Infective endocarditis in bicuspid aortic valve and mitral valve prolapse

Running Title: Infective endocarditis in BAV and MVP.

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ABSTRACT

Background: There is little information concerning infective endocarditis (IE) in patients with bicuspid aortic valve (BAV) / mitral valve prolapse (MVP), and IE antibiotic prophylaxis (IEAP) is currently not recommended for these conditions.
Objectives: To describe the clinical and microbiological features of IE in patients with BAV and MVP and compare them with those of IE patients with and without IEAP indication, to determine the potential benefit of IEAP in these conditions.
Methods: This analysis involved 3,208 consecutive IE patients prospectively included in the GAMES registry at 31 Spanish hospitals. Patients were classified as high-risk IE with IEAP indication (high-risk group; n=1,226), low and moderate-risk IE without IEAP indication (low/moderate-risk group; n=1,839), and IE with BAV (n=54) or MVP (n=89).
Results: BAV and MVP patients had a higher incidence of viridans group Streptococci (VGS) IE than high-risk group and low/moderate-risk group patients (35.2% and 39.3% vs 12.1% and 15%, respectively, all $p<0.01$). A similar pattern was seen for IE from suspected odontological origin (14.8% and 18% vs 5.8% and 6%, all $p<0.01$). BAV and MVP patients had more intracardiac complications than low/moderate-risk group (50% and 47.2% vs 30.6%, both $p<0.01$) and similar to high-risk group patients.
Conclusions: IE in patients with BAV and MVP have higher rates of VGS IE and IE from suspected odontological origin than in other IE patients, with a clinical profile similar to that of high-risk IE patients. Our findings suggest that BAV and MVP should be classified as high-risk IE conditions and the case for IEAP should be reconsidered.

Keywords: Endocarditis, Bicuspid aortic valve, Mitral valve prolapse, antibiotic prophylaxis.

Condensed abstract: We sought to describe the clinical and microbiological features of IE in BAV and MVP and compare them with those of IE patients with and without IEAP indication. Data from 3,208 consecutive IE patients were analyzed. When comparing BAV (n=54) and MVP (n=89) with IE patients with (n=1,226) and without (n=1,839) IEAP indication, BAV and MVP exhibited higher incidence of viridans group streptococci IE (35.2% and 39.3% vs 12.1% and 15%, all $p<0.01$) and higher suspected odontological origin (14.8% and 18% vs 5.8% and 6%, all $p<0.01$). BAV and MVP are high-risk IE conditions for which IEAP should be reconsidered.

Abbreviations
IE=infective endocarditis
BAV=bicuspid aortic valve
MVP=mitral valve prolapse
IEAP=infective endocarditis antibiotic prophylaxis
AHA=American Heart Association
ESC=European Society of Cardiology
CHD=congenital heart disease
HF=Heart Failure
VGS=viridans group streptococci

Introduction

Infective endocarditis (IE) is a rare disease with a high in-hospital mortality of 25% to 30% despite early diagnosis and advances in surgical and antibiotic treatments (1). Thus, it is important that efforts are directed towards preventive strategies that reduce the number of patients with IE. Antibiotic prophylaxis for IE (IEAP) is one of the strategies proposed to prevent IE.

IEAP was initially proposed in 1955 (2) and it has evolved over the past 50 years (3-9) founded on expert opinion and small case-control studies (10-14). Based on the risk of IE throughout life and the risk of complications from IE, predisposing cardiac conditions are classified as low-, intermediate- and high-risk, and IEAP was initially recommended for both intermediate and high-risk conditions (8). However, due to the lack of solid data the American Heart Association (AHA) in 2007 (9) and the European Society of Cardiology (ESC) in 2009 (15), restricted the recommendation for IEAP to only high-risk patients.

Bicuspid aortic valve (BAV) and mitral valve prolapse (MVP) are frequent cardiac abnormalities that show a higher incidence of IE than the general population (16-19). BAV and MVP are currently considered intermediate-risk cardiac conditions, and were among the conditions for which IEAP was restricted.

Several studies have shown a nationwide increase in the incidence of IE in individuals at high- and moderate-risk in the United Kingdom (20) and a rise in streptococcal IE in those at moderate-risk in the United States (21), Canada (22), Germany (23) and the Netherlands (24) after the IEAP restriction. Accordingly, there remains controversy regarding the benefits of IEAP and which patients should receive it. Specifically, there is very little information on IE in

intermediate-risk cardiac conditions like BAV and MVP, and data about the potential usefulness of IEAP in individuals with these diseases are limited.

The aim of this study was twofold: first, to describe the clinical and microbiological features of BAV and MVP patients with IE; and second, to compare these features with those of patients with and without IEAP indication, in order to gain insight about the potential usefulness of IEAP to prevent IE in these situations.

Methods

From January 2008 to September 2016, 3,524 consecutive patients with confirmed or possible IE according to the modified Duke criteria were prospectively included in the Spanish Collaboration on Endocarditis–*Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España* (GAMES) registry, at 31 Spanish hospitals (25-30). Of the 31 hospitals participating in the GAMES registry, 24 are tertiary centers with cardiac surgery onsite and 7 are community hospitals. Regional and local ethics committees approved the study and patients gave their informed consent. Multidisciplinary IE teams completed a standardized case report document with each IE episode, which included clinical, microbiological and echocardiographic sections. Patients were classified according to underlying cardiac conditions and IEAP indication. IEAP indications were based on current AHA/ESC recommendations (9,15). Hence, patients with previous IE, prosthetic valves, unrepaired cyanotic congenital heart disease (CHD), repaired CHD with residual defects, and patients with CHD and less than 6 months since surgery, were considered high-risk patients with an established indication of IEAP (high-risk group). IE was considered prosthetic when it occurred in biological or mechanical prostheses or in reconstructed native heart valves.

The remaining low- and moderate-risk patients without an established indication of IEAP constituted the low/moderate-risk group, after excluding those individuals with BAV and MVP (**Figure 1**). Patients with isolated device-related IE (n=316) were excluded from the analysis.

Major IE adverse events considered were heart failure (HF), peripheral embolism, embolic stroke, persistent bacteremia (>7 days) and intracardiac complications. Indication for cardiac surgery was decided by treating IE teams based on ESC recommendations (15,31).

Microbiological data and the suspected portal of entry were recorded prospectively by the participating centers in the GAMES form. Regarding the determination of the causal microorganism, the centers recorded the isolated microorganism in blood cultures or in the surgically removed valve during admission. To consider a microorganism as causal at least 2 positive cultures were required. The flora of the oral microbiome comprised all microorganisms whose main reservoir is the oropharynx (32,33).

In relation to the suspected portal of entry, this was established prospectively by the local teams during admission, based on patient history and physical examination. Teams determined the probable portal of entry at their discretion if factors like poor oral hygiene, previous odontological procedures, previous phlebitis or concomitant line infection were present.

Clinical, echocardiographic, microbiological features and adverse events of BAV and MVP patients were compared with those of patients from high-risk group and low/moderate-risk group.

Statistical analysis

Variables with normal distribution were expressed as mean and standard deviation (SD), while non-normal distribution variables were described with median and interquartile range (IQR). Univariate analysis of data comparisons between two groups was performed using the

unpaired Student t-test for continuous variables with normal distribution, or by the Mann-Whitney U test in the case of variables with non-normal distribution. Chi square or Fisher exact tests were used for the categorical variables. A value of $p<0.05$ was considered statistically significant. All hypothesis tests were bilateral. All statistical analysis was performed with SPSS Statistics (version 16.0).

Results

A total of 3,208 patients with definite (n=2593, 80.8%) or possible (n=615, 19.2%) IE were included in the study. Of these, 54 were patients with BAV (1.6%), 89 were patients with MVP (2.7%), 1,226 (38.2%) were high-risk patients with IEAP indication (Group 1), and 1,839 (57.3%) were low/moderate-risk patients without IEAP indication (Group 2).

Infective endocarditis in patients with bicuspid aortic valve

The BAV group comprised 54 patients; the majority were male (43, 79.6%), with a median age of 43 years (IQR: 36–55) and low comorbidity. At the time of IE diagnosis, 33 patients (61%) had moderate/severe aortic valve dysfunction (**Table 1**). Concomitant involvement of the other valve was observed in 10 (18.5%) patients. The median time of hospitalization was 33 days (IQR: 18–50).

Most cases of IE (46, 85.1%) had been acquired in the community. The most common organisms causing IE were microorganisms present in the oral cavity (42.6%), mainly *viridans group streptococci* (VGS) (35.2%), and the most frequently identified entry portal was the oral cavity (14.8%) (**Table 2**).

Intracardiac complications and HF were common (50% and 40.7%, respectively). Cardiac surgery was indicated in 75.9% and performed in 68% of patients. The in-hospital mortality was 5.6% (**Table 3**).

Infective endocarditis in patients with mitral valve prolapse

The MVP group comprised 89 patients; the majority were male (60, 67.4%), with a median age of 63 years (IQR: 45–71). At the time of IE diagnosis, moderate/severe mitral regurgitation was present in 50 patients (56%) (**Table 1**). The median time of hospitalization was 32 days (IQR: 19–45).

Again, most cases of IE were due to bacteria of the oral microbiome (46.1%), mainly VGS (39.3%), and the oral cavity was the most frequent suspected entry portal (18%) (**Table 2**).

Intracardiac complications and HF were also very frequent and were present in 47.2% and 34.8% of patients, respectively. Cardiac surgery was indicated in 56 (62.9%) and performed in 35 (39.3%) patients. The majority of individuals who underwent surgery received a mechanical prosthesis (60%), and 59 patients (66.3%) had severe mitral regurgitation at discharge. The in-hospital mortality of individuals who underwent cardiac surgery was 3% and 10% in the entire MVP group (**Table 3).**

Infective endocarditis in BAV and MVP versus infective endocarditis in patients with and without IEAP indication

BAV and MVP patients were younger and had fewer comorbidities than patients from Groups 1 and 2 (**Table 1**).

There was a higher incidence of VGS IE in BAV and MVP patients than in high-risk group (35.2% and 39.3% vs 14.6%, both $p<0.01$) and low/moderate-risk group (35.2% and 39.3% vs 15%, both $p<0.01$) patients. Furthermore, BAV and MVP patients showed higher rates

of IE from suspected odontological origin than did high-risk group (14.8% and 18% vs 5.8%, both $p<0.01$) and low/moderate-risk group (14.8% and 18% vs 6%, both $p<0.01$) patients. While VGS were the most frequent causal microorganisms in BAV and MVP groups, staphylococci were the most frequent organisms in high-risk and low/moderate-risk groups (**Table 2**). Furthermore, these findings were mantained when BAV and MVP groups were compared with isolated native aortic valve IE and isolated mitral valve IE, respectively (Online Appendix).

As nosocomial IE was more frequent in high-risk and low/moderate-risk groups than in BAV and MVP (**Table 2**), a subgroup analysis was performed including only those patients with community-acquired IE. Again, BAV and MVP groups showed a higher proportion of VGS IE and suspected oral cavity entry portal than did high-risk and low/moderate-risk groups (**Central Illustration** and Online Appendix). Again, BAV and MVP groups showed a higher proportion of VGS IE when they were compared with isolated native aortic valve and isolated mitral valve community-adquired IE, respectively (Online Appendix).

As shown in **Table 3**, BAV and MVP patients had similar intracardiac complications to those of the high-risk group (50% and 47.2% vs 44.8%, $p<0.53$ and $p<0.74$, respectively), which were more frequent than those in patients from the low/moderate-risk group (50% and 47.2% vs 30.6%, both $p<0.01$) (Central illustration). BAV patients had a significantly higher need for surgical treatment than did patients in the low/moderate-risk group (75.9% indicated and 68% performed vs 62.2% indicated and 40.6% performed, $p<0.05$ and $p<0.01$, respectively). In comparison with the high-risk group, a significantly higher number of BAV patients underwent surgery (68% vs 40%, $p<0.01$). No differences were found regarding surgery indicated and performed in the MVP group versus the high-risk and low/moderate-risk groups.

In-hospital mortality of BAV and MVP groups (5.6% and 10.1%, respectively) was significantly lower than that of the high-risk and low/moderate-risk groups, which showed similar mortality rates (29% and 28.3%, respectively, both $p<0.01$). To further investigate these differences in in-hospital mortality, we analyzed several factors known to be associated with an adverse prognosis in IE. Results of this analysis showed that patients from high-risk and low/moderate-risk groups were older, had higher comorbidity rates and higher surgical risk, and contracted nosocomial IE and staphylococcal IE more frequently than did patients with BAV and MVP (**Table 4**). When a propensity score analysis was performed between MVP and BAV individuals and high- and low/intermediate-risk subjects matched according to age, Charlson index, nosocomial IE, staphylococcal IE and LogEuroscore, in-hospital mortality rates between the BAV and MVP groups and the high-risk and low/moderate-risk groups were not statistically different (Online Appendix).

Discussion

This study presents the largest series yet described of IE in patients with BAV and MVP. It shows that patients with these cardiac conditions who contract IE are young and predominantly male individuals with few comorbidities. Despite this, the analysis of the clinical characteristics in BAV and MVP patients with IE revealed an aggressive clinical course with a similar proportion of IE complications to that of IE patients with high-risk cardiac conditions, and more intracardiac complications than in patients of the low- and intermediate-risk groups. Moreover, this study shows that the microbiological and epidemiological profile of IE in BAV and MVP patients differs substantially from that found in patients with other low- and intermediate-risk cardiac conditions, with a particularly high rate of VGS IE and also a more frequent rate of IE from suspected odontologic origin. Overall, our findings open the debate to consider IEAP

before dental procedures not only in high-risk cardiac conditions, but also in patients with BAV and MVP.

BAV is the most common form of congenital heart disease (prevalence of 0.5–2%). Patients with BAV have an IE incidence of 236 cases per 100,000 individuals/year (16,17), which represents a ~30-fold higher risk of IE than in the general population (5–7 cases per 100,000 individuals/year).(1) MVP is also a frequent cardiac condition (prevalence of 2–3%) and it is thought to be the most frequent predisposing cardiac condition for IE in developed countries. Accordingly, MVP patients have been reported to present an IE incidence of 87 per 100,000 habitants/year, which is higher than that for flail leaflet or mitral regurgitation (18,19). In spite of the abovementioned facts, BAV and MVP are considered intermediate-risk cardiac conditions and IEAP is presently not recommended.

Current AHA and ESC recommendations for IE prevention restrict IEAP to patients with high-risk cardiac conditions based on the hypothesis that the potential risks associated with IEAP (antibiotic side-effects and increase in resistant microorganisms) could exceed its benefits in those who are not high-risk.

The benefits were questioned because of the lack of randomized-controlled data of IEAP efficacy to prevent IE, and because IE seems to be most frequently caused by bacteremia provoked by routine daily activities; therefore, even if IEAP is effective, it would prevent only a small number of IE cases (9).

Nevertheless, the reality is that previous studies on IE in intermediate-risk cardiac conditions like BAV and MVP are scarce and insufficient to evaluate IE characteristics and prognosis in these patients; however, a very recent study has shown that several intermediate-risk

conditions present a similar risk of developing or dying from IE than some of those conditions currently considered high-risk (34).

Furthermore, whereas several nationwide studies performed in North America and Europe have shown an epidemiological increase in IE and streptococcal IE following IEAP restrictions (20-24), other studies have not found this to be the case (35-37). Moreover, a recent nationwide population-based cohort study has shown a protective effect of IEAP in individuals with prosthetic heart valves, and the only available meta-analysis on IEAP in dental procedures has also suggested a protective effect, despite the limitation of the poor quality of the primary studies (38,39). In addition, if the increase in the population trends of IE is assumed to be due to IEAP restriction, IEAP would be cost-effective (40).

It is unlikely that a prospective randomized placebo-controlled trial will ever be conducted to evaluate the efficacy of IEAP in dental procedures in intermediate- or even in high-risk cardiac conditions. This is due to the generally low incidence of IE, the wide variety of predisposing heart conditions, and the different types of dental procedures, which make it very difficult to carry out such types of studies. Because of this, registry-based investigations addressing clinical, microbiological and echocardiographic characteristics of IE in patients with intermediate-risk cardiac conditions, and on which patients might benefit more from IEAP, are extremely necessary.

In the present study, we analyzed clinical and microbiological findings in the largest series of BAV and MVP with IE reported to date, and compared these with those of IE in patients with high-risk cardiac conditions where IEAP is advocated, and of IE patients with low and other intermediate risk cardiac conditions for whom IEAP is currently not recommended.

Until now, IE data in BAV were almost restricted to BAV series where a maximum of 4 to 13 individuals had this complication (16,17). In those series, around 70% of patients with BAV and IE underwent cardiac surgery, which is similar to the percentage of individuals operated upon in our registry (68%). Of note, the number of BAV patients with IE requiring cardiac surgery (75.9% indicated and 68% performed) was much higher than in the low/intermediate group (indicated in 62.2% and performed in 40.6%, $p<0.05$ and $p<0.01$, respectively) and also in the high-risk group (indicated in 64.3% and performed in 40.9%, $p<0.11$ and $p<0.01$, respectively). The number of individuals operated upon is also higher than what has been reported in both native and prosthetic IE series (surgical treatment around 50%) (41,42). The high surgery rate found in these patients illustrates the importance of preventing IE to avoid risks associated with cardiac surgery, but also long-term complications derived from prosthetic valves and anticoagulation therapy.

The clinical course of IE in MVP patients has never been described in detail in the literature due to the small number of cases reported. In the largest contemporary series of individuals with MVP, only 8 subjects developed IE, 2 of whom required emergent surgery (19). However, it is important to mention the high risk of IE reported in MVP patients with moderate/severe mitral regurgitation and those with flail leaflet: 289.5 cases/100.000 person-years and 715.5 cases/100.000 person-years, respectively (19).

In our series, we found that the need for cardiac surgery in the MVP group was similar to that found in low/intermediate and high-risk groups. However, a non-negligible percentage of MVP patients with IE (66.3%) had severe mitral regurgitation at discharge, which carries substantial risk of developing HF and requiring cardiac surgery during follow-up.

We also found a relatively low in-hospital mortality rate both in BAV and MVP patients. Nevertheless, an in-hospital mortality of 5 to 10% should be still considered very high given the young age and the few comorbidities of patients included in these groups.

One of the most interesting findings of our work was the profound differences between groups regarding the IE microbiological profile and the rate of IE from suspected odontological origin. While staphylococci were the predominant IE-causing agents in patients with IEAP indication and also in the non-indicated IEAP group, VGS were the most frequent in patients with BAV and MVP (35.2% and 39.3% of cases, respectively). Furthermore, the odontological portal of entry was the most common origin of IE identified in BAV and MVP patients (14.8% and 18%, respectively), and it was significantly higher than that in the high-risk group (5.8%) and low/intermediate-risk group (6%). To determine whether IEAP is effective in preventing IE is beyond the scope of our study, but it is interesting to hypothesize that the microbiological spectrum found in patients with IEAP indication could have been influenced by IEAP, while the microbiological spectrum in IE patients with BAV and MVP reflects the absence of IEAP and an increased risk of IE compared with other low/intermediate-risk conditions.

Regarding IE adverse events, both BAV and MVP groups had more intracardiac complications than the low/intermediate-risk group (50% and 47.2% vs 30.6%, respectively, both $p<0.01$) and similar to the high-risk group (50% and 47.2% vs 44.8%, $p<0.53$ and $p<0.74$). Of note, the incidence of intracardiac complications found in BAV and MVP patients are higher than that previously reported in native valve IE and is similar to that described in prosthetic valve IE (43).

In any case, the microbiological spectrum, the increased odontological origin and the high rate of intracardiac complications and surgery (comparable to the high-risk group) (central

illustration) poses the question of whether IEAP should be reconsidered for patients with BAV and MVP.

Limitations

This study has some limitations. The information regarding IEAP prior to odontological procedures was not included in the GAMES registry database. However, all the study participants were included after the publication of the 2007 IE guidelines that restricted IEAP to high-risk patients (11). The total number of BAV and MVP patients among the population under care at the 31 participating centers is unknown, so we cannot provide incidence or prevalence data. However, ours is the largest series yet described of IE in patients with BAV and MVP.

Conclusions

IE patients with BAV and MVP present a distinct clinical and microbiological profile that includes young age, male preponderance and low comorbidity. They also present higher rates of VSG IE and increased IE from suspected dental origin than other IE patients. IE patients with BAV and MVP present a clinical course similar to that of high-risk patients, with more intracardiac complications than the low/intermediate-risk group and a higher need for surgery in the case of IE BAV patients. Based on these indirect data, we suggest that BAV and MVP should be considered high-risk IE cardiac conditions, and that IEAP indication should be reconsidered for this group of patients.

Perspectives

Competency in medical knowledge: Individuals with BAV and PVM have a higher risk of developing IE than the general population. IE in BAV and PVM is characterized by an aggressive clinical course, comparable to that of high-risk patients in terms of adverse events, and with a higher surgical need in BAV patients.

Translational outlook: Further studies are needed to assess IEAP efficacy and to determine which patients might benefit from IEAP.

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Figure Legends

Central illustration. Main distinctive microbiological and clinical findings in BAV and MVP patients with IE compared with high-risk and low/intermediate-risk IE cardiac conditions. IE patients with BAV and MVP present higher rates of viridans group streptococci IE and increased IE from suspected dental origin. They present more intracardiac complications than the low/intermediate-risk group and a higher need of surgery in IE BAV patients. IE: infective endocarditis; VGS: viridans group streptococci

Figure 1. Study overview. Data from 3,524 consecutive IE patients prospectively included in the GAMES registry. IE: infective endocarditis; IEAP: infective endocarditis antibiotic prophylaxis; BAV: bicuspid aortic valve; MVP: mitral valve prolapse.

Table 1. Baseline characteristics in bicuspid aortic valve and mitral valve prolapse patients in comparison with high-risk and low/moderate-risk groups

Variable	BAV (n = 54)	MVP (n = 89)	High-risk group (n = 1226)	Low/moderate-risk group (n =1839)	BAV vs High-risk group, p-value	BAV vs Low/moderate-risk group , p-value	MVP vs High-risk group, p-value	MVP vs Low/moderate-risk group, p-value
Male, n (%)	43 (79.6)	60 (67.4)	730 (59.5)	1115 (60.6)	**<0.01**	**<0.01**	0.17	0.24
Age (years), median (IQR)	43 (36–55)	63 (45–71)	69 (59–77)	69 (56–77)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Diabetes mellitus 2, n (%)	7 (13)	10 (11.2)	314 (25.6)	538 (29.3)	**<0.03**	**<0.03**	**<0.01**	**<0.01**
Arterial hypertension, n (%)	12 (22.2)	33 (37.1)	714 (58.4)	998 (54.4)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Dyslipidemia, n (%)	9 (16.7)	14 (15.7)	484 (39.6)	577 (31.5)	**<0.01**	**<0.04**	**<0.01**	**<0.01**
Ischemic heart disease, n (%)	5 (9.4)	13 (14.6)	398 (32.5)	363 (19.8)	**<0.01**	0.16	**<0.01**	0.46
Atrial fibrillation, n (%)	2 (3.7)	12 (13.5)	485 (39.7)	333 (18.1)	**<0.01**	**<0.02**	**<0.01**	0.36
CKD mod/sev, n (%)	1 (1.9)	5 (5.6)	177 (14.4)	308 (16.8)	**<0.03**	**<0.01**	0.06	**<0.01**
Hepatic disease, n (%)	2 (3.7)	7 (7.8)	95 (7.7)	240 (13)	0.4	0.06	0.86	0.2
Neoplasia, n (%)	1 (1.9)	13 (14.8)	170 (13.9)	337 (18.4)	**<0.01**	**<0.01**	0.81	0.65
Immunossuppresive therapy, n (%)	-	3 (3.4)	51 (4.2)	148 (8.1)	0.26	0.07	0.72	0.19
HIV, n (%)	3 (5.6)	3 (3.4)	12 (1)	44 (2.4)	**<0.01**	0.33	0.12	0.72
Charlson index (adjusted by age), median (IQR)	1 (0–2)	3 (1–4)	5 (3–6)	5 (3–7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Valve dysfunction, n (%)	Aortic regurgitation -Moderate, 14 (26) -Severe, 19 (35.1) Aortic stenosis -Moderate, 4 (7.4) -Severe, 2 (3.7)	Mitral regurgitation -Mild, 8 (9) -Moderate, 21 (23.6) -Severe, 29 (32.5)	NA	NA	NA	NA	NA	NA
Cardiac risk conditions, n (%)	NA	Cardiac device, 1 (1.1)	Prosthesis, 1055 (86.1%) Previous IE, 230 (18.4%) CHD, 145 (11.8%) Cardiac device, 179 (14.6)	Rheumatic, 99 (5.3) Cardiac device, 123 (6.7)	NA	NA	NA	NA

BAV:bicuspid aortic valve; MVP: mitral valve prolapse; CKD: chronic kidney disease; HIV: human immunodeficiency virus; HCM: hypertrophic cardiomyopathy; NA=not applicable; IQR: interquartile range; CHD: congenital heart disease

Table 2. Microbiological profile of the study groups

	BAV (n = 54)	**MVP (n = 89)**	**High-risk group (n = 226)**	**Low/moderate-risk group (n = 1839)**	**BAV vs High-risk group p-value**	**BAV vs Low/moderate-risk group p-value**	**MVP vs High-risk group p-value**	**MVP vs Low/moderate-risk group p-value**
Nosocomial IE, n (%)	5 (9.2)	7 (7.8)	441 (35.9)	456 (24.7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
IE portal of entry, n (%)	13 (24)	33 (37)	484 (39.4)	957 (51)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
• Odontological	8 (14.8)	16 (18)	71 (5.8)	111 (6)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
• Vascular	4 (7.4)	4 (4.5)	226 (18.4)	361 (19.6)	**<0.03**	**<0.02**	**<0.01**	**<0.01**
• Gastrointestinal	-	6 (6.7)	82 (6.7)	146 (7.9)	**<0.04**	**<0.03**	0.98	0.68
• Cutaneous	1 (1.9)	2 (2.2)	53 (4.3)	139 (7.6)	0.37	0.11	0.34	0.06
• Genitourinary	-	4 (4.5)	42 (3.4)	124 (6.7)	0.17	**<0.04**	0.59	0.40
• Respiratory	-	1 (1.1)	10 (0.8)	30 (1.6)	0.55	0.34	0.75	0.71
Microbiology:								
Flora of the oral microbiome	23 (42.6)	41 (46.1)	179 (14.6)	309 (16,8)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
VGS, n (%)	19 (35.2)	35 (39.3)	148 (12.1)	275 (15)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Granullicatella sp.	1 (1.9)	1 (1.1)	4 (0.3)	3 (0,2)	0.52	0.24	0.77	0.45
Abiotrophia sp.	-	2 (2.2)	6 (0.5)	5 (0,3)	0.61	0.33	0.17	**<0.03**
Gemella sp.	1 (1.9)	1 (1.1)	4 (0.3)	7 (0,4)	0.51	0.56	0.77	0.82
HACEK	2 (3.7)	2 (2.2)	17 (1.4)	19 (1,0)	0.42	0.23	0.84	0.57
Non-oral streptococci								
Nasopharynx streptococci	2 (3.7)	1 (1.1)	8 (0,7)	31 (1,7)	0.08	0.55	0.88	0.98
S. *gallolyticus*	1 (1.9)	1 (1.1)	21 (1,7)	36 (2,0)	0.64	0.65	0.99	0.86
S. *agalactiae*	1 (1.9)	2 (2.2)	15 (1,2)	47 (2,6)	0.82	0.9	0.74	0.86
Staphylococci								
S. *aureus*, n (%)	5 (9,3)	13 (14.6)	178 (14.5)	500 (27.2)	0.37	**<0.01**	0.89	**<0.01**
MARSA	-	-	34 (2.7)	70 (3.8)	0.41	0.27	0.21	0.11
CNS, n (%)	4 (7.4)	5 (5.6)	308 (25.1)	206 (11.2)	**<0.01**	0.51	**<0.01**	0.14
Enterococcus *faecalis*, n (%)	1 (1.9)	8 (9.0)	186 (15.2)	230 (12.5)	**<0.01**	**<0.03**	0.15	0.41
Non-HACEK gram-negative bacilli, n (%)	1 (1.9)	1 (1.1)	30 (2.4)	48 (2.6)	0.86	0.92	0.66	0.59
Negative blood cultures, n (%)	6 (11.1)	6 (6.7)	116 (9.5)	158 (8.6)	0.86	0.68	0.50	0.67
Polymicrobial, n (%)	1 (1.9)	-	18 (1.5)	33 (1.8)	0.72	0.62	0.49	0.39

BAV: bicuspid aortic valve; MVP: mitral valve prolapse; IE: infective endocarditis; VGS: *viridans group streptococci;* HACEK: *hemophilus parainfluenzae*, H.*aphrophilus*, H.*paraphrophilus*, H. *influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium homini*, *Eikenella corrodens*, *Kingella Kingae* and K.*denitrificans; MRSA: methicilin-resistant s. aureus; CNS: coagulase-negative staphylococci*

Table 3. Infective endocarditis related adverse events in bicuspid aortic valve and mitral valve prolapse patients in comparison with high-risk and low/moderate-risk groups

Variables	BAV (n = 54)	MVP (n = 89)	High-risk group (n = 1226)	Low/moderate-risk group (n = 1839)	BAV vs High-risk group, p-value	BAV vs Low/moderate-risk group, p-value	MVP vs High-risk group, p-value	MVP vs Low/moderate-risk group, p-value
Admission (days), median (IQR)	33 (18–50)	32 (19–45)	38 (20–54)	36 (22–51)	0.4	0.37	0.23	0.18
Heart failure, n (%)	22 (40.7)	31 (34.8)	473 (38.5)	826 (45)	0.8	0.64	0.26	0.06
Cardiac complication*, n (%)	27 (50)	42 (47.2)	549 (44.8)	563 (30.6)	0.53	**<0.01**	0.74	**<0.01**
Type of cardiac complication:					-	-	-	-
▪ Abscess	12 (22.2)	6 (6.7)	317 (25.9)	188 (10.2)				
▪ Fistula	8 (14.8)	-	53 (4.3)	24 (1.3)				
▪ Perforation	17 (31.5)	33 (37.1)	54 (4.4)	355 (19.3)				
▪ Pseudoaneurysm	5 (9.3)	3 (3.4)	97 (7.9)	73 (4)				
▪ Prosthetic dehiscence	-	-	259 (23.5)	-				
Neurological events, n (%)	11 (20.3)	19 (21.3)	265 (21.6)	379 (20.6)	0.96	0.89	0.94	0.97
▪ CNS embolism, n (%)	5 (9.2)	5 (5.6)	141 (11.5)	203 (11)	0.77	0.84	0.12	0.15
▪ CNS embolism with haemorrhagic transformation, n (%)	1 (1.8)	5 (5.6)	41 (3.3)	59 (3.2)	0.83	0.86	0.4	0.42
▪ Intracranial haemorrhage, n (%)	2 (3.7)	2 (2.2)	40 (3.2)	35 (1.9)	0.83	0.65	0.8	0.86
Peripheral embolism [Ø], n (%)	9 (18.4)	19 (21.3)	204 (16.7)	443 (24.1)	0.6	0.3	0.51	0.83
Persistent bacteriemia, n (%)	3 (5.6)	2 (2.2)	129 (10.6)	231 (12.6)	0.25	0.16	**<0.04**	**<0.01**
Cardiac surgery indication, n (%)	41 (75.9)	56 (62.9)	789 (64.3)	1145 (62.2)	0.11	**<0.05**	0.87	0.98
▪ *LogEuroscore*, median (IQR)	4 (3–18)	6 (4–21)	34 (16–60)	15 (6–36)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
▪ Cardiac surgery rejected, n (%)	4 (9.7)	21 (37.5)	287 (36.3)	397 (34.7)	**<0.01**	**<0.01**	0.97	0.77
Cardiac surgery performed, n (%)	37 (68)	35 (39.3)	502 (40.9)	748 (40.6)	**<0.01**	**<0.01**	0.97	0.77
Surgical procedures, n (%)					-	-	-	-
• Mechanical prosthesis implant	32 (62.9)	21 (23.5)	353 (28.8)	468 (25.4)				
• Biological prosthesis implant	9 (16.6)	12 (13.4)	81 (6.6)	280 (15.2)				
• Valve repair	5 (9.2)	9 (10)	72 (5.8)	122 (6.6)				
• Ascending aorta replacement	2 (3.7)	-	55 (4.5)	21 (1.1)				
In-hospital mortality, n (%)	3 (5.6)	9 (10.1)	356 (29)	521 (28.3)	**<0.01**	**<0.01**	**<0.01**	**<0.01**

BAV: bicuspid aortic valve; MVP: mitral valve prolapse; CNS: central nervous system; IQR: interquartile range; * number of patients with ≥1 cardiac complication ;

[Ø] number of patients with ≥1 peripheral embolism

Table 4. In-hospital mortality according to poor prognosis factors

Variables	**BAV (n = 54)**	**MVP (n = 89)**	**High-risk group (n = 1226)**	**Low/moderate-risk group (n = 1839)**	**BAV vs High-risk group p-value**	**BAV vs Low/moderate-risk, p-value**	**MVP vs High-risk group, p-value**	**MVP vs Low/moderate-risk , p-value**
Age (years), median (IQR)	43 (36–55)	63 (45–71)	69 (59–77)	69 (56–77)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Charlson index (adjusted by age), median (IQR)	1 (0–2)	3 (1-4)	5 (3–6)	5(3–7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Nosocomial IE, n (%)	5 (9.2)	7 (7.8)	441 (35.9)	456 (24.7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Staphylococcal IE, n (%)	8 (14.8)	16 (18)	450 (37)	765 (41)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
LogEuroscore, median (IQR)	4 (3–18)	6 (4–21)	34 (16–60)	15 (6–36)	**<0.01**	**<0.01**	**<0.01**	**<0.01**

BAV: bicuspid aortic valve; MVP:mitral valve prolapse; IE:infective endocarditis; CCI: Charlson comorbidity index; IQR:interquartile range