ORIGINAL RESEARCH

Impact of Valve Morphology on the Prevalence of Coronary Artery Disease: A Systematic Review and Meta-Analysis

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***Background*—**Literature studies suggested a lower prevalence of coronary artery disease (CAD) in bicuspid aortic valve (BAV) than in tricuspid aortic valve (TAV) patients. However, this finding has been challenged. We performed a meta-analysis to assess whether aortic valve morphology has a different association with CAD, concomitant coronary artery bypass grafting (CABG), and postoperative mortality.

***Methods and Results*—**Detailed search was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline to identify all patients with BAV or TAV and presence of CAD, concomitant myocardial surgical revascularization, and the postoperative mortality. Thirty-one studies on 3017 BAV and 4586 TAV patients undergoing aortic valve surgery were included. BAV patients showed a lower prevalence of CAD (odds ratio [OR]: 0.33; 95% CI: 0.17, 0.65), concomitant CABG (OR, 0.45; 95% CI: 0.35, 0.59), and postoperative mortality (OR, 0.62; 95% CI: 0.40, 0.97) than TAV. However, BAV subjects were significantly younger than TAV (mean difference: −7.29; 95% CI: −11.17, −3.41) were more frequently males (OR, 1.61; 95% CI: 1.33, 1.94) and exhibited a lower prevalence of hypertension (OR, 0.58; 95% CI: 0.39, 0.87) and diabetes (OR, 0.71; 95% CI: 0.54, 0.93). Interestingly, a metaregression analysis showed that younger age and lower prevalence of diabetes were associated with lower prevalence of CAD (Z value: −3.03; P=0.002 and Z value: −3.10; P=0.002, respectively) and CABG (Z value: −2.69; P=0.007 and Z value: −3.36; P=0.001, respectively) documented in BAV patients.

***Conclusions*—**Analysis of raw data suggested an association of aortic valve morphology with prevalence of CAD, concomitant CABG, and postoperative mortality. Interestingly, the differences in age and diabetes have a profound impact on prevalence of CAD between BAV and TAV. In conclusion, our meta-analysis suggests that the presence of CAD is independent of aortic valve morphology. **(*J Am Heart Assoc*. 2016;5:e003200 doi: 10.1161/JAHA.116.003200)**

Key Words: aortic valve morphology • bicuspid aortic valve • coronary artery disease

Aortic valve stenosis (AVS) is considered the most prevalent form of valve disease.[1,2] The number of people affected by this progressive and debilitating pathology will increase because of the aging population, causing an ever-increasing public health burden.[3] Traditionally, it was thought that AVS was related to valve degeneration attributed to aging, caused by several years of mechanical stress and biological response to such injury. However, more recently, several risks factors have been linked to the development of AVS, including male sex, hypertension, hyperlipidemia, smoking, advanced age, and congenital bicuspid valve morphology.[4,5] Overall, AVS pathogenesis is a multifactorial process and seems to be related to coronary atherosclerosis. In detail, an important link between AVS and early stages of coronary

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Accompanying Figures S1 and S2 and Table S1 are available at http://jaha.ahajournals.org/content/5/5/e003200/DC1/embed/inline-supplementary-material-1.pdf

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atherosclerotic plaque has been hypothesized,[6–8] and a multitude of studies have been published regarding the associations between AVS, coronary artery disease (CAD), and coronary artery bypass grafting (CABG).[9–12] In addition, a very recent study by Boudoulas et al.[13] describes the association between aortic stenosis and CABG focusing on valve morphology and concluding that "the incidence of coronary artery disease is extremely high in patients with aortic stenosis and tricuspid aortic valve." However, literature data are not consistent about this issue, and data about such an association have been challenged. In addition, the critical review of available studies highlights that, in most cases, only univariate unadjusted analyses were used, seldom taking into account for potential confounders. Thus, the aim of this study was to perform a meta-analysis of literature studies enrolling patients undergoing aortic valve surgery to assess whether aortic valve morphology (tri- or bicuspid) impacts on prevalence of CAD, concomitant CABG, and postoperative mortality. In addition, to assess the presence of potential confounders, we evaluated the impact of distribution of major clinical and demographic variables between patients with bi- or tricuspid aortic valve.

Methods

A protocol for this review was prospectively developed, detailing the specific objectives, criteria for study selection, outcomes, and statistical methods.

Search Strategy

To identify all available studies pertaining to prevalence of CAD, defined by atherosclerosis of 1 or more arteries that supply blood to the heart causing oxygen deficiency in the myocardium, we included articles with anamnestic CAD also when it was not specified whether it was anatomical CAD (70% stenosis or greater in at least 1 major coronary artery) or clinical CAD (previous acute myocardial infarction or percutaneous coronary intervention). A detailed search was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines[14] to identify all concomitant myocardial surgical revascularization (CABG) and postoperative mortality in patients with bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) undergoing aortic valve surgery. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, and EMBASE), using the following search terms in all possible combinations: tricuspid aortic valve; bicuspid aortic valve; coronary artery disease; coronary artery bypass; myocardial infarction; mortality; and death. The last search was performed in November 2015. The search strategy was developed without any language or publication year restriction. In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, the authors were contacted by e-mail to try to retrieve original data. Two independent authors (P.P. and M.N.D.D.M.) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (L.C.). Discrepancies were resolved by consensus. Selection results have been reported according to the PRISMA flow chart (Figure 1).

Data Extraction and Quality Assessment

According to the prespecified protocol, all studies evaluating prevalence of CAD or use of CABG or postoperative mortality in patients with BAV and in those with TAV undergoing aortic valve replacement were included in the analysis. Case reports, reviews, animal studies, and studies on natural history of patients with aortic valve disease (not undergoing surgery) were excluded. In each study, data regarding sample size, major clinical and demographic variables, number of patients with CAD, and number of those undergoing CABG and those dying postoperatively were extracted. Formal quality score adjudication was not used, because previous investigations failed to demonstrate its usefulness.[15]

Statistical Analysis and Risk of Bias Assessment

Statistical analysis was carried out using Comprehensive Meta-analysis (version 2 [2005]; Biostat, Englewood, NJ). Differences among BAV and TAV subjects were expressed as mean difference (MD) with pertinent 95% CIs for continuous variables, and as odds ratio (OR) with pertinent 95% CI for dichotomous variables. Overall effect was tested using Z scores, and significance was set at $P<0.05$. Statistical heterogeneity among studies was assessed with the chi-square Cochran's Q test and with the I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is, attributed to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25% to 50% moderate, and 50% high heterogeneity.[16]

Publication bias was assessed by the Egger test and represented graphically by funnel plots of the standard difference in means versus SE. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, as well as the Egger test to address publication bias, over and above any subjective evaluation. $P<0.10$ was considered statistically significant.[17] In order to be as conservative as possible, the random-effect method

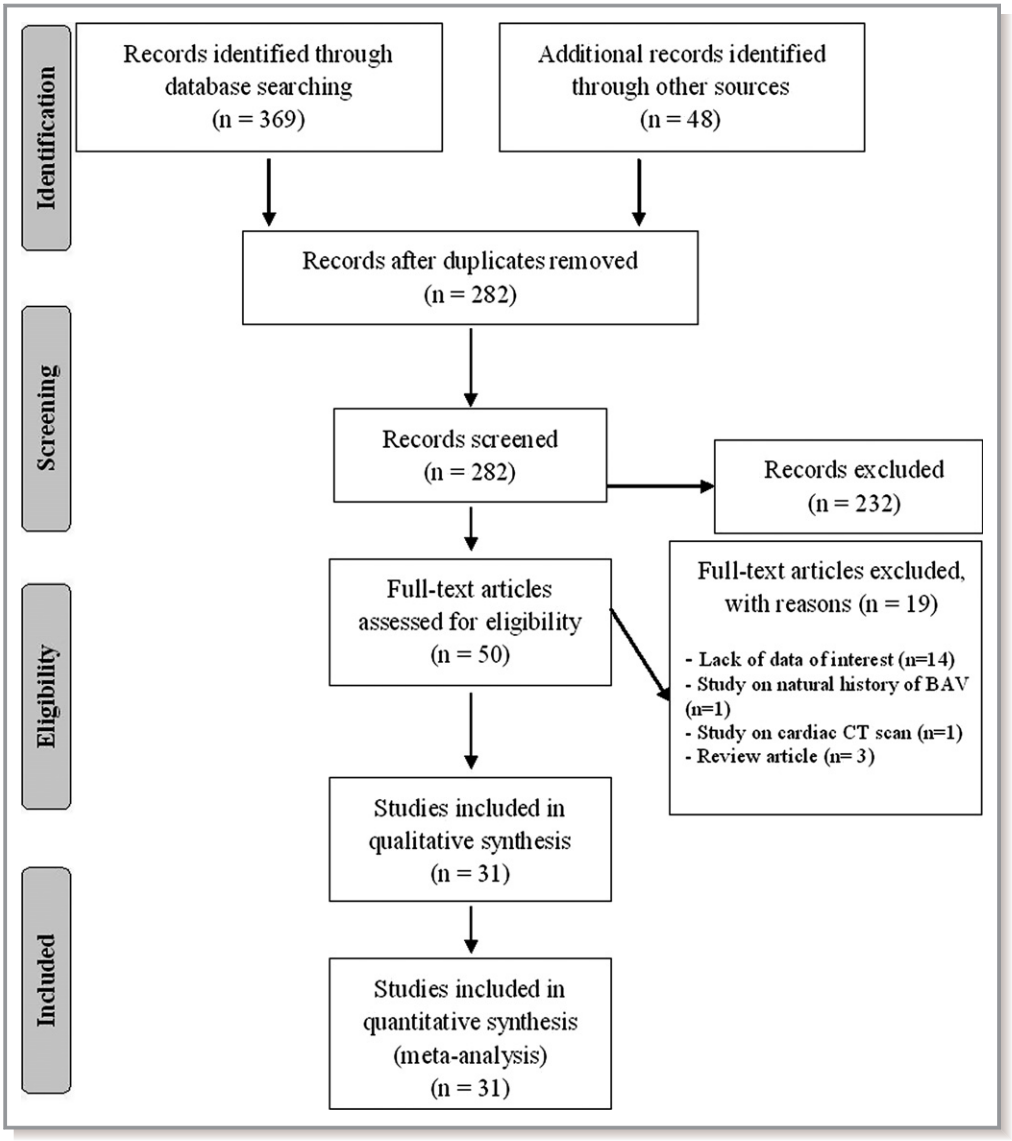

Figure 1. PRISMA flow diagram. BAV indicates bicuspid aortic valve; CT, computed tomography.

was used to take into account the variability among included studies.

Metaregression Analyses

We hypothesized that differences in prevalence of CAD, use of CABG, or postoperative mortality between BAV and TAV patients may be affected by differences in clinical and demographic characteristics of patients included in different studies (mean age, sex, body mass index [BMI], hypertension, diabetes mellitus, hyperlipidemia, and smoking habit). To assess the possible effect of such variables in explaining the different results observed across studies, we planned to perform metaregression analyses after implementing a regression model with prevalence of CAD, use of CABG, or postoperative mortality between BAV and TAV patients as dependent variables (y) and the variables mentioned above as independent variables (x).

Results

After excluding duplicate results, the search retrieved 282 articles. Of these studies, 232 were excluded because they were off the topic after scanning the title and/or the abstract and 19 because they were reviews/comments/case reports or they lacked data of interest.

Thus, 31 articles (3017 BAV patients and 4586 TAV patients) were included in the final analysis (Figure 1). In detail, 15 studies with data on prevalence of CAD (1163 BAV and 2234 TAV patients), 16 reporting on use of CABG (1782 BAV and 1886 TAV patients), and 16 on postoperative mortality rate (1067 BAV and 2399 TAV patients) were included.

Table 1. Demographic and Clinical Data of BAV and TAV

Author (Year)	Reported Outcomes	Observation Time		Subjects	Age, y	Males	Hypertension	Hyperlipidemia	Diabetes	BMI	Smoking
Abdulkareem 2013[18]	CABG		BAV	192	58	71.3					
			TAV	203	65	62.5					
Ali 2010[19]	CABG, mortality	7 years	BAV	90	63	78.9	31.1	12.2	5.6		
			TAV	125	70	58.4	32.0	16.8	11.2		
Asano 2012[20]	CABG, mortality	5 years	BAV	86	46.3						
			TAV	58	70						
Badiu 2010[21]	CAD, CABG, mortality	5 years	BAV	11	37	100.0	45.5	9.1			
			TAV	91	48	63.7	69.2	36.3	4.4		
Boudoulas 2015[13]	CABG		BAV	95	62	71.6	70	61	31		53
			TAV	175	71	55.4	87	60	47		48
Branchetti 2014[22]	CAD		BAV	74	55.5	64.9	31.1	27.0	5.4		43.2
			TAV	61	64.4	70.5	42.6	42.6	13.1		19.7
Costopoulos 2014[23]	Mortality	1 year	BAV	21	76.7	57.1	66.7		28.6	26.6	
			TAV	447	79.8	47.4	77.2		30.2	26.1	
Davies 1996[24]	CABG		BAV	296							
			TAV	125							
Delius 1998[25]	Mortality	10 years	BAV	16							
			TAV	31							
Eleid 2013[26]	CAD, CABG		BAV	47	58	76.6	68.1	48.9	8.5		23.4
			TAV	53	66	75.5	86.8	49.1	11.3		13.2
Etz 2015[27]	CAD, mortality	Inhospital	BAV	32	46.7	71.9	46.9				15.6
			TAV	347	61.6	63.7	72.0		9.2		10.7
Girdauskas 2014[28]	Mortality	10 years	BAV	153	54	73.2	48.4		11.1		35.9
			TAV	172	64	47.7	57.0		15.7		40.1
Holubec 2014[29]	CAD, CABG, mortality	2 years	BAV	60	45*	81.7	45.0				
			TAV	40	59*	67.5	75.0				
Hwang 2011[30]	CAD, mortality	10 years	BAV	45	59.6	60.0	44.4	2.2	6.7		26.7
			TAV	43	58.3	48.8	23.3	2.3	9.3		9.3
Jackson 2014[9]	CAD		BAV	292	61.1	73.6	51.0		11.3		
			TAV	355	717	69.9	74.6		14.9		
Kochman 2014[31]	CAD, mortality	1 year	BAV	28	77.6	46.4	60.7		39.3		
			TAV	84	79.1	47.6	65.5		34.5		
Kvitting 2013[32]	CABG		BAV	63	43	79.4	36.5		4.8	26	
			TAV	170	36	67.6	25.9		2.4	24	
Liu 2015[33]	CAD, mortality	30 days	BAV	15	75.4	60.0	33.3			23.6	
			TAV	25	75.8	68.0	56.0		12.0	21.7	
Mosalanezhad 2014[34]	CABG, mortality	8 years	BAV	30	42	93.3					
			TAV	20	59	75.0					

Continued

Table 1. Continued

Author (Year)	Reported Outcomes	Observation Time		Subjects	Age, y	Males	Hypertension	Hyperlipidemia	Diabetes	BMI	Smoking
Nakamura 2014[35]	CAD		BAV	17	70	76.5	58.8	35.3	17.6		35.3
			TAV	59	77	52.5	79.7	33.9	20.3		40.7
Philip 2015[10]	CAD		BAV	200	57		23.5	21.5	10.5		
			TAV	200	78		76.5	78.5	31.5		
Roberts 2003[11]	CABG		BAV	232	64.7	72.0					
			TAV	267	74	51.3					
Roberts 2007a[36]	CABG, mortality	5 years	BAV	102							
			TAV	18							
Roberts 2007b[37]	CABG, mortality	4 years	BAV	187							
			TAV	235							
Roberts 2007c[38]	CABG		BAV	54							
			TAV	142							
Roberts 2007d[39]	CABG, mortality	13 years	BAV	180							
			TAV	107							
Rylski 2014[12]	CAD, mortality	Inhospital	BAV	41	55*	63.4	56.1		9.8		
			TAV	588	61*	64.1	81.1		9.2		
Shim 2011[40]	CAD		BAV	50	52	78.0	40.0	20.0	12.0	24.7	32.0
			TAV	50	52	78.0	50.0	28.0	8.0	25.2	42.0
Stephan 1997[41]	CABG		BAV	57	67	57.9					
			TAV	57	73	54.4					
Warner 2013[42]	CAD		BAV	10	46.5	60.0	50.0	40.0	10.0	30.1	10.0
			TAV	13	46.3	76.9	38.5	46.2			23.1
Yuan 2010[43]	CAD		BAV	241	56.1	77.2	30.7	24.1	10.8		
			TAV	225	62.8	64.0	41.8	24.9			

*Data reported as median value. BAV indicates bicuspid aortic valve; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; TAV, tricuspid aortic valve.

Study Characteristics

Major characteristics of the 31 studies included in the meta-analysis are shown in Table 1.

The number of patients varied from 23 to 647, mean age from 36 to 79.8 years, and prevalence of male sex from 47.4% to 100%. Presence of hypertension was reported by 23.3% to 87.0% of patients, smoking habit by 9.3% to 53.0%, diabetes mellitus by 2.4% to 47.0%, and hyperlipidemia by 2.2% to 78.5%. Mean BMI varied from 21.7 to 30.1 kg/m^2. Length of follow-up for mortality assessment ranged from in-hospital stay period to 13 years with a median of 5 years.

Coronary Artery Disease

Fifteen studies,* for a total of 1163 BAV and 2234 TAV patients, showed that CAD was reported by 13.5% of BAV and 30.3% of TAV patients (OR, 0.33; 95% CI: 0.17, 0.65; P=0.001; Figure 2). Heterogeneity among studies was significant (I^2=86%; P<0.001), and it was not reduced by the exclusion of one study at a time. In addition, after excluding 2 studies by Kochman et al.[31] and Liu et al.,[33] including patients undergoing transcatheter aortic valve implantation (TAVI), the results were entirely confirmed (OR, 0.31; 95% CI: 0.14, 0.66; P=0.002; I^2=88%; P<0.001).

Concomitant CABG

Sixteen studies,** reporting on 1782 BAV and 1886 TAV patients, showed that the number of patients undergoing concomitant CABG was significantly lower between BAV than TAV patients (31.0% vs 45.7%; OR, 0.45; 95% CI: 0.35, 0.59; P<0.001; Figure 3). Heterogeneity among studies was significant (I^2=56%; P=0.003). However, after excluding the study by

*References 9, 10, 12, 21, 22, 26, 27, 29–31, 33, 35, 40, 42, 43.

**References 11, 13, 18–21, 24, 26, 29, 32, 34, 36–39, 41.

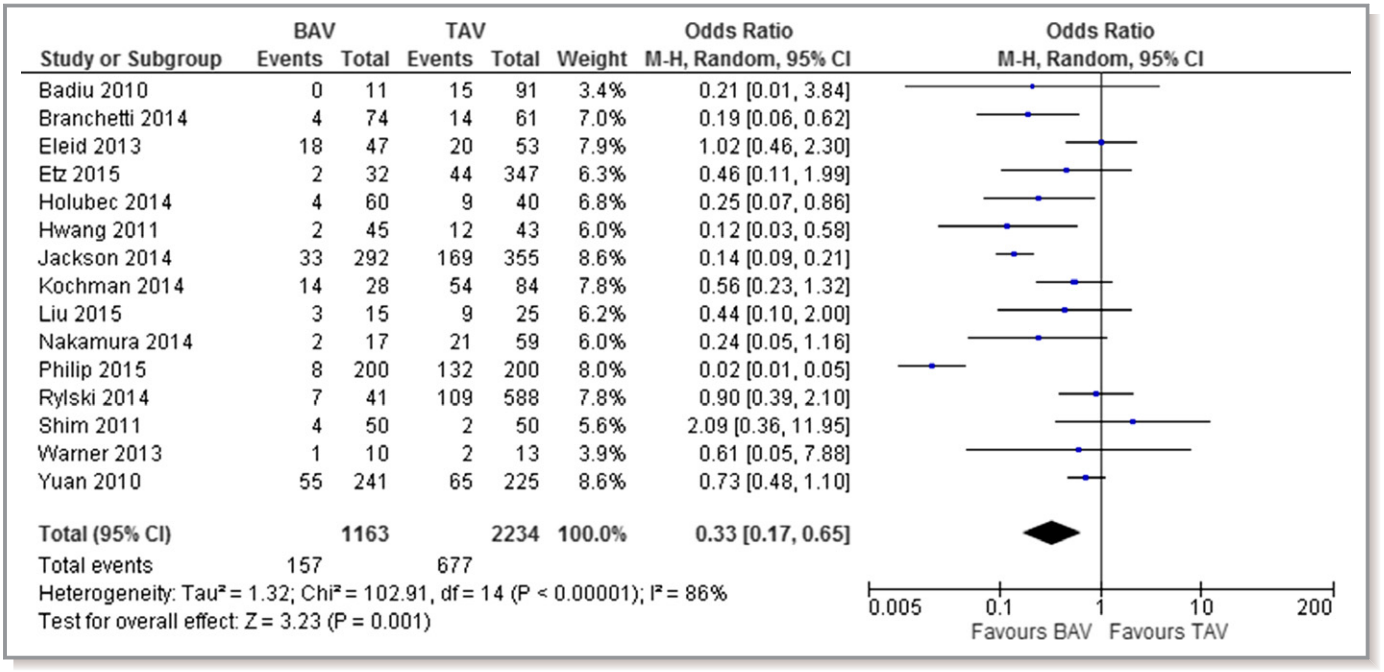

Figure 2. Prevalence of coronary artery disease in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

Asano et al.,[20] all results were confirmed without heterogeneity (OR, 0.49; 95% CI: 0.39, 0.61; $P<0.001$; $I^2=37\%$; $P=0.07$).

Postoperative Mortality

The 16 studies*** evaluating postoperative mortality showed a slightly significant difference in rate of mortality between BAV and TAV patients (16.2% vs 18.8%; OR, 0.62; 95% CI: 0.40, 0.97; $P=0.04$; $I^2=65\%$; $P<0.001$; Figure 4). Interestingly, a metaregression analysis showed that the mortality rate was independent by the length of the observation (Z value: −1.17; $P=0.240$). In addition, we conducted a subanalysis removing the 3 studies[23,31,33] that analyzed patients undergoing TAVI; the results did not differ from the previous ones (OR, 0.51; 95% CI: 0.32, 0.84; $P=0.006$; $I^2=63\%$; $P=0.001$).

Clinical and Demographic Variables

As showed in Figure S1, when major clinical and demographic characteristics have been compared between BAV and TAV patients, we found that BAV subjects were significantly younger than TAV (MD, −7.29; 95% CI: −11.17, −3.41; $P<0.001$). In addition, BAV subjects were more frequently males (72.7% vs 60.1%; OR, 1.61; 95% CI: 1.33, 1.94; $P<0.001$) and exhibited a lower prevalence of hypertension (43.0% vs 65.4%; OR, 0.58; 95% CI: 0.39, 0.87; $P<0.001$) and diabetes (11.6% vs 16.3%; OR, 0.71; 95% CI: 0.54, 0.93; $P=0.01$) than TAV. In contrast, no significant differences were found in prevalence of hyperlipidemia and smoking habit as well as in mean BMI between BAV and TAV patients.

Interestingly, a metaregression analysis showed that younger age and lower prevalence of diabetes were associated with lower prevalence of CAD (Z value: −3.03; $P=0.002$ and Z value: −3.10; $P=0.002$, respectively; Figure 5) and CABG (Z value: −2.69; $P=0.007$ and Z value: −3.36; $P=0.001$, respectively; Figure 6) documented in BAV patients as compared to TAV patients.

Sensitivity Analysis

Given the statistically significant difference in distribution of age, sex, hypertension, and diabetes between BAV and TAV patients, all the analyses have been repeated after including only studies enrolling patients comparable for all these variables.[30,33,40–42] Interestingly, the difference in prevalence of CAD (OR, 0.65; 95% CI, 0.33, 1.26; $P=0.20$) and mortality rate (OR, 1.77; 95% CI, 0.81, 3.87; $P=0.15$) were no longer significant. None of the 5 studies enrolling patients comparable for age, sex, hypertension, and diabetes provided information about concomitant CABG in BAV and TAV subjects. Thus, the sensitivity analysis was not performed for this outcome. When stratifying results according to the study design (retrospective or prospective), we found that the difference in CAD, concomitant CABG, and postoperative mortality between BAV and TAV patients were consistently confirmed only by retrospective studies. Interestingly, all the differences between the 2 groups were no longer significant in prospective studies (Table 2).

***References 12, 19–21, 23, 25, 27–31, 33, 34, 36, 37, 39.

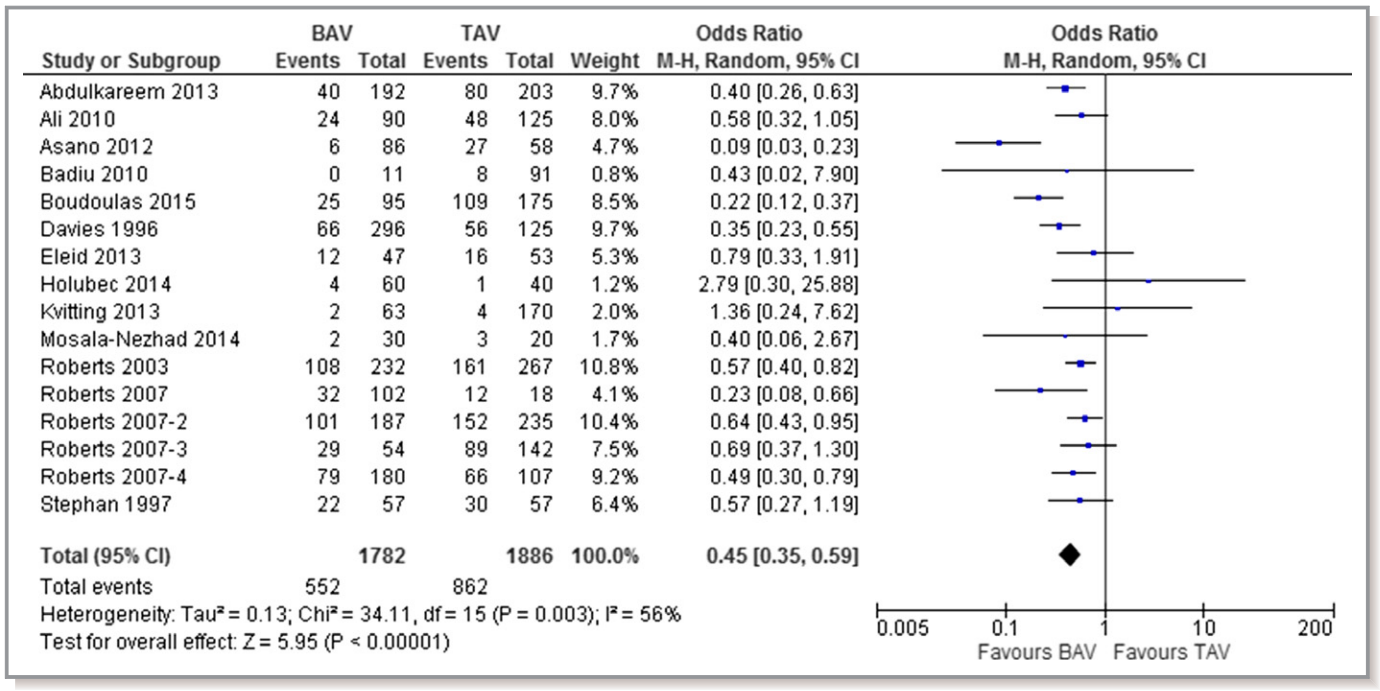

Figure 3. Prevalence of coronary artery bypass grafting (CABG) in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

Publication Bias

Because it is recognized that publication bias can affect results of meta-analyses, we attempted to assess this potential bias using funnel plot visual analysis (Figure S2).

Visual inspection of funnel plots of effect size versus SE for studies evaluating CAD, CABG, and mortality in BAV and in TAV patients suggested a symmetric distribution of studies around the effect size, and the Egger test confirmed the lack of publication bias for all these outcomes (CAD, P=0.868; CABG, P=0.914; mortality, P=0.403).

Discussion

This meta-analysis, which includes more than 7500 patients undergoing aortic valve surgery, shows, in agreement with

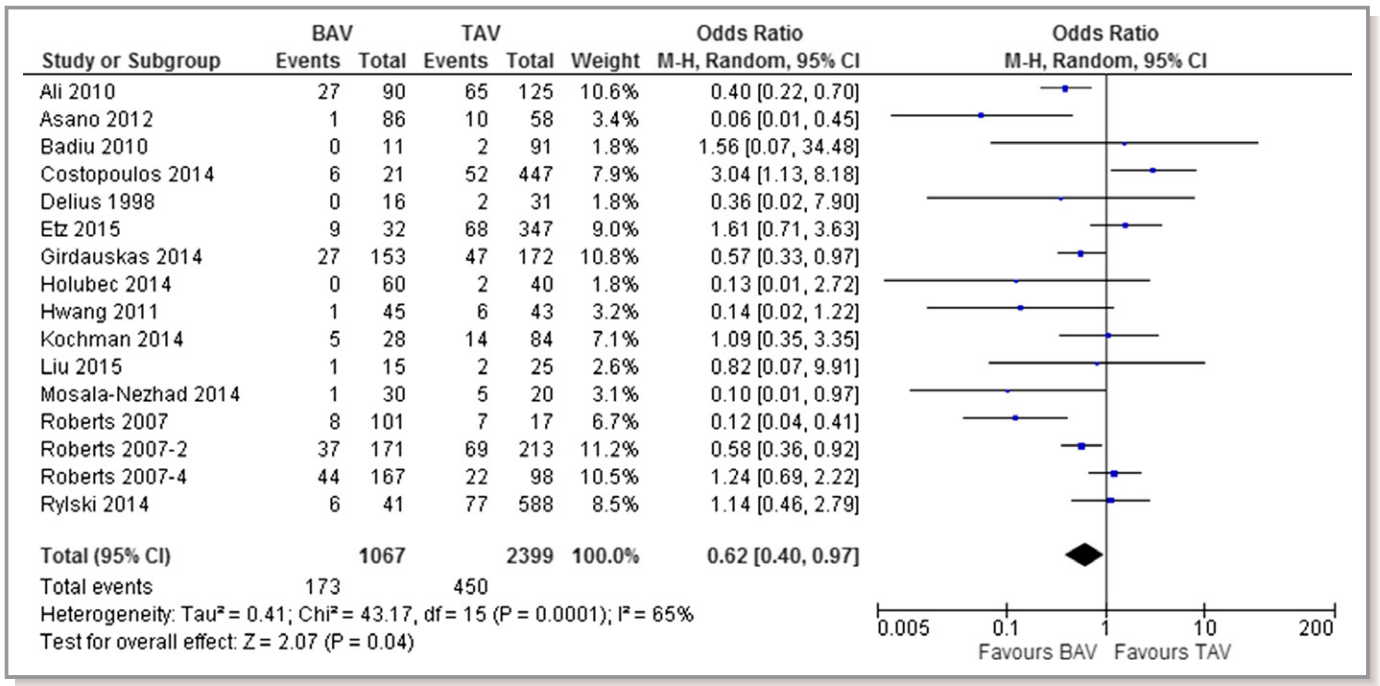

Figure 4. Post-operative mortality in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

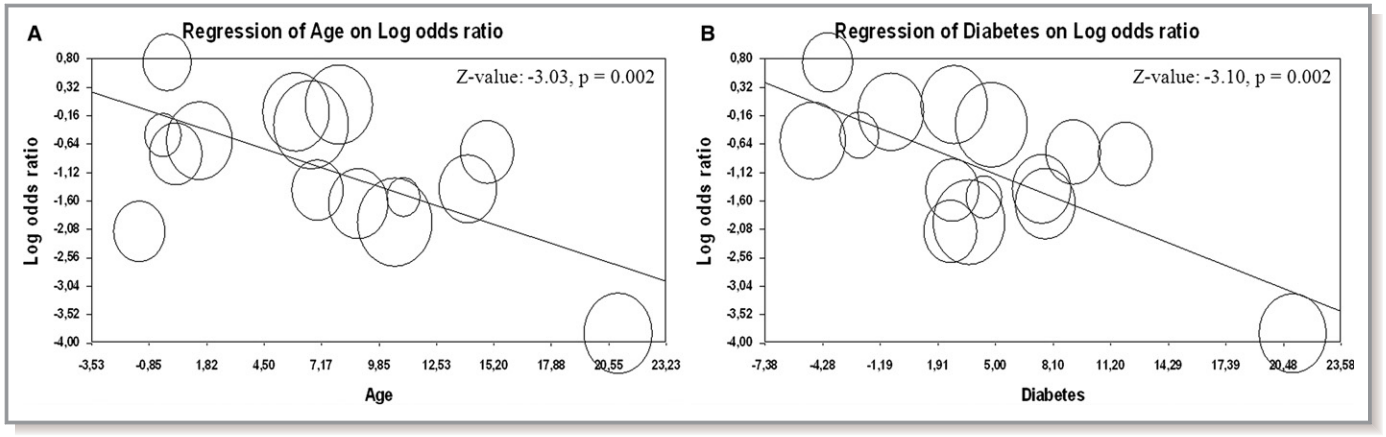

Figure 5. Meta-regression analysis. Effect of the difference in mean age (A) and in prevalence of diabetes (B) on prevalence of coronary artery disease in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

previously published data, a lower prevalence of CAD (13.5% vs 30.3%) and concomitant CABG (31% vs 45.7%) in BAV than in TAV patients, accompanied by a marginally lower rate of postoperative mortality (16.2% vs 18.8%). We also show that BAV patients enrolled in the included studies were ≈7 years younger, more often males (72.7% vs 60.1%), and exhibited lower prevalence of hypertension (43.0% vs 65.4%) and diabetes (11.6% vs 16.3%) compared to TAV patients (Table S1).

Altogether, these data suggest that the lower cardiovascular risk reported in BAV patients may be partly explained by younger age and lower prevalence of some cardiovascular risk factors in this clinical setting. Interestingly, a meta-regression analysis confirmed and extended this hypothesis, showing that age and diabetes have a profound impact on the difference in prevalence of CAD and CABG between BAV and TAV patients. Moreover, when the analyses have been repeated after including only those studies enrolling patients matched for age, sex, hypertension, and diabetes, the difference in prevalence of CAD and postoperative mortality were no longer significant between the 2 groups of patients. Thus, patients with BAV typically develop aortic stenosis at a younger age, usually before 65 years, compared to aortic stenosis in patients with TAV, which more often develops after age 70.[44]

Several studies analyzed prevalence of CAD in BAV and TAV patients, concluding that this atherosclerotic disease is uncommon in BAV, but is associated with TAV disease.[9,24] However, recent developments suggest that "incidence of CAD is high in patients with aortic valve degeneration, both in those with tricuspid and bicuspid aortic valve."[13]

Our analysis shows that although the incidence of all the considered variables is lower in BAV compared to TAV patients, a higher mean age and a higher prevalence of hypertension and diabetes is found in the TAV group. The potential impact of these confounding covariates should be taken into account. Indeed, our sensitivity analysis shows that once hypertension, sex, diabetes, and age are taken into

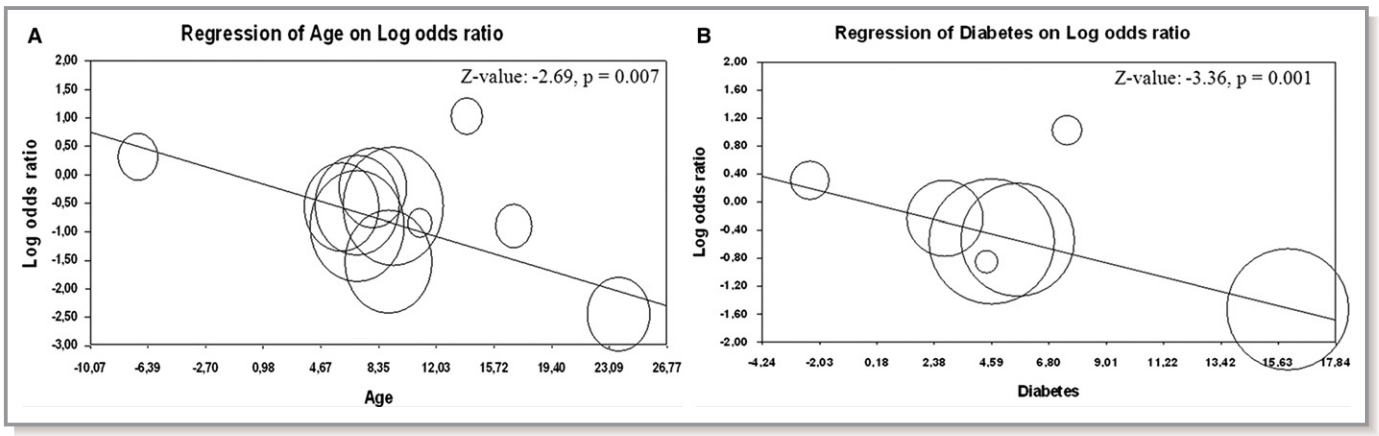

Figure 6. Meta-regression analysis. Effect of the difference in mean age (A) and in prevalence of diabetes (B) on prevalence of concomitant coronary artery bypass grafting in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

Table 2. Stratification of the Studies: Retrospective and Prospective

	No. of Studies	OR (95% CI)	Heterogeneity
CAD			
Retrospective studies	8	0.37 (0.18, 0.76; P=0.007)	I^2: 84%; P<0.001
Prospective studies	7	0.30 (0.07, 1.32; P=0.11)	I^2: 87%; P<0.001
CABG			
Retrospective studies	15	0.45 (0.35, 0.59; P<0.001)	I^2: 59%; P=0.002
Prospective studies	1	0.43 (0.02, 7.90; P=0.57)	Not evaluable
Mortality			
Retrospective studies	13	0.57 (0.34, 0.94; P=0.03)	I^2: 72%; P<0.001
Prospective studies	3	1.08 (0.41, 2.86; P=0.88)	I^2: 0%; P=0.95

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; OR, odds ratio.

account and only studies with patients comparable for these variables are included, the differences in prevalence of CAD between BAV and TAV patients is no longer significant.

The finding that, in the TAV group, higher mean age and increased prevalence of diabetes and hypertension are paralleled by a higher prevalence of CAD, concomitant CABG, and postoperative mortality somehow supports the hypothesis that the etiopathogenetic mechanism underling aortic valve degeneration is similar or complementary to coronary atherosclerosis. Indeed, recent evidence suggested that risk factors responsible for pathogenesis of atherosclerosis are also related to development of aortic calcification and stenosis.[13,45,46] However, the reasons why many patients with CAD do not develop aortic stenosis are still under debate. The major explanation may reside in the anatomic variation in size and diameter in normal tricuspid aortic valve[47] and the genetic predisposition to aortic calcification, such as lipoprotein(a) expression levels encoded by the lipoprotein(a) gene.[48]

Another finding of our analysis is the marginally lower postoperative mortality in BAV than in TAV patients. Evaluating the risk of post operative mortality in BAV and TAV patients, it is interesting to highlight that the only study[19] providing an adjusted multivariate analysis showed that valve morphology did not impact on mortality rate. Moreover, similar findings have been confirmed by Roberts et al.[37,39] by means of an unadjusted analysis. On the other hand, it is noteworthy to stress that 4 studies[20,27,28,32] consistently highlighted that an increasing age was the main predictor of postoperative mortality. Overall, these evidences confirm and extend our data suggesting that the difference in mean age between BAV and TAV might, at least in part, explain the difference in postoperative mortality documented in these 2 groups. Indeed, when we have analyzed only studies on patients comparable for age, sex, hypertension, and diabetes, the differences in postoperative mortality rate between BAV and TAV patients were no longer significant. In addition, after stratifying results according to study design, we found that differences between BAV and TAV patients were confirmed only by retrospective studies. Interestingly, all the differences between the 2 groups were no longer significant in prospective studies.

We recognize that our study has several potential limitations. The studies included in our meta-analysis have different inclusion and exclusion criteria with no clear definition of CAD. In addition, most of the patients included in the analysis had concomitant cardiovascular risk factors. Given that meta-analysis is performed on aggregate data and some missing information is present in each study, the multivariate approach allowed for the adjustment for some (but not all) potential confounders. Thus, although results of metaregression analyses were able to refine analyses by assessing the influence of most clinical and demographic variables on the observed results, caution is necessary in overall results interpretation. Moreover, heterogeneity among the studies was generally significant. Although it was not possible to conclusively ascertain sources of heterogeneity, publication bias did not affect results of our meta-analysis.

In conclusion, patients undergoing aortic valve replacement might represent a potential bias. Patients undergoing surgery are a subset of patients with BAV or TAV, and this could influence the results. This might limit the reproducibility of reported results. However, a large study[49] reporting on natural history of BAV and TAV patients not undergoing surgery confirmed the lack of difference in cardiovascular mortality between the 2 groups. In addition, the studies included analyzed not only aortic valve stenosis pathology, but also aortic valve regurgitation. However, in the studies analyzing both aortic valve pathologies,[18,22,26,27,35] there are no significative differences between BAV and TAV groups.

A further potential confounder is represented by inclusion of studies analyzing patients' candidate for TAVI, who, besides the older age, have a greater prevalence of comorbidities.

However, a subanalysis excluding these 3 studies[23,31,33] confirmed all our findings.

In conclusion, the results of the meta-analysis here presented shows that analysis of raw data clearly suggests an association of aortic valve morphology with prevalence of CAD, concomitant CABG, and postoperative mortality. Interestingly, differences in age and diabetes have a profound impact on prevalence of CAD and concomitant CABG between BAV and TAV patients. Thus, based on our analysis, BAV patients do not exhibit a lower risk of CAD compared to TAV patients. However, further studies or patient-level meta-analysis are needed to adjust results for potential confounders and definitely address this issue.

Author Contributions

Paolo Poggio and Matteo Nicola Dario Di Minno conceived and designed the study, performed statistical analysis, interpreted results, and drafted the manuscript; Laura Cavallotti, Paola Songia, Alessandro Di Minno, Pasquale Ambrosino, and Liborio Mammana acquired clinical data and drafted the manuscript; Alessandro Parolari and Elena Tremoli interpreted results and performed critical revisions. All authors read and approved the final version of the manuscript. Paolo Poggio and Matteo Nicola Dario Di Minno had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

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Disclosures

None.

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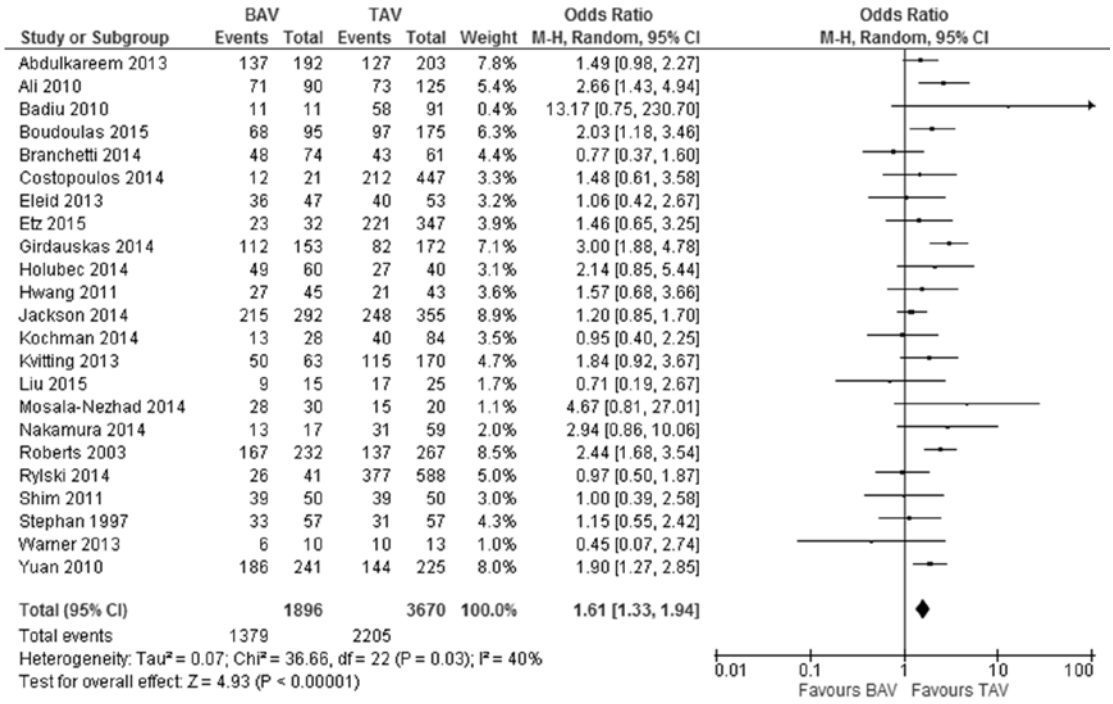
SUPPLEMENTAL MATERIAL

Impact of Valve Morphology On the Prevalence of Coronary Artery Disease:

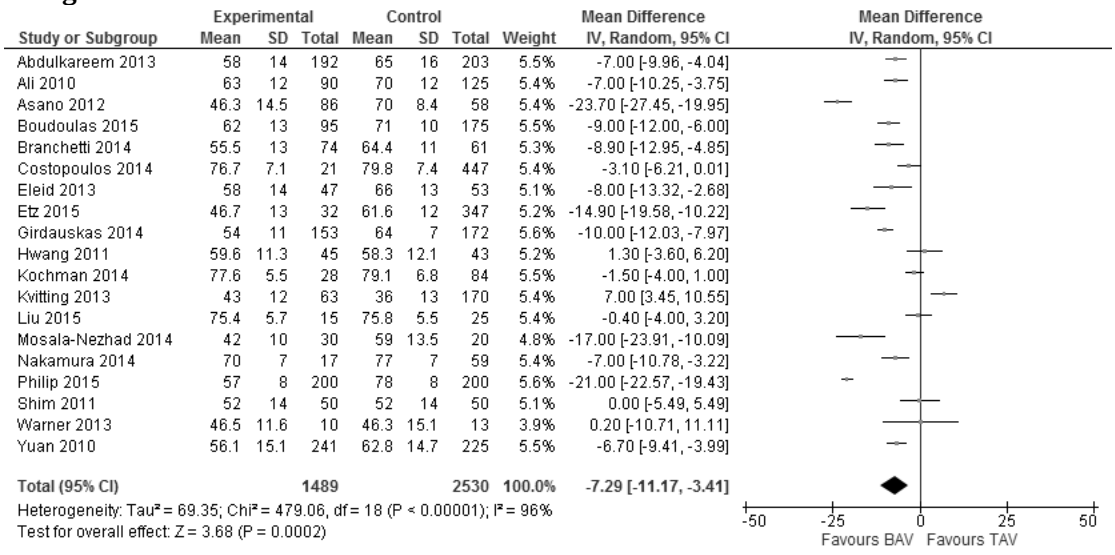
A Systematic Review and Meta-Analysis

Figure S1.Distribution of major clinical and demographic characteristics in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).(A) sex, (B) age, (C) hypertension, (D) diabetes, (E) hyperlipedimia, (F) BMI and (F) smoking.

A: Sex



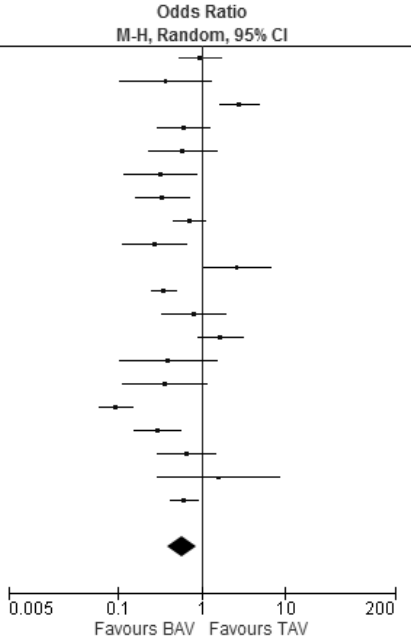
B: Age



C: Hypertension

Study or Subgroup	BAV Events	BAV Total	TAV Events	TAV Total	Weight	Odds Ratio M-H, Random, 95% CI
Ali 2010	28	90	40	125	5.6%	0.96 [0.54, 1.72]
Badiu 2010	5	11	63	91	3.9%	0.37 [0.10, 1.32]
Boudoulas 2015	70	95	87	175	5.7%	2.83 [1.64, 4.88]
Branchetti 2014	23	74	26	61	5.3%	0.61 [0.30, 1.23]
Costopoulos 2014	14	21	345	447	4.7%	0.59 [0.23, 1.50]
Eleid 2013	32	47	46	53	4.5%	0.32 [0.12, 0.89]
Etz 2015	15	32	250	347	5.2%	0.34 [0.16, 0.71]
Girdauskas 2014	74	153	98	172	5.9%	0.71 [0.46, 1.10]
Holubec 2014	27	60	30	40	4.9%	0.27 [0.11, 0.66]
Hwang 2011	20	45	10	43	4.8%	2.64 [1.05, 6.62]
Jackson 2014	149	292	265	355	6.1%	0.35 [0.25, 0.49]
Kochman 2014	17	28	55	84	4.8%	0.81 [0.34, 1.97]
Kvitting 2013	23	63	44	170	5.5%	1.65 [0.89, 3.05]
Liu 2015	5	15	14	25	3.7%	0.39 [0.10, 1.49]
Nakamura 2014	10	17	47	59	4.2%	0.36 [0.11, 1.16]
Philip 2015	47	200	153	200	5.8%	0.09 [0.06, 0.15]
Rylski 2014	23	41	477	588	5.4%	0.30 [0.16, 0.57]
Shim 2011	20	50	25	50	5.1%	0.67 [0.30, 1.47]
Warner 2013	5	10	5	13	3.0%	1.60 [0.30, 8.49]
Yuan 2010	74	241	94	225	6.0%	0.62 [0.42, 0.90]
Total (95% CI)		**1585**		**3323**	**100.0%**	**0.58 [0.39, 0.87]**
Total events	681		2174			

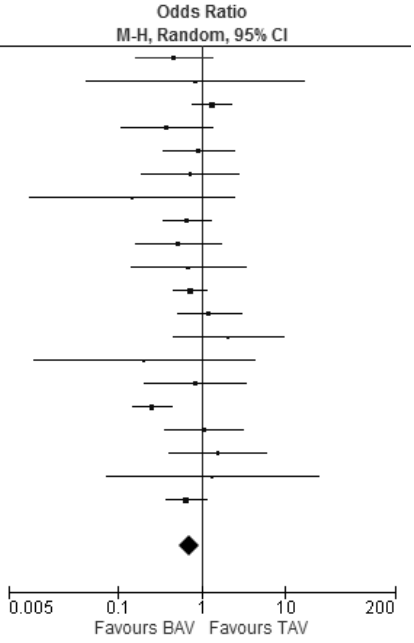
Heterogeneity: Tau² = 0.67; Chi² = 138.10, df = 19 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.62 (P = 0.009)



D: Diabetes

Study or Subgroup	BAV Events	BAV Total	TAV Events	TAV Total	Weight	Odds Ratio M-H, Random, 95% CI
Ali 2010	5	90	14	125	4.8%	0.47 [0.16, 1.35]
Badiu 2010	0	11	4	91	0.8%	0.85 [0.04, 16.74]
Boudoulas 2015	31	95	47	175	10.5%	1.32 [0.77, 2.27]
Branchetti 2014	4	74	8	61	3.7%	0.38 [0.11, 1.32]
Costopoulos 2014	6	21	135	447	5.5%	0.92 [0.35, 2.43]
Eleid 2013	4	47	6	53	3.4%	0.73 [0.19, 2.76]
Etz 2015	0	32	32	347	0.9%	0.15 [0.01, 2.50]
Girdauskas 2014	17	153	27	172	8.9%	0.67 [0.35, 1.29]
Holubec 2014	6	60	7	40	4.1%	0.52 [0.16, 1.69]
Hwang 2011	3	45	4	43	2.6%	0.70 [0.15, 3.31]
Jackson 2014	33	292	53	355	11.8%	0.73 [0.46, 1.16]
Kochman 2014	11	28	29	84	6.2%	1.23 [0.51, 2.96]
Kvitting 2013	3	63	4	170	2.7%	2.08 [0.45, 9.54]
Liu 2015	0	15	3	25	0.8%	0.21 [0.01, 4.30]
Nakamura 2014	3	17	12	59	3.1%	0.84 [0.21, 3.40]
Philip 2015	21	200	63	200	10.5%	0.26 [0.15, 0.44]
Rylski 2014	4	41	54	588	4.8%	1.07 [0.37, 3.11]
Shim 2011	6	50	4	50	3.4%	1.57 [0.41, 5.93]
Warner 2013	1	10	1	13	0.8%	1.33 [0.07, 24.32]
Yuan 2010	26	241	35	225	10.5%	0.66 [0.38, 1.13]
Total (95% CI)		**1585**		**3323**	**100.0%**	**0.71 [0.54, 0.93]**
Total events	184		542			

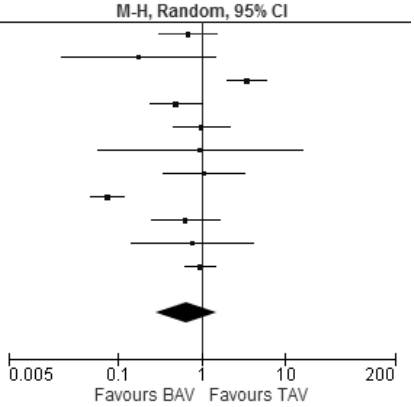
Heterogeneity: Tau² = 0.11; Chi² = 28.34, df = 19 (P = 0.08); I² = 33%
Test for overall effect: Z = 2.45 (P = 0.01)



E: Hyperlipidemia

Study or Subgroup	BAV Events	BAV Total	TAV Events	TAV Total	Weight	Odds Ratio M-H, Random, 95% CI
Ali 2010	11	90	21	125	10.0%	0.69 [0.31, 1.51]
Badiu 2010	1	11	33	91	6.5%	0.18 [0.02, 1.43]
Boudoulas 2015	61	95	60	175	10.5%	3.44 [2.04, 5.80]
Branchetti 2014	20	74	26	61	10.2%	0.50 [0.24, 1.03]
Eleid 2013	23	47	26	53	10.0%	1.00 [0.45, 2.18]
Hwang 2011	1	45	1	43	4.9%	0.95 [0.06, 15.76]
Nakamura 2014	6	17	20	59	9.2%	1.06 [0.34, 3.30]
Philip 2015	43	200	157	200	10.6%	0.08 [0.05, 0.12]
Shim 2011	10	50	14	50	9.7%	0.64 [0.25, 1.63]
Warner 2013	4	10	6	13	7.7%	0.78 [0.15, 4.13]
Yuan 2010	58	241	56	225	10.7%	0.96 [0.63, 1.46]
Total (95% CI)		**880**		**1095**	**100.0%**	**0.65 [0.28, 1.51]**
Total events	238		420			

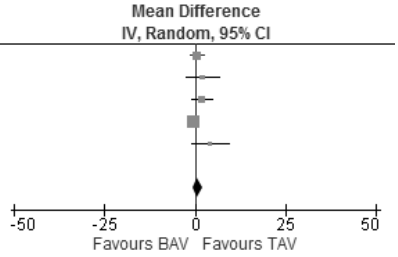
Heterogeneity: $Tau^2 = 1.67$; $Chi^2 = 124.99$, df = 10 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: $Z = 1.00$ ($P = 0.32$)



F: BMI

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Costopoulos 2014	26.6	4.4	21	26.1	4.6	447	26.6%	0.50 [-1.43, 2.43]
Kvitting 2013	26	16	63	24	15	170	7.5%	2.00 [-2.55, 6.55]
Liu 2015	23.6	4.8	15	21.7	3.1	25	17.1%	1.90 [-0.82, 4.62]
Shim 2011	24.7	2.9	50	25.2	2.7	50	43.0%	-0.50 [-1.60, 0.60]
Warner 2013	30.1	6.8	10	25.8	5.8	13	5.7%	4.30 [-0.96, 9.56]
Total (95% CI)		**159**			**705**	**100.0%**		**0.64 [-0.69, 1.97]**

Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 6.09$, df = 4 ($P = 0.19$); $I^2 = 34\%$
Test for overall effect: $Z = 0.95$ ($P = 0.34$)



G: Smoking habit

Study or Subgroup	BAV Events	BAV Total	TAV Events	TAV Total	Weight	Odds Ratio M-H, Random, 95% CI
Boudoulas 2015	53	95	48	175	15.1%	3.34 [1.98, 5.64]
Branchetti 2014	32	74	12	61	12.8%	3.11 [1.42, 6.79]
Eleid 2013	11	47	7	53	10.5%	2.01 [0.71, 5.70]
Etz 2015	5	32	37	347	10.7%	1.55 [0.56, 4.27]
Girdauskas 2014	55	153	69	172	15.7%	0.84 [0.53, 1.31]
Hwang 2011	12	45	4	43	9.1%	3.55 [1.04, 12.04]
Nakamura 2014	6	17	24	59	9.9%	0.80 [0.26, 2.44]
Shim 2011	16	50	21	50	12.5%	0.65 [0.29, 1.47]
Warner 2013	1	10	3	13	3.7%	0.37 [0.03, 4.23]
Total (95% CI)		**523**		**973**	**100.0%**	**1.52 [0.90, 2.59]**
Total events	191		225			

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 27.49$, df = 8 ($P = 0.0006$); $I^2 = 71\%$
Test for overall effect: $Z = 1.56$ ($P = 0.12$)

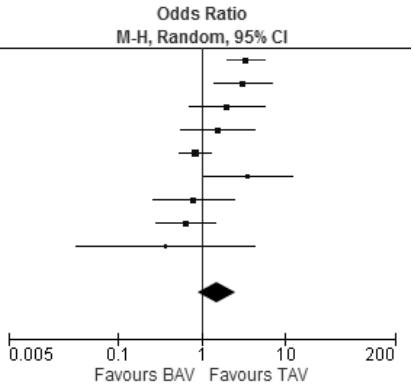
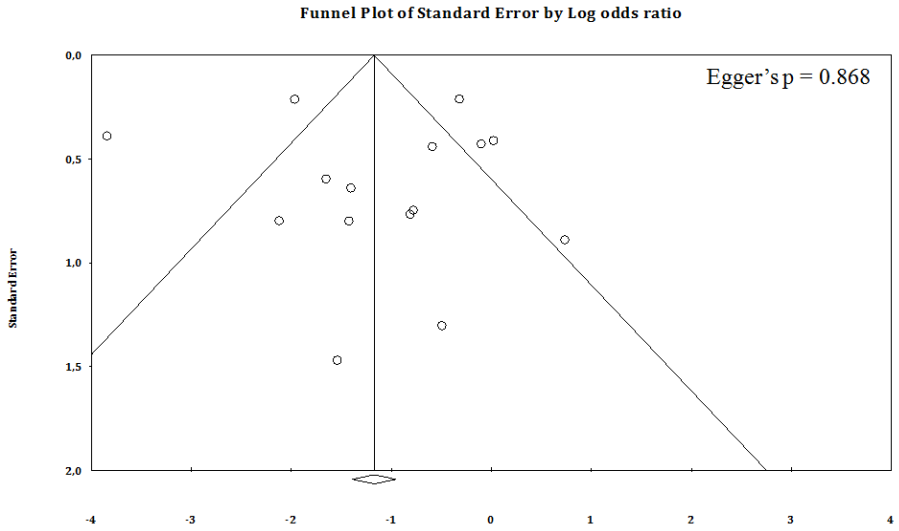
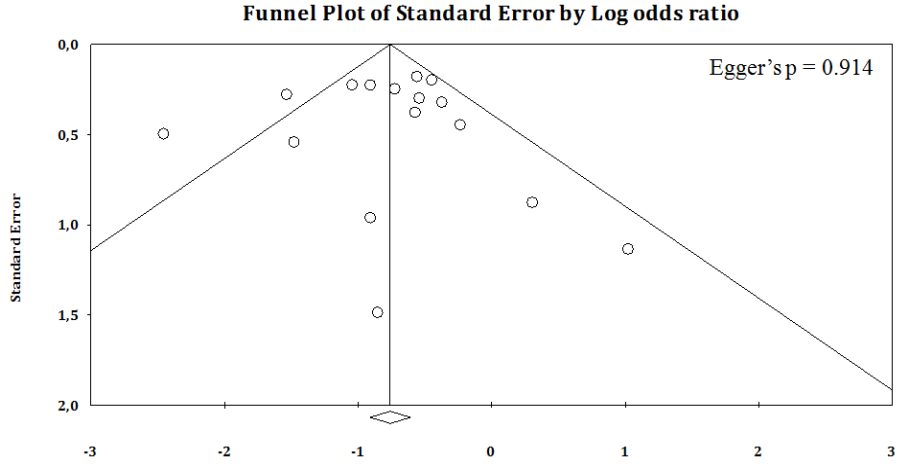


Figure S2.Funnel plots of effect size versus standard error for studies evaluating the prevalence of coronary artery disease (A), coronary artery bypass grafting (B), post-operative mortality (C) in patients with bicuspid (BAV) and tricuspid aortic valve (TAV).

A: Coronary artery disease



B: Coronary artery bypass grafting



C: Post-operative mortality

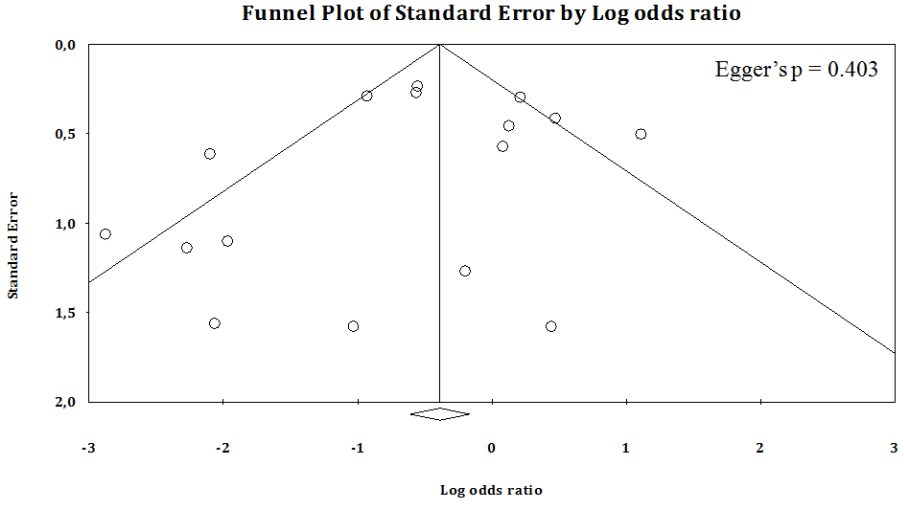


Table S1. Summary table of meta-analysis results

Outcome	Number of studies	Effect size
CAD	15 studies 1,163 BAV and 2,234 TAV	OR: 0.33, 95%CI: 0.17, 0.65, p = 0.001
CABG	16 studies 1,782 BAV and 1,886 TAV	OR: 0.45, 95%CI: 0.35, 0.59, p < 0.001
Mortality	16 studies 1067 BAV and 2399 TAV	OR: 0.62, 95%CI: 0.40, 0.97, p = 0.04
Age	19 studies 1489 BAV and 2530 TAV	MD: -7.29, 95%CI: -11.17, -3.41, p < 0.001
Male gender	23 studies 1896 BAV and 3670 TAV	OR: 1.61, 95%CI: 1.33, 1.94, p < 0.001
Hypertension	20 studies 1585 BAV and 3323 TAV	OR: 0.58, 95%CI: 0.39, 0.87, p < 0.001
Diabetes	20 studies 1585 BAV and 3323 TAV	OR: 0.71, 95%CI: 0.54, 0.93, p = 0.01
Hyperlipidemia	11 studies 880 BAV and 1095 TAV	OR: 0.65, 95%CI: 0.28, 1.51, p = 0.32
BMI	5 studies 159 BAV and 705 TAV	MD: 0.64, 95%CI: -0.69, 1.97, p = 0.34
Smoking habit	9 studies 523 BAV and 973 TAV	OR: 1.52, 95%CI: 0.90, 2.59, p = 0.12

CAD: coronary artery disease; CABG: Coronary artery bypass grafting; BMI: body mass index; BAV: bicuspid aortic valve; TAV; tricuspid aortic valve; OR: odds ratio; MD: mean difference; 95%CI: 95% confidence intervals