

# Percutaneous Heart Valve Replacement for Aortic Stenosis: State of the Evidence

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Surgical aortic valve replacement (SAVR) is the only treatment known to improve symptoms and survival in patients with severe, symptomatic aortic stenosis. Perioperative mortality, however, is high among many patients for whom SAVR may be indicated. Percutaneous heart valve replacement (PHVR) is an emerging, catheter-based technology that allows for implantation of a prosthetic valve without open heart surgery.

This review describes the available literature on PHVR for aortic stenosis, which comprised 84 published reports representing 76 distinct studies and 2375 unique patients. Successful implantation was achieved in 94% of patients; 30-day survival was 89%. Differences between patients undergoing

PHVR and those typically selected for SAVR make full interpretation of these results difficult.

A large, multicenter, randomized, controlled trial comparing PHVR with SAVR or medical management was recently completed, with initial results expected in September 2010. Pending publication of findings from that trial, the available evidence is inadequate to determine the most appropriate clinical role of PHVR or the specific patient populations for whom it might eventually be indicated.

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**A**ortic stenosis is one of the most common valvular disorders in older adults, with a prevalence of approximately 8% at age 85 (1). The typical symptoms of aortic stenosis include angina, syncope, and heart failure. In adults with severe, symptomatic aortic stenosis, 2-year mortality is approximately 50% (2), and open surgical aortic valve replacement (SAVR) is the only treatment that has been shown to improve symptoms, functional status, and survival (3).

Surgical aortic valve replacement is the most common heart valve operation, accounting for 60% to 70% of all valve surgery performed in elderly persons. Surgical aortic valve replacement is associated with a perioperative mortality risk of approximately 3% to 4%, increasing to 5.5% to 6.8% when combined with coronary artery bypass grafting (3). However, a substantial number of patients who would potentially benefit from SAVR do not undergo the procedure (4). One survey of 92 European heart centers found that 31.8% of patients with severe, symptomatic, single-valve disease did not undergo intervention, most frequently because of comorbid conditions that placed the patient at high surgical risk (5).

A new catheter-based technology allows implantation of a prosthetic heart valve within the diseased native aortic valve without the need for open heart surgery or cardiopulmonary bypass. In percutaneous (catheter-based or transcatheter) heart valve replacement (PHVR) a prosthetic

valve, manufactured with bovine or porcine pericardium and mounted within a stent, is delivered by catheter across the stenotic aortic valve either through the femoral artery (transfemoral), subclavian artery, axillary artery, or ascending aorta (all retrograde approaches) or (using an antegrade approach) through the femoral vein or directly through the apex of the heart by means of thoracotomy incision (transapical). The first successful PHV implantation in a human was reported in 2002 (6). Two PHVs have been approved for use in Europe since 2007 for symptomatic, severe aortic stenosis in persons at exceptionally high surgical risk or with other contraindications to open heart surgery, with approximately 15 000 patients treated with PHVR globally to date. No PHV is currently approved by the U.S. Food and Drug Administration.

In this review, we describe the available published literature on PHVR for aortic stenosis and consider the evidence for a range of variables that may affect short-term clinical outcomes.

## METHODS

We based our review on a technical brief commissioned by the Agency for Healthcare Research and Quality (7). For the previous report, we searched PubMed and EMBASE from 1 January 1990 to 15 October 2009 to identify articles published in English that described studies of PHVR for aortic stenosis in adults. For the current review, we updated the PubMed search through 1 June 2010. **Appendix Table 1** (available at [www.annals.org](http://www.annals.org)) provides detailed search strategies. Included articles were required to report at least 1 clinical outcome (for example, mortality, hemodynamic measurements of success, and successful implantation rates). We abstracted data from eligible articles into evidence tables (**Appendix Table 2**, available at [www.annals.org](http://www.annals.org)). Abstracted data included date of publication; country; study design; study objectives;

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duration of follow-up; number, age, and sex of participants; valve name; size of catheter; implementation approach; implantation rates; and clinical outcomes, including hemodynamic measurements, 30-day survival rates, complications, and device dysfunction rates.

We focused on device implantation success rates and 30-day survival rates as outcome measures. In addition, we evaluated the published literature for variables associated with surgery or setting that may affect short-term clinical outcomes for PHVR.

## RESULTS

### Characteristics of Included Studies

We screened published reports at the full-text stage; 21 of these did not meet eligibility criteria. The 84 included publications described 76 separate studies assessing the feasibility and short-term safety of implanting PHVs. Pertinent data from these studies, which represent 2375 apparently unique patients, are summarized in Table 1. Fifty of the publications were single or multiple case reports, and 34 were case series, the latter representing a total of 2311 patients (Table 2).

All studies included only adults with symptomatic, severe aortic stenosis who were considered to be at high surgical risk with conventional SAVR. The mean age of patients was older than 80 years. The scores from the European System for Cardiac Operative Risk Evaluation (EuroSCORE), which predicts risk for death associated with open heart surgery, were reported in 21 of the 34 case series. Mean or median logistic EuroSCOREs among the patients represented ranged from 11% to 41%, with 15 studies (71%) reporting a mean or median EuroSCORE greater than 23%.

Six PHV manufacturers were represented in the included studies, but most patients received valves produced either by Edwards Lifesciences, Irvine, California ( $n = 1040$ ), or Medtronic, Minneapolis, Minnesota ( $n = 1316$ ) (Table 2). Delivery through the femoral artery was used in 1804 patients (76%), and the transapical approach (Ascendra valve system by Edwards Lifesciences only) was used in 514 patients (22%). Fifty-seven patients (2%) had prostheses delivered through the femoral vein, subclavian artery, axillary artery, or ascending aorta.

The largest uncontrolled case series included 646 patients. Twenty-two case series (65%) included follow-up data 30 days after the procedure or until death of the patient. Seven case series (698 patients) provided clinical outcomes data 1 or more years after the procedure.

### Outcomes

Acute procedural success—successful PHV implantation without major adverse cardiac or cerebral events—has increased over the period of the published reports to nearly 97% in recent series. Of the 1967 attempts to implant a prosthetic valve in the aortic position reported in the studies identified in this report, 1843 (94%) were

### Key Summary Points

Surgical aortic valve replacement is the only proven effective treatment of aortic stenosis.

Percutaneous heart valve replacement (PHVR) is an emerging technology that allows implantation of a prosthetic heart valve without open heart surgery.

Successful implantation and 30-day survival rates for PHVR for aortic stenosis in a recent series were approximately 97% and 92%, respectively.

To date, little overlap exists between the patient populations who have received surgical versus percutaneous aortic valve replacement, and long-term outcomes associated with PHVR have rarely been reported.

Partial, preliminary findings of the first randomized, controlled trial comparing PHVR with medical therapy, including balloon aortic valvuloplasty, are expected in September 2010.

The available evidence is inadequate to determine the most appropriate clinical role for PHVs or the specific patient populations for whom these valves might eventually be indicated.

successful (Table 1). Serious adverse events potentially attributable to the PHV procedure included (in descending order of frequency) peripheral vascular complications; device malfunction, misplacement, or migration; injury to valves or myocardium; arrhythmia requiring intervention or resulting in death; cerebrovascular events; myocardial infarction; and hemodynamic collapse. Procedural complication rates reported in the 2 largest published series identified by our search strategy (8, 9), representing 339 and 646 patients who had PHVR with Edwards Lifesciences or Medtronic CoreValve devices, respectively, were major access site complications (13%), life-threatening arrhythmias (8.1%), and need for hemodynamic support (4.1%) with the Edwards SAPIEN valve, and valve-in-valve implantation or implantation of a second valve (2.6%), vascular access site complications (1.9%), and ventricular perforation (1.7%) with the CoreValve. A recently published prospective registry (1038 patients) of the Edwards SAPIEN valve reported a 12.8% risk for vascular access site complications (17.9% for transfemoral and 2.4% for transapical), with a clinically significant association between vascular complications and higher 30-day mortality in the transapical approach (10).

The 30-day survival rate across all studies was 89% (1996 of 2197 patients), including 56 patients who were included in 2 published studies and excluding patients for whom 30-day survival was not reported. The overall

**Table 1. Published Studies of Percutaneous Heart Valve Implantation for Aortic Stenosis**

Study, Year (Reference), by Manufacturer*	Patients (Unique Patients), n (n)	Approach (Unique Patients)	Successful Implantation Rate, n/n (%)	Survival at 30 Days, n/n (%)
<b>Edwards Lifesciences</b>				
Cribier et al, 2004 (29)	6	Femoral vein	5/6 (83)	3/6 (50)
Eltchaninoff et al, 2003 (30)	1 (0)			
Cribier et al, 2002 (6)	1 (0)			
Bauer et al, 2004 (31)	8	Femoral vein (n = 6); femoral artery (n = 2)	8/8 (100)	5/8 (63)
Hanzel et al, 2005 (32)	1	Aborted femoral vein to femoral artery	1/1 (100)	NR
Cribier et al, 2006 (33)	36 (34)†	Femoral vein (n = 24); femoral artery (n = 7); aborted femoral artery to femoral vein (n = 1); aborted procedures (n = 1); death before procedure (n = 1)	27/36 (75)	21/36 (58)
Chandavimol et al, 2006 (34)	1	Femoral artery	1/1 (100)	1/1 (100)
Webb et al, 2007 (35)	50	Femoral artery	43/50 (86)	44/50 (88)
Webb et al, 2006 (36)	18 (0)			
Clavel et al, 2009 (24)	50 (0)			
Gutiérrez et al, 2009 (37)	33 (0)			
Lichtenstein et al, 2006 (38)	7	Transapical	7/7 (100)	6/7 (86)
Ye et al, 2007 (39)	7 (0)			
Walther et al, 2007 (40)	59‡	Transapical	55/59 (93)	51/59 (86)
Walther et al, 2007 (41)	30 (0)‡			
Walther et al, 2008 (42)	50 (20)‡	Transapical	50/50 (100)	46/50 (92)
Zierer et al, 2008 (43)	26	Transapical	25/26 (96)	22/26 (85)
Svensson et al, 2008 (44)	40	Transapical	35/40 (88)	33/40 (83)
Rodés-Cabau et al, 2008 (45)	22	Femoral artery (n = 10); transapical (n = 11); aborted femoral artery to femoral vein (n = 1)	21/23 (91); 2 procedures in 1 patient	20/22 (91)
Al-Attar et al, 2009 (46)	1	Transapical	1/1 (100)	1/1 (100)
Bagur et al, 2009 (47)	1	Femoral artery	1/1 (100)	1/1 (100)
Clavel et al, 2009 (48)	1	Transapical	1/2 (50); 2 procedures in 1 patient	0/1 (0)
Dvir et al, 2009 (49)	1	Femoral artery	1/1 (100)	1/1 (100)
Dvir et al, 2009 (50)	1	Femoral artery	1/1 (100)	1/1 (100)
Klaaborg et al, 2009 (51)	1	Transapical	1/1 (100)	NR
Moreno et al, 2009 (52)	1	NR	1/1 (100)	0/1 (0)
Wendt et al, 2009 (53)	1	Transapical	1/1 (100)	1/1 (100)
Wong et al, 2009 (54)	1	NR	1/1 (100)	1/1 (100)
Ye et al, 2009 (55)	1	Transapical	1/2 (50); 2 procedures in 1 patient	1/1 (100)
Ng et al, 2009 (56)	1	Transapical	1/1 (100)	1/1 (100)
Himbert et al, 2009 (25)	75	Femoral artery (n = 51); transapical (n = 24)	Femoral artery, 46/51 (90); transapical, 24/24 (100)	Femoral artery, 47/51 (92); transapical, 22/24 (92)
Webb et al, 2009 (22)	25	Femoral artery	25/25 (100)	25/25 (100)
Chiam et al, 2009 (57)	1	Femoral artery	1/1 (100)	1/1 (100)
Dumonteil et al, 2009 (58)	1	Femoral artery	1/1 (100)	1/1 (100)
Rodés-Cabau et al, 2009 (59)	1	Repeated transapical valve-in-valve procedure (n = 1)	1/2 (50)	1/1 (100)
Scherner et al, 2009 (60)	1	Transapical	1/1 (100)	1/1 (100)
Sheiban et al, 2009 (61)	1	Femoral artery	1/1 (100)	1/1 (100)
Taramasso et al, 2009 (62)	1	Femoral artery	1/1 (100)	NR
Bleiziffer et al, 2009 (63)§	25	Femoral artery (n = 4); transapical (n = 21)	NR by device	NR by device
Kolettis et al, 2009 (64)	1	Transapical	1/1 (100)	NR
Bartorelli et al, 2010 (65)	1	Femoral artery	1/1 (100)	1/1 (100)
Bagur et al, 2010 (12)	213 (may have duplicates with other studies)	Femoral artery (n = 111); transapical (n = 102)	NR	192/213 (90)
Kahlert et al, 2010 (11)§	22	Femoral artery (n = 22)	22/22 (100)	NR
Messika-Zeitoun et al, 2010 (66)	34	Femoral artery (n = 25); transapical (n = 9)	33/34 (97)	NR by device
Pilgrim et al, 2010 (67)	1	Femoral artery	1/1 (100)	1/1 (100)
Rodés-Cabau et al, 2010 (8)	339	Femoral artery (n = 161); transapical (n = 172); aborted femoral artery to transapical (n = 5); repeated femoral artery (n = 1)	322/345 (93)	303/339 (89)
Ruiz-Salmerón et al, 2010 (68)	1	Femoral artery	0/1 (0)	NR

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Table 1—Continued

Study, Year (Reference), by Manufacturer*	Patients (Unique Patients), n (n)	Approach (Unique Patients)	Successful Implantation Rate, n/n (%)	Survival at 30 Days, n/n (%)
Stabile et al, 2010 (69)	1	Successful femoral artery, followed by a valve-in-valve repeated femoral artery procedure 6 mo later	2/2 (100)	1/1 (100)
Webb et al, 2010 (70)	10	Femoral artery (n = 1); transapical (n = 8); aborted femoral artery to transapical (n = 1)	10/11 (91)	10/10 (100)
Taramasso et al, 2010 (71)§	1	Femoral artery, Medtronic CoreValve implantation followed by valve-in-valve procedure with an Edwards SAPIEN valve	1/1 (100)	1/1 (100)
Total	1212 (1040)	Femoral vein (n = 37); femoral artery (n = 492); transapical (n = 507); aborted procedure (n = 1); NR (n = 2); death before procedure (n = 1)	783/846 (93)	868/986 (88)
<b>Medtronic CoreValve ReValving System</b>				
Grube et al, 2005 (72)	1	Femoral artery	1/1 (100)	NR
Grube et al, 2006 (73)	25	Femoral artery	22/25 (88)	20/25 (80)
Grube et al, 2007 (74)	86 (76)¶	Femoral artery	76/86 (88)	76/86 (88)
Grube et al, 2008 (23)	136 (122)¶	Femoral artery	Generation 1, 7/10 (70); generation 2, 17/24 (71); generation 3, 93/102 (92)	Generation 1, 6/10 (60); generation 2, 22/24 (92); generation 3, 91/102 (89)
Marcheix et al, 2007 (75)	10	Femoral artery	10/10 (100)	7/10 (70)
Berry et al, 2007 (76)	13	Femoral artery	11/13 (85)	11/13 (85)
Berry et al, 2007 (77)	1 (0)			
Lamarche et al, 2007 (78)	1	Femoral artery	1/1 (100)	1/1 (100)
Lange et al, 2007 (79)	1	Transapical	1/1 (100)	NR
Wenaweser et al, 2007 (80)	1	Femoral artery	1/1 (100)	1/1 (100)
Ruiz et al, 2008 (81)	1	Femoral artery	1/1 (100)	1/1 (100)
Bojara et al, 2009 (82)	1	Subclavian artery	1/1 (100)	1/1 (100)
Geist et al, 2009 (83)	1	NR	1/1 (100)	1/1 (100)
Piazza et al, 2009 (84)	5	Femoral artery (valve-in-valve)	5/5 (100)	4/5 (80); NR for 1 patient
Piazza et al, 2009 (85)	3	Femoral artery	3/3 (100)	2/2 (100); NR for 1 patient
Piazza et al, 2009 (86)	114	Femoral artery	NR	103/114 (90)
Piazza et al, 2008 (9)	646	Femoral artery	628/646	594/646
Tamburino et al, 2009 (87)	30	Femoral artery	29/30 (97)	28/30 (93)
Ussia et al, 2009 (88)	1	Femoral artery	1/1 (100)	1/1 (100)
Ussia et al, 2009 (89)	1	Femoral artery	1/2 (50); valve-in-valve after failed implantation	1/1 (100)
Bauernschmitt et al, 2009 (90)	1	Ascending aorta	1/1 (100)	NR
Bollati et al, 2009 (91)	2	Ascending aorta	2/2 (100)	NR
Asgar et al, 2009 (92)	1	Axillary artery	1/1 (100)	1/1 (100)
Bruschi et al, 2009 (93)	4	Femoral artery (n = 4)	4/4 (100)	4/4 (100)
Olsen et al, 2009 (94)	4	Femoral artery	4/4 (100)	NR
Bleiziffer et al, 2009 (63)§	127	Femoral artery (n = 117); transapical (n = 5); subclavian artery (n = 3); ascending aorta (n = 2)	NR by device	NR by device
Avanzas et al, 2010 (95)	108	Femoral artery (n = 103); subclavian artery (n = 5)	106/108 (98)	100/108 (93)
Bruschi et al, 2010 (96)	1	Femoral artery	1/1 (100)	1/1 (100)
Kahlert et al, 2010 (11)§	10	Femoral artery (n = 10)	10/10 (100)	NR
Khawaja et al, 2010 (97)	4	Femoral artery (n = 4)	4/4 (100)	4/4 (100)
Zahn et al, 2010 (98)	1	Repeated femoral artery valve-in-valve procedure (n = 1)	1/2 (50)	1/1 (100)
Taramasso et al, 2010 (71)§	1 (0)	Femoral artery, Medtronic CoreValve implantation followed by valve-in-valve procedure with an Edwards SAPIEN valve	0/1 (0)	NA
Total	1227 (1202)	Femoral artery (n = 1294); transapical (n = 6); subclavian artery (n = 9); ascending aorta (n = 5); axillary artery (n = 1); NR (n = 1)	1044/1102 (95)	1082/1193 (91)

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Table 1—Continued

Study, Year (Reference), by Manufacturer*	Patients (Unique Patients), n (n)	Approach (Unique Patients)	Successful Implantation Rate, n/n (%)	Survival at 30 Days, n/n (%)
<b>Endoluminal Technology Research</b>				
Paniagua et al, 2005 (17)	1	Femoral artery	1/1 (100)	0/1 (0)
<b>Sadra Medical</b>				
Buellesfeld et al, 2008 (18)	1	Femoral artery	1/1 (100)	1/1 (100)
<b>Direct Flow Medical</b>				
Schofer et al, 2008 (21)	15	Femoral artery	12/15 (80)	14/15 (93)
<b>Ventor Technologies</b>				
Falk et al, 2009 (20)	1	Transapical	1/1 (100)	NR
<b>Manufacturer not reported</b>				
Kapadia et al, 2009 (99)	1	Femoral artery	1/1 (100)	1/1 (100)
<b>Totals for all valves</b>	2458 (2261)	Femoral vein (n = 37); femoral artery (n = 1804); transapical (n = 514); subclavian artery (n = 9); ascending aorta (n = 5); axillary artery (n = 1); other (n = 5)	1843/1967 (94)**	1996/2197 (89)††

NR = not reported.

\* Locations of manufacturers are as follows (listed in alphabetical order by manufacturer): Direct Flow, Santa Rosa, California; Edwards Lifesciences, Irvine, California; Endoluminal Technology Research, Houston, Texas; Medtronic CoreValve, Minneapolis, Minnesota; Sadra Medical, Los Gatos, California; Ventor Technologies, Netanya, Israel.

† Data from 2 patients in this series are also reported in reference 29.

‡ References 40–42 have overlapping patients (see Appendix Table 2, available at www.annals.org, for details). These 3 studies combined reports on 79 unique patients.

§ Reports on both Edwards Lifesciences and Medtronic CoreValve.

¶ References 23, 73, and 74 have overlapping patients (see Appendix Table 2 for details). These 3 studies combined reports on 223 unique patients.

|| Twenty-four patients were counted twice. Survival was not reported for 6 patients. A total of 127 patients from reference 63 were not included.

\*\* Fifty-six patients were counted twice; 5 patients with 2 procedures. The count includes an overall implantation success rate of 150/152 patients (99%) reported in reference 63, which was not stratified by device manufacturer.

†† Fifty-six patients were counted twice; survival was not reported for 9 patients. The count includes an overall 30-d survival rate of 134/152 patients (88%) reported in reference 63, which was not stratified by device manufacturer.

30-day mortality rate of 11% is higher than rates reported for conventional SAVR (3% to 4% overall, with higher rates in patients older than 65 years in low-volume centers) but substantially 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 end point of major adverse cardiovascular and cerebral events (death from any cause, myocardial infarction, or stroke), with rates of approximately 8% in recent large series. Improvement in functional status, measured by the New York Heart Association classification, was reported in most of the series, with a reduction in severity from New York Heart Association class III to IV at baseline to class I to II soon after PHV implantation.

In addition to major adverse cardiovascular events, a few studies examined the effect of the PHV procedure on other organ function. Kahlert and coworkers (11) reported a higher rate of new foci of restricted diffusion on cerebral diffusion-weighted magnetic resonance brain imaging days after transfemoral PHVR (27 of 32, 84%) compared with a historical control group who had SAVR (10 of 21, 48%). However, these imaging findings were not associated with measurable impairment of neurocognitive function or clinically apparent events. In a cohort of 213 patients

undergoing either transfemoral or transapical PHVR, Bagur and colleagues (12) found acute kidney injury (reduction in estimated glomerular filtration rate >25% within 48 hours of the procedure or need for hemodialysis) in 11.7%, with 1.4% requiring hemodialysis. In a propensity-adjusted comparison using data from 104 patients who had SAVR, acute kidney injury occurred in 9.2% of patients who had PHVR compared with 25.9% of patients who had SAVR.

**Variables That May Affect Short-Term Clinical Outcomes for PHVs**

We summarize the limited available evidence about the effect of patient characteristics, prosthesis characteristics, and implantation approach on short-term clinical outcomes in patients undergoing PHVR further in the following section. The available reports provided insufficient details about treatment setting, operator characteristics, and type of anesthesia to determine whether these variables may affect outcomes.

**Patient Characteristics**

A patient’s clinical status, coexisting medical conditions, and corresponding operative risk all significantly affect clinical outcomes for surgical procedures in general

**Table 2. Important Variables in Published Studies of Percutaneous Heart Valve Implantation**

Variable	Reports, n	Patients, n
<b>Total numbers</b>	84	2375
<b>Valve manufacturers*</b>		
Edwards Lifesciences	50	1040
Medtronic CoreValve	32	1316
Paniagua heart valve (manufacturer not reported)	1	1
Sadra Medical	1	1
Direct Flow Medical	1	15
Ventor Technologies	1	1
Manufacturer not reported	1	1
<b>Study type†</b>		
Case reports	50	67
Case series	34	2311
<b>Approach‡</b>		
Femoral vein	5	37
Femoral artery	55	1804
Transapical	22	514
Subclavian artery	3	9
Ascending aorta	2	5
Axillary artery	1	1
Other	5	5

\* Three publications included reports on both Edwards Lifesciences and Medtronic CoreValve valves. See the asterisked footnote in Table 1 for manufacturer locations.

† Four publications categorized as case reports reported data on more than 1 patient, and 3 case report publications included patients ( $n = 3$ ) who were also described in case series; the latter are counted twice here.

‡ Ten publications reported on several approaches.

(13). Specific characteristics, such as age, functional status, cardiac status, and medical comorbidity, have been shown to be associated with mortality in conventional heart valve surgery (1, 14–16). It is unknown, however, whether these factors also affect outcomes for PHVR, and if they do, whether their effect is directly related to the PHV device or procedure (8).

All patients in the included PHVR studies had symptomatic aortic stenosis and a high predicted operative mortality for SAVR, as measured by validated surgical risk models (the logistic EuroSCORE or the Society of Thoracic Surgeons Predicted Risk of Mortality). The amount and quality of the published data, and the way in which the data are reported, make it difficult to identify any specific patient characteristics related to outcomes associated with PHVR. However, in case series, it is notable that actual 30-day mortality rates with PHVR were substantially lower than the expected perioperative mortality rates with major surgery as predicted by the EuroSCORE.

#### Prosthesis Characteristics

We analyzed outcomes by valve manufacturer as a proxy for more detailed prosthesis characteristics. Five manufacturers reported implantation in a total of 19 patients, providing insufficient evidence to evaluate a rela-

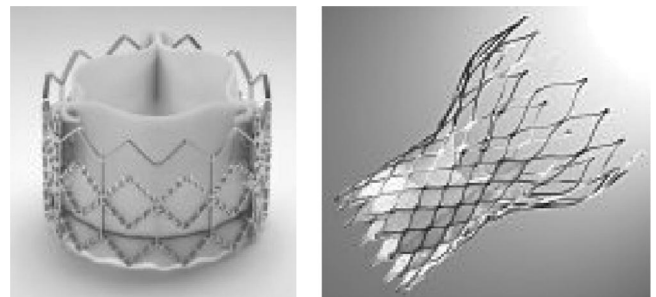
tionship between valve design or manufacturer and short-term clinical outcomes (17–21).

In contrast, 50 reports representing 1040 patients and 32 reports representing 1316 patients were identified for the Edwards SAPIEN transcatheter heart valve and the Medtronic CoreValve ReValving System, respectively. Implantation success and 30-day survival rates were 93% and 88%, respectively, for the Edwards SAPIEN transcatheter heart valve (including its precursors, the Percutaneous Heart Valve and the Cribier–Edwards valve), and 95% and 91%, respectively, for the Medtronic CoreValve ReValving System. The available data do not support definitive conclusions about the possible superiority of one of these devices over the other.

The Edwards SAPIEN transcatheter heart valve, a balloon-mounted bovine pericardial valve within a stainless steel stent (Figure), is currently available in 2 valve diameters (23 and 26 mm) and is delivered on maneuverable catheters with diameters of 22 French and 24 French, respectively. These valve diameters are suitable for implantation in aortic annulus diameters from 18 to 25 mm. The large diameters of these catheters currently require minimal vessel diameters of 7 mm and 8 mm, respectively, for the transfemoral approach. Modifications to the device—including availability of larger valve diameter, longer intravascular sheath to facilitate delivery of the device to the descending aorta, and improved maneuverability in the ascending aorta—have been made during the publication period of the included case series, potentially affecting short-term outcomes for PHVR with this device. In the near future, change in stent material to cobalt–chromium to allow thinner struts is expected to reduce the delivery profile to 18 French or 19 French, increasing the population of patients amenable to this therapy and possibly reducing vascular complications (22).

The Medtronic CoreValve ReValving System, a porcine pericardial valve sewn within a self-expanding nitinol frame (Figure), is currently available in diameters of 26

**Figure. Valves used in percutaneous heart valve replacement.**



**Left.** Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, California). **Right.** Medtronic CoreValve ReValving aortic bio-prosthesis (Medtronic, Minneapolis, Minnesota).

mm and 29 mm to allow implantation in aortic valve annulus diameters of 20 to 24 mm and 24 to 27 mm, respectively. The delivery catheter diameter has also undergone generational changes to reduce the diameter from 25 French to the current 18 French. This smaller diameter allows transfemoral implantation in patients with iliac artery diameter of 6 mm or more. Comparison of newer generation CoreValve PHVs with older, larger delivery catheters demonstrates a lower rate of major adverse cardiac and cerebrovascular events and, thus, a higher rate of acute procedural success, but this finding is confounded by increased operator experience (23).

The reported hemodynamics of PHVs, as measured by Doppler echocardiography, are similar to those of conventional valves. Mean PHV gradients were uniformly less than 15 mm Hg in short-term follow-up. In 1 series with matched comparison of PHV (50 patients) versus biologic (50 patients) or mechanical (50 patients) SAVR, superior hemodynamics (transvalvular gradient and effective orifice area) were found for PHV versus surgical procedures (24). Despite the limited PHV diameters available, the reported incidence of patient–prosthesis mismatch (insufficient effective orifice area for body surface area) is low (24). In contrast, paravalvular regurgitation, predominantly mild or moderate in severity, has been reported in most patients after PHVR. Although the mechanism of paravalvular regurgitation after PHVR is probably related to incomplete apposition of the frame to the aortic annulus, oversizing of the PHV diameter relative to the aortic annulus diameter has not been associated with a lower rate or degree of regurgitation (24). To date, no studies have evaluated the associations between short-term hemodynamics and clinical outcomes or long-term durability of PHVs compared with conventional valves.

### **Implantation Approach**

Six delivery or implantation approaches have been reported for PHVR: femoral vein, femoral artery, subclavian artery, axillary artery, ascending aorta, and directly through the apex of the heart by means of thoracotomy incision (transapical). The femoral artery and transapical approaches are most commonly used in current practice. In the femoral artery approach, a catheter is introduced through the groin and passed through the femoral and iliac arteries to the aorta and then across 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 with aortic stenosis. Angiography of the entire aorta and iliofemoral vessels is an essential preprocedural evaluation in order to assess feasibility of device delivery across the aortic valve. Limitations of the aortoiliac anatomy, including peripheral arterial disease and vessel tortuosity, have excluded nearly one third of patients considered for PHVR (25). The femoral vein, femoral artery,

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

Transapical aortic valve replacement (Edwards Lifesciences Ascendra system) is a recently developed option for patients with unfavorable aortic or iliac artery anatomy for the transfemoral approach and is done by cardiac surgeons through a left thoracotomy incision without cardiopulmonary bypass. 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 risks associated with surgical access and general anesthesia.

In the published literature reviewed here, reported implantation success and 30-day survival rates were 93% and 90%, respectively, for the femoral artery approach and 94% and 88%, respectively, for the transapical approach. Single-center comparisons of these 2 implantation approaches have not found significant differences in procedural success or complication rates, with the exception of longer stays in the intensive care unit after transapical aortic valve replacement (25). In the multicenter SOURCE registry, the transapical approach had a lower rate of vascular access complications (4.7%) but higher EuroSCORE and 30-day mortality rate compared with the transfemoral approach (10).

### **DISCUSSION**

The existing published literature on PHVR consists of case reports and series that focus almost exclusively on the Edwards SAPIEN transcatheter heart valve and Medtronic CoreValve ReValving System. This literature demonstrates the feasibility of PHVR in the treatment of aortic stenosis among patients whose high perioperative risk profile places them at significantly higher risk for poor outcome from SAVR. Reported short-term outcomes are generally good, with successful implantation and 30-day survival rates of 94% and 89%, respectively.

Cohorts with follow-up extending beyond successful implantation and 30-day survival have demonstrated continued mortality consistent with advanced age and presence of several comorbid conditions of patients treated with PHVR. Among PHVR cohorts, 1-year survival rates of 70% to 75% have been reported (22, 25), with approximately half of the deaths not directly attributable to cardiac causes. This underscores the importance of appropriate patient selection because if therapy becomes more widely available, it raises questions about whether PHVR could improve long-term results in lower-risk patients. Of

importance, no data have been published about longer-term outcomes or the safety or efficacy of PHVR in patients for whom SAVR is associated with typical or acceptable operative risk, limiting comparison of the outcomes associated with this novel technology versus SAVR. Studies evaluating the possible extension of this technology to younger patients with fewer comorbid conditions should include comparison with an SAVR control group with attention to the hemodynamic durability of PHVs over time.

Other important limitations of the currently available data exist. First, no results from prospective, randomized, controlled trials of PHVR have yet been reported. Although case series demonstrate technical feasibility, they do not evaluate efficacy. Comparison of procedural PHVR mortality rates with the predicted SAVR mortality rates by logistic EuroSCORE may be one way of assessing short-term benefits or harms associated with PHVR. Other limitations include the lack of uniformly assessed outcomes; the subjective nature of patient selection as “too high risk for surgery” in the absence of EuroSCORE or another validated risk-assessment tool; and inadequate data to determine which factors, such as patient, prosthetic, or implantation characteristics, may be associated with better outcomes. The association between aortic stenosis and coronary artery disease and the potentially combined effect of concomitant revascularization with aortic valve replacement may also confound evaluation of long-term outcome after PHVR. Finally, rapid improvements in PHV devices, implantation techniques, and operator experience during the publication period of these reports introduce dynamic, time-dependent factors that confound assessment of acute and longer-term outcomes.

To date, the U.S. Food and Drug Administration has not approved any PHV for the indication of aortic stenosis, but both the Edwards SAPIEN transcatheter heart valve and the Medtronic CoreValve ReValving System have received a 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. Ongoing, large, prospective registries of these devices across Europe and Canada provide real-world insights into the application and outcome of PHVR.

A randomized, controlled trial of PHVR in adults with aortic stenosis is ongoing at 26 sites in the United States, Canada, and Germany. The PARTNER (Placement of Aortic Transcatheter) valve trial (ClinicalTrials.gov registration number: NCT00530894), sponsored by Edwards Lifesciences, was initiated in April 2007 and has a completed enrollment of approximately 1040 participants (26). In this 2-group study, participants with symptomatic, severe, aortic stenosis and a Society of Thoracic Surgeons Predicted Risk of Mortality risk score of 10 or more who are candidates for SAVR were randomly allocated to receive the Edwards SAPIEN transcatheter heart valve (by means of the transfemoral or transapical approach) or un-

dergo SAVR (cohort A); participants who are not candidates for SAVR (defined as operative mortality or serious, irreversible morbidity of 50% or more) were randomly allocated to the Edwards SAPIEN transcatheter heart valve or medical management, including balloon aortic valvuloplasty, as indicated (cohort B; 350 patients). The primary outcome measure is 1-year survival; secondary outcomes include major adverse cardiac or cerebrovascular events and other safety events, functional and quality-of-life improvement, evidence of prosthetic valve dysfunction, and rehospitalization. Preliminary results of cohort B, which completed enrollment in March 2009, are expected to be presented at the Transcatheter Cardiovascular Therapeutics meeting in Washington, DC, in September 2010. This trial comparing PHVR with either conventional heart surgery or medical management will be critical in evaluating the relative safety and efficacy of PHVR for both surgical and nonsurgical candidates.

Two other relevant randomized, controlled trials were recently initiated in Denmark. One will compare PHVR using the Medtronic CoreValve ReValving System with SAVR among 280 patients with severe aortic valve stenosis who are least 70 years of age (27). The primary outcome is the combined rate of death from any cause, myocardial infarction, and stroke at 1 year. Short-term procedural success and selected longer-term outcomes (some up to 5 years) will also be assessed. The estimated study completion date is December 2018. The second Danish trial, which focuses primarily on short-term (1 month) safety issues, compares PHVR using the Edwards SAPIEN transcatheter heart valve with insertion of a biological valve through conventional aortic valve surgery (28). The anticipated sample size is 200 patients, and the estimated study completion date is December 2015.

In summary, PHVR for severe aortic stenosis remains an investigational procedure in the United States but is a promising therapeutic option for patients with severe, symptomatic aortic stenosis who have a higher risk for poor outcome with SAVR. The rapid adoption of PHVR in Europe supports its role in fulfilling an unmet clinical need. Pending the results of the randomized PARTNER trial later this year, little published evidence directly informs whether PHVR might also be indicated for patients for whom SAVR is a treatment option. Further studies are needed to evaluate factors related to improved long-term results, particularly those that assess the effect of noncardiac conditions on outcomes, and the effectiveness and cost-effectiveness of the various PHVs compared with conventional heart valves and other PHVs. The potential availability of lower-profile PHV devices with options for device type and implantation technique will place greater importance on patient selection for the therapy—SAVR, PHVR, or medical therapy—that is most appropriate for individual patients with symptomatic, severe, aortic stenosis.

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