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Characteristics and prognosis of patients with left-sided native bivalvular infective endocarditis

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ABSTRACT

Background: Most cases of left-sided native valve infective endocarditis (IE) involve a single valve and little is known concerning IE that simultaneously affects both the aortic and mitral valves.

Methods: We aimed to determine the characteristics, identify the prognostic factors, and define the impact of early surgery for patients with left-sided native bivalvular IE. This analysis included 1,340 consecutive patients presenting with definite acute left-sided native valve IE in a two-center cohort study.

Results: A bivalvular involvement was present in 257 patients(19%). Patients with bivalvular IE had more embolic events($p=0.044$), congestive heart failure($p=0.016$), vegetations, and perivalvular complications(both $p<0.001$) than those with monovalvular IE. Early surgery was more frequent for patients with bivalvular IE ($p<0.001$). 30-day mortality was higher for patients with bivalvular IE than those with monovalvular IE (24.5% vs. 17.6%; $p=0.008$), even after adjustment (OR[95% CI]:1.86[1.26-2.73]; $p<0.001$). Estimated 10-year survival was 70±1% for monovalvular IE and 59±3% for bivalvular IE($p=0.002$). Bivalvular IE was still associated with mortality following multivariable Cox analysis, after adjustment for covariates including age, neurological events, congestive heart failure, Staphylococcus spp. infection, perivalvular complications, and early surgery (HR[95%CI]:1.70[1.31-2.11], $p<0.001$). Early surgery was associated with increased survival for patients with bivalvular IE (79±4% vs. 35±6%, $p< 0.001$).

Conclusions: Bivalvular involvement is frequent in left-sided native valve IE, is associated with more embolic events and congestive heart failure than monovalvular IE, and patients are at a high risk of death. Early surgery is associated with improved survival and should be systematically discussed in the absence of contraindication.

Keywords: infective endocarditis; bivalvular endocarditis; mitroaortic endocarditis; native valve endocarditis; surgery; prognosis

SUMMARY

In left-sided native valve infective endocarditis (IE), bivalvular involvement is frequent (19%) and is associated with more embolic events and congestive heart failure than isolated aortic or mitral IE. Bivalvular IE is an independent predictor of 30-day mortality and long-term mortality. Early surgery for patients with mitroaortic IE is independently associated with reduced 30-day and long-term mortality and should be widely considered in the absence of contraindication to improve outcomes.

INTRODUCTION

Infective endocarditis (IE) is a deadly disease(1,2). Despite advances in diagnosis and surgical management, IE is still associated with high mortality and severe complications(1-5). The epidemiology of IE has significantly changed over the years and its diagnosis is more common now than in the past(5). This higher frequency of patients with IE is partially due to an increase in staphylococcus(6) and healthcare-associated IE(7), as well as the advent of new predisposing factors, such as the presence of prosthetic valves or intracardiac materials, hemodialysis, immunodeficiency, the increased use of injectable treatment, and, most importantly, the aging population, with an increasing burden of degenerative diseases(8,9). Most left-sided native valve IE cases involve a single valve and little is known concerning patients with IE that simultaneously affects both the aortic and mitral valves. Only a few small series(10,11) focused on mitroaortic endocarditis have been studied. These studies, which enrolled a limited number of patients, reported more heart failure in cases of bivalvular involvement(10), but good in-hospital and 10-year survival after surgery(11). We thus conducted a larger-scale study to describe the characteristics and assess the prognosis of mitroaortic endocarditis to improve the management and outcomes of such patients. Indeed, the prognosis is more likely to be poor in patients with bivalvular than monovalvular left-sided IE and these patients may require early surgery.

This registry, focusing on a large series of consecutive patients with definite acute IE, according to the Duke criteria, enrolled between 1990 and 2017 in two French tertiary centers (Amiens and Marseille), was retrospectively analyzed to determine clinical and echocardiographic characteristics, identify prognostic factors, and define the impact of early surgery for patients with left-sided native bivalvular IE.

MATERIAL AND METHODS

Inclusion and Exclusion Criteria

This study was conducted in the departments of cardiology of two university-affiliated tertiary care hospitals for adults in France (Amiens and Marseille), which are referral centers for IE in their regions. A specific database was created to collect information on patients with a diagnosis of suspected IE. We reviewed all consecutive patients with definite acute IE diagnosed at each center, according to the Duke criteria(12,13), from January 1990 to September 2017 (n=2,421). The exclusion criteria were prosthetic valve IE(n=680), isolated pacemaker or defibrillator lead IE(n=299), and right-sided IE (n=102). The present analysis was based on 1,340 patients with native aortic and/or mitral valve IE: 582 with isolated native aortic valve IE, 501 with isolated native mitral valve IE, and 257 with bivalvular IE. The study was approved by an independent ethics committee and conducted in accordance with institutional policies, national legal requirements, and the tenets of the revised Declaration of Helsinki.

Baseline data and echocardiography

The following data were collected at admission and during the hospital stay: age, sex, hypertension, diabetes, history of myocardial infarction, prior IE, comorbidity included in the Charlson index, and causative pathogen (determined by blood cultures, serology testing, valve culture, or polymerase chain reaction on a valve specimen, according to international guidelines[5]). Transthoracic and transesophageal echocardiographic studies were performed in all patients (in the absence of contraindication) by experienced physicians during the acute phase of IE and the data from the first echocardiographic study were collected as previously described(14). Briefly, echocardiographic data included the presence, localization (aortic, mitral, or both), mobility, and maximal length of vegetations (vegetation length was measured in various planes and the maximal length was used), and the presence and localization of perivalvular complications, defined as an abscess, pseudoaneurysm, or fistula, according to accepted definitions(5). The severity of valvular regurgitation was assessed according to international guidelines(5).

Monovalvular IE was defined as the presence of a vegetation and/or perivalvular complication on a single valve (i.e. mitral or aortic) and bivalvular IE as the presence of a vegetation, perforation, and/or perivalvular complication on both the mitral and aortic valves. The following acute clinical events present at admission or occurring during hospitalization were also recorded: heart failure, neurological events, and peripheral embolism. The severity of heart failure was assessed according to the New York Heart Association (NYHA) classification with stage III and IV corresponding to congestive heart failure. The diagnosis of embolism was based either on clinical signs or on data derived from non-invasive procedures (cerebral and thoracoabdominal computed tomography performed in the absence of severe renal insufficiency or hemodynamic instability). A neurological event was defined by the development of a confirmed ischemic stroke, hemorrhagic stroke, cerebral abscess, or a cerebral mycotic aneurysm and was not included in the count of embolic events. Clinical decisions concerning medical management and referral for surgery were made by the cardiac team with the approval of the patient's referring cardiologist, in accordance with current practice guidelines(5).

Follow-up and Endpoints

The median follow-up was 65.0(interquartile range:37-115) months (mean 85±78 months). Patients were followed by clinical consultations and echocardiography in the outpatient clinics of the two tertiary centers. A few patients were followed in public hospitals or private practices by referring cardiologists working in collaboration with the tertiary centers. During follow-up, events were ascertained by direct patient interview and clinical examination and/or repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. Given the retrospective nature of the study, informed consent was waived and all of the patients agreed to participate in the study when contacted for follow-up. Early surgery was defined as surgery performed within 30 days after the diagnosis of IE(14,15). Emergency surgery was defined as surgical intervention performed during the first 24 h after the diagnosis of IE, urgent surgery as surgical intervention between 24 h and seven days after the diagnosis, and elective surgery as surgery more than seven days after the diagnosis of IE(5). Patients operated on after more than 30 days following the diagnosis were considered to be medically managed. The primary endpoint was 30-day mortality and the secondary endpoint was long-term mortality.

Statistical analysis

SPSS version 18.0 software (IBM, Armonk, New York) was used for statistical analysis. The study population was divided into two groups according to the localization of IE: monovalvular IE or bivalvular IE. Patients with bivalvular IE were then compared according to their vital status and management (medical or surgical). Continuous variables are expressed as the mean value±one standard deviation or the median (25th and 75th percentiles) and categorical variables as frequency percentages and counts. The relationship between baseline continuous variables and the groups was explored by one-way ANOVA tests (for normally distributed variables) or Kruskal-Wallis tests (for non-normally distributed variables). Pearson's χ^2 statistic or Fisher's exact test were used to examine the association between the groups and baseline categorical variables. Estimated survival rates ± one standard error were estimated according to the Kaplan Meier method and compared using two-sided log-rank tests. Factors independently associated with bivalvular endocarditis and those associated with 30-day mortality were investigated using multivariable logistic regression analyses.

Multivariable analyses of long-term all-cause mortality were performed using Cox proportional hazards models. We did not use model-building techniques but entered covariates considered to be of potential prognostic impact, on an epidemiological basis, into the model. These covariates were: age, sex, the Charlson comorbidity index (not including age), diabetes, prior IE, neurological events, peripheral embolism, congestive heart failure, Staphylococcus infection, perivalvular complication, left ventricular ejection fraction (LVEF)<50%, and early surgery. The limit of statistical significance was $p<0.05$. All tests were two tailed.

RESULTS

Baseline characteristics

Of the 1,340 patients included (73.5% males, mean age 61.9 years), 1,083 had monovalvular IE (582 aortic and 501 mitral) and 257 bivalvular endocarditis. Vegetations were visualized in 84.5% of cases and a perivalvular complication was identified in 19.2% of cases. Neurological events were observed in 236 patients (17.6%), embolic events (after exclusion of isolated neurological events) in 529 patients (39.5%), and 383 patients (28.6%) were in NYHA class III or IV. Streptococcus spp. were the microorganism responsible for IE in 32.9% of patients and Staphylococcus spp were isolated in 25.2% of cases. Early surgery was performed in 566 patients (42.2%), with a mean interval between admission and surgery of 10±8 days. Emergency surgery was performed on 85 patients (15%) and urgent surgery on 265 (46.8%), whereas surgery was performed on 216 patients (38.2%) more than seven days after the diagnosis of IE (Table 1).

Patients with bivalvular IE had more embolic events ($p=0.017$) and congestive heart failure ($p=0.016$) than those with monovalvular IE. Streptococcus bovis ($p=0.012$) and Enterococcus spp. ($p=0.009$) were more frequently responsible for bivalvular IE, whereas staphylococcus aureus was more common in monovalvular IE (p<0.001). Vegetations, perivalvular complications, and perforations were more frequently observed in bivalvular IE (all p<0.001). Early surgery (p<0.001) and, in particular, urgent surgery (p=0.003), were more frequent for patients with bivalvular IE. Age, gender, comorbidity, prior IE, neurological events, creatinine levels, and white blood cell counts were comparable between the two groups (Table 1).

Factors associated with bivalvular endocarditis

Following multivariate logistic regression analysis, bivalvular IE was associated with congestive heart failure (adjusted odds ratio [OR]:1.50, 95% confidence interval [CI]:1.04-2.16, p=0.029), IE due to streptococcus bovis (OR[95%CI]:1.52[1.01-2.15], p=0.023), the presence of a perivalvular complication (OR [95%CI]:1.37[1.02-2.06], p=0.044), and LVEF <50% (OR[95%CI]:1.63 [1.11-2.40], p=0.013) (Table 2).

Outcome analysis

30-day mortality

The 30-day mortality rate was 19.0% for the total population (n=254). Thirty-day mortality was higher for patients with bivalvular IE than those with monovalvular IE (24.5% vs. 17.6%, p=0.008). Following multivariable logistic regression analysis, bivalvular IE was still an independent predictor of 30-day mortality (adjusted OR[95%CI]:1.86[1.26-2.73], p<0.001) (Table 3).

Long-term mortality

During follow-up, 408 deaths (30.5%) occurred. Estimated 10-year survival was 70±1% for monovalvular IE and 59±3% for bivalvular IE (Log rank p=0.002). Among patients with single-valve IE, there were no differences in terms of survival between aortic IE and mitral IE

(70±2% vs. 67±3%, p=0.76). Mortality was higher for bivalvular IE than isolated aortic valve IE (Log rank p=0.006) or isolated mitral valve IE (Log rank p=0.017) (Figure 1A).

Following multivariable Cox analysis, bivalvular IE was still associated with mortality after adjustment for age, sex, the Charlson comorbidity index, diabetes, prior IE, neurological events, peripheral embolism, congestive heart failure, Staphylococcus spp. infection, perivalvular complication, LVEF <50%, and early surgery (adjusted HR[95%CI]:1.70[1.31-2.11], p<0.001) (Table 4). Among single-valve IE patients, there was no difference in terms of survival between aortic valve IE and mitral valve IE after adjustment (p=0.26). Mortality was higher for bivalvular IE than isolated aortic (p=0.004) or mitral valve IE (p=0.002) (Figure 1B).

Outcomes and management of bivalvular endocarditis

30-day mortality

The 30-day mortality rate for patients with bivalvular IE was 24.5% (n=63). Following multivariate logistic regression analysis, the independent predictors of 30-day mortality were neurological events (adjusted OR[95%CI]:2.31[1.10-5.50], p=0.041), congestive heart failure (adjusted OR[95%CI]:2.25[1.16-4.30], p=0.032), and perivalvular complication (adjusted OR[95%CI]:1.92[1.01-4.52], p=0.040), whereas early surgery was associated with better 30-day survival (adjusted OR[95%CI]:0.27[0.12-0.50], p<0.001) (supplementary Table S1).

Long-term mortality

During follow-up, 101 patients (38.3%) with bivalvular IE died. Following multivariable Cox analysis, the independent predictors of long-term mortality of patients with bivalvular IE were perivalvular complication (adjusted HR[95%CI]:2.33[1.33-4.08], p=0.003), the Charlson index (adjusted HR[95%CI]:1.44[1.19-1.72], p<0.001), and LVEF<50% (adjusted HR[95%CI]:2.24 [1.16-4.37], p=0.017) (Supplementary Table S2).

Management

Among the 257 patients with bivalvular IE, 123 were initially medically managed and 134 (52.1%) underwent early surgery (22[16.4%] during the first 24 hours, 67[50%] between days 2 and 7, and 45[33.6%] between days 7 and 30). Patients who were initially medically managed were older (p=0.013), more often diabetic (p=0.019), had a higher Charlson index (p=0.024), fewer vegetations, and fewer perivalvular complications (p<0.001) than those who underwent early surgery (supplementary Table S3). Early surgery was associated with better 10-year survival than medical management of patients with bivalvular IE (79±4% vs. 35±6%, Log rank p<0.001) (Figure 2A), even after adjustment (Adjusted HR[95%CI]:0.22 [0.12-0.30], p<0.001) (Supplemental Table S2, Figure 2B) and after exclusion of patients with neurological events (Adjusted HR[95%CI]:0.18[0.14-0.33], p<0.001). The distribution of surgical interventions in the early surgery group is reported in supplementary Table S4. There were no differences in terms of 30-day and long-term survival regardless of the type of surgical intervention (p=0.95 and p=0.45 respectively).

Of the 123 patients who were initially managed medically, 50 (43%) underwent surgery during follow-up (mean delay of 5±7months, 56% within 3 months following IE diagnosis). There was no difference in survival between patients who underwent surgery after 30 days and those who were medically managed during the full follow-up period (44±1% vs. 32±6%, Log rank p=0.52), even after adjustment (p=0.07).

DISCUSSION

This cohort study of 1,340 patients with left-sided native valve IE is, to our knowledge, the first large-scale study specifically devoted to the comparison of bivalvular and monovalvular IE. The main findings of our study are the following: (i) bivalvular involvement occurs frequently in left-sided native IE (19%) and is associated with more embolic events and congestive heart failure than monovalvular IE, (ii) bivalvular IE is more often related to streptococcus spp. or enterococcus spp. infection than monovalvular IE, (iii) bivalvular IE is an independent predictor of 30-day mortality and long-term mortality, in addition to established predictors of outcome such as age, comorbidity, heart failure, staphylococcus infection, perivalvular complications, and neurological events, (iv) patients with mitroaortic IE presenting with a perivalvular complication have a higher risk of intra-hospital and long-term mortality; and (v) early surgery is associated with improved survival in patients with left-sided native bivalvular IE (Figure 3).

In our study, vegetations were more frequent in bivalvular than single-valve IE (95% vs.82%), as previously reported in patients with multiple valve endocarditis (left or right-sided) (16).Perivalvular complications and perforation were also more common in patients with a bivalvular IE, which is consistent with previous reports(16,17) and understandable from a pathophysiological perspective. Indeed, left-sided bivalvular lesions can result from simultaneous seeding of bacteria on previously damaged valves. However, the second valve involvement is secondary to the infection of the first valve in most cases, which is usually the aortic valve(18). The most common mechanism of bivalvular left-sided IE involves infection of the mitral valve following the formation of a "jet lesion" due to aortic regurgitation(19). The regurgitation jet can be directed towards the mitral valve and induce a vegetation, perforation, or pseudoaneurysm of the anterior mitral leaflet. A second important cause may be infection, which spreads into the adjacent periaortic fibrous tissue by the formation of an abscess, resulting in secondary destruction of the mitral anulus with or without associated mitral regurgitation(20). This form of mitroaortic IE seems more severe as, in our study, perivalvular complication (present in 20% of patients with bivalvular IE) were independently associated with increase 30-day and long-term mortality in patients with a bivalvular involvement. Another less-described mechanism of mitral valve secondary infection is called 'mitral kissing vegetation': large aortic vegetations prolapse into the left ventricular outflow tract during diastole and contact the anterior mitral leaflet, thus causing secondary infection(18). Aortic IE is therefore a predisposing factor for secondary mitral-valve infection, whereas primary mitral IE does not specifically predispose patients to secondary aortic involvement.

Selton-Suty et al.(17) reported that 66% of patients with multivalvular IE from a 1999 French database of 88 patients with definite IE with multivalvular location had a Streptococcal infection, whereas only 12% had a Staphylococcal infection. Accordingly, we found a higher prevalence of Streptococci (especially for the bovis type) and Enterococci and a lower prevalence of Staphylococci (especially for the aureus type) in patients with bivalvular IE than those with single-valve IE. Indeed, the rapidity of structural alterations induced by Staphylococcus leads to early diagnosis and probably does not allow the infection to spread to another valve. In our study, patients with bivalvular IE experienced more embolic events than those with monovalvular IE. This is in accordance with the results of a study by Rohmann et al.(21). Indeed, the potential for embolism is greater when there are vegetations on both the aortic and mitral valves. In this study(21), 10 of the 20 patients with bivalvular IE had an embolic episode. Congestive heart failure was also more common for patients with mitroaortic IE than those with isolated aortic or mitral IE. Kim et al(10), Lopez et al(16) and Selton-Suty et al(17) also reported a higher incidence of heart failure in patients with multivalvular IE, but they did not exclude those with right-sided valve involvement or those with prosthetic valves. In these three studies(10,16,17), there was a trend towards greater 30-day mortality for patients with multivalvular IE relative to patients with monovalvular IE (21% vs. 18%, 30% vs. 28%, and 23% vs. 17%, respectively), which did not reach statistical significance, likely due to the relatively small number of patients. In our cohort, bivalvular IE was associated with an increase of 86% in the relative risk of 30-day mortality after adjustment for covariates of prognostic importance. We also report, for the first time, that these patients have poorer long-term survival than those with single-valve IE. Indeed, after adjustment for age, sex, the Charlson comorbidity index, diabetes, prior IE, neurological events, peripheral embolism, congestive heart failure, Staphylococcus spp., perivalvular complications, LVEF<50%, and early surgery, bivalvular IE was still associated with a 70% increase in the relative risk of long-term mortality.

The frequency of surgery during hospital admission in patients with multivalvular IE is high(16,17). Accordingly, of the 257 patients with bivalvular IE in our study, 134 (52.2%) underwent early surgery and 50(19.5%) underwent delayed surgery. Gilinov et al.(11) reported that 10-year survival was good (73%) in a series of 54 patients with mitroaortic IE who underwent surgery during hospitalization for IE. Accordingly, early surgery in our study was associated with better 30-day survival (85.8% vs. 63.3%) and 10-year survival (79±4% vs. 35±6%) than medical management for patients with bivalvular IE, even after adjustment for established outcome predictors. Nevertheless, surgery was sometimes contraindicated because of a prohibitive operative risk related to severe clinical features and comorbidities. The results of our study show that bivalvular involvement is frequent in left-sided native valve IE and associated with more embolic events and congestive heart failure than monovalvular IE, resulting in a higher risk of death for patients. Since early surgery is associated with improved survival in patients with bivalvular IE, it should be systematically discussed within the endocarditis team in the absence of contraindications and according to the operative risk.

Limitations

This study is subject to the inherent limitations of those based on retrospective follow-up data. We cannot rule out the possibility that our patients may represent a selected cohort from referral centers with more severe disease than that of the average population. However, most IEs in our regions are generally referred to our institutions at least for the initial evaluation and management. In this observational study, the decision to perform surgery was based on the clinical judgement of the medico-surgical team. Thus, there was bias in the selection of therapy. However, a randomized trial comparing surgical and medical strategies has never been performed and would likely be ethically unacceptable in this setting. It is therefore not surprising that several differences in clinical characteristics were observed between the surgical and medical groups. Information on residual heart failure and on changes in LVEF during follow-up were not available in our database. This study was not designed to investigate the impact of the type of surgical procedure on survival. The absence of difference is potentially related to the relatively small number of patients with bivalvular IE who underwent early surgery and to the small number of events in this group of operated patients. Unfortunately, information on associated coronary bypass were not available in our database. Finally, our study focused only on left-sided native valve IE and does not provide data on right-sided multivalvular IE or patients with prosthetic valves. Further specific studies are needed to assess the prognosis of these patients.

CONCLUSION

Bivalvular involvement is frequent in left-sided native valve IE, affecting one fifth of patients, and is associated with more embolic events and congestive heart failure than isolated aortic or mitral IE. Bivalvular IE is an independent predictor of 30-day and long-term mortality, in addition to established predictors of outcome, such as age, comorbidity, heart failure, staphylococcus infection, perivalvular complications, and neurological events. Despite the widespread use of surgery in this context, the prognosis is still dismal. With advances in cardiac imaging, cardiologists should be able to recognize and diagnose endocarditis earlier to prevent the spread of infection to the adjacent valves. Our results also highlight the importance of early echocardiography for patients with bacteremia, in particular that caused by streptococcus spp. or enterococcus spp., which evolve relatively slowly and more often lead to multivalvular alterations. Early surgery for patients with mitroaortic IE is independently associated with reduced 30-day and long-term mortality and should be widely considered to improve outcomes.

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Table 1: Baseline demographic, clinical and biological characteristics of the study population

Variables	Total (n=1340)	Bivalvular endocarditis (n=257)	Monovalvular endocarditis (n=1083)	p value
Patients' characteristics				
Age(years)	61.9±15.4	61.9±15.2	62±14.3	0.913
Male gender (n,%)	985(73.5)	195(75.9)	790(72.9)	0.190
Hypertension (n,%)	473(35.3)	81(31.5)	392(36.2)	0.090
Diabetes mellitus (n,%)	196(14.6)	29(11.3)	167(15.4)	0.186
History of myocardial infarction (n,%)	93(6.9)	17(6.6)	76(7.0)	0.473
Previous endocarditis (n,%)	40(3.0)	7(2.7)	33(3.0)	0.488
Charlson comorbidity index (without age).	1.2±1.4	1.2±1.5	1.2±1.4	0.755
Clinical presentation and complications*				
Neurological event (n,%)				
Embolic events (n,%)**	236(17.6)	48(18.7)	188(17.4)	0.338
NYHA class (n,%)	529(39.5)	117(45.5)	412(38.0)	**0.017**
I-II	957(71.4)	169(65.8)	788(72.8)	**0.016**
III-IV(CHF)	383(28.6)	88(34.2)	295(27.5)	
Biochemistry				
Serum creatinine (µmol/l)	136±120	137±101	131±117	0.579
White blood cells (10^3/ mm^3)	10.9±4.8	10.9±4.9	10.9±4.7	0.984
Microorganism				
Staphylococcus spp (n,%)	338(25.2)	47(18.4)	291(26.1)	**0.001**
Staphylococcus Aureus (n,%)	263(19.6)	31(12.1)	232(21.4)	**<0.001**
Staphylococcus coagulase negative (n,%)	74(5.5)	15(5.8)	59(5.4)	0.452
Streptococcus spp (n,%)	441(32.9)	98(38.1)	343(31.6)	**0.038**
Oral streptococci	221(16.5)	43(16.7)	178(16.4)	0.486
Streptococcus Bovis	220(16.4)	55(21.0)	165(15.2)	**0.012**
Enterococcus spp (n,%)	153(11.4)	41(16.0)	112(10.3)	**0.009**
Other or negative blood culture (n,%)	408(30.5)	71(27.6)	337(31.2)	0.052
Echocardiography				
Vegetation (n,%)	1132(84.5)	244(94.9)	888(82.0)	**<0.001**
Vegetation length (mm)	12±8.3	12.9±7.7	11.8±8.4	0.078
Vegetation length>10 mm (n,%)	696(51.9)	164(63.8)	532(49.1)	**<0.001**
Perivalvular complication (n,%)	258(19.2)	67(26.0)	191(17.6)	**<0.001**
Perforation (n,%)	452(33.7)	153(59.5)	299(27.6)	**<0.001**
LVEF<50% (n,%)	362(27.0)	59(23.0)	303(28.0)	0.059
Treatment and evolution				
Early surgery (n,%)	566(42.2)	134(52.1)	432(39.9)	**<0.001**
Emergency surgery (n,%)	85/566 (15.0)	22/134(16.4)	63/432(14.6)	0.510
Urgent surgery (n,%)	265/566(46.8)	67/134(50.0)	198/432(45.8)	**0.003**
Elective surgery (n,%)	216/566(38.2)	45/134(33.6)	171/432(39.6)	**0.046**
30-day mortality (n,%)	254(19.0)	63(24.5)	191(17.6)	**0.008**
length of stay (days)	36±21	37±25	36±20	0.707

IE recurrence (n,%)	108(8.1)	23(8.9)	85(7.8)	0.318

Normally distributed continuous variables are expressed as mean±1 standard deviation, non-normally distributed continuous variables are expressed as median(25th and 75th percentiles), and categorical variables are expressed as percentages and numbers.
*at admission or occurring during hospitalization**after exclusion if isolated neurological events
Abbreviations:CHF: congestive heart failure, NYHA:New York Heart Association LVEF:left ventricular ejection fraction IE:infective endocarditis

Table 2: Factors independently associated with bivalvular endocarditis by multivariate logistic regression.

Variables	**Bivalvular endocarditis**	
	OR(95% CI)	**p**
Age	1.00(0.99-1.01)	0.87
Male sex	1.14(0.79-1.64)	0.48
Charlson index(without age)	0.93(0.81-1.06)	0.27
Prior endocarditis	0.78(0.31-1.92)	0.59
Bicuspid aortic valve	0.71(0.42-1.41)	0.38
Diabetes	0.85(0.53-1.37)	0.52
Neurological event	1.21(0.80-1.82)	0.26
Embolic event	1.21(0.88-1.67)	0.26
Congestive heart failure	1.50(1.04-2.16)	**0.029**
Staphyloccocus aureus	0.53(0.33-0.91)	**0.041**
Streptococcus bovis	1.52(1.01-2.15)	**0.023**
Enterococcus	1.21(0.75-1.96)	0.44
Vegetation length	1.01(0.99-1.03)	0.20
Perivalvular complication	1.37(1.02-2.06)	**0.045**
Ejection fraction<50%	1.63(1.11-2.40)	**0.013**

OR:odds ratio, CI:confidence interval

Table 3: Multivariate logistic regression for predictors of 30-day mortality

Variables	30-day mortality	
	Multivariate logistic regression	
	OR(95% CI)	**p**
Age	1.02(1.01-1.03)	**0.001**
Male sex	1.13(0.80-161)	0.48
Charlson index(without age)	1.23(1.09-1.39)	**<0.001**
Diabetes	0.96(0.63-1.46)	0.85
Prior endocarditis	0.57(0.18-1.80)	0.31
Neurological event	1.79(1.02-2.50)	**0.014**
Embolic event	0.88(0.23-1.11)	0.47
Congestive heart failure	2.22(1.54-3.20)	**<0.001**
Staphylococcus	1.88(1.33-2.66)	**<0.001**
Perivalvular complication	2.03(1.38-3.01)	**<0.001**
Ejection fraction<50%	1.09(0.76-1.56)	0.64
Bivalvular endocarditis	1.86(1.26-2.73)	**0.002**
Early surgery	0.21(0.16-0.31)	**<0.001**

OR:odds ratio, CI:confidence interval

Table 4: Multivariate Cox analysis for predictors of long-term mortality

Variables	Long-term mortality	
	Multivariate Cox analysis	
	HR(95% CI)	p
Age	1.02(1.01-1.03)	**<0.001**
Male sex	1.04(0.83-1.31)	0.72
Charlson index(without age)	1.23(1.14-1.32)	**<0.001**
Diabetes	0.96(0.73-1.26)	0.77
Prior endocarditis	0.64(0.33-1.24)	0.18
Neurological event	1.08(1.01-1.87)	**0.049**
Embolic event	0.97(0.98-1.19)	0.76
Congestive heart failure	1.78(1.41-2.18)	**<0.001**
Staphylococcus	1.45(1.16-1.82)	**0.001**
Perivalvular complication	1.59(1.23-2.05)	**<0.001**
Ejection fraction<50%	1.09(0.85-1.40)	0.48
Bivalvular endocarditis	1.70(1.31-2.11)	**<0.001**
Early surgery	0.33(0.21-0.37)	**<0.001**

HR:Hazard ratio, CI:confidence interval

FIGURE LEGENDS

Figure 1

Kaplan-Meier (A) and adjusted (B) survival curves according to the localization of the infective endocarditis: isolated mitral, isolated aortic or bivalvular endocarditis

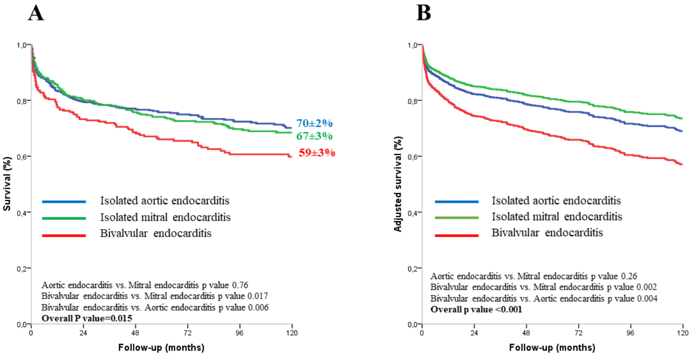
Figure 2

A Kaplan-Meier survival curves and **B** Adjusted survival curves according to the management of patients with bivalvular endocarditis.

Figure 3

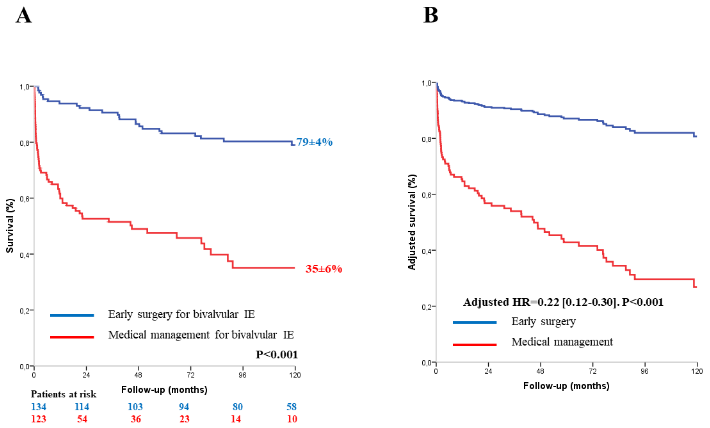
Bivalvular versus monovalvular left-sided native valve endocarditis, summary of the study.

IE:infective endocarditis, HR=hazard ratio, OR:odds ratio



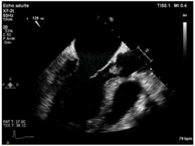
Patients at risk

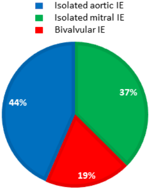
582	409	354	288	221	179
501	343	282	229	180	129
257	171	142	120	96	70


A
Survival (%)
1,0
0,8
0,6
0,4
0,2
0,0
79±4%
35±6%
Early surgery for bivalvular IE
Medical management for bivalvular IE
P<0.001
0
24
48
72
96
120
Follow-up (months)
Patients at risk
134 114 103 94 80 58
123 54 36 23 14 10
B
Adjusted survival (%)
1,0
0,8
0,6
0,4
0,2
0,0
Adjusted HR=0.22 [0.12-0.30]. P<0.001
Early surgery
Medical management
0
24
48
72
96
120
Follow-up (months)

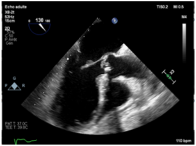
1340 patients with left-sided native valve IE

Monovalvular left-sided native valve IE

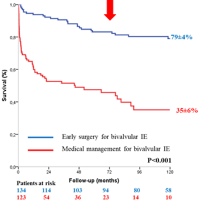




Bivalvular left-sided native valve IE



- **Heart failure** 27.2%
- **Neurological events** 17.4%
- **Perivalvular complications** 17.6%
- **30-day mortality** 17.6%
- **10-year mortality** 30%
- **Early surgery** 39.9%



- **Heart failure** 34.2%
- **Neurological events** 18.7%
- **Perivalvular complications** 26%
- **30-day mortality** 24.5% ↑ OR=1.86
- **10-year mortality** 41% ↑ HR=1.70
- **Early surgery** 52.1%