The Silzone effect: how to reconcile contradictory reports?

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Abstract

Objective: To attempt to reconcile reports containing contradictory findings with the St. Jude Medical Silzone heart valve. Methods: Major leak and thromboembolism data were extracted from available Silzone valve studies. Linearized rates were used to summarize and compare the events rates among the studies. Results: The Artificial Valve Endocarditis Reduction Trial (AVERT) study reported significant higher rate of major leak and the Cardiff Embolic Risk Factor Study (CERFS) reported significant higher rate of thromboembolism with Silzone compared to non-Silzone valves. But, current updates of these studies show a diminution of these differences. Three other comparative studies reported no difference between Silzone and non-Silzone valves, and three single arm studies reported acceptable results with Silzone valves. Conclusion: The contradictory findings could be partly due to clinical and technical reasons. No new events have been reported since the original AVERT (major leak) and CERFS (mitral thromboembolism) publications.

Keywords: St. Jude Medical heart valve; Silzone heart valve; Paravalvular leak; Thromboembolism

1. Introduction

The various publications on the St. Jude Medical (SJM) Silzone heart valve experience raise an interesting and clinically important question: How should we interpret reports containing disparate findings with the same treatment? The treatment in this case is the Silzone heart valve, identical to the non-Silzone SJM valve except for a silver-coated sewing ring intended to avert prosthetic valve endocarditis. The findings are major paravalvular leak and thromboembolism. The randomized Artificial Valve Endocarditis Reduction Trial (AVERT) study [1] reported a significantly higher risk of major leak, but not thromboembolism, with Silzone compared to non-Silzone SJM valves. The prospective Cardiff Embolic Risk Factor Study (CERFS) reported significantly higher rates of thromboembolism, but not leak, with Silzone compared to non-Silzone [2,3]. Other comparative studies found no increased rates of leak [4,5] or thromboembolism [5,6] with Silzone. Other single-arm studies reported no increased rates of leak or thromboembolism with Silzone valves [7–9].

The randomized AVERT study should provide the highest level of evidence; however, it contains only 403 of the estimated 36 000 Silzone valve patients. Among the non-AVERT reports are 485 additional Silzone valve patients. These disparate reports provide an opportunity to attempt to reconcile their apparently contradictory results, and to include some recently updated information from the AVERT and CERFS studies [10,11].

We do not try to evaluate the Silzone effect on endocarditis since it is the least controversial aspect of the Silzone valve’s performance, and, according to the AVERT protocol [12], a 4-year study comprising 4400 valves may be necessary to reach a definitive conclusion about the efficacy of the Silzone treatment.

2. Clinical material

We used the PubMed search service (http://www.ncbi.nlm.nih.gov/) to find papers that included the word ‘Silzone’ in any field of the citation. This produced the following papers, listed in order of their putative strength of evidence.
2.1. Randomized studies

AVERT is a multicenter randomized trial of Silzone versus non-Silzone valves, designed to be a 4-year study enrolling 4400 valves [12]. However, patient accrual was stopped in January 2000, after 807 operations at 12 North American and 7 European centers, because of a significantly higher rate of explant for paraavalvular leak in the Silzone arm of the study. The published report included 878 patient-years of follow-up [1]. Updated information on AVERT, with 1823 follow-up years, recently became available [11]. Another, single center study, undertaken with the same goals as AVERT, randomized 95 patients to receive Silzone or non-Silzone SJM valves [4].

2.2. Matched study

A letter to the editor [6] found no TE in a matched group of 81 Silzone and 81 non-Silzone SJM valve patients from the German Experience with Low Intensity Anticoagulation (GELIA) database.

2.3. Comparative studies

The Cardiff CERFS study implanted 51 Silzone and 118 non-Silzone SJM valves as part of a prospective study to find risk factors for thromboembolism, described in two early abstracts [2,3] and a recent paper [10]. Another recent study compared 113 Silzone and 111 non-Silzone valves [5].

2.4. Single-arm (Silzone only) series

A three-institution study reported on 38 Silzone patients [7]. Two single-institution studies reported on 126 [8] and 111 [9] Silzone patients. 

2.5. Case reports

Silzone efficacy in prosthetic valve endocarditis was reported in single patients [13,14] and in 10 patients [15]. Endocarditis and/or leak in Silzone patients was also reported [16–19]. These case reports are not considered further.

The complications extracted from the series reports were major leak (leading to reoperation) and all thromboembolism. We did not exclude leaks associated with endocarditis, as recommended by the STS/AATS guidelines for reporting heart valve performance [20], since not every study included that information.

3. Statistical methods

Linearized rates were used to summarize and compare the rates of major leak and thromboembolism. Only late events and late follow-up years should be used to calculate linearized rates, because they assume that the risk is constant, but the early risk is usually higher. Both early and late events were used to compute the linearized rates since not every study gave them separately. Even during the late period the risk may be changing; in such cases, a time-related method such as Kaplan–Meier should be used [21]. Some reports used Kaplan–Meier event-free curves, but most did not. So, in order to proceed with tabular and graphical comparisons, we used linearized rates, deriving them from the raw data when they were not given directly.

Some papers combined aortic, mitral and double valve replacement patients. Combining the positions impairs the clinical usefulness of the data, and is proscribed by the guidelines for reporting [20]. But since the distribution among positions is similar for both valve types and for most of these series (Table 1), comparisons should still be valid. So, to enable comparisons, we combined all valve positions. Confidence intervals for the linearized rates were computed using the method suggested by Cox [22,23].

4. Results

The first set of two columns in Table 1 contains data from the AVERT study: the top section is from the 2002 publication [1] and the bottom section is updated information [11]. The second set of two columns contains the comparable data from CERFS: the top section is from a 1999 abstract [2] and the bottom section is from a recent update [10]. The remaining columns in the table are from the other reports. The major leak and the thromboembolism rates in the table are in bold type. Below the point estimates of these rates are their 90% confidence intervals.

These rates and confidence intervals are compared graphically for major leak (Fig. 1) and thromboembolism (Fig. 2). In these figures, the interval estimates for Silzone from the first CERFS study [2] are truncated since, with only 31 patient-years, they are quite large (the complete intervals are given in the table). For comparison, the rates corresponding to the FDA’s Objective Performance Criteria (OPC) for mechanical heart valves [24] are shown in the figures by solid horizontal lines. To gain approval, the valve’s upper confidence limit should be less than twice the OPC, shown by dashed horizontal lines. (Note: FDA recommends using only late events, whereas the rates in these figures include both early and late events.)

5. Discussion

There are both clinical and technical reasons why different studies reach different conclusions. Clinical reasons include differences in patient risk factors, operative techniques and patient management. Technical reasons include differences in sample sizes, definitions, follow-up methods, data management and statistical analyses. In comparative studies within the same institution(s), especially when the valve
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Patients</td>
<td>403</td>
<td>404</td>
<td>51</td>
<td>46</td>
<td>81</td>
<td>81</td>
<td>113</td>
<td>101</td>
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<td>Mean age (year)</td>
<td>61</td>
<td>61</td>
<td>65</td>
<td>59</td>
<td>61</td>
<td>Matched</td>
<td>57</td>
<td>58</td>
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<tr>
<td>Male (%)</td>
<td>59</td>
<td>41</td>
<td>50</td>
<td>43</td>
<td>59</td>
<td>Matched</td>
<td>68</td>
<td>60</td>
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<td>Positions (%)</td>
<td>Aortic</td>
<td>59</td>
<td>63</td>
<td>61</td>
<td>52</td>
<td>65</td>
<td>69</td>
<td>64</td>
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<tr>
<td></td>
<td>Mitral</td>
<td>32</td>
<td>25</td>
<td>30</td>
<td>24</td>
<td>20</td>
<td>27</td>
<td>33</td>
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<tr>
<td></td>
<td>Double</td>
<td>9</td>
<td>12</td>
<td>8</td>
<td>2</td>
<td>14</td>
<td>4</td>
<td>3</td>
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<td>Follow-up (patient-years)</td>
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<td></td>
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<tr>
<td>Total</td>
<td>437</td>
<td>441</td>
<td>31</td>
<td>244</td>
<td>58</td>
<td>62</td>
<td>108</td>
<td>227</td>
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<td>1.1</td>
<td>0.6</td>
<td>2.1</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
<td>2.3</td>
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<td>Linearized rate (%/year)</td>
<td>3.2</td>
<td>0.5</td>
<td>0.0</td>
<td>0.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.9</td>
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<td>90% Confidence interval</td>
<td>2.0–4.9</td>
<td>0.1–1.3</td>
<td>0.0–6.2</td>
<td>0.1–1.6</td>
<td>0.0–3.3</td>
<td>0.0–3.1</td>
<td>0.2–3.6</td>
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<tr>
<td>All thromboembolism</td>
<td>Linearized rate (%/year)</td>
<td>5.9</td>
<td>3.9</td>
<td>45.2</td>
<td>10.2</td>
<td>0.0</td>
<td>0.0</td>
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<td>90% Confidence interval</td>
<td>4.3–8.1</td>
<td>2.5–5.7</td>
<td>28.6–68.6</td>
<td>7.3–14.1</td>
<td>0.5–5.1</td>
<td>0.5–3.1</td>
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<tr>
<td>Total</td>
<td>900</td>
<td>922</td>
<td>153</td>
<td>529</td>
<td></td>
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<tr>
<td>Mean</td>
<td>2.2</td>
<td>2.3</td>
<td>3.0</td>
<td>4.7</td>
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<td>Reoperation for leak</td>
<td>Linearized rate (%/year)</td>
<td>1.4</td>
<td>0.2</td>
<td>0.7</td>
<td>0.2</td>
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<td></td>
<td>90% Confidence interval</td>
<td>0.9–2.2</td>
<td>0.1–0.6</td>
<td>0.1–2.5</td>
<td>0.0–0.7</td>
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<tr>
<td>All thromboembolism</td>
<td>Linearized rate (%/year)</td>
<td>4.1</td>
<td>3.0</td>
<td>8.5</td>
<td>6.8</td>
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<tr>
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<td>90% Confidence interval</td>
<td>3.1–5.3</td>
<td>2.2–4.1</td>
<td>5.3–13.1</td>
<td>5.1–8.9</td>
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</table>

* Provided by the author.
patients are randomized or matched, most of the clinical differences should be neutralized.

Sample size can be crucial since with too little data, clinically important differences will not be statistically significant, while with enough data, even clinically unimportant difference can become statistically significant. Thus, the failure of a study to detect differences could be due to small sample size, an example of statistical Type 2 (false negative) error. Accordingly, insignificant results (large P-values) should be interpreted as ‘a significant difference was not detected’ rather than ‘there is no difference’ or ‘the treatments are the same’. With more data, estimates become more precise, as indicated by smaller confidence intervals. Because of the pronounced heterogeneity in results among these series, we did not attempt a formal meta-analysis, nor even produce any P-values; we used an estimation rather than a hypothesis-testing approach, emphasizing qualitative, graphical comparisons. In the figures, we have purposely made the point estimates, indicated by square symbols, small, to focus attention on the confidence ranges (vertical lines).

5.1. Major leak

Both AVERT reports have a higher leak rate for Silzone than for non-Silzone valves (Fig. 1), while the other comparative reports either do not, or have widely overlapping confidence intervals. The rate for Silzone is much lower in the more recent AVERT study [11] than in the original report [1]. In fact, no new major leaks have been reported with Silzone valves in the AVERT study between the earlier publication (which included reports through November 2000) and the updated information (through August 2002) in spite of more than twice as many patient years of follow-up. In such a situation, the linearized rate will continue to fall as the follow-up increases, and the Kaplan–Meier method is better for summarizing and comparing such risks [11].

5.2. Thromboembolism

In all of the comparative reports, Silzone valves have a higher thromboembolism rate than non-Silzone valves (Fig. 2). But, except for the original CERFS report, the 90% confidence intervals overlap. Confidence intervals from one study are not plotted since follow-up years were not given; however, those confidence intervals would also overlap. The high thromboembolism rate for Silzone valves from the original CERFS report [2] has since become lower [10]. Unfortunately, pooling the positions and using linearized rates has concealed an important element in the CERFS data: namely that the thromboembolism risk was confined to the mitral position and to the relatively early postoperative period. In fact, no new events have been reported between the earlier abstracts and the updated paper. And none have occurred beyond 3 months after operation, despite follow-up out to 3 years. The Kaplan–Meier method is better for summarizing and comparing such risks, separately by valve position [10].

5.3. Conclusion

Contradictory reports with the Silzone valve have created a continuing dilemma [25]. The AVERT and CERFS studies
found significantly higher rates of major leak, and thromboembolism, respectively, with Silzone compared to non-Silzone SJM valves. Several smaller studies found no differences between Silzone and non-Silzone SJM valves in comparative studies; others found acceptable results with Silzone valves in single-arm studies. These negative findings could be due to small sample sizes; however, with further experience the differences found by AVERT and CERFS become smaller. Indeed, no more major leaks in AVERT or mitral thromboembolism in CERFS have been reported between their original and recent (2003) reports, with 1.1 and 2.4 additional years of follow-up, respectively. This should be welcome news, especially for patients.

References


