JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 24, 2018

PUBLISHED BY ELSEVIER

Infective Endocarditis in Patients With Bicuspid Aortic Valve or Mitral Valve Prolapse

Isabel Zegri-Reiriz, MD, PhD,[a] Arístides de Alarcón, MD, PhD,[b] Patricia Muñoz, MD, PhD,[c] Manuel Martínez Sellés, MD, PhD,[d] Victor González-Ramallo, MD, PhD,[e] Jose M. Miro, MD, PhD,[f] Carles Falces, MD, PhD,[g] Claudia Gonzalez Rico, MD,[h] Xabier Kortajarena Urkola, MD,[i] José Antonio Lepe, MD,[b] Regino Rodriguez Alvarez, MD,[j] Jose Maria Reguera Iglesias, MD,[k] Enrique Navas, MD,[l] Fernando Dominguez, MD, PhD,[a,m] Pablo Garcia-Pavia, MD, PhD,[a,n] for the Spanish Collaboration on Endocarditis–Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES)

ABSTRACT

BACKGROUND There is little information concerning infective endocarditis (IE) in patients with bicuspid aortic valve (BAV) or mitral valve prolapse (MVP). Currently, IE antibiotic prophylaxis (IEAP) is not recommended for these conditions.

OBJECTIVES This study sought 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 (Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España) 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 IE than did high-risk group and low/moderate-risk group patients (35.2% and 39.3% vs. 12.1% and 15.0%, respectively; all $p < 0.01$). A similar pattern was seen for IE from suspected odontologic origin (14.8% and 18.0% vs. 5.8% and 6.0%; all $p < 0.01$). BAV and MVP patients had more intracardiac complications than did low/moderate-risk group (50% and 47.2% vs. 30.6%, both $p < 0.01$) patients and were similar to high-risk group patients.

CONCLUSIONS IE in patients with BAV and MVP have higher rates of viridans group streptococci IE and IE from suspected odontologic 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. (J Am Coll Cardiol 2018;71:2731–40) © 2018 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Cardiology, Hospital Universitario Puerta de Hierro, CIBERCV, Madrid, Spain; [b]Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine Infecious Diseases Research Group, Institute of Biomedicine of Seville, University of Seville/CSIC/University Hospitals Virgen del Rocío and Virgen Macarena, Seville, Spain; [c]Department of Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERES, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain; [d]Department of Cardiology, Hospital General Universitario Gregorio Marañón, CIBERCV, Universidad Europea, Universidad Complutense, Madrid, Spain; [e]Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [f]Department of Infectious Diseases, Hospital Clínic- Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [g]Department of Cardiology, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [h]Department of Infectious Diseases, Hospital Universitario Marqués de Valdecilla, Santander, Spain; [i]Department of Infectious Diseases, Hospital Universitario de Donostia, San Sebastián, Spain; [j]Department of Infectious Diseases, Hospital Universitario de Cruces, Bilbao, Spain; [k]Department of Infectious Diseases, Hospital Regional Universitario de Málaga, Málaga, Spain; [l]Department of Infectious Diseases, Hospital Universitario Ramón y Cajal, Madrid, Spain; [m]Fundación Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain; and the [n]University Francisco de Vitoria, Pozuelo de Alarcon, Madrid, Spain.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.03.534

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

BAV = bicuspid aortic valve

CHD = congenital heart disease

ESC = European Society of Cardiology

HF = heart failure

IE = infective endocarditis

IEAP = infective endocarditis antibiotic prophylaxis

IQR = interquartile range

MVP = mitral valve prolapse

VGS = viridans group streptococci

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 toward preventive strategies that reduce the number of patients with IE. IE antibiotic prophylaxis (IEAP) is one of the strategies proposed to prevent IE.

SEE PAGE 2741

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, owing 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 such as BAV and MVP, and data about the potential usefulness of IEAP in individuals with these diseases are limited.

The aim of this study was 2-fold: 1) to describe the clinical and microbiological features of BAV and MVP patients with IE; and 2) to compare these features with those of patients with and without IEAP indication, 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-GAMES (Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España) registry, at 31 Spanish hospitals (25–30). Of the 31 hospitals participating in the GAMES registry, 24 are tertiary centers with cardiac surgery on site 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 <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

This work was supported in part by the Instituto de Salud Carlos III (grants RD012/0042/0066 and CB16/11/00432). Dr. Miro received a personal 80:20 research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain during 2017 to 2019. The CNIC is supported by the Ministry of Economy, Industry and Competitiveness and the ProCNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505). Grants from the Instituto de Salud Carlos III and the Spanish Ministry of Economy and Competitiveness are supported by the Plan Estatal de I+D+I 2013-2016—European Regional Development Fund "A way of making Europe." The funders played no role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Bernard Prendergast, BMedSChi, BM BS, DM, served as Guest Editor for this paper.

Manuscript received February 21, 2018; revised manuscript received March 16, 2018, accepted March 17, 2018.

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 such as poor oral hygiene, previous odontologic procedures, previous phlebitis, or concomitant line infection were present.

Clinical, echocardiographic, and 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 ± SD, while non-normal distribution variables were described with median and interquartile range (IQR). Univariate analysis of data comparisons between 2 groups was performed using the unpaired Student's *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 p value <0.05 was considered statistically significant. All hypothesis tests were bilateral. All statistical analysis was performed with SPSS Statistics version 16.0 (IBM Corporation, Armonk, New York).

RESULTS

A total of 3,208 patients with definite (n = 2,593, 80.8%) or possible (n = 615, 19.2%) IE were included in the study. Of these, 54 were patients with BAV (1.6%), 89 (2.7%) were patients with MVP, 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).

IE IN PATIENTS WITH BAV. The BAV group comprised 54 patients; the majority were men (n = 43, 79.6%), with a median age of 43 years (IQR: 36 to 55 years) and low comorbidity. At the time of IE diagnosis, 35 (64.8%) patients had moderate or 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 to 50 days).

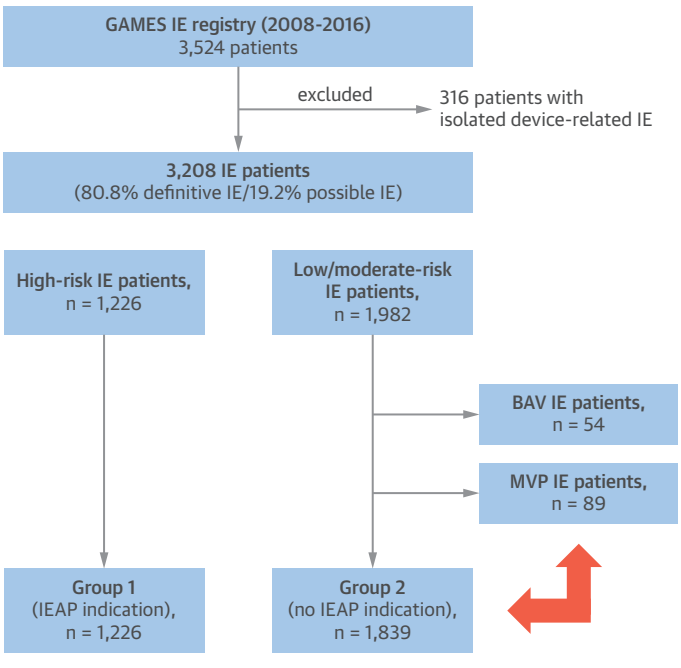
Most cases of IE (n = 49, 90.7%) had been acquired in the community. The most common organisms causing IE were microorganisms present in the oral cavity (42.6%), mainly viridans group streptococci (VGS) (35.2%), and the most frequently identified entry portal was the oral cavity (14.8%) (Table 2).

Intracardiac complications and HF were common (50.0% and 40.7%, respectively). Cardiac surgery was indicated in 75.9% and performed in 68.0% of patients. The in-hospital mortality was 5.6% (Table 3).

IE IN PATIENTS WITH MVP. The MVP group comprised 89 patients; the majority were men (n = 60, 67.4%), with a median age of 63 years (IQR: 45 to 71 years). At the time of IE diagnosis, moderate or severe mitral regurgitation was present in 50 patients (56%) (Table 1). The median time of hospitalization was 32 days (IQR: 19 to 45 days).

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 (18.0%) (Table 2).

FIGURE 1 Study Overview



Data from 3,524 consecutive infective endocarditis (IE) patients prospectively included in the GAMES (Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España) registry. BAV = bicuspid aortic valve; IEAP = infective endocarditis antibiotic prophylaxis; MVP = mitral valve prolapse.

TABLE 1 Baseline Characteristics in BAV and MVP Patients in Comparison With High-Risk and Low/Moderate-Risk Groups

	BAV (n = 54)	MVP (n = 89)	High-Risk Group (n = 1,226)	Low/Moderate-Risk Group (n =1,839)	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	43 (79.6)	60 (67.4)	730 (59.5)	1,115 (60.6)	**<0.01**	**<0.01**	0.17	0.24
Age, yrs	43 (36–55)	63 (45–71)	69 (59–77)	69 (56–77)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Type 2 diabetes mellitus	7 (13.0)	10 (11.2)	314 (25.6)	538 (29.3)	**<0.03**	**<0.03**	**<0.01**	**<0.01**
Arterial hypertension	12 (22.2)	33 (37.1)	714 (58.4)	998 (54.4)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Dyslipidemia	9 (16.7)	14 (15.7)	484 (39.6)	577 (31.5)	**<0.01**	**<0.04**	**<0.01**	**<0.01**
Ischemic heart disease	5 (9.4)	13 (14.6)	398 (32.5)	363 (19.8)	**<0.01**	0.16	**<0.01**	0.46
Atrial fibrillation	2 (3.7)	12 (13.5)	485 (39.7)	333 (18.1)	**<0.01**	**<0.02**	**<0.01**	0.36
CKD moderate/severe	1 (1.9)	5 (5.6)	177 (14.4)	308 (16.8)	**<0.03**	**<0.01**	0.06	**<0.01**
Hepatic disease	2 (3.7)	7 (7.8)	95 (7.7)	240 (13.0)	0.40	0.06	0.86	0.20
Neoplasia	1 (1.9)	13 (14.8)	170 (13.9)	337 (18.4)	**<0.01**	**<0.01**	0.81	0.65
Immunosuppressive therapy	–	3 (3.4)	51 (4.2)	148 (8.1)	0.26	0.07	0.72	0.19
HIV	3 (5.6)	3 (3.4)	12 (1.0)	44 (2.4)	**<0.01**	0.33	0.12	0.72
Charlson index (adjusted by age)	1 (0–2)	3 (1–4)	5 (3–6)	5 (3–7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Valve dysfunction					-	-	-	-
Aortic regurgitation								
Moderate	14 (25.9)	NA	NA	NA				
Severe	19 (35.1)	NA	NA	NA				
Aortic stenosis								
Moderate	4 (7.4)	NA	NA	NA				
Severe	1 (1.9)	NA	NA	NA				
Mitral regurgitation								
Mild	NA	8 (9.0)	NA	NA				
Moderate	NA	21 (23.6)	NA	NA				
Severe	NA	29 (32.5)	NA	NA				
Cardiac risk conditions					-	-	-	-
Cardiac device	0 (0.0)	1 (1.1)	179 (14.6)	123 (6.7)				
Prosthesis	NA	NA	1,055 (86.1)	NA				
Previous IE	NA	NA	230 (18.4)	NA				
CHD	NA	NA	145 (11.8)	NA				
Rheumatic	NA	NA	NA	99 (5.3)				

Values are n (%) or median (interquartile range). **Bold** p values are statistically significant.

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

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 (60.0%), and 59 (66.3%) patients had severe mitral regurgitation at discharge. The in-hospital mortality of individuals who underwent cardiac surgery was 3.0% and 10.0% in the entire MVP group (Table 3).

IE IN BAV AND MVP VERSUS IE 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. 15.0%; both $p < 0.01$) patients. Furthermore, BAV and MVP patients showed higher rates of IE from suspected odontologic origin than did high-risk group (14.8% and 18.0% vs. 5.8%; both $p < 0.01$) and low/moderate-risk group (14.8% and 18.0% vs. 6.0%; both $p < 0.01$) patients (Central Illustration). While VGS were the most frequent causal microorganisms in the BAV and MVP groups, staphylococci were the most frequent organisms in high-risk and low/moderate-risk groups (Table 2). Furthermore, these findings were maintained when the BAV and MVP groups were compared with isolated native aortic valve IE and isolated mitral valve IE, respectively (Online Tables 1 and 2).

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, the BAV and MVP groups showed a higher

TABLE 2 Microbiological Profile of the Study Groups

	BAV (n = 54)	MVP (n = 89)	High-Risk Group (n = 1,226)	Low/ Moderate-Risk Group (n = 1,839)	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	5 (9.2)	7 (7.8)	441 (35.9)	456 (24.7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
IE portal of entry	13 (24.0)	33 (37.0)	484 (39.4)	957 (51.0)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Odontological	8 (14.8)	16 (18.0)	71 (5.8)	111 (6.0)	**<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	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
Nonoral 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*	5 (9.3)	13 (14.6)	178 (14.5)	500 (27.2)	0.37	**<0.01**	0.89	**<0.01**
MRSA	–	–	34 (2.7)	70 (3.8)	0.41	0.27	0.21	0.11
CoNS	4 (7.4)	5 (5.6)	308 (25.1)	206 (11.2)	**<0.01**	0.51	**<0.01**	0.14
Enterococcus faecalis	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	1 (1.9)	1 (1.1)	30 (2.4)	48 (2.6)	0.86	0.92	0.66	0.59
Negative blood cultures	6 (11.1)	6 (6.7)	116 (9.5)	158 (8.6)	0.86	0.68	0.50	0.67
Polymicrobial	1 (1.9)	–	18 (1.5)	33 (1.8)	0.72	0.62	0.49	0.39

Values are n (%). **Bold** p values are statistically significant.

CoNS = coagulase-negative staphylococci; IE = infective endocarditis; HACEK = *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Haemophilus influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium homini*, *Eikenella corrodens*, *Kingella kingae*, and *Kingella denitrificans*; MRSA = methicillin-resistant *Staphylococcus aureus*; VGS = viridans group streptococci; other abbreviations as in Table 1.

proportion of VGS IE and suspected oral cavity entry portal than did high-risk and low/moderate-risk groups (Online Table 1). Again, the 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-acquired IE, respectively (Online Table 1).

As shown in **Table 3**, BAV and MVP patients had similar intracardiac complications to those in the high-risk group (50.0% and 47.2% vs. 44.8%; $p < 0.53$ and $p < 0.74$, respectively), which were more frequent than were those in patients from the low/moderate-risk group (50.0% 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 68.0% 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 (68.0% vs. 40.9%; $p < 0.01$). 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 (29.0% 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

TABLE 3 IE-Related Adverse Events in BAV and MVP Patients in Comparison With High-Risk and Low/Moderate-Risk Groups

	BAV (n = 54)	MVP (n = 89)	High-Risk Group (n = 1,226)	Low/ Moderate-Risk Group (n = 1,839)	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	33 (18–50)	32 (19–45)	38 (20–54)	36 (22–51)	0.40	0.37	0.23	0.18
Heart failure	22 (40.7)	31 (34.8)	473 (38.5)	826 (45.0)	0.80	0.64	0.26	0.06
Cardiac complication*	27 (50.0)	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 (4.0)				
Prosthetic dehiscence	–	–	259 (23.5)	–				
Neurological events	11 (20.3)	19 (21.3)	265 (21.6)	379 (20.6)	0.96	0.89	0.94	0.97
CNS embolism	5 (9.2)	5 (5.6)	141 (11.5)	203 (11.0)	0.77	0.84	0.12	0.15
CNS embolism with hemorrhagic transformation	1 (1.8)	5 (5.6)	41 (3.3)	59 (3.2)	0.83	0.86	0.4	0.42
Intracranial hemorrhage	2 (3.7)	2 (2.2)	40 (3.2)	35 (1.9)	0.83	0.65	0.8	0.86
Peripheral embolism†	9 (18.4)	19 (21.3)	204 (16.7)	443 (24.1)	0.60	0.30	0.51	0.83
Persistent bacteremia	3 (5.6)	2 (2.2)	129 (10.6)	231 (12.6)	0.25	0.16	**<0.04**	**<0.01**
Cardiac surgery indication	41 (75.9)	56 (62.9)	789 (64.3)	1145 (62.2)	0.11	**<0.05**	0.87	0.98
logEuroSCORE	4 (3–18)	6 (4–21)	34 (16–60)	15 (6–36)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Cardiac surgery rejected	4 (9.7)	21 (37.5)	287 (36.3)	397 (34.7)	**<0.01**	**<0.01**	0.97	0.77
Cardiac surgery performed	37 (68.0)	35 (39.3)	502 (40.9)	748 (40.6)	**<0.01**	**<0.01**	0.97	0.77
Surgical procedures					–	–	–	–
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 (10.0)	72 (5.8)	122 (6.6)				
Ascending aorta replacement	2 (3.7)	–	55 (4.5)	21 (1.1)				
In-hospital mortality	3 (5.6)	9 (10.1)	356 (29.0)	521 (28.3)	**<0.01**	**<0.01**	**<0.01**	**<0.01**

Values are median (interquartile range) or n (%). **Bold** p values are statistically significant. *Patients with ≥1 cardiac complication. †Patients with ≥1 peripheral embolism.
CNS = central nervous system; EuroSCORE = European System for Cardiac Operative Risk Evaluation; other abbreviations as in Table 1.

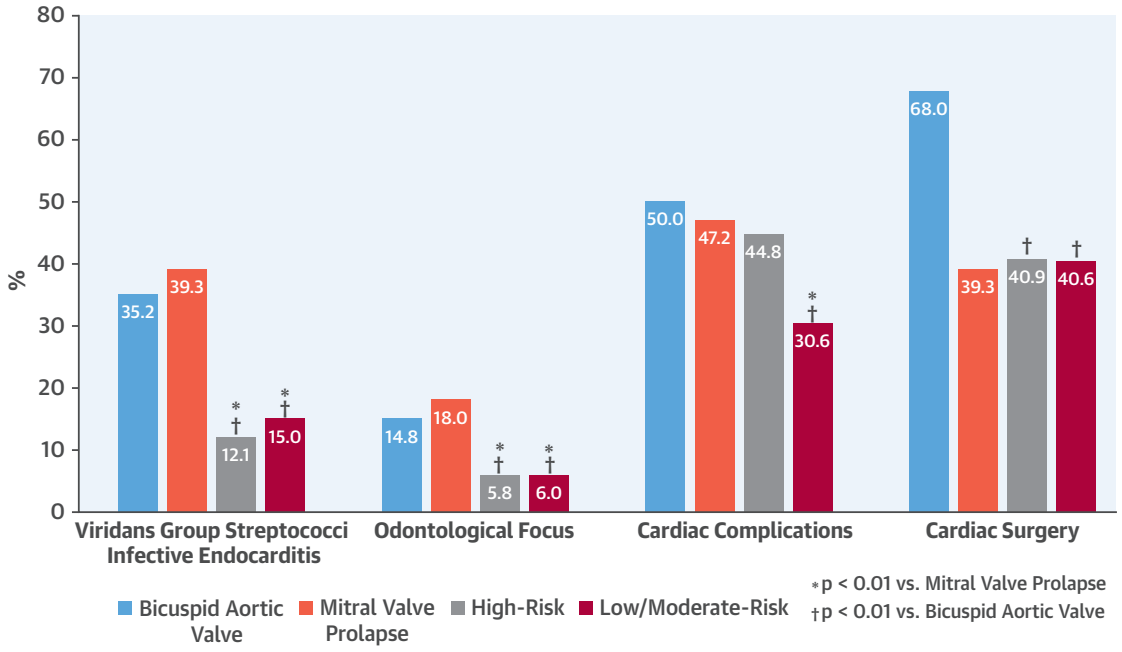
MVP and BAV individuals and high- and low/intermediate-risk subjects matched according to age, Charlson index, nosocomial IE, staphylococcal IE, and logEuroSCORE, in-hospital mortality rates between the BAV and MVP groups and the high-risk and low/moderate-risk groups were not statistically different (Online Tables 4 and 5).

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-risk 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-risk 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% to 2.0%). 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 to 7 cases per 100,000 individuals/year) (1). MVP is also a frequent cardiac condition (prevalence of 2.0% to 3.0%) 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 in patients with flail leaflet or mitral regurgitation (18,19). Despite the

CENTRAL ILLUSTRATION **Infective Endocarditis in Bicuspid Aortic Valve and Mitral Valve Prolapse**



Zegri-Reiriz, I. et al. J Am Coll Cardiol. 2018;71(24):2731-40.

Main distinctive microbiological and clinical findings in bicuspid aortic valve (BAV) and mitral valve prolapse (MVP) patients with infective endocarditis (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.

previously mentioned 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).

TABLE 4 **In-Hospital Mortality According to Poor Prognosis Factors**

	BAV (n = 54)	MVP (n = 89)	High-Risk Group (n = 1,226)	Low/Moderate-Risk Group (n = 1,839)	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, yrs	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)	1 (0–2)	3 (1–4)	5 (3–6)	5 (3–7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Nosocomial IE	5 (9.2)	7 (7.8)	441 (35.9)	456 (24.7)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Staphylococcal IE	8 (14.8)	16 (18.0)	450 (37.0)	765 (41.0)	**<0.01**	**<0.01**	**<0.01**	**<0.01**
logEuroSCORE	4 (3–18)	6 (4–21)	34 (16–60)	15 (6–36)	**<0.01**	**<0.01**	**<0.01**	**<0.01**

Value are median (interquartile range) or n (%). **Bold** p values are statistically significant.
Abbreviations as in Tables 1 and 3.

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 may 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 70.0% of patients with BAV and IE underwent cardiac surgery, which is similar to the percentage of individuals operated on in our registry (68.0%). Of note, the number of BAV patients with IE requiring cardiac surgery (75.9% indicated and 68.0% performed) was much higher than in the low or 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 on is also higher than what has been reported in both native and prosthetic IE series (surgical treatment around 50.0%) (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 or severe mitral regurgitation and those with flail leaflet: 289.5 cases per 100,000 person-years and 715.5 cases per 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 the low/intermediate-risk 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 5.0% to 10.0% 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 odontologic origin. While staphylococci were the predominant IE-causing agents in patients with IEAP indication and also in the nonindicated IEAP group, VGS were the most frequent in patients with BAV and MVP (35.2% and 39.3% of cases, respectively). Furthermore, the odontologic portal of entry was the most common origin of IE identified in BAV and MVP patients (14.8% and 18.0%, respectively), and it was significantly higher than that in the high-risk group (5.8%) and low/intermediate-risk group (6.0%). 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 (50.0% and 47.2% vs. 30.6%, respectively; both $p < 0.01$) and similar to the high-risk group (50.0% 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 odontologic 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.

STUDY LIMITATIONS. The information regarding IEAP before odontologic 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.

ADDRESS FOR CORRESPONDENCE: Dr. Pablo Garcia-Pavia OR Dr. Fernando Dominguez, Department of Cardiology, Hospital Universitario Puerta de Hierro, Manuel de Falla, 2, Majadahonda, Madrid, 28222, Spain. E-mail: pablogpavia@yahoo.es OR fdominguezrodriguez@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Individuals with BAV and MVP have a higher risk of developing IE than the general population does. IE in BAV and MVP 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 determine which patients may benefit from IEAP.

REFERENCES

1. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2015;387:882–93.

2. Jones TD, Baumgartner L, Bellows MT, et al. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation 1955;11:317–20.

3. Rammelkamp CH, Breese BB, Griffeath HI, et al. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation 1957;15:154–8.

4. Wannamaker LW, Denny FW, Diehl A, et al. Prevention of bacterial endocarditis. Circulation 1965;31:953–4.

5. Kaplan EL, Anthony BF, Bisno A, et al. Prevention of bacterial endocarditis. Circulation 1977;56:139–43.

6. Shulman ST, Amren DP, Bisno AL, et al. Prevention of bacterial endocarditis: a statement for health professionals by the Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease in the Young. Circulation 1984;70:1123–7.

7. Dajani AS, Bisno AL, Chung KJ, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. JAMA 1990;264:2919–22.

8. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. JAMA 1997;277:1794–801.

9. Wilson W, Taubert K, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation 2007;116:1736–54.

10. Horstkotte D, Rosin H, Friedrichs W, et al. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J 1987;8:379–81.

11. Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. Am J Med 1990;88:131–6.

12. Van der Meer JTM, Michel MF, Valkenburg HA, et al. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135–9.

13. Lacassin F, Hoen B, Leport C, et al. Procedures associated with infective endocarditis in adults. Eur Heart J 1995;16:1968–74.

14. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. Ann Intern Med 1998;129:761–9.

15. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis. Eur Heart J 2009;30:2369–413.

16. Ward C. Clinical significance of the bicuspid aortic valve. Heart 2000;83:81–5.

17. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;25:2789–800.

18. Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. Lancet 2005;365:507–18.

19. Katan O, Michelena HI, Avierinos JF, et al. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. Mayo Clin Proc 2016;91:336–42.

20. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. Lancet 2015;385:1219–28.

21. Pant S, Patel NJ, Deshmukh A, Gowala H, Patel N, Badheka A. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol 2015;65:2070–6.

22. Mackie AS, Liu W, Savu A, Marelli AJ, Kaul P. Reply to Letter From Thornhill. Infective endocarditis hospitalizations before and after the 2007 American Heart Association Prophylaxis Guidelines. Can J Cardiol 2016;32:1578.e11.

23. Keller K, von Bardeleben RS, Ostad MA, et al. Temporal trends in the prevalence of infective endocarditis in Germany between 2005 and 2014. Am J Cardiol 2017;119:317–22.

24. Van den Brink FS, Swaans MJ, Hoogendijk MG, et al. Increased incidence of infective endocarditis after the 2009 European Society of Cardiology guideline update: a nationwide study in the Netherlands. Eur Heart J Qual Care Clin Outcomes 2016;3:141–7.

25. Ramos-Martínez A, Roque F, Fariñas MC, et al. Prognostic factors of infective endocarditis in patients on hemodialysis: a case series from a National Multicenter Registry. Int J Cardiol 2017;241:295–301.

26. Martínez-Sellés M, Bouza E, Díez-Villanueva P, et al. Incidence and clinical impact of infective endocarditis after transcatheter aortic valve implantation. EuroIntervention 2016;11:1180–7.

27. Fernández-Cruz A, Cruz-Menárguez M, Muñoz P, et al. The search for endocarditis in patients with candidemia: a systematic recommendation for echocardiography? A prospective cohort. Eur J Clin Microbiol Infect Dis 2015;34:1543–9.

28. Ruiz-Morales J, Ivanova-Georgieva R, Fernández-Hidalgo N, et al. Left-sided infective endocarditis in patients with liver cirrhosis. J Infect 2015;71:627–41.

29. Dominguez F, Ramos A, Bouza E, et al. Infective endocarditis in hypertrophic cardiomyopathy: A multicenter, prospective, cohort study. Medicine (Baltimore) 2016;95:e4008.

30. Rivoisy C, Vena A, Schaeffer L, et al. Prosthetic valve Candida spp endocarditis: new insights into long term prognosis-the ESCAPE study. Clin Infect Dis 2018;66:825–32.

31. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36:3075–123.

32. Facklam R. What happened to the streptococci: overview of taxonomic and nomenclature changes. Clin Microbiol Rev 2002;15:613–30.

33. Parahitiyawa NB, Jin LJ, Leung WK, et al. Microbiology of odontogenic Bacteremia: beyond Endocarditis. Clin Microbiol Rev 2009;22:46–64.

34. Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. Eur Heart J 2018;39:586–95.

35. 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.

36. Desimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation 2012;126:60–4.

37. Dayer M, Thornhill M. Antibiotic prophylaxis guidelines and infective endocarditis: cause for concern? J Am Coll Cardiol 2015;65:2077–8.

38. Tubiana S, Blotiere PO, Hoen B, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and case crossover study. BMJ 2017;358:j3776.

39. Cahill TJ, Harrison JL, Jewell P, et al. Antibiotic prophylaxis for infective endocarditis: a systematic review and meta-analysis. Heart 2017;103:937–44.

40. Franklin M, Wailoo A, Dayer MJ, et al. The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis. Circulation 2016;134:1568–78.

41. Tornos P, Lung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005;91:571–5.

42. Piper C, Korfer R, Horstkotte D. Prosthetic valve endocarditis. Heart 2001;85:590–3.

43. Graupner C, Vilacosta I, San Roman J, et al. Periannular extension of infective endocarditis. J Am Coll Cardiol 2002;39:1204–11.

KEY WORDS antibiotic prophylaxis, bicuspid aortic valve, endocarditis, mitral valve prolapse

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.