Supplementary

Appendix 1

Search terms

Embase

(aorta/exp OR 'aorta surgery'/de OR 'aorta reconstruction'/de OR aortoplasty/de OR 'aortic root surgery'/de OR 'aortic valve repair'/de OR 'aorta valve'/de OR 'aorta valve disease'/exp OR 'aorta disease'/exp OR 'aortic root aneurysm'/de OR (aort* OR Valsalva* OR root OR bav OR tav):ab,ti,kw) AND ('David operation'/de OR 'david procedure'/de OR 'aortic valve David reimplantation'/de OR 'aortic valve sparing procedure'/de OR 'valve sparing aortic root replacement'/de OR 'valve sparing root replacement'/de OR (((valve*) NEAR/6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5):ab,ti,kw OR (david):ti) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim AND [english]/lim

Medline ALL Ovid

(exp Aorta / OR exp Aortic Diseases / OR aortic root aneurysm/ OR (aort* OR Valsalva* OR root OR bav OR tav).ab,ti,kw.) AND ((((valve*) ADJ6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david ADJ3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5).ab,ti,kw. OR (david).ti.) NOT (exp animals/ NOT humans/) AND english.la.

Cochrane

((aort* OR Valsalva* OR root OR bav OR tav):ab,ti) AND ((((valve*) NEAR/6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5):ab,ti OR (david):ti)

Web of science

TS=(((aort* OR Valsalva* OR root OR bav OR tav)) AND ((((valve*) NEAR/5 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/2 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5))) NOT DT=(Meeting Abstract OR Meeting Summary) AND LA=(english)

Google Scholar

Aorta|aortic|Valsalva|root "valve sparing|spare|preserving|reimplantation"|"david technique|surgery |operation|procedure|reimplantation|repair|intervention|resuspension|type"

Appendix 2

Background mortality

For the overall group and bicuspid/tricuspid subgroup separately, the background mortality of the general population was acquired for the pooled median year of intervention within each country among included studies from that country. Country, year and sex-specific background mortality estimates were obtained from the Human Mortality Database (https://www.mortality.org/). Brazil, Turkey and China are not included in this database, but only 8% of included patients originated from these countries, and they were not present in the subgroups. Proportion of individuals of the included countries are presented in Table S3. Survival was matched with the corresponding year and sex-specific background survival in the countries of origin separately for each subgroup.

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Excess mortality

We compared the survival simulated by the microsimulation model with the observed survival in our Kaplan-Meier meta-analysis for time-to-event outcomes to estimate the risk ratio of additional excess mortality not directly resulting from valve-related morbidity relative to the probability of background mortality observed in the general population. We temporarily excluded early mortality, since early mortality was a separate input in our microsimulation model. During the simulation, we iteratively simulated the survival of 10.000 patients with an age deriving from the mean ± SD distribution and proportion of males of the study population using the same mortality due to valve-related events and background mortality, but with varying risk ratios of excess mortality for different timeframes. Subsequently, the risk ratio resulting in the smallest difference between the simulated and observed survival according to the least squares method was chosen as the suitable risk ratio for excess mortality. The iterative procedure (by minimizing least squares) is based on the golden section search method (Kiefer, J. (1953), "Sequential minimax search for a maximum").

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis (PSA) was performed to consider the uncertainty in input parameters of our microsimulation and to reflect the implications for uncertainty in outcomes. In the PSA, the model considered a sample size of 1,000 patients per set and ran for 1000 different sets of randomly drawn input parameters. Values of the input parameters were randomly drawn from the following distributions: beta distributions for early mortality risk and probabilities of re-interventions and death after valve-related events, log-normal distributions for late events and normal distributions for the RR of mortality after reintervention and excess mortality, varied with +/-10%. For all sets of coefficients, the mean outcome in the 1000 patients was recorded and the mean (point estimate) and the 2.5% and 97.5% percentiles (credible interval) over all the 1000 mean values for each outcome were computed. PSA allows the microsimulation to take into account both first-order uncertainty (random variation in outcomes between identical patients) and second-order uncertainty (uncertainty in the input parameters).

Appendix 3

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Table S1 Input parameters microsimulation and their source

Parameter	Source
Baseline	
Age	Sample size weighted summarized age
SD Age	Sample size weighted summarized SD age
Sex	Proportion of males included studies
Early events	
Early mortality	Meta-analysis (pooled proportion)
Early endocarditis	Meta-analysis (pooled proportion)
Early Valve thrombosis	Meta-analysis (pooled proportion)
Early bleeding	Meta-analysis (pooled proportion)
Early MI	Meta-analysis (pooled proportion)
Risk ratio early mortality reintervention	Calculated by dividing early mortality by mortality due to AV reintervention
Late events	
Late mortality (background)	HMD life tables
Observed mortality	Reconstructed-IPD KM of late mortality
Late mortality excess mortality risk ratio	Calculated by difference between background mortality + valve related mortality and observed mortality
Late mortality valve related	Mortality caused by early mortality, late bleeding, late stroke, late endocarditis, overall AV reintervention
Late AV reintervention	Reconstructed-IPD KM of overall AV reintervention*
Late Bleeding	Meta-analysis (pooled adverse event rate)
Late Stroke	Meta-analysis (pooled adverse event rate)
Late endocarditis	Meta-analysis (pooled adverse event rate)
Late Valve thrombosis	Meta-analysis (pooled adverse event rate)
Consequences of events	
Reintervention due to endocarditis	Summarized proportion reported intervention for endocarditis
Reintervention due to valve thrombosis	Summarized proportion reported intervention for endocarditis
Mortality due to bleeding	Summarized proportion reported mortality for bleeding
Mortality due to stroke	Summarized proportion reported mortality for stroke
Mortality due to endocarditis	Summarized proportion reported mortality for endocarditis
Mortality due to valve thrombosis	Summarized proportion reported mortality for valve thrombosis
Mortality due to AV reintervention (only used to calculate RR early mortality intervention)	Summarized proportion reported mortality for AV reintervention

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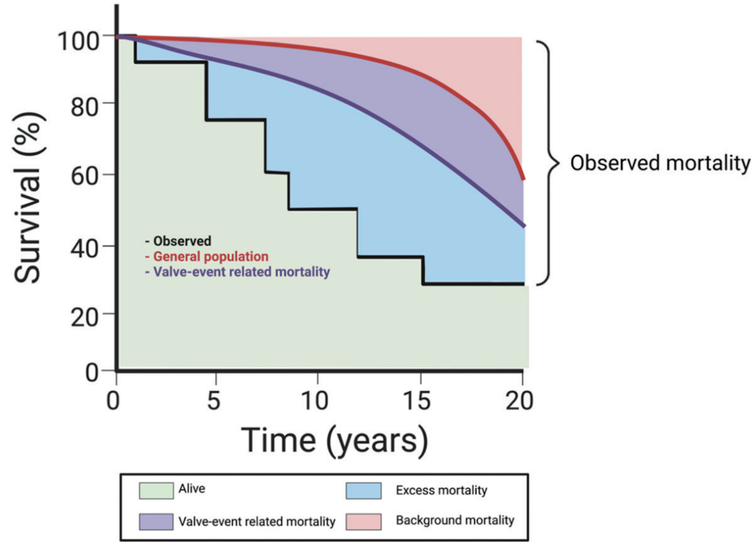

Figure S1 Explanation of different microsimulation based sources of mortality. Background mortality is mortality in the matched background population. Valve-related event mortality is the mortality due to valve related events (AV reintervention, endocarditis, stroke, thrombo-embolism, bleeding, valve-thrombosis). Excess mortality is the additional mortality patients exhibit minus valve related event mortality and background mortality.

Table S2 Estimated risk ratios of excess mortality for specific timeframes

Group	0–3 months	4–12 months	13–120 months	121–240 months
Total group	3.754	3.754	0.88	0.981
BAV group	0.43	0.43	0.43	0.43
TAV group	11.5	0.96	0.96	0.96

BAV, Bicuspid aortic valve; TAV, tricuspid aortic valve.

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Table S3 Proportion of individuals from included countries

Country	Year	Overall group		Bicuspid subgroup		Tricuspid subgroup	
		Proportion	Adjusted proportion	Proportion	Adjusted proportion	Proportion	Adjusted proportion
Belgium	2008	4.2%	4.4%	12.5%	12.5%	14.3%	14.3%
Brazil	–	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%
China	–	4.2%	0.0%	0.0%	0.0%	0.0%	0.0%
Canada	2004	2.1%	4.4%	0.0%	0.0%	0.0%	0.0%
Finland	2011	2.1%	2.2%	12.5%	12.5%	0.0%	0.0%
France	2011	6.3%	6.7%	12.5%	12.5%	0.0%	0.0%
Germany	2011	25.0%	26.7%	0.0%	0.0%	14.3%	14.3%
Italy	2007	12.5%	13.3%	0.0%	0.0%	14.3%	14.3%
Japan	2018	4.2%	4.4%	0.0%	0.0%	0.0%	0.0%
Lithuania	2010	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Netherlands	2008	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Poland	2015	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Korea	2004	2.1%	2.2%	0.0%	0.0%	14.3%	14.3%
Spain	2011	4.2%	4.4%	0.0%	0.0%	0.0%	0.0%
Switzerland	2015	2.1%	2.2%	0.0%	0.0%	14.3%	14.3%
Turkey	–	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%
USA	2009	20.8%	22.2%	62.5%	62.5%	28.6%	28.6%

Table S4 Types of distribution fit to pooled time-to-event data for all time-varying risks in the microsimulation model

Bicuspid aortic valve	Linearized occurrence rate
Tricuspid aortic valve	Gamma distribution
Total group	Royston-Parmar distribution

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Table S5 Pre and perioperative characteristics in TAV and BAV

Variable	Pooled Data	Range	Included Studies (n)	Included Patients (n)
Tricuspid Aortic Valve (TAV)				
Total patient number (n)	2054	58–448	11	2054
Surgical period (years)	1995–2020		11	2054
Age (years), mean ± SD	48.6±14.2	36–57.5	10	1996
Gender, male (%)	80.7	56.9–93.1	11	2054
Comorbidity				
Renal insufficiency (dialysis) (%)	0.6	0–0.9	3	482
LV dysfunction (EF <30%)	2.9	1.3–6.4	3	375
Hypertension (%)	50.1	22.0–79.4	8	1365
Coronary artery disease (%)	16.3	2.9–38.1	6	1106
Connective tissue disease (%)	30.2	0–100	8	1112
Bicuspid aortic valve (%)	0	0	11	2054
Prior cardiac operation (%)	4.9	0–16.2	6	1424
Emergency surgery (%)	3.3	0–17.2	9	1965
Reexploration for bleeding (%)	5.0	0–15.9	10	1884
Concomitant procedure (n)	745	14–168	10	1726
Mitral valve plasty (%)	7.0	1.4–9.8	10	1726
Mitral valve replacement (%)	0.2	0–1.7	7	982
Tricuspid valve surgery (%)	1.7	0–6.4	7	1262
CABG (%)	9.5	0–23.6	10	1726
Hemiarch repair (%)	20.7	9.5–90.2	6	916
Arch repair (%)	12.0	1.9–10.0	7	903
Other (VSD repair, MAZE etc.) (%)	8.9	1.9–25.3	9	1637
Extracorporeal circulation time, min., mean ± SD	164.3±40.6	127–227	11	2054
Aortic cross-clamping time min., mean ± SD	133.9±30.6	99–231	11	2054
Bicuspid Aortic Valve (BAV)				
Total patient number (n)	865	29–189	12	865
Surgical period (years)	1993–2022		12	865
Age (years), mean ± SD	44.0±12.3	40.1–47.4	12	865
Gender, male (%)	89.1	79.4–100	12	865
Comorbidity				
Renal insufficiency (dialysis) (%)	0	0	3	190
LV dysfunction (EF <30%)	0	0	2	246
Hypertension (%)	41	17.5–79.5	12	865
Coronary artery disease (%)	8.7	3.5–20.7	4	254
Connective tissue disease (%)	3.8	0–9.1	6	426
Bicuspid aortic valve (%)	100	100	12	865
Prior cardiac operation (%)	2.6	0–6.4	8	628
Emergency surgery (%)	1.6	0–4.6	8	506
Reexploration for bleeding (%)	2.5	0–5.1	9	556
Concomitant procedure (n)	321	0–63	12	865
Mitral valve plasty (%)	2.2	0–7.2	11	808
Mitral valve replacement (%)	0	0	8	562
Tricuspid valve surgery (%)	0.2	0–0.5	8	645
CABG (%)	5.00	0–10.3	11	808
Hemiarch repair (%)	20.1	0–64.1	7	603
Arch repair (%)	22.6	0–76.2	9	541
Other (VSD repair, MAZE etc.) (%)	2.8	0–11.1	9	690
Extracorporeal circulation time, min., mean ± SD	190.9±33.8	122–309	12	865
Aortic cross-clamping time min., mean ± SD	159.8±27.1	97–242	12	865

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Table S6 Univariable meta regression for re-exploration for bleeding and late mortality

Characteristic	B estimate (SE)	P-value	% heterogeneity explained
Re-exploration for bleeding			
Mean year of surgery	0.05 (0.03)	0.10	0%
Age	0.04 (0.01)	0.002	26%
Males (per 1% increase)	0.01 (0.01)	0.32	0%
Mean follow-up years	0.02 (0.05)	0.64	0%
BAV (vs TAV) (per 1 % increase)	–0.01 (0.01)	0.16	1%
Cardiopulmonary bypass time	–0.004 (0.003)	0.08	0%
Late mortality			
Mean year of surgery	–0.03 (0.03)	0.35	0%
Age	0.06 (0.01)	<.001	50%
Males (per 1% increase)	0.03 (0.02)	0.03	0%
Mean follow-up years	0.02 (0.06)	0.70	0%
BAV (vs TAV) (per 1 % increase)	–0.003 (0.004)	0.39	9%
Cardiopulmonary bypass time	–0.004 (0.002)	0.03	1%

BAV, Bicuspid aortic valve; TAV, tricuspid aortic valve.

Table S7 Pooled early risks and linearized occurrence rates of the total group after temporarily excluding studies with the lowest 25th sample size or patient years (in case of late outcomes)

Outcome	Risk (%)	95% CI	Studies included (n)
Early Outcomes			
Early mortality	1.5	1.1–1.9	33
Reintervention on the aortic valve	0.4	0.3–0.6	24
Reexploration for bleeding	5.1	4.1–6.4	30
Stroke	0.9	0.6–1.4	27
Late Outcomes			
Late mortality	0.86	0.67–1.11	28
Reintervention on the aortic valve	0.67	0.52–0.86	25
Endocarditis	0.21	0.14–0.30	26
Stroke	0.22	0.16–0.33	20
Bleeding	0.14	0.07-0.29	14

https://dx.doi.org/10.21037/acs-2023-avs1-0038

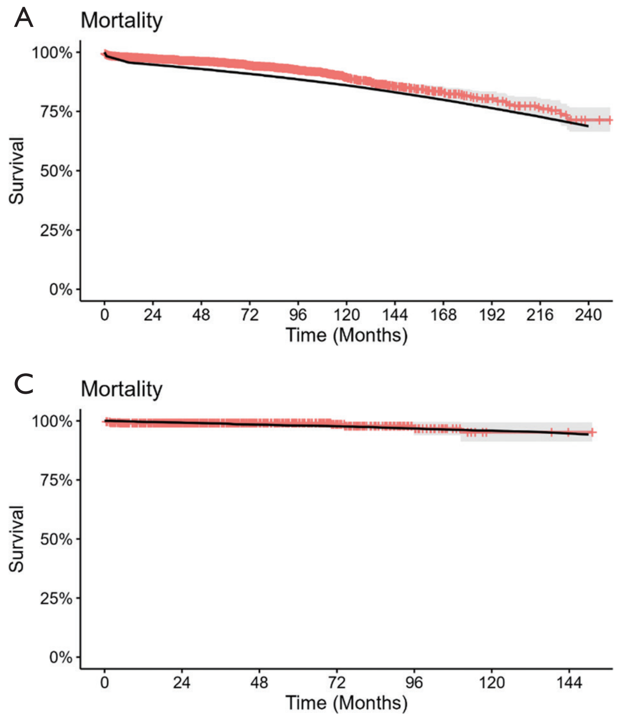

Figure S2 Calibration plots of microsimulation based mortality (black line) and observed mortality (KM curves, red line) for total group (A), bicuspid group (B) and tricuspid group (C).

https://dx.doi.org/10.21037/acs-2023-avs1-0038