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STS/AATS/SCAI POSITION STATEMENT

The Clinical Development of Percutaneous Heart Valve Technology

A Position Statement of the Society of Thoracic Surgeons (STS), the American Association for Thoracic Surgery (AATS), and the Society for Cardiovascular Angiography and Interventions (SCAI)

Endorsed by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA)

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PREAMBLE

This joint position statement represents the combined efforts of four professional societies (Society of Thoracic Surgeons [STS], American Association for Thoracic Surgery [AATS], American College of Cardiology [ACC], and Society for Cardiovascular Angiography and Interventions [SCAI]), two government agencies (the U.S. Food and Drug Administration [FDA] and the Centers for Medicare and Medicaid Services [CMS]), and numerous industry representatives to assess the foreseeable directions of a class of emerging technologies being developed to enable the percutaneous treatment of cardiac valve dysfunction. Percutaneous heart valve technology (PHVT) is a less invasive means of treating valvular heart disease. The goals of the interdisciplinary group have been to establish cooperation, identify consensus and controversy, and formulate clinical guidelines for the continued development of PHVT.

PROCESS

On April 22, 2004, the STS/AATS Committee/Workforce for the Assessment of New Technology (Appendix 1) organized a workshop on PHVT. Included were representatives from the STS, the AATS, the ACC, and SCAI. Also in attendance were representatives from the FDA's Division of Cardiovascular Devices, Circulatory Support and Prosthetic Devices Branch, CMS, and industry representatives (Appendix 2). Clinical aspects of PHVT were initially addressed in small groups with representatives from each of the constituencies followed by a summary report and discussion amongst the entire group. All participants of the workshop and writing group members completed a disclosure questionnaire documenting all outside relationships that might be perceived as real or potential conflicts of interest (1). Current crucial issues addressed were: 1) trial design, 2) control groups, 3) end points for assessment, 4) rate of technological change, 5) institutional and investigator requirements, and 6) safety. Consideration of these issues is undertaken with the acknowledgement that for most patients with heart valve disease, open cardiac surgical procedures provide an established form of treatment.

BACKGROUND

For decades, percutaneous interventional therapy has been an option for patients with pulmonic (2–4), mitral (5,6), and aortic valvular disease (7,8). For selected patients with pulmonic or mitral stenosis, percutaneous valvuloplasty is

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aortic stenosis, balloon aortic valvuloplasty (BAV) (11,12) has been used as a bridge to aortic valve replacement as noted by the current ACC/American Heart Association (AHA) guidelines (13). Hospital mortality for BAV varies from 3.5% to 13.5%, and as many as 25% of the patients have at least one serious complication (14). The durability of BAV is limited. Therefore, open aortic valve replacement remains the definitive therapy for aortic stenosis in patients who are viable candidates for surgery.

Currently, multiple new concepts for the percutaneous treatment of valvular heart disease are under evaluation in a variety of stages from bench testing to early clinical trials (15). Most involve either mitral valve repair via annular or leaflet manipulation, or percutaneous valve insertion for pulmonic or aortic valve disease. Using a stent-based valve (16,17), percutaneous pulmonary valve insertion has been successfully carried out in more than 60 cases, primarily outside the U.S., usually for the treatment of conduit stenosis (18). However, late follow-up is limited and future trials will need to focus on the issues of patient selection with degenerated conduits, durability and the inability of the device to grow. Although percutaneous aortic valve insertion has been carried out on a compassionate use for extremely high-risk patients (19,20), significant paravalvular regurgitation and early mortality characterize the experience thus far (21). Currently, there are no approved percutaneous aortic valve devices in the U.S.

The goal of the following discussion is to provide a framework for clinical research directed at further testing of PHVT.

GENERAL GUIDELINES REGARDING CLINICAL TRIAL DESIGN FOR PHVT

The testing of new medical technology usually begins with bench testing (in vitro) and in vivo animal testing, followed by clinical investigation. Initial clinical investigation begins with a feasibility study: a small, unblinded, and uncontrolled trial designed to test safety. Following the feasibility trials, a larger, prospective, controlled trial is performed to evaluate both safety and efficacy (Pivotal trial). The most rigorous design for establishing the safety and effectiveness of new technology is the controlled, randomized trial. It is the consensus of the participants of the Workshop that no adequate historical controls exists for the evaluation of PHVT sufficient to eliminate the influence of confounding variables. Therefore, randomized controlled trials are necessary to evaluate safety and efficacy properly for these devices.

At each institution participating in clinical trials, the study team should include at least an interventionalist, a cardiac surgeon, a non-interventional clinical investigator charged with monitoring patient welfare, and an echocardiographer. All members of the study team should be teraction will aid trial completion and, it is hoped, lead to improvement in device placement, function, and assessment.

Use of PHVT requires skill sets independent of the operator's base discipline, and specific training should be required before engaging in any percutaneous valve procedure. Those individuals eligible for the procedural training should be confined to experienced interventionalists and surgeons. Feasibility studies in adults should be restricted to a small number of high-volume cardiology and cardiac surgery programs where at least 100 to 150 surgical valve operations per year are performed (22). Participating cardiac surgeons should perform a minimum of 40 to 50 valve repairs or replacements annually (23). In addition, the surgeon's valve experience should be specific for the device under consideration (i.e., a surgeon with a large volume of aortic valve replacement and minimal mitral valve repair would only qualify for an aortic device study). Although most interventionalists are likely to be cardiologists, or rarely interventional radiologists, surgeons with appropriate training in percutaneous procedures may directly participate, in addition to providing patient selection, guidance, and back-up services. Interventionalists should perform at least 100 percutaneous procedures each year, and have experience with the catheter-based techniques required for PHVT (e.g., trans-septal and/or coronary sinus access techniques) and with the assessment and management of valvular heart disease (24–26). Clinical trials should also be limited to centers with a proven track record of close collaboration between the aforementioned disciplines and experience in trials.

A major problem with all new devices is how to evaluate a first-generation product against the established "gold standard," in this case the open cardiac surgical procedure. How should a new device that avoids cardiac surgery but perhaps is less effective—especially initially—be best evaluated? At the design stage of a clinical trial it is essential to state clearly the purpose of the study and the specific hypothesis to be evaluated (27). Randomized controlled trial designs can be broadly viewed as evaluating the superiority or non-inferiority (clinical equivalence) of the test arm with regard to effectiveness. Critical differences exist between these two approaches, which affect sample size, study feasibility, and credibility of conclusions (28). It is important to point out that it is statistically, and practically, impossible to demonstrate equivalence between two treatment arms, as some differences are always likely to exist. Therefore, a "clinically acceptable" difference ("delta") between the two treatment arms must be specified at the outset and the null hypothesis constructed such that its rejection supports the claim of non-inferiority (Table 1).

Sample size estimation would be most appropriately determined by power calculations for the specific end point and study results published in the literature. Study end

Table 1. Randomized Controlled Trial Designs

Trial Design Type	Null Hypothesis for Effectiveness	Alternate Hypothesis for Effectiveness
Superiority	Treatment A success rate ≤ treatment B rate	Treatment A success rate > treatment B rate
Non-inferiority	Treatment A success rate ≥ treatment B rate + "delta"	Treatment A success rate < treatment B rate + "delta"

necessary documentation, and 3) having independent core laboratories, blinded to the treatment assignment, adjudicate the cases whenever possible. Meaningful outcome measurements could include components such as death, myocardial infarction, need for surgical repair (including the need for valve replacement when repair was the preoperative intent), stroke or embolic events, hemodynamic deterioration, ejection fraction, measures of reverse remodeling, valvular regurgitation, endocarditis, hemolysis, and functional testing. Although the timing of end point measurements was discussed at the Workshop, the consensus was that it is too early in PHVT development to answer this question.

Finally, in any trial designed to evaluate an intervention, "crossovers" are likely to occur. Crossover patients can be analyzed using several methods, including "intent to treat," "as treated," and "per protocol" (29,30). In addition, a large amount of missing end point data can make interpretation of trial results difficult and threaten the success of the trial. Every effort should be made to collect all data specified in the trial. Additionally, the importance of a knowledgeable and active Data Safety and Monitoring Board cannot be overemphasized. This board should be independent of the investigators, of the company sponsoring the trial, and of any contracted data analysis organizations involved in the trial.

PERCUTANEOUS MITRAL VALVE REPAIR (PMVR) FOR MITRAL REGURGITATION

The pathophysiologic triad describing mitral regurgitation (MR) is composed of etiology (cause of the disease), valve lesions (resulting from the disease), and valve dysfunction (resulting from the lesion) (31). These distinctions are relevant because long-term prognosis depends on etiology, whereas surgical treatment strategy—and future PMVR—depends on valve dysfunctions and lesions. Mild to moderate MR is seen in approximately 20% of the general population (32,33). The most common causes of MR in Western countries are degenerative, ischemic, and dilated cardiomyopathy (34).

The STS National Adult Cardiac Surgery Database 2003 notes a countrywide mortality for first time elective mitral these figures are 6.1% (males) to 12.2% (females), respectively (35). Patients undergoing reoperation are also at increased risk (36). Mitral valve repair is considered superior to mitral valve replacement because of lower operative mortality, improved late survival, a reduced risk of endocarditis, fewer thromboembolic complications, and better preservation of left ventricular function (37–42). However, the majority of mitral valve operations done in the U.S. in 2003 remained mitral valve replacement (43). Individual surgeon experience remains the key factor in predicting the likelihood of mitral valve repair or replacement for any given patient.

To discuss patient selection for PMVR for MR and to consider comparative outcomes with surgical approaches, it is possible to consider two classifications: one focusing on etiology and the other on leaflet dysfunction, realizing that both can influence patient outcome. For the purposes of this discussion, we will focus on leaflet dysfunction as opposed to etiology (33). This classification is based on the opening and closing motions of the mitral leaflets. Patients with type I dysfunction have normal leaflet motion. Mitral regurgitation in these patients is due to annular dilatation or leaflet perforation. There is increased leaflet motion in patients with type II dysfunction with the free edge of the leaflet overriding the plane of the annulus during systole (leaflet prolapse). The most common lesions responsible for type II dysfunction are chordal elongation or rupture and papillary muscle elongation or rupture. Patients with type IIIa dysfunction have restricted leaflet motion during both diastole and systole. The most common lesions are leaflet thickening/retraction, chordal thickening/shortening or fusion, and commissural fusion. The mechanism of MR in type IIIb dysfunction is restricted leaflet motion during systole: left ventricular enlargement with apical papillary muscle displacement due to ischemic or idiopathic cardiomyopathy causes this type of valve dysfunction.

Currently, there are two concepts for percutaneous mitral valve repair: 1) partial mitral annuloplasty by device placement in the coronary sinus to reduce the circumference of the posterior mitral annulus; and 2) anterior and posterior leaflet attachment using an edge-to-edge clip or suture (44–46). Posterior annuloplasty faces multiple anatomic challenges including dilation of the trigone-to-trigone area (47,48), leaflet tethering by papillary muscle displacement (49), mitral annular calcification, inability to fix the annuloplasty to the fibrous trigones (50), and the potential for compromise of the circumflex coronary artery. The edge-to-edge repair concept has been used in surgically treated patients, but the best results have been obtained when combined with an annuloplasty (51). The results of edge-to-edge repair have been suboptimal in patients with restricted leaflet motion (type III dysfunction), including a recent surgical series where it was used in combination with a posterior annuloplasty in patients with ischemic regurgi-

annular remodeling technology should consist of 20 to 30 patients with severe symptomatic MR caused by annular dilation with normal leaflet motion (type I dysfunction) or by restricted leaflet motion (type IIIb dysfunction), or by a combination of these two mechanisms. A feasibility study to evaluate PMVR with leaflet edge-to-edge repair should consist of 20 to 30 patients with excessive leaflet motion (type II dysfunction).

These studies will have safety as the primary end point and will assess adverse events including residual (equal or worse) MR, myocardial infarction, stroke, tamponade, coronary artery injury, death, and leaflet damage compromising subsequent mitral valve repair. The secondary end points of the study will include quantitative echocardiographic assessment of MR diminution, left ventricular function, and symptom status. The design of Pivotal trials will need to await safety and durability data from the feasibility study, but will include: 1) comparison of PMVR to open surgical mitral valve repair in patients with types I, II, and IIIb dysfunction; or 2) comparison of PMVR to optimal medical therapy (53) in non-surgical candidates with either end-stage cardiomyopathy and type IIIb severe MR or elderly patients with significant comorbidities and type II dysfunction.

PERCUTANEOUS AORTIC VALVE REPLACEMENT (PAVR)

Aortic valve replacement is the most common heart valve operation. Aortic stenosis (AS) affects from 2% to 7% of individuals older than 65 years in the U.S., a prevalence that will continue to increase as more people live to older ages (54,55). Aortic stenosis is consistently progressive (56–59), and because it occurs in an elderly age group it is often associated with comorbid risk factors and previous bypass surgery (60). The goals of therapy for patients with AS include both improvement of symptoms and prolongation of life (61). Percutaneous strategies for the treatment of AS began with percutaneous balloon valvuloplasty, but data from single-center studies and the multicenter National Heart, Lung, and Blood Institute (NHLBI) registry noted only a modest improvement in early hemodynamics, a substantial incidence of peripheral vascular complications, a 30-day mortality of 7%, and a high incidence of restenosis within 6 months (7,62).

The disappointing results of BAV have led to investigation of the possibility of percutaneous placement of prosthetic aortic valves. Such devices have been used clinically in a small number of cases in high-risk patients (63). A feasibility study designed to evaluate PAVR might consist of 20 to 30 patients with severe symptomatic AS (aortic valve area ≤ 0.70 cm^2), or severe aortic valve regurgitation (AR). Initial feasibility trials have treated only AS patients feasibility trials will initially enroll only patients with severe AS.

In addition, differences in the age and comorbidity between patients with AS and AR dictate each study population be fairly pure, with a cohort of one or the other but not a mixture. These initial patients should be judged to be at extremely high operative risk as calculated by an established risk scoring system (64–67). Selection of a risk scoring system as well as the definition of inoperability should be clearly defined in the protocol. Such inoperability will almost always be caused by non-cardiac morbid conditions. In such a feasibility trial it is not acceptable to use such devices for patients who simply refuse open surgery on the basis of personal preference. Study end points will include death, stroke, myocardial infarction, para-prosthetic leak, device migration, symptom status, angiographic gradient, and rehospitalization. Pivotal trials will depend upon the safety data from the feasibility trial, and a variety of control groups may be possible including patients having balloon valvuloplasty and high-risk open surgery.

MINIMALLY INVASIVE VALVE SURGERY

The procedural goal of PHVT is to reliably repair or replace dysfunctional heart valves percutaneously and without the need for cardiopulmonary bypass (CPB). An alternate approach has been to repair or replace valves off-pump through small incisions, thereby simplifying device delivery. Concepts along these lines include anterior and posterior pads connected by a subvalvular cord designed to draw the posterior leaflet and annulus of the mitral valve toward the anterior leaflet (68); a transatrial off-pump edge-to-edge mitral valve repair (69); and off-pump AR antegrade through the ascending aorta or retrograde through the left ventricular apex (70). The minimally invasive surgical approach is an avenue of treating heart valve disease that not only has benefit on its own merit but also supports development of PHVT.

REGULATORY CONSIDERATIONS

At this Workshop, the general considerations of the FDA, as expressed by Bram Zuckerman, Director of Cardiovascular Devices, Office of Device Evaluation (ODE), Center for Devices and Radiologic Health, were as follows. Percutaneous heart valve systems are considered class III devices; they will be reviewed as pre-market approval (PMA) applications (71) and, as such, controlled, randomized clinical trials will be the gold standard for meeting FDA requirements. Industry or independent study investigators should solicit the assistance and guidance of the FDA before

SUMMARY

Although percutaneous devices for the repair or replacement of heart valves appear promising, they are clearly in an early stage of development. Many critical questions remain unanswered, including the durability of these devices and the potential adverse effects they may have on subsequent heart valve surgery. Therefore, one cannot justify the use of these experimental technologies in patients for whom published guideline indications do not exist or in situations of prophylactic therapy until data on safety and effectiveness are gathered from well-designed clinical trials. Study candidates should consist of symptomatic patients in whom long-term survival is already severely compromised. Such a strategy would allow the collection of mid-term device durability data while providing much needed clinically relevant safety and effectiveness data.

Prospective, randomized, clinical trials provide the most reliable evidence of the effectiveness of the treatment. Without such trials, ineffective treatments (or worse, harmful treatments) may be accepted in medical practice. Our collective enthusiasm for new, less-invasive cardiovascular approaches should not divert us from the importance of evaluating these devices in the context of a controlled clinical trial environment. Success of these clinical trials ultimately depends upon a sincere commitment to collaboration between cardiology and cardiac surgery.

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