Effective Health Care Program

Technical Brief Number 2

Percutaneous Heart Valve Replacement

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Technical Brief

Number 2

Percutaneous Heart Valve Replacement

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments and Comparative Effectiveness Reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care. Technical Briefs are the most recent addition to this body of knowledge.

A Technical Brief provides an overview of key issues related to a clinical intervention or health care service—for example, current indications for the intervention, relevant patient population and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions. The emphasis, therefore, is on providing an early objective description of the state of science, a potential framework for assessing the applications and implications of the new interventions, a summary of ongoing research, and information on future research needs. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly, while Technical Briefs will serve to inform new research development efforts.

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Abstract

Objectives. To describe the types of prosthetic heart valves now in use and in development, summarize clinical studies completed or under way, and discuss factors that may impact clinical outcomes for percutaneous heart valve (PHV) replacement.

Data Sources. MEDLINE®, EMBASE®, and gray literature sources.

Review Methods. We searched the English-language literature to identify systematic reviews and comparative clinical studies of conventional heart valves and studies of PHVs in adults. We define PHV replacement as the delivery of a prosthetic heart valve via a catheter inserted either through a vein or artery (femoral vein; femoral, subclavian, or axillary arteries; or the ascending aorta) or through the apex of the heart via an incision in the chest wall (transapical approach).

Results. We identified numerous mechanical and bioprosthetic heart valves. Six systematic reviews compared various conventional valves; the single high-quality review found better short-term hemodynamic performance but longer operating times with stentless compared to stented bioprosthetic valves. A large primary literature (57 randomized controlled trials [RCTs], 40 observational studies) compares various conventional heart valves.

Seven manufacturers of PHVs were identified in 62 fully published case reports or non-comparative case series that studied 856 unique patients. All but 19 of these patients received valves produced by one of two PHV manufacturers. The route of access was via the femoral artery in 580 patients (68 percent). The transapical approach was used in 223 patients (26 percent). The route of access for the remaining 53 patients (6 percent) was via the femoral vein, subclavian artery, axillary artery, or ascending aorta. All but two of the prosthetic valves were implanted in the aortic valve position in patients with symptomatic aortic stenosis at high operative risk. Successful implantation was achieved in 92 percent of patients; 30-day survival was 86 percent. The lack of comparative studies limits the ability to determine which variables associated with PHV replacement are causally related to outcomes. A multicenter RCT comparing PHV to conventional heart valve replacement or medical management is currently underway in the United States.

Conclusions. A large number of heart valve prostheses are in use, but there are limited data to inform the selection of one valve over another. There is sufficient existing primary literature to support systematic reviews or meta-analyses to help inform several important clinical questions pertaining to conventional heart valve replacement. PHV replacement is a rapidly emerging technology that has been proven feasible and is a promising therapeutic option for patients with severe, symptomatic aortic stenosis who have a higher risk of poor outcome with surgical aortic valve replacement. Well-designed observational studies and decision modeling could help inform clinical and health policy in the absence of RCTs.

Introduction

Background

As the proportion of older adults increases in the U.S. population, the prevalence of degenerative heart valve disease is also increasing. Calcific aortic stenosis (narrowing) and ischemic and degenerative mitral regurgitation (leakage) are the most common valvular disorders in adults aged 70 years and older.[1,2] For patients with severe valve disease, heart valve replacement involving open heart surgery can improve functional status and quality of life.[3-5] A variety of conventional mechanical and bioprosthetic heart valves are readily available. However, some individuals are considered too high risk for open heart surgery. These patients may benefit from a less invasive procedure.

Percutaneous heart valve replacement is a relatively new interventional procedure involving the insertion of an artificial heart valve using a catheter, rather than through open heart surgery.[6] The portal of entry is typically either via the femoral vein or artery, or directly through the myocardium via the apical region of the heart. An expandable prosthetic heart valve is delivered and deployed at the site of the diseased native valve. The percutaneous heart valve replacement procedure usually takes less time to perform and is less invasive than open heart surgery.

The Agency for Healthcare Research and Quality (AHRQ) has commissioned this Technical Brief to:

- Describe the types of conventional and percutaneous heart valves now in use or in development and their theoretical advantages and disadvantages for different patient populations.
- Describe the literature comparing various types of conventional heart valves in adults and determine whether a systematic review of this literature is feasible and needed.
- Describe the literature evaluating percutaneous heart valves in adults, including the patient populations and major outcomes studied to date.
- Describe implantation techniques for percutaneous heart valves and the factors associated with surgery or setting that may impact outcomes.

The intended audience of this Technical Brief includes policymakers, decisionmakers for third-party payers, clinicians, patients, and investigators.

Epidemiology

Aortic stenosis and mitral regurgitation are the most common valvular disorders in older adults. The prevalence of at least moderate aortic stenosis in the general population increases from 2.5 percent at age 75 to 8.1 percent at age 85.[7] Once moderate aortic stenosis (valve area 1.0 to 1.5 cm^2) is present, the valve area decreases at an average rate of 0.1 cm^2 per year. After a long latent period, patients may develop symptoms of angina, syncope, or heart failure, with moderate or, more commonly, severe stenosis. The decision to replace the aortic valve is based largely on the presence or absence of symptoms.[8] After the onset of symptoms, the risk of sudden death is high, and survival averages 2 to 3 years.[9-12]

Aortic valve replacement (AVR) is the most common heart valve operation, accounting for 60 to 70 percent of all valve surgery performed in the elderly. In adults with severe, symptomatic, calcific aortic stenosis, AVR is the only effective treatment.[8] In patients with symptomatic aortic stenosis, AVR improves symptoms, functional status, and survival. The 2006 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines make a Class I recommendation for AVR in symptomatic patients with severe aortic stenosis.[8] AVR is also recommended in certain circumstances for patients with severe stenosis who are asymptomatic, and for patients with mild to moderate stenosis undergoing coronary artery bypass graft (CABG) when there is evidence that progression may be rapid.[8] Aortic valve repair using balloon valvuloplasty has been performed in older adults, but results in poor outcomes and is only considered for patients considered too high risk for valve replacement.

AVR carries a perioperative mortality risk of approximately 3.0 to 4.0 percent, increasing to 5.5 to 6.8 percent when combined with coronary artery bypass grafting.[8] In patients over the age of 65, the average in-hospital mortality is 8.8 percent in low-volume centers.[8] Operative risks can be estimated with validated online risk calculators[7,13-15] that include age, sex, functional status, cardiac factors, and medical comorbidity. Although age alone is not a contraindication to surgery, a survey of Dutch cardiologists found age to be a primary determinant in the decision to recommend AVR.[16] Based on high-risk features or age, a significant subset of patients with indications for valve surgery are deemed ineligible for conventional valve replacement.[17] One survey of 92 European heart centers found that 31.8 percent of patients with severe, symptomatic, single valve disease did not undergo intervention, most frequently because of comorbidities.[18]

Mitral valve regurgitation affects approximately 2.3 percent of 60- to 69-year-olds and 5.5 percent of adults older than 70.[1] It is the second most common reason for valve surgery in older adults. The most common causes of mitral regurgitation in older adults are myxomatous degeneration and ischemic heart disease.[19-21] With mild to moderate disease, individuals may remain asymptomatic for many years. Patients with chronic severe mitral regurgitation have a high likelihood of becoming symptomatic after 6 to 10 years. The 2006 ACC/AHA guidelines recommend mitral valve surgery for patients with chronic severe mitral regurgitation who have impaired functional status or meet specific hemodynamic criteria (Level of Evidence = C, which represents consensus opinion of experts, case studies, or standard of care).[8] In contrast to the recommendations for patients with aortic stenosis, valve repair—rather than replacement—is considered an option and is recommended for "the majority of patients with severe chronic mitral regurgitation who require surgery."[8]

Conventional Valve Replacement

Conventional valve replacement requires general anesthesia, a sternotomy, and heart-lung bypass. The surgeon removes the diseased valve and replaces it with a mechanical or biological valve. Surgery averages 3 to 6 hours, and most patients are discharged from the hospital after 5 to 6 days. Recovery generally takes 6 to 12 weeks. Patients who receive a mechanical valve will be placed on life-long anticoagulation that requires regular monitoring. Like mechanical valves, bioprosthetic heart valves are readily available and have a simple and standard implantation technique. Unlike mechanical valves, they do not require chronic anticoagulation. Bioprosthetic heart valves are also less durable than mechanical valves. Minimally invasive valve surgery is similar to traditional surgery but uses smaller incisions, with the potential advantages of less

bleeding, less pain, and decreased recovery time. All of these procedures have associated cardiovascular risks, including stroke.

Selecting the specific heart valve involves both clinical and technical considerations. Clinical considerations include: concurrent indications for anticoagulation (e.g., chronic deep venous thrombosis) or contraindications to anticoagulation; the patient's life expectancy; and patient preference. Technical considerations include: surgeon experience with particular valves; the technical difficulty of implanting differing valves; valve durability; and the size of the valve annulus.

Percutaneous Valve Replacement

Percutaneous (or "catheter-based" or "transcatheter") heart valve replacement is an experimental procedure in which a valve is crimped onto a catheter and deployed without removing the diseased native valve. The procedure does not require heart-lung bypass. Potential advantages include decreased recovery time and lower surgical risk. Potential disadvantages include a greater risk for valve migration (since the valve is not sewn into place), complications associated with catheter-based delivery, and uncertain valve durability.

Six percutaneous techniques have been described in the published literature. In the early stages of development, percutaneous valves were delivered via the femoral vein or artery. More recently, they have also been successfully implanted through the heart wall (the "transapical" approach), through the subclavian artery, through the axillary artery, and through the ascending aorta. For the purpose of this report, we consider the femoral vein, femoral artery, transapical, subclavian artery, axillary artery, and ascending aorta approaches all to fall within the scope of percutaneous heart valve replacement.

The procedure using the transapical approach is performed by cardiac surgeons, using direct left ventricular apical puncture through a small thoracotomy. The procedure does not require a sternotomy. The other five approaches all involve cannulation of an artery or vein. Of these, four approaches (femoral artery, subclavian artery, axillary artery, and ascending aorta) are considered to be *retrograde* approaches because the catheter is directed through a vessel against the direction of blood flow. The femoral vein approach, by contrast, is considered to be an *antegrade* (or anterograde) approach because the catheter is directed to the heart through the venous system, in the direction of blood flow.

Methods

Key Questions

AHRQ, the sponsor of this report, originally identified four key questions to be addressed in this Technical Brief. The research team at the Duke Evidence-based Practice Center (EPC) further clarified and refined the overall research objectives and the key questions in consultation with the AHRQ Task Order Officer assigned to the project.

The key questions addressed are as follows:

Question 1. What are the different types of heart valves in use and in development (including tissue, mechanical, and percutaneous valves)?

a. What are the existing or potential U.S. Food and Drug Administration (FDA) indications for each valve (patient characteristics, etc.)?
b. What are the theoretical advantages and disadvantages of different valves for different patient populations?

Question 2. From a systematic literature scan of studies on different types of tissue and mechanical valves, describe the types of comparative studies, including basic study design, size of study, length of followup, and outcomes assessed. This literature scan will provide data to determine if a systematic review of this literature is possible and needed, and to provide needed context for understanding the evaluation and development of percutaneous heart valves.

Question 3. From a systematic literature scan of studies on different types of percutaneous heart valves, provide a synthesis of the following variables:

a. Number for each type of valve.
b. Type of studies—comparative and non-comparative randomized controlled trials (RCTs), non-randomized controlled clinical trials, case series, etc.
c. Variables associated with surgery (implantation technique), setting, etc.
d. Size of studies/length of followup.
e. Patient population/concurrent and prior treatments.
f. Hemodynamic success rates reported.
g. Harms reported.

Question 4. What are the variables associated with surgery or setting that may impact outcomes for percutaneous heart valves?

a. What are the different implantation techniques (i.e., position of implantation, delivery, and axis techniques)? What is the evidence of success (i.e., absence of narrowing and regurgitation) and harms?
    i. For percutaneous aortic valves.
    ii. For percutaneous mitral valves.

Sources of Information and Review Methods

The sources of information consulted and review methods used by the Duke team varied considerably by key question. Question 1 involved gathering and collating information from the

FDA, device manufacturers, and other sources. Question 2 and Questions 3-4 required separate literature reviews using distinct sources, search strategies, and review methods. Because of this variability, we describe the methods used for each key question separately.

Question 1. Heart Valves in Use and Development

We used four approaches to identify heart valves now in use or in development. First, we identified valves described in the published literature abstracted in answer to Question 2 (conventional valves) and Questions 3 and 4 (percutaneous valves). Next, we generated a list of valve manufacturers based on the published literature and expert knowledge. On our behalf, the Scientific Resource Center (SRC) at the Oregon EPC then contacted 14 companies believed to manufacture percutaneous heart valves and requested information on percutaneous valves in use or in development. (They attempted to contact a 15th manufacturer, but were unable to identify any current contact information for the company.) Of the 14 manufacturers contacted, 7 did not respond, 6 responded that they had nothing to submit, and 1—Edwards Lifesciences, LLC—responded with the requested information. Finally, we supplemented these approaches by searching the Web sites of valve manufacturers.

To identify valves with FDA approval, we first contacted the FDA, who provided a list of approved valves. For valves known to us but not included in the list provided by the FDA, we searched the Internet (via Google) using terms for the manufacturer, the specific valve, and "FDA." Using this strategy, we discovered and accepted manufacturer press releases claiming FDA approval.

Percutaneous heart valves are an emerging technology, and none are FDA approved. For this valve class, we relied on the published literature and experts to describe potential FDA indications.

To determine the theoretical advantages and disadvantages of different valves for different populations, we relied on discussions and recommendations in clinical guidelines, review articles, and consultations with experts. Using these sources, we developed a narrative description of the valve classes, goals in valve design, and the theoretical advantages and disadvantages of different types of valves.

Question 2. Studies Comparing Various Types of Conventional Heart Valves

Approach. For Question 2, we scanned the existing literature comparing different types of conventional (i.e., tissue and mechanical) heart valves in order to determine whether a systematic review of this literature is possible and needed, and to provide a context for understanding the development and evaluation of percutaneous heart valves. We sought to describe the available comparative studies in terms of the number of available studies, interventions compared, basic study design, size of study, length of followup, and outcomes assessed.

We began by searching for relevant, high-quality systematic reviews. We then expanded beyond these to a scan of available RCTs and select observational studies.

Literature sources and search strategies. We used separate strategies to identify systematic reviews, RCTs, and observational studies:

- For potentially relevant ***systematic reviews,*** we searched PubMed® (1949 to October 17, 2008) using the detailed search strategy given in Appendix A. We also searched the

Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database using the terms "heart valve" OR "heart valve prosthesis."

- We identified potentially relevant ***RCTs*** in two ways: (1) By reviewing the individual studies included in the systematic reviews that met our full-text inclusion criteria; and (2) by searching PubMed® (1949 to October 17, 2008) using the detailed search strategy given in Appendix A.
- We identified potentially important ***observational studies*** primarily by reviewing the individual studies included in the systematic reviews that met our full-text inclusion criteria. A few additional observational studies were picked up by the RCT search described in Appendix A. We also searched PubMed® (search date December 13, 2008) for recent (published during the past 5 years) observational studies that were large ($n \geq 1000$), *or* that had followup of 10 years or longer, *or* that evaluated valves not studied in RCTs using the detailed search strategy described in Appendix A.

Screening for inclusion/exclusion—systematic reviews. A single reviewer screened the titles and abstracts of all citations for potential inclusion. Articles were included if they concerned conventional heart valves and appeared to be a review article.

Citations included at the title-and-abstract stage were reviewed in full-text form independently by two researchers. Articles meeting the following criteria were **included** for data abstraction:

- The article was a systematic review, defined as a review including both a Methods section describing a search strategy and analytic approach, and abstractions of primary literature; *and*
- The review directly compared two or more different types of conventional heart valves; *and*
- The review concerned valve replacement (rather than repair); *and*
- The review focused on adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- The review was published in English in the year 2000 or later.

When the two reviewers arrived at different conclusions about whether to include or exclude an article, they were asked to reconcile the difference.

Screening for inclusion/exclusion—RCTs. A single investigator screened titles and abstracts and then full texts of potentially relevant RCTs. The inclusion criteria applied at both screening stages were:

- Comparison of two or more heart valves for valve replacement (rather than repair); *and*
- Randomized allocation to treatment; *and*
- Study conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- Study published in English.

If there was any uncertainty about whether an article should be included, a second investigator was consulted.

Screening for inclusion/exclusion—observational studies. A single investigator screened titles and abstracts and then full texts using the following inclusion criteria:

- Observational study design; *and*
- Comparison of two or more heart valves for valve replacement (rather than repair); *and*
- Large study population (n ≥ 1000) *or* followup ≥ 10 years *or* study evaluated a valve not evaluated in RCTs; *and*
- Study conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- Study published in English.

A second investigator was consulted in cases where there was uncertainty about whether an article should be included.

Data abstraction. For Question 2, we completed detailed evidence tables only for the included systematic reviews (Appendix B, Evidence Table 1). Data abstracted included the number and designs of included studies, patient descriptors, heart valves compared, and outcomes reported.

For RCTs and observational studies that met our inclusion criteria, we abstracted basic information on the interventions compared, study design, size of study, length of followup, and outcomes assessed into summary tables (Appendix C, Tables C1 and C2).

Quality assessment. The methodological quality of the included systematic reviews was evaluated independently by two investigators using a quality assessment tool developed specifically for this project. This tool was adapted from a similar instrument used in a previous evidence report prepared for AHRQ,[22] which in turn was based on the Quality Of Reporting Of Meta-analyses (QUOROM) statement.[23]

The 10 quality criteria assessed were stated in question form; possible responses were "Yes," "Partially," "No," or "Can't tell." The criteria used are presented in detail in Appendix D. When the two investigators disagreed in their assessments, they met to reconcile the difference. The results of quality assessments for individual systematic reviews are reported in Evidence Table 1 (Appendix B).

The RCTs and observational studies reviewed for this question were not assessed for methodological quality.

Question 3. Studies of Percutaneous Heart Valves

Approach. We scanned the existing published and gray literature on different types of percutaneous heart valves to synthesize information on the variables specified in Question 3. We limited our search to human studies of percutaneous heart valves in adults.

Literature sources and search strategies. We searched PubMed® and EMBASE® through October 15, 2009, for relevant published studies using the detailed search strategies given in Appendix A.

We also conducted an extensive search of the gray literature for this question (last search date December 31, 2008). We were assisted in this effort by a librarian with expertise in gray literature searching, who suggested sources and search terms. The gray literature sources consulted, search terms used, and results are described in Table 1.

Finally, colleagues working in AHRQ's Effective Health Care Program at Oregon Health & Science University contacted companies known or believed to manufacture percutaneous heart valves on our behalf to request any additional information they wished to submit in the form of "Scientific Information Packets." Requests to companies were sent out on August 5, 2008; the deadline for responding was September 16, 2008. Table 2 provides a list of the companies contacted and their responses.

Screening for inclusion/exclusion—published studies. Citations to published studies retrieved through searches of PubMed® and EMBASE® were supplemented by information provided in the Scientific Information Packet submitted by Edwards Lifesciences, LLC. A single reviewer screened the titles and abstracts of all citations for potential inclusion. All citations that appeared to report primary data on studies of percutaneous heart valves in humans were included at this stage, with no limit by language or heart valve position (e.g., aortic vs. mitral).

Citations included at the title-and-abstract stage were reviewed in full-text form independently by two researchers. Articles meeting the following criteria were **included** for data abstraction:

- Interventions included percutaneous heart valves; *and*
- Study involved valve replacement (rather than repair); *and*
- Primary data were reported; *and*
- Study was conducted in humans; *and*
- Study was conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- At least 1 clinical outcome was reported (e.g., mortality, hemodynamic parameters of success, successful implantation rates); *and*
- Study was published in English.

Note that no restrictions were imposed regarding:

- Study design (all designs acceptable); *or*
- Sample size ($n \geq 1$ acceptable).

When the two reviewers arrived at different conclusions about whether to include or exclude an article, they were asked to reconcile the difference.

Screening for inclusion/exclusion—gray literature. A single investigator searched the general gray literature sources listed in Table 1 and screened the material identified for potential relevance using the inclusion/exclusion criteria described above for published studies.

A single investigator also searched the sources listed in Table 1 for potentially relevant abstracts from recent scientific meetings. Titles and abstracts were screened online, and potentially relevant abstracts were then reviewed in full using the inclusion/exclusion criteria described above for published studies. Abstracts meeting the inclusion criteria were further screened to eliminate those abstracts that duplicated information reported more fully in published studies.

A single investigator searched ClinicalTrials.gov for potentially relevant ongoing studies of percutaneous heart valves.

Finally, a single investigator reviewed information on four relevant registries of percutaneous heart valve implantation included in the Scientific Information Packet provided by Edwards Lifesciences, LLC.

Data abstraction. For Question 3, we created detailed evidence tables only for published studies (Appendix B, Evidence Table 2). Data abstracted included: date of publication; country; study design; study objectives; duration of followup; number, age, and sex of participants; indication for percutaneous heart valve; valve name; size of catheter; implementation approach; implantation rates; and clinical outcomes, including hemodynamic measurements and 30-day mortality rates, complications, and device dysfunction rates.

Important data from the included gray literature and Scientific Information Packets were abstracted into summary tables included in the Results section.

Purely descriptive statistics are used to summarize and analyze the data abstracted from the fully published reports, as is appropriate for a horizon scan of literature comprised solely of non-comparative studies.

Quality assessment. The studies included for this question were not formally assessed for methodological quality.

Question 4. Variables that May Affect Outcomes for Percutaneous Heart Valves

Approach. Question 4 focused on variables associated with surgery or setting that may impact outcomes for percutaneous heart valves. In consultation with experts in cardiology and cardiac surgery, we elected to broaden our focus beyond the specific variables listed in the question to include other variables that usually impact outcomes for surgical procedures and that we expected would be reported in published reports identified by our search strategy. In the end, we considered six general categories of variables: (1) prosthesis characteristics; (2) implantation approach; (3) treatment setting; (4) operator characteristics; (5) type of anesthesia; and (6) patient characteristics. The specific variables considered under each category are listed in Table 3.

For the purpose of answering this question, we focused on device implantation success rates and 30-day survival rates as outcome measures. These two outcomes were consistently reported in most of the studies, and they serve as reasonable proxy measures for the feasibility of delivering prosthetic heart valves percutaneously, as well as for short-term clinical outcomes.

Sources and methods. For Question 4, we considered a subset of the literature identified for Question 3, namely, the 62 fully published reports that met the inclusion criteria for that question. The methods used to search the published literature, screen potentially relevant citations, and abstract and evaluate data are described above, under Question 3. For Question 4 we also consulted with experts in cardiology and cardiac surgery and incorporated information and perspectives from pertinent, published review articles.[6,8,24-30]

For the present question, we excluded data presented at scientific meetings but not yet published in peer-reviewed journals for the following reasons: (1) the data reported in meeting abstracts were insufficient to create sufficiently detailed evidence tables; (2) data presented at scientific meetings often differ from those that later appear in published reports; (3) data presented at meetings are often derived from a subset of patients whose data have undergone

only preliminary analysis; and (4) insufficient data are usually presented in the abstracts to identify new patients in ongoing series for which preliminary findings were previously published.

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the project to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include the following: three progressively stricter screening opportunities for each article (abstract screening, full-text screening, and data abstraction); involvement of at least two individuals (an abstractor and an over-reader) in each data abstraction; and agreement of at least two investigators on all included studies.

Our principle external quality-monitoring device is the peer review process. Nominations for peer reviewers were solicited from several sources, including the clinical content experts on the Duke research team, AHRQ, and staff at the SRC at the Oregon EPC. The list of nominees was forwarded to AHRQ for vetting and approval. A list of peer reviewers who submitted comments on a draft version of this report is provided in Appendix E.

Results

Question 1. Heart Valves in Use and in Development

Listing of Valves

Table 4 (conventional valves) and Table 5 (percutaneous valves) summarize the information we were able to compile, using the methods described above, on heart valves now in use or in development and their FDA status. In many instances, valve names used in the published literature were incomplete and did not precisely match device names provided by manufacturers or the FDA. In such cases, we attempted to match names based on other device characteristics, such as valve type, or from narrative descriptions in the literature. When matches could not be made with confidence, we listed all valve device names. Thus, Tables 4 and 5 may list some valves more than once using different names. Some of the valves listed are no longer manufactured, but may be encountered in patients with past valve replacements. These obsolete valves are also described in reviews and primary comparative studies. For these reasons, we included these valves in our summary tables.

To date, no PHV has received FDA approval for the indication of aortic stenosis, but both the Edwards SAPIEN valve and the CoreValve ReValving System have received Conformité Européenne (European conformity, or CE) mark certification in Europe. The CE mark indicates that a medical device has met acceptable safety standards, but does not necessarily indicate that the device is efficacious.

Classes of Heart Valves

Diseased heart valves can be replaced with mechanical or biological valves. Mechanical valves employ caged-ball, tilting disc, and bileaflet designs. The first artificial heart valve was a caged-ball design which utilized a metal cage to house a silicone coated ball.[31] Tilting disc valves employ a disc controlled by a metal strut, which opens and closes with each cardiac cycle. Bileaflet valves utilize two semicircular leaflets that rotate around struts attached to the valve housing. At least six companies manufacture tilting disc or bileaflet mechanical valves that are currently available in the U.S. market (Table 4).

Biological valves (bioprosthesis or tissue valves) are classified into two major categories: xenografts made from bovine, porcine, or equine tissue; and homografts obtained from cadaveric donors. Xenografts may have a supporting frame (stent) or no supporting frame (stentless). Xenografts are much more readily available than homografts. We identified seven different manufacturers of FDA-indicated xenografts, including bovine, porcine, stented, and stentless models (Table 4).

Percutaneous heart valves are stent-based xenografts that are collapsed onto a catheter and are expanded at the time of implantation. Percutaneous valves are an emerging technology. We identified seven manufacturers of percutaneous valves (Table 5); none of these valves are FDA approved.

Heart Valve Design

Replacement heart valves must be durable in order to minimize the risk of reoperation due to device failure. Factors that affect durability include: valve position; valve design; valve

materials; and, for bioprostheses, the processes used to fix tissue and prevent calcification. A second goal is to replicate natural valve function as closely as possible. Desirable functional characteristics are: a non-thrombotic surface; materials that do not predispose to endocarditis; and favorable hemodynamic profiles, including laminar flow, small transvalvular gradients, and minimal regurgitant volumes. One measure of hemodynamic efficiency is captured by the effective orifice area (EOA); larger EOAs provide better flow.

Theoretical Advantages and Disadvantages of Different Heart Valves

Mechanical heart valves are more durable than bioprostheses and are readily available. Mechanical valves have a simple and standard implantation technique. However, mechanical valves require lifelong anticoagulation because of a greater risk of thrombosis. Anticoagulation significantly increases the risk for bleeding that may require transfusion, and therefore requires careful monitoring. Because of shear forces, mechanical valves may also cause hemolytic anemia. Mechanical valves are hemodynamically inefficient in smaller sizes, a limitation for AVR in patients with a small aortic annulus. Caged-ball valves have the disadvantages of noise, hemodynamic inefficiency, and higher rates of thrombotic complications, necessitating a higher degree of anticoagulation than other mechanical valves.[8] Edwards Lifesciences, LLC, discontinued production of the caged-ball valve in 2007. Caged-ball valves are no longer marketed in the United States and other developed countries. Tilting disc designs have superior hemodynamic efficiency to caged-ball designs, but have the disadvantage of severe hemodynamic compromise if disc thrombosis or immobility occurs. Bileaflet mechanical valves have greater EOA than tilting disc valves and may be less thrombogenic than other mechanical valves. Because mechanical valves have the longest durability, they are recommended for younger patients (< 65 years old) who are willing to take oral blood thinners (e.g., warfarin) and participate in anticoagulation monitoring.[8]

Bioprosthetic heart valves are also readily available and do not require chronic anticoagulation. In addition, they have a simple and standard implantation technique and may have fewer infectious complications than mechanical valves. However, bioprosthetic valves are less durable than mechanical valves. Structural deterioration is age-related, occurring more rapidly in younger age groups. Biological valves carry the theoretical risk of transmitting infection; at least one bovine valve has been recalled due to concern about transmission of bovine spongiform encephalopathy. Methods for tissue fixation and anticalcification have evolved since early bioprosthetic heart valves. Second-generation valves of this type are glutaraldehyde fixed under low pressure (compared with high pressure with the first generation), which is thought to increase durability. Stented bovine pericardial valves appear to have better hemodynamic performance and longer durability than stented porcine valves, especially in smaller sizes. Because stentless valves have less supporting material than stented bioprostheses, they have the potential for improved EOA and improved hemodynamic performance. Stentless valves may also be more durable than stented valves. However, stentless valves may be more technically difficult to implant, increasing operating room time and possibly surgical risk. Tissue-engineered valves using regeneration or repopulation approaches represent an emerging bioprosthetic technology; no such FDA-approved valves were identified.[32] Regeneration involves the implantation of a restorable matrix that is expected to remodel in vivo and yield a functional valve composed of the cells and connective tissue of the patient. Repopulation involves implanting a porcine or human valve that has been depopulated of native cells, where

the remaining scaffold of connective tissue is repopulated with the patient's own cells. The theoretical advantage is a living tissue that responds to growth and physiological forces in the same way a native valve does. The 2006 ACC/AHA guidelines recommend a bioprosthesis for patients of any age who will not take or have major contraindications to warfarin therapy, for patients ≥ 65 years of age who do not have risk factors for thromboembolism, and for patients under age 65 who choose this approach for lifestyle reasons.[8]

The durability of homograft heart valves depends upon how the valve is recovered, processed, and preserved. Homograft aortic valves are supplied as a composite valve, aortic root, and part of the anterior mitral leaflet. This additional tissue is useful for severe disease due to endocarditis, and homografts are most frequently used for this indication. Durability of homografts does not appear to be superior to xenografts. Like xenografts, homograft (human) heart valves do not require chronic anticoagulation, risk of thromboembolism is very low, and these valves may be less likely to calcify than xenografts. Implantation procedures and reoperation for a failed valve are more complex than for standard mechanical or stented xenografts. The supply of homografts is much more limited than for mechanical valves or xenografts.

Because they are delivered via a catheter, percutaneous heart valves have the potential advantage of lower perioperative morbidity and mortality than valves implanted using conventional surgical approaches. There are six percutaneous approaches, one that uses direct apical heart puncture (the transapical approach), and five that involve cannulation of either the femoral vein, femoral artery, subclavian artery, axillary artery, or ascending aorta. None of these procedures requires cardiopulmonary bypass or a sternotomy, and the femoral and subclavian approaches may not require general anesthesia. The major theoretical advantages of the percutaneous approach are lower perioperative risk and less morbidity, leading to faster recovery times. Percutaneous valves have been used experimentally in patients deemed too high risk for conventional valve replacement surgery. Compared with valves implanted by open heart surgery, however, these valves are not sewn in, so there is an increased risk of migration. In addition, there are risks associated with cannulation, including thromboembolic events or perforation of major vessels. There is no long-term experience with percutaneous valves, so durability is uncertain and the implantation approach is evolving. Finally, percutaneous heart valves are not FDA approved, but the ongoing Placement of AoRTic TraNscathetER (PARTNER) trial is evaluating one of these valves in the United States.[33]

Question 2. Studies Comparing Various Types of Conventional Heart Valves

Scan of Systematic Reviews

Reviews identified. Our literature search identified 325 potentially relevant citations. Of these, 283 were excluded at the title-and-abstract screening stage, and 35 at the full-text screening stage. Seven publications, describing six distinct systematic reviews, addressed the comparative efficacy of various conventional prosthetic heart valves and met our other inclusion criteria.[34-40] Major characteristics of these reviews are summarized in Table 6, and a detailed abstraction of each review is provided in Evidence Table 1 (Appendix B). Only one of the included reviews[35] met all 10 of the quality assessment criteria we applied. Common limitations of other reviews included: inadequate or poorly described search strategies (5 of 6 reviews); failure to assess the

quality of primary studies (5 of 6); and failure to examine for publication bias (4 of 6). Furthermore, observational studies and systematic reviews of observational studies are inherently limited in their ability to provide unbiased comparisons between different patient populations.

The included reviews are described in greater detail below, organized by valve comparison.

Mechanical vs. bioprosthetic valves. Four systematic reviews, described in five papers,[34,36-38,40] compared mechanical and bioprosthetic valves. Kassai et al.[34] identified two RCTs in adults (n = 1011) and one in children (n = 218) comparing mechanical with bioprosthetic valves in aortic or mitral valve position. Specific valves compared were the Bjork-Shiley or Lillehei-Kaster mechanical valves; and the Hancock, Carpentier-Edwards, or Angell-Shiley bioprosthetic valves. These valves are no longer in widespread use. Meta-analysis of the three trials showed no difference between mechanical and bioprosthetic valves for all-cause mortality at 5 years (relative risk [RR] 1.16, 95 percent confidence interval [CI] 0.97 to 1.39) or at 11 years (RR 0.94, 95 percent CI 0.84 to 1.06). Subjects receiving mechanical valves were less likely to undergo reoperation at 11 years (RR 0.4, 95 percent CI 0.29 to 0.58; x^2 for heterogeneity, p = 0.059), and less likely to have endocarditis (RR 0.6, 95 percent CI 0.3 to 0.95; x^2 for heterogeneity, p = 0.0001), but were more likely to have a bleeding complication (RR 1.65, 95 percent CI 1.26 to 2.18). A major limitation of this review is that the search only went through 1997.

A more recent systematic review[36] also compared mechanical and bioprosthetic valves in the aortic position, limiting the literature to observational studies with at least 10 years of patient followup. The review identified 32 articles describing 38 case series and reporting outcomes in 17,439 patients. Studies with more than 10 percent obsolete valve types and studies that did not report mortality outcomes were excluded. Valves compared were the St. Jude bileaflet disc, CarboMedics, Sorin bileaflet and single disc, ATS, On-X, Edwards Mira, Edwards Duromedics, Tekna valve, or Medtronic-Hall tilting disc mechanical valves; and the Carpentier-Edwards Perimount pericardial, Carpentier-Edwards porcine standard, Carpentier-Edwards porcine supra-annular, Hancock II and MO porcine, Sorin Mitroflow pericardial, Medtronic Mosaic, Edwards Prima stentless, St. Jude x-cell, and Biocor porcine bioprosthetic valves. Statistical analysis using regression approaches showed no difference in mortality after adjusting for age, New York Heart Association class, and presence of aortic regurgitation (0.23 fewer deaths per 100 patient-years with bioprosthetic valves; 95 percent CI -0.99 to 0.63). The advantage of this review is that it focuses on studies describing experiences in clinical practice with currently used valves. However, an important limitation is the reliance on case series that do not directly compare mechanical with bioprosthetic valves. Indirect comparisons are more subject to bias and provide lower quality evidence.

Rizzoli et al.[40] reviewed the outcomes for mechanical vs. bioprosthetic valves implanted in the tricuspid position. Eleven studies reporting "intra-institutional comparisons" of mechanical (n = 646) vs. biological (n = 514) valves were included. Specific study designs and valve types were not described, but a review of the primary literature cited showed these to be observational studies. Median duration of followup was 6.5 years. In seven studies reporting mortality, the hazard ratio was 1.07 (95 percent CI 0.84 to 1.35), indicating a small, statistically insignificant increase for mechanical vs. bioprosthetic valves. For three studies reporting freedom from reoperation, the pooled hazard ratio was 1.24 (95 percent CI 0.67 to 2.31) for mechanical vs. bioprosthetic valves. There are a number of limitations to this review, including: primary data

from observational studies that are at increased risk for bias; lack of quality assessments for the primary data; and no evaluation for publication bias. Observational studies are at risk for confounding by indication, with particular valves being selected based on clinical indications, leading to important baseline imbalances in prognostic factors between the mechanical and bioprosthetic groups.

A 2004 review and microsimulation described in two publications compared selected bileaflet mechanical valves and stented porcine bioprosthesis in the aortic position.[37,38] Specific mechanical valves considered were the St. Jude Medical bileaflet valves (standard and hemodynamic plus models); bioprosthetic valves were the Carpentier-Edwards standard and supra-annular valves, Hancock standard and modified orifice, and Hancock II valves. Studies in adult populations with predominately first-time AVR, valve events ascertained using standard definitions, and international normalized ratio values between 1.8 and 4.5 were included for review. Nine observational studies on St. Jude Medical valves and 13 studies on stented porcine bioprosthesis met inclusion criteria from the 144 identified in the search. Most of the 22 included studies were case series; 15 were retrospective designs, 5 were prospective, and 2 were not described. Meta-analysis showed the following event rates per 100 patient-years for mechanical vs. bioprosthetic valves: valve thrombosis (0.16 vs. 0.01); thromboembolism (1.6 vs. 1.3); hemorrhage (1.6 vs. 0.4); and endocarditis (3.9 vs. 3.2 in first 6 months). Incorporating these estimates into a microsimulation model for a 65-year-old man, life expectancy was projected at 10.4 years for mechanical vs. 10.7 years for bioprosthesis. Study limitations include the following: primary literature is predominately case series; lack of assessment for study quality; poorly described search strategy; and life expectancy results that depend on valid modeling.

In summary, two RCTs in adults showed no difference between mechanical and bioprosthetic valves in the aortic or mitral positions. However, the specific valves tested in these RCTs have been replaced by new models that may perform differently, and the study populations differ substantially from adults most commonly undergoing valve replacement today. In addition, standards for anticoagulation have changed to a lower international normalized ratio range, such that bleeding complications would now be expected to be lower. A large body of observational studies describing experiences with heart valve replacement has been summarized in systematic reviews. Although observational studies are at greater risk for bias than RCTs, and the systematic reviews evaluating them are of low to moderate quality, findings from those reviews are consistent with the findings from systematic reviews of RCTs.

Stented vs. stentless bioprosthetic valves. Left ventricular (LV) hypertrophy is a complication of aortic stenosis, and maximizing hemodynamic results from AVR is theorized to facilitate LV mass regression and improve clinical outcomes. Stentless valves are xenografts that have no additional structure (stent) allowing for larger valve sizes to be implanted, maximizing the EOA-to-tissue annulus ratio. Maximizing this ratio offers the potential for improved hemodynamic and clinical outcomes.

Only one systematic review evaluated stented vs. stentless bioprosthetic valves.[35] This high-quality review included 11 RCTs of AVR conducted in Western Europe and Canada and reported between 1996 and 2006. A total of 445 subjects were randomized to stented valves: Carpentier Edwards Perimount, More, Mosaic, Intact, and Hancock II. The Prima Plus, Freedom, Freestyle and Toronto Stentless valves were implanted in 474 subjects. Six studies (n = 599) reported the primary outcome LV mass index at 6 months, and five studies (n = 550) reported this outcome at 12 months or later. LV mass index was lower for stentless valves at 6 months

(weighted mean difference [WMD] -6.42, 95 percent CI -11.63 to -1.21), but this improvement disappeared after 12 months (WMD 1.19, 95 percent CI -4.15 to 6.53), and the meta-analysis showed significant heterogeneity that could not be explained by subgroup analyses. Secondary outcomes showed improved hemodynamic results for stentless valves (mean aortic gradient, WMD -3.57 mm Hg, 95 percent CI -4.36 to -2.78; peak aortic gradient, WMD -5.80, 95 percent CI -6.90 to -4.69), but longer operative cross-clamp time (WMD 23.5 minutes greater, 95 percent CI 20.4 to 26.1) and bypass time (WMD 29, 95 percent CI 24.4 to 34.0). There was no difference in mortality for stentless vs. stented valves at 1-year followup (odds ratio [OR] 0.91, 95 percent CI 0.52 to 1.57).

The primary limitations of this review are the short followup duration, the lack of symptom or functional status outcomes, and the significant unexplained heterogeneity across studies. These short-term studies suggest tradeoffs—improved hemodynamics at the expense of longer procedure times for stentless valves—and no evidence for improved cardiac function or lower mortality for stentless vs. stented valves at 12 months.

Comparisons of one bioprosthetic valve vs. another. A 2006 review and microsimulation[39] compared two bioprosthetic valves, the Carpentier-Edwards pericardial valve and the Carpentier-Edwards supra-annular valve, both in the aortic position. These "second generation" valves were introduced in the 1980s and incorporated improvements in valve design aimed at reducing structural valvular deterioration and improving hemodynamic performance. The review included studies that focused on patients aged > 15 years with predominately first-time AVR. Additional inclusion criteria were: patients who predominately did not require long-term anticoagulation; valve sizes 19 to 31 mm; and valve events ascertained using standard definitions. Eight observational studies (n = 2685) on pericardial valves and five studies (n = 3796) on supra-annular valves met the inclusion criteria from the 48 identified in the search. Only two of these studies directly compared the two types of valves; the remaining 11 were case series of a single valve type. Meta-analysis of data from all included studies showed the following event rates per 100 patient-years for Carpentier-Edwards pericardial vs. Carpentier-Edwards supra-annular, respectively: valve thrombosis (0.03 vs. 0.02); thromboembolism (1.35 vs. 1.76); hemorrhage (0.43 vs. 0.46); endocarditis (0.62 vs. 0.39); and non-structural dysfunction (0.13 vs. 0.61). Neither CIs nor p-values were given for these comparisons. Incorporating these estimates into a microsimulation model for a 65-year-old man, life expectancy was projected at 10.8 years for the Carpentier-Edwards pericardial valve vs. 10.9 years for the Carpentier-Edwards supra-annular valve. This review and microsimulation are strengthened by model estimates from observational studies with long followup periods cited by the review authors. As in other reviews that rely on observational studies, indirect comparisons and confounding by indication may bias outcome estimates. In addition, the methods used in the review are poorly described, decreasing confidence in the estimates used in the microsimulation model in this particular instance.

Scan of Randomized Controlled Trials

As described in the Methods section, in order to supplement the information obtained from systematic reviews, we sought to identify additional relevant RCTs and large observational studies that compared two or more conventional heart valves. For each such study we abstracted key design features to inform a judgment about the feasibility and possible value of conducting a systematic review of this literature.

Of the 416 potentially relevant articles identified by our search, 329 were excluded at the title-and-abstract screening stage, and 10 more at the full-text screening stage. Seventy-seven (77) articles, describing 57 unique RCTs involving 13,379 subjects, met our inclusion criteria (Appendix C, Table C1). Sixteen of these trials were included in the systematic reviews described immediately above. The 57 trials evaluated valve replacement in the aortic position (n = 43), aortic and mitral position (n = 11), or mitral position alone (n = 3). For the 43 studies exclusively evaluating AVR, the most common comparison was of bioprosthetic stented vs. bioprosthetic stentless valves (Table 7). For the 11 studies evaluating aortic and mitral valve replacement, comparisons were: homograft vs. mechanical (n = 1); one mechanical valve vs. another (n = 7); mechanical vs. bioprosthetic (n = 2); and one bioprosthetic valve vs. another (n = 1). The three studies of mitral valve replacement all compared mechanical valves.

Within these major classes of valve types, the number of unique valves evaluated was large (Table 8). Valve technology has evolved, and some of these valves are no longer marketed in the United States. Some valves are designed for special purposes, such as a lower profile for a small annulus. A systematic review would need to carefully evaluate whether valves in a general class (e.g., mechanical) could be considered together for analytic purposes.

Other critical issues affecting the feasibility of a systematic review are the timing, types, and quality of outcomes reported. Long-term studies are important to adequately evaluate mortality, reoperation for structural device failure, and long-term adverse effects such as stroke and bleeding complications. For the 42 studies of AVR, outcomes were reported at 1 year or sooner in 29 studies (69 percent), > 1 to 5 years in 10 studies (24 percent), and > 5 to 10 years in 3 studies (7 percent). Studies of aortic or mitral replacement generally had longer followup: > 1 to 5 years for 4 studies (36 percent); > 5 to 10 years for 5 studies (45 percent); and > 10 years for 2 studies (18 percent). Mean followup for the three mitral valve studies was about 5 years. The types of outcomes reported are summarized in Table 9. Intermediate outcomes such as hemodynamic changes were the most commonly reported. Although adverse effects were reported in about three-quarters of studies, we identified considerable heterogeneity in reporting, making a valid summary estimate more difficult.

Scan of Observational Studies

Of the 1160 potentially relevant citations identified by our search, 1096 were excluded at the title-and-abstract stage, and another 24 at the full-text stage. Forty (40) articles, each describing a unique study and involving a total of 332,551 subjects, met our inclusion criteria (see Appendix C, Table C-2). Twenty-six of these studies were included in the systematic reviews described above. A single Medicare claims study accounts for 307,054 of the subjects.[41] Studies evaluated valve replacement in the aortic position (n = 22), aortic and/or other valve positions (n = 5), tricuspid position (n = 10), and mitral position (n = 2); 1 study did not report valve position. For the 27 studies evaluating aortic and/or other valve replacements, mechanical vs. bioprosthetic stented and bioprosthetic stented vs. bioprosthetic stentless were the most common comparisons, followed by comparisons of two bioprosthetic stented valves (Table 10). Of the 10 studies evaluating tricuspid valve replacement, nine compared mechanical with stented bioprosthesis.

Thirty-six different named valves are evaluated in these studies, including 21 valves not evaluated in RCTs (Table 11).

Compared with RCTs, observational studies are more likely to describe longer followup and report clinically important outcomes. Twenty-six of the 40 included studies (65 percent) had

a mean followup duration exceeding 5 years. Most studies reported mortality rates, adverse effects, and reoperation rates (Table 12). A complicating issue for a possible systematic review is variability across studies in potential confounders controlled for in the analyses.

Summary

Our literature scan identified six relevant systematic reviews, one of high quality, and a large body of RCTs and observational studies comparing different conventional heart valves with one another. The single high-quality meta-analysis evaluated 11 studies comparing stented with stentless bioprosthetic valves; we identified an additional four relevant trials and seven observational studies. There is sufficient literature to address other relevant comparisons, such as between mechanical and bioprosthetic valves, and between homografts and bioprosthetic valves, and to make selected within-class comparisons (e.g., among differing mechanical valves).

Based on varying duration of followup and types of outcomes reported, a systematic review would need to evaluate both RCTs and observational studies. RCTs of currently available valves tend to have shorter followup and thus are unable to evaluate critical outcomes such as reoperation for valve failure, late adverse effects, and long-term survival. Observational studies with longer-term followup can supplement findings from randomized trials. Systematic reviews will be complicated by heterogeneity in study design, valve position, and valve types. Other challenges include: whether to include studies of valves no longer marketed that may perform differently from modern valves; accounting for changes in anticoagulation targets and thus the risk for bleeding; and accounting for observational studies that vary by whether outcomes are adjusted for potential confounders. A systematic review that carefully develops a conceptual framework and evaluates the association between intermediate outcomes (such as hemodynamic changes) and long-term outcomes of importance to patients would be particularly useful.

Question 3. Studies of Percutaneous Heart Valves

Studies Identified

A total of 77 published reports were screened at the full-text stage; of these, 15 were excluded. The remaining 62 publications, describing 55 separate studies, assessed the feasibility and short-term safety of implanting percutaneous heart valves and met our other inclusion criteria.[42-103]

Important data from these studies, which represent 856 unique patients, are summarized in Tables 13 and 14; detailed abstractions of the included studies are provided in Evidence Table 2 (see Appendix B).

Our gray literature scan identified 12 scientific meeting abstracts that presented data on 11 studies not described in the published reports.[104-115] These abstracts, which are summarized in Table 15, report data on 923 patients who underwent percutaneous heart valve replacement. Insufficient evidence was reported in the abstracts to make it possible to determine with confidence how many patients may be represented in more than one abstract, or in both an abstract and a fully published report.

We identified four ongoing clinical trials via the ClinicalTrials.gov Web site (www.clinicaltrials.gov) (Table 16). Finally, the Scientific Information Packet provided by Edwards Lifesciences, LLC, included information on four relevant registries of percutaneous heart valve implantation (Table 17).

Results from Published Studies

Table 13, Table 14, and the paragraphs below summarize the most important findings from our scan of published studies. Data presented in abstract form at scientific meetings but not yet published in peer-reviewed journals are not included in this information synthesis for the following reasons: (1) meeting abstracts usually contain insufficient information to create sufficiently detailed evidence tables; (2) data presented at scientific meetings often differ from those that later appear in published reports, thereby putting into question the accuracy of the data presented in the abstracts; and (3) information presented at meetings is often derived from a subset of patients whose data have undergone only preliminary analysis. We describe the results from the abstracts we identified briefly in a separate section, below.

Number of studies and patients for each type of valve. We identified seven manufacturers of percutaneous heart valves through the published, peer-reviewed medical literature. The first published report of percutaneous valve replacement in an adult[42] involved a valve that was initially manufactured by Percutaneous Heart Valve, Inc. The device is referred to as "Percutaneous Heart Valve" in the initial published studies. In 2004, Percutaneous Heart Valve, Inc., was acquired by Edwards Lifesciences, LLC. Subsequently, the same device was referred to as the Cribier-Edwards valve in published reports. More recent publications refer to that same device as the "Edwards SAPIEN Transcatheter Heart Valve" (or "SAPIEN THV"). Reports in the non-peer-reviewed literature describe the Ascendra Aortic Heart Valve Replacement System as the Cribier-Edwards valve for use in transapical, rather than transfemoral, delivery. The literature identified by our search strategy does not describe whether or how the differently named percutaneous heart valves acquired or manufactured by Edwards Lifesciences, LLC, have been modified over time. We identified 35 published reports, describing 28 studies, that reported results on a total of 412 unique patients who received a device manufactured by Edward Lifesciences, LLC, or Percutaneous Heart Valve, Inc.[42-76]

The second valve to appear in the published literature is the CoreValve ReValving System. The first generation was delivered via a femoral artery approach using a 25 French (Fr) catheter. The second generation of the valve was delivered via a 21 Fr catheter. The third and current generation is delivered via an 18 Fr catheter. We identified 22 reports, describing 21studies, that reported on a total of 424 unique patients who underwent percutaneous heart valve replacement with a CoreValve device.[74,77-97]

One report included in the above counts[74] described two series of patients: one that received an Edwards Lifesciences valve (n = 25), and one that received a CoreValve valve (n = 127).

We identified a single published report for each of the five additional percutaneous heart valve manufacturers, plus one case report in which the names of the valve and manufacturer were not reported.[103] A case report of the Paniagua Heart Valve, manufactured by Endoluminal Technology Research, was published in 2005.[98] Case reports of the Lotus Valve (Sadra Medical)[99] and the Melody Valve (Medtronic)[100] were published in 2008. A case series that reported on the initial experience of the first 15 patients who received a Direct Flow Medical valve (Direct Flow Medical, Inc.) via using the femoral artery approach was also published in 2008.[101] In 2009, a case report was published that involved the Ventor Embracer valve manufactured by Ventor Technologies.[102]

Type of studies. Thirty-five of the published reports were case reports, and 27 were case series, the latter representing a total of 822 patients. We did not identify any published RCTs. One study described the procedure and reported clinical outcomes on five patients who underwent a valve-in-valve procedure, whereby a CoreValve Revalving device was implanted within a previously implanted prosthetic heart valve in the aortic position.[90] A single study compared clinical outcomes of 50 patients who underwent percutaneous heart valve (PHV) replacement at the aortic position with the Cribier-Edwards valve to historical controls comprised of 50 patients who underwent surgical valve replacement with a stented valve and 50 patients who underwent surgical valve replacement with a stentless valve.[51] The controls were matched for sex, aortic annulus diameter, left ventricular ejection fraction, body surface area, and body mass index. Compared to the two surgically implanted valve groups, PHV replacement was associated with a lower transprosthetic gradient, more frequent aortic regurgitation, lower incidence of severe prosthesis-patient mismatch, and higher incidence of adverse reactions. Interpretation of these findings is complicated, however, by the many potential biases inherent to indirect comparisons between two or more patient populations whose clinical characteristics are significantly different between groups.

Variables associated with the procedure. Five reports described an antegrade approach via the femoral vein, 32 described a retrograde approach via the femoral artery, and 17 described a transapical approach, representing 37, 578, and 223 patients, respectively. Only 12 of the reports described the setting in which the procedure took place (e.g., operating suite, catheter lab), and only four described the training or specialty of the person performing the procedure. Successful implantation of a heart valve percutaneously was achieved in 92 percent of cases.

Size of studies and length of followup. All of the published reports were non-comparative case reports or series. The largest series involved 136 patients. All but seven included followup data 30 days after the procedure or until death of the patient. Eleven reports (18 percent) provided followup data 1 or more years after the procedure.

Patient population and concurrent and prior treatments. All of the studies included only adult patients. One reported on implantation of a prosthetic valve in the pulmonic position in a young adult with congenital heart disease,[100] and one reported on implantation in the mitral valve position in an 80-year-old male with mitral stenosis.[76] The remaining studies were conducted in patients with severe aortic stenosis who were considered to be at high surgical risk for conventional aortic replacement surgery (n = 854 patients). The mean age of patients was greater than 80 years. A small minority of patients had undergone heart valve replacement prior to undergoing percutaneous heart valve replacement. European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores, which predict risk of death associated with open heart surgery, were reported in 15 of the 27 case series. Mean or median logistic EuroSCOREs among the patients represented in these 15 studies ranged from 11 to 41 percent, with 10 studies (67 percent) reporting a mean or median EuroSCORE greater than 23 percent.

Hemodynamic success rates. In nearly all patients, successful implantation of a prosthetic heart valve resulted in significant improvement in both valve area and either mean or peak pressure gradient across the replaced valve. Mild to moderate (Grade 1 or 2) paravalvular leaks were reported after the procedure in the majority of patients. LV ejection fraction was generally not

significantly improved. In one series with matched comparison of PHV (n = 50) vs. biologic (n = 50) or mechanical (n = 50) SAVR, superior hemodynamics (transvalvular gradient and effective orifice area) were found for PHV vs. surgical procedures.[51] Despite the limited PHV diameters available, the reported incidence of patient-prosthetic mismatch (insufficient effective orifice area for body surface area) is low.[51]

Clinical outcomes and harms reported. Thirty-day survival across all studies was 781/903 (86 percent), including 56 patients who were included in two published studies, and excluding patients for whom 30-day survival was not reported. We were unable to calculate a precise rate because there was some overlap of patients in a few of the published series, resulting in double counting of 56 patients (Table 13). This estimate remains unchanged after excluding studies with overlapping patients from the 30-day survival calculation. The most common causes of death attributed to the heart valve replacement procedure were myocardial infarction or stroke, arrhythmia, perforation of the vessels or heart wall, and heart failure.

The overall 30-day mortality rate of 14 percent is higher than rates reported for conventional aortic valve replacement (3 to 4 percent overall, with higher rates in patients over 65 in low-volume centers) but significantly lower than the operative mortality rate predicted by the logistic EuroSCORE for the patients in these published reports. Thirty-day outcomes were also reported as a composite endpoint of major adverse cardiovascular and cerebral events (defined as death from any cause, myocardial infarction, or stroke), with rates approximately eight percent in recent large series. Improvement in functional status, measured by the New York Heart Association (NYHA) classification, was reported in most of the series, with a reduction in severity from NYHA III-IV at baseline to I-II soon after PHV implantation. Among two PHV cohorts, 70-75% one-year survival rates have been reported,[70,71] with approximately half of the deaths deemed non-cardiac in causation.

Results from Scientific Meeting Abstracts

Table 15 briefly summarizes data from the 12 abstracts identified by our search of scientific meeting presentations. All of the eligible abstracts identified were presented in the year 2008; otherwise eligible abstracts presented in prior years were excluded because the studies they represented were subsequently published in full reports. The 12 abstracts represent 923 patients; despite our attempt to exclude studies that overlapped entirely with fully published reports, it is likely that some of the 923 patients represented in the abstracts listed in Table 15 are represented in the fully published reports summarized elsewhere in this report.

Four abstracts reported on a total of 128 patients who received the Edwards SAPIEN THV, and 6 abstracts reported the results of 5 case series involving 768 patients who underwent percutaneous heart valve replacement with the CoreValve ReValving System. An additional 2 studies involving 27 patients did not report the name of the device, but circumstantial evidence suggests that the Edwards SAPIEN THV was used in both of these studies.

One of the studies presented as an abstract compared a transapical approach (n = 21) with sternotomy (n = 30) in a series of 51 consecutive patients.[115] This study is one of only two studies we identified in our searches of the published and gray literature that involved a direct, albeit non-randomized, comparison. Three abstracts specified that they used a transapical approach, and six used the term “percutaneous” or “transcatheter” without specifying which specific approach was used. None of the studies represented by the meeting abstracts were conducted in the United States; all were conducted in Europe.

Ongoing Clinical Trials

We identified four pertinent ongoing trials on the ClinicalTrials.gov website (www.clinicaltrials.gov) (Table 16). Three of these are non-randomized, open-label, single group assignment treatment studies involving three different valves: the Melody Transcatheter Pulmonary Valve, Edwards SAPIEN THV, and Ventor Embracer Heart Valve. Pulmonary valve insufficiency is the clinical indication for the former, whereas the latter two are enrolling patients with either "heart valve disease" or "aortic valve disease."

The fourth ongoing trial represents the first RCT of percutaneous heart valves. The Placement of AoRtic TraNscathetER valve trial, or PARTNER Trial, is sponsored by Edwards Lifesciences, LLC. According to the listing in ClinicalTrials.gov, "the purpose of this study is to determine the safety and effectiveness of the device and delivery systems (transfemoral and transapical) in high-risk, symptomatic patients with severe aortic stenosis."[33]

The start date of the PARTNER Trial was in April 2007. Estimated study completion date is September 2014. Anticipated enrollment is 1040. Eligible patients with aortic stenosis who are at high surgical risk (defined as operative mortality of ≥ 15 percent and/or Society of Thoracic Surgeons risk score ≥ 10) will be randomly allocated to receive the Edwards SAPIEN THV percutaneously or undergo conventional surgical valve replacements. Eligible patients who are not candidates for conventional surgical valve replacement (defined as operative mortality or serious, irreversible morbidity ≥ 50 percent) will be randomly allocated to the Edwards SAPIEN THV or medical management (or balloon aortic valvuloplasty, as indicated).

Registries

Our systematic search of the published literature and our extensive search of the gray literature did not identify any ongoing or recently-closed-but-as-yet-unpublished registries of percutaneous heart valves. Information about the four registries summarized in Table 17 was provided by Edwards Lifesciencs, LLC. These four registries include patients with the Edwards SAPIEN THV in up to 30 sites in Europe. None appears to include patients in the United States.

Question 4. Variables that May Affect Outcomes for Percutaneous Heart Valves

The evidence derived from the 62 fully published reports identified by our search strategy that pertains to the 6 categories of variables identified above is summarized in the sections that follow. Because we did not identify any published reports that included primary data from human studies of percutaneous mitral valve replacement, this section of the report focuses exclusively on percutaneous AVR.

Prosthesis Characteristics

Five of the seven companies identified as percutaneous heart valve manufacturers are each represented by a single report in the published literature. Four of these are case reports,[98-100,102] and one is a case series involving 15 patients;[101] none of the five reports included a direct comparator. This is insufficient evidence to comment on potential relationships between the design or manufacturer of a valve and clinical outcomes for these devices.

In contrast, we identified 35 reports representing 412 patients and 22 reports representing 424 patients for the Edwards SAPIEN THV and the CoreValve ReValving System, respectively.

Implantation success and 30-day survival were 92 percent and 85 percent, respectively, for the Edwards SAPIEN THV (including its precursors, the Percutaneous Heart Valve and the Cribier-Edwards valve), and 89 percent and 87 percent, respectively, for the CoreValve ReValving System. These data do not support definitive conclusions regarding the possible superiority of one of these devices over the other. All of the included studies were either case reports or case series.

Given the absence of an experimental design or direct control group, comparisons across studies are limited by numerous confounding factors, including patient and operator characteristics, clinical indication for the procedure, treatment setting, and secular trends. The inability to distinguish between causative and confounding factors applies to all of the variables considered here that may theoretically impact clinical outcomes associated with percutaneous heart valve replacement.

Larger catheter sizes may limit patient eligibility due to insufficient iliac artery size; they are also associated with greater risk of vascular trauma to iliac or aortic arteries. The potential relationship between decreasing catheter size and improved clinical outcomes is illustrated by the study by Grube et al.,[80] which demonstrated an implantation survival rate of 92 percent and a 30-day survival rate of 89 percent with the smaller, third-generation of the CoreValve system compared with rates of 70 percent and 60 percent, respectively, with the larger, first-generation delivery system. It is possible, however, that the improved outcomes observed over time in the series of patients reported in this study are due to factors independent of the smaller catheter size, such as operator experience with the procedure or other variables that may have changed over time.

Although clearly important for approaches that involve cannulation of major vessels, the size of the delivery system catheter is theoretically less important for the transapical approach. There is also a theoretical advantage of devices that permit either post-deployment adjustment or intraoperative deployment of a second percutaneously delivered heart valve within a malpositioned prosthetic valve. The reports we reviewed were not designed to address either of these issues.

Implantation Approach

Six delivery or access approaches have been reported for percutaneous AVR: femoral vein, femoral artery, subclavian artery, axillary artery, ascending aorta, and directly through the wall of the left ventricle (transapical). The femoral vein approach offers the theoretical advantage of femoral venous rather than arterial access, potentially reducing complications related to injury to arterial vessels. In this approach, a catheter is introduced through the groin into the femoral vein, and then maneuvered to the right atrium and across the intra-atrial septum and mitral valve to reach the aortic valve. This approach carries the risk of residual atrial septal defect from the large delivery catheter required, as well as the risk of procedure-associated mitral regurgitation. In addition, the complexity of this technique prevented widespread adoption of the procedure, particularly with first-generation devices.

In current practice, the femoral vein approach has largely been replaced by the femoral artery approach, which allows a simpler route of delivery. In this approach, a catheter is introduced through the groin into the femoral and iliac arteries to the aorta and then to the aortic valve. Limitations of this approach include the large diameter of the delivery catheter that must be accommodated by the iliac artery, and the tortuosity and atherosclerosis of the aorta in many patients who have aortic stenosis. The femoral vein, femoral artery, subclavian artery, axillary

artery, and ascending aorta approaches all have risks associated with vessel cannulation, including vessel wall injury, and in the case of retrograde (i.e., arterial) approaches, thromboembolic complications related to traversing the aorta with a catheter.

Transapical AVR is a recently developed option for patients with unfavorable aortic or iliac artery anatomy for the transfemoral approach, and is performed by cardiac surgeons via a left thoracotomy incision. Compared with transfemoral approaches, transapical valve replacement has theoretical advantages associated with the straight-line approach to the aortic valve, including potentially reducing complications of aortic atheroembolic events, bleeding at the site of vascular access, and mitral valve damage. However, this technique carries the potential risks associated with surgical access and general anesthesia. Reported implantation success and 30-day survival rates are 89 percent and 89 percent, respectively, for the femoral artery approach, and 94 percent and 87 percent, respectively, for the transapical approach.

Treatment Setting

Percutaneous heart valve replacements have generally been performed in cardiac catheterization laboratory settings because of the availability of appropriate devices and fluoroscopic imaging equipment for the procedural aspects. To date, the majority of percutaneous valve implantations have occurred under general anesthesia, with the subsequent requirement that the catheterization laboratories used must allow for anesthesia equipment and personnel. Because the procedure involves implantation of a prosthetic device, the maintenance of a sterile setting is important to reduce the risk of infection.

The advent of percutaneous AVR via a transapical approach emphasizes the overlap between cardiac catheterization laboratory and operating suite settings for these procedures. This overlap has led to the development of "hybrid" catheterization laboratories developed and equipped to perform procedures traditionally done in operating suites. In addition to standard catheterization imaging equipment, these hybrid settings may involve ceiling-supported lighting equipment to provide higher lighting output, and heating, ventilation, and air conditioning systems to provide laminar flow diffusion of air typically found in operating suites.

Too few published reports identified by our literature reviewed reported sufficient detail about the treatment setting to determine whether this variable impacts outcomes associated with percutaneous valve replacement.

Operator Characteristics

The intersection of procedural elements described above may stimulate increased collaboration between cardiologists (including both interventional cardiologists and echocardiographers), cardiothoracic surgeons, and cardiac anesthesiologists. Although interventional cardiologists by training have greater experience with percutaneous transfemoral procedures and devices, cardiac surgeons are experienced with techniques necessary for transapical valve replacement, as well as possible repair for vascular access complications and cardiopulmonary bypass and ventricular support. Cross-specialty training may develop, with incorporation of simulation technology for endovascular training.

Too few published reports identified by our literature review reported sufficient detail about operator characteristics to determine whether this variable impacts outcomes associated with percutaneous valve replacement; however, some authors reported improved outcomes with increased operator experience with a given percutaneous heart valve replacement procedure.[59,80]

Type of Anesthesia

A theoretical advantage of approaches that involve cannulation of a vessel compared with either a transapical approach for percutaneous heart valve replacement or conventional aortic valve surgery is that the former can be administered using conscious sedation, as opposed to general anesthesia. The literature we reviewed did not provide sufficient evidence to comment on the independent risk contribution of general anesthesia vs. conscious sedation as they apply to percutaneous heart valve replacement.

Patient Characteristics

A patient's clinical status, coexisting medical conditions, and corresponding operative risk are all variables that significantly impact clinical outcomes for any surgical procedure.[116] With the sole exceptions of a 21-year-old woman with congenital heart disease with a pulmonic valve prosthesis,[100] and an 80 year-old man with mitral stenosis,[76] all of the patients in the published reports identified by our systematic literature search had symptomatic aortic stenosis with a correspondingly relatively high predicted operative mortality for conventional AVR by cardiac surgery with cardiopulmonary bypass, as measured by validated surgical risk models (either the logistic EuroSCORE or the Society of Thoracic Surgeons Predicted Risk of Mortality. The amount and quality of the published data, and the way the data are reported, render it difficult to identify any specific patient characteristics related to outcomes associated with PHV replacement. However, in case series, it is notable that actual 30-day mortality rates with PHV replacement were substantially lower than the expected perioperative mortality rates with major surgery, as predicted by the EuroSCORE.

The reports identified by our literature search did not provide sufficient evidence to determine which patient characteristics impact outcomes associated with percutaneous valve replacement. Factors associated with mortality in conventional valve surgery may be applicable to percutaneous valve replacement. These factors include age, functional status, cardiac factors, and medical comorbidity.[7,13-15]

Discussion

Summary of Findings

Conventional mechanical and bioprosthetic heart valves are readily available in the U.S. market. Tissue-engineered valves are in development, but none currently have an FDA indication. Important clinical issues in selecting a valve include the technical difficulty of valve replacement, valve durability, hemodynamic performance, complication rates, the need for anticoagulation, and effects on patient-important outcomes such as functional status and mortality. From a policy perspective, device costs, procedure costs, availability of specific valve types, and availability of experienced operators are additional considerations.

A large number of published RCTs and observational studies have evaluated the comparative effectiveness of conventional heart valves in adults. Existing systematic reviews compare mechanical with bioprosthetic valves in the aortic or mitral and tricuspid position, but all of these reviews have important methodological limitations that may bias results. A recent high-quality review compared stented with stentless bioprosthetic valves and found mixed short-term hemodynamic benefits for stentless valves, but with the tradeoff of longer cross-clamp and heart-lung bypass times.[35] Only one review compared two different stented bioprosthetic valves,[39] and we did not identify any systematic reviews comparing differing mechanical valves.

Systematic reviews that aim to compare valves are challenging. Surgical and anesthetic techniques have improved over time, potentially confounding comparisons across time periods. Valve designs have also changed over time, and those changes are not always reliably reflected by changes to valve names; moreover, valve names are not reported in a uniform manner, complicating accurate valve classification. Many currently marketed valves have not been evaluated in long-term RCTs, necessitating the incorporation of observational studies, which are more subject to bias.

Percutaneous heart valves have been developed and evaluated by at least seven companies. Some of these valves are approved for use in Europe, and most of the published literature originates from this region. The current literature consists of case series and case reports focusing almost exclusively on the Edwards SAPEIN THV valve and CoreValve ReValving Systems. The peer-reviewed literature describes just over 900 patients, assessed as being at high risk for conventional valve replacement, who have received these valves. This initial experience is promising. Rates of successful implantation are high, and 30-day survival is 86 percent and is lower than mortality predicted by the EuroSCORE. In lower risk patients, the perioperative mortality rate for surgical AVR is approximately 3 to 4 percent, increasing to 5.5 to 6.8 percent when combined with coronary artery bypass grafting.[8]

The first percutaneous heart valve replacement procedures were conducted by accessing the venous system via the femoral vein and passing a catheter through the septum of the heart to reach (and traverse) that aortic valve. This antegrade approach via the femoral vein now appears to have been replaced by one of two emerging approaches: (1) a retrograde approach via the femoral artery; or (2) a transapical approach via the apex of the heart. Three other retrograde approaches—via the subclavian or axillary artery or the ascending aorta—have also been reported. Unlike the antegrade approach via the femoral vein, retrograde approaches do not require perforating and traversing the cardiac septum but present important technical challenges, in large part because of the calcified and tortuous arteries that must be navigated with a relatively large catheter. In contrast, the more recently developed transapical approach obviates the need

for maneuvering a catheter through either arteries or veins, but it requires making an incision in the chest wall and traversing the myocardium.

All six percutaneous approaches reported in the published literature may require some additional training of cardiac surgeons or interventional cardiologists, as well as some modifications to existing catheter labs or operating suites. To date, few groups in the United States have significant experience with percutaneous heart valve replacement. Although the initial experience demonstrates that percutaneous heart valves can be implanted with good short-term success, longer term survival, valve durability, and complication rates are unknown. Even comparison of short-term success to historical controls is problematic because predicted mortality is based on imperfect risk prediction models that were developed for other cardiac surgeries. A further limitation of the extant literature is the subjective nature of patient selection as "too high risk for surgery," making appropriate patient selection less certain. The ongoing PARTNER clinical trial that compares percutaneous heart valves with conventional valves will be critical in comparing the relative safety and efficacy of these technologies.[33]

Future Research

The long-term durability of mechanical heart valves is well established and has been shown to be superior to that of early generation bioprosthetic valves. Newer generation bioprosthetic valves are purported to have improved durability. Since bioprosthetic valves do not require chronic anticoagulation, durability is a critical issue in determining at what age to recommend them instead of mechanical valves. An updated, high-quality systematic review could address this issue. An updated review may also be able to evaluate specific valves within each class, including currently marketed newer vs. older valves, and valves with different design features (e.g., mechanical bileaflet vs. tilting disc). Because the number of direct comparisons is limited for many valves and some valve classes, indirect comparisons using network meta-analysis may be useful. A recent observational study using Medicare Claims data found that bioprosthetic valves were associated with a slightly lower risk of death and complications, but a higher risk of reoperation in older adults undergoing isolated AVR.[41] Claims data provide limited information for case-mix adjustment. Recognizing that RCTs are not practical for all comparisons, an observational study utilizing claims data coupled with clinical databases could improve case-mix adjustment and estimates of comparative effectiveness.

For percutaneous heart valves, the potential research agenda is broad. What are the complication rates, durability, and effects on mortality and health-related quality of life? How do these valves compare with conventional valve replacement in lower risk patients? Which procedural and setting factors, including procedural volume, are related to clinical outcomes? How does PHV replacement impact quality of life? How do discharge rates to extended care facilities, rates of rehospitalization after valve placement, and changes in functional status compare to other treatment options? In which patient populations are percutaneous heart valves indicated? The ongoing PARTNER trial will address the efficacy of percutaneous heart valves compared with medical treatment in high-risk patients, and their efficacy compared with conventional valves in patients at the higher range of acceptable risk for surgical replacement.[33]

If percutaneous heart valves become FDA approved, a prospective registry to track the specific devices implanted and the clinical characteristics of recipients could be linked to Medicare claims data for subsequent analysis.

We identified specific opportunities for improved reporting that would facilitate comparative effectiveness studies. Standardized reporting of methods and outcomes of

percutaneous heart valve replacement is especially important in light of the evolution of this technology. At least six different approaches have been reported to date. Detailed reporting of technical factors that may be associated with outcomes—such as details of the implantation approach and characteristics of the operators—would allow for retrospective analysis. Future research could also provide data on the relative costs associated with PHV procedures.

Selection of heart valves involves a number of trade-offs. From the surgeon's perspective, some valves require greater technical expertise and operating times. From the patient's perspective, valve durability and the related risk for reoperation, complication rates, and the need for chronic anticoagulation are all pertinent considerations. From the policymaker's perspective, valve prosthesis costs, costs over the life of the valve (including anticoagulation monitoring for mechanical valves), and access to competing valve replacement options may be relevant considerations. Percutaneous heart valves, if FDA approved, will introduce a new option for patients who are currently deemed too high risk for conventional valve replacement. Because these patients have multiple competing risks for mortality, the effects on all-cause mortality and health-related quality of life are uncertain. From a societal perspective, the introduction of percutaneous valves may require investment in clinician training, redesign of procedural suites, and direct costs for heart valve replacement in a population previously not eligible. If percutaneous valves are proved effective in high-risk patients, a further consideration is whether to extend this procedure to lower risk patients because of its potential for lower morbidity and lower costs. Complex clinical, reimbursement policy, and regulatory questions such as these could be addressed in part by decision modeling. For example, decision modeling could simultaneously consider the effects of patient populations (e.g., age, comorbid conditions), valve characteristics (e.g., durability), clinical issues (e.g., other indications for anticoagulation), valve-specific complication rates (e.g., major bleeding), costs, and patient preferences on survival and health-related quality of life.

Conclusions

Because the U.S. population is aging and aortic and mitral valve disease is age-related, heart valve replacement is an important issue both clinically and from the perspective of healthcare policy. Conventional heart valve replacement is a well-established intervention with many available device options, and current evidence suggests similar outcomes with mechanical and bioprosthetic valves. However, current evidence syntheses do not provide sufficient evidence to select specific valves within each of these categories.

Many older adults are not currently candidates for conventional heart valve replacement, or may be candidates for heart valve replacement, but are at especially high risk for complications associated with open-heart surgery. Percutaneous valve replacement has been demonstrated to be feasible for aortic stenosis, and short-term outcomes are promising. Several companies are developing these valves, and the reported clinical experience is increasing rapidly. Percutaneous valves have the potential to expand access to valve replacement for a large group of older adults with severe valve disease and concurrent medical conditions that currently preclude surgery. Percutaneous valves also have the potential to substitute for some conventional valve replacements and expand the indications for valve replacements. However, existing data are inadequate to determine the most appropriate clinical role for these valves or the specific patient populations for whom these valves might eventually be indicated. Many unanswered questions remain pertaining to the effects—intended or unintended—of expanding the clinical

indication for percutaneous heart valve replacement to groups of patients in whom this treatment modality has not yet been evaluated.

Decision modeling, coupled with high-quality systematic reviews, could inform clinical and policy decisions in the near future. Findings from the ongoing PARTNER clinical trial[33] should yield important efficacy data when they become available. Over the longer term, device registries could be established for the purpose of evaluating comparative effectiveness since randomized trials may not be feasible for some clinically important questions.

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Acronyms and Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AVR	Aortic valve replacement
CABG	Coronary artery bypass graft
CI	Confidence interval
EOA	Effective orifice area
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
LV	Left ventricular
OR	Odds ratio
PARTNER	Placement of AoRTic TraNscathetER trial
PHV	Percutaneous heart valve
QUOROM	Quality Of Reporting Of Meta-analyses
RCT	Randomized controlled trial
RR	Relative risk
SRC	Scientific Resource Center
WMD	Weighted mean difference

Table 1. Percutaneous heart valves—gray literature sources, search terms, and results (last search date December 31, 2008)

Source	Search Term(s)	Restrictions	Number of Citations Identified	Number of Eligible Studies
General gray literature sources				
Google Scholar (http://scholar.google.com) Advanced Scholar Search: http://scholar.google.com/advanced_scholar_search?hl=en&lr=	All of the words: "percutaneous," "heart," and "valve"	• In the title of the article • In the "Medicine, Pharmacology, and Veterinary Science" subject area • Published 2003-2008	56	0
CRISP (Computer Retrieval of Information on Scientific Projects; http://crisp.cit.nih.gov/) Query Form: http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen	"percutaneous" AND "valve"	• All award types • All IRGs • All institutes and centers • Fiscal years 2003-2008	12	0
The New York Academy of Medicine Grey Literature Report (http://www.nyam.org/library/pages/grey_literature_report) Search under "Search the Grey Literature Collection"	Subject Keyword "heart valve" anywhere in text or title	None	37	0
OAIster (University of Michigan—collection of free, otherwise difficult-to-access resources from 327 institutions; http://www.oaister.org) Search page (http://quod.lib.umich.edu/cgi/b/bib/bib-idx?c=oaister;page=simple)	"percutaneous" AND "heart" AND "valve"	None	58	0
NICHSR (National Library of Medicine, National Information Center of Health Services Research and Health Care Technology (http://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm)	"percutaneous"	None	15	0
WHO Publications (http://www.who.int/publications/en)	"percutaneous heart valve"	None	69	0
Abstracts from scientific meetings				
American Heart Association (AHA; http://scientificsessions.americanheart.org/portal/scientificsessions/ss/); Advanced Search: http://circ.ahajournals.org/search.dtl	All of the words: "percutaneous," "heart," and "valve"	• In title or abstract • Include AHA Scientific Sessions Abstracts • 2003-2008	30	1
American Cardiology Association (ACC; http://www.acc.org/) Search page: http://content.onlinejacc.org/search.dtl	All of the words: "percutaneous," "heart," and "valve"	• In title or abstract • All JACC journals 2003-2008	10	0
Transcatheter Cardiovascular Therapeutics (TCT) Abstracts 2008 meeting Search page: http://www.aievolution.com/tct0801	"percutaneous heart valve"	All abstract categories	0	0
	"percutaneous" "transapical" "transcatheter"	All abstract categories	211 (percuta-neous) 3 (transapical) 15 (trans-catheter)	7

Table 1. Percutaneous heart valves—gray literature sources, search terms, and results (last search date December 31, 2008) (continued)

Source	Search Term(s)	Restrictions	Number of Citations Identified	Number of Eligible Studies
European Society of Cardiology (ESC) http://www.escardio.org/Pages/index.aspx) Search page: http://spo.escardio.org/abstract-book/topic.aspx	Browsed "surgery and intervention in valve disease" topic	ESC Congress 2007 or ESC Congress 2008	13 (2007) 16 (2008)	1 (2 abstracts)
American Association of Thoracic Surgery (AATS) http://www.aats.org/multimedia/files/AnnualMeeting/2008/AATS08-Final-Program.pdf	Browsed (not possible to search using keywords/subject terms)	AATS Annual Meetings 2007 and 2008	NA	2
Society of Thoracic Surgeons (STS) http://www.sts.org	"transcatheter" "percutaneous" "transapical"	STS Annual Meeting 2008	NA	0
Ongoing trials				
ClinicalTrials.gov (http://www.clinicaltrials.gov) Basic Search: http://www.clinicaltrials.gov/ct2/search	(percutaneous OR transapical) AND (heart OR valve)	None	17	4

Abbreviations: IRGs = institutional research grants; JACC = Journal of the American College of Cardiology.

Table 2. Requests for Scientific Information Packets and responses from companies

Company	Response
Cardiac Dimensions	Telephone response on 5 August 2008—nothing to submit
CoreValve, Inc.	No response
Direct Flow Medical, Inc.	No response
Edwards Lifesciences, LLC	Hardcopy Scientific Information Packet received 16 September 2008
Endoluminal	Unable to contact; no contact information available from any source, may no longer be a company
Endovalve	No response
Evalve, Inc.	E-mail dated 7 August 2008—nothing to submit
Hansen Medical	E-mail dated 6 August 2008—nothing to submit
JenaValve Technology, Inc.	No response
Medtronic, Inc.	E-mail dated 29 August 2008—nothing to submit
MiCardia	E-mail dated 5 August 2008—nothing to submit
Mitralign, Inc.	No response
Myocor, Inc.	No response
Sadra Medical	No response
Viacor, Inc.	E-mail dated 5 August 2008—nothing to submit

Table 3. Variables potentially associated with outcomes for percutaneous heart valves

Prosthesis Characteristics:
- Valve design
- Valve size
- Catheter size
- Deployment
- Post-deployment adjustment

Implantation Approach:
- Transfemoral antegrade
- Transfemoral retrograde
- Transapical

Treatment Setting:
- Surgical operating room
- Cardiac catheterization suite
- Cardiac catheterization suite enhanced with operating room features ("hybrid" setting)

Operator Characteristics:
- Medical or surgical specialty
- Experience

Type of Anesthesia:
- General anesthesia
- Conscious sedation

Patient Characteristics:
- Medical conditions and comorbidities
- Operative risk
- Indication for the procedure

Table 4. Conventional heart valves in use or in development

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
Mechanical valves					
Alliance Medical Technologies	Monostrut Cardiac Valve Prosthesis	Unknown	Tilting disc	Yes (FDA)	No longer marketed (FDA)
AorTech	Ultracor	Aortic	Tilting disc	Unable to determine	
ATS Medical, Inc.	Bioflow	Unknown	Unknown	Unable to determine	
ATS Medical, Inc.	Open Pivot Bileaflet Heart Valve	Mitral & aortic	Bileaflet	Yes (FDA)	
Bjork-Shiley	Convex/Concave	Unknown	Tilting disc	Unable to determine	
Bjork-Shiley	Low Profile	Unknown	Tilting disc	Unable to determine	
Bjork-Shiley	Monostrut	Mitral & aortic	Tilting disc	Yes (non-FDA)	No longer marketed (non-FDA)
CarboMedics, Inc.	CarboMedics Prosthetic Heart Valve	Unknown	Bileaflet	Yes (FDA)	
CarboMedics, Inc.	CarboMedics Valve	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Carbo-Seal Ascending	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Carbo-Seal Valsalva	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Optiform	Mitral	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Orbis Universal	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Pediatric/Small Adult	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Reduced Series Aortic	Aortic	Bileaflet	Yes (non-FDA)	

Table 4. Conventional heart valves in use or in development (continued)

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
CarboMedics, Inc.	Standard Valve	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
CarboMedics, Inc.	Top Hat Supra-Annular	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the CarboMedics Prosthetic Heart Valve has FDA indication, but does not specify which models.
Direct Flow Medical, Inc.	Web site under construction—no information	Unknown	Unknown	Unable to determine	
Edwards Lifesciences, LLC	Edwards Duromedics	Mitral & aortic	Bileaflet	Unable to determine	No longer marketed (non-FDA)
Edwards Lifesciences, LLC	Edwards MIRA Mechanical	Mitral & aortic	Bileaflet	Unable to determine	
Edwards Lifesciences, LLC	Starr-Edwards Silastic Ball Heart Valve Prosthesis	Mitral	Caged-ball	Yes (FDA)	No longer marketed (non-FDA)
Edwards Lifesciences, LLC	Tekna	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Lillehei-Kaster	Lillehei-Kaster Heart Valve	Mitral & aortic	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Lillehei-Kaster	Low Profile	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
MedicalCV	Omnicarbon Cardiac Valve Prosthesis	Aortic	Tilting disc	Yes (FDA)	No longer marketed (FDA)
MedicalCV	Omniscience Cardiac Valve Prosthesis	Aortic	Tilting disc	Yes (FDA)	No longer marketed (FDA)
Medtronic, Inc.	Advantage Supra Bileaflet	Aortic	Bileaflet	Unable to determine	
Medtronic, Inc.	Medtronic-Hall Prosthetic Mechanical Heart Valve	Mitral & aortic	Tilting disc	Yes (FDA)	
On-X Life Technologies, Inc.	On-X Prosthetic Heart Valve	Aortic	Bileaflet	Yes (FDA)	
Sorin Biomedica Cardio	Allcarbon	Mitral & aortic	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Bicarbon Family	Mitral & aortic	Bileaflet	Unable to determine	
Sorin Biomedica Cardio	Carbocast	Mitral	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Monocast	Mitral & aortic	Tilting disc	Unable to determine	

Table 4. Conventional heart valves in use or in development (continued)

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
Sorin Biomedica Cardio	Monodisk	Mitral & aortic	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Slimline	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	High Performance	Unknown	Unknown	Unable to determine	
St. Jude Medical	St. Jude Medical Coated Aortic Valved Graft Prosthesis	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters HP Valved Graft with Gelweave Valsalva Technology	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Mechanical Heart Valve with Silzone Coating	Mitral & aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Series Aortic Valved Graft	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Series Hemodynamic Plus Valve with FlexCuff Sewing Ring	Aortic	Bileaflet	Unable to determine	No longer marketed (non-FDA)
St. Jude Medical	St. Jude Medical Masters Series Mechanical Heart Valve	Mitral & aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Valved Graft with Hemashield Technology	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Mechanical Heart Valve	Mitral & aortic	Bileaflet	Yes (FDA)	
St. Jude Medical	St. Jude Medical Mechanical Valve Hemodynamic Plus Series	Mitral & aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Regent Valve	Aortic	Bileaflet	Yes (non-FDA)	
St. Jude Medical	St. Jude Medical Regent Valve with Silzone Coating	Aortic	Bileaflet	Unable to determine	No longer marketed (non-FDA)
Unknown	Debakey	Unknown	Unknown	Unable to determine	
Unknown	Hall-Kaster	Unknown	Unknown	Unable to determine	

Table 4. Conventional heart valves in use or in development (continued)

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
Unknown	Harken	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Unknown	Smelloff-Cutter	Unknown	Unknown	Unable to determine	
Bioprosthetic valves					
ATS Medical, Inc.	ATS 3F Aortic Bioprosthesis, Model 1000	Aortic	Equine	Yes (FDA)	
Biocor	Biocor	Unknown	Porcine	Unable to determine	Stentless (non-FDA)
Bioflo	Unknown	Unknown	Bovine	Yes (non-FDA)	No longer marketed (non-FDA)
CarboMedics, Inc.	Mitroflow Aortic Pericardial Heart Valve	Aortic	Bovine	Yes (FDA)	
Cryolife	O'Brien Model 300	Aortic	Porcine	Unable to determine	Stentless (non-FDA)
Cryolife	SynerGraft Pulmonary Valve and Valved-Conduit Allograft	Pulmonary	Human	(Cleared, not approved)	Decellularized (non-FDA)
Edwards Lifesciences, LLC	Carpentier-Edwards Bioprosthesis	Aortic & mitral	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Duraflex Low Pressure Bioprosthesis	Mitral	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Magna Pericardial Bioprosthesis	Mitral & aortic	Bovine	Yes (non-FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Pericardial Bioprosthesis	Aortic & mitral	Bovine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Plus Pericardial Bioprosthesis	Mitral & aortic	Bovine	Yes (FDA)	Stented (non-FDA)
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount RSR Pericardial Bioprosthesis	Aortic	Bovine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Theon	Mitral & aortic	Bovine	Unable to determine	
Edwards Lifesciences, LLC	Carpentier-Edwards Supra-Annular Valve (SAV) Bioprosthesis	Mitral, aortic, & tricuspid	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Edwards Prima Plus Stentless Bioprosthesis	Aortic	Porcine	Yes (FDA)	

Table 4. Conventional heart valves in use or in development (continued)

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
Edwards Lifesciences, LLC	Prima Stentless Bioprosthesis (Subcoronary), Model 2500	Aortic	Porcine	Yes (FDA)	No longer marketed (FDA)
Medtronic, Inc	Medtronic Contegra Pulmonary Valved Conduit (Models 200 and 200S)	Pulmonary	Bovine	Yes (FDA)	FDA approved for use as humanitarian use devices under HDEs (FDA).
Medtronic, Inc.	Freestyle Aortic Root Bioprosthesis	Aortic	Porcine	Yes (FDA)	Stentless (non-FDA)
Medtronic, Inc.	Intact	Aortic	Porcine	Unable to determine	
Medtronic, Inc.	Medtronic Hancock I (Standard) Porcine Bioprosthesis	Mitral	Porcine	Yes (FDA)	
Medtronic, Inc.	Medtronic Hancock II Bioprosthetic Heart Valve	Mitral & aortic	Porcine	Yes (FDA)	Stented (non-FDA)
Medtronic, Inc.	Medtronic Hancock Modified Orifice (MO) Porcine Bioprosthesis	Aortic	Porcine	Yes (FDA)	
Medtronic, Inc.	Medtronic Mosaic Porcine Bioprosthesis	Mitral & aortic	Porcine	Yes (FDA)	Stented (non-FDA)
Shelhigh	Biomitral	Mitral	Porcine	Unable to determine	
Shelhigh	Injectable Pulmonic Valve System	Apical approach pulmonic	Bovine	Unable to determine	
Shelhigh	NR2000 Plus SemiStented	Aortic	Porcine	Unable to determine	
Shelhigh	NR2000 Super Stentless	Aortic	Porcine	Unable to determine	
Shelhigh	NR900A	Tricuspid	Porcine	Unable to determine	
Shelhigh	Pulmonic Valve Conduit, No-React Treated, Model NR-4000 Series	Pulmonary	Bovine & porcine	Yes (FDA)	FDA approved for use as humanitarian use devices under HDEs (FDA).
Sorin Biomedica Cardio	Pericarbon Freedom Solo	Aortic	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Pericarbon Freedom Stentless	Aortic	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Pericarbon More	Aortic & mitral	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Soprano	Aortic	Bovine pericardium	Unable to determine	

Table 4. Conventional heart valves in use or in development (continued)

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?†	Notes‡
St. Jude Medical	St. Jude Medical Biocor Porcine Stentless Bioprosthetic Heart Valve	Aortic	Porcine	Unable to determine	
St. Jude Medical	St. Jude Medical Biocor Valve and Biocor Supra Valve	Mitral & aortic	Porcine	Yes (FDA)	
St. Jude Medical	St. Jude Medical Epic Tissue Valve with Silzone Coating	Mitral & aortic	Porcine	Unable to determine	No longer marketed (non-FDA)
St. Jude Medical	St. Jude Medical Epic Valve and Epic Supra Valve	Aortic	Porcine	Yes (FDA)	Stented (non-FDA)
St. Jude Medical	St. Jude Medical Toronto SPV Valve (Stentless Porcine Aortic), Model SPA-101	Aortic	Porcine	Yes (FDA)	
Unknown	Ionescu-Shiley	Unknown	Bovine	Unable to determine	Stented (non-FDA)
Wessex Medical	Wessex	Unknown	Porcine	Unable to determine	Stented (non-FDA)

* Valve type for mechanical valves is either Caged-ball, Tilting disc, Bileaflet, or Unknown; and for bioprosthetic valves either Bovine, Equine, Porcine, Human, or Unknown.
† FDA indication column identifies the source of the FDA status as determined by the FDA (FDA) or a non-FDA source (non-FDA), or as Unable to determine.
‡ Notes column indicates the source of the note as determined by an FDA source (FDA) or a non-FDA source (non-FDA).
Abbreviations: FDA = U.S. Food and Drug Administration; HDE = humanitarian device exemptions.

Table 5. Percutaneous heart valves in use or in development

Company	Valve Name	Valve Position	Valve Type*	FDA Indication?
CoreValve, Inc.	CoreValve ReValving System	Aortic	Porcine	No
Direct Flow Medical, Inc.	Direct Flow Medical Valve	Aortic	Equine	No
Edwards Lifesciences, LLC	Edwards SAPIEN, SAPIEN XT, Cribier Edwards & Percutaneous Heart Valve Technologies	Aortic	Equine	No
Medtronic, Inc.	Melody Valve	Aortic	Bovine	No
Sadra Medical	Lotus Valve	Aortic	Bovine	No
Unknown	Paniagua Heart Valve	Aortic	Unknown	No

*Valve type for percutaneous valves is either Bovine, Equine, Porcine, Human, or Unknown.
Abbreviation: FDA = U.S. Food and Drug Administration.

Table 6. Characteristics of included systematic reviews comparing various conventional heart valves

Review	Included Study Designs	Numbers of Studies and Subjects	Valve Comparison	Main Outcomes Reported
Kassai et al., 2000[34]	RCT	2 studies 1011 subjects	Aortic and/or mitral: Mechanical vs. bioprosthetic	Mortality, reoperation, bleeding
Kunadian et al., 2007[35]	RCT	11 studies 919 subjects	Aortic: Stented vs. non-stented bioprosthetic	Left ventricular mass regression, surgical procedure times
Lund and Bland, 2006[36]	Observational	38 studies 17,439 subjects	Aortic: Mechanical vs. bioprosthetic	Mortality
Puvimanasinghe et al., 2004[37] and Puvimanasinghe et al., 2003[38]	Observational	22 studies 13,281 subjects	Aortic: St. Jude mechanical vs. porcine bioprosthetic	Life expectancy, thrombotic and bleeding complications
Puvimanasinghe et al., 2006[39]	Observational	13 studies 6481 subjects	Aortic: Carpentier-Edwards pericardial aortic vs. Carpentier-Edwards supra-annular bioprosthetic	Life expectancy, thrombotic and bleeding complications
Rizzoli et al., 2004[40]	Observational	11 studies 1160 subjects	Tricuspid: Bioprosthetic vs. mechanical valves	Survival, reoperation

Abbreviation: RCT = randomized controlled trial.

Table 7. Types of valves compared in the aortic position—randomized controlled trials*

	Homograft	Autograft	Mechanical	BP: Stented	BP: Stentless
Homograft	0	3	0	1	3
Autograft	-	0	1	0	0
Mechanical	-	-	12	2	2
BP-stented	-	-	-	7	15
BP-stentless	-	-	-	-	1

*Number of studies is given for each comparison. The total number of comparisons exceeds the number of studies because some studies included more than one comparison.
Abbreviation: BP = bioprosthetic.

Table 8. Conventional valves evaluated in randomized controlled trials

Mechanical	Bioprosthetic: Stented	Bioprosthetic: Stentless
AorTech Ultracor ATS Medical Bioflow Bjork-Shiley Monostrut* Bjork-Shiley Low Profile* Bjork-Shiley Convex/Concave* CarboMedics (unspecified) CarboMedics Reduced bileaflet Edwards Duromedics Edwards Mira Lillehei-Kaster* Lillehei-Kaster Low Profile* OnX Medtronic Hall Medtronic Advantage Supra Sorin Slimline St. Jude Hemodynamic Plus St. Jude High Performance St. Jude Regent St. Jude Silzone* Starr Edwards	Carpentier-Edwards Pericardial Carpentier-Edwards Perimount Carpentier-Edwards Perimount Magna Medtronic Hall Hancock II Medtronic Mosaic Hancock standard* Sorin More	Carpentier Edwards Prima Plus Cryolife O'Brien Model 300* Medtronic Freestyle Sorin Freedom Biocor St. Jude Toronto

*No longer commercially available.

Table 9. Number of randomized controlled trials reporting various outcomes

Outcomes	Aortic (n = 43)	Aortic/Mitral (n = 11)	Mitral (n = 3)
Mortality	33	9	3
Clinical	22	7	3
Hemodynamic	39	2	2
Cardiac function	36	1	1
Reoperation	12	9	3
Adverse effects	29	10	3

Table 10. Types of valves compared in the aortic and/or other position*

	Homograft	Autograft	Mechanical	BP: Stented	BP: Stentless	BP: Mixed
Homograft	0	0	0	2	0	0
Autograft	-	0	0	0	0	0
Mechanical	-	-	3	7	0	1
BP-stented	-	-	-	5	7	0
BP-stentless	-	-	-	-	1	0
BP-mixed	-	-	-	-	-	0

*Number of studies is given for each comparison. Two studies that did not specify the type of bioprosthetic valve (stented vs. stentless) are omitted.[41,117] The total number of comparisons exceeds the number of studies because some studies made more than one comparison.

Abbreviation: BP = bioprosthetic.

Table 11. Conventional valves evaluated in observational studies

Mechanical	Bioprosthetic: Stented	Bioprosthetic: Stentless
AorTech Ultracor	Biocor porcine	Carpentier Edwards Prima
ATS Medical Bioflow	Carpentier-Edwards Perimount	Medtronic Freestyle
Bjork-Shiley Monostrut*	Carpentier-Edwards porcine	Shelhigh Super stentless
CarboMedics (unspecified)	Hancock Standard*	St. Jude Toronto
Debakey	Ionescu-Shiley bovine	
Edwards Duromedics	Medtronic Intact	
Edwards Tekna	Medtronic Mosaic	
Hall-Kaster	Mitroflow	
Harken	Sorin Pericarbon	
OnX	Wessex Medical porcine	
Medtronic Hall		
Omniscience		
Smelloff-Cutter		
Sorin Allcarbon		
Sorin Bicarbon		
Sorin Carbocast		
Sorin Monocast		
Sorin Monodisc		
St. Jude Medical		
St. Jude High Performance		
St. Jude Regent		
Starr Edwards*		

*No longer commercially available.

Table 12. Number of observational studies reporting various outcomes*

Outcomes	Aortic/Other (n = 27)	Tricuspid (n = 10)	Mitral (n = 2)
Mortality	22	10	1
Clinical	5	3	0
Hemodynamic	9	0	0
Cardiac function	9	0	0
Reoperation	17	8	1
Adverse effects	19	8	2

*One study that did not specify valve position is omitted.[118]

Table 13. Summary of published studies of percutaneous heart valve implantation

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Edwards Lifesciences, LLC								
Cribier et al., 2004[44] Eltchaninoff et al., 2002[43] Cribier et al., 2002[42]	Percutaneous Heart Valve	6 1 (0) 1 (0)	3	Aortic stenosis	5/6 (83%)	Femoral vein	24 Fr	3/6 (50%)
Bauer et al., 2004[45]	Percutaneous Heart Valve	8	1	Aortic stenosis	8/8 (100%)	Femoral vein (n = 6) Femoral artery (n = 2)	NR	5/8 (63%)
Hanzel et al., 2005[46]	Percutaneous Heart Valve	1	5 days	Aortic stenosis	1/1 (100%)	Aborted femoral vein to femoral artery	24 Fr	NR
Cribier et al., 2006[47]	Percutaneous Heart Valve	36 (34)[a]	26	Aortic stenosis	27/36 (75%)	Femoral vein (n = 24) Femoral artery (n = 7) Aborted femoral artery to femoral vein (n = 1) Aborted procedures (n = 1) Death prior to procedure (n = 1)	NR	21/36 (58%)
Chandavimol et al., 2006[48]	Percutaneous Heart Valve	1	12	Aortic stenosis	1/1 (100%)	Femoral artery	24 Fr	1/1 (100%)
Webb et al., 2007[49] Webb et al., 2006[50] Clavel et al., 2009[51] Gutierrez et al., 2009[52]	Cribier Edwards Cribier Cribier Edwards or Edwards SAPIEN Edwards-SAPIEN	50 18 (0) 50 (0) 33 (0)	12 12 1	Aortic stenosis	43/50 (86%)	Femoral artery	NR	44/50 (88%)
Lichtenstein et al., 2006[53] Ye et al., 2007[54]	Cribier-Edwards Cribier-Edwards	7 7 (0)	6	Aortic stenosis	7/7 (100%)	Transapical	NA	6/7 (86%)
Walther et al., 2008[55] Walther et al., 2007[56]	Edwards SAPIEN THV Cribier-Edwards	59 30 (0)[b]	3	Aortic stenosis	55/59 (93%)	Transapical	NA	51/59 (86%)

Table 13. Summary of published studies of percutaneous heart valve implantation (continued)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Walther et al., 2008[57]	Edwards SAPIEN THV	50 (20)[b]	18	Aortic stenosis	50/50 (100%)	Transapical	NA	46/50 (92%)
Zierer et al., 2008[58]	Edwards SAPIEN THV	26	1	Aortic stenosis	25/26 (96%)	Transapical	NA	22/26 (85%)
Svensson et al., 2008[59]	Edwards	40	11	Aortic stenosis	35/40 (88%)	Transapical	NA	33/40 (83%)
Rodes-Cabau et al., 2008[60]	Edwards-Sapien	22	> 6	Aortic stenosis	21/23 (91%) (2 procedures in 1 patient)	Femoral artery (n = 10) Transapical (n = 11) Aborted femoral artery to femoral vein (n = 1)	24 Fr (n = 10) 22 Fr (n = 12)	20/22 (91%)
Al-Attar et al., 2009[61]	Edwards SAPIEN THV	1	3	Aortic stenosis	1/1 (100%)	Transapical	NR	1/1 (100%)
Clavel et al., 2009[62]	Edwards SAPIEN	1	0	Aortic Stenosis	1/2 (50%) (2 procedures in 1 patient)	Transapical	NR	0/1 (0%)
Dvir et al., 2009[63]	Edwards SAPIEN	1	4	Aortic Stenosis	1/1 (100%)	Femoral artery	24 Fr	1/1 (100%)
Klaaborg et al., 2009[64]	Edwards SAPIEN THV	1	0	Aortic Stenosis	1/1 (100%)	Transapical	26 Fr	NR
Moreno et al., 2009[65]	Edwards SAPIEN	1	0	Aortic Stenosis	1/1 (100%)	NR	NR	0/1 (0%)
Wendt et al., 2009[66]	Edwards SAPIEN	1	1	Aortic Stenosis	1/1 (100%)	Transapical	NR	1/1 (100%)
Wong et al., 2009[67]	Edwards SAPIEN	1	1	Aortic Stenosis	1/1 (100%)	NR	NR	1/1 (100%)
Ye et al., 2009[68]	Edwards SAPIEN	1	16	Aortic Stenosis	1/2 (50%) (2 procedures in 1 patient)	Transapical	NR	1/1 (100%)
Ng et al., 2009[69]	Edwards-Sapien	1	1	Aortic Stenosis	1/1 (100%)	Transapical	NR	1/1 (100%)
Himbert et al., 2009[70]	Edwards-SAPIEN	75	10	Aortic Stenosis	Femoral artery: 46/51 (90%) Transapical 24/24 (100%)	Femoral artery (n = 51) Transapical (n = 24)	NR	Femoral artery: 47/51 (92%) Transapical: 22/24 (92%)
Webb et al., 2009[71]	SAPIEN SAPIEN XT	22 3	1	Aortic Stenosis	25/25 (100%)	Femoral artery	22/24 Fr	25/25 (100%)

Table 13. Summary of published studies of percutaneous heart valve implantation (continued)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Chiam et al, 2009[72]	Sapien THV	1	1	Aortic Stenosis	1/1 (100%)	Femoral artery	22 Fr	1/1 (100%)
Dumonteil et al., 2009[73]	Edwards Sapien	1	1	Aortic Stenosis	1/1 (100%)	Femoral artery	NR	1/1 (100%)
Bleiziffer et al., 2009[74] NOTE: reports on both Edwards and CoreValve	Edwards-Sapien	25	6	Aortic Stenosis	NR by device	Femoral artery (n = 4) Transapical (n = 21)	22/24 Fr NR	NR by device
Kolettis et al., 2009[75]	23 mm pericardial stented xenograft prosthesis	1	0	Aortic stenosis	1/1 (100%)	Transapical	NR	NR
Cheung et al., 2009[76]	Cribier Edwards 9000MIS	1	1	Mitral stenosis	1/1 (100%)	Transapical	33 Fr	1/1 (100%)
Totals: Edwards Lifesciences, LLC		**584 (412)**			**386/422[c] (92%)**	**Femoral vein (n = 36) Femoral artery (n = 153) Transapical (n = 216) Aborted femoral vein to femoral artery (n = 1) Aborted femoral artery to femoral vein (n = 2) Aborted procedure (n = 1) Not reported (n = 2) Death prior to procedure (n = 1)**		**355/416[d] (85%)**
CoreValve ReValving System								
Grube et al., 2005[77]	CoreValve Revalving System	1	0.5	Aortic stenosis	1/1 (100%)	Femoral artery	25 Fr	NR
Grube et al., 2006[78]	CoreValve Revalving System	25	12	Aortic stenosis	22/25 (88%)	Femoral artery	24 Fr (n = 10) 21 Fr (n = 15)	20/25 (80%)

Table 13. Summary of published studies of percutaneous heart valve implantation (continued)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Grube et al., 2007[79]	CoreValve Revalving System	86 (76)[e]	> 1	Aortic stenosis	76/86 (88%)	Femoral artery	21 Fr (n = 50) 18 Fr (n = 36)	76/86 (88%)
Grube et al., 2008[80]	CoreValve Revalving System	136 (122)[e]	> 12	Aortic stenosis	Generation 1: 7/10 (70%) Generation 2: 17/24 (71%) Generation 3: 93/102 (92%)	Femoral artery	25 Fr (n = 10) 21 Fr (n = 24) 18 Fr (n = 102)	Generation 1: 6/10 (60%) Generation 2: 22/24 (92%) Generation 3: 91/102 (89%)
Marcheix et al., 2007[81]	CoreValve Revalving System	10	1	Aortic stenosis	10/10 (100%)	Femoral artery	21 Fr	7/10 (70%)
Berry et al., 2007[82] Berry et al., 2007[83]	CoreValve Revalving System	13 1 (0)	10	Aortic stenosis	11/13 (85%)	Femoral artery	21 Fr	11/13 (85%)
Lamarche et al., 2007[84]	CoreValve Revalving System	1	3	Aortic stenosis	1/1 (100%)	Femoral artery	21 Fr	1/1 (100%)
Lange et al., 2007[85]	CoreValve Revalving System	1	10 days	Aortic stenosis	1/1 (100%)	Transapical	NA	NR
Wenaweser et al., 2007[86]	CoreValve Revalving System	1	12	Aortic stenosis	1/1 (100%)	Femoral artery	21 Fr	1/1 (100%)
Ruiz et al., 2008[87]	CoreValve Revalving System	1	12	Aortic stenosis	1/1 (100%)	Femoral artery	25 Fr	1/1(100%)
Bojara et al., 2009[88]	CoreValve Revalving System	1	1	Aortic stenosis	1/1 (100%)	Subclavian artery	18 Fr	1/1(100%)
Geist et al., 2009[89]	CoreValve Revalving System	1	3	Aortic stenosis	1/1 (100%)	NR	18 Fr	1/1(100%)
Piazza et al., 2009[90]	CoreValve Revalving System	5	10	Aortic stenosis	5/5 (100%)	Femoral artery (valve-in-valve)	NR	4/5 (80%) NR for 1 pt

Table 13. Summary of published studies of percutaneous heart valve implantation (continued)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Piazza et al., 2009[91]	CoreValve Revalving System	3	3	Aortic stenosis	3/3 (100%)	Femoral artery	NR	2/2 (100%) NR for 1 pt
Tamburino et al., 2009[92]	CoreValve Revalving System	30	1	Aortic stenosis	29/30 (97%)	Femoral artery	18 Fr	28/30 (93%)
Ussia et al., 2009[93]	CoreValve Revalving System	1	2	Aortic stenosis	1/1 (100%)	Femoral artery	18 Fr	1/1(100%)
Ussia et al., 2009[94]	CoreValve Revalving System	1	6	Aortic stenosis	1/2 (50%) (valve-in-valve after failed implantation)	Femoral artery		1/1(100%)
Bauernschmitt et al., 2009[95]	CoreValve Revalving System	1	0	Aortic stenosis	1/1 (100%)	Ascending aorta	NR	NR
Bollati et al., 2009[96]	CoreValve Revalving System	2	0	Aortic stenosis	2/2 (100%)	Ascending aorta	18 Fr	NR
Asgar et al., 2009[97]	CoreValve self-expanding nitinol prosthesis	1	5	Aortic stenosis	1/1 (100%)	Axillary artery	18 Fr	1/1 (100%)
Bleiziffer et al., 2009[74] NOTE: reports on both Edwards and CoreValve	CoreValve Revalving System	127	6	Aortic stenosis	NR by device	Femoral artery (n = 117) Transapical (n = 5) Subclavian artery (n = 3) Ascending aorta (n = 2)	18 Fr	NR by device
Totals: CoreValve ReValving System		**449 (424)**			**286/323[f] (89%)**	**Femoral artery (n = 407)** **Transapical (n = 6)** **Subclavian artery (n = 4)** **Ascending aorta (n = 5)** **Axillary artery (n = 1)** **NR (n = 1)**		**275/315[g] (87%)**

Table 13. Summary of published studies of percutaneous heart valve implantation (continued)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Followup (months)	Clinical indication	Successful implantation rate	Approach (no. of unique patients)	Catheter size	30-day survival
Paniagua Heart Valve								
Paniagua et al., 2005[98]	Paniagua Heart Valve	1	5 days	Aortic stenosis	1/1 (100%)	Femoral artery	NR	0/1 (0%)
Lotus Valve								
Buellesfeld et al., 2008[99]	Lotus Valve	1	3	Aortic stenosis	1/1 (100%)	Femoral artery	21 Fr	1/1 (100%)
Melody Valve								
Rodés-Cabau, et al., 2008[100]	Melody valve	1	3	Pulmonary stenosis	1/1 (100%)	Femoral vein	NR	1/1 (100%)
Direct Flow Medical, Inc.								
Schofer et al., 2008[101]	Direct Flow Medical aortic valve	15	1	Aortic stenosis	12/15 (80%)	Femoral artery	NR	14/15 (93%)
Ventor Technologies								
Falk et al., 2009[102]	Ventor Embracer valve	1	0.5	Aortic stenosis	1/1 (100%)	Transapical	27 Fr	NR
Manufacturer not reported								
Kapadia et al., 2009[103]	NR	1	18	Aortic stenosis	1/1 (100%)	Femoral artery	NR	1/1 (100%)
Totals for all valves:		**1053 (856)**		**Aortic stenosis (n = 854)** **Pulmo-nary stenosis (n = 1)** **Mitral Stenosis (n = 1)**	**839/917[n] (92%)**	**Femoral vein (n = 37)** **Femoral artery (n = 578)** **Transapical (n = 223)** **Subclavian artery (n = 4)** **Ascending aorta (n = 5)** **Axillary artery (n = 1)** **Other (n = 8)**		**781/903[l] (86%)**

[a]Data from two patients in this series are also reported in Cribier et al., 2004.[44]
[b]Walther et al., 2008;[55] Walther et al., 2007;[56] and Walther et al., 2008[57] have overlapping patients (see Evidence Table 2 in Appendix B for details). These three studies combined report on 79 unique patients.
[c]Thirty-five (35) patients counted twice; 25 patients from Bleiziffer et al., 2009[74] not included.

[d]Thirty-two (32) patients counted twice; survival not reported for 3 patients; 25 patients from Bleiziffer et al., 2009[74] not included.
[e]Grube et al., 2006;[78] Grube et al., 2007;[79] and Grube et al., 2008[80] have overlapping patients (see Evidence Table 2 in Appendix B for details). These three studies combined report on 223 unique patients.
[f]Twenty-six (26) patients counted twice; 127 patients from Bleiziffer et al., 2009[74] not included.
[g]Twenty-four (24) patients counted twice; survival not reported for 6 patients; 127 patients from Bleiziffer et al., 2009[74] not included.
[h]Fifty-six (56) patients counted twice; 5 patients with 2 procedures. Count includes 150/152 (99%) overall implantation success rate reported by Bleiziffer et al., 2009,[74] which was not stratified by device manufacturer.
[i]Fifty-six (56) patients counted twice; survival not reported for 9 patients. Count includes 134/152 (88%) overall 30-day survival rate reported by Bleiziffer et al., 2009,[74] which was not stratified by device manufacturer.
Abbreviations: Fr = French; n = number of patients; NA = not applicable; NR = not reported; pt = patient.

Table 14. Important variables in published studies of percutaneous heart valve implantation

Variable	Number of publications	Number of patients
Total numbers	62	856
Position:		
Aortic	60	854
Pulmonic	1	1
Mitral	1	1
Valve manufacturers:*		
Edwards Lifesciences	35	412
CoreValve	22	424
Endoluminal Technology Research	1	1
Sadra Medical	1	1
Medtronic	1	1
Direct Flow Medical	1	15
Ventor Technologies	1	1
Manufacturer not reported	1	1
Study type:**		
Case reports	35	37
Case series	27	822
Approach:***		
Femoral vein	5	37
Femoral artery	32	578
Transapical	17	223
Subclavian artery	2	4
Ascending aorta	2	5
Axillary artery	1	1
Other	7	8

*One publication included reports on both Edwards Lifesciences and CoreValve valves.
**One publication included case reports on 3 patients, and three case report publications included patients (n = 3) who were also described in case series; the latter are counted twice here.
***Four publications reported on multiple approaches.

Table 15. Summary of scientific meeting abstracts describing studies of percutaneous heart valve implantation

Valve Name	Meeting and Year	Abstract Reference	Sample Size	Date Last Patient Enrolled (actual or expected)	Clinical Indication	Approach	Country or Countries
Edwards SAPIEN							
	TCT 2008	Sack et al., 2008[104]	30	NR	NR	Antegrade (n = 2) Retrograde (n = 28)	Germany
	TCT 2008	Colombo et al., 2008[105]	29	5/08	Aortic stenosis	Transfemoral (n = 23) or transapical (n = 6)	Italy, France
	AHA 2008	Clavel et al., 2008[106]	50	NR	Aortic stenosis	NR ("percutaneous")	Canada
	AATS 2008	Ye et al., 2008[107]	19	2006	Aortic stenosis	Transapical	Canada
Subtotal: Edwards SAPIEN			**128**				
CoreValve ReValving System							
	TCT 2008	Behan et al., 2008[108]	12	NR	Aortic stenosis	NR ("percutaneous")	France
	TCT 2008	Maier et al., 2008[109]	33	06/08	Aortic stenosis	NR ("percutaneous")	Netherlands
	TCT 2008	Piazza et al., 2008[110]	646	04/08	Aortic stenosis	NR ("transcatheter")	Germany, Netherlands, France
	TCT 2008	De Jaegere et al., 2008[111]	47	05/08	Aortic stenosis	NR ("percutaneous")	Netherlands
	ESC 2008	Jilaihawi et al., 2008[112] Jilaihawi et al., 2008[113]	30	NR	Aortic stenosis	NR ("transfemoral")	United Kingdom
Subtotal: CoreValve			**768**				

Table 15. Summary of scientific meeting abstracts describing studies of percutaneous heart valve implantation (continued)

Valve Name	Meeting and Year	Abstract Reference	Sample Size	Date Last Patient Enrolled (actual or expected)	Clinical Indication	Approach	Country or Countries
Unnamed							
	TCT 2008	Masson et al., 2008[114]	6	NR	Failed mitral (n = 2) or aortic (n = 4) valve bioprosthesis	NR ("transcatheter")	Netherlands
	AATS 2008	Doss et al., 2008[115]	21	NR	Aortic stenosis	Transapical (n = 21) vs. sternotomy (n = 30)	Germany
Subtotal: Unnamed			**27**				
Total			**923**				

Abbreviations: AATS = American Association of Thoracic Surgery; AHA = American Heart Association; ESC = European Society of Cardiology; n = number of patients; NR = not reported; TCT = Transcatheter Cardiovascular Therapeutics.

Table 16. Summary of ongoing studies of percutaneous heart valves

Valve Name	ClinicalTrials.gov Identifier	Sponsor	Name of Study	Anticipated Enrollment	Study Start Date	Condition Treated	Study Design	Country or Countries
Edwards SAPIEN	ClinicalTrials.gov ID: NCT00530894	Edwards Lifesciences, LLC	PARTNER trial (Placement of AoRTic TraNscathetER valve trial)	1040	4/07	Critical aortic stenosis	Randomized clinical trial. 4 arms: Cohort A: Edwards SAPIEN THV valve vs. surgical valve Cohort B: Edwards SAPIEN THV vs. medical therapy	23 centers in United States, Canada, Germany
Melody Transcatheter Pulmonary Valve	ClinicalTrials.gov ID: NCT00688571	Medtronic Bakken Research Center	Melody Transcatheter Pulmonary Valve (TPV) Post-Marketing Surveillance Study	60	10/07	Heart valve disease	Non-randomized, open label, single group assignment treatment study	Germany
Edwards SAPIEN THV	ClinicalTrials.gov ID: NCT00676689	Edwards Lifesciences, LLC	Pulmonic Feasibility Study of the SAPIEN Transcatheter Heart Valve (COMPASSION study)	30	4/08	Pulmonary valve insufficiency	Non-randomized, open label, single group assignment treatment study	United States
Ventor Embracer Heart Valve Prosthesis	ClinicalTrials.gov ID: NCT00677638	Ventor Technologies	Catheter-Based Transapical Implantation of the Ventor Embracer Heart Valve Prosthesis in Patients with Severe Aortic Valve Disease	30	6/08	Aortic valve disease	Non-randomized, open label, single group assignment treatment study	Germany

Table 17. Summary of registries of percutaneous heart valve implantation*

Registries	Name of Study	Purpose	Anticipated Enrollment	Study Period	Condition Treated	Study Design	Country or Countries
Edwards SAPIEN THV	Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial (formerly I-REVIVE) registry	To demonstrate that the Edwards SAPIEN THV is a safe and effective treatment for elderly patients who are at a high risk, and therefore poor candidates for AVR surgery.	106	1-year followup to be completed in January 2009	NR	Edwards SAPIEN THV with retrograde transfemoral delivery system	France
Edwards SAPIEN THV	TRAVERCE (TRAnsapical Surgical DeliVERy of the Cribier-Edwards aortic bioprosthesis)	A first-in-man pilot study to evaluate the feasibility and safety of the transapical surgical delivery and implantation of the Edwards SAPIEN THV.	172	12/04 to 4/08	NR		Germany, Austria
Edwards SAPIEN THV	SOURCE post-market registry		350	NR	NR	Post-market registry	30 European sites
Edwards SAPIEN THV*	PARTNER EU trial (Placement of AoRTic TraNscathetER valve trial)	NR	132	NR	Severe aortic stenosis	Non-randomized, open label, multicenter single group assignment treatment study using either a transapical or transfemoral delivery approach	European sites

*Information provided by Edwards Lifesciences, LLC.
Abbreviations: AVR = aortic valve replacement; NR = not reported.

Appendix A. Exact Search Strategies

PubMed® Search Strategy Used to Identify Systematic Reviews of Conventional Heart Valves (Question 2) – Date of search: October 17, 2008

#1 Heart Valve Prosthesis (29083)
#2 Heart Valve Prosthesis Implantation (7798)
#3 (Aortic Valve/surgery OR Aortic Valve/transplantation) (8179)
#4 (Mitral Valve/surgery OR Mitral Valve/transplantation) (8271)
#5 #1 OR #2 OR #3 OR #4 (34134)
#6 #5 AND systematic[sb] (169)
#7 Cochrane database syst Rev (5467)
#8 Search [tw] (5467)
#9 Meta-analysis [pt] (18848)
#10 Systematic review [tw] (13902)
#11 #7 OR #8 OR #9 OR #10 (121097)
#12 #5 AND #11 (150)
#13 #6 OR #12 (266)

PubMed® Search Strategy Used to Identify Randomized Controlled Trials of Conventional Heart Valves (Question 2) – Date of search: October 17, 2008

#1 Heart Valve Prosthesis (29083)
#2 Heart Valve Prosthesis Implantation (7798)
#3 (Aortic Valve/surgery OR Aortic Valve/transplantation) (8179)
#4 (Mitral Valve/surgery OR Mitral Valve/transplantation) (8271)
#5 #1 OR #2 OR #3 OR #4 (34134)
#6 randomized controlled trial[Publication Type] (257078)
#7 (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) (36383)
#8 #6 OR #7 (266338)
#9 #5 AND #8 (483)
#10 Limit to English and Human (416)

PubMed® Search Strategy Used to Identify Observational Studies of Conventional Heart Valves (Question 2) – Date of search: December 13, 2008

#1 Heart Valve Prosthesis [Majr] (16659)
#2 Heart Valve Prosthesis Implantation [Majr] (3989)
#3 (Aortic Valve/surgery [Majr] OR Aortic Valve/transplantation [Majr]) (4604)
#4 (Mitral Valve/surgery [Majr] OR Mitral Valve/transplantation [Majr]) (4555)
#5 #1 OR #2 OR #3 OR #4 (23965)
#6 Longitudinal OR cohort studies OR (relative risk OR (relative AND risk)) OR follow up studies (1615952)
#7 #5 AND #6 (7319)

#8 (Randomized[Title/Abstract] AND controlled [Title/Abstract]) OR randomized controlled trial[pt] (285005)
#9 #7 NOT #8 (7087)
#10 #9 Limits: Review (432)
#11 #9 NOT #10 (6655)
#12 #11 Limits: English, Humans, Adult: 19-44, Middle Aged+ Aged 45+ years, added to PubMed in the last 5 years (1157)

PubMed® Search Strategy Used to Identify Studies of Percutaneous Heart Valves (Questions 3-4) – Date of search: October 15, 2009

#1 Percutaneous OR transapical OR transcatheter OR CoreValve OR Edwards OR Sapien (120603)
#2 (("Heart Valve Prosthesis"[Majr] OR "Heart Valve Prosthesis Implantation"[Majr]) OR ("Aortic Valve/surgery"[Majr] OR "Aortic Valve/transplantation"[Majr])) OR ("Mitral Valve/surgery"[Majr] OR "Mitral Valve/transplantation"[Majr] OR ("Pulmonic Valve/surgery"[Majr] OR "Pulmonic Valve/transplantation"[Majr] OR "Pulmonary Valve/surgery"[Majr] OR "PulmonaryValve/transplantation"[Majr]) (25756)
#3 #1 AND #2 Limits: Humans, Clinical Trial, Case Reports (616)

EMBASE® Search Strategy Used to Identify Studies of Percutaneous Heart Valves (Questions 3-4) – Date of search: October 15, 2009

#1 Heart Valve Prosthesis/de (18,068)
#2 Aorta Valve/de or mitral valve/de or pulmonary valve/de (23,587)
#3 #1 or #2 (35,879)
#4 (Percutaneous or transapical or transcatheter or CoreValve or Edwards or Sapien) (158,669)
#5 #3 and #4 (2,299)
#6 clinical trial/exp or case report/de (2,419,486)
#7 #5 and #6 and [embase]/lim (341)

Appendix B. Evidence Tables

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
Kassai, Gueyffier, Cucherat, et al., 2000[1]	**No. of included studies:** RCTs: 3 (2 in adults) Observational: 0 **Study countries:** NR **Study intervention:** Mechanical heart valves (Bjork-shiley, Lillehei-Kaster-children) **Comparator treatment(s):** Bioprosthetic heart valves (Carpentier-Edward, Hancock, Angell-Shiley-children) **Clinical setting – 1:** OR: All 3 **Clinical setting – 2:** NR **Implantation technique:** Surgical: 3 Percutaneous: 0 **Surgeon characteristics:** NR	**No. of patients:** RCTs: 1229 (1011 adults) Observational: 0 **Age:** Adults – 2 trials Children – 1 trial **Race/ethnicity:** NR **Comorbidities:** NR **Surgical indication(s):** **Aortic valve disease:** 605 **Mitral valve disease:** 553 **Aortic and mitral valve disease:** 61	**Primary:** 1) All-cause mortality **Secondary:** 2) In-hospital mortality 3) Cardiac mortality 4) Reoperation 5) Bleeding 6) Thromboembolism 7) Endocarditis **Length of follow-up:** Mean of 11-12 yr for adults	Relative risks (with 95% CIs) for mechanical heart valves compared to bioprosthetic for 2 adult studies at 11 yr **Primary outcome:** 1) All-cause mortality at 11 yr: 0.94 (0.84 to 1.06) **Secondary outcomes:** 2) In-hospital mortality: 0.75 (0.5 to 1.13) 3) Cardiac mortality: 0.98 (0.79 to 1.21) 4) Reoperation: 0.4 (0.28 to 0.58); p = 0.059 for heterogeneity 5) Bleeding at 11 yr: 1.65 (1.25 to 2.18) 6) Thromboembolism: 0.97 (0.71 to 1.34) 7) Endocarditis: 0.57 (0.34 to 0.95); p = 0.001 for heterogeneity	**Comments:** Internal inconsistencies make some results suspect **Quality assessment:** Focused clinical question?: Yes Detailed and exhaustive search?: Can't tell; databases appropriate, search terms not given Inclusion/exclusion criteria defined and appropriate?: Yes Included studies evaluated for quality?: No Assessments reproducible?: Yes Analysis for variability?: Yes Results combined appropriately?: Yes Publication bias assessed?: Yes Both benefits and harms assessed?: Yes Conclusions supported by data?: Yes **Objective(s) of review:** To compare effects on mortality and morbidity for mechanical vs. bioprosthetic heart valves

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
Kunadian, Vijaya-lakshmi, Thornley, et al., 2007[2]	**No. of included studies:** RCTs: 11 Observational: 0 **Study countries:** UK (5) Italy (3) Germany (2) Canada (1) **Study intervention:** Stentless valve (Prima Plus-Edwards Lifesciences, Freedom-Sorin Bomedica Cardio, Freestyle-Medtronic, Toronto-St Jude, Biocor-Sorin Biomedica) **Comparator treatment(s):** Stented valve (Perimount-Carpentier-edwards, Edwards Lifesciences, More-Sorin Biomedica, Mosaic-Medtronic, Intact-Medtronic, Hancock II-Medtronic) **Clinical setting – 1:** NR, but all presumably OR **Clinical setting – 2:** NR	**No. of patients:** RCTs: 919 (474 stentless; 445 stented) Observational: 0 **Age:** NR **Race/ethnicity:** NR **Comorbidities:** NR **Surgical indication(s):** Aortic valve replacement	**Primary:** 1) Left ventricular mass regression index **Secondary:** 2) Cross-clamp time 3) Bypass time 4) Post-operative mean and peak aortic gradient 5) Effective orifice area index 6) Mortality at ≤ 1 yr **Length of follow-up:** NR	**Primary outcome:** 1) LVMI at 6 mo (6 studies, n = 599): WMD -6.42 (95% CI, -11.63 to -1.21) for stentless vs. stented; p < 0.01 for heterogeneity LVMI at ≥ 12 mo (5 studies, n = 550): WMD 1.19 (-4.15 to 6.53) for stentless vs. stented; p = 0.35 for heterogeneity **Secondary outcomes:** 2) Cross-clamp time (10 studies): WMD 23.5 min longer (20.4 to 26.1) for stentless vs. stented 3) Bypass time (9 studies): WMD 29.0 min longer (24.4 to 34.0) for stentless vs. stented 4) Mean aortic gradient (number of studies NR): WMD -3.57 mmHg for stentless (-4.36 to -2.78) vs. stented Peak gradient (number of studies NR): WMD -5.80 mmHg for	**Comments:** None **Quality assessment:** Focused clinical question?: Yes Detailed and exhaustive search?: Yes (though only 1995-2006) Inclusion/exclusion criteria defined and appropriate?: Yes Included studies evaluated for quality?: Yes Assessments reproducible?: Yes Analysis for variability?: Yes Results combined appropriately?: Yes Publication bias assessed?: Yes Both benefits and harms assessed?: Yes Conclusions supported by data?: Yes **Objective(s) of review:** To determine whether stentless valves vs. conventional stented valves give greater left ventricular mass regression

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
	Implantation technique: Surgical: 11 Percutaneous: 0 **Surgeon characteristics:** NR			stentless (-6.90 to -4.69) vs. stented 5) Effective orifice area index (number of studies NR): Higher for stentless vs. stented; value NR, p < 0.01 6) Mortality at ≤ 1 yr (7 trials, n = 807): OR = 0.91 (0.52 to 1.57) for stentless vs. stented; p = 0.70 for heterogeneity	
Lund and Bland, 2006[3]	**No. of included studies:** RCTs: 0 Observational: 32 articles describing 38 case series **Study countries:** NR **Study intervention:** Mechanical heart valves (St. Jude bileaflet disc, mixed disc valves, Medtronic-Hall tilting disc) **Comparator treatment(s):** Bioprosthetic heart valves (Carpentier-Edwards [CE] Perimount pericardial, CE porcine standard,	**No. of patients:** RCTs: 0 Observational: 17,439 **Age:** Mean mechanical: 58.0 Mean bioprosthetic: 68.8 **Race/ethnicity:** NR **Comorbidities:** Concomitant CABG: 15.7% mechanical 34.1% bioprosthetic NYHA class III or IV: 64.6% mechanical, 69.6% bioprosthetic **Surgical indication(s):** Aortic valve replacement for the	**Primary:** 1) Mortality **Secondary:** None **Length of follow-up:** Mean 6.4 yr for mechanical (range, 3.9 to 10.8), and 5.3 yr (2.6 to 10.1) for bioprosthetic	**Primary outcome:** 1) -0.23 deaths (95%CI, -0.99 to 0.63) per 100 patient-years for bioprosthetic vs. mechanical, adjusting for age, proportion with NYHA class III or IV, and aortic regurgitation as the indication **Secondary outcomes:** None	**Comments:** None **Quality assessment:** Focused clinical question?: Yes Detailed and exhaustive search?: Partially; well-described strategy, but may be too narrow Inclusion/exclusion criteria defined and appropriate?: Yes Included studies evaluated for quality?: No Assessments reproducible?: No Analysis for variability?: Yes, graphically Results combined appropriately?: Yes Publication bias assessed?: No Both benefits and harms assessed?: Yes Conclusions supported by data?: Yes **Objective(s) of review:** To determine whether currently available mechanical heart valves (bileaftet and single disc) vs. stented bioprosthetic (porcine and bovine) have differential effects on crude

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
	CE porcine supra-annular, Hancock II and MO porcine, Mitroflow pericardial, mixed biologic, Biocor porcine) **Clinical setting – 1:** NR, but all presumably OR **Clinical setting – 2:** NR **Implantation technique:** Surgical: 32 Percutaneous: 0 **Surgeon characteristics:** NR	following indications: - Aortic regurgitation (28.7% mechanical; 16.5% bioprosthetic) - Aortic stenosis (50.9% mechanical; 68.6% bioprosthetic); - Endocarditis (6.8% mechanical, 2.2% bioprosthetic)			mortality
Puvimana-singhe, Takken-berg, Edwards, et al., 2004[4] **and** **Puvimana-singhe, Takken-berg, Eijkemans, et al., 2003**[5]	**No. of included studies:** NR by study design – 9 reports for St. Jude aortic valve prostheses (7 retrospective, 2 prospective) and 13 reports for stented porcine bioprostheses (8 retrospective, 3 prospective, 2 NR) **Study countries:** NR **Study intervention:** St. Jude mechanical aortic valve prosthesis **Comparator**	**No. of patients:** NR by study design; St. Jude mechanical: 4274 pts Porcine bioprostheses: 9007 pts **Age:** Mean St. Jude: 59.1 Mean porcine: 65.4 **Race/ethnicity:** NR **Comorbidities:** Concomitant CABG: 30% St. Jude 37% porcine **Surgical indication(s):**	**Primary:** 1) Life expectancy based on microsimulation 2) Event-free life expectancy based on microsimulation **Secondary:** Occurrence rate per 100 patient-years of following: 3) Valve thrombosis 4) Thromboembolism 5) Hemorrhage	**Primary outcome:** 1) Life expectancy for a 65 y/o man: 10.4 yr mechanical vs. 10.7 yr bioprostheses 2) Event-free life expectancy for 65 y/o man: 7.7 yr mechanical vs. 8.4 yr bioprosthesis Concomitant CABG decreased life expectancy **Secondary outcomes:** Occurrence rate per 100 patient-years:	**Comments:** None **Quality assessment:** Focused clinical question?: Yes Detailed and exhaustive search?: Probably no; search terms not clear, PubMed and references of included studies only Inclusion/exclusion criteria defined and appropriate?: Can't tell Included studies evaluated for quality?: No Assessments reproducible?: No Analysis for variability?: No Results combined appropriately?: Partially; required standard definitions as part of inclusion criteria, but didn't discuss further Publication bias assessed?: No Both benefits and harms assessed?: Yes Conclusions supported by data?: Uncertain

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
	treatment(s): Stented porcine bioprosthesis **Clinical setting – 1:** NR, but presumably all OR **Clinical setting – 2:** NR **Implantation technique:** Surgical: 22 Percutaneous: 0 **Surgeon characteristics:** NR	Aortic valve replacement	6) Endocarditis 7) Non-structural dysfunction 8) Structural valvular deterioration **Length of follow-up:** Total follow up in patient-years was 25,726 for St. Jude mechanical, and 54,151 for porcine bioprosthesis	3) Valve thrombosis: Mechanical: 0.16 Bioprosthesis: 0.01 4) Thromboembolism: Mechanical: 1.6 Bioprosthesis: 1.3 5) Hemorrhage: Mechanical: 1.6 Bioprosthesis: 0.4 6) Endocarditis: Mechanical: 3.9 in first 6 mo, 0.66 after 6 mo Bioprosthesis: 3.2 in first 6 mo; 0.48 after 6 mo 7) Non-structural dysfunction: Mechanical: 0.29 Bioprosthesis: 0.3 8) Structural valvular deterioration: Mechanical: 0 Bioprosthesis: 1.2	**Objective(s) of review:** To predict age and sex-specific outcomes of patients after aortic valve replacement with St. Jude mechanical valves and stented porcine bioprosthesis
Puvimana-singhe, Takken-berg, Eijkemans, et al., 2006[6]	**No. of included studies:** NR by study design – 8 reports on the Carpentier-Edwards pericardial valve, and 5 on the Carpentier-Edwards supraannular valve **Study countries:** NR	**No. of patients:** NR by study design; C-E pericardial: 2685 pts C-E porcine supra-annular: 3796 pts **Age:** Mean C-E pericardial: 66.9 Mean C-E porcine	**Primary:** 1) Life expectancy based on microsimulation 2) Event-free life expectancy based on microsimulation **Secondary:** Occurrence rate per 100 patient-years of	**Primary outcome:** 1) Life expectancy for a 65 y/o man: 10.8 yr CE pericardial vs. 10.9 yr CE supraannular 2) Event-free life expectancy for 65 y/o man: 9.0 yr CE pericardial vs.	**Comments:** None **Quality assessment:** Focused clinical question?: Yes Detailed and exhaustive search?: No, only 7 yr, only English, restrictive terms Inclusion/exclusion criteria defined and appropriate?: Can't tell Included studies evaluated for quality?: No Assessments reproducible?: No

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
		supraannular: 69.8	following:	8.8 yr CE supraannular	Analysis for variability?: No Results combined appropriately?: No
	Study intervention: Carpentier-Edwards pericardial aortic valve replacement	**Race/ethnicity:** NR	3) Valve thrombosis	**Secondary outcomes:** Occurrence rate per 100 patient-years:	Publication bias assessed?: No Both benefits and harms assessed?: Yes Conclusions supported by data?: Uncertain
	Comparator treatment(s): Carpentier-Edwards supraannular bioprosthetic aortic valve replacement	**Comorbidities:** NR	4) Thromboembolism	3) Valve thrombosis: CE pericardial: 0.03 CE supraannular: 0.02	**Objective(s) of review:** To compare long-term outcomes in patients undergoing aortic valve replacement with Carpentier-Edwards bovine pericardial vs. Carpentier-Edwards porcine supraannular bioprosthesis.
	Clinical setting – 1: NR, but presumably all OR	**Surgical indication(s):** NR	5) Hemorrhage	4) Thromboembolism: CE pericardial: 1.35 CE supraannular: 1.76	
	Clinical setting – 2: NR		6) Endocarditis	5) Hemorrhage: CE pericardial: 0.43; CE supraannular: 0.46	
	Implantation technique: Surgical: 13 Percutaneous: 0		7) Non-structural dysfunction	6) Endocarditis: CE pericardial: 0.62 CE supraannular: 0.39	
	Surgeon characteristics: NR		**Length of follow-up:** 18 yr for C-E pericardial valves, and up to 20 yr for C-E porcine supraannular valves	7) Non-structural dysfunction: CE pericardial: 0.13 CE supraannular: 0.61	
Rizzoli, Vendramin, Nesseris, et al., 2004[7]	**No. of included studies:** NR by study design – 11 studies referenced	**No. of patients:** NR by study design; Bioprosthetic: 646 Mechanical: 514	**Primary:** 1) Late survival of pts after operation	**Primary outcome:** 1) Survival: Hazard ratio for mechanical vs. bioprosthetic (8 studies) = 1.07 (0.84 to 1.35)	**Comments:** None
	Study countries: Belgium = 1; Canada = 3; France = 2; Japan = 1; UK = 2; Turkey = 1; Italy = 1	**Age:** Mean for all pts: 49.3	**Secondary:** 2) Freedom from reoperation	**Secondary outcomes:** 2) Freedom from reoperation: Hazard ratio for mechanical vs. bioprosthetic (3 studies)	**Quality assessment:** Focused clinical question?: No Detailed and exhaustive search?: Partially; appropriate databases, poor search terms Inclusion/exclusion criteria defined and appropriate?: No; only criteria was “intra-institutional comparison of results of biological or mechanical TVR” Included studies evaluated for quality?: No
	Study intervention:	**Race/ethnicity:** NR **Comorbidities:** Ratio of NYHA class III	3) Reoperation-free survival **Length of follow-up:**		

Evidence Table 1. Systematic reviews comparing various conventional heart valves (Question 2) (continued)

Study	Studies and interventions	Patients	Outcomes assessed	Relative risks/other summary effect measures	Comments/quality scoring
	Bioprosthetic valve replacement in the tricuspid position **Comparator treatment(s):** Mechanical valve replacement in the tricuspid position **Clinical setting – 1:** NR, but presumably all OR **Clinical setting – 2:** NR **Implantation technique:** Surgical: 11 Percutaneous: 0 **Surgeon characteristics:** NR	and IV in bioprosthetic to mechanical valves: 0.81 **Surgical indication(s):** Tricuspid valve replacement	Mean duration: 6.8 yr For individual studies: Van Nooten: 7.8 yr Scully: 6.3 yr Munro: 3.7 yr Farinas: 9.5 yr Hayashi: 6.7 yr Ratnatunga: NR Dalrymple: 8.1 yr Do: 5.6 yr Kaplan: 6.3 yr Carrier: 4.0 yr Local Data: 7.4 yr	= 1.24 (0.67 to 2.31) 3) Reoperation-free survival: Hazard ratio for mechanical vs. bioprosthetic (2 studies) = 0.86 (0.70 to 1.05)	Assessments reproducible?: No Analysis for variability?: No Results combined appropriately?: No Publication bias assessed?: No Both benefits and harms assessed?: No Conclusions supported by data?: Yes **Objective(s) of review:** In patients needing tricuspid valve replacement, does mechanical or bioprosthetic heart valve lead to better survival?

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Al-Attar, Raffoul, Himbert, et al., 2009[8]	**Country/countries:** France **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 3 months	**No. of patients:** 1 **Age:** 81 **Sex:** Male **Medical/functional status:** NYHA III **Surgical indication(s):** Low cardiac output & acute renal failure **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Edwards SAPIEN THV **Size of catheter:** 26 mm **Self- or balloon-expanding?:** Balloon-expandable **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: Echocardiography 2) Change in valve area: NR 3) Change in valve gradient: NR **Clinical status outcomes:** 1) Change in NYHA functional class: NR **Survival:** 1/1 (100%) at 3 months	**Complications:** - Pericardial effusion at 2 weeks - False aneurysm of LV **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: Negligible posterior leak (< 1/4)	
Asgar, Mullen,Delahunty, et al., 2009[9]	**Country/countries:** United Kingdom **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 5 months	**No. of patients:** 1 **Age:** 71 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Severe AS **Inclusion criteria:** NR	**Valve name:** CoreValve **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self **Implantation approach:** Axillary **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** NR **Clinical status outcomes:** NR **Survival:** 1/1 (100%)	**Complications:** None reported **Major cardiovascular/ cerebrovascular events:** None reported **Valve dysfunction:** None reported	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		Exclusion criteria: NR				
Bauer, Eltchani-noff, Tron, et al., 2004[10]	**Country/countries:** France **Setting:** NR **Basic design:** Case series **Study objective(s):** Apply tissue Doppler imaging to detect subtle improvement in global and regional LV systolic function immediately after PHV implantation **Duration of follow-up:** 1 mo after PHV implantation	**No. of patients:** 8 **Age:** 77 to 88 (mean 83 ± 3) **Sex:** Female: 6 (75%) Male: 2 (25%) **Medical/functional status:** NYHA class IV: 8 (100%) 2 (25%) in cardiogenic shock **Surgical indication(s):** - 8 (100%) had severe AS, with AVA averaging 0.59 ± 0.11 cm^2 - Peak pressure gradient 78 ± 19 mm Hg - Mean pressure gradient 46 ± 15 mm Hg - LVEF averaged 48 ± 18% (22% to 73%), and LVEF was lower than 45% in 3 (38%) pts I**nclusion criteria:** - Symptomatic	**Valve name:** Cribier Edwards (Not named in report) **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon inflation: 23 mm diameter **Implantation approach:** Arterial retrograde in 2 (25%) Transseptal anterograde in 6 (75%) **Operator(s):** NR	**Successful implantation:** 8/8 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.59 ± 0.11 → 1.69 ± 0.11 cm^2 2) Change in valve gradient: mean 46 ± 15 → 8 ± 3 mm Hg 3) Other: EF 48 ± 18% → 57 ± 12% **Clinical status outcomes:** Change in NYHA functional class: NR 30-day survival: 5/8 (63%)	**Complications:** LVEF increased from 48 ± 18% to 57 ± 12% ($p < 0.0001$) at 24 hr follow-up **Valve dysfunction:** - Leak: NR - Hemolysis: NR - Migration: NR - Infection: NR - Need for re-intervention: NR	Authors state that "percutaneous aortic valve replacement is characterized by an immediate enhancement of global and regional systolic function, even in patients with low ejection fraction."

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		despite maximal medical therapy - Declined by 2 independent surgeons due to hemodynamic instability and associated severe comorbidities **Exclusion criteria:** NR				
Bauernschmitt, Schreiber, Bleiziffer, et al., 2009[11]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** NR	**No. of patients:** 1 **Age:** 80 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Critical AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** CoreValve Revalving System **Size of catheter:** NR **Self- or balloon-expanding?:** Self-expanding Implantation approach: Retrograde, via ascending aorta **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Aortography: NR 2) Echocardiography: NR 3) Change in valve gradient: NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** NR	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** NR	
Berry, Asgar, Lamarche, et al., 2007[12] **and**	**Country/countries:** Canada **Setting:** NR **Basic design:** Case series **Study objective(s):**	**No. of patients:** 13 informed consent **Age:** Median 82 (64 to 90) **Sex:** Female: 5 (46%); Male: 6 (54%)	**Valve name:** CoreValve porcine bioprosthesis **Size of catheter:** 21 Fr **Self- or balloon-expanding?:** Self-expanding nitinol valve frame	**Successful implantation:** 11/13 (85%) **Hemodynamic outcomes:** 1) Change in valve area: $0.56 \pm 0.19 \rightarrow 1.3 \pm 0.4$ cm^2 ($p < 0.0001$)	**Complications:** - 2 (18%) non-cardiac deaths - 3 (27%) CKMB > 5X ULN - 3 (27%) new permanent pacemaker - 4 (36%) new LBBB	Author states this report provides "novel information on the versatility of PAVR, which in our hands was combined with percutaneous left heart circulatory support, PCI and

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Berry, Cartier, and Bonan, 2007[13]	Investigate whether novel therapeutic approaches may facilitate AVR outcomes for high-risk pts **Outcomes:** - 30-day mortality - In-hospital mortality - LVEF change - NT-BNP concentration change **Duration of follow-up:** 305 (270 to 326) days (from PAVR until 2/20/2007 [or until death])	**Medical/functional status:** NYHA class III: 8 (73%) NYHA class IV: 3 (27%) **Surgical indication(s):** Severe AS **Inclusion criteria:** - Severe AS (aortic valve area index ≤ 0.6 cm2/m2 - Aorticannulus diameter of 20-23 mm - Sinotubular junction diameter ≤ 45 mm - Either pt age ≥ 80 yr with a logistic Euro-Score ≥ 20%, or age ≥ 65 yr plus at least one major disincentive for surgery (previous cardiac surgery, pulmonary artery systolic pressure > 60 mm Hg) **Exclusion criteria:** Peripheral arterial disease associated with significant tortuosity or an internal lumen diameter ≤ 7 mm	**Implantation approach:** Transfemoral retrograde **Operator(s):** NR	2) Change in valve gradient: mean 51 ± 19 → 9 ± 4 mm Hg (p < 0.00001) 3) Other: Mean LVEF 49 ± 17% → 56 ± 11% at 30 days Mean NT-BNP 10,059 ± 12,117 → 5,036 ± 7,790 pg/ml at 30 days **Clinical status outcomes:** Change in NYHA functional class: 1 patient improved by 2 points, and the other survivors improved by 1 point (p = 0.0006) **30-day survival:** 1) 11/13 (85%) at 30 days 2) 7/13 (54%) at 1 year 3) 0 cardiac deaths within 30 days	- 8 (82%) blood transfusion - 2 (18%) platelet transfusion - 1 male had periprocedural stroke and died 5 days post-PAVR **30-day AEs:** - 4 (36%) bradyarrhythmia - 2 (18%) major bleeding **Valve dysfunction:** Leak: Grade I (64%) Grade II (36%)	PTA. A multidisciplinary approach with careful screening and postprocedure follow-up is necessary to ensure optimal procedural outcomes."

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Bleiziffer, Ruge, Mazzitelli, et al., 2009[14]	**Country/countries:** Germany **Setting:** Hybrid operating room with permanent angiography unit **Basic design:** Case series **Study objective(s):** "We will discuss the various techniques currently in use, all of which are now being performed at the German Heart Center I Munich. Furthermore, we will discuss the results that have been obtained to date, with follow-up times of up to 6 months." **Duration of follow-up:** 6 months	**No. of patients:** 152 **Age:** 81 ± 7 **Sex:** Female: 87 (57%) Male: 65 (43%) **Medical/functional status:** 97% NYHA III or IV **Surgical indication(s):** Patients either had a specific contraindication to conventional surgical aortic valve replacement, such as severe, extensive calcification of the ascending aorta, or they were very old and had major comorbidities **Inclusion criteria:** Specific contraindication to conventional surgical aortic valve replacement, or very old and had major comorbidities **Exclusion criteria:** NR	**Valve name:** Edwards-Sapien & CoreValve **Size of catheter:** E-S: 22-24 Fr CV: 18 Fr **Self- or balloon-expanding?:** E-S: Balloon-expanding CV: Self-expanding **Implantation approach:** Transfemoral retrograde (n = 121) Transapical (n = 26) Subclavian artery (n = 3) Ascending aorta (n = 2) **Operator(s):** NR	**Successful implantation:** 150/152 (99%) **Hemodynamic outcomes:** 1) Method of assessment: Echocardiography 2) Change in valve area: 0.65 ± 0.19 to 1.56 ± 0.4 cm^2 at 6 mo 3) Change in valve gradient: Mean: 49 ± 17 to 11 ± 4 at 6 mo **Clinical status outcomes:** Change in NYHA functional class: 86% class I or II at 3 months; 83% class I or II at 6 months **Survival:** 134/152 alive at 30 days; 12 patients died later in 6-month course of follow-up	**Complications:** 1 pt – ruptured ascending aorta 1 pt – supravalvular dislocation of prosthesis 4 pts – intraoperative cardiac depression **Major cardiovascular/ cerebrovascular events:** 31 pts - third-degree atrioventricular block necessitating pacemaker 25 pts - vascular complications 8 pts – cerebrovascular events **Valve dysfunction:** Leak: Frequency of paravalvular leaks of grade ≥ 2 was 11% at time of discharge and 7% at 6 mo	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Bojara, Mumme, Gerckens, et al., 2009[15]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** Focus on an alternative arterial access for retrograde aortic valve implantation in patients in which the femoral/iliac arteries are not accessible **Duration of follow-up:** 30 days	**No. of patients:** 1 **Age:** 82 **Sex:** Male **Medical/functional status:** NYHA Class IV **Surgical indication(s):** Recurrent resting dyspnea **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Third-generation CoreValve **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Subclavian artery approach **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: C-cath 2) Change in valve area: 0.6 cm^2 to NR 3) Change in valve gradient: Peak: 85 mm Hg to "almost zero" intraoperatively **Clinical status outcomes:** Change in NYHA functional class: Class II/III **Survival:** 1/1 (100%) at 30 days	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** NR	
Bollati, Moretti, Omede, et al., 2009[16]	**Country/countries:** Italy **Setting:** NR **Basic design:** Case series **Study objective(s):** NR **Duration of follow-up:** 12 days for one patient, and 3 weeks for the second patient.	**No. of patients:** 2 **Age:** Pt 1: 81 Pt 2: 70 **Sex:** Female: 2 (100%) **Medical/functional status:** NYHA III **Surgical indication(s):** Pt 1: Dyslipidemia, asymptomatic carotid	**Valve name:** CoreValve Revalving System **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 2/2 (100%) Hemodynamic outcomes: 1) Method of assessment: TTE C-cath 2) Change in valve area: NR 3) Change in valve gradient: "Almost complete resolution of aortic valve gradient"	**Complications:** - A third-degree atrioventricular block (requiring permanent pacemaker implantation) - Bleeding from the right femoral artery access (requiring implantation of two covered stents and blood transfusion) **Major cardiovascular/ cerebrovascular**	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		artery disease, coronary artery disease symptomatic for effort angina Pt 2: Hypertension, insulin-dependent diabetes, obesity, previous episode of DVT and severe hepatic cirrhosis with secondary pancytopenia which had already caused severe esophageal bleeding in 2004 **Inclusion criteria:** NR **Exclusion criteria:** NR		**Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Alive at discharge, 12 days, and 3 weeks after admission	**events:** NR **Valve dysfunction:** - Leak: "Moderate" - Other: Persistent bleeding from femoral site	
Buellesfeld, Gerckens, and Grube, 2008[17]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 3 mo	**No. of patients:** 1 **Age:** 93 **Sex:** Female **Medical/functional status:** NYHA class IV Logistic euroSCORE (mortality): 22.9% **Surgical indication(s):** Severe symptomatic aortic stenosis **Inclusion criteria:** Surgical valve	**Valve name:** Lotus Valve (nitinol frame with implemented bovine pericardial leaflets) **Size of catheter:** 21 Fr Lotus **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.36 → 1.7 cm^2 2) Change in valve gradient: 59 → 23 mm Hg (peak to peak) **Clinical status outcomes:** Change in NYHA functional class: IV → II	**Complications:** New complete AV block **Valve dysfunction:** None	Authors state that "successful percutaneous aortic valve replacement can be performed using the new self-expanding and repositionable Lotus valve for treatment of high-risk patients with aortic valve stenosis."

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		replacement had been declined by 2 independent cardiovascular surgeons due to comorbidities **Exclusion criteria:** NR		**30-day survival:** 1 (100%) at 3 mo		
Chandavimol, McClure, Carere, et al., 2006[18]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 12 mo	**No. of patients:** 1 **Age:** 85 **Sex:** Male **Medical/functional status:** NYHA class III euroSCORE: 30% **Surgical indication(s):** Severe AS **Inclusion criteria:** "Surgical risk" deemed excessive by two cardiac surgeons **Exclusion criteria:** NR	**Valve name:** Edwards Lifesciences **Size of catheter:** 24 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.7 → 1.8 cm^2 2) Change in valve gradient: Mean 58 → 16 mm Hg **Clinical status outcomes:** Change in NYHA functional class: NR **30-day survival:** 1 (100%) at 1 yr	**Complications:** NR **Valve dysfunction:** Leak: Trivial paravalvular aortic regurgitation	
Cheung, Webb, Wong, et al., 2009[19]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report	**No. of patients:** 1 **Age:** 80 **Sex:** Male **Medical/functional status:** NR	**Valve name:** 26-mm Cribier-Edwards 9000MIS **Size of catheter:** 33 Fr **Self- or balloon-expanding?:** Balloon-expanding	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: TEE C-cath	**Complications:** Three episodes of ventricular tachycardia requiring defibrillation, and a new LV apical thrombus **Major**	Valve-in-valve implantation

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	Study objective(s): "We report a transcatheter mitral valve-in-valve implant in a patient." **Duration of follow-up:** Until death at 47 days	**Surgical indication(s):** Symptomatic bioprosthetic mitral stenosis **Inclusion criteria:** NR **Exclusion criteria:** NR	**Implantation approach:** Transapical **Operator(s):** NR	2) Change in valve area: 0.7 cm^2 to NR 3) Change in valve gradient: Mean: 17 to 3 mm Hg **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Pt died 47 days after implantation from multiple organ dysfunction	**cardiovascular/ cerebrovascular events:** Pt sustained embolic stroke after 3 days **Valve dysfunction:** Leak: No paravalvular or transvalvular mitral regurgitation	
Chiam, Koh, Chao, et al., 2009[20]	**Country/countries:** Singapore **Setting:** Cath lab **Basic design:** Case report **Study objective(s):** "Describe the first ever percutaneous aortic valve implantation for symptomatic severe AS in Asia." **Duration of follow-up:** 30 days	**No. of patients:** 1 **Age:** 77 **Sex:** Male **Medical/functional status:** NYHA class III **Surgical indication(s):** Severe AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Sapien THV **Size of catheter:** 22 Fr **Self- or balloon-expanding?:** Balloon **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: Mean: 57 to 6 mm Hg immediately post-deployment, and 20 mm Hg at 30-day f/u 3) Other: LVEF 46% **Clinical status outcomes:** NYHA Class I at 30-day f/u **Survival:** 1/1 (100%) at 30 days	**Complications:** None reported **Major cardiovascular/ cerebrovascular events:** None reported **Valve dysfunction:** Leak: trivial	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Clavel, Dumont, Pibarot, et al., 2009[21]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report **Study objective(s):** "We report two life-threatening complications associated with percutaneous aortic valve implantation, and we discuss their potential causes and solutions." **Duration of follow-up:** Until death at 2 days post-operative	**No. of patients:** 1 **Age:** 79 **Sex:** Male **Medical/functional status:** NR **Surgical indication(s):** Low-flow, low-gradient AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** 26-mm Edwards SAPIEN valve **Size of catheter:** 26 Fr **Self- or balloon-expanding?:** NR **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** First attempt failed due to severe central aortic regurgitation; second implantation led to postoperative progress for 2 days **Hemodynamic outcomes:** 1) Method of assessment: TEE TTE 2) Change in valve area: 0.76 cm^2 to NR 3) Change in valve gradient: Mean: 20 mm Hg to NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Patient developed refractory cardiogenic shock with irreversible metabolic acidosis and disseminated intravascular coagulation, and subsequently died during weaning from cardiopulmonary bypass	**Complications:** Central aortic regurgitation requiring implantation of second "valve-in-valve" in the same procedure. TWo days after the procedure, both prostheses were found to have migrated into the left ventricle, causing obstruction of the LV outflow tract. **Major cardiovascular/ cerebrovascular events:** Pt developed cardiogenic shock and death secondary to migration of aortic bioprosthesis into the LV outflow tract **Valve dysfunction:** Leak: No periprosthetic leak 2 days after the procedure, by TTE	
Cribier, Eltchaninoff, Tron, et al., 2004[22]	**Country/countries:** France **Setting:** Cath lab	**No. of patients:** 6 (1 death at surgery, 5 evaluable) **Age:** 75 ± 12 (57 to	**Valve name:** Percutaneous Valve Technologies, Inc. **Size of catheter:** 22 to 23	**Successful implantation:** 5/6 (83%) **Hemodynamic outcomes:**	**Complications:** Hemodynamic collapse: 2 (33%) **Valve dysfunction:**	2-patient overlap between Cribier, Eltchaninoff, Tron, et al., 2004[22] and Cribier, Eltchaninoff,

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
and **Eltchaninoff, Tron, and Cribier, 2003**[23] **and** **Cribier, Eltchaninoff, Bash, et al., 2002**[24]	**Basic design:** Case series **Study objective(s):** Assess the results of PHV implantation in non-surgical patients with end-stage calcific aortic stenosis **Duration of follow-up:** 8 to 18 wk	91) **Sex:** Female: 1 (17%) Male: 5 (83%) **Medical/functional status:** NYHA class IV **Surgical indication(s):** End-stage aortic stenosis **Inclusion criteria:** - Severe calcific aortic stenosis and multiple comorbidities - Declined for surgery by cardiac surgeons owing to hemodynamic instability and/or comorbidities - Aortic valve area ≤ 0.6 cm^2 **Exclusion criteria:** NR	mm **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral anterograde **Operator(s):** NR	1) Change in valve area: Mean 0.49 ± 0.08 → 1.66 ± 0.13 cm^2 2) Change in valve gradient: Mean 38 ± 11 → 5.6 ±3.4 mm Hg 3) Other – EF: Mean 24 ± 9.5 → 41 ± 12% Clinical status outcomes: **Change in NYHA functional class:** NR **30-day survival:** 1) 2 (33%) at 8 wk 2) Deaths (intra-operative to 18 wk): - Complications of leg amputation (n = 1) - Acute abdominal syndrome (n = 1) - Rectal cancer (n = 1)	Leak: - Severe paravalvular AR 2/5 (40%) - Mild paravalvular AR 3/5 (60%) Migration: 1/6 (17%)	Tron, et al., 2006[25] (i.e., the same 2 patients are described in both study reports)
Cribier, Eltchaninoff, Tron, et al., 2006[25]	**Country/countries:** France **Setting:** NR **Basic design:** Case series **Study objective(s):**	**No. of patients:** 36 enrolled; 33 underwent procedure (1 death prior to procedure, 1 death during pre-dilation, 1 procedure cancelled because annulus too large)	**Valve name:** Percutaneous Valve Technologies, Inc. (later became known as CoreValve) **Size of catheter:** NR **Self- or balloon-**	**Successful implantation:** 27/35 taken to cath lab (77%) 27/33 PHV placement attempted (82%) 2 procedures aborted; 2 acute PHV migrations; 3	**Complications:** Stroke: 1 (3%) **Valve dysfunction:** Leak: Paravalvular AR 10 (37%) Grade 1 12 (44%) Grade 2 5 (19%) Grade 3	2-patient overlap with Cribier, Eltchaninoff, Tron, et al., 2004[22] (i.e., the same 2 patients are described in both study reports)

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	Primary: Study the feasibility, safety, efficacy, and durability of PHV implantation in the aortic position Secondary: Obtain data regarding the efficacy and durability of the PHV **Duration of follow-up:** Up to 26 mo	**Age:** 80 ± 7 (62 to 91) **Sex:** Female: 15 (43%) Male: 21 (57%) **Medical/functional status:** NYHA class IV euroSCORE: 12 ± 2% **Surgical indication(s):** Inoperable AS **Inclusion criteria:** - Severe aortic valve stenosis with associated symptoms that were expected to benefit from isolated valve replacement - Formally declined for surgery by two independent cardiac surgeons on basis of high risk for surgery - Severe comorbidities - Aortic valve area ≤ 0.7 cm^2 - NYHA functional class IV **Exclusion criteria:** - Vascular disease that precluded access	**expanding?:** NR **Implantation approach:** Transfemoral retrograde: 7 Transfemoral antegrade: 26 Aborted retrograde to antegrade: 1 **Operator(s):** NR	failures to cross **Hemodynamic outcomes:** 1) Change in valve area: 0.6 ± 0.11 → 1.7 ± 0.1 cm^2 ($p < 0.0001$) 2) Change in valve gradient: Mean 37 ± 13 → 9 ± 2 mm Hg ($p < 0.0001$) 3) Other – LVEF: 45 ± 18 → 53 ± 14% at 1 wk ($p = 0.02$) **Clinical status outcomes:** Change in NYHA functional class (for 30-day survivors): To class I: 5 (24%) To class II: 14 (67%) To class III: 2 (10%) No improvement: 0% **Survival:** 1) 21 (78%) among patients with successful implantation at 30 days; 17 (63%) at 6 mo 2) Deaths associated with the procedure: - Tamponade (n = 2) - Brain death post-resuscitation (n = 1) - Ventriculararrhythmia (n = 1) - Unknown etiology (n = 1)	PHV migrations: 2	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		- Severe deformation of the chest - Intracardiac thrombus - Unprotected stenosis of the left main coronary artery not amenable to percutaneous intervention - MI within 7 days - Prosthetic heart valves - Active infection - Leukopenia - Coagulopathy - Active bleeding - Acute anemia - Pts who could not be fully dilated with a 23 mm aortic valvuloplasty balloon and pts with a native aortic valve annulus size > 24 mm or < 19 mm were also excluded				
Dumonteil, Marcheix, Berthoumieu et al., 2009[26]	**Country/countries:** France **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 1 month	**No. of patients:** 1 **Age:** 82 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Severe aortic stenosis, with a	**Valve name:** Edwards Sapien **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: TEE Fluoroscopy 2) Change in valve area: NR 3) Change in valve	**Complications of procedure:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Grade 1 aortic prosthesis leak	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		history of mitral valve replacement 25 years prior **Inclusion criteria:** NR **Exclusion criteria:** NR		gradient: NR. "Normal mitral and aortic prosthesis function with only grade 1 aortic prosthesis leak." **Clinical status outcomes:** 1) Change in NYHA functional class: Class II at 1 month **Survival:** 1/1 (100%) at 1 month		
Dvir, Assali, Vaknin, et al., 2009[27]	**Country/countries:** Israel **Setting:** NR **Basic design:** Case report **Study objective(s):** "We report a patient treated by this novel method, discuss and assess how it is implanted, report the findings conducted to date, and suggest future directions for percutaneous treatment of aortic valve disease." **Duration of follow-up:** 4 months	**No. of patients:** 1 **Age:** 87 **Sex:** Male **Medical/functional status:** NR **Surgical indication(s):** Deteriorating functional capacity secondary to weakness and dyspnea **Inclusion criteria:** NR **Exclusion criteria:** NR	Valve name: Edwards SAPIEN valve **Size of catheter:** 24 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** A multidisciplinary team of experts in echocardiography, intensive care, vascular surgery, radiology, cardiothoracic surgery, and invasive cardiology.	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: TEE C-cath 2) Change in valve area: 0.55 to 1.7 cm^2 3) Change in valve gradient: 101/62 to 33/16 mm Hg intraoperatively **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** 1/1 (100%) at 4 months	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: No paravalvular leakage immediately post-procedure	
Falk, Schwam-	**Country/countries:** Germany and Israel	**No. of patients:** 1	**Valve name:** Ventor Embracer Valve	**Successful implantation:** 1/1 (100%)	**Complications:** NR	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
menthal, Kempfert, et al., 2009[28]	**Setting:** Surgical hybrid suite **Basic design:** Case report **Study objective(s):** "Here we report implantation of this new valve in a patient." **Duration of follow-up:** 19 days	**Age:** 85 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Symptomatic AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Size of catheter:** 27 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Hemodynamic outcomes:** 1) Method of assessment: Echocardiogram 2) Change in valve area: NR 3) Change in valve gradient: Mean: NR to 4 mm Hg Peak: NR to 8 mm Hg **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Alive at discharge on day 19; no further f/u reported	**Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: Minimal paravalvular leak (grade < 1)	
Geist, Sherif, and Khattab, 2009[29]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 3 months	**No. of patients:** 1 **Age:** 79 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Non-ST elevation myocardial infarction **Inclusion criteria:** NR **Exclusion criteria:**	**Valve name:** CoreValve ReValving System **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** NR **Operator(s):** NR	**Successful implantation:** 1/1, but the article deals with successful coronary artery intervention 3 mo after valve implantation **Hemodynamic outcomes:** 1) Method of assessment: NR 2) Change in valve area: NR 3) Change in valve gradient: Peak: 60 to 5 mm Hg	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** NR	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		NR		**Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** 1/1 (100%) at 3 months		
Grube, Buellesfeld, Mueller, et al., 2008[30]	**Country/countries:** Germany **Setting:** NR **Basic design:** Prospective single site safety and performance study **Study objective(s):** "To demonstrate the progress among the various CoreValve Revalving device generations and to evaluate the current feasibility, safety, and efficacy status up to 12 months postimplantation, particularly of the third generation 18F CoreValve ReValving prosthesis compared with device generations 1 (25F) and 2 (21F)" **Duration of follow-up:** NR	**No. of patients:** 136 **Age:** 82 ± 7 **Sex:** Female: 79 (58%) Male: 57 (42%) **Surgical indication(s):** AS **Inclusion criteria:** - Severe AS (area < 1cm^2) *and* - ≥ 80 yr with a logistic euroSCORE (mortality) ≥ 20% (21 Fr group) - *or* ≥ 75 yr with a logistic euroSCORE (mortality) ≥ 15% (18 Fr group) - *or* ≥ 65 yr *plus* additional prespecified risk factors **Exclusion criteria:** - Hypersensitivity or contraindication to any study medication - Sepsis or active	**Valve name:** CoreValve ReValving system **Size of catheter:** 25 Fr (n = 10) 21 Fr (n = 24) 18 Fr (n = 102) **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** Generation 1: 7/10 (70%) Generation 2: 17/24 (71%) Generation 3: 93/102 (92%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: 41.6 ± 16.4 → 8.1 ± 3.8 mm Hg in generation 3 **Clinical status outcomes:** Change in NYHA functional class: 3.3 ± 0.5 → 1.7 ± 0.7 **30-day survival:** Generation 1: 6/10 (60%) Generation 2: 22/24 (92%) Generation 3: 91/102 (89%) **12-month survival:** Generation 1: 60% Generation 2: 79% Generation 3: 84%	**Procedural major adverse CV and cerebral events:** Generation 1: 20.0% Generation 2: 16.7% Generation 3: 3.9% **Complications:** 3 (2%) incorrect valve positioning, requiring deployment of 2nd prosthesis **Valve dysfunction:** Worsening of preinterventional AR in 33 patients (26%). Of these, 2 had postintervention AR of grade 3+. No grade 4+ AR.	10-patient overlap with Grube, Laborde, Gerckens, et al., 2006[31] and Grube, Schuler, Buellesfeld, et al., 2007[32] (i.e., the same 10 patients are described in all 3 study reports) *plus* An additional 4-patient overlap with Grube, Schuler, Buellesfeld, et al., 2007[32]

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		endocarditis - Excessive femoral, iliac or aortic atherosclerosis				
Grube, Laborde, Gerckens, et al., 2006[31]	**Country/countries:** Germany **Setting:** NR **Basic design:** Single-site case series **Study objective(s):** "To evaluate the feasibility and safety of implantation of the self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic valve disease using a retrograde percutaneous approach." **Duration of follow-up:** Up to 1 yr	**No. of patients:** 25 **Age:** 80 (range 68-94) **Sex:** Female: 20 (80%) Male: 5 (20%) **Surgical indication(s):** AS **Inclusion criteria:** - Severe AS (area < 1cm^2) - Aortic valve annulus diameter ≥ 20 and ≤ 23 mm) - Contraindication to surgery **Exclusion criteria:** - Hypersensitivity or contraindication to any study medication - Sepsis or active endocarditis - Excessive femoral, iliac or aortic atherosclerosis	**Valve name:** CoreValve ReValving system **Size of catheter:** 24 Fr (n = 10) 21 Fr (n = 15) **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 22/25 (88%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: 44.2 ± 10.8 → 12.4 ± 3.0 Clinical status outcomes: NR **30-day survival:** 20/25 (80%)	**Complications:** - Urgent open heart surgery (n = 1) - Severe AI - Left ventricle perforation - Hemodynamic failure - Disseminated intravascular coagulation **Valve dysfunction:** Valve leakage: Grade 0: 10 Grade 1+: 7 Grade 2+: 4 Grade 3-4+: 0	10-patient overlap with Grube, Buellesfeld, Mueller, et al., 2008[30] and Grube, Schuler, Buellesfeld, et al., 2007[32] (i.e., the same 10 patients are described in all 3 study reports)

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Grube, Laborde, Zickmann, et al., 2005[33]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 2 wk	**No. of patients:** 1 **Age:** 73 **Sex:** Female **Medical/functional status:** NYHA class IV **Surgical indication(s):** Severe symptomatic AS **Inclusion criteria:** Surgical valve replacement had been declined for the pt because of comorbidities, including previous bypass surgery **Exclusion criteria:** NR	**Valve name:** CoreValve, composed of three bovine pericardial leaflets inserted within a self-expanding nitinol stent **Size of catheter:** 25 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: Mean 45 → 8 mm Hg 3) Other – EF: 45 → 76% **Clinical status outcomes:** Change in NYHA functional class: IV → II **30-day survival:** 1 (100%)	**Complications:** None **Valve dysfunction:** None	
Grube, Schuler, Buellesfeld, et al., 2007[32]	**Country/countries:** Germany and Canada **Setting:** NR **Basic design:** Prospective multicenter, single-arm safety and performance study **Study objective(s):** To determine both the procedural	**No. of patients:** 86 50 = 21 Fr 36 = 18 Fr **Age:** 21-Fr: Mean 81± 5 yr 18-Fr: Mean 83 ± 7 yr **Sex:** Female: 56 (65%) Male: 30 (35%) **Medical/functional status:**	**Valve name:** CoreValve **Size of catheter:** 21 Fr (2nd generation) 18 Fr (3rd generation) **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** Acute device success 76/86 (88%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: NR **Clinical status outcomes:**	**Complications:** - Conversion to operative valve placement due to misplacement of valve: 6 - Stroke: 9 (10%) - Cardiac tamponade: 9/64 (14%) - Death or MI or tamponade or stroke or conversion to surgery/valvulo-plasty or emerging	10-patient overlap with Grube, Laborde, Gerckens, et al., 2006[31] and Grube, Buellesfeld, Mueller, et al., 2008[30] (i.e., the same 10 patients are described in all 3 study reports) *plus* An additional 4-patient overlap with

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	performance and safety of percutaneous implantation of the second (21-Fr) and third (18-Fr) generation CoreValve aortic valve prosthesis **Duration of follow-up:** 30 days	71 (83%) NYHA class III or IV **Logistic euroSCORE (mortality):** 21-F: 23 ± 14% 18-F: 19 ± 11% **Surgical indication(s):** Symptomatic severe AS **Inclusion criteria:** - Severe AS (area < 1 cm^2) - *And* ≥ 80 yr with a logistic euroSCORE (mortality) ≥ 20% (21-F group) - *Or* ≥ 75 yr with a logistic euroSCORE (mortality) ≥ 15% (18-F group) - *Or* ≥ 65 yr *plus* additional prespecified risk factors **Exclusion criteria:** - Hypersensitivity or contraindication to any study medication - Sepsis or active endocarditis - Excessive femoral, iliac or aortic atherosclerosis		Change in NYHA functional class: Mean class 2.85 ± 0.73 → 1.85 ± 0.6 ($p < 0.0001$) **30-day survival:** 76 (88%) at 30 days	DCI: 22 (26%) **Valve dysfunction:** Leak (paravalvular): - Grade 3+ or 4+ AR: 0 - Worsening to grade 2+: 15 (20%) - Worsening to grade 1+: 11 (14%)	Grube, Buellesfeld, Mueller, et al., 2008[30] Authors state that "percutaneous valve replacement with the CoreValve revalving system for selected patients with severe AS provides an encouraging device success rate, results in marked hemodynamic and clinical improvement, and is associated with a comparably low acute and 30-day mortality rate in this high-risk population."

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Hanzel, Harrity, Schreiber, et al., 2005[34]	**Country/countries:** United States **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 5 days (until death)	**No. of patients:** 1 **Age:** 84 **Sex:** Male **Medical/functional status:** NYHA class IV **Surgical indication(s):** Critical AS **Inclusion criteria:** Deemed too high-risk for surgical aortic valve replacement by two surgeons **Exclusion criteria:** NR	**Valve name:** Percutaneous Valve Technologies (trileaflet bovine pericardial valve mounted within a stainless steel tubular-slotted stent) **Size of catheter:** 24 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde (successful implantation) Transfemoral antegrade (unsuccessful attempt) **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.55 → 1.7 cm^2 2) Change in valve gradient: 45 → 4 mm Hg 3) Other – EF: 20 → 20% **Clinical status outcomes:** Change in NYHA functional class: NR **30-day survival:** 0 (0%) at 30 days	**Complications:** Day 1: Pt developed pulseless electrical activity requiring chest compressions, removal of guidewire, intubation, vasoactive drugs, and intra-aortic balloon pump insertion; antegrade approach abandoned; AV crossed retrograde Day 3: Pt developed VT requiring 1 electrical shock Day 4: Pt developed worsening hypotension requiring addition of norepinephrine and neosynephrine to dopamine and dobutamine Day 5: Pt developed pulseless electrical activity, and was resuscitated after 25 min; decision made to withhold further resuscitative efforts, and patient died **Valve dysfunction:** Leak: Mild/moderate paravalvular AR	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Himbert, Des-coutures, Al-Attar, et al. 2009[35]	**Country/countries:** France **Setting:** NR **Basic design:** Case series **Study objective(s):** "We sought to describe the results of a strategy offering either transfemoral or transapical aortic valve implantation (TAVI) in high-risk patients with severe aortic stenosis." **Duration of follow-up:** 10 months (SD 6); range 1-27	**No. of patients:** 75 (51 transfemoral, 24 transapical) **Age:** 82 (SD 8) **Sex:** Female n=34 (45%) Male n=43 (55%) **Medical/functional status:** NYHA class II: 4 (5%) III: 40 (53%) IV: 32 (41%) **Surgical indication(s):** AS **Inclusion criteria:** Among all patients with severe symptomatic AS consecutively referred for TAVI by primary or tertiary hospitals or by independent cardiologists, with a high surgical risk or contraindications to surgical aortic valve replacement. Inclusion criteria included EuroSCORE ≥20% or STS-PROM ≥10%, life expectancy > 1yr, anatomy suitable for intervention, and no need for CABG. **Exclusion criteria:** NR	**Valve name:** Edwards-SAPIEN **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon **Implantation approach:** Transfemoral retrograde as first option; transapical approach used when there were contraindications to the transfemoral route **Operator(s):** Cardiac surgeon	**Successful implantation:** Overall: 70/75 (93%) Transfemoral: 46/51 (90%) Transapical: 24/24 (100%) **Hemodynamic outcomes:** 1) Method of assessment: TTE 2) Change in valve area: NR 3) Change in valve gradient: NR **Clinical status outcomes:** 1) Change in NYHA functional class: NYHA functional class among survivors at last f/u: I: 20 (33%) II: 35 (57%) III: 6 (10%) 2) Survival (at 30 days: Overall: 69/75 (92%) Transfemoral: 47/51 (92%) Transapical: 22/24 (92%)	**Complications:** Hemopericardium in 1 pt from perforation of left ventricle, leading to intraprocedural death **Major cardiovascular/cerebrovascular events:** Stroke: n = 3 (all in transfemoral group) **Valve dysfunction:** Leak: Grade II or greater: 13 (17%) Grade III or greater: 4 (5%) Redilation for paravalvular leak: 5 (7%) AV blocks requiring pacemaker: 4 (5%) Emergent implantation of a second valve ("valve-in-valve") in 1 pt Second valve implanted in a higher position because of misplacement of first valve in 2 pts Iliac dissections: 4 (5%) Tamponade: 4 (5%)	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Kapadia, Svensson, and Tuzcu, 2009[36]	**Country/countries:** United States **Setting:** NR **Basic design:** Case report **Study objective(s):** "We report an uncommon complication of left main trunk occlusion with deployment of the valve and its successful percutaneous management with clinical follow-up." **Duration of follow-up:** 18 months	**No. of patients:** 1 **Age:** 82 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Severe aortic stenosis, presenting with NSTEMI and heart failure **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** NR **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** 1/1 (100%) at 18 months	**Complications of procedure:** Left main trunk occlusion **Major cardiovascular/ cerebrovascular events:** Left main trunk occlusion **Valve dysfunction:** NR	
Klaaborg, Egeblad, Jakobsen, et al., 2009[37]	**Country/countries:** Denmark **Setting:** NR **Basic design:** Case report **Study objective(s):** "We report transapical treatment of a stenosed 21 mm Mitroflow aortic valve prosthesis using the Edwards SAPIEN THV." **Duration of follow-up:** 1 month	**No. of patients:** 1 **Age:** 82 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** **Severe stenosis, shortness of breath, chest pain, overt heart failure** **Inclusion criteria:**	**Valve name:** Original: 21-mm Mitroflow Replacement: 23-mm Edwards SAPIEN THV **Size of catheter:** 26 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Method of assessment: TTE 2) Change in valve area: 0.4 to 1.0 cm^2 3) Change in valve gradient: Peak: 100 to 40 mm Hg **Clinical status outcomes:**	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: Mild central aortic valve regurgitation	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	Duration of follow-up: 2 weeks post-procedure; no further f/u data reported	NR **Exclusion criteria:** NR		Change in NYHA functional class: NR **Survival:** Alive at discharge 2 weeks after the procedure; no further f/u reported		
Kolettis, Spargias, and Stavridis, 2009[38]	**Country/countries:** Greece **Setting:** Cardiac cath lab **Basic design:** Case report **Study objective(s):** "We present a case of on-pump coronary artery bypass grafting with beating heart, combined with transapical aortic valve implantation, in a young man with porcelain aorta, severe AS and critical stenosis of the left main coronary artery." **Duration of follow-up:** 6 days	**No. of patients:** 1 **Age:** 48 **Sex:** Male **Medical/functional status:** NR **Surgical indication(s):** Severe AS, left main coronary artery disease, and porcelain aorta **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** 23-mm Edwards SAPIEN pericardial stented xenograft prosthesis **Size of catheter:** **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical (in combination with CABG via sternotomy) **Operator(s):** Interventional cardiologist	**Successful implantation:** 1/1 (100%) Hemodynamic outcomes: 1) Method of assessment: TEE C-cath 2) Change in valve area: NR 3) Change in valve gradient: NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Alive at discharge on day 6	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: Mild aortic insufficiency without any paravalvular leak	Postoperative echocardiography revealed mild aortic insufficiency without any paravalvular leak
Lamarche, Cartier, Denault, et al., 2007[39]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report	**No. of patients:** 1 **Age:** 64 **Sex:** Female **Medical/functional**	**Valve name:** ReValving System (CoreValve, Paris) **Size of catheter:** 21 Fr **Self- or balloon-expanding?:** Self-	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.61 → 1.4 cm^2	**Complications:** None **Valve dysfunction:** Leak: Trace paravalvular	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		status: NYHA class IV Parsonnet score 35 **Surgical indication(s):** - Critical AS - Idiopathic pulmonary fibrosis **Inclusion criteria:** Refused for AVR surgery **Exclusion criteria:** NR	expanding Implantation approach: **Transfemoral retrograde** Operator(s): **NR**	2) Change in valve gradient: NR 3) Other – LVEF: 20 → 35% **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** 1 (100%) at 3 mo		
Lange, Schreiber, Gotz, et al., 2007[40]	**Country/countries:** Germany **Setting:** Hybrid operation theater **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 10 days	**No. of patients:** 1 **Age:** 87 **Sex:** Female **Medical/functional status:** NYHA class III Logistic euroSCORE (mortality) 36% euroSCORE 13 **Surgical indication(s):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** CoreValve TAVR ReValving (Irvine, CA) **Size of catheter:** 18 Fr sheath **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: Peak gradient of 100 mm Hg to mean gradient of 15 mm Hg 3) Other – EF: Unchanged: 50% **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** 1 (100%) at 10 days	**Complications:** None **Valve dysfunction:** Leak: Trace paravalvular leak	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Lichtenstein, Cheung, Ye, et al., 2006[41] and **Ye, Cheung, Lichtenstein, et al., 2007**[42]	**Country/countries:** Canada **Setting:** Operating room with fluoroscopy **Basic design:** Case series **Study objective(s):** NR **Duration of follow-up:** 6 mo	**No. of patients:** 7 **Age:** 77± 10 **Sex:** Female: 2 (29%) Male: 5 (71%) **Medical/functional status:** NYHA class II: 2 (29%) NYHA class III: 4 (58%) NYHA class IV: 1 (13%) Logistic euroSCORE (mortality): 31±23% **Surgical indication(s):** Symptomatic AS **Inclusion criteria:** Judged to be at unacceptably high risk for routine open-heart AVR with CPB because of significant comorbidity **Exclusion criteria:** NR	**Valve name:** Cribier-Edwards Valve (Edwards Lifesciences, Inc.) equine pericardial trileaflet valve **Size of catheter:** 24 Fr **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** 7 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.7 ± 0.3 → 1.8 ± 0.7 cm^2 2) Change in valve gradient: Mean 32 ± 8 → 10 ± 5 mm Hg at 1 mo 3) Other: LVEF 49 ± 9% → 52 ± 13% No change in valve function after procedure to one month later **Clinical status outcomes:** Change in NYHA functional class: “Improved” in 4 “Unchanged” in 1 **30-day survival:** 1) 6/7 (86%) 2) 4/7 (57%) at 6 mo 3) 1 death from pneumonia on day 12 4) 1 death from lung disease 5) 1 death from cancer	**Complications:** None **Valve dysfunction:** Leak: paravalvular leak: Trivial: 4 (59%) Mild: 2 (29%) Moderate: 1 (14%)	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Marcheix, Lamarche, Berry, et al., 2007[43]	**Country/countries:** Canada **Setting:** Sterile cardiologic interventional suite **Basic design:** Case series **Study objective(s):** Report the experience with retrograde endovascular bioprosthesis implantation with brief cardiopulmonary bypass support in high-risk older patients **Duration of follow-up:** 1 mo	**No. of patients:** 10 **Age:** Mean 81 (64 to 85) **Sex:** Female: 5 (50%) Male: 5 (50%) **Medical/functional status:** NYHA class III: 7 (70%) NYHA class IV: 3 (30%) Median euroSCORE: 32% (21% to 40%) **Surgical indication(s):** - Severe AS - Deemed by 2 cardiothoracic surgeons to be at prohibitively high surgical risk for conventional open chest AVR **Inclusion criteria:** High or prohibitive risk with conventional surgery **Exclusion criteria:** NR	**Valve name:** CoreValve (Paris) **Size of catheter:** 21 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Retrograde **Operator(s):** NR	**Successful implantation:** 10 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.57 → 1.2 cm^2 2) Change in valve gradient: Mean 51 ± 19 → 11 ± 3 mm Hg **Clinical status outcomes:** Change in NYHA functional class: Median III → II (p = 0.01) **30-day survival:** 7/10 (70%) **Deaths:** - 2 from stroke; - 1 in hospital (cause NR)	**Complications:** - Vascular access site complication: 3 (30%) - Confusion: 3 (30%) - Respiratory infection: 1 (10%) - Hemopericardium requiring pericardiocentesis: 1 (10%) - Stroke: 2 (20%) - Acute renal failure: 1 (10%) - Non-sustained atrial fibrillation: 2 (20%) - Major bleeding: 2 (20%) - Ophthalmoplegia: 1(10%) **Valve dysfunction:** Leak: - Mild intraprosthesis 5 (50%) - Grade 1 periprosthetic leak 7 (70%) - Grade 2 periprosthetic leak 1 (10%) Need for re-intervention: 0; 2 patients required reoperation, but not cardiac	
Moreno, Dobarro,	**Country/countries:** Spain	**No. of patients:** 1	**Valve name:** 26-mm Edwards SAPIEN	**Successful implantation:** Without complication	**Complications:** AV block requiring	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Lopez de Sa, et al., 2009[44]	**Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 3 days	**Age:** 79 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Symptomatic severe AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** NR **Operator(s):** NR	*except* complete atrialventricular block requiring transvenous pacemaker stimulation **Hemodynamic outcomes:** NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Sudden cardiac death 3 days post-op (caused by RV perforation)	transvenous pacemaker **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** NR	
Ng, van der Kley, Delgado, et al., 2009[45]	**Country/countries:** The Netherlands **Setting:** NR **Basic design:** Case report **Study objective(s):** "We would like to share our experience with an 82 y/o man referred for percutaneous aortic valve replacement for treatment of grade 3 paravalvular aortic regurgitation with a 'valve-in-valve' procedure." **Duration of follow-up:** 30 days	**No. of patients:** 1 **Age:** 82 **Sex:** Male **Medical/functional status:** NYHA class III **Surgical indication(s):** NR **Inclusion criteria:** Patient had history of aortic valve replacement with a Medtronic Freestyle stentless aortic valve **Exclusion criteria:** NR	**Valve name:** CoreValve Revalving System **Size of catheter:** NR **Self- or balloon-expanding?:** NR **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** First attempt unsuccessful because of increased aortic regurgitation severity due to nondeployment of a single aortic cusp. Second implantation successful. **Hemodynamic outcomes:** Method of assessment: TTE Cardiac computed tomography **Change in valve area:** NR **Change in valve gradient:** NR Clinical status outcomes:	**Complications:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: "Minimal" residual paravalvular leak and mild central aortic regurgitation	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
				Change in NYHA functional class: NR **Survival:** 1/1 (100%) at 30 days		
Paniagua, Condado, Besso, et al., 2005[46]	**Country/countries:** Venezuela **Setting:** Cath lab **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 5 days (until death)	**No. of patients:** 1 **Age:** 62 **Sex:** Male **Medical/functional status:** Clinical description consistent with NYHA class IV **Surgical indication(s):** Inoperable calcific aortic stenosis and multiple severe comorbidities, including pulmonary edema, CHF, and pulmonary HTN **Inclusion criteria:** Pt was declined by three surgical groups because of low EF, comorbidities, and generally hopeless situation **Exclusion criteria:** NR	**Valve name:** Paniagua Heart Valve (Endoluminal Technology Research, Miami, FL) **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1 (100%) Hemodynamic outcomes: 1) Change in valve area: 0.6 → 1.6 cm^2 2) Change in valve gradient: 36 → < 5 mm Hg 3) Other – LVEF: 15% unchanged Clinical status outcomes: Change in NYHA functional class: NR **30-day survival:** 0% at 30 days Death on day 5 from reoperation failure	**Complications:** - Cardiac arrest requiring resuscitation and intubation - Complete atrioventricular block - Suspected pulmonary embolism **Valve dysfunction:** Leak: Mild paravalvular leak	
Piazza, Schultz, de Jaegere,	**Country/countries:** The Netherlands	**No. of patients:** 5 **Age:**	**Valve name:** CoreValve Revalving System	**Successful implantation:** Not applicable, because only patients with failure of	**Complications:** 79 yo female – Cardiac tamponade	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
et al., 2009[47]	**Setting:** NR **Basic design:** Case series **Study objective(s):** To evaluate the procedural, imaging, and clinical outcomes of patients who underwent transcatheter valve-in-valve implantation with two self-expanding aortic valve bioprostheses during the same procedure **Duration of follow-up:** Up to 351 days	Mean: 79 Range: 73 - 84 **Sex:** Female: 2 (40%) Male: 3 (60%) **Medical/functional status:** 79 yo female – NYHA IV 73 yo male – NYHA IV 79 yo male – NYHA III 80 yo male – NYHA IV 84 yo female – NYHA IV **Surgical indication(s):** Dyspnea, angina **Inclusion criteria:** 5 case reports of valve-in-valve implantation, from a series of 59 patients (54 of whom did not undergo a valve-in-valve procedure) **Exclusion criteria:** Patients in whom 2 sequential valves were implanted.	**Size of catheter:** NR **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	implantation of a first valve are included in this report. Of the 5 patients who underwent valve-in-valve implantation, 5/5 (100%) second valves were successfully implanted. **Hemodynamic outcomes:** Method of assessment: Computed tomography TTE **Change in valve area:** NR **Change in valve gradient:** NR Clinical status outcomes: Change in NYHA functional class: NR **Survival:** 79 yo female – died day 6 from septic shock and renal failure 73 yo male – alive at 351 days 79 yo female – alive at 316 days 80 yo male – alive at 64 days 84 yo female – alive at 8 days	(LAA and LV perforation) 79 yo male – Stroke and PPM for complete AVB 80 yo male – Recurrent SOB; ↑ peak TAVG to 49 mm Hg 73 yo male & 84 yo female – no complications **Major cardiovascular/ cerebrovascular events:** See above **Valve dysfunction:** NR	
Piazza, Serruys, and de	**Country/countries:** The Netherlands	**No. of patients:** 3 **Age:**	**Valve name:** CoreValve Revalving System	**Successful implantation:** 3/3 (100%)	**Complications:** NR **Major**	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Jaegere, 2009[48]	**Setting:** NR **Basic design:** Case reports **Study objective(s):** To describe the feasibility of the combination of percutaneous coronary intervention and percutaneous aortic valve implantation with peripheral left ventricular assist device (TandemHeart) support **Duration of follow-up:** 4-86 days	Mean: 87.3 Range: 81-93 **Sex:** Female 3 (100%) **Medical/functional status:** 1 pt – NYHA III 2 pts – NYHA IV **Surgical indication(s):** Dyspnea, angina Inclusion criteria: NR Exclusion criteria: NR	**Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde Operator(s): NR	**Hemodynamic outcomes:** Method of assessment: Intracardiac echocardiography **Change in valve area:** Pt #1: 0.7 to 1.4 cm^2 Pt #2: Baseline NR to 1.7 cm^2 Pt. #3: NR **Change in mean valve gradient:** Pt #1: 20 to 9 mm Hg Pt #2: Baseline NR to 8 mm Hg Pt. #3: NR **Clinical status outcomes:** Change in NYHA functional class: NR **Survival:** Alive at 86, 57, and 4 days follow-up, respectively	**cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** NR	
Rodés-Cabau, Dumont, De LaRochellière, et al., 2008[49]	**Country/countries:** Canada **Setting:** Cath lab for transfemoral procedure, and operating room for transapical procedure **Basic design:** Case series **Study objective(s):**	**No. of patients:** 24 enrolled, but 2 died awaiting the procedure, for actual sample size of 22 **Age:** 84 (range 62-91) **Sex:** Female: 12 (55%), Male: 10 (45%)	**Valve name:** Edwards-Sapien. 23 mm (n = 12) 26 mm (n = 10) **Size of catheter:** 22 Fr (n = 12) 24 Fr (n = 10) **Self- or balloon-expanding?:** Balloon-expanding	**Successful implantation:** 21/23 (91%) **Note:** 2 procedures in 1 patient **Hemodynamic outcomes:** 1) Change in valve area: 0.63 ± 0.18 → 1.45 ± 0.48 cm^2 2) Change in valve	**Complications:** - Intraoperative death (n = 1) from electromechanical dissociation immediately after aortic valve implantation - Severe AR (n = 1) - Cardiac tamponade (n = 1) - Myocardial apical tear (n = 1)	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	"To evaluate the results of…a multidisciplinary percutaneous aortic valve implantation program, focusing on patient and approach selection criteria, procedural results, and complications, as well as mid-term follow-up" **Duration of follow-up:** Median 6 mo	**Medical/functional status:** NYHA IV **Surgical indication(s):** Mixed aortic valve disease with severe AR and moderate AS. Patient was a candidate for surgical AVR, but she declined. **Inclusion criteria:** All patients who underwent the procedure at the study center from Apr 2007 to Jan 2008 **Exclusion criteria:** NR	**Implantation approach:** Transfemoral retrograde (n = 10); transapical (n = 11); aborted transfemoral to transapical (n = 1) **Operator(s):** Cardiac surgeons and interventional cardiologists	gradient: 34 ± 10 → 9 ± 2 mm Hg **Clinical status outcomes:** 1) Change in NYHA functional class: Not reported in a way that can be readily summarized **30-day survival:** 20/22 (91%)	**Valve dysfunction:** Paravalvular AR in 13 patients (1+ in 9 patients, 2+ in 4 patients)	
Rodés-Cabau, Houde, Perron, et al. 2008[50]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 3 mo	**No. of patients:** 1 **Age:** 21 **Sex:** Female **Medical/functional status:** NR **Surgical indication(s):** Moderate pulmonary insufficiency. Patient was status post Ross procedure at age 10 for bicuspid aortic valve with severe aortic stenosis.	**Valve name:** Melody valve Size of catheter: NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral antegrade **Operator(s):** NR	**Successful implantation:** 1/1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: 0.65 → 0.96 cm^2 2) Change in peak valve gradient: 75 mm → 75 mm Hg 24 hr after the procedure **Clinical status outcomes:** Change in NYHA functional class: NR	**Complications:** None **Valve dysfunction:** None	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		Inclusion criteria: See under "Surgical indications," above **Exclusion criteria:** NR		**30-day survival:** 1/1 (100%)		
Ruiz, Laborde, Condado, et al., 2008[51]	**Country/countries:** NR (authors from United States, France, and Venezuela) **Setting:** Cath lab **Basic design:** Case report **Study objective(s):** "To report the clinical, hemodynamic, and iconographic outcomes of the longest term survivor of the global CoreValve experience" **Duration of follow-up:** 3 yr	**No. of patients:** 1 **Age:** 58 **Sex:** Female **Medical/functional status:** NYHA IV **Surgical indication(s):** - Mixed aortic valve disease with severe AR and moderate AS - Patient was a candidate for surgical AVR, but she declined **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** CoreValve **Size of catheter:** 1st generation 25 Fr delivery system **Self- or balloon-expanding?:** NR **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1/2 (50%). First valve was deployed too proximal, necessitating deployment of a second valve ("valve in valve") during the same 6-hr procedure. **Hemodynamic outcomes:** 1) Method of assessment: TEE 2) Change in valve area: NR 3) Change in valve gradient: NR 4) Other: NR **Clinical status outcomes:** 1) Change in NYHA functional class: IV → II 2) Other: Resolution of CHF symptoms **30-day survival:** 1/1 (100%). 100% survival beyond 3 yr.	**Complications:** Severe AR from incorrect placement of first valve **Valve dysfunction:** - Leak: Trivial paravalvular - New moderate MR	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Schofer, Schluter, Treede, et al., 2008[52]	**Country/countries:** Germany, United States **Setting:** NR **Basic design:** Case series **Study objective(s):** "To assess the feasibility and safety of retrograde transarterial implantation of a novel nonmetallic aortic valve prosthesis" **Duration of follow-up:** NR	**No. of patients:** 15 **Age:** NR **Sex**: NR **Surgical indication(s):** AS **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Direct Flow Medical aortic valve prosthesis **Size of catheter:** NR **Self- or balloon-expanding?:** NR **Implantation approach:** Retrograde **Operator(s):** NR	**Successful implantation:** 12/15 (80%) **Hemodynamic outcomes:** 1) Change in median valve area: 1.64 → 0.60 cm^2 2) Change in valve gradient: 54.0 → 14.0 mm Hg **Clinical status outcomes:** NR **30-day survival:** 14/15 (93%)	**Complications:** - Death (n = 1) - Stroke (n = 1) **Valve dysfunction:** NR	Data abstracted from abstract only; trying to obtain copy of full text
Svensson, Dewey, Kapadia, et al., 2008[53]	**Country/countries:** United States **Setting:** "…mostly in hybrid fluoroscopy operating rooms. Early attempts to perform the procedure with mobile fluoroscopy units were abandoned." **Basic design:** Case series **Study objective(s):** Evaluate "feasibility of… transcatheter approach"	**No. of patients:** 40 **Age:** Mean 83 (69 to 93) **Sex:** Female: 19 (48%) Male: 21 (52%) **Medical/functional status:** Mean STS score: 13.4% (4% to 47%) Logistic euroSCORE (mortality): 35.5% ± 15.3% **Surgical indication(s):**	**Valve name:** Edwards Sapien Tanscatheter Heart Valve **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** 40 (100%) valves successfully delivered (35 [88%] successfully seated) Hemodynamic outcomes: 1) Change in valve area: 0.62 ± 0.13 → 1.61 ± 0.37 cm^2 2) Change in valve gradient: mean gradient 40 ± 9.8 → 7.7 ± 2.5 mm Hg 3) Other – AR: 1.4 → 1.2 (NS) **Clinical status**	**Complications:** - 3 deaths on day of operation - MI: 7 (18%) - Stroke: 2 (5%) - MACCE: 21 (53%) - Serious AE: 29 (73%) **Valve dysfunction:** - Leak: 0 - Migration: 1 (3%) - Need for re-intervention: 3 (8%) - Embolization: 3 (8%) - Severe AR: 1 (3%) - Leak at 30 days: 0 = 19% 1+ = 46%	Author states that "this new method may offer previously untreated patients or turned-down patients a new avenue of treatment provided procedural difficulties can be overcome."

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		Critical AS **Inclusion criteria:** - Age > 70 - Valve area ≤ 0.6 cm^2 - Society of Thoracic Surgeons score > 15% - *Or* deemed inoperable **Exclusion criteria:** NR		**outcomes:** Change in NYHA functional class: 3.33 → 2.25 (p < 0.0001) **30-day survival:** 33/40 (83%). 7 died within 30 days. An additional 2 died after 30 days.	2+ = 31% 3+ = 4% 4+ = 0%	
Tamburino, Capodanno, Mule, et al., 2009[54]	**Country/countries:** Italy **Setting:** NR **Basic design:** Prospective, nonrandomized study **Study objective(s):** To report acute and short-term outcomes of PAVR with the 18 Fr CoreValve Revalving System **Duration of follow-up:** Range: 1-13 months Mean: 4.9 ± 4 months	**No. of patients:** 30 **Age:** Mean: 82 ± 5 Range: 73-88 **Sex:** Female: 17 (57%) Male: 13 (43%) **Medical/functional status:** 10 pts NYHA I/II 20 pts NYHA III/IV **Surgical indication(s):** **Severe AS** **Inclusion criteria:** Native aortic valve stenosis with an aortic valve are < 1 cm^2 (< 0.6 cm^2/m^2) determined by echocardiography;	**Valve name:** Third-generation CoreValve Revalving System **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 29/30 (97%) **Hemodynamic outcomes:** Method of assessment: Echocardiography C-cath **Change in valve area:** 0.61 ± 0.18 to 1.49 ± 0.39 cm^2 (p < 0.001) **Change in valve gradient:** Peak: 85.6 ± 22.0 to 1.8 ± 4.0 mm Hg **Clinical status outcomes:** Change in NYHA functional class: 2.72 ± 0.59 pre-op to 1.31 ± 0.47 post-op (p < 0.001)	**Complications:** 1 pt required implantation of second CoreValve device due to unfavorable placement of first valve **Major cardiovascular/ cerebrovascular events:** Hemorrhagic stroke: 1 (3%) **Valve dysfunction:** Paravalvular leaks: 1+ in 12 pts 2+ in 2 pts	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		aortic valve annulus diameter ≥ 20 mm and ≤ 27 mm; sinotubular junction ≤ 43 mm; diameter of iliac and femoral arteries ≥ 6 mm; contraindications to surgery because of concomitant comorbid conditions assessed and agreed to by both an independent cardiologist and a cardiovascular surgeon **Exclusion criteria:** Femoral, iliac, or aortic pathologies, aortic aneurysm, carotid or vertebral artery obstruction ≥ 70%, coagulopathies, myocardial infarction or cerebrovascular accident within the previous month, severe tricuspid or mitral valvular regurgitation, left ventricular or atrial thrombus, uncontrolled atrial fibrillation, sepsis or active endocarditis, hypersensitivity or contraindications to any medication used in the study		**Survival:** At 30 days – 1 pt had died of hemorrhagic stroke and 1 had died as result of ischemic stroke which did not appear to be related to procedure		

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Ussia, Mule, and Tamburino, 2009[55]	**Country/countries:** Italy **Setting:** NR **Basic design:** Case report **Study objective(s):** "We report on a case o self-expandable biological valve prosthesis malpositioned high respect to the aortic valve annulus, resulting in severe aortic regurgitation treated with a second device implantation." **Duration of follow-up:** 6 months	**No. of patients:** 1 **Age:** 84 **Sex:** Female **Medical/functional status:** NYHA III **Surgical indication(s):** Severe aortic valve stenosis and mitral regurgitation **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** CoreValve Revalving System **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding (though balloon was dilated for second implantation to ensure earlier problem would not reoccur) **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** First implantation failed due to malposition ("the valve slipped upward just above the aortic cusps"). Second prosthesis was implanted successfully. **Hemodynamic outcomes:** C-cath Echocardiography **Change in valve area:** 0.36 to NR **Change in valve gradient:** Peak: 50 to 5 mm Hg (intraoperatively) Mean: 30 to 10 mm Hg (at 6 mos f/u) **Clinical status outcomes:** Change in NYHA functional class: NYHA class I **Survival:** 1/1 (100%) at 60 days	**Complications:** Pseudo-aneurism of right femoral artery treated with surgical reduction **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: 1+ paravalvular	
Ussia, Barbanti, and Tamburino, 2009[56]	**Country/countries:** Italy **Setting:** NR **Basic design:** Case report **Study objective(s):**	**No. of patients:** 1 **Age:** 85 **Sex:** Female **Medical/functional status:** NYHA class IV	**Valve name:** Third-generation CoreValve Revalving System **Size of catheter:** 18 Fr **Self- or balloon-expanding?:** Self-expanding	**Successful implantation:** Yes **Hemodynamic outcomes:** Method of assessment: TTE C-cath	**Complications of procedure:** NR **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:**	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	NR **Duration of follow-up:** 60 days	**Surgical indication(s):** Angina pectoris, severe dyspnea **Inclusion criteria:** NR **Exclusion criteria:** NR	**Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Change in valve area:** NR **Change in valve gradient:** Peak: 45 to 15 mm Hg **Clinical status outcomes:** Change in NYHA functional class: NYHA class I (after discharge**)** **Survival:** 1/1 (100%) at 60 days	Leak: 2+ paravalvular leak	
Walther, Falk, Kemfert, et al. 2008[57]	**Country/countries:** Germany, Austria, United States **Setting:** Hybrid operating theater **Basic design:** Case series **Study objective(s):** "To analyze the results of the initial 50 patients receiving transapical aortic valve implantation at a single center." **Duration of follow-up:** Up to 18 mo	**No. of patients:** 50 **Age:** 82.4 ± 4.6 **Sex:** Female: 39 (78%) Male: 11 (22%) **Medical/functional status:** NYHA: 3.4 ± 0.5 Logistic euroSCORE (mortality): 27.6 ± 12.2% **Surgical indication(s):** Severe symptomatic AS and high perioperative risk **Inclusion criteria:** - Age > 75 - Surgical high risk as judged by a EuroSCORE of > 9	**Valve name:** Edwards SAPIEN THV **Size of catheter:** 14 Fr introducer sheath **Valve diameter:** 23 mm (n = 13) 26 mm (n = 37) **Self- or balloon-expanding?:** NR **Implantation approach:** Transapical **Operator(s):** Cardiac surgeons and cardiologists	**Successful implantation:** 50/50 (100%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: NR **Clinical status outcomes:** Change in NYHA functional class: NR **30-day survival:** 46/50 (92%) **6-mo survival:** 73.9% ± 6.2% **12-mo survival:** 71.4% ± 6.5%	**Complications:** - Valve dislocation - Aortic root dissection - Coronary occlusion **Valve dysfunction:** NR	30-patient overlap with Walther, Simon, Dewey, et al. 2007[58] and Walther, Falk, Borger, et al., 2007[59] (i.e., the same 30 patients are described in all 3 study reports)

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		- Aortic annulus diameter < 24 mm - Symmetrically distributed calcification of the stenotic native aortic valve cusps **Exclusion criteria:** NR				
Walther, Simon, Dewey, et al. 2007[58] **and** **Walther, Falk, Borger, et al., 2007**[59]	**Country/countries:** Germany, Austria, United States **Setting:** Routine operative theater **Basic design:** Multicenter case series **Study objective(s):** "To present the initial multicenter results of the first ethically approved clinical trial for transapical minimally invasive aortic valve implantation" **Duration of follow-up:** Mean 110 days (range, 1 to 255 days)	**No. of patients:** 59 By site: Leipzig (n = 30); Vienna (n = 24) Frankfurt (n = 3) Dallas (n = 2) **Age:** 81 ± 6 **Sex:** Female: 44 (75%) Male: 15 (25%) **Medical/functional status:** NYHA: 3.4 ± 0.5 Logistic euroSCORE risk score (mortality): 27 ± 14% euroSCORE: 11.2 ± 1.8 **Surgical indication(s):** Severe symptomatic AS **Inclusion criteria:** - Age > 75 - Surgical high risk as	**Valve name:** Edwards SAPIEN THV **Size of catheter:** 14 Fr soft sheath **Self- or balloon-expanding?:** Balloon-expanding Implantation approach: Transapical **Operator(s):** Cardiac surgeons and cardiologists	**Successful implantation:** 54 (92%) patients, with one successful conversion to conventional valve replacement **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: mean gradient 43 ± 14 → 9 ± 6 mm Hg (95% CI: 7.3, 10,7) **Clinical status outcomes:** Change in NYHA functional class: NR **30-day survival:** 1) 51/59 (86%) 2) 3 deaths in hospital from non-valvular causes	**Complications:** - Perioperative conversion to sternotomy (n = 4) - New pacemaker (n = 2) - Stroke (n = 2) - Pleural effusion (n = 18) - Supraventricular arrhythmia (n = 18) - Tracheostomy (n = 8) **Aortic incompetence at time of hospital discharge (n = 40):** Leak: - None: 14 (35%) - Trace/mild: 23 (58%) - Mod/severe: 3 (8%)	30-patient overlap with Walther, Falk, Kemfert, et al. 2008[57] (i.e., the same 30 patients are described in all 3 study reports)

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		judged by a EuroSCORE of > 9 - Aortic annulus diameter < 24 mm - Symmetrically distributed calcification of the stenotic native aortic valve cusps **Exclusion criteria:** NR				
Webb, Altwegg, Masson, et al., 2009[60]	**Country/countries:** Canada **Setting:** Cath lab **Basic design:** Case series **Study objective(s):** "We describe a new delivery system and next-generation balloon-expandable valve in a case series of 25 high-risk patients undergoing transarterial AVR." **Duration of follow-up:** 30 days	**No. of patients:** 25 **Age:** Mean 85; range, 79-88 **Sex:** Female: 13 (52%) Male: 12 (48%) **Medical/functional status:** NYHA class I: 1 (4%) II: 2 (8%) III: 14 (56%) IV: 8 (32%) **Surgical indication(s):** AS **Inclusion criteria:** Symptomatic AS in whom the risk associated with open heart surgery was considered prohibitive by a team of cardiologists and	**Valve name:** SAPIEN (n = 22) SAPIEN XT (n = 3) **Size of catheter:** 22 Fr or 24 Fr **Self- or balloon-expanding?:** Balloon **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** SAPIEN 22/22 (100%) SAPIEN XT 3/3 (100%) **Hemodynamic outcomes:** 1) Method of assessment: Echocardiography 2) Change in valve area: 0.59 ± 0.15 to 1.6 ± 0.27 cm^2 3) Change in valve gradient: 49.3 ± 17.9 to 10.6 ± 2.9 mm HG 4) Other: All patients had normal prosthetic valve function at 1-month f/u **Clinical status outcomes:** 1) Change in NYHA functional class: NR	**Complications:** None reported **Major cardiovascular/ cerebrovascular events:** 2/25 (4%) with stroke or MI during 30-day f/u **Valve dysfunction:** 1 patient had more than mild valvular regurgitation	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		cardiac surgeons. **Exclusion criteria:** Annulus diameter < 18 or > 26 mm or severe iliofemoral arterial disease, or if reasonable quality or duration of life was unlikely		2) 30-day survival: 25/25 (100%)		
Webb, Pasupati, Humphries, et al., 2007[61] **and** **Webb, Chandavimol, Thompson, et al., 2006**[62] **and** **Clavel, Webb, Pibarot, et al., 2009**[63] **and** **Gutierrez M, Rodes-Cabau J, Bagur R, et al.,**	**Country/countries:** Canada **Setting:** Cath lab **Basic design:** Case series **Study objective(s):** "We report the early and late outcomes with this procedure in the initial 50 high-risk patients." **Duration of follow-up:** Median 359 days	**No. of patients:** 50 **Age:** 82 ± 7 (62 to 94) **Sex:** Female: 20 (40%) Male: 30 (60%) **Medical/functional status:** NYHA class II: 5 (10%) NYHA class III: 32 (64%) NYHA class IV: 13 (26%) Logistic euroSCORE (mortality): 28% **Surgical indication(s):** Severe AS **Inclusion criteria:** Not candidates for surgery **Exclusion criteria:** NR	**Valve name:** Cribier Edwards **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 43/50 (86%) success **Reasons for failure:** - Inaccessible iliac access: 1 - Inability to cross aortic valve: 3 - Defective delivery catheter: 1 - Malpositioning: 2 **Hemodynamic outcomes:** 1) Change in valve area: 0.6 ± 0.2 → 1.7 ± cm^2 2) Change in valve gradient: Mean 46 ± 17 → 11 ± 5 mm Hg 3) Other: LVEF 53 ± 15% → 57 ± 13% MR decreased from median Grade 2 → 1 **Clinical status**	**Complications:** - Death from aortic injury: 1 (2%) - Stroke: 2 (4%) - MI: 1 (2%) - Iliac artery perforation: 1(2%) - Ventricular fibrillation: 2 (4%) - Tamponade: 1 (2%) - Heart block: 2 (4%) **Valve dysfunction:** Leak: Moderate paravalvular insufficiency 3 (6%) AR Grade improved in 32%, was unchanged in 24%, and worsened in 44%	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
2009[64]				**outcomes:** Change in NYHA functional class: 50% of patients improved ≥ 1 class at 30 days **30-day survival:** 44/50 (88%)		
Wenaweser, Buellesfeld, Gerckens, et al., 2007[65]	**Country/countries:** Germany **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 12 mo	**No. of patients:** 1 **Age:** 80 **Sex:** Male **Medical/functional status:** NYHA class: IV Logistic euroSCORE (mortality): 35.6% **Surgical indication(s):** - Severe AR of a bioprosthesis - Prior surgical valve replacement - History of endocarditis - History of 2 prior thoracotomies - Refuses surgery **Inclusion criteria:** See "Surgical indications," above **Exclusion criteria:** NR	**Valve name:** CoreValve ReValving System (2nd generation) **Size of catheter:** 21 Fr **Self- or balloon-expanding?:** NR **Implantation approach:** Transfemoral retrograde **Operator(s):** NR	**Successful implantation:** 1 (100%) **Hemodynamic outcomes:** 1) Change in valve area: NR 2) Change in valve gradient: NR 3) Other – cardiac output: 2.6 → 4.4 L/min **Clinical status outcomes:** Change in NYHA functional class: Class IV → Class I **30-day survival:** 1 (100%). 100% survival at 1 yr as well.	**Complications:** None **Valve dysfunction:** None	Article discusses the first "Valve in Valve" procedure

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
Wendt, Eggebrecht, Kahlert, et al., 2009[66]	**Country/countries:** Germany **Setting:** Hybrid OR **Basic design:** Case report **Study objective(s):** "We report a successful transapical aortic valve implantation performed in a 96 y/o woman demonstrating the potential o the novel technique as an alternative treatment option in old and multimorbid patients at high risk for conventional AR." **Duration of follow-up:** 30 days	**No. of patients:** 1 **Age:** 96 **Sex:** Female **Medical/functional status:** NYHA class III/IV **Surgical indication(s):** Dyspnea and recurrent syncope based on severe aortic valve stenosis **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Edwards SAPIEN **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** Yes **Hemodynamic outcomes**: Method of assessment: TTE C-cath **Change in valve area:** 0.4 to 1.7 cm^2 at 30-day f/u **Change in valve gradient:** Mean: 61 to 6 mm Hg at 30 day f/u **Clinical status outcomes:** Change in NYHA functional class: NYHA class I at 30 days **Survival:** 1/1 at 30 days	**Complications:** Mild renal impairment **Major cardiovascular/ cerebrovascular events:** NR **Valve dysfunction:** Leak: "No signs of paravalvular leakage"	
Wong, Boone, Thompson, et al., 2009[67]	**Country/countries:** Canada **Setting:** NR **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 13 months	**No. of patients:** 1 **Age:** 88 **Sex:** Male **Medical/functional status:** NR **Surgical indication(s):** Symptomatic severe AS **Inclusion criteria:**	**Valve name:** Edwards SAPIEN **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** NR **Operator(s):** NR	**Successful implantation:** Suboptimal valve placement, but successful **Hemodynamic outcomes:** TTE **Change in valve area:** NR **Change in valve gradient:** NR **Clinical status**	**Complications:** Moderate paravalvular AR treated with repeated balloon redilation without altering the valve position **Major cardiovascular/ cerebrovascular events:** None **Valve dysfunction:** Leak: Paravalvular	Pt presented 11 months post-op with fever and streptococcus in blood culture (from dental procedure without endocarditis prophylaxis) – treatment was complicated by renal failure, pneumonia, delirium, and dysphagia

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
		NR **Exclusion criteria:** NR		**outcomes:** Change in NYHA functional class: NR **Survival:** Alive at 11-month f/u		
Ye, Webb, Cheung, et al., 2009[68]	**Country/countries:** Canada **Setting:** Operating room **Basic design:** Case report **Study objective(s):** NR **Duration of follow-up:** 16 months	**No. of patients:** 1 **Age:** 85 **Sex:** Male **Medical/functional status:** NYHA III/IV **Surgical indication(s):** Severe aortic regurgitation, associated with pulmonary hypertension and preserved LV systolic function **Inclusion criteria:** NR **Exclusion criteria:** NR	**Valve name:** Edwards SAPIEN **Size of catheter:** NR **Self- or balloon-expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	**Successful implantation:** This was a valve-in-valve implantation after earlier prosthesis was failing **Hemodynamic outcomes:** Echocardiography Fluoroscopy **Change in valve area:** NR **Change in valve gradient:** NR **Change in NYHA functional class:** Class I at 16 months **Survival:** Yes, at 16 months	**Complications:** None **Major cardiovascular/ cerebrovascular events:** None **Valve dysfunction:** None	
Zierer, Wimmer-Greinecker, Martens, et al., 2008[69]	**Country/countries:** Germany **Setting:** Specially equipped angiography suite (hybrid operating room) **Basic design:** Case	**No. of patients:** 26 **Age:** 84 ± 7 **Sex:** Female: 20 (77%) Male: 6 (23%) **Medical/functional**	**Valve name:** Cribier-Edwards 23 mm (n = 11) 26 mm (n = 15) **Size of catheter:** 14 Fr soft sheath **Self- or balloon-**	**Successful implantation:** 25/26 (96%) **Hemodynamic outcomes:** 1) Method of assessment: TEE 2) Change in valve area:	**Complications:** - 2 (8%) conversion to open surgery - 2 (8%) left main stem obstruction - 3 (12%) severe hypotension - 1 (4%) intraoperative death	

Evidence Table 2. Published studies of percutaneous heart valves (Questions 3-4) (continued)

Study	Study characteristics	Patients	Intervention	Outcomes	Adverse events	Comments
	series **Study objective(s):** "To report our initial clinical experience in 26 consecutive patients who underwent antegrade placement of a catheter-deliverable aortic valve" **Duration of follow-up:** NR	**status:** NYHA class 3.5 ± 0.4 **Surgical indication(s):** AS **Inclusion criteria:** - Age ≥ 75 - Severe symptomatic AS - Aortic valve orifice ≤ 0.8 cm^2 - High surgical risk (EuroSCORE predicted risk > 20%) - Aortic valve diameter ≤ 24 mm **Exclusion criteria:** - Aortic annulus diameter > 25 mm - Non-calcified AS - Subvalvular AS - Bicuspid aortic valve - Intracardiac thrombus - Endocarditis - Untreated symptomatic coronary artery disease - Recent ME - EF < 20% - Recent stroke - Hypertrophic obstructive cardiomyopathy	**expanding?:** Balloon-expanding **Implantation approach:** Transapical **Operator(s):** NR	NR 3) Change in valve gradient: NR **Clinical status outcomes:** NR **30-day survival:** 22/26 (85%)	from aortic root dissection - 1 (4%) death from right ventricle perforation - 1 (4%) aortic annulus rupture **Valve dysfunction:** Mild-moderate AI due to paravalvular leakages	

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Appendix C. Additional Tables Relevant to Question 2

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Aklog, Carr-White, Birks, et al., 2000[1] **Systematic review citation?:** No	**N:** 182 **Adult only?:** Mixed **Follow-up timing:** (median) 33.9 mo	**Valve position:** Aortic **Valve 1:** Pulmonary autograft **Valve 2:** Aortic homograft	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Ali, Halstead, Cafferty, et al., 2006[2] **and Ali, Halstead, Cafferty, et al., 2007**[3] **Systematic review citation?:** Yes	**N:** 161 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 23 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Perimount **Valve 2:** Edwards Prima Plus	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	
Angell, Angell, & Sywak, 1977[4] **Systematic review citation?:** No	**N:** 99 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 60 mo	**Valve position:** Aortic and mitral **Valve 1:** Starr-Edwards composite-seat (6320 mitral; 2310 aortic) **Valve 2:** Homografts provided by Northern California Transplant Bank (fresh human aortic valves)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Anonymous, 1985[5] and Hammermeister, Henderson, Burchfiel, et al., 1987[6] and Khuri, Folland, Sethi, et al., 1988[7] and Hammermeister, Sethi, Henderson, et al., 1993[8] and Hammermeister, Sethi, Henderson, et al., 2000[9] Systematic review citation?: Yes	**N:** 575 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 180 mo	**Valve position:** Aortic = 394 Mitral = 181 **Valve 1:** Bjork-Shiley spherical disc **Valve 2:** Hancock porcine-heterograft bioprosthetic	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	VA Cooperative Study
Autschbach, Walther, Falk, et al., 2000[10] Systematic review citation?: No	**N:** 300 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** ATS Medical, Inc. **Valve 2:** Carbomedics	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Bakhtiary, Abolmaali, Dzemali, et al., 2006[11] Systematic review citation?: Yes	**N:** 40 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 5 days	**Valve position:** Aortic **Valve 1:** Medtronic Hall tilting disc OR Medtronic ADVANTAGE bileaflet **Valve 2:** Medtronic Mosaic OR Medtronic Freestyle	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	Data from abstract only. Patient population may overlap with that in Bakhtiary, Schiemann, Dzemali, et al., 2006,[12] but unable to verify.
Bakhtiary, Schiemann, Dzemali, et al., 2006[12] Systematic review citation?: No	**N:** 24 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle **Valve 2:** Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	Patient population may overlap with that in Bakhtiary, Abolmaali, Dzemali, et al., 2006,[11] but unable to verify.
Berg, McLaughlin, Akar, et al., 1998[13] Systematic review citation?: No	**N:** 40 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards SAV stented bioprosthesis **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Bloomfield, Kitchin, Wheatley, et al., 1986[14] **and Bloomfield, Wheatley, Prescott, et al., 1991**[15] **and Oxenham, Bloomfield, Wheatley, et al., 2003**[16] **Systematic review citation?:** Yes	**N:** 541 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 240 mo	**Valve position:** Aortic = 211 Mitral = 262 Both = 60 Assoc. tricuspid = 8 **Valve 1:** Bjork-Shiley ABP/MBRP-60º spherical stilting disc **Valve 2:** Hancock 242/342 OR later Carpentier-Edwards 2625/6625	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Carr-White, Glennan, Edwards, et al., 1999[17] **Systematic review citation?:** No	**N:** 47 **Adult only?:** Mixed **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Pulmonary autograft **Valve 2:** Aortic homograft	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Chambers, Rimington, Hodson, et al., 2006[18] **Systematic review citation?:** Yes	**N:** 160 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Stentless Porcine Valve **Valve 2:** Edwards Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	
Chambers, Rimington, Rajani, et al., 2007[19] **Systematic review citation?:** No	**N:** 78 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Cryolife O'Brien model 300 **Valve 2:** St. Jude Medical Stentless Porcine Valve	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	
Chambers, Roxburgh, Blauth, et al., 2005[20] **Systematic review citation?:** No	**N:** 52 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** CarboMedics Top Hat Supraanular **Valve 2:** Medical Carbon Research Institute (MCRI) On-X	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Cohen, Christakis, Campbell, et al., 2002[21] **Systematic review citation?:** Yes	**N:** 99 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards pericardial **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Dalmau, Gonzalez-Santos, Lopez-Rodriguez, et al., 2007[22] **Systematic review citation?:** No	**N:** 86 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Edwards Perimount Magna **Valve 2:** Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	
de la Fuente, Sanchez, Romero, et al., 2000[23] **Systematic review citation?:** No	**N:** 200 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 67 mo	**Valve position:** Aortic **Valve 1:** CarboMedics mechanical **Valve 2:** Monostrut mechanical tilting disc	**Hemodynamic:** NR **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	
Doss, Martens, Wood, et al., 2002[24] **Systematic review citation?:** Yes	**N:** 40 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Perimount **Valve 2:** Edwards Prima Plus	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	Completely different population than in Doss, Wood, Martens, et al., 2005[25]
Doss, Wood, Martens, et al., 2005[25] **Systematic review citation?:** No	**N:** 40 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Pulmonary autograft **Valve 2:** Edwards MIRA	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	Completely different population than in Doss Martens, Wood, et al., 2002[24]
Dunning, Graham, Thambyrajah, et al., 2007[26] **Systematic review citation?:** No	**N:** 60 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Sorin Freedom **Valve 2:** Sorin More	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Efskind, Nitter-Hauge, Hall, et al., 1973[27] **Systematic review citation?:** No	**N:** 115 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 18–30 mo	**Valve position:** Aortic = 68 Mitral = 47 **Valve 1:** Lillehei-Kaster low profile **Valve 2:** Bjork-Shiley low profile	**Hemodynamic:** NR **Cardiac function:** Yes **Mortality:** NR **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** NR	
Eichinger, Botzenhardt, Keithahn, et al., 2004[28] **and Eichinger, Botzenhardt, Guenzinger, et al., 2004**[29] **Systematic review citation?:** No	**N:** 136 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 10 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Carpentier-Edwards Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	
Fiore, Barner, Swartz, et al., 1998[30] **Systematic review citation?:** No	**N:** 156 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 61 mo	**Valve position:** Mitral **Valve 1:** St. Jude Medical bileaflet **Valve 2:** Medtronic Hall tilting disc	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Fiore, Swartz, Grunkmeier, et al., 1997[31] **Systematic review citation?:** No	**N:** 80 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 40.5 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical bileaflet **Valve 2:** Medtronic Hall tilting disc	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	Subgroup population analysis from a 456-patient RCT
Graham, Thambyrajah, Stewart, et al., 2005[32] **Systematic review citation?:** Yes	**N:** 54 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Sorin Freedom stentless **Valve 2:** Sorin More stented	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	Data from abstract only
Gross, Harringer, Mair, et al., 1995[33] **and Gross, Harringer, Beran, et al., 1999**[34] **Systematic review citation?:** No	**N:** 139 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 45 mo	**Valve position:** Aortic **Valve 1:** Cryopreserved homograft **Valve 2:** Edwards Prima stentless model 2500	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Guenzinger, Eichinger, Hettich, et al., 2008[35] **Systematic review citation?:** No	**N:** 80 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Medtronic Advantage Supra **Valve 2:** St. Jude Medical Regent	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** es	
Horstkotte, Haerten, Herzer, et al., 1983[36] **Systematic review citation?:** Yes	**N:** 150 **Adult only?:** Mixed **Follow-up timing:** (mean or longest value given) 60 mo	**Valve position:** Mitral **Valve 1:** Bjork-Shiley standard **Valve 2:** Lillehei-Kaster **Valve 3:** Starr-Edwards 6120	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Jasinski, Ulbrych, Kolowca, et al., 2004[37] **Systematic review citation?:** Yes	**N:** 16 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 1 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Medtronic Freestyle	**Hemodynamic:** NR **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	
John, Khan, Kuo, et al., 2006[38] **Systematic review citation?:** No	**N:** 242 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 40 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Carpentier-Edwards SAV porcine bioprosthesis	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	Data from abstract only
Kim, Lesaffre, Scheys, et al., 1994[39] **Systematic review citation?:** No	**N:** 403 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 61 mo	**Valve position:** Aortic and mitral **Valve 1:** Monostrut tilting disc **Valve 2:** Medtronic-Hall tilting disc	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Kleine, Hasenkam, Nygaard, et al., 2000[40] **Systematic review citation?:** No	**N:** 24 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Medtronic-Hall tilting disc **Valve 2:** St. Jude Medical bileaflet	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Kuntze, Blackstone, and Ebels, 1998[41] **and Kuntze, Ebels, Eijgelaar, et al, 1989**[42] **Systematic review citation?:** No	**N:** 419 **Adult only?:** Yes **Follow-up timing:** (median) 98.5 mo	**Valve position:** Aortic = 254 Mitral = 111 Both = 54 **Valve 1:** Bjork-Shiley Convex-Concave (later replaced by Bjork-Shiley Monostrut) **Valve 2:** Medtronic-Hall **Valve 3:** Edwards-Duromedics bileaflet	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** No **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	Edwards-Duromedics was added as a third arm after approx 2.5 years – therefore shorter follow-up and smaller n
Kvidal, Bergstrom, Malm, et al., 2000[43] **Systematic review citation?:** No	**N:** 424 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 120 mo	**Valve position:** Aortic **Valve 1:** Bjork-Shiley Monostrut **Valve 2:** Edwards Duromedics	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	
Lehmann, Walther, Kempfert, et al., 2007[44] **Systematic review citation?:** No	**N:** 223 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 94.2 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle OR St. Jude Toronto Stentless Porcine Valve **Valve 2:** Carpentier-Edwards porcine xenograft	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** No **Adverse Events:** Yes	
Levang, 1978[45] **and Levang, 1979**[46] **and Levang, Nitter-Hauge, Levorstad, et al., 1979**[47] **and Levang, Levorstad, Jaugland, 1980**[48] **Systematic review citation?:** No	**N:** 300 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 24 mo	**Valve position:** Aortic **Valve 1:** Bjork-Shiley **Valve 2:** Lillehei-Kaster	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** NR	
Lim, Caputo, Ascione, et al., 2002[49] **and Bryan, Rodgers, Bayliss, et al., 2007**[50] **Systematic review citation?:** No	**N:** 485 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 120 mo	**Valve position:** Aortic = 288 Mitral = 160 Both = 37 **Valve 1:** CarboMedics bileaflet mechanical **Valve 2:** St. Jude bileaflet mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Lundblad, Hagen, Smith, et al., 2001[51] **Systematic review citation?:** No	**N:** 17 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 3 mo	**Valve position:** Aortic **Valve 1:** CarboMedics Top Hat Supraannular **Valve 2:** CarboMedics Intraannular valve	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Maselli, Pizio, Pasquale, et al., 1999[52] **Systematic review citation?:** Yes	**N:** 40 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 8 mo	**Valve position:** Aortic **Valve 1:** Aortic homograft **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve **Valve 3:** Medtronic Freestyle **Valve 4:** Medtronic Intact	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** Yes **Reoperation:** NR **Adverse Events:** NR	
Melina, DeRoebrts, Gaer, et al., 2004[53] **and Meline, Mitchell, Amrani, et al., 2002**[54] **Systematic review citation?:** No	**N:** 147 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 45 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle **Valve 2:** Homograft	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Mikaeloff, Jegasen, Ferrini, et al., 1989[55] **Systematic review citation?:** No	**N:** 357 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 64.7 mo	**Valve position:** Mitral **Valve 1:** St. Jude Medical prosthesis **Valve 2:** Bjork-Shiley valve OR Starr-Edwards 6120 valve	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Miraldi, Spagnesi, Tallarico, et al., 2006[56] **Systematic review citation?:** No	**N:** 80 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Perimount **Valve 2:** Sorin Freedom	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** Yes	Small aortic annulus
Murday, Hochstitzky, Mansfield, et al., 2003[57] **Systematic review citation?:** No	**N:** 389 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 96 mo	**Valve position:** Aortic = 267 Mitral = 122 **Valve 1:** St. Jude Medical mechanical **Valve 2:** Starr-Edwards	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Otero, Pomar, Revuelta, et al., 2005[58] **Systematic review citation?:** No	**N:** 80 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Sorin Slimline **Valve 2:** St. Jude Medical High Performance	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	Small aortic annulus

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Perez de Arenaza, Lees, Flather, et al., 2005[59] **Systematic review citation?:** Yes	**N:** 190 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle **Valve 2:** Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Rostad, Simonsen, and Nitter-Hauge, 1979[60] **Systematic review citation?:** No	**N:** 48 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 27 mo	**Valve position:** Aortic and mitral **Valve 1:** Bjork-Shiley **Valve 2:** Lillehei-Kaster	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	
Santini, Bertolini, Montalbano, et al., 1998[61] **Systematic review citation?:** Yes	**N:** 77 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 14.5–18.5 mo	**Valve position:** Aortic **Valve 1:** Hancock II porcine **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve OR Biocor stentless	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	
Santini, Dyke, Edwards, et al., 1997[62] **Systematic review citation?:** No	**N:** 70 **Adult only?:** mixed **Follow-up timing:** (mean or longest value given) 16 mo	**Valve position:** Aortic **Valve 1:** Aortic homograft **Valve 2:** Pulmonary autograft	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** NR	
Schaff, Carrell, Steckelberg, et al., 1999[63] **and** **Schaff, Carrell, Jamieson et al., 2002[64]** **and** **Englberger, Schaff, Jamieson, et al. 2005[65]** **and** **Grunkemeier, Jin, Im, et al., 2006[66]** **Systematic review citation?:** No	**N:** 807 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 54 mo	**Valve position:** Aortic = 476 Mitral = 258 Both = 73 **Valve 1:** St. Jude Medical Silzone-coated prosthesis **Valve 2:** St. Jude Medical mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	AVERT trial

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Seitelberger, Bialy, Gottardi, et al., 2004[67] **Systematic review citation?:** No	**N:** 86 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Edwards Lifescience pericardial **Valve 2:** Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** Yes **Reoperation:** NR **Adverse Events:** NR	
Sensky, Loubani, Keal, et al., 2003[68] **Systematic review citation?:** No	**N:** 56 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** ATS Medical bileaflet OR Ultracor tilting disc **Valve 2:** Carpentier-Edwards Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	
Totaro, Degno, Zaidi, et al., 2005[69] **Systematic review citation?:** Yes	**N:** 63 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 1 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Perimount Magna **Valve 2:** Carpentier-Edwards Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	
Vitale, Caldarera, Muneretto, et al., 2001[70] **Systematic review citation?:** No	**N:** 140 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Hemodynamic Plus **Valve 2:** St. Jude Medical standard cuff	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse Events:** Yes	
Walther, Falk, Langebartels, et al., 1999[71] **and** **Walther, Falk, Langebartels, et al., 1999[72]** **Systematic review citation?:** Yes	**N:** 180 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle OR St. Jude Medical Toronto Stentless Porcine Valve **Valve 2:** Carpentier-Edwards porcine	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse Events:** Yes	
Walther, Lehmann, Falk, et al., 2004[73] **Systematic review citation?:** No	**N:** 100 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 14.6 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Edwards Lifesciences Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	

Table C1. Randomized controlled trials comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Wheatley, Tolland, Pathi, et al., 1995[74] **and Chaudry, Raco, Murithi, et al., 2000**[75] **Systematic review citation?:** No	**N:** 170 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 98 mo	**Valve position:** Aortic = 94 Mitral = 54 Both = 22 **Valve 1:** Bioflo pericardial bioprosthesis **Valve 2:** Carpentier-Edwards Supraannular porcine bioprosthesis	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse Events:** Yes	
Williams, Muir, Pathi, et al., 1999[76] **Systematic review citation?:** Yes	**N:** 40 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 32 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Stentless Porcine Valve stentless **Valve 2:** Carpentier-Edwards SAV	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	Data from abstract
Wiseth, Haaverstad, Vitale, et al., 2005[77] **Systematic review citation?:** No	**N:** 20 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 6 mo	**Valve position:** Aortic **Valve 1:** CarboMedics Reduced bileaflet **Valve 2:** Medtronic Hall	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse Events:** NR	Data from abstract only

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Akins, Hilgenberg, Vlahakes, et al., 2002[78] **Systematic review citation?:** Yes	**N:** 750 **Adult only?:** Yes **Follow-up timing:** (mean) 68 mo	**Valve position:** Aortic **Valve 1:** Bioprosthetic (Carpentier-Edwards porcine, Carpentier-Edwards pericardial) **Valve 2:** Mechanical (St. Jude Medical, Medtronic Hall, Starr-Edwards, Bjork-Shiley, CarboMedics)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Bernet, Bakut, Grize, et al., 2007[79] **Systematic review citation?:** No	**N:** 1161 **Adult only?:** NR **Follow-up timing:** (mean or longest value given) 55 mo	**Valve position:** NR **Valve 1:** St. Jude Medical **Valve 2:** ATS Medical mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** Yes	Data from abstract only
Bleiziffer, Eichinger, Wagner, et al., 2005[80] **Systematic review citation?:** Yes	**N:** 40 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 24 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Root **Valve 2:** Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** NR	
Borger, Carson, Ivanov, et al., 2005[81] **Systematic review citation?:** Yes	**N:** 737 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 79 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Stentless Porcine Valve OR Medtronic Freestyle **Valve 2:** Carpentier-Edwards Perimount OR Medtronic Mosaic	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** Yes	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Bottio, Rizzoli, Caprili, et al., 2005[82] **Systematic review citation?:** No	**N:** 379 **Adult only?:** Yes **Follow-up timing:** (mean) Sorin = 180 mo Hancock = 158 mo	**Valve position:** Aortic **Valve 1:** Sorin Monocast **Valve 2:** Hancock standard	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	Data from abstract only
Bove, Belleghem, Francois, et al., 2006[83] **Systematic review citation?:** Yes	**N:** 255 **Adult only?:** Yes **Follow-up timing:** 12 to 136 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Stentless Porcine Valve **Valve 2:** Carpentier-Edwards Perimount	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse events:** Yes	
Carrier, Hebert, Pellerin, et al., 2003[84] **Systematic review citation?:** Yes	**N:** 97 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 60 mo	**Valve position:** Tricuspid **Valve 1:** Carpentier-Edwards pericardial bioprosthetic **Valve 2:** Bileaflet mechanical (CarboMedics AND St. Jude Medical)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** NR	
Dalrymple-Hay, Leung, Ohri, et al., 1999[85] **Systematic review citation?:** Yes	**N:** 87 **Adult only?:** mixed **Follow-up timing:** (mean or longest value given) 97 mo	**Valve position:** Tricuspid and/or aortic **Valve 1:** Tissue **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
de la Fuente, Sanchez, Imizcoz, et al., 2003[86] **Systematic review citation?:** Yes	**N:** 215 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 72 mo	**Valve position:** Aortic **Valve 1:** Medtronic Intact **Valve 2:** Carpentier-Edwards SAV	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse events:** Yes	
Del Rizzo and Abdoh, 1998[87] **Systematic review citation?:** No	**N:** 995 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 36 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical Toronto Stentless Porcine Valve **Valve 2:** Medtronic Freestyle	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** Yes	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Do, Pellerin, Carrier, et al., 2000[88] **Systematic review citation?:** Yes	**N:** 29 **Adult only?:** Yes **Follow-up timing:** (mean) 70 ± 64 mo	**Valve position:** Tricuspid **Valve 1:** Bileaflet mechanical **Valve 2:** Bioprosthetic valve	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse events:** Yes	
Eberlein, von der Emde, Rein, et al., 1990[89] **Systematic review citation?:** Yes	**N:** 1668 **Adult only?:** mixed **Follow-up timing:** (mean) 77 mo	**Valve position:** Mitral **Valve 1:** Starr-Edwards model 6520 **Valve 2:** Bjork-Shiley plane prosthesis **Valve 3:** Bjork-Shiley convexo-concave 60º **Valve 4:** St. Jude Medical **Valve 5:** Carpentier-Edwards tissue	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse events:** Yes	
Hayashi, Saito, Yamamoto, et al., 1996[90] **Systematic review citation?:** Yes	**N:** 29 **Adult only?:** mixed **Follow-up timing:** (mean or longest value given) 80 mo	**Valve position:** Tricuspid **Valve 1:** Carpentier-Edwards porcine **Valve 2:** St. Jude Medical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse events:** Yes	
Houel, Le Besnerais, Soustelle, et al.,[91] **Systematic review citation?:** Yes	**N:** 212 **Adult only?:** Yes **Follow-up timing: (**mean or longest value given) 98 to 118 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards standard porcine **Valve 2:** Mitroflow pericardial	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Jamieson, von Lipinski, Mitagishima, et al., 2005[92] **Systematic review citation?:** No	**N:** 1782 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 180 mo	**Valve position:** Mitral **Valve 1:** Bioprosthesis (Carpentier-Edwards SAV, Carpentier-Edwards Perimount, Medtronic Mosaic) **Valve 2:** Mechanical (St. Jude Medical, CarboMedics)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Jasinski, Hayton, Kadziola, et al., 2002[93] **Systematic review citation?:** Yes	**N:** 28 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Medtronic Freestyle	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse events:** NR	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Jin, Zhang, Gibson, et al., 1996[94] **Systematic review citation?:** Yes	**N:** 137 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 36 mo	**Valve position:** Aortic **Valve 1:** Aortic homograft **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve **Valve 3:** Carpentier-Edwards porcine OR St. Jude Medical bileaflet	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** NR **Clinical:** NR **Reoperation:** NR **Adverse events:** NR	
Kaplan, Kut, Demirtas, et al., 2002[95] **Systematic review citation?:** Yes	**N:** 122 **Adult only?:** mixed **Follow-up timing:** (mean or longest value given) 228 mo	**Valve position:** Tricuspid **Valve 1:** Mechanical (St. Jude Medical, CarboMedics, Medtronic, Sorin, Bjork-Shiley, Hall-Kaster, Omniscience) **Valve 2:** Bioprosthetic (Biocor porcine, Wessex Medical porcine, Medtronic Hancock, Carpentier-Edwards, Ionescu-Shiley bovine)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Kulik, Bedard, Lam, et al., 2006[96] **Systematic review citation?:** No	**N:** 659 **Adult only?:** Yes **Follow-up timing:** (mean) AVR = 59 mo MVR = 66 mo	**Valve position:** Aortic and/or mitral **Valve 1:** Mechanical (Medtronic-Hall, St. Jude Medical, CarboMedics, MCRI On-X) **Valve 2:** Bioprosthetic (homograft, Medtronic Hancock, Edwards pericardial)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Kurlansky, Williams, Traad, et al., 2006[97] **Systematic review citation?:** No	**N:** 1104 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 64 mo	**Valve position:** Aortic = 703 Mitral = 488 Tricuspid = 5 Pulmonic = 1 (93 pts had multi-valve procedures) **Valve 1:** Carpentier-Edwards porcine **Valve 2:** St. Jude Medical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** NR **Adverse events:** NR	
Le Tourneau, Savoye, McFadden, et al., 1999[98] **Systematic review citation?:** Yes	**N:** 162 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 53 to 58 mo	**Valve position:** Aortic **Valve 1:** Sorin Pericarbon model SA **Valve 2:** Carpentier-Edwards model 2900	**Hemodynamic:** Yes **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse events:** Yes	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Le Tourneau, Vinventelli, Fayad, et al., 2002[99] **Systematic review citation?:** Yes	**N:** 150 **Adult only?:** Yes **Follow-up timing:** (mean) 78 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Supraannular model 2650 **Valve 2:** Carpentier-Edwards pericardial model 2900	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse events:** Yes	
Milano, Guglielmi, Carlo, et al., 1998[100] **Systematic review citation?:** Yes	**N:** 355 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 120 mo	**Valve position:** Aortic **Valve 1:** Mechanical (St. Jude Medical valve, St. Jude Medical HP, Sorin Bicarbon, CarboMedics, Duromedics) **Valve 2:** Biological (Carpentier-Edwards standard porcine, Medtronic Hancock II, Edwards-Prima, St. Jude Medical X-cell, Medtronic Mosaic	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Munro, Jamieson, Tyers, et al., 1995[101] **Systematic review citation?:** Yes	**N:** 94 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 44 mo	**Valve position:** Tricuspid **Valve 1:** Bioprosthetic **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Ninet, Tronc, Robin, et al., 1998[102] **Systematic review citation?:** Yes	**N:** 206 **Adult only?:** Yes **Follow-up timing:** (mean) Valve 1 = 53 mo Valve 2 = 64 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical **Valve 2:** Mitroflow pericardial	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse events:** Yes	
Peterseim, Cen, Cheruvu, et al., 1999[103] **Systematic review citation?:** Yes	**N:** 841 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 120 mo	**Valve position:** Aortic **Valve 1:** St. Jude Medical model A102 **Valve 2:** Carpentier-Edwards model 2625	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Prasongsukam, Jamieson, Lichtenstin, 2005[104] **Systematic review citation?:** No	**N:** 1587 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 144 to 189 mo	**Valve position:** Aortic or mitral **Valve 1:** Bioprosthetic **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** NR **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	Data from abstract only

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Ratnatunga, Edwards, Dore, et al., 1998[105] **Systematic review citation?:** Yes	**N:** 425 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 120 mo	**Valve position:** Tricuspid **Valve 1:** Biological **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** NR	
Rizzoli, Vendramin, Nesseris, et al., 2004[106] **Systematic review citation?:** No	**N:** 101 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 89 mo	**Valve position:** Tricuspid **Valve 1:** Bioprosthesis **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** NR	
Ruel, Chan, Bedard, et al., 2007[107] **Systematic review citation?:** No	**N:** 567 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 240 mo	**Valve position:** Aortic = 314 Mitral = 214 Both = 39 **Valve 1:** Mechanical (Bjork-Shiley, CarboMedics, Harken, Lillehei-Kaster, Medtronic-Hall, Starr-Edwards, St. Jude Medical) **Valve 2:** Bioprosthesis (Carpentier-Edwards, homograft, Ionescu-Shiley, Medtronic Hancock)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** NR **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Schelbert, Vaughan-Sarrazin, Welke, et al., 2008[108] **Systematic review citation?:** No	**N:** 307,054 **Adult only?:** Yes **Follow-up timing:** (range) 8 to 158 mo	**Valve position:** Aortic **Valve 1:** Bioprosthesis **Valve 2:** Mechanical	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Scully and Armstrong, 1995[109] **Systematic review citation?:** Yes	**N:** 60 **Adult only?:** Yes **Follow-up timing:** (mean) 75 mo	**Valve position:** Tricuspid **Valve 1:** Bioprosthetic (Medtronic Hancock II, Carpentier-Edwards porcine, Ionescu-Shiley pericardial, Medtronic Intact, Medtronic Hancock) **Valve 2:** Mechanical (Bjork-Shiley Monostrut, Bjork-Shiley welded outlet strut 60º or 70º, St. Jude Medical bileaflet)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** Yes **Reoperation:** Yes **Adverse events:** Yes	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Smedira, Blackstone, Roselli, et al., 2006[110] **Systematic review citation?:** No	**N:** 1222 **Adult only?:** Yes **Follow-up timing:** (mean) Pericardial = 180 mo Allograft = 67 mo	**Valve position:** Aortic **Valve 1:** Stented bovine pericardial **Valve 2:** Cryopreserved allograft	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** NR	
Tsialtas, Bolognesi, Beghi, et al., 2007[111] **Systematic review citation?:** Yes	**N:** 68 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 12 mo	**Valve position:** Aortic **Valve 1:** Carpentier-Edwards Perimount **Valve 2:** St. Jude Medical Toronto Stentless Porcine Valve OR Shelhigh Super Stentless	**Hemodynamic:** Yes **Cardiac function:** Yes **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** NR	
Valfre, Rizzoli, Zussa, et al., 2006[112] **Systematic review citation?:** No	**N:** 1931 **Adult only?:** Yes **Follow-up timing:** (median) 144 mo	**Valve position:** Aortic and mitral **Valve 1:** Medtronic Hancock **Valve 2:** Medtronic Hancock II	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Van Nooten, Caes, Taeymans, et al., 1995[113] **Systematic review citation?:** Yes	**N:** 146 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 30 mo	**Valve position:** Tricuspid **Valve 1:** Bioprosthetic (Carpentier-Edwards porcine & bovine, Medtronic Hancock, CarboMedics Mitroflow) **Valve 2:** Mechanical (Smeloff-Cutter, Kay-Shiley, DeBakey, Bjork-Shiley tilting disc, St. Jude Medical)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Vitale, De Feo, Siena, et al., 2004[114] **Systematic review citation?:** Yes	**N:** 2734 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 49 to 114 mo	**Valve position:** Aortic **Valve 1:** Tilting disc (Bjork-Shiley, Medtronic-Hall, Sorin Monodisc standard, Sorin Monodisc Allcarbon, Sorin Monodisc Carbocast Ultracor) **Valve 2:** Bileaflet (Aortec, ATS Medical, CarboMedics, CarboMedics TH, Edwards, Duromedics, Edwards TEKNA, Edwards Mira, Onyx, St. Jude Medical, St. Jude Medical HP, St. Jude Medical Regent, Sorin Bicarbon)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	

Table C2. Observational studies comparing two or more conventional heart valves for valve replacement (continued)

Study and status vis-à-vis systematic reviews	Population and follow-up	Valve location and valve comparisons	Outcomes reported	Notes
Westaby, Horton, Jin, et al., 2000[115] **Systematic review citation?:** Yes	**N:** 407 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 60 mo	**Valve position:** Aortic **Valve 1:** Medtronic Freestyle **Valve 2:** Carpentier-Edwards model 2650	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	
Westaby, Jonson, Payne, et al., 2001[116] **Systematic review citation?:** No	**N:** 2082 **Adult only?:** Yes **Follow-up timing:** (mean or longest value given) 1 mo	**Valve position:** Aortic **Valve 1:** Medtronic Mosaic **Valve 2:** Medtronic Freestyle	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** NR **Adverse events:** NR	
Wu, Gregorio, Renzulli, et al., 2004[117] **Systematic review citation?:** No	**N:** 1873 **Adult only?:** mixed **Follow-up timing:** (mean) Valve 1 = 139 mo Valve 2 = 54 mo	**Valve position:** Aortic **Valve 1:** Single disc (Bjork-Shiley, Medtronic-Hall, Lillehei-Kaster, Omnicarbon, Sorin standard, Sorin Allcarbon, Sorin Carbocast) **Valve 2:** Bileaflet (ATS-Medical Edwards MIRA, Sorin Bicarbon, CarboMedics standard, CarboMedics HP, Duromedics, Edwards TEKNA, St. Jude Medical standard, St. Jude Medical HP, St. Jude Medical Regent)	**Hemodynamic:** NR **Cardiac function:** NR **Mortality:** Yes **Clinical:** NR **Reoperation:** Yes **Adverse events:** Yes	

References to Appendix C

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Appendix D. Criteria Used To Assess the Quality of Systematic Reviews Included for Question 2

The following 10 criteria were used to assess the quality of systematic reviews included for Question 2 (evaluating comparisons of various types of conventional heart valves). Possible responses were "Yes," "Partially," "No," or "Can't tell." Text in italics provides notes on how to interpret and operationalize the various criteria.

The quality assessment tool described here was adapted from a similar instrument used in a previous evidence report prepared for the Agency for Healthcare Research and Quality (AHRQ),[1] which in turn was based on the Quality Of Reporting Of Meta-analyses (QUOROM) statement.[2]

1. Was a focused clinical question clearly stated?
   For "yes," should at least identify population and interventions; does not have to be in PICO format (Patient population, Intervention, Comparison, Outcomes).

2. Was the search for relevant studies detailed and exhaustive?
   Consider and rate 2 components: (a) Search methods described in enough detail to permit replication? (b) Databases and search terms appropriate? Consider any restrictions imposed (e.g., years, age groups, language).

3. Were inclusion/exclusion criteria clearly defined and appropriate?
   Consider and rate 2 components: (a) Were the criteria specified clearly enough to permit replication? (b) Were these criteria likely to capture all relevant studies? Consider criteria related to study population, intervention, outcomes, and study design.

4. Were the primary studies evaluated for quality, and were quality assessments done appropriately?
   Consider and rate 2 components: (a) Was study quality assessed? (b) Was quality assessment performed using a validated instrument?

5. Were assessments of studies reproducible?
   Consider and rate 2 components: (a) Did 2 or more independent raters abstract data? (b) Was an appropriate method used for resolving disagreements?

6. Were analyses conducted to measure variability in effect?
   Consider and rate 2 components: (a) Was there a check for heterogeneity statistically or graphically? (b) Were possible sources of any observed heterogeneity explored (e.g., differences in study design or population)?

7. Were results combined appropriately?
   Was an accepted quantitative or qualitative method of pooling used?

8. Was publication bias assessed?
   Consider whether any of the following methods were employed: Funnel plots, test statistics, or search of trials registry for unpublished studies.

9. Were both benefits and harms assessed?

10. Were the author's conclusions supported by the data presented?

References to Appendix D

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Appendix E. Peer Reviewers

The Duke Evidence-based Practice Center is grateful to the following peer reviewers who read and commented on a draft version of this report:

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- Jeffrey Shuhaiber, M.D.; Cincinnati Children's Hospital Medical Center; Cincinnati, OH
- John Webb, M.D.; St. Paul's Hospital; Vancouver, BC, Canada
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