SUMMARY OF KEY STUDIES RELATING TO THE GUIDELINES AND IMAGING AND ACOUSTIC RESEARCH

From the many articles referenced in the Bibliography, we have selected fourteen which were chosen because they provide an excellent summary of the most important findings of the research completed for the Panel. In other words, a review of the summaries of these fourteen articles will help patients and their physicians to have a bird's eye view of relevant information. This summary is divided into two parts: key epidemiological and clinical studies that have been done for developing the guidelines and key studies in the imaging and acoustics research directed at developing a technique to diagnose single leg fracture/separation (SLS) of the BSCC heart valve. These key papers cover or refer to other studies published on valve fracture and valve replacement surgery.

Articles relating to the Guidelines.

1. We begin the list with the Dutch study published in 1992 in the *Lancet* in which Yolanda van der Graaf et al conducted a cohort study on all 2303 patients implanted with 60- or 70- degree valves. After an average follow-up period of 6.6 years, the investigators studied 42 patients with outlet strut fracture (OSF). They identified "...wide opening angle (70^0), large valve size ($\geq$29 mm diameter), and young age (<50 years) as risk factors for outlet strut fracture."

2. In a publication in *Circulation* in 1995, Alexander Walker et al reported on a case-control study of 60^0 valves implanted in the United States 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 younger patients, patients with larger valves in the mitral position, and valves welded from mid-1981 through March 1984 were more likely to fracture. In addition, larger body surface area was associated with increased fracture risk (body surface area is related to gender in that women have smaller areas).

3. The third study was a follow-up to the 1992 Dutch study in which the manufacturing characteristics that predicted OSF in large 60^0 degree valves were studied. In this investigation, published in 1999 in the *Journal of Thoracic Cardiovascular Surgery*, Kallewaard and colleagues followed all Dutch patients with implanted valves until fracture, death, reoperation, or 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 discs used, and the fracture percentage of a given lot as independent risk factors of fractures.

4. A study authored by Omar and colleagues and published in *Heart* (2001) reported on OSF in the United Kingdom. The risk of fracture was investigated in a cohort of 2977 patients with a follow-up of 18 years when 56 OSFs occurred. The investigators

confirmed earlier findings of younger age, larger body surface area, larger valve size, shop order with higher fracture rate, and the manufacturing period from 1981 to 1984 as risk factors for OSF.

5. A study published by Blot and colleagues in 2001 in *The Journal of Heart Valve Disease* reported on the combined experience of the three cohort studies conducted in UK, Netherlands, and the USA. The three cohorts included 15,770 patients with 60-degree valves who were followed for up to 18 years looking for the occurrence of OSF. The article contains a summary of risk factors and confidence intervals according to patient and valve characteristics in the three countries. The authors concluded, "The risk of OSF decreased steadily with advancing patient age. Fracture rates were lower among women than men, and also varied significantly with valve size and position, and OSF status of other valves in the same shop order." Furthermore, the authors found that OSF rates declined with time since implantation.

6. The sixth paper summarizes the 25-year experience with the valve fracture and valve replacement surgery. The paper, authored by Blot and most of the Supervisory Panel members, was published in *Circulation* in 2005. It contains information on the type, location, number of patients, and follow-up period of the studies. In addition, it includes data on the numbers of OSFs reported through 2003, the risk factors for OSF, and the mortality from valve replacement surgery. The paper concludes that, twenty-five years after the initial BSCC valve implants, fractures continue to occur, albeit at a reduced rate. Furthermore, "continued monitoring of BSCC patients is needed to track and quantify risks and enable periodic updating of guidelines for patients and their physicians."

7. A study was conducted in 2005-2006 by Blackstone and colleagues at the request of the Supervisory Panel. This cohort study covered the period from January 1, 1972 to January 1, 2005 and included about 2000 adults who underwent elective valve prosthesis explant (aortic, mitral, or both) at the Cleveland Clinic, which is one of the largest heart surgery centers in the world. We include excerpts from the report submitted to the panel which includes a summary and four figures. The outcomes measured were 30-, 60-, and 90-day mortality and /or stroke in patients according to their status classified by the risk assessment tool of the New York Heart Association (NYHA)—classes I and II are presumed to be "healthier patients." Of special interest, are the graphs for the 90-day mortality or stroke in NYHA I and II patients. These graphs formed the basis for the calculations in the amended 2006 proposed guidelines.

8. The eighth study was authored by Blot and colleagues and published in 2007 in *The Journal of Heart Valve Disease*. The aim of the study was to estimate the prevalence of SLS, a potential precursor for OSF. Various data sources and calculations based on valve size, position and angle were used to derive the estimated prevalence. The findings indicated that that SLS may be present in four to nine percent of all BSCC valves. The authors stated that "Such estimates help frame the context for potential patient screenings, should imaging and acoustic techniques to detect SLS become available."

9. This study is the result of a self-administered questionnaire from 585 patients who had been part of the patient imaging study. It was carried out an average of about 4 years after the patients had been imaged and assessed the quality of life in 31 patients who had their BSCC valve explanted as compared to the quality of life in 554 patients who had not had explantation. There was no statistical difference in the quality of life between the two groups; however, it was noted that over one-half of both groups had poor quality of life in their follow-up. This was due to half being hospitalized for heart failure in the 4 years; over half were unable to walk up one flight of stairs; and more than 10% had received pacemakers. The fragile nature of these patients needs to be taken into account when heart valve explantation is being considered.

Articles relating to Imaging and Acoustics research.

Following the early recognition of BSCC heart valve fractures and patient deaths, a major effort to detect the status of the BSCC heart valve in the 86,000 individual patients was undertaken. Two promising techniques were pursued, namely acoustical recordings of heart sounds from patients with the valves and specific imaging of the valves by modified cineradiologic x-ray studies. Initially, it was recognized that the sounds emitted by the closure of the valve would be different if one of the legs of the outlet strut was broken (SLS). It was assumed that SLS was the first step toward total fracture of the valve (OSF). Therefore, several studies were initiated to determine the acoustical techniques which would identify SLS of the BSCC heart valve.

10. Study #10 is by Bjork of Sweden, who invented the BSCC heart valve, outlined the history and development of the valve (*Canadian Journal of Cardiology*, 1989). It also described the results of early Swedish experience with surgical implantation of the heart valve, which were the studies that led to the widespread use of the valve in the U.S. and its approval by the FDA. Because of some of the problems, including thrombosis and congestive heart failure, Bjork and his colleagues developed modifications of the BSCC heart valve. This was designed to be a mono-strut valve, which became widely used after 1984. As pointed out in this article, there have been no valve fractures in this advanced and modified mono-strut valve since 1984.

11. & 12. Study #11 by Dow and others was published in *Circulation* and outlined the development of a very complex technique of differentiating heart sound recordings made from patients with single leg separations of their BSCC valve from patients with intact legs of their valve. The work focused on both alterations in the intensity of the sound and the frequency of sound changes. Another acoustical approach is discussed in Study #12, in which modeling studies of how the valve disc closed were used to identify the varying frequency of acoustic signals from intact, partially separated, and fully separated valve struts. These studies were used to evaluate sound recordings made from patients with BSCC heart valves. While these two, and other acoustical studies, did

identify some patients who had SLS, there were many misidentifications resulting in false-negative and false-positive findings (Eberhardt, et. al, *Journal of Heart Valve Disease*, 1995).

13 & 14. The second approach to identify faulty BSCC valves in patients was specialized imaging techniques of cineradiography. Study #13 was published in the *New England Journal of Health* in 1995 and was a report of patients determined to be at a higher risk of strut separation. These patients were studied at 6-month intervals by modified imaging techniques at Beaumont, Stanford, and Glasgow, Scotland. In order to read the imaging studies, a rating scale had been previously tested in sheep implanted with known intact and separated leg BSCC valves. These imaging studies were used to train readers for the imaging studies (Study #14 authored by Hopper and published by *The Journal of Thoracic Cardiovascular Surgery* in1998). Five categories of the likelihood of single leg separation were developed by the responses of several readers. It was observed that there was considerable variability in the interpretation of the imaging studies by various observers and that a team of readers gave better results. The highest likelihood of the five categories was noted to be those in which there was general agreement among the readers. These techniques were then utilized to read the results of the clinical studies from Study #13.

When the two highest likelihoods of SLS (Categories IV and V) were noted by the readers, the patients had explant of their BSCC heart valve and re-implantation of another valve. The agreement between the imaging studies and the status of the valve upon removal were generally good in these two categories. However, there were many false-negative and false-positive results in that in some of the patients had lower imaging scores (Categories I, II and III). In two cases fractures developed in the 6-month interval between studies, even though the initial study reported the valve as intact. Also, in some patients having moderate likelihood of separation, valves were removed and found to be intact, which resulted in unnecessary surgery. To date, an imaging study in only the highest level of categorization by multiple readers can be reliably determined to represent true positive findings.

Concluding Comments

Today the Panel continues to be vigilant for issues which may require updating the Guidelines. We are also considering further research in an effort to develop an acoustic diagnostic device which may provide patients and their physicians with valuable information about the status of their BSCC heart valve. For a more complete summary of the activities of the Panel, please refer to the document entitled "Update on the Status of the Continuing Operation Plan of the Supervisory Panel, Approved by the Court April 28, 2005" found elsewhere on this website.

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