The Björk-Shiley Convexo-Concave Heart Valve Experience from the Perspective of the Supervisory Panel

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The 20-year activities of a medical supervisory panel appointed under the terms of a settlement agreement of the Bowling v. Pfizer class action suit involving the Björk-Shiley convexo-concave (BSCC) heart valve are detailed. Of approximately 86,000 valves implanted, catastrophic failure of the valve was reported in 663 patients from 1978 to 2012. In 1994, a 7-member medical panel consisting of cardiologists, cardiovascular surgeons, epidemiologists, and a nontechnical chairman was appointed by the federal court. The panel collected clinical and manufacturing data, supported epidemiologic studies assessing risk factors for valve fracture, and developed guidelines for payment for explanting potentially defective valves in patients. Three sets of guidelines, based on comparisons of estimated risks of valve fracture versus risks of valve replacement surgery, were issued by the panel to help guide patients and their physicians in decisions about explanting valves. In addition, the panel supported research directed at identifying valves at risk for outlet strut fracture. The primary techniques evaluated included analyzing acoustic signals from the valves, imaging valves for potential cracks in the struts, and structural analyses of Björk-Shiley convexo-concave valves, but none proved applicable for large-scale surveillance of the patient population. The panel also became a patient advocate and acted as an intermediary between the manufacturer and the attorneys initiating the legal settlement. The panel's experiences may help inform future strategies for guideline development for other medical devices or procedures involving risk-benefit comparisons.   © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1921–1931)

The past 1/2 century has witnessed enormous advances in the development and refinement of implantable medical devices such as heart valves, joint replacements, and pacemakers/defibrillators. For the most part, these devices have improved the quality and, in some cases, the duration of human life. Unfortunately, occasional unexpected adverse events have and will continue to occur (e.g., the recently reported problems with hip replacements and cardiac pacemaker/defibrillator leads), with the result that very careful monitoring of new devices is now recognized to be an essential component of the evaluation of health services and the protection of patients. Fracture of the outlet strut of the Björk-Shiley convexo-concave (BSCC) heart valve was one of the first and most catastrophic of these adverse events.

The BSCC valve, originally released in 1978,[1] was approved by the Food and Drug Administration (FDA) in 1979, after which large numbers were distributed by Pfizer Inc., for implantation worldwide. During the next several years, multiple instances of catastrophic failure of the BSCC valve, often with patient death, were reported.[2–5] These reports resulted in numerous wrongful death lawsuits. A class action lawsuit, known as Bowling v. Pfizer, was filed in 1992, the principal purpose of which was to deal with class members' fear of further injury or death.[6]

The settlement agreement provided for implantees to be members of the class and receive certain benefits, unless they opted out. It also provided that a supervisory panel (the panel) of experts would be appointed for the purposes of (1) establishing and modifying guidelines under which monetary benefits would be paid to class members who elected to have their BSCC valve(s) explanted, (2) conducting "research and development of diagnostic techniques to identify implantees who had significant risk of strut fracture", and (3) "conducting research concerning the characterization and/or reduction of the risks of valve replacement surgery, including improvement of the techniques for such surgery".[6] The panel was appointed and began its work in 1994; it consisted of 7 members, 6 of whom were medical doctors who were experts in cardiology, cardiovascular surgery, and epidemiology and a nonscientist chairperson who organized the efforts of the panel. A significant sum of money was committed under the supervision of the federal court to support the research mandated in the settlement, which was unique at the time for a settlement of this sort.[6]

Our purposes in this publication are to (1) summarize the panel's activities over the 20 years of its existence, (2) review

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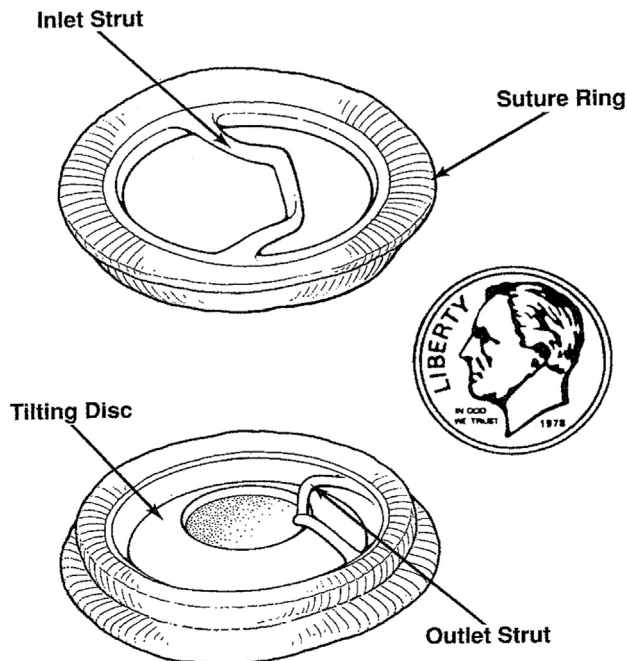E-mail address: don@clsvc.com (D.C. Harrison).

Figure 1. Views of a 60° BSCC heart valve in a closed position. The inlet strut is molded into the metal valve ring, which is covered by fabric suture ring. The outlet strut is welded into the metal ring. The tilting disc is shown in the valve's closing position. The quarter is shown to illustrate size. Illustration by Michael P. Schenk.

the history and current status of the BSCC heart valve issue, and (3) highlight those lessons that may be useful to other similar panels tasked with assessing the risk and promoting research into failures of other medical technologies that might be implanted in patients.

Background

The BSCC valve: The BSCC tilting disc valve was designed to replace the original radial spherical (R/S) model, which was prone to valve thrombosis. The BSCC heart valve was considered an improvement over the earlier version because its strength was increased by making the inlet strut part of the orifice ring and doubling the cross-section area, thus improving hydrodynamics and eliminating the area of stagnant and low flow behind the disc (thereby decreasing the thrombosis risk). The valve also contained an outlet strut made of Haynes 25 alloy (M. Vincent and Associations, Ltd., US Distribution, Inc., Windfall, Indiana) whose legs were welded into the valve ring. The tip of the outlet strut was bent downward to form a rounded hook that fit into a circular depression on the downstream side of the disc (the well) and served to hold the disc in the valve housing as it rotated between the open and closed positions (Figure 1). Valve closure occurred in 2 phases: translation, in which the disc moved backward toward the valve ring, terminating when the edge of the occluder impacted the ring, followed by rotation about this axis to the closed position. By design, the axis of rotation was close to the base of the outlet strut so that the major force of the rotational impact was applied to the larger molded inlet strut, with any slight overrotation impacting the base of the outlet strut. All the initial valves produced had

a 60° opening angle; a second version of the valve with a 70° opening angle was introduced >1 year later and was frequently implanted in Europe, but it was never approved for implantation in the United States (US).[7]

Worldwide, nearly 86,000 valves (54% aortic and 46% mitral) were shipped and not returned and, therefore, were assumed to have been implanted. More than 31,000 were in the US; other countries with significant numbers of implanted valves included Canada, England, France, Germany, India, Italy, Japan, Spain, Sweden, and the Netherlands.[8–10]

Outlet strut fractures: The first fracture of the outlet strut of a 60° valve occurred during clinical trials in 1978; as increasing numbers of valves were implanted, additional reports of similar fractures were received by the manufacturer. Although the number of fractures was small compared with the number of valves implanted, the fact that they all occurred near the weld site of the outlet strut suggested either a design or a manufacturing flaw. The fractures themselves were catastrophic, leading to embolism of the disc, abrupt volume overload, and death in most cases, with significant morbidity reported in many of those who survived to emergent surgery. As a result, although the overall mortality rate for the BSCC was similar to that of other valves implanted during the same period, the 70° valve was withdrawn from the market in 1983, and the 60° valves were withdrawn in 1986. The fractures of the 70° valves were considered to be more common, accounting for its earlier removal from the market.[10]

Mechanism: As the number of fractures began to increase, the Shiley Heart Valve Research Center initiated a number of studies to determine the cause of the outlet strut fractures (OSFs). Pulse duplicator studies demonstrated that (1) uneven pressure distribution across the disc at closure resulted in a tendency for the disc to overrotate, (2) there was a linear relation between outlet strut loads and the closing velocity, (3) outlet strut loads increased with increasing dP/dt and heart rate, and (4) valve-related factors such as the hook-to-well distance and hook deflection correlated with outlet strut load.[11]

Studies of BSCC valves with strain gauges implanted in sheep showed that the overall strut loads increased with increasing exercise associated with increasing dP/dt and pressure at valve closure. Thus, it was concluded that increasing closure forces, most notable during exercise, caused overrotation of the disc that pushed the tip of the outlet strut upward, creating a bending force at the weld site at the base of the strut legs, which at some point exceeded the tolerance of the Haynes 25 alloy. Over time, repeated stresses led to cracking and ultimate fracture of 1 or both outlet struts. This led the manufacturer to increase the hook-to-well distance, and these modified valves were introduced in April 1984. To date, none of these valves has ever fractured, but these data did not become available until long after the BSCC valves were withdrawn from the market.

Activities of the Supervisory Panel

Establishment of guidelines for valve replacement surgery: The Bowling-Pfizer settlement agreement provided monetary benefit for those who had been injured by BSCC failure and for their families, as well as certain costs associated with valve replacement for those those in whom the risk of valve failure exceeded the surgical mortality/serious morbidity involved in valve replacement.
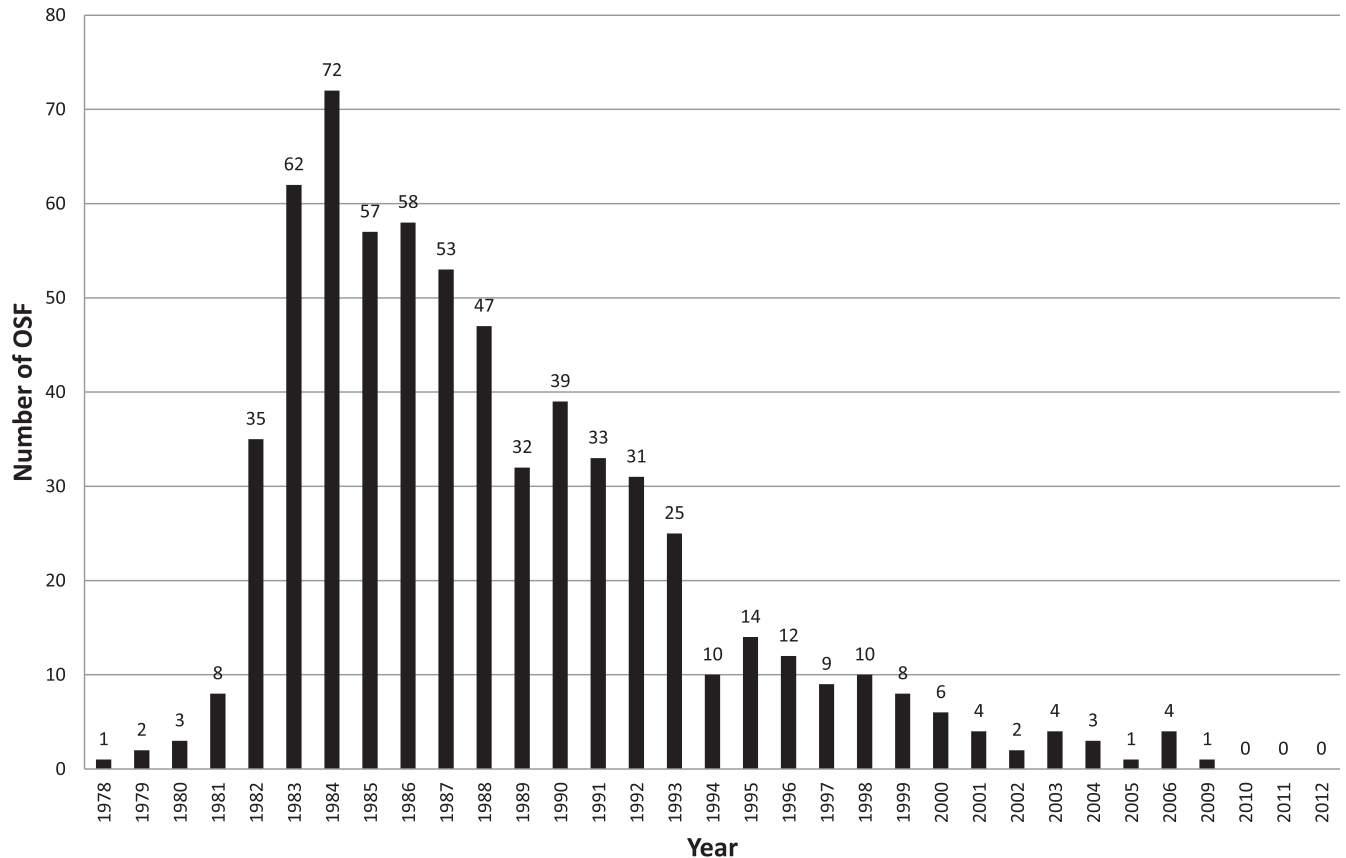
Figure 2. The number of OSFs occurring each year from the earliest reported case in 1978. No fractures have been reported in 2010, 2011, and 2012.

The guidelines were therefore intended to identify patients in whom the meaningful extension of life expectancy provided by reoperation exceeded the potential loss due to valve fracture. In calculating this risk, the panel assumed that the patient was in optimal health for his or her age and that the facility where the surgery was to be performed had an excellent operative mortality record. This in turn required assembling data on the incidence of strut fracture, the risk factors associated with fracture, and the surgical mortality and morbidity data for valve reoperation.

Incidence of strut fracture: OSFs occurring worldwide have been regularly reported to Pfizer from 1979 to the present. As of the end of 2012, a total of 663 fractures (491 in 60° valves and 155 in 70° valves) have been reported, including 17 reported to Pfizer without serial number identification.[12] The average annual fracture rate over the entire period is 0.04% for 60° valves and 0.26% for 70° valves, although actual fracture rates are believed to be somewhat higher because not all OSFs are believed to be reported to Pfizer.

Figure 2 shows the numbers of OSFs reported annually from the worldwide database. The number of fractures increased to a peak in the mid-1980s and began a steady decrease thereafter.

Risk factors for OSF: The factors affecting risk of OSF were originally examined in a retrospective cohort study on all 2,303 Dutch patients implanted with 60° or 70° valves.[13] After an average follow-up period of 6.6 years, the investigators identified 42 cases of OSF. Multivariate analysis

identified wide opening angle (70°), large valve size ($\geq$29 mm diameter), and young age (<50 years) as risk factors for OSF. To further explore the determinants of risk and their relative contribution to OSF, the panel sponsored additional case-control and cohort studies in both the US and Europe. In the first of these studies, Walker et al[14] conducted a case-control study of 60° valves implanted in the US and Canada and manufactured from January 1, 1979 to March 31, 1984. Cases included all verified OSFs reported to the manufacturer from January 1979 through January 1992. Clinical data were available from medical records for 96 cases and 634 controls. The investigators concluded that "[t]here was a strong inverse gradient of risk with age … Large mitral valves were at greatest risk of strut fracture … valves welded from mid-1981 through March 1984 were more likely to fracture than those manufactured in 1979 and 1980 … Body surface area <1.5 m² was associated with 1/16 the risk of body surface area of $\geq$2.0 m²". It was noted that differences in body surface area are related to gender, with women having smaller areas.

The panel also sponsored follow-up to the 1992 Dutch study in which the manufacturing characteristics that predicted OSF in large 60° degree valves were studied.[15] In this investigation, Kallewaard et al followed all patients with implanted valves until fracture, death, reoperation, or the end of study on July 1, 1996. Manufacturing records were available for 637 valves, including 23 fractured valves. Results indicated that "age at implantation …, lot size …, number of hook deflection tests performed …, number of

Table 1
Valve-related risk factors for outlet strut fracture (OSF) in 60° Björk-Shiley convexo-concave heart valves

Risk Factor	Category	Estimated Relative Risk of OSF	Estimated No. (%) of Valves With Attribute	No. (%) of OSF With Attribute
Angle	70°	5.0	4,000 (5)	154 (24)
	60°	1.0*	81,700 (95)	479 (76)
Size (mm)	33	9.6	1,600 (2)	58 (10)
	31	5.5	10,300 (12)	205 (33)
	29	4.0	14,900 (17)	181 (28)
	27, 23	2.8	32,200 (38)	155 (24)
	25, 21	1.0*	26,500 (31)	34 (5)
Weld date	>1980	1.0*	7,600 (9)	35 (5)
	1980	0.5	18,400 (22)	45 (7)
	January 1981 to June 1982	1.6	33,100 (39)	463 (74)
	July 1982 to March 1984	1.0	18,500 (22)	89 (14)
	April 1984 onward	0.0	8,000 (9)	0 (0)
Shop order[†]	OSF in other valves in batch <1%	1.0*	69,800 (81)	231 (36)
	OSF in other valves in batch 1%−5%	1.9	12,100 (14)	247 (39)
	OSF in other valves in batch >5%	2.4	3,800 (4)	155 (24)
Welder group[‡]	A or B	1.0*	70,700 (82)	391 (62)
	C	1.5	15,100 (18)	242 (38)
Position	Mitral	2.5	38,100 (45)	496 (78)
	Aorta	1.0*	47,200 (55)	137 (22)
Rework status[§]	No crack or rework	1.0*	78,100 (91)	538 (85)
	Crack, rework, or missing	1.6	7,700 (9)	95 (15)

* Reference (baseline) category.

[†] Batch in which valve was produced.

[‡] Refers to categorization of welders who welded the outlet strut to the valve flange.

[§] Refers to whether valve was reworked because of a crack or other fault detected during manufacturing process; those with missing information on this factor were also at increased risk and thus grouped with those known to have rework. The risk factors identified for OSF are listed and compared with a reference baseline category of 1. The highest risks occur in 70° valves, larger mitral valves, and valves with a crack or that had been reworked.

Table 2
Rates of outlet strut fracture (OSF) incidence (percentage of valves experiencing OSF by the year of follow-up) according to patient age at follow-up

Age (yrs)	No. of OSF	Incidence Rate (% per yr)	95% CI
<45	30	0.29	0.19−0.39
45−54	23	0.15	0.09−0.21
55−64	41	0.15	0.10−0.19
65−74	13	0.04	0.02−0.07
75+	2	0.02	0.00−0.04

The rate of valve fracture per year is shown for the age of patients at the reported fracture occurrence. Younger patients had the highest incidence with almost none in the >75-year group. Data from combined Dutch/British/American cohort studies.[16]

CI = confidence interval.

discs that were used …, and lot fracture percentage … as independent predictors of fractures". The manufacturing data were provided by Pfizer for this review.

Also sponsored by the panel was a study by Omarand et al[8] who reported on OSF in the United Kingdom cohort of 2,977 patients with a follow-up of 18 years. There were 56 OSFs. The investigators identified age, body surface area, valve size, shop order, fracture rate, and manufacturing period as risk factors for OSF. They also noted that the risk

of OSF in valves manufactured from 1981 to 1984 was 4× greater than that of valves manufactured before 1981.[8]

The results of these studies and the calculated relative valve-related risks are summarized in Table 1. This table has been updated as each new set of fracture data are made available to the panel.

Risk factors therefore included those related to the valve. Valve opening angle (70° vs 60°) and diameter size (33 vs 21 mm) are the strongest determinants of fracture risk. Other significant but weaker determinants were related to specific aspects of the manufacturing process such as the fracture rate of the batch from which the valve originated, the amount of rework of valves, and the welder group.[10,16]

Age and gender are the most important patient-related characteristics. The risk of fracture was only 1/2 as high among women compared with men, and risk decreased with increasing age. Fewer than 14% of the fractures occurred in those aged ≥65 years (Table 2).

To determine OSF rates for purposes of the guidelines, we used the periodic reports of OSF data prepared by the manufacturer and submitted to the FDA and the Bowling-Pfizer Trustees (Table 1) as numerators and the estimated valve-years of follow-up as denominators. Unlike the individual studies reported previously, this reporting system includes fractures worldwide. Because not all OSFs are believed to be captured by this system, an upward adjustment of the estimated rates was made by the panel to account for underreporting. The upward adjustment

contained the higher observed rates of OSFs in the Netherlands and the United Kingdom cohorts, in which the reporting is considered to be highly accurate. An additional 10% was added to compensate for potential underreporting suggested by these cohorts.[9,10]

Risk factors to mechanisms of fracture: These epidemiologic data are consistent with the factors known to increase stress on the valve. Specifically, closing stresses increase with increasing cardiac output, heart rate, and valve size and are greatest during periods of intense exercise. All these parameters tend to be greater in men than women and tend to decrease as patients age. They are also consistent with the observation that fracture rate is associated with body mass index. Although one might assume that the cumulative effect of multiple closures over time would increase risk, only those that increased closure forces above the tolerance limit of the strut appear critical.

Risks associated with reoperation: The supervisory panel's guidelines were heavily dependent on surgical mortality and morbidity data for explantation of prosthetic valves. This was complicated by the fact that data for elective operation for prosthetic valve replacement are limited.[17−19] Nevertheless, the panel gathered data from the most reliable sources, including the database of the Society of Thoracic and Cardiovascular Surgery and from the Cleveland Clinic, which is the largest center in the world performing heart valve replacement. The surgical mortality and morbidity within 90 days were obtained from the Society of Thoracic and Cardiovascular Surgery database, and early and later-stage mortalities and morbidities were determined from the Cleveland Clinic database.[20] The panel periodically collected data from these sources and corrected its estimates based on improvements in surgical results as it modified the guidelines from time to time.[21,22] Because the mortality and morbidity for replacement of aortic valves differed from that of the replacement of mitral valves, each was addressed separately.

Because patient age is an important factor in surgical mortality and the average age of the patients with BSCC valves was greater than many of the reports in the literature, the panel needed to make adjustments for these differences. Concomitant disease is also an important contributor to surgical mortality; however, as the panel was required by a binding settlement protocol to assume that the patients were in optimal health and individual patient status was unknown to the panel, risk was based on that for patients in class I and II. It was assumed that the patient's health would be taken into account by his or her personal physician in deciding on reoperation irrespective of the patient's qualification for monetary benefits. It is also well known that the surgical mortality and morbidity is much greater at low-volume centers, but the charge to the panel was to determine the optimal surgical mortality and morbidity. Thus, it used the data from the Cleveland Clinic database together with the significant numbers of explants carried out at the Stanford and William Beaumont Hospitals to determine optimal results.[20,21]

Although the observed operative mortality improved slightly as each of the new guidelines was developed, the decreasing risk of cardiac surgery was counterbalanced by the concomitant aging of the population, with the result that changes that were used in the development of each set of guidelines were relatively small.

In 1997, the court approved the first set of guidelines established by the panel. Since then, the guidelines have been revised 3 times, with the current version being approved in 2007. Because of the relatively small annual fracture rate and the age of the population, the number of patients who were initially expected to achieve an actual improvement in life expectancy was relatively small and consisted mainly of young patients with larger mitral valves. With each revision of the guidelines, this number decreased because of the decreasing fracture rate and the advancing age and decreasing size of the population of patients with BSCC valves.

Issues involved in applying guidelines to individual patients: The first issue relates to the difficulty in applying information obtained from group data to individual patients. The value of the guidelines is in identifying the subgroup of patients for whom, on average, BSCC heart valve reoperation will result in a gain in life expectancy. However, for some individual patients, there can be an immediate loss of life expectancy (if death results from reoperation), whereas for other patients there can be a significant gain (if a strut fracture is avoided by a successful operation). Furthermore, for some patients who undergo reoperation, there may well be no change in life expectancy, even if they survive the reoperation because they may not have had an OSF if the valve had been left in place. Accordingly, it is important to understand that the guidelines are based on a statistical analysis of group data and that the risk for an individual patient may differ from that of the group.

The second issue is that the qualification for a monetary benefit should not be equated with the recommendation that replacement surgery is appropriate for a particular patient. This is because many patients are not in optimal health, and some facilities do not have significant experience in valve replacement surgery. Thus, when either of these assumptions is not met, the risk of surgery would increase and the likelihood of benefit to the patient would decrease.

Finally, although the guidelines define patients who are most likely to benefit from valve replacement surgery, they are based on probabilities, and thus on occasion, patients deemed at low risk may experience fracture. Although the percentage of fractures is considerably less than in the high-risk group, because the low-risk group itself is many-fold larger, the absolute numbers will be greater.

Single leg separation: Experimental studies indicated that a break in a single leg of the outlet strut would occur first, followed after a variable time by complete fracture of the strut, and therefore this phenomenon, termed single leg separation (SLS), was considered a precursor of OSF. Because SLS was considered to place patients with BSCC valves at particularly high risk, monetary benefits were included in the settlement to cover certain costs associated with explant surgery for these patients.[6] This led to a number of research studies to develop methods to detect SLS in patients with BSCC valves.

Over time, individual prophylactically explanted valves returned to the manufacturer after explantation showed evidence of SLS by visual inspection or microscopic examination. The prevalence of SLS in these valves was 8.2%, but this varied by valve size, position, and opening angle. The size-, position-, and angle-specific SLS rates were applied to the corresponding valve distribution in the worldwide database. This resulted in an estimated SLS prevalence of 6.8% (95% confidence limits 4.1% to 9.4%) in all valves.[23]

Research into Development of Diagnostic Techniques to Identify Implantees Who Have Significant Risk of Strut Fracture Due to SLS

At the time of its appointment, the panel assumed responsibility for ongoing studies initiated by Pfizer, which primarily focused on acoustic and imaging methods to detect SLS and modeling studies to further characterize the nature of the forces acting on the valve and their resulting stress. The panel also assumed responsibility for certain specialized instruments and 2 small herds of sheep implanted with BSCC valves.

There were also 3 large clinical/imaging and acoustic trials ongoing at the Western Infirmary in Glasgow, Stanford University, and the William Beaumont Hospital.[24,25] These studies enrolled high-risk patients, predominantly those with larger mitral valves who were likely to undergo explantation. These centers were chosen because of their excellent combination of cardiology and cardiac surgical teams. Each center was to enroll up to 300 patients, and each successfully did so.[24–26] These patients were scheduled for 6-month follow-ups, evaluating their clinical status and undergoing special acoustical and imaging studies. These acoustical studies were standard phonocardiographic recordings, and the imaging studies used advanced radiologic imaging techniques that required special positioning of the patients to provide opportunities to examine the individual outlet struts. A total of 57 patients underwent prophylactic explants at these centers.[10] These patients received careful follow-up, and the status of their valves was compared with the results from their acoustical and imaging studies to determine the sensitivity and specificity of these methods to detect SLS (see later). It was expected that acoustic studies, which were relatively simple to record and analyze, could be made widely available and would be used to screen for high-risk patients who would then be referred to a few specialized centers for definitive radiologic diagnosis. After completion of these research studies, the panel retained these centers as places in which members of the settlement in the high-risk categories under the guidelines could go for ongoing special studies and an explanation of the clinical relevance of the guidelines.

In addition to continuing ongoing studies that offered promise, the panel issued a series of requests for proposal to identify potential new or improved methods for the detection of SLS. The scope of the resulting research program was quite wide; however, the projects could be broadly grouped into those dealing with the acoustic signatures of the valve, imaging to visualize strut fracture, and structural analyses to further understand the factors responsible for strut fracture.

Acoustic studies: Early studies based on strain gauge recording of BSCC valves in pulse duplicators reported that the average outlet strut resonant frequency for intact valves was 7.8 kHz compared with 2.2 kHz for SLS valves with separation between the 2 ends of the fractured strut. The dominant resonance frequency for SLS valves in which the end of the cracked strut remained in contact was 4.3 kHz, with a range of 3.0 to 6.5 kHz depending on the degree of apposition.[27,28] Based on these observations, a number of studies were conducted in excised valves, pulse duplicators, and experimental animals implanted with BSCC valves, together with analyses of the clinical recordings from the Stanford, Beaumont, and Glascow trials. These studies differed in the sound analyzed (opening vs closing), the time window sampled (fixed vs overlapping), and the nature of the analysis (varying from simple analysis of the fundamental resonant frequency and its harmonics to complex weighted parametric models). Although these approaches showed promise, none reached a level of accuracy acceptable for clinical decision making (i.e., a recommendation for valve explantation).

Nevertheless, the results were encouraging enough that in 2003, the panel approved a proposal from Advanced Computation Engineering Systems (ACES)[21] for an advanced passive acoustical detection system using an array of extremely sensitive microphones to be placed around the chests of patients. Before using this technique in patients, a number of sheep implanted with BSCC valves were studied. The passive acoustic detection system worked well in 5 of 6 sheep, with the results suggesting that the second harmonic frequency might represent a superior identifying characteristic.

To further refine these findings, the panel supported a study carried out by Hemolab Cardiovascular Engineering group in the Netherlands in 2009.[29] Its work confirmed the reported results by the ACES group when studies were carried out in the air. However, when valves were placed in a pulse duplicator with conditions similar to those of functioning hearts in patients, the identification of the acoustic signals for the second harmonic was inconclusive.

Because of the quality of the work in sheep, the ACES group was supported to carry out a study in volunteers with BSCC valves. Fourteen valves were studied in 12 patients with surprisingly good quality recordings. Six of the valves studied were manufactured after April 1984 and were expected to be intact, whereas the other 8 patients were at low risk for fracture and would not have qualified for explant under the guidelines. Acoustical patterns for all were designated as intact, as expected, but in the absence of a gold standard (explanted valves), it was impossible to prove that these findings were accurate or estimate the sensitivity of the method in detecting clinical SLS. In an attempt to overcome this problem, the ACES group was asked to convert and reanalyze the acoustical recordings from the 78 expanded patient group in the Stanford and Beaumont cohorts whose valves had been explanted and whose status was known. Unfortunately, these recordings were not of high enough quality to permit analysis because of limited frequency resolution and noise contamination.

Because the outlet strut vibrations used in the passive acoustic studies were of limited amplitude, accounting for

only 0.5% of the total amplitude of the closing sound, and could only be temporally separated from the higher amplitude components during a brief time window at the end of closure, several groups proposed using focused high-intensity sound to produce vibration of the outlet strut.[12] This approach had the advantage that the strut could be activated at any point during diastole and thus isolated from the higher amplitude vibrations of the other components of the valve sounds present during opening and closing.

Unfortunately, although these acoustic studies were being performed it became apparent that, because of the declining fracture rate and rarity of valve explants, it would never be possible to perform the studies necessary to validate the accuracy of these methods in the clinical setting. Thus, the panel concluded that further studies were no longer justified.

Imaging studies: The second clinical approach to identify SLS was based on specialized radiographic studies with particular focus on the outlet strut. In a report by O'Neill et al,[26] 315 patients with BSCC valves were studied at the Beaumont Hospital on 2 occasions separated by 6 months. To establish a standardized grading system for determining strut integrity, cineradiographic studies were first performed on 25 BSCC valves, 14 with intentionally manufactured strut fractures imaged in a pulse duplicator. A grading system of 0 to 5 was developed based on the number of views and frames in each view in which a radiolucent area was evident at the base of the outlet strut. In this system, 0 represented an inadequate image, 1 was a normal valve, 2 indicated minimal suspicion, 3 indicated suspicion, 4 meant probable separation, and 5 meant definite separation. Using these criteria, expert reviewers gave grades of ≥ 2 to 1 intact valve and missed 1 SLS in the test valves. In the clinical studies, images were interpreted by 1 of 3 experts with knowledge of the clinical status and access to the online digital images and cine review. There were 5 patients with grade 5, 6 with grade 4, 1 with grade 2, and 277 with grade 1 valves. Twenty-one of these valves were subsequently available for analysis, with all SLS valves classified as grade 4 or 5 and 1 intact classified as grade 4. Assuming that a grade 4 or 5 indicated an SLS, this yielded an overall prevalence of 3.5% (compared with the rate of 8.2% in valves returned to the manufacturer). In 2 cases, fractures developed during follow-up, 1 during the 6-month interval between studies and a second 7 months after the second evaluation. In both cases, the imaging studies had reported the valves as intact.

To determine whether outside observers could independently interpret these images, a panel of expert observers composed of 1 cardiovascular radiologist and 5 cardiologists conducted blinded reviews of 571 of the 670 images obtained. Mean panel scores were <4 in 9 of the 10 documented SLS patients. The kappa statistics were 0.20 for agreement between the onsite readings and the panel's ratings and 0.19 for agreement among members of the panel, emphasizing the need for studies to be performed only at institutions with special expertise in recording and interpreting these images.[24,26]

In another study of 964 BSCC valves in 842 patients, radiographic imaging correctly identified 1 aortic and 25 mitral SLS valves with 4 false positives and 1 false negative verified at explantation.[24] Here again, only a small fraction of the valves were explanted, so overall sensitivity of the method could not be assessed.

Given the limited number of valves explanted in these patient studies, and thus the inability to assess the true sensitivity of the imaging methods, the panel reviewed data from a study conducted at Pennsylvania State University Milton S. Hershey Medical Center designed to compare the diagnostic sensitivity of the Seimens Hi-Coroskop cine-radiographic system (Seimens GMBH, Cologne, Germany) used in the clinical studies described previously with a newly developed geometric magnification system developed by Feinfocus in Germany.[29] The study was conducted in 25 sheep with surgically implanted valves (6 intact, 10 mechanically induced SLS, and 5 clinical SLS valves). Five views were acquired for each valve with reading according to a block design requiring 28 blocks of 16 image sets each and 8 reviewers. Each reviewer read 7 blocks of image sets per modality for a total of 224 image sets. Prevalence of SLS among the 1,792 ranged from 15% to 19%. Using a cut point of 4 to define SLS, sensitivity varied markedly by reviewer. Taking the 5 clinical SLS valves as a whole, over both technologies, SLS was detected in 40 of 80 blinded reviewer interpretations (50%), whereas the 7 intentional SLSs were detected significantly less often (13 of 112 cases, 12%). The results of these multiple studies to determine the valve imaging for detecting SLS as a precursor to OSF suggested to the panel that the sensitivity and specificity that could be achieved was too poor for clinical application at this time.

Despite this conclusion, in September 2000, the panel approved a study to be carried out at Penn State University (Hershey) in which improved x-ray imaging technology would be used to study high-risk patients with BSCC valves in the mitral position who qualified for benefits and were considering explants.[30] Hershey was approved because of their extensive experience in BSCC valve imaging, in both patients and sheep with implanted valves. Valves were categorized using the 5 categories previously described. From 2000 to 2009, there were 59 imaging sessions in 39 patients. Only 7 of these patients underwent explantation, and 2 valves were correctly identified as intact. There was 1 false positive and 1 false negative, and in 3 patients, the team of readers could not agree on the presence or absence of SLS. Based on these results, the panel concluded that there was no further likelihood that currently available radiographic techniques could reliably differentiate intact from SLS valves, and these studies were terminated.

However, by 2008, as a result of ongoing advances in imaging technology such as multislice computerized tomography, magnetic resonance imaging, and computer interpretation of radiographic images the panel appointed a subcommittee to evaluate their potential value for SLS detection. After considerable study, the panel concluded that, based on the physics of clinical x-ray, it would be impossible in the short term to reliably detect SLS in patients with BSCC valves and that even if such a technique were to become available, in view of the limited number of BSCC heart valves likely to be explanted, the clinical accuracy of the method could never be validated.

Electromagnetic methods to detect SLS: In addition to the imaging and acoustic studies, the panel received proposals

to study a variety of other methods to detect SLS. These included electromagnetic studies in which a magnetic field, generated either externally or by a locally activated catheter,[31] is applied to the valve to induce current in the partial loops that contain the outlet strut. These methods were based on the theory (supported by preliminary investigation) that when the strut was in contact with the valve ring, stationary current was produced. However, when the strut was fractured, the current could not flow, and the transiently induced current terminated following initial oscillations. When the contact was resistive (partial fracture), exponentially decaying current was excited with a decay rate dependent on the impedance included in the loop, which in turn was related to the degree of crack propagation. Here again, these methods showed promise in experimental models, static valves, and pulse duplicator studies. However, in those cases in which the experiments progressed to the more complex experimental animal stage, the in vitro results could not be duplicated. Other proposals based on magnetic excitation were also studied, including the electromechanical acoustic transducer technique performed at Michigan State, in which 2 magnetic fields, one static and the other time varying, were used to generate forces (Lorentz forces) in the valve to excite the resonant modes of the outlet strut.[31] Because the outlet strut resonance varied with strut integrity, it was necessary to sweep the beat excitation frequency over the expected range, assuming that the frequency at which the strut vibration velocity was greatest would correspond to the underlying resonant frequency. The results of ex vivo studies were again impressive, but problems involved in scaling the equipment to the size necessary for clinical studies and the strength of the magnetic fields required were prohibitive for human studies.

Modeling studies: Early work demonstrated that OSF in BSCC valves was the result of progressive fatigue crack growth during the lifetime of the valve. Based on the early strain gauge studies, it was assumed that most of the valve lifetime is spent below a stress threshold at which crack propagation occurs, whereas above this threshold fatigue crack growth rates exhibit a strong dependence on the design features of the valve, the level of stress applied, the microstructure of the material, and the environment in which crack growth occurs. Although the importance of increased stress had been demonstrated, the stress level at which crack propagation occurred, the determinants of these stresses, and their impact on the various components of the valve, as well as the design variables that influence the rate of progression had never been determined, particularly for aortic valves. Therefore, in an attempt to relate valve failure to design and manufacturing parameters that could be measured in situ or obtained from the manufacturing records, the panel sponsored a number of modeling studies using advanced stress analysis techniques. Furthermore, because epidemiologic studies identified several factors associated with the welding process as risks, and welding of the outlet strut to the ring is known to produce local changes in the microstructure of the Haynes 25 alloy at the critical location at which fracture occurred, the impact of welding technique on microstructure was examined.[32]

Finally, combined computational fluid dynamics studies demonstrated that the fluid momentum, rather than that of the occluder, is the primary determinant of the impulsive moment/ force on the occluder at closure and that the rotational velocity of the occluder at impact provides a direct measure of this parameter. In addition, these studies demonstrated that the difference between a valve that lasts a lifetime and one that could fracture in a much shorter time, perhaps months, was a matter of a difference of hundredths of millimeters in the hook to well distance. They further confirmed the importance of dP/dt and cardiac output, systolic duration (heart rate), and aortic compliance on valve stress. Welding studies identified characteristics of the welding process that increased strut rigidity and altered the microstructural composition of the alloy just distal to the weld.

In addition to these primary areas of investigation for detecting potential failure of BSCC valves, the panel reviewed a wide range of diverse proposals, ranging from development of a portable device for routine telephonic monitoring of heart sounds to a magnetic resonance imaging study of the brain to detect microinfarct caused by fragments of metal released during the process of fracture. These proposals either did not provide consistent data or were considered to be impractical for widespread application.

Medical Literature Review and the Bowling-Pfizer Website

During the 20 years of the panel's existence, medical technology, especially improvements in heart valves and diagnostic techniques, has advanced considerably. Therefore, the panel needed to monitor the medical literature for advances in heart valve technology and diagnostic methods for evaluating valve integrity and function. The panel established a subcommittee to regularly monitor the medical literature for relevant information relating to heart valves, and specific journals were assigned to each member of the subcommittee for regular review. The subcommittee convened quarterly by telephone to discuss selected reports and to decide if they belonged in a bibliographic section of the Bowling-Pfizer website. These reports were selected to aid physicians and patients in understanding how relevant advances might be important in providing ongoing care to patients with BSCC heart valves. This process continues, and the bibliographic references are available online to all physicians and patients (*www.bowling-pfizer.com*).

Discussion

The Bowling-Pfizer settlement agreement specified that the supervisory panel focuses on 3 general areas: development of guidelines, detection of SLS, and improvement in surgical techniques. In the development of guidelines, the panel was aided enormously by the FDA requirement that the manufacturer maintain a database of all fractures occurring worldwide. In addition, the manufacturer performed detailed analyses of all returned valves so that data on the prevalence of SLS were also available. These sources of data formed the basis for fracture rate determinations. In determining factors related to the risk of fracture, the panel was aided by the detailed records of all implants maintained by the government health systems in the United Kingdom and the Netherlands and by talented local investigators who were committed to discovering these risks. US registries

such as the Medic Alert database and the Social Security death index were also useful. Without these resources and collaborators, it would have been impossible for the panel to compute the risk estimates used in the guidelines.

In their attempts to identify methods to detect SLS, the panel worked with a broad range of investigators, including engineers, physicists, physical acousticians, and experts in hydrodynamics, computational fluid dynamics, and finite element modeling. These investigators were uniformly committed to their various approaches, but, with few exceptions, none had attempted to apply their methods to prosthetic heart valves or been involved in attempts to use their techniques in the clinical environment. Thus, although all these methods showed promise in excised valves and in vitro models, various problems were encountered as they were tested in increasingly complex in vivo experiments. These varied from difficulties in exciting the partially obscured moving valve to adapting the equipment for clinical use. For example, scaling the magnets for the electromechanical acoustic transducer studies to a size required for clinical recording would have resulted in a device that filled a large room; had never been produced, tested, or approved for clinical study; and would have been available only at the engineering site. Also, when the panel initiated these studies, the fracture and valve explant rates were such that it seemed possible for reasonable estimates of their accuracy to be obtained. However, over time, as both of these rates decreased (in some years to zero), it became progressively clear that such data on the sensitivity and specificity of the method could never be obtained. Furthermore, the chronic animal models were so complicated and expensive to create and maintain that there were a very limited number of valves available for these studies. Thus, although the advanced passive and active acoustics methods attained accuracies in the chronic experimental studies that were comparable with clinical methods to diagnose ischemia and recommend catheterization in patients with coronary artery disease, the validation sample was very limited and the results did not appear to justify their use as stand-alone criteria for explantation.

The mandate to sponsor studies to improve surgical techniques and decrease mortality proved more aspirational than practical. This goal was formulated as part of the legal settlement apparently without significant clinical input and was beyond the resources or time available to the panel. Although several small studies were funded, these were mainly retrospective comparisons of techniques, and the impact was modest. Surgical techniques for valve explantation and replacement with newer models have improved over these 20 years, but this gain was largely offset by the advancing age of this cohort of patients.

Because the panel was established as part of a legal settlement, its work was not conducted in isolation. The regular semiannual meetings of the panel were attended by the 2 trustees appointed by the court, class counsel, special counsel, a representative from Public Citizen, and counsel for the manufacturer. Investigators were often invited to attend these meetings both to present their proposals and to discuss progress. All parties were involved in these discussions, which were occasionally colored by feelings generated during the original lawsuits. These particularly related to the reliability of the manufacturer's original investigation and

stimulated confirmatory studies, but in the end, the early data proved reliable given the methods available at the time and formed the basis for the ongoing research. The discussions also exposed differences in the interpretation of the same data by clinicians and lawyers. For example, the guidelines were incorporated into the settlement agreement to prevent patients from undergoing valve explantation unless it was likely to improve their ultimate outcome, not because monetary benefits were available and without appreciating the associated risks. The panel agreed with these goals and developed the guidelines. The guidelines identified only a small percentage of the total implant population as being at high risk. Some of the attorneys, focusing on the fact that sporadic fractures continued to occur in the much larger population of low-risk patients, believed that the guidelines, which were based on relative probabilities, were invalid and that monetary benefits should be available to any patients with BSCC valve seeking explantation. Although such debates were frustrating at times, in the end, they proved to be beneficial as they sharpened our arguments and perhaps made us more critical scientists. Regular reports of the activities of the panel were required by the court and presented by the panel chairman with the representative attorneys present. Although the judge generally approved the recommendations of the panel, on occasion, individual members or the entire panel were called on to support these recommendations.

As illustrated in Figure 2, the reported BSCC heart valve fractures followed the shape of an infectious disease outbreak, except that they happened over a period of years rather than days, weeks, or months. Just as the infectious disease epidemic recedes when the most susceptible persons are exhausted from the population and immunity develops in the remainder, the epidemic of OSFs began to recede as the valves at highest risk were removed by fracture or explantation and "immunity" developed—in this case, as a result of aging, when OSF appeared to be less frequent.

The panel concluded that it is possible that a handful of fractures might continue to occur in the future, but they will most likely be due to metal fatigue, because most valves have now been implanted for >30 years. For all these reasons, we conclude that the present set of guidelines will be the last to be issued under the imprimatur of the panel. The panel plans to continue to review incoming data related to valve fractures and surgical mortality and review the pertinent medical literature for advances that may benefit the class members. Publications of relevance to heart valves are periodically added to the bibliography maintained on the Bowling-Pfizer website.

Lessons Learned by the BSCC Supervisory Panel

Over almost 20 years of activity, the panel identified several areas worthy of consideration for future monitoring of FDA class II and III implantable devices in patients. One of the most obvious needs is the ability to track the patients into whom these devices are implanted. The importance of this cannot be overemphasized, especially once a clinical problem is encountered with a device. Although it was possible in our deliberations to track data in the US and in some parts of Europe, this accounted for fewer than 1/2 of the valves implanted worldwide. Considerable progress, due

to activities of the FDA, Congress, and the Institute of Medicine, has been made in this area, but more emphasis should be given to an international system for tracking a device and matching it with a particular patient.

Another issue is communication with both physicians and patients. Although a subset of patients identified themselves by joining the class, most, not included in the several national databases, were unknown. Communication with this latter group was possible only through publication of the guidelines, but these are generally read only by physicians. In addition, many patients are unaware of the specific type of valve that they have been implanted with, valve serial numbers may be difficult to find, and manufacturing records for those class members who did not register were complicated to obtain or interpret. Early in the experience of the panel, direct communication with registered class members and their physicians could be accomplished only by a letter (occasionally returned unopened). Today, it would be much easier to use the Internet, e-mail, or social network programs, and it is important that improved methods of communication with patients be developed and standardized.

The panel also came to appreciate that experts with interdisciplinary backgrounds were absolutely essential for sifting through and weighing the data arising from clinicians and investigators once a device failure had been identified. Such an expert panel can become the intermediary between industry and legal representatives. In many ways, the Bowling-Pfizer Supervisory Panel became patient advocates to ensure that neither legal representatives nor industry overreached in their conclusions and recommendations. The panel also understood that once a class action settlement had been reached, the expert committee could work with the court to ensure that unwarranted and misguided decisions would not be reached, resulting in either widespread explantation of a device without clear evidence of a benefit and considerable surgical risks or leaving devices in place that continued to have high levels of potential risk. Such expert panels could also aid in developing ways to continue to evaluate devices that had been implanted in patients that might be putting them at risk.

From the panel's observations, it is possible to suggest some strategies by which device manufacturers could improve the safety of implantable cardiac devices. Emphasis on determining early signs of mechanical or material failure could be strengthened. Although device manufacturers give considerable time and effort to assessing the likelihood of failure in bench studies before device implantation, less attention is directed to specific sources of in vivo failure. Mechanisms for continuing to monitor the in vivo implanted devices for impending failure could be developed by the time of device approval by the FDA from those patients implanted in the clinical studies required for approval. These approaches would give physicians and patients more confidence in continuing high-quality performance of the devices. It should be noted that progress has been made in this area for some cardiac devices, including the monitoring of pacemakers and implantable defibrillators for continuing quality performance. Measures such as this could be developed for other implantable devices as well.

Although the panel did not develop definitive diagnostic methods to detect SLS in the implanted BSCC valves, the studies they supported provided valuable information on prosthetic heart valve function and highlighted how minute changes in valve design and manufacture can lead to dramatic failure. In addition, the refinements in acoustics, imaging, and more exotic technologies should add to the diagnostic armamentarium of the cardiologist in evaluating future expected failures of cardiovascular devices. It should also be apparent that the panel was aided immensely by being able to consult with and contract for research with a wide variety of scientists for academic and research organizations.

Finally, for a supervisory panel to carry out the programs discussed in this report, it is necessary to be provided with sufficient funding for its activities. In the case of the Bowling-Pfizer settlement agreement, the panel received funds for its ongoing activities, its consultations with experts, and contracting for relevant research.

The 20-year experience of the panel, working within the constraints of the legal system, has been frustrating at times but has been extremely rewarding. The interaction among scientists, lawyers, and court has been beneficial for the class members' best clinical interests. The acoustic and imaging research projects have contributed new information that can guide future research. The work on the guidelines used objective methods to quantify the risk factors related to valve fractures and resulted in a formulation for identifying those eligible for financial benefits. The panel's implementation of the guidelines helped patients and their physicians to balance the benefits of undergoing surgical replacement of a potentially high-risk valve against the possible dangers of nonintervention. The panel's conservative approach in implementing meaningful extension of life when considering valve replacement surgery has probably saved the lives of many patients and prevented the occurrence of serious morbidity in many others.

Disclosures

The authors' only conflict is their official work as panel members, for which they were paid.

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