Transcatheter Aortic-Valve Implantation for Aortic Stenosis

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Section: Surgery
Place(s) of Service: Inpatient

I. Description

Transcatheter aortic valve implantation (TAVI) is a potential alternative treatment for patients with severe aortic stenosis. Many patients with aortic stenosis are very elderly and/or have multiple medical comorbidities, thus indicating a high-risk, often prohibitive, for surgery. This procedure is being evaluated as an alternative to open surgery for high-risk patients with aortic stenosis and as an alternative to nonsurgical therapy for patients with a prohibitive risk for surgery.

Two transcatheter aortic valves have U.S. Food and Drug Administration (FDA) approval for the treatment of aortic stenosis, the Edwards SAPIEN™ balloon-expandable valve (Edwards LifeSciences, Irvine, CA) and the self-expanding Medtronic CoreValve Transcathether Aortic Valve Replacement System (Medtronic Inc., Minneapolis, MN).

For patients who are not surgical candidates due to excessive surgical risk, the PARTNER B trial reported results for patients treated with TAVI by the transfemoral approach compared with continued medical care with or without balloon valvuloplasty. There was a large decrease in mortality for the TAVI patients at 1 year compared with medical care. This trial also reported improvements on other relevant clinical outcomes for the TAVI group. There was an increased risk of stroke and vascular complications in the TAVI group. Despite these concerns, the overall balance of benefits and risks from this trial indicate that health outcomes are improved. For patients who are not surgical candidates, no randomized trials have compared the self-expandable valve with best medical therapy. However, results from the single-arm CoreValve Extreme Risk Pivotal Trial met the authors’ prespecified objective performance goal. In a randomized controlled trial (RCT) directly comparing the self-expandable with the balloon-expandable valve among surgically high-risk patients, the devices had similar 30-day mortality outcomes, although the self-expandable valve was associated with higher rates of residual aortic regurgitation and requirement for a new permanent pacemaker.

For patients who are high risk for open surgery, but are operable candidates, the PARTNER A trial reported noninferiority for survival at 1 year for the balloon-expandable valve compared with open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in mortality or in rates of stroke between the 2 procedures. Since
the publication of the PARTNER A trial, the CoreValve High Risk study demonstrated noninferiority for survival at 1 year for the self-expanding prosthesis. This study reported no significant differences in stroke rates between the groups.

The PARTNER A trial also included a subgroup analysis comparing the transfemoral and transapical approaches and reported no outcome differences between the 2 approaches. Some nonrandomized comparative studies have reported higher mortality in patients treated by the transapical approach, but these comparisons are inconclusive because patients treated by the transapical route had a higher baseline risk for mortality. In 2013, FDA expanded approved of TAVI by the transapical approach to include both patients who are not candidates for open surgery and patients who are at high risk for open surgery. In 2014, FDA granted approval for the CoreValve system for patients at extreme risk or who are not suitable candidates for open surgery. FDA labeling indicates that the device can be delivered via femoral, subclavian/axillary, or ascending aortic access.

Evidence from randomized and nonrandomized studies suggests that TAVI with a self-expanding device is associated with higher rates of requirements for permanent pacemakers postprocedure. However, survival rates appear to be similar between device types. There is ongoing research into predictors of conduction abnormalities after TAVI. At this point, the evidence is insufficient to support the superiority of one particular device over another in all patients.

Based on the available evidence, the FDA approvals, and the results of clinical input, TAVI may be considered medically necessary in patients who are not suitable candidates for open surgery, and in patients who are operable candidates but at high risk for open surgery, with an FDA-approved self-expanding or balloon-expandable device according to its labeled indication.

II. Criteria/Guidelines

Transcatheter aortic valve replacement with an FDA approved transcatheter heart valve system, performed via an approach consistent with the device’s FDA approved labeling, is covered (subject to Limitations/Exclusions and Administrative Guidelines) for patients with aortic stenosis when all of the following conditions are present:

1. Severe aortic stenosis * with a calcified aortic annulus; AND
2. NYHA heart failure Class II, III or IV symptoms (See Appendix for class definitions); AND
3. Left ventricular ejection fraction greater than 20% AND
4. Patient is not an operable candidate for open surgery, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon) OR
5. Patient is an operable candidate but is at high risk for open surgery defined as:
   a. Society of Thoracic Surgeons predicted operative risk score of 8% or higher; or
   b. Judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery.

* For the use of the Sapien or CoreValve device, severe aortic stenosis is defined by the presence of one or more of the following criteria:
   - An aortic valve area of less than or equal to 1 cm²
   - An aortic valve area index of less than or equal to 0.6 cm²/m²
A mean aortic valve gradient greater than 40 mm Hg
A jet velocity greater than 4.0 m/s

III. Limitations/Exclusions
A. Transcatheter aortic valve replacement is not covered for all other indications, including but not limited to, patients with a degenerated bio-prosthetic valve ("Valve in Valve" implantation)

B. Devices without FDA approval are not covered.

IV. Administrative Guidelines
A. Precertification is required. Complete HMSA's Precertification Request and fax or mail the form as indicated. Include the following documentation:
   1. History and physical
   2. Documentation indicating that the patient is not an operable candidate for open surgery, confirmed by two cardiovascular specialists
   3. Diagnostic studies confirming severe aortic stenosis

B. Applicable codes:

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<th>Inpatient Procedure Code</th>
<th>Description</th>
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<td>35.05</td>
<td>Endovascular replacement of aortic valve</td>
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<table>
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<tr>
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<th>Description</th>
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<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach</td>
</tr>
<tr>
<td>33362</td>
<td>;open femoral artery approach</td>
</tr>
<tr>
<td>33363</td>
<td>;open axillary artery approach</td>
</tr>
<tr>
<td>33364</td>
<td>;open iliac artery approach</td>
</tr>
<tr>
<td>33365</td>
<td>;transaortic approach (e.g., median sternotomy, mediastinotomy)</td>
</tr>
<tr>
<td>33366</td>
<td>;transapical exposure (e.g. left thoracotomy)</td>
</tr>
</tbody>
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C. The following add-on codes are covered if performed with one of the primary procedures listed above:

<table>
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<th>CPT</th>
<th>Description</th>
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<td>cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (e.g., femoral vessels) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>33368</td>
<td>cardiopulmonary bypass support with open peripheral arterial and venous cannulation (e.g., femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)</td>
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Aortic stenosis is defined as narrowing of the aortic valve opening, resulting in obstruction of blood flow from the left ventricle into the ascending aorta. Progressive calcification of the aortic valve is the most common etiology in North America and Europe, while rheumatic fever is the most common etiology in developing countries. Congenital abnormalities of the aortic valve, most commonly a bicuspid valve, increase the risk for aortic stenosis, but aortic stenosis can also occur in a normal aortic valve. Risk factors for calcification of a congenitally normal valve mirror those for atherosclerotic vascular disease, including advanced age, male gender, smoking, hypertension, and hyperlipidemia. Thus, the pathogenesis of calcific aortic stenosis is thought to be similar to that of atherosclerosis, i.e., deposition of atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification.

The natural history of aortic stenosis involves a long asymptomatic period, with slowly progressive narrowing of the valve until the stenosis reaches the severe stage. At this time, symptoms of dyspnea, chest pain, and/or dizziness/syncope often occur and the disorder progresses rapidly. Treatment of aortic stenosis is primarily surgical, involving replacement of the diseased valve with a bio-prosthetic or mechanical valve by open heart surgery.

Burden of illness. Aortic stenosis is a relatively common disorder of elderly patients and is the most common acquired valve disorder in the United States. Approximately 2-4% of individuals older than 65 years of age have evidence of significant aortic stenosis, increasing up to 8% of individuals by age 85 years. In the Helsinki Aging Study, a population-based study of 501 patients aged 75-86 years, the prevalence of severe aortic stenosis by echocardiography was estimated to be 2.9%. In the US, more than 50,000 aortic valve replacements are performed annually due to severe aortic stenosis.

Aortic stenosis does not cause substantial morbidity or mortality when the disease is mild or moderate in severity. By the time it reaches the severe stage, there is an untreated mortality rate
of approximately 50% within 2 years. Open surgical repair is an effective treatment for reversing aortic stenosis, and artificial valves have demonstrated good durability for periods up to 20 years. However, these benefits are accompanied by a perioperative mortality of approximately 3-4% and substantial morbidity, both of which increase with advancing age.

Unmet needs. Many patients with severe, symptomatic aortic stenosis are poor operative candidates. Approximately 30% of patients presenting with severe aortic stenosis do not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities. For patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of aortic stenosis but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes. Balloon valvuloplasty can improve symptoms and increase flow across the stenotic valve but is associated with high rates of complications such as stroke, myocardial infarction (MI), and aortic regurgitation. In addition, restenosis can occur rapidly, and there is no improvement in mortality. As a result, there is a large unmet need for less invasive treatments for aortic stenosis in patients who are at increased risk for open surgery.

Transcatheter aortic valve implantation (TAVI) has been developed in response to this unmet need and is intended as an alternative treatment for patients in whom surgery is not an option due to prohibitive surgical risk or for patients who are at high risk for open surgery. The procedure is performed percutaneously, most often through the transfemoral artery approach. It can also be done through the subclavian artery approach and transapically using mediastinoscopy. Balloon valvuloplasty is first performed in order to open up the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve and is then expanded and secured to the underlying aortic valve annulus. The procedure is performed on the beating heart without the need for cardiopulmonary bypass.

There are at least two transcatheter aortic valve devices being tested. The Edwards SAPIEN heart-valve system (Edwards Lifesciences, Irvine, CA) is a tri-leaflet bioprosthetic porcine valve that is contained within a stainless steel frame. This device has been commercially available in Europe since 2007 and received U.S. Food and Drug Administration (FDA) approval in November 2011, with expanded indications for approval granted in 2012 and 2013.

The Medtronic CoreValve ReValving System is a second transcatheter valve system under testing. This device is a porcine bioprosthetic valve that is sewn within a self-expanding nitinol frame. It is inserted via the transfemoral artery approach and has also been inserted via the subclavian artery approach. This device has also been approved for use in Europe since 2007 and received FDA approval in the U.S. in 2014.

Regulatory Status

The Sapien Transcatheter Heart Valve System received FDA approval in November 2011 for patients with severe aortic stenosis who are not eligible for open-heart procedures and have a calcified aortic annulus. In 2012, an additional FDA premarket approval (PMA) was granted for the Edwards SAPIEN transcatheter heart valve Model 9000TFX with expanded indications for use. Approval was granted for both the transfemoral and transapical approach. Patient indications were
broadened to include patients who are at high risk for open surgery. For the transapical approach, approval was granted for patients who are at high risk for open surgery. In September 2012, FDA expanded the indications for the transapical approach to include both inoperable patients and patients who are at high risk for open surgery. As a result, the Sapien Transcatheter Heart Valve System is approved for both high risk and inoperable patients when used by either the transapical or transfemoral approach. In June 2014, the next-generation Sapien XT Transcatheter Heart Valve (model 9300TFX) was approved by FDA for use with the NovaFlex+ delivery system.

The Medtronic CoreValve Transcatheter Aortic Valve Replacement System (Medtronic Inc., Minneapolis, MN) received FDA approval in January 2014 for patients with symptomatic heart disease due to severe native calcific aortic stenosis and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (see Policy Guidelines section). In June 2014, FDA expanded the indications for the CoreValve to include patients at high risk for open surgery. FDA labeling indicates that the device can be delivered via femoral, subclavian/axillary, or ascending aortic access.

VI. Rationale:

The evidence on TAVI consists of many uncontrolled case series and one pivotal randomized controlled trial (RCT) - the PARTNER trial. These studies report on two potential populations for TAVI: 1) patients who are not surgical candidates, and 2) patients who are high risk for surgery but still considered to be surgical candidates. The evidence on these two groups of patients will be discussed separately.

Outcomes for TAVI in patients who are not Surgical Candidates

Systematic Reviews:

Systematic reviews on this question consist of studies that evaluate results from case series. An Agency for Healthcare Research and Quality (AHRQ)-sponsored review in 2010 reviewed 84 publications enrolling 2,375 patients. Implantation was successful in 94% of patients overall, with higher success rates reported in more recent publications. The aggregate 30-day survival was 89% across all studies. Adverse event rates were reported in the larger case series, with an estimated 30-day rate of major cardiovascular adverse events and stroke of 8%.

A second systematic review was published in 2011 by Figulla et al. This review included studies that enrolled symptomatic patients with severe aortic stenosis, had a mean age of 75 years or older, reported on 10 or more patients, and had a follow-up duration of 12 months or more. A total of 12 studies met these criteria and were compared to a group of 11 studies that treated severe aortic stenosis with nonsurgical therapy. The procedural success in these studies ranged from 86-100%, and the 30-day mortality ranged from 5.3-23%. The combined mean survival rate at 1 year was 75.9% (95% confidence interval [CI] 73.3-78.4). This 1-year survival rate compared favorably to medical therapy, which was estimated to be 62.4% (95% CI 59.3-65.5).

Randomized controlled trials

The PARTNER trial was a pivotal multicenter RCT of TAVI performed in the U.S., Canada, and Germany, using the SAPIEN heart-valve system. Leon et al. reported results of patients from the
PARTNER trial with severe aortic stenosis who were not candidates for open surgery. In order to be classified as unsuitable for open surgery, patients had to have a predicted probability of ≥50% for death or a serious irreversible condition at 30 days post-surgery. This probability was determined by two surgeon investigators using clinical judgment and the Society of Thoracic Surgery (STS) risk score. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as unsuitable for surgery. A total of 3,105 patients were screened for aortic-valve surgery, and 12% of these were eventually included in the cohort of patients deemed unsuitable for surgery.

A total of 358 patients were randomized to TAVI or usual care. TAVI was performed by the transfemoral approach under general anesthesia. Standard therapy was determined by the treating clinicians. In most cases (83.8%), standard treatment included balloon valvuloplasty of the aortic valve. A small number of patients (6.7%) underwent open surgical valve replacement despite the high risk, and another 2.2% of patients underwent TAVI at a center outside the U.S. that was not participating in the trial. The primary outcome was death from any cause over the course of the trial (median follow-up 1.6 years). A “coprimary” endpoint was the composite of time to death from any cause or time to repeat hospitalization related to aortic stenosis or TAVI. Secondary endpoints were cardiovascular mortality, New York Heart Association (NYHA) functional class, the rate of hospitalizations due to aortic stenosis or TAVI, the 6-minute walk test, valve performance as measured by echocardiography, and procedural complications (myocardial infarction [MI], stroke, acute kidney injury, vascular complications, and bleeding).

The mean age of enrolled patients was 83.2 years. There were some baseline imbalances in the patient population indicating that the standard therapy group may have had a higher severity of illness. Standardized scores of surgical risk were higher in the standard therapy group. The Logistic EuroSCORE was significantly higher in the standard therapy group compared to the TAVI group (30.4±19.1 vs. 26.4±17.2, p=0.04) and the Society of Thoracic Surgery (STS) score was numerically higher but did not reach statistical significance (12.1±6.1 vs. 11.2±5.8, p=0.14). Significantly more patients in the standard therapy group had chronic obstructive pulmonary disease (COPD) (52.5% vs. 41.3, p=0.04) and atrial fibrillation (48.8% vs. 32.9%, p=0.04), and there was a nonsignificant trend for more patients in the standard therapy group having a lower ejection fraction (51.1 vs. 53.9%) and frailty, as determined by prespecified criteria (28.0 vs. 18.1%).

Death from any cause at 1 year following enrollment was lower for the TAVI group (30.7% vs. 49.7%, p<0.001). This represents a 19% absolute risk reduction, a 38.2% relative risk reduction, and a number needed to treat of 5.3 to prevent one death over a 1-year follow-up. Most secondary outcomes also favored the TAVI group. Cardiovascular death was lower in the TAVI group (19.6% vs. 44.1%, p<0.001). The composite of all-cause mortality and repeat hospitalizations was reached by 42.5% of the patients in the TAVI group compared with 70.4% in the standard therapy group. Symptoms and functional status were also superior in the TAVI group. The percent of patients in NYHA Class I or II at 1 year was higher for the TAVI group (74.8% vs. 42.0%, p<0.001), and there was a significant improvement in the 6-minute walk test for the TAVI group but not for the standard therapy group (between group comparisons not reported). Subgroup analysis did not report any significant differences in outcomes according to clinical and demographic factors.
Complication rates were higher for the TAVI group. Stroke or transient ischemic attack (TIA) at 1 year was more than twice as frequent for the TAVI group (10.6% vs. 4.5%, p=0.04). Major bleeding and vascular complications occurred in a substantial percent of patients undergoing TAVI, and were significantly higher than in the standard therapy group (22.3% vs. 11.2%, p=0.007; and 32.4% vs. 7.3%, p<0.001 respectively).

Quality of life (QOL) outcomes from this trial were reported by Reynolds et al in 2012.(11) QOL outcomes were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score, the Medical Outcomes Study 12-Item Short-Form (SF-12), and the EuroQol (EQ-5D). The number of participants who completed the QOL measures was not clearly reported; estimates from graphical representation show that between 149 and 170 patients in the TAVI group and 138 and 157 patients in the medical therapy group completed baseline QOL measures. At the follow-up time points of 30 days, 6 months, and 12 months, the change in the QOL scores was greater for the TAVI group. At 30 days, the mean difference in the KCCQ was 13.3 points (95% CI, 7.6 to 19.0; p<0.001). This mean difference increased at later time points to 20.8 points (95% CI, 14.7 to 27.0; p<0.001) at 6 months and 26.0 points (95% CI, 18.7 to 33.3; p<0.001) at 12 months. Changes in the SF-12 and EQ-5D measures showed similar patterns.

Two-year outcomes were reported from the PARTNER trial in 2012. Mortality at 2 years was 43.3% in the TAVI group compared to 68.0% in the medical therapy group (hazard ratio [HR], 0.58; 95% CI, 0.36 to 0.92; p=0.02). Cardiovascular mortality was also lower in the TAVI group compared to medical therapy (31.0% vs. 62.4%, p<0.001). The rate of hospitalization over the 2-year period was lower in the TAVI group compared to medical therapy (35.0% vs 72.5%, p<0.001).

In 2014, Svensson et al reported detailed mortality outcomes for both arms of the PARTNER trial: the PARTNER B RCT previously described that compared surgical repair with TAVI in prohibitive surgical risk patients, and the PARTNER A RCT that compared surgical repair with TAVI in high surgical risk patients, described next. For the 358 patients who were considered inoperable and enrolled in the PARTNER B RCT, at last follow-up, 237 patients had died. Those randomized to standard therapy exhibited an early peak in mortality that was higher than those randomized to TAVI and prolonged beyond 6 months. Compared with standard therapy, the estimated net lifetime benefit added by transfemoral TAVI was 0.50 years (90% CI, 0.30 to 0.67).

Case series/Cohort Studies

Many case series of TAVI have been published in the last 10 years, the majority of which have included patients who are not candidates for open surgery. However, the selection process for TAVI has largely been subjective, with the expert opinion of the surgeons and/or cardiologists as the main factor determining suitability for open surgery. As a result, there may be some overlap in these series with patients who are surgical candidates, but the distinction cannot be easily made from the reported studies. Some of the larger case series are discussed below.

In 2014, Popma et al published results of the CoreValve Extreme Risk Pivotal Trial, which was designed to evaluate the CoreValve self-expanding valve among patients with severe aortic stenosis who were considered to be at extreme risk for surgical aortic valve replacement. The study included patients with severe aortic stenosis and NYHA class II or greater symptoms who were considered to be at extreme risk for open aortic valve repair. A patient was judged to be extreme
risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 50% or greater risk for mortality or irreversible morbidity at 30 days with surgical repair. The study’s primary end point was the 12-month rate of all-cause mortality or major stroke in the “attempted implant” population. This population included all patients who underwent a documented valve implant via an iliofemoral approach. The study defined an objective performance goal of 43% for all-cause mortality or major stroke at 12 months postprocedure. This goal was based on 2 sources: a weighted meta-analysis of 7 balloon aortic valvuloplasty studies, which yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% CI, 34.0% to 51.4%). This estimate was adjusted based on the lower 95% confidence bound of 43% in the standard therapy arm of inoperable patients in the PARTNER trial.

Four hundred eighty-nine patients were included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study prior to treatment, 6 of whom did not complete the procedure with iliofemoral access). The Kaplan-Meier rate of the primary end point (all-cause mortality or major stroke) was 26.0% (upper bound of 95% CI, 29.9%), which was lower than the prespecified performance goal of 43% (p<0.001). The rate of all-cause mortality at 1 year following enrollment was 24.3%, while the rate of major stroke at 12 months was 4.3%. These rates are comparable or better than those seen in the TAVI arm of the PARTNER pivotal trial, although patients in the PARTNER pivotal trial had a higher baseline STS score (12.1% in the PARTNER trial vs 10.3% in the Popma et al study).

In 2014, Reardon et al reported outcomes for the group of patients enrolled in the CoreValve Extreme Risk Pivotal Trial who received the device through an approach other than the iliofemoral approach. Inclusion criteria and procedures were the same as for the primary CoreValve Extreme Risk Trial. One hundred fifty patients with prohibitive iliofemoral anatomy were included and received the CoreValve device through an open surgical approach via the subclavian artery (N=70) or a direct aortic approach via a median hemisternotomy or right thoracotomy (N=80). Included patients were elderly (mean age, 81.3 years) and significantly symptomatic, with 92% of subjects having NYHA class III or IV heart disease. At 30 days post-procedure, 23 patients (15.3%) had met the primary end point of all-cause mortality or major stroke; of the 23 patients, 17 (11.3%) had died and 11 (7.5%) had experienced a major stroke. At 12 months postprocedure, 59 patients (39.4%) had met the primary end point; of those, 54 (36%) had died and 13 (9.1%) had experienced a major stroke. The 30-day mortality of 11.3% was higher than that reported in the studies of TAVI that used a transfemoral approach or an iliofemoral approach (PARTNER B RCT and the CoreValve Extreme Risk Pivotal Trial), but similar to the 30-day mortality reported by the patients treated with a transapical approach (PARTNER A trial).

The two largest series included in the AHRQ review reported on 646 patients treated with the Medtronic CoreValve and 339 patients treated with the Edwards SAPIEN valve. The CoreValve study by Piazza et al. study was notable in that it used more objective patient selection criteria than is common in this literature. Their criteria for eligibility included the following: 1) Logistic EuroScore ≥15%, 2) age ≥75 or, 3) age ≥65 with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns or radiation precluding open surgery, or body mass index (BMI) ≤18 kg/m². Procedural success was 97% and 30-day survival was 92%. The 30-day combined rate of death, MI or stroke was 9.3%. The study by Rodes-Cabou et al. was performed in
Canada and used Edwards SAPIEN valve. This study had subjective inclusion criteria, relying on the judgment of the participating surgeons to determine eligibility for TAVI. The procedural success rate was 93.3% and the 30-day mortality was 10.4%. The authors also reported a mortality rate of 22.1% at a median follow-up of 8 months.

Another larger study from Germany reporting on 697 patients treated with the CoreValve system. Procedural success was 98.4% and 30-day mortality was 12.4%. Another large case series from Italy included 663 patients treated with the CoreValve device. Procedural success was 98% and mortality at 1 year was 15%. A notable study was published by Gurvitch et al. in 2011 that reported on durability and longer clinical outcomes up to 3 years. Seventy patients who underwent TAVI and survived for greater than 30 days were included. Survival at 1, 2, and 3 years was 81%, 74%, and 61%, respectively. One patient (1.5%) required reoperation during this time period. The valve area decreased from 1.7 ± 0.4 cm² following the procedure to 1.4±0.3 cm² at 3 years. Aortic incompetence was trivial or mild in 84% of patients and did not worsen over time.

In 2013, Mack et al reported outcomes after TAVI from 224 hospitals participating in the Edwards SAPIEN device post Food and Drug Administration (FDA) approval registry. From November 2011 to May 2013, the registry included at total of 7710 patients who underwent TAVI placement, of whom 1559 (20%) patients were considered inoperable, and 6151 (80%) were considered high-risk but operable. Of those considered inoperable, 1139 underwent device placement via transfemoral access, while 420 underwent device placement via nontransfemoral access. In-hospital mortality was 5.4% and 7.1% for the inoperable patients who underwent TAVI via transfemoral and nontransfemoral access, respectively. Thirty-day clinical outcomes were reported for 694 inoperable patients; of those, 30-day mortality was 6.7% and 12.6% for patients who underwent TAVI via transfemoral and nontransfemoral access, respectively.

**Section Summary:**

Numerous case series have demonstrated feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at 1 year for TAVI compared to standard therapy. Baseline group differences were present, indicating that the TAVI group may have been healthier. While these differences are unlikely to account for the degree of mortality benefit reported, they may have resulted in an overestimation of the mortality benefit.

The benefit in mortality was accompanied by an increased stroke risk, as well as substantial increases in vascular complications and major bleeding. There is also uncertainty concerning the generalizability of these results, since patient selection was primarily determined by the judgment of the cardiovascular surgeons and/or cardiologists. It is not known whether this type of decision making by surgeons and cardiologists is reliable across the range of practicing clinicians.

**Outcomes for TAVI in Patients who are at High Risk for Open Surgery**

**Systematic Reviews.**

Several systematic reviews have been published on this question. The evidence in these studies is derived largely from nonrandomized comparative studies, as only 1 RCT has been published (the PARTNER trial). Panchal et al reported results from a meta-analysis of 17 studies that included 4659
patients, 2267 treated with TAVI, and 2392 treated with open surgery. Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality that was higher by a mean of 3.7 points compared to patients undergoing open surgery. On combined analysis, there were no differences between groups on 30-day mortality, mortality at longest follow-up, cardiovascular mortality, MI, stroke, or TIA. Patients in the open surgery group had a higher incidence of major bleeding complications (relative risk, 1.42; 95% CI, 1.20 to 1.67; p<0.001). In a similar meta-analysis that included 17 studies reporting on 4873 patients, there were no differences between TAVI and open surgery in early mortality (odds ratio [OR], 0.92; 95% CI, 0.70 to 1.2) or mid-term mortality, defined as between 3 months and 3 years (HR=0.99; 95% CI, 0.83 to 1.2).

Randomized controlled trials.

The PARTNER A Trial

Results from the cohort of patients in the PARTNER trial who were high risk for open surgery, but still suitable candidates, were published in June 2011. The inclusion and exclusion criteria were generally the same as for the prior cohort, except that these patients were classified as high risk for surgery rather than unsuitable for surgery. For high risk, patients had to have a predicted perioperative mortality of ≥15%, as determined by a cardiac surgeon and cardiologist using clinical judgment. An STS score of ≥10 was included as a guide for high-risk, but an STS score threshold was not a required criterion for enrollment. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as high risk for surgery. A total of 3,105 patients were screened for aortic valve surgery, and 22.5% of these were eventually included in the cohort of patients deemed high-risk for surgery.

A total of 699 patients were randomized to TAVI or usual care. The primary hypothesis was that TAVI was non-inferior to open aortic valve replacement (AVR), using a one-sided non-inferiority boundary of 7.5% absolute difference in mortality at 1 year. TAVI was performed under general anesthesia using the transfemoral approach if possible (n=492). If the transfemoral approach was not possible, transapical approach was used (n=207). The comparison group underwent open AVR. Details of the open procedure were not provided in presentation slides.

The primary outcome was death from any cause at 1-year follow-up. A second powered endpoint was non-inferiority at 1 year for the patients undergoing TAVI by the transfemoral approach. Secondary endpoints were cardiovascular mortality, NYHA functional class, rehospitalizations, the 6-minute walk test, valve performance as measured by echocardiography, and procedural complications (MI, stroke, acute kidney injury, vascular complications, and bleeding). The mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographics and clinical characteristics were generally well-balanced, except for a trend toward an increased percent of patients in the TAVI group with a creatinine level >2.0 (11.1% vs. 7.0%, p=0.06).

Death from any cause at 1 year following enrollment was 24.2% for the TAVI group compared to 26.8% for the open AVR group (p=0.44 for difference between groups). The upper limit of the 95% confidence interval (CI) for the difference between groups was a 3.0% excess mortality in the TAVI group, which was well within the non-inferiority boundary of 7.5%. Thus the criterion of non-
inferiority was met, with a p value of 0.001. For the subgroup of patients who underwent TAVI by the transfemoral approach, results were similar with 22.2% mortality in the TAVI group compared with 26.4% mortality in the open AVR group (p=0.002 for non-inferiority). The secondary outcomes of cardiovascular mortality (14.3% vs. 13.0%, p=0.63) and rehospitalizations (18.2% vs. 15.5%, p=0.38) were not significantly different for the TAVI versus open AVR groups. The percent of patients in NYHA Class I or II at 1 year was similar between groups at 1 year, as was the improvement in the 6-minute walk test. On subgroup analysis, there was a significant effect for gender, with women deriving greater benefit than men (p=0.045), and a significant effect for prior coronary artery bypass graft (CABG), with patients who had not had prior CABG deriving greater benefit in the TAVI group.

Certain complication rates showed significant differences between groups. Stroke or TIA at 1 year was higher for the TAVI group (8.3% vs. 4.3%, p=0.04). Vascular complications occurred in 18.0% percent of patients undergoing TAVI, compared with 4.8% in the open AVR group (p=0.01), and major vascular complications were also higher in the TAVI group (11.3% vs. 3.5%, p=0.01). On the other hand, major bleeding was more common in the open group compared to TAVI (25.7% vs. 14.7%, p=0.01).

Reynolds et al published QOL results from the PARTNER trial in 2012. QOL outcomes were evaluated using the KCCQ summary score, the SF-12, and the EQ-5D. Of 699 patients in the trial, 628 completed baseline QOL measures. Patients in both the TAVI group and the surgical AVR group demonstrated significant improvements in all QOL measures over the 12 months following treatment. The TAVI group had superior improvement at 1 month on the KCCQ (mean difference, 9.9; 95% CI, 4.9 to 14.9; p<0.001), but this difference was no longer present at 6 or 12 months. A similar pattern of results was reported for the SF-12 and EQ-5D measures.

Generereux et al published a follow-up study from the PARTNER A trial reporting on bleeding complications. Using an as-treated approach, this analysis included 313 patients treated with surgical repair, 240 patients treated with transfemoral TAVI, and 104 patients treated with transapical TAVI. Seventy-one patients treated with surgery (22.7%) had major bleeding complications within 30 days of the procedure, compared with 27 (11.3%) of those treated with transfemoral TAVI and 9 (8.8%) of those treated with transapical TAVI (p<0.001). A major bleeding complication was independently associated with worse prognosis at 1 year.

The U.S. CoreValve High Risk Study

In 2014, Adams et al published results of the U.S. CoreValve High Risk Study. This was an RCT comparing surgical aortic valve replacement with TAVI using a self-expanding transcatheter aortic valve prosthesis (CoreValve device) in patients who had severe aortic stenosis and were considered at increased risk of death during surgery. The study randomized 795 patients in a 1:1 ratio to TAVI or open aortic valve replacement. Patients were considered to be at “increased surgical risk” if 2 cardiac surgeons and 1 interventional cardiologist estimated that the risk of death within 30 days after surgery was 15% or more and that the risk of death or irreversible complications within 30 days after surgery was less than 50%. The primary analysis was based on the as-treated population, which included all patients who underwent an attempted implantation. For the study’s primary outcome, the rate of death from any cause at 1 year was lower in the TAVI group than in the surgical group (14.2% vs 19.1%; absolute risk reduction, 4.9%; upper boundary of 95% CI, -0.4,
which was less than the predefined noninferiority margin of 7.5% point difference between the groups; noninferiority, p<0.001, superiority p=0.04). Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVI group than in the surgical group: at 30 days, major vascular complications occurred in 5.9% of the TAVI group compared with 1.7% of the surgical group (p=0.003), while permanent pacemaker implantation was required in 19.8% of the TAVI group compared with 7.1% of the surgical group (p<0.001). In contrast to the PARTNER trial, the TAVI group did not have a higher rate of any stroke at 1 year postprocedure than the surgical group: 8.8% for the TAVI group compared with 12.6% for the surgical group (p=0.10).

Section summary:
The PARTNER RCT in high-risk patients who were eligible for surgical AVR reported differences between TAVI and open AVR in terms of mortality at 1 year and most major secondary outcomes. The non-inferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality, but in actuality, the reported mortality for the TAVI group was lower than for the open group, although not significantly different. QOL was also similar at 1 year between the TAVI and AVR groups. Stroke or TIA was significantly more common for the TAVI group, occurring at a rate of almost 2 times that reported for open surgery. Other secondary outcomes was similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern for generalizability of results given that the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. The U.S. CoreValve High Risk Study reported that TAVI was noninferior to open surgical repair. Although, in contrast to the PARTNER A RCT, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group.

In addition to these two RCTs, several meta-analyses have compared outcomes between TAVI and open surgery using evidence that is primarily from nonrandomized comparative trials. These meta-analyses have concluded that there are no clear differences in mortality, or in secondary morbidity outcomes, between the two procedures.

Comparisons of Different TAVI Devices
As of 2014, there are 2 FDA-approved TAVI devices, one of which relies on a self-expanding mechanism and one which relies on a balloon-expanding mechanism. A relatively small body of evidence has addressed whether different TAVI devices are associated with differences in outcomes.

Systematic Reviews
In 2014, Athappan et al published results from a systematic review and meta-analysis to evaluate the risk of stroke for patients undergoing TAVI, comparing the transfemoral with transapical access approaches and the self-expanding (CoreValve) valve design with the balloon-expandable (SAPIEN) valve design. The authors identified 25 multicenter studies and 33 single-center studies that met their inclusion and exclusion criteria, including 3 randomized comparisons, all from the PARTNER
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study. At 30 days postprocedure, there were no differences in stroke rates. In multicenter studies, the incidence of stroke 30 days postprocedure was 2.4% (95% CI, 1.9% to 3.2%) for centers using the self-expanding valve and 3.0% (95% CI, 2.4% to 3.7%) for centers using the balloon-expanding valve. In pooled analysis, there was no difference in the in-hospital/30-day stroke rate between the self-expanding and balloon-expanding valve groups (pooled OR=1.03; 95% CI, 0.78 to 1.35). Findings were similar for single center studies. Stroke rates improved with increasing center experience with TAVI.

Randomized Controlled Trials

In 2014, Abdel-Wahab et al published results of an RCT that directly compared the CoreValve self-expandable valve with the SAPIEN balloon-expandable valve among patients at high risk for surgery with severe aortic stenosis.31 Two hundred forty-one patients were randomized, 121 to the balloon-expandable valve group and 120 to the self-expandable valve group. The study’s primary end point was device success, a technical composite end point including (1) successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system; (2) correct position of the device in the proper anatomic location; (3) intended performance of the prosthetic heart valve; and (4) only 1 valve implanted in the proper anatomic location. Device success occurred in 116 of 121 (95.9%) of patients in the balloon-expandable group, compared with 93 of 120 (77.7%) patients in the self-expandable valve group (RR=1.24; 95% CI, 1.12 to 1.37). This difference was driven largely by differences in rates of residual aortic regurgitation, which occurred in 4.1% of the balloon-expandable valve group and 18.3% of the self-expandable valve group (RR=0.23; 95% CI, 0.09 to 0.58; p<0.001). Cardiovascular mortality at 30 days and bleeding and vascular complications were not significantly different between the groups. Patients in the balloon-expandable group less frequently required placement of a new permanent pacemaker (17.3% vs 37.6%, p=0.001).

Nonrandomized Comparative Studies

In 2014, Van Belle et al compared rates of postprocedural aortic regurgitation for TAVI with balloon-expandable or self-expandable valves, using data from a large, national French registry of patients undergoing TAVI from January 2010 to October 2011.32 Significant postprocedural aortic regurgitation (>grade 1) has been associated with worsened long-term outcomes. For this analysis, the authors included 3195 patients, of whom 1872 (67.6%) received a balloon-expandable valve and 897 (32.4%) received a self-expandable valve. Postprocedural aortic regurgitation greater than grade 1 occurred in 15.8% of all patients, and in 21.5% of patients who received a self-expandable valve (vs 13.0% of those who received a balloon-expandable valve; p<0.001); this difference remained significant after controlling for potential confounding factors.

Dworakowski et al used data from a registry of TAVI procedures from the United Kingdom, the UK TAVI Registry, to compare differences between balloon-expandable and self-expandable valves in terms of paraprosthetic aortic regurgitation post-TAVI. The analysis included 2440 patients enrolled at 25 UK centers, 52.7% and 47.2% of whom received a balloon-expandable or self-expandable device, respectively. Ten percent of patients had moderate or severe post-TAVI paraprosthetic aortic regurgitation. The use of a self-expanding valve was associated with paraprosthetic aortic regurgitation, with 13.6% of those with a self-expanding valve experiencing moderate or severe aortic regurgitation (vs 7.6% of those with balloon-expandable valve; p<0.001).
However, overall mortality did not differ between devices. In regression modeling, moderate-to-severe aortic regurgitation was a significant predictor of mortality in patients treated with a balloon-expandable valve (HR=1.97; 95% CI, 1.47 to 2.61), but not in patients treated with a self-expanding valve (HR=1.13; 95% CI, 0.83 to 1.51). The authors note that the reason for this difference in aortic regurgitation-related mortality risk is not well understood.

Kasel et al prospectively compared sequential patients treated at a single institution with the CoreValve and Sapien devices. Patients treated with TAVI from December 2007 to April 2010 (N=were treated with the CoreValve device; those treated after April 2010 received the Sapien device. The present study included 50 patients treated with transfemoral TAVI with each device; of 185 patients considered candidates for TAVI, the first 25 of those treated in the 2007-2010 period were excluded to avoid a learning curve effect. In addition, 60 of those who were treated with transapical TAVI in the post-2010 period were excluded. Sapien- and CoreValve-treated patients differed at baseline in relation to sex, history of dyslipidemia, previous cardiovascular surgery, previous chest irradiation, STS score, and presence of rhythm disturbances. Device success rates were similar between groups (98% with the Sapien valve vs 90% with the CoreValve; p=0.20). For the primary end point of Valve Academic Research Consortium-combined safety events, in multivariable analysis, the Sapien device was associated with significantly fewer AEs (OR=0.21; 95% CI, 0.05 to 0.84; p=0.03). More patients treated with the CoreValve required a permanent pacemaker placement (38% vs 8%; p<0.001).

Section Summary

A single RCT that compared TAVI devices with different mechanisms (self-expanding [CoreValve] vs balloon-expandable [Sapien]) reported no significant differences in cardiovascular mortality at 30 days post-procedure. However, the balloon-expandable valve was associated with higher rates of device success due to lower rates of paraprosthetic regurgitation and with lower rates of permanent pacemaker requirement. These findings are supported by results from nonrandomized comparisons between the two currently-available types of TAVI devices.

Comparisons of Alternative TAVI

The majority of all patients treated with TAVI, and all the patients enrolled in the PARTNER B trial, have been by the transfemoral approach. Other approaches, such as the transapical approach, have been used in patients with inadequate femoral access. There is a limited amount of evidence comparing outcomes from different approaches. In the PARTNER A trial, slightly less than one-third of procedures were performed by the transapical approach, and there were no substantial differences in outcomes between the 2 approaches. The Edwards SAPIEN transcatheter heart-valve system has FDA approval for use by the transfemoral and transapical approach. The Medtronic CoreValve device has FDA approval for use by the transfemoral, transsubclavian/transaxillary, and transaortic approaches.

Systematic Reviews

A systematic review and meta-analysis of 20 nonrandomized studies comparing outcomes from the transfemoral and transapical approaches was published by Li et al in 2013. This review included 20 studies, 19 of which were prospective and one of which was retrospective. There were a total of 4267 patients treated by the transfemoral approach and 2242 patients treated by the transapical
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approach. Patients treated by the transfemoral approach had lower 30-day mortality (7.5% vs. 11.3%). There were no differences between groups in the incidence of stroke (3.8% vs. 4.0%) or heart block requiring pacemaker (8.5% vs. 7.5%).

Garcia et al conducted a meta-analysis comparing 30-day outcomes after TAVI via transfemoral, transapical, and transsubclavian approaches. The authors included studies that reported 30-day outcomes stratified by different access routes, with a final sample of 7 studies that included 2636 patients (1526 who received transfemoral access, 882 who received transapical access, 228 who received trans-subclavian access). Compared with transfemoral access, transapical access was associated with higher odds of 30-day mortality (OR=1.54; 95% CI, 1.09 to 2.16; p=0.01); all patients studied for this comparison used the SAPIEN valve. Compared with transfemoral access, transsubclavian access was associated with no significant difference in 30-day mortality (OR=0.64; 95% CI, 0.31 to 1.32; p=0.23), but was associated with a decreased risk of vascular complications (OR=0.53; 95% CI, 0.29 to 0.95; p=0.03).

Nonrandomized comparative studies. Some nonrandomized, comparative studies have compared outcomes for the transfemoral approach compared to the transapical approach. In a retrospective, multicenter from 4 centers in Europe enrolling 882 patients, outcomes were compared between the transfemoral (n=793, 89.9% of total) and transapical (n=89, 10.1% of total) approaches. Patients treated by the transapical approach were more severely ill, as demonstrated by a higher median EuroSCORE (27.0 vs 20.0, p<0.001) and a higher median Society of Thoracic Surgeons Score (10.2 vs 6.7, p<0.001). Patients treated by the transapical approach had a higher 30-day mortality (OR=3.1, 95% CI, 1.4 to 6.8; p=0.004) and a higher overall mortality at a median follow up of 365 days (HR=1.9; 95% CI, 1.2 to 2.9; p=0.004). The transapical approach was associated with a lower risk for major bleeding complications (OR=0.33; 95% CI, 0.12 to 0.90; p=0.03).

Ewe et al. included 107 consecutive patients undergoing TAVI. 47 by the transfemoral approach and 50 by the transapical approach. Mortality was not significantly different for the transfemoral approach versus the transapical approach at 30 days (11.1% vs. 8.5%, respectively, p=0.74) or at 1 year (19.8% vs. 14.3% respectively). Vascular complications were more common in the transfemoral group (18% vs. 5%, respectively, p=0.05). Fluoroscopy time and total radiation exposure was more reduced for the transapical approach.

A nonrandomized, comparative study reported higher complication rates with the transapical approach. Thomas et al. used data from a European registry to compare patients undergoing TAVI by the transfemoral (n=463) with patients undergoing TAVI by the transapical approach (n=575). Complications were more frequent in the transapical group, but the transapical group also may have been more severely ill as judged by a higher Eurogual risk score. A publication from the UK TAVI registry evaluated risk factors for adverse outcomes in 877 TAVI procedures. On univariate analysis, TAVI by the transapical approach was associated with lower survival, although this relationship did not persist after controlling for demographic and clinical factors.

Tanawuttiwat et al conducted a retrospective, single-institution cohort study to compare the incidence of new-onset atrial fibrillation after aortic valve replacement using different approaches, including TAVI by the transfemoral, transapical, and transaortic approaches, and surgical aortic valve replacement. The authors included 231 consecutive who underwent aortic valve replacement, of whom 82 underwent surgical replacement and 149 underwent TAVI with a balloon-expandable
implant (SAPIEN device). After exclusion of patients with evidence of preexisting atrial arrhythmia (n=80), a bicuspid aortic valve (n=24), or who died within 48 hours of the procedure (n=4), the final study population was 123. TAVI was performed via the transfemoral approach if there was an appropriate iliofemoral arterial diameter; otherwise, transapical or transaortic TAVI was performed. Postprocedural new-onset atrial fibrillation occurred in 52 patients (42.3%), most commonly in surgical replacement, occurring in 21 of 35 patients (60%), compared with 19 of 36 patients (53%) undergoing transapical TAVI, 8 of 24 patients (33%) undergoing transaortic TAVI, and 4 of 28 patients (14%) undergoing transfemoral TAVI (p=0.001).

Subsequent to the RCT portion of the PARTNER trial, the study investigators conducted a nonrandomized continued-access study that allowed patients meeting the inclusion and exclusion criteria for the RCT portion of the trial to undergo TAVI. Dewey et al used data from the transapical cohort of the PARTNER trial combined with data from patients who underwent transapical TAVI in the continued-access study to report outcomes after transapical procedures. Patients included in their analysis included 104 patients who underwent transapical TAVI as part of the PARTNER trial, 92 patients who had been in the transapical cohort in the PARTNER trial and were randomized to conventional surgical valve repair, and 975 patients who underwent transapical TAVI as part of the continued-access registry. Thirty-day or in-hospital mortality was similar across groups: 10.6% for patients who received transapical TAVI as part of the PARTNER trial; 12.0% for patients who underwent surgical valve repair; and 8.8% for patients who received transapical TAVI as part of the continued-access registry (p=0.54). Compared with those who received transapical TAVI as part of the PARTNER trial, those in the continued-access registry had a lower rate of stroke at 1 year (3% vs 10.8%; p=0.004).

Van der Boon et al analyzed data from a multicenter European database of TAVI patients to compare outcomes after transapical TAVI with those after transfemoral TAVI. The authors included 944 consecutive patients who underwent TAVI, 793 (94%) via transfemoral approach, 89 (9.4%) via transapical approach, 58 (6.1%) via subclavian approach, and 4 by direct transaortic valve implantation. Compared with the transfemoral TAVI group, those undergoing transapical TAVI had higher rates of coronary artery bypass graft, coronary artery disease, hypertension, chronic kidney disease, and peripheral vascular disease. Compared with the transfemoral TAVI group, after adjustment for clinical variables, the all-cause in-hospital mortality was higher for those undergoing transapical TAVI (adjusted OR=3.12; 95% CI, 1.43 to 6.82; p=0.004). In contrast, major vascular complications were less common in the transapical TAVI group (adjusted OR=0.33; 95% CI, 0.12 to 0.90; p=0.031). Although this study used multivariate analysis to adjust for observable sources of bias between the groups, the possibility of residual confounding and confounding due to differences in the valve types used between the groups remains.

Section Summary.

There is some evidence comparing different approaches for TAVI. The highest quality evidence is for the transapical approach. This evidence includes a subgroup analysis from the PARTNER RCT, and nonrandomized comparative studies. In the RCT, there was not a mortality difference between the two approaches. In the nonrandomized studies, mortality is higher for patients treated by the transapical approach. However, patients treated by the transapical approach were more severely ill, with a higher predicted mortality at baseline. It is not possible to determine whether this
difference in mortality is due to noncomparability of groups or due to the specific approach. In addition, since the transapical approach is generally used in patients who are not suitable for the transfemoral approach due to advanced vascular disease, the transapical approach is usually done out of necessity, not by choice of the surgeon. There is very little evidence on other approaches such as the transaxillary, transaortic and transiliac.

In 2013, the FDA expanded approved TAVI by the transapical approach to include both patients who are not candidates for open surgery and patients who are at high risk for open surgery.

**What is the complication rate following TAVI?**

A systematic review of complications associated with TAVI was published by Khatri et al in 2013. This study included all publications with at least 100 patients that had data on at least 1 type of complication. A total of 49 studies enrolling 16,063 patients were identified. The most common adverse event was heart block requiring a pacemaker insertion, which occurred in 13.1% of patients. Vascular complications occurred in 10.4% of patients. The third most common complication was acute renal failure requiring therapy in 4.9% of patients, and stroke was reported in 2.9% of patients. Other complications included moderate to severe aortic regurgitation in 4.5%, valve embolization in 1.3%, MI in 1.1% and coronary obstruction in 0.8%.

Giordana et al published a systematic review and meta-analysis of predictors of all-cause mortality after TAVI. The authors included 25 studies with 8874 patients who underwent TAVI for severe symptomatic aortic stenosis that reported predictors of mortality at 30 days or at mid-term follow-up. Most patients (51.1%) underwent the procedure via the transfemoral approach, with 33.7% and 1.7% receiving a transapical or direct aortic/subclavian approach, respectively. A Sapien balloon-expandable valve was used in 5392 patients (60.8%), while a CoreValve self-expandable valve was used in 1899 patients (21.4%). Three studies did not report the type of valve implanted. At 30 days, 663 patients (7.5%), 712 developed AKI (8.02%), 1224 (13.8%) developed major bleeding, 782 (8.8%) developed major vascular complications, and 1106 (12.5%) required pacemaker implantation. At mid-term follow-up (median, 365 days), 1917 patients (21.6%) had died. The strongest predictors of 30-day mortality were higher AKI stage (≥2; OR=18.0; 95% CI, 6.25 to 52), preprocedural hospitalization for at least 1 week (OR=9.36; 95% CI, 2.55 to 35); periprocedural acute myocardial infarction (OR=8.54; 95% CI, 2.57 to 33.52); and preprocedural increased pro-brain natriuretic peptide (BNP) levels (OR=5.35; 95% CI, 1.74 to 16.5). The strongest predictors of mid-term mortality were increased pro-BNP levels (OR=11; 95% CI, 2.55 to 35), stage 3 AKI (OR=6.80; 95% CI, 2.55 to 15.66), left ventricular ejection fraction less than 30% (OR=6.67; 95% CI, 3.5 to 12.76), and periprocedural acute myocardial infarction (OR=6.52; 95% CI, 2.34 to 18.14).

Some studies have specifically reported on 1 or more complications in large numbers of patients. Representative studies of this type will be reviewed here.

**Vascular Access Complications**

The most common complications following TAVI are vascular complications related to the access site. Van Mieghem et al pooled results from prospective databases on 986 patients undergoing transfemoral TAVI from 5 clinical centers in Europe. The rate of major vascular complications was 14.2%. Major bleeding occurred at a rate of 17.8% and life-threatening/disabling bleeding occurred
at a rate of 11%. Czerwinska-Jelonkiewicz et al reported vascular complication rates for 89 consecutive patients treated at a single institution; 44 patients had vascular complications, 17 of which (20.5% of the total) were considered major incidents.

**Acute Kidney Injury**

AKI is also relatively common following TAVI. In 218 patients treated at 1 academic medical center in the U.S., stage 2 or higher AKI occurred in 8.3% (18/218). Half of the patients with AKI (9/18) required dialysis. Mortality at 30 days (44.4% vs. 3.0%, p<0.001) and 1 year (55.6% vs. 16.0%, p<0.001) was much higher in patients with AKI compared to those without AKI. In a similar study of 248 patients from an academic center in Europe, stage 2 or higher AKI was more common, occurring in 35.9% of patients (89/248). Mortality was also increased at 30 days (13.5% vs. 3.8%, p<0.001) and at 1 year (31.5% vs. 15.0%, p<0.001) for patients with AKI.

**Permanent Pacemaker Requirement**

A pacemaker requirement due to conduction abnormalities is another relatively frequent complication following TAVI. Siontis et al conducted a systematic review and meta-analysis to determine predictors of permanent pacemaker implantation after TAVI. The authors included 41 studies that made available individual patient-level data, which included 11,210 patients treated with TAVI, of whom 17% required a permanent pacemaker after aortic valve implantation. Between 2% and 51% of patients across the individual studies required a permanent pacemaker. For the patients receiving the Medtronic CoreValve, the median rate of permanent pacemaker placement was 28% (interquartile range, 24%-35%), whereas for those receiving the Edwards Sapien valve, the median permanent pacemaker placement rate was 6% (interquartile range, 5%-7%). In pooled analyses, factors significantly associated with permanent pacemaker requirement after TAVI included male sex (RR=1.23, p<0.01); baseline first-degree atrioventricular block (RR=1.52, p<0.01); and intraprocedural atrioventricular block (RR=1.75, p=0.04). Several studies that were not included in the Siontis review have addressed the need for permanent pacemaker placement after TAVI. Gensas et al reported rates and predictors of permanent pacemaker requirements after TAVI in patients enrolled in a multicenter Brazilian registry. Four hundred eighteen patients were treated with TAVI between 2008 and 2012. The authors reported outcomes for 353 who survived the procedure and who did not have a previous permanent pacemaker. About a quarter (25.2%) of patients required a permanent pacemaker by 30 days postprocedure. In multivariable analysis, CoreValve device (vs Sapien XT; OR=4.24; 95% CI, 1.56 to 11.49; p<0.001), baseline right bundle branch block (OR=4.41; 95% CI, 2.20 to 8.82; p<0.001), and requirement for balloon predilatation of the aortic valve (OR=1.75; 95% CI, 1.02 to 3.02; p=0.04) were independent predictors of a requirement for permanent pacemaker.

As previously described, Abdel-Wahid et al reported results of an RCT comparing the CoreValve and the Sapien valves and found that patients in the balloon-expandable group less frequently required placement of a new permanent pacemaker (17.3% vs 37.6%, p=0.001).

Lenders et al compared permanent pacemaker requirement rates based on depth of implantation for patients treated with the CoreValve device. Two hundred thirty-two patients were treated with a CoreValve device, some with a newer-generation delivery catheter (the Accutrak; N=112) and some with an older-generation delivery catheter (N=120). Groups were similar at baseline. The
mean depth of implantation was 8.4 in the non-Accutrak group and 7.1 in the Accutrack group (p=0.034). In patients without a permanent pacemaker before valve implantation, 33 patients in the non-Accutrak group (32.3%) received a permanent pacemaker after implantation, compared with 21 in the Accutrack group (21.4%; p=0.094). Among all patients, the mean depth of implantation was significantly lower (lower in relation to a reference line connecting the lower edges of the 3 aortic valve cusps) in patients who required a new permanent pacemaker compared with those who did not (8.9 mm vs 6.9 mm; p=0.002).

Boerlage-Van Dijk et al reported predictors of cardiac conduction abnormalities in 121 patients who received a CoreValve implant at a single center between October 2007 and June 2011. For the analysis of new left bundle branch block, 34 patients were excluded because of preprocedural left bundle branch block or a ventricular-paced rhythm. For the analysis of permanent pacemaker implantation, 16 patients were excluded, 10 patients because of preprocedural pacemaker implantation, 5 because they died before the required observation period for possible pacemaker indication, and 1 because the patient needed a pacemaker implantation due to a sick sinus syndrome, which was not related to TAVI and was discovered in the observation period after TAVI. After the TAVI procedure, 23 patients (21.9%) required pacemaker implantation, most commonly due to total atrioventricular block (N=21; 91.3%). Forty-seven patients developed a new left bundle branch block after the TAVI procedure, which was temporary in 19%. Significant predictors of pacemaker requirement were mitral annular calcification and pre-existing right bundle branch block, while prosthesis size and prosthesis depth were significant predictors of new left bundle branch block.

Section Summary

In addition to complication rates that are reported in randomized and nonrandomized studies evaluating outcomes after TAVI, 2 systematic reviews and a number of cohort studies have reported specifically on complications after TAVI. Given the high requirements for new permanent pacemakers after TAVI, particularly with the CoreValve, a number of studies have focused on predictors of new conduction abnormalities.

**Outcomes for TAVI “valve-in-valve” approach**

The evidence on this question consists of case series, most of which are small. The largest case series published to date is from the Global Valve-in-Valve registry. This study included 202 patients from 38 cardiac centers with a prior surgical bioprosthetic valve replacement that had failed. The procedure was successful in 93.1% of attempts, and 95% of patients had 1 degree or less of aortic regurgitation postprocedure. Early adverse events occurred in 15.3%, with the most common events being malposition of the device and ostial coronary obstruction. Overall mortality was 8.3% at 30 days and 16.3% at 1 year. At 30 days’ follow-up, 83.7% of patients were in New York Heart Association functional Class I or II.

Other case series are smaller and generally from a single-center. A case series from Europe using the Medtronic CoreValve enrolled 27 patients from 1 cardiology center. There were 2 deaths within 30 days. Improvements in the aortic valve gradient and the degree of regurgitation were noted. Adverse events included stroke (7.4%), kidney failure (7.4%), life-threatening bleeding (7.4%), and access site complications (11.1%). Another case series from Europe treated 18 patients with a
degenerated bio-prosthetic valve and symptoms due to valve dysfunction. Implantation was successful in 17/18 patients. Complications included AKI in 3/18 patients, major bleeding in 4/18 patients, and major access site complications in 1/18 patients. At a median follow-up of 11 months, mortality was 5.6% and symptoms were improved with all patients in NYHA Class II or lower.

Smaller case series have reported on valve-in-valve implantation for patients with failed TAVI. For example, a publication from Canada reported on 21 patients with transcatheter valve failure due to aortic regurgitation. The procedure was successful in 19/21 patients; the remaining 2 patients required conversion to open surgery. Mortality at 30 days was 14.3% and at 1 year was 24%. Aortic regurgitation was absent in 4 patients, mild in 13 patients, and moderate in 2 patients.

In 2014, Raval et al reported results from a systematic review of multiple types of valve-in-valve replacement procedures, including 31 studies that reported outcomes after transcatheter aortic valve-in-valve replacement, 13 of which were case reports. Pooled analyses of study results are not reported, but the authors report a relatively high rate (90%-90%) of success for valve-in-valve TAVI procedures.

Section Summary
The evidence related to the use of TAVI for valve-in-valve replacement after failed TAVI or degenerated bioprosthetic valve consists primarily of small case series and 1 systematic review of available case series. The evidence is insufficient to permit conclusions about outcomes after TAVI for valve-in-valve replacement compared with surgical repair.

Ongoing Clinical Trials
A search of online site ClinicalTrials.gov returned numerous ongoing trials of TAVI in various stages of evolution. The majority of these are single-arm trials evaluating the safety and efficacy of TAVI, using various types of valves, delivery systems, ancillary treatments, and outcomes. The following RCTs were identified compared TAVI to alternative treatments, or compared outcomes of different types of valves:

- **NCT01057173.** Transcatheter compared to surgical valve implantation in patients with severe aortic stenosis. This is an RCT underway in Europe that is comparing TAVI with open surgical valve replacement using the Medtronic CoreValve. Estimated completion date is December 2018.

- **NCT01314313.** The PARTNER II Trial: Placement of Aortic Transcatheter Valves. This is an RCT underway in the U.S. that is comparing 2 types of the Edwards SAPIEN Valve system, the SAPIEN valve with RetroFlex3 and the SAPIEN XT with NovaFlex. Estimated completion date is March 2018.

- **NCT01586910.** Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). This is an RCT of 2,500 patients at intermediate risk for surgery comparing TAVI with open AVR. The study is listed as recruiting, but no estimated completion date was provided.
- NCT01645202. A Comparison of Transcatheter Heart Valves in High Risk Patients with Severe Aortic Stenosis: The CHOICE trial. This is an RCT of 240 patients that compares TAVI using the Edwards SAPIEN valve to TAVI using the Medtronic CoreValve system. Estimated completion date for the primary outcomes is estimated to be March 2014.

- NCT01240902. Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement. This is an RCT underway in the U.S. that is comparing TAVI with open surgical valve repair using the Medtronic CoreValve in patients who are at high risk for open surgery. Estimated completion date November 2017.

- NCT01982032. Edwards SAPIEN Periprosthetic Leakage Evaluation Versus Medtronic CoreValve in Transfemoral Aortic Valve Implantation (the ELECT trial). This is an RCT including 108 patients to compare the incidence of postprocedural paravalvular aortic regurgitation between the SAPIEN and CoreValve valves, among patients with severe, symptomatic aortic stenosis who are judged to be inoperable or high risk for open surgery. The estimated study completion date is November 2016.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Clinical input was received from 6 academic medical centers and one specialty society in 2011. At the time of vetting, FDA approval had not yet been granted for any TAVI device. Reviewers were mixed in support for a medically necessary indication for patients who are not surgical candidates. However, all reviewers indicated that they would consider this procedure medically necessary if FDA approval was granted. None of the reviewers expressed support for medical necessity in other patient populations, including patients who were at high risk for surgery, but were surgical candidates. Concerning patient selection criteria, most reviewers referred to the study selection criteria in the PARTNER trial and did not offer further options for objective patient selection.

2014 Input

In 2014, clinical input was received from 6 academic medical centers and 2 specialty societies, 1 of which provided 2 responses. All reviewers who provided a response considered TAVI medically necessary for patients with severe aortic stenosis with a calcified aortic annulus and NYHA heart failure class II, III, or IV symptoms, and who are not operable candidates for open surgery or who are operable candidates but are at high risk for open surgery. Most reviewers would require a patient to have a left ventricular ejection fraction greater than 20% for the procedure to be medically necessary. All reviewers indicated support for limiting the use of TAVI to patients who are not operable candidates for open surgery or who are operable candidates but are at high risk for open surgery, and most supported using FDA’s definition of high risk and extreme risk for surgery.

Most reviewers noted that self-expanding valves have been associated with higher rates of post-procedural requirements but that neither type of valve was clearly superior to the other.
Summary of Evidence

For patients who are not surgical candidates due to excessive surgical risk, the PARTNER B trial reported results for patients treated with TAVI by the transfemoral approach compared to continued medical care with or without balloon valvuloplasty. There was a large decrease in mortality for the TAVI patients at 1 year compared to medical care. This trial also reported improvements on other relevant clinical outcomes for the TAVI group. There was an increased risk of stroke and vascular complications in the TAVI group. Despite these concerns, the overall balance of benefits and risks from this trial indicate that health outcomes are improved. For patients who are not surgical candidates, no randomized trials have compared the self-expandable valve with best medical therapy. However, results from the single-arm CoreValve Extreme Risk Pivotal Trial met the authors’ prespecified objective performance goal. In a randomized controlled trial directly comparing the self-expandable to the balloon-expandable valve among surgically high-risk patients, the devices had similar 30-day mortality outcomes, although the self-expandable valve was associated with higher rates of residual aortic regurgitation and requirement for a new permanent pacemaker.

For patients who are high risk for open surgery, but are operable candidates, the PARTNER A trial reported noninferiority for survival at 1 year for the balloon-expandable valve compared to open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in mortality or in rates of stroke between the two procedures. Since the publication of the PARTNER A trial, the CoreValve High Risk study demonstrated noninferiority for survival at 1 year for the self-expanding prosthesis. This study reported no significant differences in stroke rates between the groups.

The PARTNER A trial also included a subgroup analysis comparing the transfemoral and transapical approaches and reported no outcome differences between the 2 approaches. Some nonrandomized comparative studies have reported higher mortality in patients treated by the transapical approach, but these comparisons are inconclusive because patients treated by the transapical route had a higher baseline risk for mortality. In 2013, the FDA expanded approved of TAVI by the transapical approach to include both patients who not candidates for open surgery and patients who are at high risk for open surgery. In 2014, FDA granted approval for the CoreValve system for patients at extreme risk or who are not suitable candidates for open surgery. FDA labeling indicates that the device can be delivered via femoral, subclavian/axillary, or ascending aortic access.

Evidence from randomized and nonrandomized studies suggests that TAVI with a self-expanding device is associated with higher rates of requirements for permanent pacemakers postprocedure. However, survival rates appear to be similar between device types. At this point, the evidence is insufficient to support the superiority of 1 particular device over another in all patients.

Based on the available evidence, the FDA approvals, and the results of clinical input, TAVI may be considered medically necessary in patients who are not suitable candidates for open surgery, and in patients who are operable candidates but at high risk for open surgery, with an FDA-approved self-expanding or balloon-expandable device according to its labeled indication.
TAVI has also been used as a “valve-in-valve” treatment for degenerated bio-prosthetic valves and for failed transcatheter valves. The evidence on this indication consists only of case series and is insufficient to determine whether outcomes are improved compared to alternatives. As a result, TAVI used for a “valve-in-valve” approach does not meet payment determination criteria.

Supplemental Information

Practice Guidelines and Position Statements

In 2014, the American Heart Association and the American College of Cardiology published guidelines for the management of valvular heart disease. These guidelines make the following recommendations regarding the choice of surgical or transcatheter intervention for treatment of aortic stenosis:

- **Class I recommendations:**
  - Surgical AVR [aortic valve replacement] is recommended in patients who meet an indication for AVR with low or intermediate surgical risk (Level of Evidence: A).
  - For patients in whom TAVR [transcatheter aortic valve replacement] or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care (Level of Evidence: C).
  - TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 mo (Level of Evidence: B).

- **Class IIa recommendations:**
  - TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk (Level of Evidence: B).

- **Class IIb recommendations:**
  - Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS (Level of Evidence: C).

- **Class III recommendations (no benefit):**
  - TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (Level of Evidence: B).

In 2012, the European Society for Cardiology and the European Association for Cardio-Thoracic Surgery published guidelines for the management of valvular heart disease. These guidelines make the following recommendations regarding the use of TAVI:

- **Class I recommendations:**
  - TAVI should only be undertaken with a multidisciplinary ‘heart team’ including cardiologists and cardiac surgeons and other specialists if necessary (Level of Evidence: C).
  - TAVI should only be performed in hospitals with cardiac surgery on-site (Level of Evidence: C).
  - TAVI is indicated in patients with severe symptomatic AS [aortic stenosis] who are not suitable for AVR [aortic valve replacement] as assessed by a ‘heart team’ and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities (Level of Evidence: B).

- **Class IIa recommendations:**
Transcatheter Aortic-Valve Implantation for Aortic Stenosis

TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a ‘heart team’ based on the individual risk profile and anatomic suitability (Level of Evidence: B).

A “Professional Society Overview” on transcatheter valve therapy was published July 2011 by the American College of Cardiology Foundation and the Society of Thoracic Surgeons. The purpose of this document was to enumerate the core issues that will be anticipated in integrating TAVI into general clinical care. As part of this document, a list of necessary components for the successful introduction of Transcatheter Heart Valve Therapies was developed:

- Specialized heart centers with experienced multidisciplinary physicians and paramedical personnel
- Professional multidisciplinary heart team:
  - Primary cardiologists
  - Cardiac surgeons
  - Interventional cardiologists
  - Echocardiographers and imaging specialists
  - Heart failure specialists
- Proper procedure and facilities
  - Modified conventional cardiac laboratory
  - Hybrid operating room
- Development of and participation in clinical database and registries
- Knowledge of, and evaluation of, evidence-based medical literature concerning patient selection, procedural performance, and complication management
- Specific standardized protocols for management strategies, procedural performance, problem-solving, and complication management

The European Society of Cardiology published guidelines for the management of grown-up congenital heart disease in 2010. The guidelines state, “Transcathether aortic valve implantation currently has no place in the treatment of congenital AS [aortic stenosis].”

Medicare National Coverage Determinations

The Centers for Medicare and Medicaid Services (CMS) published a decision memo on the use of transcatheter aortic valve replacement in May 2012. This memo indicated that CMS covers TAVI when used according to FDA indications when the following conditions are met:

- Device has FDA approval
- Two cardiac surgeons agree with indications for the procedure
- The patient is under the care of a heart team, and the hospital meets qualifications for performing TAVI.

The memo also stated that TAVR could be covered for non FDA-approved indications under the Coverage with Evidence Development (CED) program. The following is a summary of the main conditions required for CED:
Transcatheter Aortic-Valve Implantation for Aortic Stenosis

- TAVI is performed within a clinical study that has the following characteristics:
  - The clinical study must adhere to the standards of scientific integrity and relevance to the Medicare population
  - The study must address quality of life and adverse events at follow-up periods of 1 year or longer.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

9. FDA. Labeling and Approval Letter -- Medtronic CoreValve System (P130021). 2014
10. Piazza N, Grube E, Gerckens U et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. 
    *Clin Res Cardiol* 2011; 100(4):265-76.


VIII. Appendix

New York Heart Association Functional Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.</td>
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