortic valve replacement, bioprostheses were implanted more frequently than mechanical prostheses (61% vs 39%; p=0.06) whilst for mitral valve surgery, bioprostheses were less commonly implanted (34% vs 66%; p=0.002). Intracardiac abscesses were more frequent in the bioprosthesis group (30% vs 23%; p=0.0044). Both in-hospital and 1-year death rates were higher in the bioprosthesis group, 20.6% vs 14.0% (p=0.0009) and 25.3% vs 16.6% (p<.0001), respectively. For patients undergoing isolated aortic valve replacement, 1-year mortality after biologic versus mechanical valve replacement was 21.9% and 13.1% respectively; for patients undergoing isolated mitral valve replacement, 1-year mortality after biologic valve replacement was 26.3% compared to 20.3% for mechanical valve replacement.

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Only three variables independently predicted the implantation of a biological or a mechanical prosthesis. Compared to bioprostheses, mechanical prostheses were less commonly implanted in patients with increased age (OR: 0.64 for every 10 years; 95% CI: 0.561 - 0.733), and in patients with a history of cancer (OR: 0.72; 95% CI: 0.526 - 0.979), but were more commonly utilized in mitral valve replacements (OR: 1.60; 95% CI: 1.289 - 1.996).

Multivariable analysis of 1-year mortality predictors is presented in Table 2. Bioprosthesis use was independently associated with 1-year mortality; the risk of death was increased by 30% (hazard ratio: 1.298 [1.011 - 1.665]; p = 0.0406). The hazard ratio was significantly higher in patients < 65 years of age (1.620 [1.123-2.339]) but not in patients ≥ 65 years of age (0.845 [0.596-1.199]). Kaplan-Meier 1-year mortality estimates were 28.4% in the bioprosthesis group and 19.7% in the mechanical prosthesis group (p < 0.001) (Figure 2). After covariate adjustment, 1-year mortality estimates for biologic and mechanical prostheses were 24.7% and 20.5%, respectively (p = 0.0362).

DISCUSSION

In the present study, 1,467 patients received valve prostheses during the acute phase of IE with 37% receiving biologic valve replacement and 63% a mechanical prosthesis. Both in-hospital and one-year mortality were higher in the bioprosthesis group. The higher mortality associated with bioprosthesis extended beyond the in-hospital acute phase of IE, and was independently associated with 1-year mortality in multivariable analysis. These results have relevance to current clinical practice, as biologic valve replacements were used in approximately 60% of valve replacement surgeries for IE in the United States from 2002 to 2008.[12]

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A few randomized trials have compared the outcome of biological versus mechanical prostheses, but none have included patients with IE. [13-15] In a Veterans' Administration trial involving 575 patients undergoing single aortic or mitral valve replacement randomized to receive a biological or mechanical valve, the 15-year mortality after aortic valve replacement was higher with a bioprosthesis than mechanical prosthesis, but not after mitral valve replacement.[14] Bloomfield et al. randomized 533 patients to biological or mechanical prosthesis, and there was a non significant trend toward higher mortality after 12 years with the bioprosthesis.[13] However, in a meta-analysis of three trials, 5-year and 11-year mortality were not statistically different between the two types of prosthetic valves.[16]

Other observational studies have compared the results of biologic or mechanical valve prosthesis for IE. In a previous study of 185 patients who received a valve prosthesis during the acute phase of IE, the 4-year mortality was higher in the bioprosthesis group.[17] In a small study of patients undergoing aortic valve replacement for aortic valve IE, 5-year mortality of patients who received biologic replacements (bioprostheses or homografts) was two-fold higher than for patients who received mechanical valve replacement, yet the increased mortality was evident only in patients less than 65 years of age.[18] Other studies have found no significant difference in mortality for biologic compared to mechanical valve replacement, but a higher rate of reoperation in younger patients who received biologic prosthesis.[19, 20] In a recent, retrospective study of patients on dialysis with IE who underwent valve surgery, no difference in longer term mortality was evident between type of valve prosthesis.[21] However, this cohort included patients treated with surgery beyond the acute phase of IE and the very high one-year mortality rate may have overshadowed any valve-related effect.[21]

In the current study, the increased in-hospital and 1-year mortality associated with biologic valve replacement was evident only in patients younger than 65 years of age. This

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early, increased mortality in younger patients was a surprising finding. Furthermore, the odds ratio associated with bioprosthetic valve type was modest relative to other variables related to 1-year mortality. Although it is unlikely that biologic prostheses had valve degeneration or failure within 1-year follow up, data regarding post-operative echocardiographic assessment of the prostheses were not available. The selection of mechanical or biologic prosthetic valve in the setting of IE involves multiple considerations, including surgeon's preference and experience, size and expected hemodynamics of the prosthetic valve, patient's predicted longevity and valve durability, and risk of bleeding complications related to long-term anticoagulation. Although biologic valve replacement remained statistically associated with higher mortality after adjustment for certain chronic medical conditions, other variables which may have influenced type of valve prosthesis were not available for analysis in this study. Implantation of a biologic prosthesis in a younger patient may reflect other comorbid condition with reduced expected survival. On the other hand, among patients > 65 years of age, other medical conditions may be a greater determinant of mortality than the type of prosthesis implanted. The low C-statistic for the survival model may also indicate that baseline clinical characteristics associated with the acute IE episode are NOT strongly associated with 1 year survival in patients treated with surgery. Previous survival analyses have focused largely on in-hospital or shorter term mortality, but intermediate term mortality may be related to other factors not captured at baseline.

This study has several other limitations. Since this is an observational study, the results are subject to selection bias such that unidentified variables may have influenced surgical decision-making regarding the type of prosthesis implanted. We could not ascertain whether in-hospital or 1-year mortality was due to a mechanical cardiac, infectious, or unrelated cause. Data regarding the use of anticoagulation after valve replacement and relapse of IE were not collected in this study, yet may have influenced outcome.

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In conclusion, in a large, contemporary cohort of patients undergoing valve replacement surgery for active IE, bioprosthetic valve replacement was associated with higher in-hospital and 1-year mortality, particularly in patients younger than 65 years of age. Further studies are needed to determine factors related to type of prosthesis implanted in the setting of active IE and the valve-related outcome of these interventions.

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References

1. Que YA, Moreillon P. Infective endocarditis. *Nat Rev Cardiol* 2011;**8**:322-36
2. Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: Three successive population-based surveys. *J Am Coll Cardiol* 2012;**59**:1968-76
3. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The international collaboration on endocarditis-prospective cohort study. *Arch Intern Med* 2009;**169**:463-73
4. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The task force on the prevention, diagnosis, and treatment of infective endocarditis of the european society of cardiology (ESC). Endorsed by the european society of clinical microbiology and infectious diseases (ESCMID) and the international society of chemotherapy (ISC) for infection and cancer. *Eur Heart J* 2009;**30**:2369-13
5. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease): Endorsed by the society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, and society of thoracic surgeons. *Circulation* 2008;**118**:e523-661
6. Newton S, Hunter S. What type of valve replacement should be used in patients with endocarditis? *Interact Cardiovasc Thorac Surg* 2010;**11**:784-8

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7. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Early lessons from the international collaboration on endocarditis investigation. *Infect Dis Clin North Am* 2002;**16**:255-72, vii

8. Fowler VG, Jr., Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: A consequence of medical progress. *JAMA* 2005;**293**:3012-21

9. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633-8

10. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: A reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;**137**:791-7

11. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: Importance of non-nosocomial acquisition. *Ann Intern Med* 2009;**150**:586-94

12. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: A simplified risk scoring system. *J Thorac Cardiovasc Surg* 2011;**141**:98-106 e101-2

13. Bloomfield P, Wheatley DJ, Prescott RJ, et al. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* 1991;**324**:573-9

14. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: Final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000;**36**:1152-8

15. Vallejo JL, Gonzalez Santos JM, Albertos J, et al. [Long-term experience with multivalve replacement with the Medtronic-Hall mechanical prosthesis]. *Rev Esp Cardiol* 1990;**43**:610-8

ACCEPTED MANUSCRIPT

16. Kassai B, Gueyffier F, Cucherat M, et al. Comparison of bioprosthesis and mechanical valves, a meta-analysis of randomised clinical trials. *Cardiovasc Surg* 2000;**8**:477-83

17. Reul GJ, Sweeney MS. Bioprosthetic versus mechanical valve replacement in patients with infective endocarditis. *J Card Surg* 1989;**4**:348-51

18. Nguyen DT, Delahaye F, Obadia JF, et al. Aortic valve replacement for active infective endocarditis: 5-year survival comparison of bioprostheses, homografts and mechanical prostheses. *Eur J Cardiothorac Surg* 2010;**37**:1025-32

19. Moon MR, Miller DC, Moore KA, et al. Treatment of endocarditis with valve replacement: The question of tissue versus mechanical prosthesis. *Ann Thorac Surg* 2001;**71**:1164-71

20. Wos S, Jasinski M, Bachowski R, et al. Results of mechanical prosthetic valve replacement in active valvular endocarditis. *J Cardiovasc Surg (Torino)* 1996;**37**:29-32

21. Leither MD, Shroff GR, Ding S, et al. Long-term survival of dialysis patients with bacterial endocarditis undergoing valvular replacement surgery in the United States. *Circulation* 2013;**128**:344-51

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Figure 1 - Disposition of subjects enrolled in the ICE-PCS cohort

Figure 2 - One-year covariate-adjusted survival according to the type of valve prosthesis (Kaplan-Meier curves)

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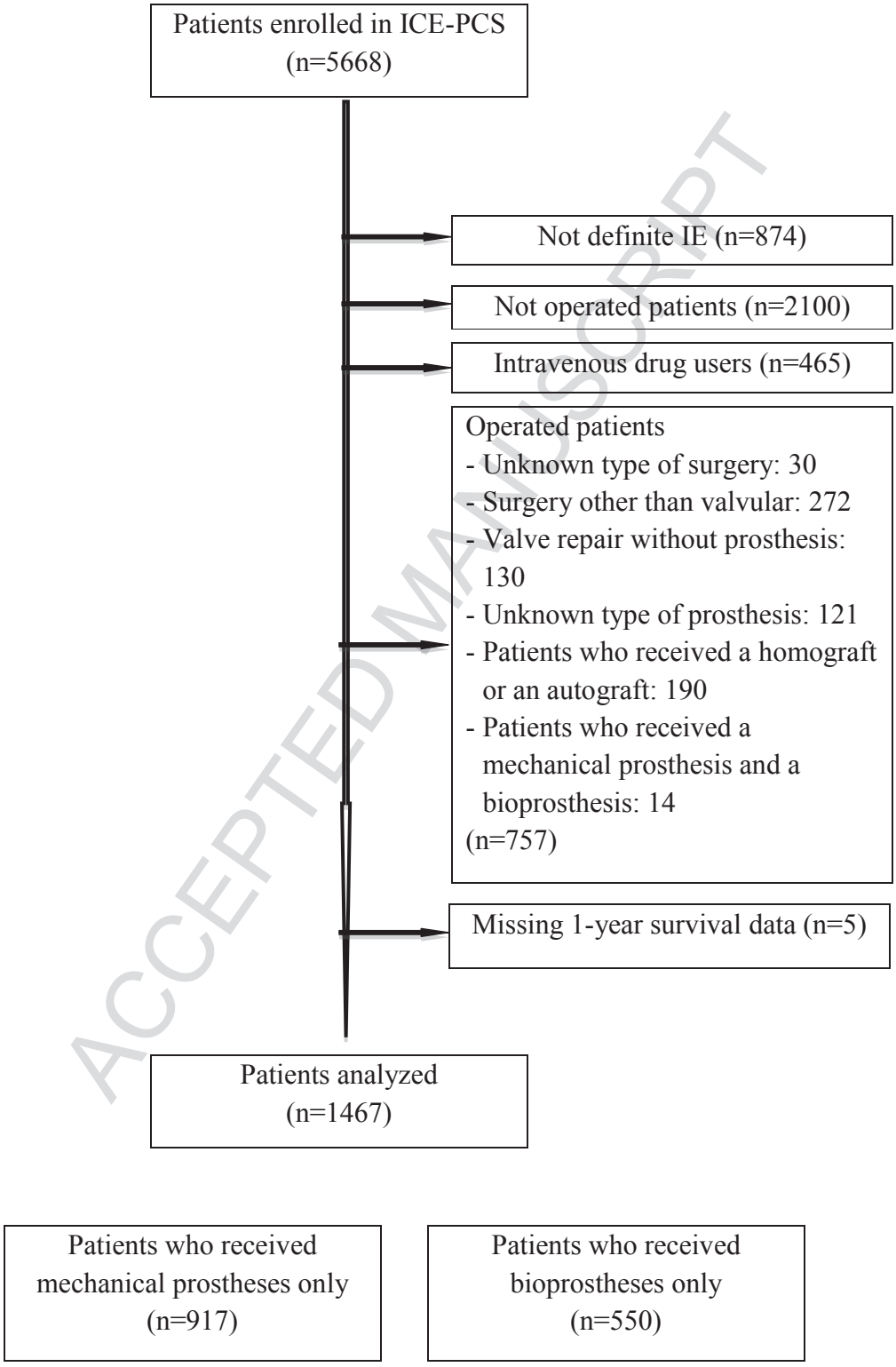

Fig. 1

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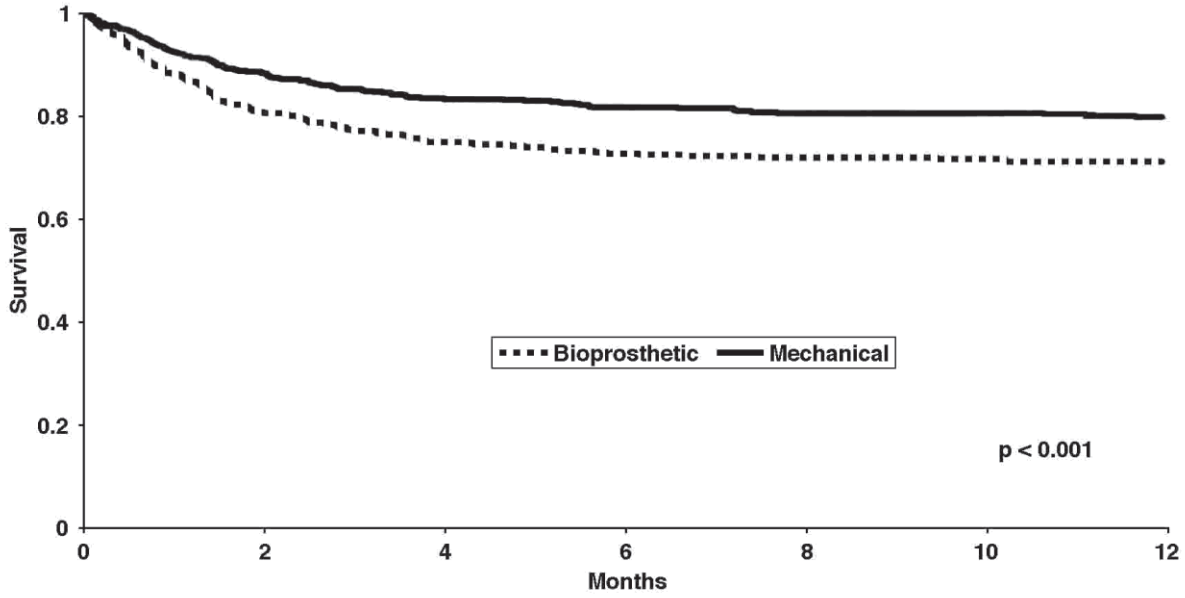

Fig. 2

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Table 1 - Comparison of patients who received biological or mechanical prostheses

Variable	Level	Overall		Mechanical		Bioprosthetic		P-value
		N	%	N	%	N	%	
Total		1467	100	917	62.5	550	37.5	
Age < 65 years old		950	64.8	682	71.8	268	28.2	<.0001
Age ≥ 65 years old		517	35.2	235	45.4	282	54.6	
Age (N=1466)	Mean	1466	56.63	917	53.62	549	61.65	<.0001
	STD		15.66		15.16		15.21	
Gender (N=1465)	Men	1053	71.88	665	72.68	388	70.55	0.3794
Region (N=1467)	North America	199	13.57	82	8.94	117	21.27	
	South America	157	10.70	69	7.52	88	16.00	
	Australia/New Zealand/Africa	227	15.47	156	17.01	71	12.91	<.0001
	Europe	830	56.58	571	62.27	259	47.09	
	Asia/Mid East	54	3.68	39	4.25	15	2.73	

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Medical history							
History of cancer (N=1439)		106	7.37	54	5.98	52	9.70	0.0090
Mild renal insufficiency (N=637)		51	8.01	25	6.41	26	10.53	0.0622
Moderate or severe renal disease or haemodialysis dependent (N=1467)		88	12.61	39	9.49	49	17.07	0.0030
Previous IE episode (N=1460)		123	8.42	65	7.13	58	10.58	0.0213
Known native valve disease (N=1430)		472	33.01	312	35.14	160	29.52	0.0285
Valve status at beginning of episode (N=1466)								
Aortic valve	Native	1134	77.35	726	79.26	408	74.18	
	Mechanical prosthesis	142	9.69	105	11.46	37	6.73	<.0001
	Bioprosthesis	122	8.32	30	3.28	92	16.73	
	Other	66	4.64	53	6.00	13	2.36	
Mitral valve	Native	1225	83.56	740	80.70	485	88.34	
	Mechanical prosthesis	132	9.00	106	11.56	26	4.74	<.0001
	Bioprosthesis	30	2.05	11	1.20	19	3.46	

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	Other	79	5.39	60	6.54	19	3.46	
Tricuspid valve	Native	1394	95.09	862	94.10	532	96.73	
	Mechanical prosthesis	4	0.27	2	0.22	2	0.36	0.0118
	Bioprosthesis	4	0.27	1	0.11	3	0.55	
	Other	64	4.37	51	5.57	13	2.36	
Pulmonic valve	Native	1405	95.84	870	94.98	535	97.27	
	Mechanical prosthesis	2	0.14	0	0.00	2	0.36	0.0084
	Other	59	4.02	46	5.02	13	2.36	
	Present IE							
Health care-associated IE (N=1467)		295	20.11	154	16.79	141	25.64	<.0001
Type of IE (N=1405)	Native	1025	72.03	653	74.04	372	68.76	0.0938
	Prosthetic	380	26.70	218	24.72	162	29.94	
Location of vegetation (N=1371)	No vegetation	101	7.32	54	6.24	47	9.14	0.0200
	Left heart only	1220	88.41	782	90.30	438	85.21	

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	Right heart only	22	1.59	8	0.92	14	2.72	
	Both left and right heart	28	2.03	16	1.85	12	2.33	
Fever > 38° C (N=1344)		1169	86.98	759	89.82	410	82.16	<.0001
Worsening of old murmur or new murmur (N=1467)		870	59.30	587	64.01	283	51.45	<.0001
Elevated C-reactive protein (N=1296)		983	75.85	644	77.87	339	72.28	0.0238
Microorganisms (N=1467)								
Staphylococcus aureus		267	18.20	160	17.45	107	19.45	0.3350
Coagulase negative staphylococci		177	12.07	100	10.91	77	14.00	0.0781
Viridans group streptococci		273	18.61	188	20.50	85	15.45	0.0162
Group D streptococci		122	8.32	81	8.83	41	7.45	0.3546
Enterococcus		147	10.02	74	8.07	73	13.27	0.0013
HACEK		17	1.16	9	0.98	8	1.45	0.4124
Gram negative rods		37	2.52	21	2.29	16	2.91	0.4642
Culture negative		143	9.75	98	10.69	45	8.18	0.1173
Echocardiography								

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New regurgitation (N=1457)	1127	78.26	728	81.16	399	73.48	0.0006
Intracardiac vegetations (N=1461)	1277	88.43	810	90.00	467	85.85	0.0168
Paravalvular complications (N=1459)	516	35.78	311	34.59	205	37.75	0.2253
Surgery							
Aortic valve surgery (N=1465)	976	66.62	594	64.85	382	69.58	0.0629
Mitral valve surgery (N=1464)	773	52.80	512	55.90	261	47.63	0.0022
Complications							
Embolisation (N=1448)	324	22.38	217	24.06	107	19.60	0.0484
Intracardiac abscess (N=1453)	377	25.95	212	23.40	165	30.16	0.0044
Persistent positive blood cultures (N=1446)	91	6.29	46	5.09	45	8.29	0.0155
In-hospital mortality (N=1466)	241	16.44	128	13.96	113	20.58	0.0009
One-year mortality (N=1467)	291	19.84	152	16.58	139	25.27	<.0001

IE: infective endocarditis; N=: number of patients for whom information is available; Health care-associated IE: inpatient, hospital acquired infection or health care related infection, non-hospital acquired (e.g. hemodialysis, outpatient chemotherapy, home intravenous antibiotics)

No significant difference between the two groups for the following parameters:

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- Medical history: chronic pulmonary disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, endocavitary device, diabetes mellitus, end organ damage, peptic ulcer disease, liver disease, connective tissue disease, hemiplegia, dementia, HIV infection
- Complications: stroke, congestive heart failure, mycotic aneurysm

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Table 2 - Parameters independently influencing 1-year mortality (multivariable analysis)

Parameter	Hazard ratio	95% confidence limits	p-value
Biological vs. mechanical prosthesis	1.298	1.011 - 1.665	0.0406
Age in ten-year intervals	1.278	1.164 - 1.404	<.0001
Type of IE: prosthetic valve	1.312	1.012 - 1.700	0.0404
Elevated C-reactive protein	0.681	0.520 - 0.891	0.0050
Diabetes mellitus	1.461	1.110 - 1.922	0.0069
Haemodialysis-dependent	2.278	1.514 - 3.428	<.0001
Viridans group streptococci	0.577	0.381 - 0.875	0.0096
Healthcare-associated IE	1.430	1.082 - 1.889	0.0118
Mitral valve vegetation	1.542	1.217 - 1.956	0.0003
Congestive heart failure	1.681	1.322 - 2.139	<.0001
Intracardiac abscess	1.697	1.318 - 2.184	<.0001
Persistent positive blood cultures	1.575	1.080 - 2.298	0.0184
Europe vs. other regions	1.869	1.411 - 2.476	<.0001

C-index = 0.491

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Highlights

- In a large, contemporary cohort of 1,467 patients
- undergoing biological (37% of patients) or mechanical (63% of patients) valve replacement surgery for definite active infective endocarditis,
- bioprosthetic valve replacement was independently associated with higher in-hospital and 1-year mortality, particularly in patients younger than 65 years of age.

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