"Our complication rates are lower than theirs": Statistical critique of heart valve comparisons

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Objectives: From the widely differing complication rates published for every heart valve, is it possible to determine a true rate for each valve and to compare the rates of two different valves? We investigated this question for the two most popular bileaflet valves.

Methods: Aortic valve data were abstracted from 14 St Jude Medical (St Jude Medical Inc, Minneapolis, Minn; 33,125 patient-y) and 11 Carbomedics (Sulzer Carbomedics Inc, Austin, Tex; 19,141 patient-y) series, and mitral valve data were abstracted from 11 St Jude Medical (21,553 patient-y) and 8 Carbomedics (8368 patient-y) series. Regression analysis was used to accommodate heterogeneity among rates with the same valve model, to estimate hazard ratios and 95% confidence intervals for the valve model effect, and to incorporate other series-level risk factors.

Results: Most of the complication rates with both valve models exhibited significant heterogeneity. For thromboembolism and bleeding, the relative risks for valve model were not significantly different from unity. Valve thrombosis rates exhibited less heterogeneity: the Carbomedics valve had a lower rate in the aortic position (hazard ratio 0.2, 95% confidence interval 0.1-0.6) and a higher rate in the mitral position (hazard ratio 1.9, 95% confidence interval 1.0-3.8).

Conclusions: Unlike simple weighted averages of valve complication rates, regression methods can incorporate heterogeneity related to center effects and allow for inclusion of other risk factors. Thromboembolism and bleeding rates were not significantly different with St Jude Medical and Carbomedics valves. Valve thrombosis appeared to differ between the two valves, but the absolute differences in rates were small. Because of the variability among rates with the same valve, statistical comparisons must be interpreted cautiously.

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Most currently used mechanical heart valve prostheses have complication rates in the same clinical range, because those with extreme rates are eventually discarded. This clinical range is still wide, however, approximately 0.5% to 3.5% per year for aortic valve thromboembolism, for example, and one may ask, "What is the true rate for a particular valve?" and "Which valve has the lowest rate?" Because of the variability observed from one study to another with the same prosthesis, a single observational study obviously cannot give the definitive answer. A review of many published, good quality studies may provide our best possibility of answering these questions. To illustrate, we selected the two most successful bileaflet valves, St Jude Medical (St Jude Medical Inc, Minneapolis, Minn) and Carbomedics (Sulzer Carbomedics Inc, Austin, Tex) and performed comparisons of thromboembolism, valve thrombosis, and bleeding rates in both the aortic and mitral positions.

Material and Methods

Clinical Material

From sources identified by MEDLINE searches of the English-language journals, we selected aortic and mitral valve series published in the last 10 years with at least 400 patient-years of follow-up. This amount of follow-up conforms to the minimum requirements for Food and Drug Administration marketing approval of a new heart valve prosthesis.¹ We used only articles that claimed conformance to either the original² or the current³ guidelines for reporting and that had at least 95% completeness of follow-up, as the guidelines require. There was some inconsistency in the reporting of linearized rates. Most reports considered late events only, but it was often difficult to determine this for certain. Some other data limitations are described in Appendix 1.

From each published series we extracted by position (aortic or mitral) the linearized event rates, the components of the rates (number of events and total patient-years), and some potential risk factors that may affect the rates, including follow-up completeness, mean follow-up time, and longest follow-up time. If there was a decrease in risk with time, then series with longer follow-ups would be at an advantage. Inclusion of mean follow-up as a potential risk factor allowed us to consider this possibility. Patient age and gender were also collected but often were not given separately by valve position. Other potential risk factors abstracted were the journal (which was converted to the journal's impact factor), year of publication, number of valves, whether late events only were reported, and whether major events only were reported (for thromboembolism and bleeding).

Statistical Methods

"Linearized" rates, which assume that the risk (hazard) is constant with time, are used to summarize many time-related complications of heart valve replacement. For some complications, such as tissue valve failure, this assumption is clearly inappropriate because the hazard for failure increases with time. For several other complications, however, including thromboembolism, valve thrombosis, and bleeding, the assumption of a constant hazard rate is considered an acceptable approximation. The Food and Drug Administration has formulated objective performance criteria for new heart valve approvals that are based on linearized rates. A practical advantage of linearized rates is that most studies provide them. If not, the rate can be easily computed from the number of events and the total follow-up years by simple division ($\text{Rate} = 100 \times \text{Events/Year}$) to provide events per 100 valve-years, usually given as percent per patient-year or percent per year.

A convenient statistic for expressing the relationship between two linearized rates, for example thromboembolism with two heart valve models, is their ratio, called the *relative risk* or more specifically the *hazard ratio* (HR). If the two risks are equal, HR equals 1; the further HR is from unity, the greater is the valve model effect. The 95% confidence interval (CI) gives the range of values that are consistent with the observed data. There is a relationship between hypothesis testing and 95% CI estimation. If the two rates are significantly different ($P < .05$), then the 95% CI does not include 1. Conversely, if the rates are not significantly different, the 95% CI does include 1. Because they are intrinsically related, we tended to emphasize the estimation (95% CI) approach instead of the hypothesis testing (P value) approach. The 95% CIs

for individual linearized rates were calculated with a method suggested by Cox.⁴

Given several studies of the same valve model, one might be tempted to compute a weighted mean linearized rate (the sum of all events divided by the sum of all follow-up years) for each valve model and use these weighted averages to compute 95% CIs and to compare valve models. If the rates vary significantly among series with the same valve, however, then directly comparing the weighted averages will produce 95% CIs and P values that are too small, because the extra variability among series is not accounted for. In this case a regression approach that accommodates diversity among series and adjusts the 95% CIs and P values appropriately should be used. If the factors that cause this heterogeneity can be identified, they can be adjusted for in a Poisson regression analysis. If such variables cannot be identified, or if they do not sufficiently account for the heterogeneity among series, then a regression method that allows for heterogeneity among the rates with each valve model can be used. We used the negative binomial distribution, a generalization of the Poisson distribution (see Appendix 2 for details). These regression models provide an estimate of the HR for valve model adjusted for within-model heterogeneity and can be used to examine the simultaneous effects of other potential risk factors.

Results

Table 1 summarizes the information extracted from reports of aortic St Jude Medical valves,⁵⁻¹⁸ and Table 2 contains the information for aortic Carbomedics valves.^{6,19-28} Figures 1 through 3 contain comparison plots of the linearized rates separated by aortic valve model for thromboembolism, valve thrombosis, and bleeding, respectively. Table 3 summarizes the information extracted from reports of mitral St Jude Medical valves,^{7,8,11-16,18,29,30} and Table 4 contains the information for mitral Carbomedics valves.^{19,20,22,24-26,28,31} Figures 4 through 6 contain comparison plots of the linearized rates separated by mitral valve model for thromboembolism, valve thrombosis, and bleeding, respectively. Note that in most cases the rates vary widely for each valve model and do not appear to cluster about a central value for either model. Although we provide weighted averages (pooled values) at the bottoms of Tables 1 through 4, we therefore did not use these rates directly for analyses. For example, we did not compute 95% CIs for them, nor did we use their ratio to compute an HR. Instead, we let the regression do this, adding in the appropriate variability.

Valve Model Comparisons

Of the 12 groups of linearized rates (3 events $\times$ 2 positions $\times$ 2 valve models), all displayed significant ($P < .05$) heterogeneity (Table 5) except for two of the valve thrombosis groups. Interestingly, these latter two groups had the fewest numbers of events. Negative binomial regression was used for all six valve model comparisons (3 events $\times$ 2 positions). Table 5 contains the summary and comparison statistics. The HRs for the effect of the Carbomedics valve

TABLE 1. St Jude Medical aortic valves

Series	Reference	Valves	Follow-up				Thromboembolism		Thrombosis		Bleeding	
			Complete (%)	Mean (y)	Longest (y)	Total (pt-y)	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
A	5	73	100	7	10	535	5	0.9 (0.4-2.0)			12	2.3 (1.2-3.8)
B	6	149	96	4	7	608	8	1.3 (0.6-2.5)	0	0.0 (0.0-0.4)	25	4.1 (2.7-6.0)
C	7	611	98	3	10	1,605	19	1.2 (0.7-1.8)	3	0.2 (0.1-0.5)	14	0.9 (0.5-1.4)
D	8	275	97	6	13	1,640	10	0.6 (0.3-1.1)	0	0.0 (0.0-0.2)	16	1.0 (0.6-1.5)
E	9	270	100	6	16	1,654	18	1.1 (0.7-1.7)	0	0.0 (0.0-0.2)	21	1.2 (0.8-1.9)
F	10	412	100	4	10	1,800	18	1.0 (0.6-1.5)			22	1.2 (0.8-1.8)
G	11	194	96	10	15	1,843	37	2.0 (1.4-2.7)	3	0.2 (0.0-0.4)		
H	12	425	98	4	12	1,852	25	1.4 (0.9-2.0)	1	0.1 (0.0-0.3)	2	0.1 (0.0-0.3)
I	13	204	100	10	10	1,969	73	3.7 (2.9-4.6)	0	0.0 (0.0-0.1)	33	1.7 (1.2-2.3)
J	14	418	97	6	16	2,376	49	2.1 (1.5-2.7)	6	0.3 (0.1-0.5)	64	2.7 (2.1-3.4)
K	15	578	100	4	13	2,441	59	2.4 (1.8-3.1)	2	0.1 (0.0-0.3)	42	1.7 (1.3-2.3)
L	16	666	97	6	20	3,881	97	2.5 (2.0-3.0)	12	0.3 (0.2-0.5)	78	2.0 (1.6-2.5)
M	17	694	100	6	18	4,502	53	1.2 (0.9-1.5)	2	0.0 (0.0-0.1)	24	0.5 (0.4-0.8)
N	18	773	95	8	15	6,419	54	0.8 (0.6-1.1)	16	0.2 (0.1-0.4)	61	1.0 (0.7-1.2)
Total		5742				33,125	525	1.58	45	0.15	414	1.32

TABLE 2. Carbomedics aortic valves

Series	Reference	Valves	Follow-up				Thromboembolism		Thrombosis		Bleeding	
			Complete (%)	Mean (y)	Longest (y)	Total (pt-y)	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
O	19	209	97	2	5	522	16	3.1 (1.8-4.9)	0	0.0 (0.0-0.5)	10	1.9 (1.0-3.4)
P	6	139	97	4	7	587	9	1.5 (0.8-2.8)	0	0.0 (0.0-0.4)	19	3.2 (2.0-5.0)
Q	20	239	99	4	8	928	22	2.4 (1.5-3.5)	0	0.0 (0.0-0.3)	14	1.5 (0.9-2.5)
R	21	361	98	3	6	937	11	1.2 (0.6-2.0)	0	0.0 (0.0-0.3)	12	1.3 (0.7-2.2)
S	22	359	98	3	6	1,248	17	1.4 (0.9-2.2)	0	0.0 (0.0-0.2)	24	1.9 (1.3-2.8)
T	23	603	98	3	5	1,560	17	1.1 (0.7-1.7)	0	0.0 (0.0-0.2)	25	1.6 (1.1-2.3)
U	24	613	98	4	9	2,378	88	3.7 (3.0-4.5)	0	0.0 (0.0-0.1)	52	2.2 (1.7-2.8)
V	25	689	99	4	7	2,495	41	1.6 (1.2-2.2)	1	0.0 (0.0-0.2)	41	1.6 (1.2-2.2)
W	26	469	98	6	9	2,580	7	0.3 (0.1-0.5)	0	0.0 (0.0-0.1)	11	0.4 (0.2-0.7)
X	27	1019	100	3	9	2,730	26	1.0 (0.6-1.4)	2	0.1 (0.0-0.2)	47	1.7 (1.3-2.3)
Y	28	771	100	4	8	3,176			1	0.0 (0.0-0.1)	22	0.7 (0.5-1.0)
Total		5471				19,141	254	1.59	4	0.02	277	1.45

model and their 95% CIs from the regression models are given. None of the HRs for thromboembolism or bleeding were significantly different from 1 (the 95% CIs contained the value 1). In the aortic position, the Carbomedics valve had less valve thrombosis (HR 0.16) and the 95% CI (0.06-0.56) excluded the value 1. In the mitral position, the Carbomedics valve had more valve thrombosis (HR 1.94) and the 95% CI (0.98-3.84) almost excluded the value 1.

We used three series-level variables to try to adjust for some of the variation between valves. Levels of anticoagulation could affect the results. But international normalized ratio values were not generally available for these series, and reviewers of an earlier draft wondered whether bleeding rate could be a surrogate for anticoagulation intensity. This did not turn out to be the case (Figure 7). In fact, there was a positive (rather than inverse) relationship between bleeding and both thromboembolism and valve thrombosis in

both positions; in none of the regression models was the HR for bleeding rate less than unity, which would indicate a protective factor. So this was not considered further.

Another potentially important series-level factor was follow-up time (Figure 8). If the hazard decreases with time, then the Carbomedics series, with shorter follow-up on average, would be at a disadvantage. We allowed mean follow-up to enter every regression. In none of them was it significant ($P > .10$), and in some its HR was greater than 1, indicating increasing risk with longer follow-up. When the effect went in the "correct" direction, we forced it into the model, and it changed the results somewhat in favor of the Carbomedics valve. These results are also included in Table 5.

The final series-level factor considered in the regression models was follow-up completeness (Figure 9). It seems reasonable that more complete follow-up might result in

Figure 1. Thromboembolism (TE) rates for St Jude Medical and Carbomedics aortic valves. Each circle represents 1 series, with area of circle proportional to number of patient-years in series, as shown by calibration circle in upper left. Solid horizontal lines represent weighted average for each valve model. Horizontal dashed line (3.0%/y) represents Food and Drug Administration's objective performance criterion (OPC) for new valve approvals.

Figure 2. Thrombosis rates for St Jude Medical and Carbomedics aortic valves. Each circle represents 1 series, with area of circle proportional to number of patient-years in series, as shown by calibration circle in upper left. Solid horizontal lines represent weighted averages for each valve model. The Food and Drug Administration's criterion for new valve approvals (0.8%/y) is not shown on this graph.

higher event rates. Thus we allowed follow-up percentage to enter every model. It was never close to significant, and only in three models was its HR greater than 1 (meaning

higher percentage associated with higher event rate). When forced into these three models, it made only the slightest change, at most 0.02 decrease in the HR for valve model.

Figure 3. Bleeding rates for St Jude Medical and Carbomedics aortic valves. Each *circle* represents 1 series, with area of circle proportional to number of patient-years in series, as shown by *calibration circle* in upper left. *Solid horizontal lines* represent weighted averages for each valve model. *Horizontal dashed lines* represent Food and Drug Administration's criteria for major bleeding (1.5%/y) and all bleeding (3.0%/y).

TABLE 3. St. Jude Medical mitral valves

Series	Reference	Valves	Follow-up				Thromboembolism		Thrombosis		Bleeding	
			Complete (%)	Mean (y)	Longest (y)	Total (pt-y)	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
A	11	94	96	9	15	869	25	2.9 (1.9-4.2)	0	0.0 (0.0-0.3)		
B	29	385	99	2	5	926	47	5.1 (3.8-6.7)	3	0.3 (0.1-0.9)	8	0.9 (0.4-1.6)
C	8	166	97	6	13	930	3	0.3 (0.1-0.9)	1	0.1 (0.0-0.5)	11	1.2 (0.6-2.0)
D	7	490	98	3	10	1,287	42	3.3 (2.4-4.4)	4	0.3 (0.1-0.7)	15	1.2 (0.7-1.9)
E	13	163	100	9	10	1,520	78	5.1 (4.1-6.4)	1	0.1 (0.0-0.3)	28	1.8 (1.3-2.6)
F	18	207	95	8	15	1,580	28	1.8 (1.2-2.5)	7	0.4 (0.2-0.9)	14	0.9 (0.5-1.4)
G	15	440	100	4	12	1,782	78	4.4 (3.5-5.5)	2	0.1 (0.0-0.4)	50	2.8 (2.1-3.7)
H	14	292	97	6	16	1,868	63	3.4 (2.6-4.3)	1	0.1 (0.0-0.3)	29	1.6 (1.1-2.2)
I	16	513	97	5	20	2,662	77	2.9 (2.3-3.6)	5	0.2 (0.1-0.4)	51	1.9 (1.4-2.5)
J	12	636	98	5	12	3,252	53	1.6 (1.2-2.1)	3	0.1 (0.0-0.2)	6	0.2 (0.1-0.4)
K	30	440	98	11	19	4,877	34	0.7 (0.5-1.0)	10	0.2 (0.1-0.4)	49	1.0 (0.8-1.3)
Total		3826				21,553	528	2.45	37	0.17	261	1.26

Discussion

Comparing complication rates between established, clinically acceptable heart valves would be an ideal task for a randomized study. However, there are major implementation difficulties with such studies. They are extremely resource intensive, requiring many years and many valves to complete. The AVERT study of the St Jude Medical Silzone valve, designed to distinguish a 50% reduction in endocarditis rates, required 4400 valves and 4 years' time to complete.³² The major heart valve randomized studies have taken so long to conduct that the valves originally entered into the study were no longer in use when the study was

finished.³³ And the results of those studies only confirmed what was already known from published observational studies.

Thus observational studies provide almost all of the known valve complication information. However, observational studies have an important disadvantage. When a randomized study is begun, its existence is generally announced, and the results eventually become available. However, most reports of observational studies are ad hoc; the decision to publish is usually made after the data are collected and analyzed and the results are known. Thus the series reported in the literature may not be representative of

Figure 4. Thromboembolism rates for St Jude Medical and Carbomedics mitral valves. Each *circle* represents 1 series, with area of circle proportional to number of patient-years in series, as shown by *calibration circle* in upper left. *Solid horizontal lines* represent weighted averages for each valve model. *Horizontal dashed line* (3.0%/y) represents Food and Drug Administration’s objective performance criterion for new valve approvals.

TABLE 4. Carbomedics mitral valves

Series	Reference	Valves	Follow-up				Thromboembolism		Thrombosis		Bleeding	
			Complete (%)	Mean (y)	Longest (y)	Total (pt-y)	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
L	19	189	97	2	5	431	16	3.7 (2.2-5.9)	2	0.5 (0.1-1.5)	12	2.8 (1.5-4.7)
M	22	167	98	3	6	580	12	2.1 (1.1-3.5)	2	0.3 (0.1-1.1)	9	1.6 (0.8-2.8)
N	28	169	100	4	8	677			3	0.4 (0.1-1.2)	2	0.3 (0.1-1.0)
O	20	167	99	5	8	800	6	0.8 (0.3-1.5)	0	0.0 (0.0-0.3)	7	0.9 (0.4-1.7)
P	25	328	99	3	7	1096	16	1.5 (0.9-2.3)	2	0.2 (0.0-0.6)	25	2.3 (1.5-3.3)
Q	31	428	100	3	5	1398	30	2.1 (1.5-3.0)	7	0.5 (0.2-1.0)	21	1.5 (1.0-2.3)
R	24	447	98	4	9	1571	64	4.1 (3.2-5.2)	11	0.7 (0.4-1.2)	37	2.3 (1.7-3.2)
S	26	330	98	6	9	1815	6	0.3 (0.1-0.7)	1	0.1 (0.0-0.3)	5	0.3 (0.1-0.6)
Total		2225				8368	150	1.95	28	0.33	118	1.41

the experience in general. And this publication bias may occur preferentially when the outcomes are either favorable or unfavorable. This phenomenon has been recently demonstrated for the outcome of operative mortality after cardiac surgery.³⁴

We have previously compiled reviews of published valve complication rates and used graphic techniques to compare them visually, but we refrained from performing formal analytical comparisons because of the great variability among series.^{35,36} We therefore did not produce weighted average rates for each model, either to characterize a particular model or to make comparisons between valve models. These comparisons were purely descriptive, not inferential.

However, it is natural to pool the results across many studies of the same valve and try to draw an overall conclusion regarding complication rates, and some have done so through simple comparison of the pooled means. This study found significant heterogeneity among 10 of the 12 subgroups of event rates (Table 5). This implies that simple pooled (weighted average) rates cannot be compared directly. The reasons for the heterogeneity could include patient-specific risk factors (many are known) and center-specific factors (postoperative management and data collection methods). To this list would have been added “event definitions”; however, all these reports claim to adhere to the guidelines for reporting.

It has been claimed that thromboembolism is predomi-

Figure 5. Thrombosis rates for St Jude Medical and Carbomedics mitral valves. Each *circle* represents 1 series, with area of circle proportional to number of patient-years in series, as shown by *calibration circle* in upper left. *Solid horizontal lines* represent weighted averages for each valve model. *Horizontal dashed line* (0.8%/y) represents Food and Drug Administration's objective performance criterion for new valve approvals.

Figure 6. Bleeding rates for St Jude Medical and Carbomedics mitral valves. Each *circle* represents 1 series, with area of circle proportional to number of patient-years in series, as shown by *calibration circle* in upper left. *Solid horizontal lines* represent weighted averages for each valve model. *Horizontal dashed lines* represent Food and Drug Administration's criteria for major bleeding (1.5%/y) and all bleeding (3.0%/y).

nantly patient related, whereas thrombosis is more indicative of prosthesis function.³⁷ In this study the two valve models had similar thromboembolism and bleeding rates in both positions, but valve thrombosis rates were different. In the mitral position the Carbomedics valve's rate was higher,

as has been alluded to by some previous studies.^{24,38,39} There was a significantly lower valve thrombosis rate in the aortic position with the Carbomedics valve. Because thrombosis rates themselves are low, however, the *differences* between them (rather than the ratios) are extremely small,

Figure 7. Relationship of thromboembolism (TE) and valve thrombosis (VT) rates (in percent per year, on vertical axes) to bleeding rates (in percent per year, on horizontal axes). Open circles indicate St Jude Medical series and filled circles indicate Carbomedics series.

TABLE 5. Pooled event rates and HRs for comparison of event rates

		Pooled event rates		Valve only in model		Mean follow-up forced in	
Event	Valve	Rate (%/y)	Cochran* <i>P</i> value	HR†	95% CI	HR†	95% CI
Aortic position							
Thromboembolism	St Jude	1.58	<.001	1.06	0.68-1.66	0.98	0.55-1.76
	Carbomedics	1.59	<.001				
Valve thrombosis	St Jude	0.14	.005	0.16	0.05-0.56		
	Carbomedics	0.02	.777				
Bleeding	St Jude	1.32	<.001	1.06	0.66-1.70		
	Carbomedics	1.45	<.001				
Mitral position							
Thromboembolism	St Jude	2.45	<.001	0.72	0.38-1.38	0.54	0.27-1.09
	Carbomedics	1.95	<.001				
Valve thrombosis	St Jude	0.17	.111	1.94	0.98-3.84	1.58	0.73-3.41
	Carbomedics	0.33	.03				
Bleeding	St Jude	1.26	<.001	1.1	0.60-2.00	0.94	0.49-1.83
	Carbomedics	1.41	<.001				

*Heterogeneity among series was tested with Cochran test.

†HR for valve model effect of Carbomedics valve.

representing an incidence of fewer than 2 thromboses in 1000 patient-y. This may be a situation where statistical significance, if it exists, does not imply a clinically important difference.

The findings of this study must be viewed with caution. We have stressed the statistical limitations of combining and comparing diverse valve series. There are also limitations related to data collection (Appendix 1) and definitions.

For example, we attempted to adjust for intensity of follow-up by incorporating follow-up completeness in the models. However, completeness of follow-up may be a poor surrogate for follow-up intensity. There is a difference between a prospectively oriented follow-up system, in which patients are periodically contacted from their surgical dates forward, and a retrospective approach, where patients may be contacted for the first time perhaps 10 years after the

Figure 8. Relationship of thromboembolism (TE) and valve thrombosis (VT) rates (in percent per year, on vertical axes) to mean follow-up (FU, in years, on horizontal axes). *Open circles* indicate St Jude Medical series and *filled circles* indicate Carbomedics series.

Figure 9. Relationship of thromboembolism (TE) and valve thrombosis (VT) rates (in percent per year on vertical axes) to completeness of follow-up (FU, in percent, on horizontal axes). *Open circles* indicate St Jude Medical series and *filled circles* indicate Carbomedics series.

operation. Thus even though a retrospective and a prospective series might have the same overall percentage of completeness, the one with a retrospective approach is much less

likely to reveal intervening events, especially nonfatal ones, than is the one with a prospective approach. We tried to incorporate heterogeneity among series into our analyses

but were still unable to *explain* this heterogeneity. With so many factors able to influence the results from different centers, it is difficult to combine analyses across different studies on the basis of published results.

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Appendix 1

Data Limitations

- There is a simple relationship between the linearized rate, the number of events, and the total follow-up years. We needed all three for the analysis, so if one of them was not given in the article, we derived it from the other two. If only one of the three was given, we did not use that article. If all three were given but were inconsistent with each other, we tried to determine the two most reliable values and recalculated the third.
- When total follow-up years were not given separately by position, we calculated them from the linearized rates and numbers of events if they were available. Otherwise we derived them as proportions of the total follow-up years according to the ratios of patients with each valve position.
- If thrombosis was included in the thromboembolism rate, we recalculated that rate to exclude the valve thromboses.
- One aortic Carbomedics series²³ and 1 mitral Carbomedics series³¹ were multicenter studies; publications from one of the investigators of those studies^{24,29} may include some overlap.
- One series defined late events as those occurring after 3 months⁴⁰ and focused on anticoagulation management only, so we did not use that study.
- A few series were considered in the analyses but did not meet one of the selection criteria: 2 aortic series^{41,42} and 1 mitral series⁴² had follow-up completeness between 92% and 94%; 2 aortic series^{28,43} included only major thromboembolic events, and 1 article did not mention adherence to the guidelines for reporting.⁴⁴

- Even though 1 Carbomedics reference⁴⁵ appeared to update a previous reference,¹⁹ it did not separate thromboembolism by position, and the newer reference had fewer bleeding events because of a stricter definition of major bleeding.

Appendix 2

Statistical Details

If events occur independently at a constant rate of R per patient-year, the number of events E in Y patient-years follows a Poisson distribution (with parameter RY); the maximum likelihood estimate of R is E/Y . In the cardiac surgical literature this estimate is multiplied by 100 to convert it to events per 100 years, or percentage per year, and called the *linearized rate*.

If the rates in several series with the same valve are assumed to be equal, then their weighted average can be directly compared with, for example, a likelihood ratio test or an F test, as suggested by Cox.⁴ A more general way to compare valve models when the rates among series with each model are similar is to use Poisson regression.⁴⁶ Here the series are not directly pooled, and risk factors that differ among series can be incorporated to provide a HR for the effect of valve model adjusted for these other factors.

Before Poisson regression is used, however, series with the same valve model should be tested for homogeneity. A test for this could be a likelihood ratio test or the χ^2 goodness-of-fit test attributed to Cochran.⁴⁷ If there is significant heterogeneity among the rates for series with the same valve model, then Poisson regression should not be used directly, unless the heterogeneity can be accounted for by including other risk factors. If not, then a modification of simple Poisson regression can be used to account for the heterogeneity. One way is to use the negative binomial distribution. The negative binomial distribution is used to model count data from subgroups that have Poisson distributions but with differing rates that themselves have a gamma distribution.⁴⁸ The negative binomial distribution is a generalization of the Poisson distribution in the sense that the variance of the negative binomial has an additional dispersion parameter; if this is 0, the negative binomial collapses to the Poisson.

Another regression method is to include a random effect for medical center in the model to accommodate unmeasured variation that valves from the same center have in common but that may vary among different centers.⁴⁹ We used this method in several of the analyses but did not include the results because they were similar to those from the negative binomial regressions. The S-PLUS 2000 statistical program (Insightful Corporation, Seattle, Wash) was used for all analyses. The S-PLUS functions used for Poisson, negative binomial, and random effect regressions were *glm* (generalized linear models), *glm.nb* (generalized linear model, negative binomial) and *reglm* (random effects generalized linear model), respectively.