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Infective endocarditis risk in patients with bicuspid aortic valve: Systematic review and meta-analysis

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ABSTRACT

Background: Antibiotic prophylaxis in bicuspid aortic valve patients is currently a matter of debate. Although it is no longer recommended by international guidelines, some studies indicate a high risk of infective endocarditis. We aim to evaluate the risk of native valve infective endocarditis in bicuspid aortic valve patients and compare to individuals with tricuspid aortic valve.

Methods: Study search of longitudinal studies regarding infective endocarditis incidence in bicuspid aortic valve patients (compared with tricuspid aortic valve/overall population) was conducted through OVID in the following electronic databases: MEDLINE, CENTRAL, EMBASE; from inception until October 2020. The outcomes of interest were the incidence rate and relative risk of infective endocarditis. The relative risk and incidence rate (number of cases for each 10 000 persons-year) with their 95 % confidence intervals (95 %CI) were estimated using a random effects model meta-analysis. The study protocol was registered at PROSPERO CRD42020218639.

Results: Eight cohort studies were selected, with a total of 5351 bicuspid aortic valve patients. During follow up, 184 bicuspid aortic valve patients presented infective endocarditis, with an incidence rate of 48.13 per 10,000 patients-year (95 %CI 22.24–74.02), and a 12-fold (RR: 12.03, 95 %CI 5.45–26.54) increased risk compared with general population, after adjusted estimates.

Conclusions: This systematic review and meta-analysis suggests that bicuspid aortic valve patients have a significant high risk of native valve infective endocarditis. Large prospective high-quality studies are required to estimate more accurately the incidence of infective endocarditis, the relative risk and the potential benefit of antibiotic prophylaxis.

1. Introduction

Infective endocarditis is a serious condition that still carries a high morbidity and mortality, with in-hospital mortality risk of around 20 % despite significant advances in diagnosis, antibiotic therapy, complications management and surgical techniques [1–3]. For that reason, it is important to identify predisposing risk factors and develop preventive strategies. Under some clinical scenarios, antibiotic prophylaxis is one of the preventive measures that aimed to reduce the incidence of infective endocarditis among high-risk patients [4].

High-risk patients have found to have an estimated incidence rate of around 100 per 10,000 person-years of infective endocarditis [5–9]. The high-risk group include those with valvular prothesis, some congenital heart defects (CHD), as cyanotic and repaired CHD and previous infective endocarditis [4,10].

Previously to the most recent guidelines, antibiotic prophylaxis was indicated to patients with intermediate and high-risk of infective endocarditis [4,10]. The evidenced low level of efficacy of antibiotic

Abbreviations: BAV, bicuspid aortic valve; CHD, congenital heart defects; IE, infective endocarditis; RR, relative risk.

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prophylaxis in infection prevention led to its restriction for high-risk patients after 2007 in the United States of America and after 2009 in Europe [10].

Bicuspid aortic valve (BAV) patients are considered of intermediate risk for infective endocarditis and antibiotic prophylaxis is not indicated [11]. However, this is the most common congenital cardiac abnormality, with an estimated prevalence of 0.5–2 % [12,13]. Older cohort studies have estimated the lifetime prevalence of infective endocarditis to be between 10 % and 30 % [7]. Nevertheless, these older studies presented numerous biases and more recent incidence estimates of native valve endocarditis in this population have been substantially lower, ranging from 2 to 5 % [12,14].

Recent studies, most of them of retrospective nature, have been published, but the results continue to be unclear regarding the true incidence and risk magnitude of infective endocarditis in BAV patients [15].

In this systematic review with meta-analysis, we intended to assess the incidence and relative risk of native valve infective endocarditis in BAV patients and compare it with background population.

2. Materials and methods

This systematic review was developed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [16]. The protocol was submitted to registration in PROSPERO CRD42020218639.

2.1. Eligibility criteria

This systematic review aimed to evaluate the incidence rate and the relative risk of infective endocarditis in patients with BAV in longitudinal studies (as cohort studies either prospective or retrospective or in case-control studies).

BAV patients could be identified in the studies through imaging methods or reported by the authors as having previous or newly diagnosed BAV at the time of the endocarditis. For relative risk estimation, we allowed comparators with tricuspid aortic valves (evaluated through imaging methods) or general population (assuming a small proportion of patients with BAV in this population).

2.2. Information sources and search methods

Study search was conducted through OVID in the following electronic databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE; from inception until October 2020. Full search strategy is detailed in supplementary data 1.

2.3. Study selection, data collection process and synthesis

Two reviewers evaluated independently the titles and the abstracts resulting from the search based on the inclusion criteria. In a second phase, the full-text reports of the studies not immediately rejected were assessed independently by the reviewers to determine whether they met the inclusion criteria. Any discrepancies were resolved by agreement. The data from each included study was introduced into a pre-piloted form. The information retrieved was: study design, year of publication, study location length of follow-up, sample size, participants characteristics in BAV and control groups and outcomes of interest.

The outcomes of interest were the absolute incidence of infective endocarditis cases in BAV patients per 10,000 patients/year and the relative incidence, versus tricuspid aortic valve individuals or the general population.

2.4. Risk of bias

The risk of bias was independently evaluated by two reviewers through the Newcastle–Ottawa Scale [17,18] adapted for this research as detailed in supplementary data 2. This tool assesses the risk of bias based on the comparability of study groups, selection of subjects and assessment of exposure in both cohort and case-control studies.

2.5. Statistical analysis

STATA software version 16.0 was used for statistical analysis and to derive forest plot showing the results of individual studies and pooled analysis.

When studies did not report the estimated incidence, the crude incidence was calculated using the number of exposed and period of follow up and reported as number of cases for each 10,000 persons-year with 95 % Confidence Interval (95 % CI) [18].

Random-effects meta-analysis was performed estimate pooled risk ratios and 95 % confidence intervals (95 % CIs), irrespectively of the statistical heterogeneity assessed through the I2 statistic. For this analysis we used the reported relative risk of each study. In absence of such adjusted risk ratio, we compared the crude incidence with the reference of 10 cases for 10,000 persons-year for general population [5–9], preserving the upper confidence interval for the ratio calculation.

Publication bias was assessed through visual inspection of funnel plot asymmetry and by Egger test (supplementary data 3).

3. Results

3.1. Study selection

The search yielded 395 articles. After applying the inclusion and exclusion criteria, 292 were excluded after screening the titles and abstracts and from the remaining 103 articles subjected to full-text assessment, 8 met the inclusion criteria[19–27](Fig. 1). The main reasons for exclusion were wrong included population and wrong study design, being detailed in supplementary data 4.

3.2. Design of the studies and main characteristics

The eight included studies are detailed in Table 1; seven cohort studies [19,20,22,24–27] and one case-control study [23] were included, being mostly retrospective [20,22–27]. Most of the studies were conducted in Europe (France, Netherlands, Italy, Portugal) and in North America (United States of America and Canada), being two multinational [23,24]. Kiyota *et al.* included patients with bicuspid and tricuspid aortic valves [23]. Verheugt *et al.* included a total of 10,210 patients with multiple CHD, presenting 551 BAV as the main CHD [22].

A total of 5351 BAV patients were included in this systematic review, 184 were diagnosed with infective endocarditis during follow up. The diagnosis of infective endocarditis was established by the modified Duke criteria in three studies [20,22,23], with the remaining without clear definition of the diagnostic criteria applied [19,24–27]. The follow up period ranged from 1.8 to 18.9 years [22,25].

Three of the included studies involved more than one cohort [19,20,23]. To fit the scope of the present systematic review, were excluded from analysis the cohorts which included patients with surgical indication.

3.3. Risk of infective endocarditis

The pooled analysis of the eight included studies showed that BAV patients had a risk of native valve infective endocarditis of 48 per 10,000 patients-year (95 %CI 22.24–74.02; Fig. 2), with an adjusted increased risk of 12-fold (relative risk (RR): 12.03, 95 %CI 5.45–26.54) and an overall increased risk of 37-fold (RR: 36.57, 95 %CI 21.49–62.24; Fig. 3) compared with general population.

Due to the disparity between the adjusted and calculated/unadjusted estimates, with great variability of RR obtained from studies (21 to 224

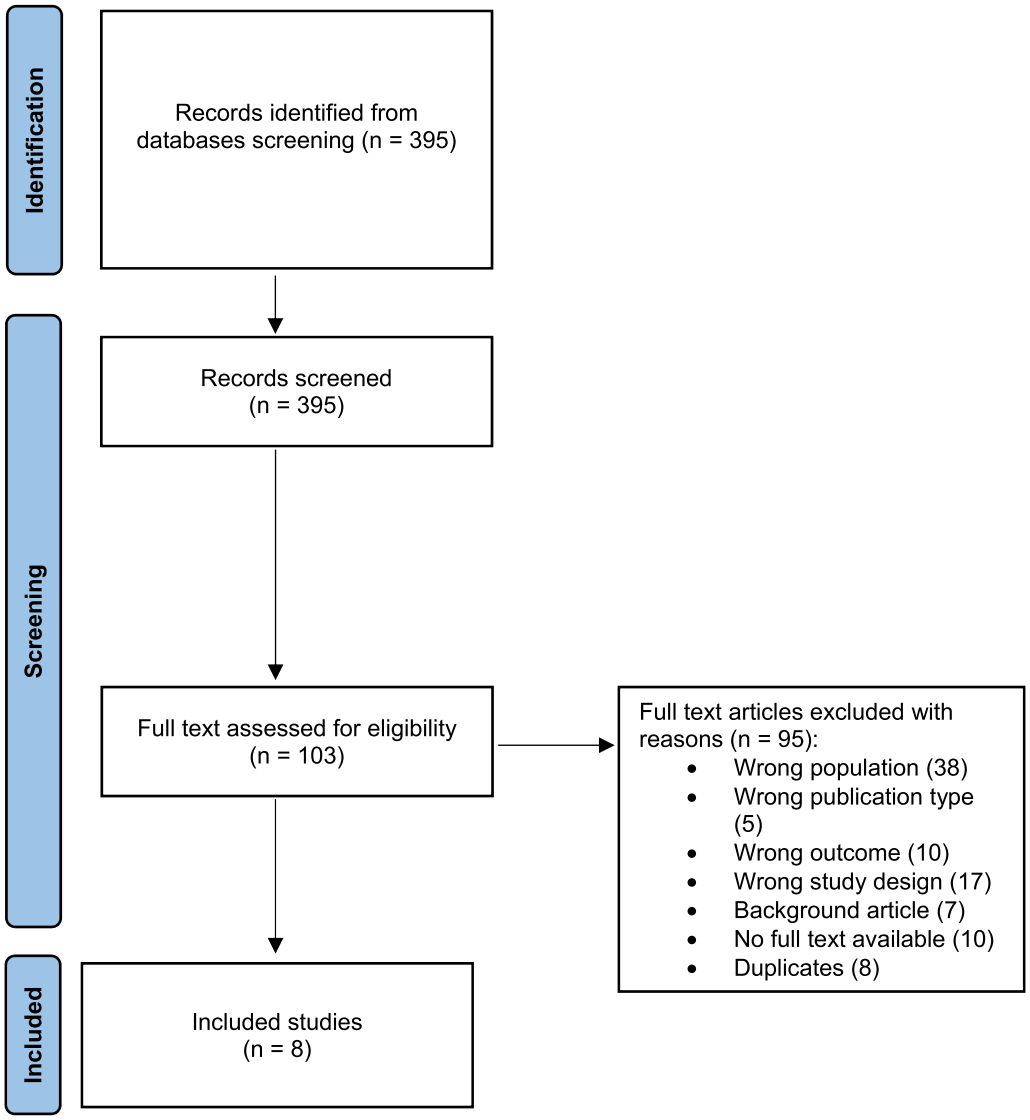

Fig. 1. Flowchart of the studies selection.

in the calculated estimates), we assume that the RR closer to the real risk of infective endocarditis in BAV patients is 12.03, 95 %CI 5.45–26.54.

The incidence rate of infective endocarditis in BAV patients from the included studies ranged from 9.90 (95 %CI 4.40, 15.40) per 10,000 patient-year in Michelena et al. to 108.80 (95 %CI 84.79, 132.82) per 10,000 patient-year in Kong *et al.* [20,21,24].

Kiyota *et al.* also included patients with tricuspid aortic valve in a case-control study. In the included US cohort, the authors found that BAV patients had a 23-fold higher relative risk of native infective endocarditis compared to tricuspid aortic valve patients (95 %CI 8.1, 100, $p < 0.0001$) [23]. Additionally, native valve endocarditis involving aortic valve was more frequent in BAV patients when compared to tricuspid aortic valve population (93 % vs 34 % in tricuspid aortic valve patients, $p < 0.0001$ in the US cohort).

Michelena *et al.* showed that male BAV patients present a higher risk of infective endocarditis when compared to women, with all patients from the community and tertiary center cohorts being males (11 patients) [20]. Nevertheless, these were expected results since there is a clear prevalence of BAV in males [28].

BAV infective endocarditis patients where significantly younger and had less comorbidities than tricuspid aortic valve patients in Kiyota *et al.*, although BAV patients presented an increased risk of native valve infective endocarditis independent of age [23].

Some of the included studies reported infective endocarditis local complications, with high rates of perivalvular abscess in BAV patients [19,23]. Kiyota *et al.* observed higher incidence of aortic root abscess in BAV patients with infective endocarditis, with higher rates of aortic valve replacement compared to tricuspid aortic valve infected patients (85 % vs 46 %). However, infective endocarditis was not an independent predictor of mortality in BAV patients. Despite the increased risk of infective endocarditis complications and aortic valve surgery, BAV did not associate with increased in 1 or 5 year mortality when compared to TAV, which can be partly explained by the younger age and fewer comorbidities verified in BAV patients [23].

Only one included study described the microbiology data: Kiyota *et al.* observed a lower incidence of high risk infectious agents such as *Staphylococcus Aureus* in BAV patients when compared to tricuspid aortic valve patients. No statistically significant differences regarding pathogens in patients with aortic root abscess were reported [23].

3.4. Publication bias

Visual inspection of funnel plot reveled no important asymmetries (supplementary data 3) and the Egger test result was non-significant result ($p = 0.15$).

Table 1
Summary of the main characteristics of the included studies.

Study, year	Study design	Location	Data source	Inclusion period	Condition	Main endpoint	Population n	Age (Y)	Males n	IE n	Definition of IE	Follow-up period
Cheng et al. 2020[19]	Prospecti-ve	France	Tertiary center Somme French Department	2005–2017	>18 years of age diagnosed with BAV; Included patients with no surgical indication	Clinical course and long term outcomes of BAV patients	BAV: 350 TAV: NA	53 ± 16	249	BAV: 5 TAV: NA	Unspecified	6.7 IQR: 2.7–9.6Y
Michelena et al. 2016 [20,21]	Retrospec-tive	USA	Community cohort from Olmsted County	1980–1999	First BAV echocardiographic diagnosis	All-cause mortality, long term outcomes	BAV: 416[1] TAV: NA	35 ± 2	288	BAV: 9 TAV: NA	Modified Duke criteria	16 ± 7Y
Verheught et al. 2011 [22]	Retrospec-tive	Netherlands	Dutch CONCOR national registry	11/2001 – 03/2009	Adults with CHD that developed IE during adulthood	Prediction of IE up to the age of 40 and 60 years old	BAV: 551 TAV: NA	NS	NS	BAV: 31 TAV: NA	Modified Duke criteria	18.9 IQR: 0.1–75.5Y
Kiyota et al. 2017 [23]	Retrospec-tive, case-control	USA - Boston, Massa-chusetts	Medical records from urban network healthcare	01/ 2000–06/ 2014	Adults with a first native valve IE and received antibiotics	Determine the risk of IE of BAV compared with TAV	BAV: 1122 TAV: 18,727	BAV with IE: <59Y: 31 TAV with IE: <59Y:176	7323	BAV: 38 TAV: 127	Modified Duke criteria	4.8 ± 3.9Y
Kong et al. 2017 [24]	Retrospec-tive	Netherlands Singapore, Australia, Canada and Romania	Multicenter regitry	1991–2015	BAV documented on transthoracic echocardiography and complete clinical record data	Sex-related differences in valve morphology, dysfunction at presentation, aortopathy, IE, and aortic dissection	BAV: 1992 TAV: NA	46.8 ± 17.5	1424	BAV: 78 TAV: NA	Unspecified	5.4Y
Pachulski et al. 1993 [25]	Retrospec-tive	Canada	Echocardiography laboratory database	1985–1989	BAV patients and serial Doppler echocardiographic examinations	Assess the pattern of valve dysfunction progression	BAV: 51[2] TAV: NA	36 IQR: 21–67	40	BAV: 2 TAV: NA	Unspecified	1.8 IQR: 0.5–3.8Y
Rodrigues et al. 2017 [26]	Retrospec-tive	Portugal - Lisbon	Hospital database	1990–09/ 2015	BAV patients not submitted to aortic valve replacement or ascending aortic graft surgery	Assess the incidence and predictors of cardiac events	BAV: 227 TAV: NA	28 ± 14	101	BAV: 11 TAV: NA	Unspecified	13 ± 9Y
Tzemos et al. 2008 [27]	Retrospec-tive	Canada	University Health Network echocardiogra-phy and CHD database	1994–2001	BAV on transthoracic echocardiography and absence of complex congenital cardiac defects	Assess the frequency and predictors of cardiac outcomes in BAV patients	BAV: 642[3] TAV: NA	31 IQR: 16–78	437	BAV: 10[3] TAV: NA	Unspecified	9 ± 5Y

n: number of patients; IE: infective endocarditis; BAV: Bicuspid aortic valve; TAV: tricuspid aortic valve; CHD: congenital heart defects; NA: not applicable; NS: not specified; Y: years; IQR: interquartile range.
[1] During follow up 5 patients were submitted to aortic valve replacement; [2]During follow up 6 patients were submitted to aortic valve replacement; [3]142 patients submitted to surgery (ascending aorta/aortic valve replacement) during follow up; 3 patients were excluded due to prothesic infective endocarditis.

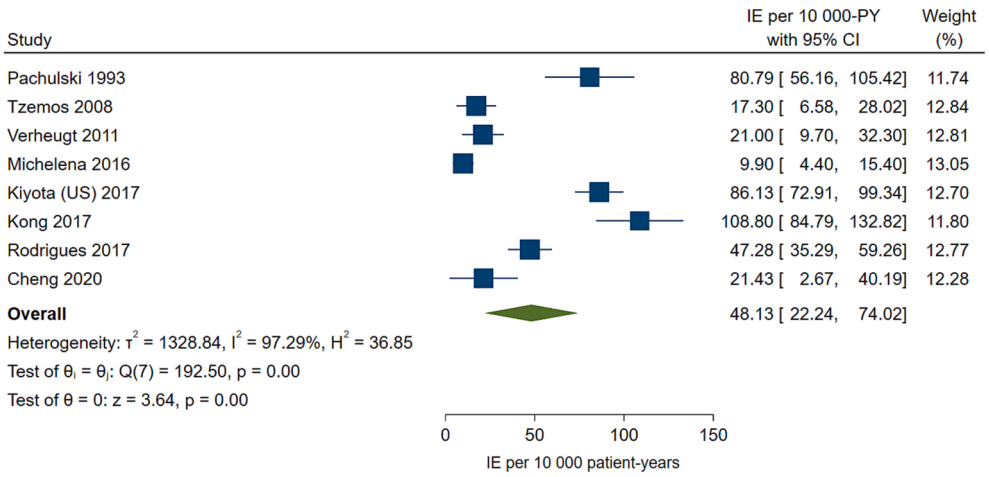

Fig. 2. Forest plot of the estimated incidence rate of infective endocarditis in bicuspid aortic valve patients, IE: infective endocarditis; PY: per year; BAV: bicuspid aortic valve.

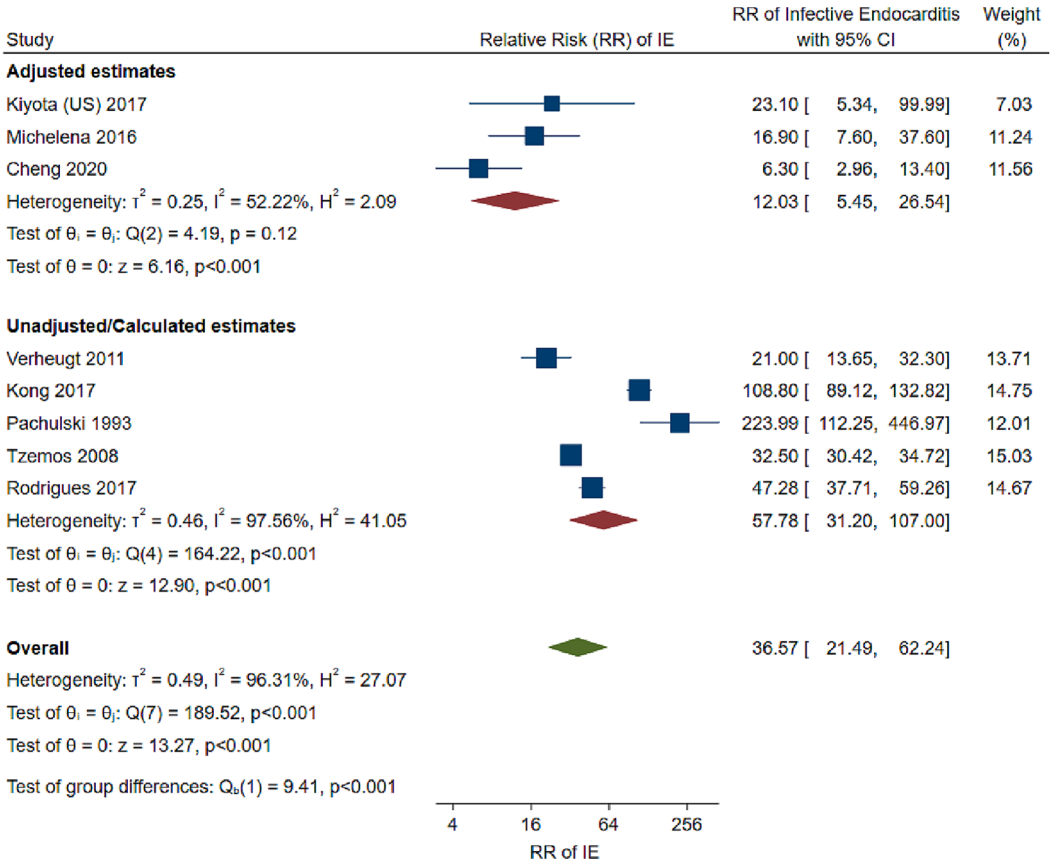

Fig. 3. Forest plot of the adjusted and calculated ratio of infective endocarditis in bicuspid aortic valve patients, IE: infective endocarditis; PY: per year; BAV: bicuspid aortic valve.

4. Discussion

The main finding of this systematic review is that the included BAV patients had a significant high risk of native valve infective endocarditis during follow up, being 12-fold higher than general population after adjusted estimates, with an estimated incidence of 48 per 10,000 patients per year. We considered that the incidence rate of infective endocarditis in background population, assuming that most of patients have tricuspid aortic valves, is 10 in 100,000 patients per year according to the available data [5–9].

In a Danish study, the high-risk patients defined by the European and American guidelines, namely prior infective endocarditis, valvular prothesis and cyanotic and repaired CHD presented an incidence rate of infective endocarditis of 161/10,000, 60/10,000 and 15/10,000 patient-years [6]. Compared to a previous old review, the incidence of infective endocarditis in patients with prior infective endocarditis (74/10,000 patient-years) and valvular prothesis (31–38/10,000 patient-years) was higher in this recent study [29].

Another study that included 3 groups of patients with moderate risk of infective endocarditis (valve disorders, cardiac implantable electronic

device, and hypertrophic cardiomyopathy) showed that the incidence risk was 8-fold higher than the background population with an incidence rate per 10,000 patient-years of 15.6, 18.9 and 7.1, respectively [30].

BAV patients in our systematic review present an estimated incidence that is higher than patients at moderate risk and similar to the reported incidence in high-risk patients. This is particularly relevant since the restriction of the indications for antibiotic prophylaxis initiated in 2007 according to the lack of evidence showing a clear risk/benefit in moderate risk patients [10]. However, the question that needs to be answered is if BAV patients have intermediate or high-risk of infective endocarditis, since there is no clearly defined incidence rate of infective endocarditis for patients at high-risk. Besides the limitations of our data, considering the incidence rate of infective endocarditis previously reported in the Danish studies for high and moderate risk groups [6,30], we believe that BAV patients are closer to the high-risk group, namely valvular prothesis and cyanotic and repaired CHD. Furthermore, some of the included studies observed higher rates of local complications as aortic root or perivalvular abscess and need of early surgery with aortic valve replacement in BAV patients, especially in the younger ones, suggesting a more aggressive course of the disease that should be taken into consideration when estimating the risk of infective endocarditis in these patients [19,23].

A study published by Tribouilly *et al.* observed that the incidence of perivalvular abscess was higher in BAV patients (50 % vs 20 %, $p < 0.001$) putting these patients at higher risk of early surgery (82 % vs 57 %, $p < 0.001$). Additionally, the authors found that the presence of BAV (odds ratio (OR) 3.79 (1.97–7.28); $p < 0.001$), as well as uncontrolled infection, were the only two independent predictors of abscess formation in infective endocarditis patients [31]. Therefore, these patients may benefit from antibiotic prophylaxis.

The pathophysiology of infective endocarditis in BAV is not well stablished. Commonly, this valvular congenital abnormality present high rates of valvular dysfunction earlier in life (4th–5th decade) [32]. The different flow patterns through a BAV may explain additional endothelial damage, with platelet and fibrinogen deposition that facilitates haematogenic bacteria or fungi seeding [33]. As shown by Kyota *et al.*, BAV patients have more often aortic valve-only infective endocarditis when compared to control population, possibly meaning that BAV constitute a preferential seeding site for bacterial growing. Additionally, the lower incidence of highly destructive pathogens as Staphylococcus Aureus observed in BAV patients is of particular interest, considering that BAV patients presented an increased risk of destructive infective endocarditis [23]. This data suggests that a more aggressive course of the disease in BAV patients does not seem to be attributed to presence of a high pathogenicity microorganism.

In necropsy studies, the incidence of infective endocarditis ranges from 15.3 to 40 % in BAV patients and was identified as the primary cause of aortic insufficiency in this population [34,35]. *Fenoglio et al.* performed autopsies in 152 BAV patients and found that infective endocarditis was the major cause of death in these patients, particularly in younger ages, with 77 % of patients being under the age of 50 years old [35]. Another study that included 91 autopsies in BAV patients identified infective endocarditis as the third major cause of death, responsible for 11 % of the deceases [36].

This systematic review did not address the relationship between significant BAV dysfunction and higher risk of infective endocarditis, neither evaluates the risk of aortic valve infective endocarditis, but the risk of native infective endocarditis in BAV patients.

The included studies had several limitations. Some studies did not adequately characterize BAV population, describing solely the incidence of infective endocarditis on characterization of BAV outcomes [19,20,25–27]. The studies included data collected over the last three decades, which can compromise the comparability between them considering the advances in diagnosis, improved antimicrobial treatment and earlier detection of complications via transesophageal echocardiography.

Moreover, some studies did not specify the applied diagnostic criteria, which can cause some doubt regarding the reliability of the established diagnosis. Most of the included studies derived from cohorts of patients from tertiary or referral centers with potential bias of selection that might also explain this high incidence of infective endocarditis [19,20,24,26,31]. The retrospective nature of most studies, with data obtained by consulting clinical records, can be a source of missing information and incomplete follow up. All included studies are unclear regarding possible infective endocarditis driven events, as dental hygiene, and prior exposition to antibiotic prophylaxis, which could be useful to better determine the clinical usefulness of the results. Additionally, none of the included studies addressed antibiotic prophylaxis of infective endocarditis in this population and no information was provided regarding the prior administration of antibiotics.

To our knowledge, this is the first systematic review that evaluates the incidence rate of infective endocarditis in BAV patients. We included a significant number of BAV patients and cohorts from different countries, in an attempt to represent the real BAV population. This study indicates that the incidence-rate of infective endocarditis in this population is higher than the one previously reported in patients with moderate risk, therefore, general measures to prevent infective endocarditis, such as good oral hygiene, should be reinforced in these patients. The use of antibiotic prophylaxis is still doubtful but may be considered in the presence of other risk factors for infective endocarditis.

Randomized controlled trials with antibiotics prior to procedures prone to bacteriemia in this BAV patients would be useful, but we anticipate difficulties in the recruitment of BAV patients and in a large sample size required to achieve robust conclusions. Finally, we consider that our findings, although with the mentioned limitations, provide useful evidence that should be considered when evaluating this subgroup of patients in clinical practice.

5. Conclusions

BAV patients have a significant risk of infective endocarditis, higher than patients at moderate risk and closer to the previously reported in high-risk patients. Large prospective high-quality studies are required to estimate more accurately the incidence of infective endocarditis, the relative risk, and the potential benefit of antibiotic prophylaxis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data 1 (search strategy used in Ovid), 2 (risk of bias), 3 (funnel plot) and 4 (key excluded studies) to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101249.

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