Current Status of Transcatheter Aortic Valve Implantation: A Systematic Review of Non-orthodox Deployment Strategies

Thesis submitted to the

University of Arizona College of Medicine - Phoenix

in partial fulfillment of the requirements for the degree of

Doctor of Medicine

Hao Pan

Class of 2012

Mentor: Michael Caskey, MD

Dedication

This project is dedicated to my mentor, Dr. Michael Caskey,

who has cultivated my interest for medicine and fostered my growth

from the very beginning.

Acknowledgements

The author thanks Jacqueline Doyle, Burt Feuerstein, Michael Caskey and Merick Kirshner for their invaluable assistance and medical expertise, without which this project would never have taken place.

Abstract

Objectives: The present systematic review objectively assessed the feasibility, safety, clinical effectiveness, and durability of different approaches in deployment of transcatheter aortic valve implantation (TAVI) for patients at high surgical risk with severe aortic stenosis.

Methods: Electronic searches were performed in 3 databases from January 2002 to November 2011 of patients undergoing TAVI via transapical, transaortic, subclavian approaches. The primary end points included feasibility, safety, efficacy, and durability.

Results: The current literature regarding TAVI is limited to observational studies. Overall procedural success rates ranged from 90% to 100%. The incidence of major adverse events included: 30-day mortality (0%-18%), major adverse cardiovascular and cerebral events ranged from 2% to 35% and the rate of postoperative multiple organ failure was 2% to 8%. There was statistically significant hemodynamic improvement demonstrated by postoperative echocardiography measurements with no significant deterioration up to 6 months postprocedure. Survival at 6 months ranged from 59% to 93%. Only

one study with long-term of transapical TAVI follow-up could reliably evaluate long-term survival of 58% at 3 years.

Significance: TAVI has proven to be feasible and potentially an effective intervention for non-surgical patients with symptomatic aortic stenosis. Although short-term efficacy based on echocardiography has been promising, there is a paucity of data concerning long-term outcomes. The evolution of TAVI will be dependent on the development of a valid tool for estimating the surgical risk to define indications for surgical aortic valve replacement versus transcatheter aortic valve implantation.

Table of Contents

List of Figures & Tables

INTRODUCTION

Aortic stenosis (AS) is the most common form of valvular heart disease in adults in the western world[1]. This disorder is rapidly becoming a large public health burden as the age of the population increases with its associated morbidity and mortality. Severe AS is universally fatal if left untreated, with a 75% mortality rate within 3 years of symptom onset[2]. Although patients are often high-risk candidates for open surgery, aortic valve replacement (AVR) with cardiopulmonary bypass (CPB) has been the longstanding treatment of choice for patients with symptomatic severe AS that not only offers symptomatic relief, but the potential to improve long-term survival[3]. However, this elderly population with symptomatic severe AS poses a difficult target because of their significant comorbidities. Surgical AVR with CPB can often be denied because of an unacceptably high preoperative risk of mortality and morbidity.

Consequently, many patients with severe AS may never even undergo surgical evaluation for various reasons such as patient refusal, advanced age, or excessive surgical risk. It is well-studied that

symptomatic patients continue to have a poor prognosis with only medical management. The reason aortic stenosis is a surgical disease is that the obstruction to the outflow tract requires mechanical relief. The long-term benefits of percutaneous balloon aortic valvuloplasty as a less-invasive, lower risk alternative was never established because of high rates of reintervention[4-6]. However, this lack of an alternative to surgical AVR led to an important clinical question. This long-term outcome was investigated thoroughly by Europe as a large proportion of the cohort over the age of 75 does not undergo surgical AVR. Yet, even as an overwhelming preponderance of data has established that AVR significantly reduces mortality, 30-40% of patients that have a class I indication for AVR are never offered surgical intervention because of their high surgical risk[7].

These findings coupled with the strength of the existing data drove interest toward reducing morbidity and mortality in this specific demographic. The need for a less invasive device to relieve a fixed mechanical obstruction led to the development of transcatheter aortic valve implantation (TAVI). Ultimately, it was this exact cohort in which TAVI was first demonstrated during the early pioneering works of Cribier et al. using a transvenous, transseptal approach[8,9]. Since

the initiation of the ongoing PARTNER (Placement of AoRTic TraNscathetER Valve) trial, the U.S. investigators have demonstrated significantly improved outcomes with good reproducibility[10-12]. One randomized control trial demonstrated an absolute reduction of 20% in all-cause mortality in extreme risk patients denied by two cardiothoracic surgeons for surgical AVR when comparing TAVI against medical therapy[13].

Since Cribier et al. began in 2002, TAVI has undergone active investigation in many medical centers. However, the development and adoption of TAVI has been somewhat limited by the inherent technical complexity, surgical resources, and the risks of transapical puncture[8,9]. Investigators evolved to a retrograde femoral arterial approach, originally used for access in balloon aortic valvuloplasty. This created a technically less challenging and a method of access many are more accustomed to[14,15]. Patient selection generally requires a comprehensive study of the different arterial approach sites, such as the aorta, aortoiliac, and femoral vasculature. However, inherent peripheral artery disease in this specific cohort may render ileofemoral access difficult or even impossible in many cases. Therefore, by simplifying this procedure, retrograde femoral access may have

excluded many elderly patients with concomitant peripheral vascular disease. This paradox of increasing the number of centers offering TAVI, yet decreasing the accessibility of this procedure to vasculopaths is secondary to data demonstrating the risk of procedure failure or vascular injury greatly increases when wiring and passing catheters across diseased and tortuous femoral and iliac vasculature[17].

This potential for vascular morbidity inherent in the elderly population led to the development of subclavian, transapical, and transaortic access techniques. Subsequently, many investigators involved in the PARTNER trial have begun to release early outcomes related to their experiences in non-orthodox access techniques at their centers[17-32,50,51]. Each of these techniques provides the advantage of avoiding access difficulty and facilitating device delivery. However, the transaortic and transapical approaches are significantly more invasive as the former requires a mini-sternotomy, meanwhile the latter requires a thoracotomy[16]. Moreover, complications specific to passing a percutaneous valve holder across the apex such as myocardial rupture and apical aneurysm formation have been reported[25]. These new approaches regarding TAVI offers more patients this unique device

and refines its deliverability while minimizing patient morbidity and mortality.

Even as ongoing TAVI data is collected, there is a definite need by investigators to demonstrate the clinical and echocardiographic efficacy of this device. The Society of Thoracic Surgeons (STS) National Cardiac Database has demonstrated that mortality for surgical AVR can range anywhere from 4.3% for first isolated AVR to 25% for redo surgery or multiple valve replacement plus coronary artery bypass grafting, with an overall mortality rate of 6.4%[33]. Consequently the drive by the ongoing PARTNER trial is to demonstrate non-inferiority of TAVI compared to the outcomes seen in high-risk patients after surgical AVR[34]. Even as the traditional retrograde femoral arterial approach has become well established and the use of TAVI has expanded with new access techniques, its adoption must be tempered with high clinical efficacy and safe, measurable outcomes. Many issues related to TAVI remain to be clarified by clinical data. The present literature review was designed to objectively assess the feasibility, safety, and clinical effectiveness of non-orthodox access in TAVI in the treatment of severe AS.

RESEARCH MATERIALS & METHODS

Literature Search Strategy

Electronic searches were performed in 3 databases from January 2002 to November 2011: PubMed and Cochrane Database of Systematic Reviews. To achieve the maximum sensitivity of the search strategy and identify all studies, we used appropriate free text and thesaurus terms: "percutaneous" OR "transcutaneous" OR "transcatheter" AND "transarterial" OR "transapical" OR "transaortic" OR "subclavian artery" OR "axillary artery" AND "aortic valve" OR "aortic valve stenosis" AND "aortic valve implantation." The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies.

Study Population

The study population was classified as patients who would be considered for TAVI in the United States, therefore of high surgical risk with AS or those deemed not suitable for surgical AVR. The criteria for patient selection for TAV implantation varied among institutions, and the definitions for nonsurgical candidates were not uniform.

Interventions

The Edwards SAPIEN bioprosthesis is a balloon-expandable stent with three bovine pericardial leaflets mounted within a cobalt-chromium frame. This device is available in two sizes: 23 mm expanded and 26 mm expanded. Current devices require either a 22F, 24F, or 26F sheath for delivery. The Medtronic Corevalve is a self-expanding percutaneous porcine aortic valve in a nitinol stent. The available valve diameters are 22, 26, and 29 mm. Delivery is via 18F, 21F or 25F sheaths.[49]

For axillary/subclavian access, a 5 cm infra- or supraclavicular skin incision for exposure was used for access. An axillary arterial diameter of 6 mm was considered adequate for implantation. Antegrade transapical aortic valve implantation was performed through a 3-5 cm left anterolateral mini-thoracotomy. Retrograde implantation directly though the ascending aorta was performed through a partial upper mini-sternotomy. A temporary pacemaker wire was placed transvenously for rapid ventricular pacing during balloon valvuloplasty of the stenotic aortic valve from 160-200 beats/min and for prophylaxis in cases of postoperative heart block requiring external rhythm support.

Outcome Measures

The findings from initial searches were discussed and arranged as criteria to incorporate into the present literature review. The primary end points included feasibility and safety (procedural success rate, mortality, major tachyarrhythmia, bradyarrhythmia requiring permanent pacemaker insertion, myocardial infarction, cardiac tamponade, cerebrovascular accident, conversion to surgical AVR, vascular complication, severe paravalvular leak, emergency percutaneous coronary intervention, endocarditis, aortic dissection/perforation, blood transfusion, procedure duration, and length of hospital stay).

The secondary outcomes that many investigators evaluated regarded the efficacy and durability of the device based on echocardiographic findings (mean aortic valve area, peak and mean pressure gradient, left ventricular ejection fraction) and clinical assessments (New York Heart Association [NYHA] functional class) improvement versus baseline, and survival at 6, 12, 24, and 36 months follow-up).

Study Design & Selection Criteria

A meta-analysis was not appropriate because no comparisons among different devices or techniques of insertion have been reported, sample sizes are relatively small, and potential differences in different generations of prostheses may also exist. Prospective and retrospective experimental or observational studies were included, however case reports, case series, abstracts, editorials, and expert opinions were excluded. This systematic review only targeted studies and patient subsets that included high-risk patients with severe AS that only received TAVI via a subclavian/axillary artery, transapical, or transaortic approach. Only the most comprehensive studies from each center were included for data extraction and qualitative appraisal. Previously published duplicate trials with smaller numbers of patients or shorter lengths of follow-up were excluded from the final review.

Data Extraction and Critical Appraisal

The 2 investigators (H.P. & M.P.C.) independently appraised each article, using a combined critical review checklist as recommended by the National Health Service Center for Reviews and Dissemination

case series quality assessment criteria[35], the Cochrane Collaboration handbook for systematic reviews of interventions[36], and the Agency for Healthcare Research and Quality systems to rate the strength of scientific evidence[37]. This agreed upon guidelines covered representativeness of study sample, explicitness of inclusionary and exclusionary criteria, specific echocardiographic and/or functional class at time of treatment, presence of follow-up, objectivity of outcome measures, and appropriateness of statistical analysis. The criteria for assessing the quality of postoperative morbidity and mortality data included whether terms were clearly defined, use of standardized or validated objective measurements and the presence of appropriate adverse effects attributed to the interventions. All data was extracted from the relevant articles' texts, tables, and figures. Clinical outcomes and technical measurements of each study were reviewed and integrated through a narrative review. Discrepancies between the 2 reviewers were resolved by discussion and consensus. The final results were reviewed by two external reviewers (M.S.K. & H.S.) and appropriate revisions were undertaken.

RESULTS

Quantity of Studies

The titles and abstracts of 164 peer-reviewed publications were identified after searching two distinct electronic databases. A cursory evaluation of these abstracts identified 38 potentially relevant publications. Manual search of the reference lists identified 13 additional publications of interest. When the inclusion and exclusion criteria were applied to these 49 publications, 18 articles[17-32,50,51] remained for assessment. Duplicative publications with accumulating numbers of patients or increased length of follow-up were identified. The publication with most complete data set from each center was retained and the initial preliminary studies were eliminated. In total, 12 studies were included for appraisal and data extraction (Table 1)[17-26,50,51]. All studies evaluated the feasibility and safety of TAVI. All except two studies[19,26] assessed the efficacy and durability of TAVI using hemodynamic measurements by use of echocardiography.

TABLE 1. Summary of relevant current publications

Investigator	Study Period	n	Access	Procedure	Procedural Success, n (%)	Age (mean ± SD)	Logistic EuroSCORE (mean ± SD)	STS Score (mean ± SD)
Ye[17]	2005-2009	71	Transapical	Edwards SAPIEN GA; no CPB	71 (100)	80 ± 8	35 ± 20	12 ± 8
Zierer[18]	2006-2008	26	Transapical	Edwards SAPIEN GA; RVP; fem-fem CPB (11)	26 (100)	84 ± 7	37 ± 6	-
Al-Attar[19]	2007-2008	18	Transapical	Edwards SAPIEN GA; RVP; no CPB	18 (100)	83 ± 8	31 ± 11	18 ± 7
Walter[20]	2006	59	Transapical	Edwards SAPIEN GA; RVP; fem-fem CPB (28)	55 (93)	81 ± 6	27 ± 14	-
Svensson[21]	2006-2008	40	Transapical	Edwards SAPIEN GA; RVP; fem-fem CPB (10)	36 (90)	83 ± 5	36 ± 15	13
Bleiziffer[22]	2007-2008	28	Transapical Transaortic Subclavian	Edwards SAPIEN & Medtronic CoreValve GA; RVP; fem-fem CPB (4)	135 (99)	81 ± 7	24 ± 15	23 ± 10
Modine[23]	2009	17	Subclavian	Medtronic CoreValve GA; RVP, no CPB	17 (100)	71 ± 11	34 ± 11	-
Petronio[24]	2007-2009	54	Subclavian	Medtronic CoreValve GA 40; RVP, no CPB	54 (100)	83	25 ± 10	-
Bruschi[25]	2008-2010	12	Transaortic Subclavian	Medtronic CoreValve GA; RVP, no CPB	11 (92)	81 ± 8	32 ± 17	11 ± 4
Bapat[26]	2008-2011	108	Transapical Transaortic	Edwards SAPIEN GA; RVP; fem-fem CPB (2)	108 (100)	82 ± 10	24 ± 14	-
Eltchaninoff[50]	2009	83	Transapical Subclavian	Edwards SAPIEN & Medtronic CoreValve GA & LA; RVP; no CPB	82 (82)	82 ± 7	26 ± 11	19 ± 13
Bosmans[51]	2010	96	Transapical Subclavian	Edwards SAPIEN & Medtronic CoreValve GA; RVP; no CPB	94 (98)	82 ± 6	33 ± 17	-

CPB, Cardiopulmonary bypass; *GA*, General anesthesia; *LA* Local Anesthesia; *RVP*, Rapid ventricular pacing; *fem*, femoral; STS, Society of Thoracic Surgeons

Quality of Studies

No randomized controlled trials or matched comparative studies were identified. All 12 included articles were experimental studies without control groups or blinding. All reports originated from specialized tertiary referral centers, while two included data from full registries accumulated by respective countries[50,51]. Eight series had ≥40 patients enrolled (range, 40-137)[17,20-22,24,26, 50,51] and the remaining 4 series had <40 patients (range, 12-26).[18,19,23,25] The definitions identified as inclusionary criteria for high-risk patients with AS unsuitable for surgical AVR varied among the institutions. For example, age ≥70[21], ≥75[18,20,22], ≥80[19] or none/undefined[50,51]; AVA ≤1 cm^2,[24,26,50] ≤0.8 cm^2,[18] ≤0.6 cm^2,[21,50]; or a peak transaortic gradient of ≥40 mm Hg.[26] Additional criteria consisted of aortic annulus diameter ≤24 mm and symmetrically distributed calcification of the stenotic native aortic valve cusps[18,20]; logistic EuroSCORE >11%,[20] >20%,[18,22,26,50] and Society of Thoracic Surgeons score ≥10[50], >15%.[21] Also to be included as a non-traditional femoral/iliac approach TAVI, all study subjects had to be excluded because of iliac-femoral arteriopathy, small size, excessive tortuosity, calcification, or abdominal aorta aneurysm.[17-26,50,51]

All centers also deemed candidates inoperable based on clinical judgement because of risk factors not covered by risk scoring (such as repeated previous cardiac surgery, porcelain aorta, severe COPD, chest deformities, and other surgeon-documented technical reasons).[17-26,50,51] In several studies, risk calculation data (EuroSCORE & STS score) was collected but not directly used as delineation for risk stratification.[17,19,23-25,51] Certain studies also implicitly acknowledged that predictive risk scores do not calculate all relevant variables. Therefore, currently there is no single risk calculator that can accurately estimate operative risk[17,19].

In 3 studies,[19,23,25] the number of patients evaluated was relatively small because of the degree of selection and the relatively small investigational site. The study samples in these series are less likely to be fully representative of the study population and were not large enough to provide definitive estimates of incidence of all adverse events. Therefore it is possible that certain adverse effects related to these procedures were never seen or were abnormally elevated because of the relatively small sample size. Seven studies reported explicit inclusionary criteria,[18,20-22,24,26,50] and 5 studies did not[17,19,23,25,51]. All studies reported procedure-related or 30-day morbidity and

mortality[17-26,50,51]. Seven studies reported follow-up data at 6 months[17,20-22,24-26]. Four studies reported follow-up data at 12 months[17,21,25,26]. Meanwhile, only one study had follow-up data beyond 2 years of 17 patients, coincidentally that investigational site also performed the first human case of successful transapical TAVI[17]. This study also provided the longest recorded follow-up to date of a successful deployment of a transapical TAVI at 37.3 months[17]. All but one study[19] evaluated hemodynamic measurements by echocardiography to some degree. Three studies performed subgroup analysis assessing procedural learning curve[17,20,24]. Mortality, morbidity, hemodynamic measurements, and survival rates were objective outcome measures, while NYHA class was based on subjective clinical assessment.

All studies clearly defined the techniques of TAVI and the description of the techniques used for each approach was relatively similar. Clinical adverse events were adjudicated by a independent clinical committee in two studies,[20,21] not in 2 other studies,[24,26] and was not reported in the remaining 8 studies[17-19,22,23,25,50,51]. The duration of follow-up was reported and the definitions of adverse events were clearly explained in all studies[17-26,50,51]. Two studies

reported data according to major adverse cardiovascular and cerebral events (MACCE)[21,24].

Assessment of Feasibility

The overall procedural success rates ranged from 90% to 100% (Table 1) [17-26,50,51]. All studies determined procedural success based on Piazza and colleagues' three distinct end points:[12] adequate technical placement, normal bioprosthesis performance, and operative outcome. Svensson et al.[21] reported that 36 of the 40 antegrade transapical implantations (90%) of Edwards SAPIEN TAV were performed successfully with 4 technical failures. In three patients the valve embolized, one of these cases was cause by the cine automatically switching off during the critical moment of deployment. In the other patient, valve migration occurred immediately after implantation during CPR. Also with the antegrade transapical Edwards SAPIEN TAV, Walther and associates[20] achieved successful implantation in 55 patients (93%). Reasons for failure in the four patients were all due to incorrect positioning of the valve. Two of these malpositions occurred early in the series and one was secondary to the lack of fluoroscopic imaging because of technical problems (only TEE was used) during a deployment. The remaining case occurred due to the presence of

severe focal calcification of only one of the native aortic valve cusps.

There was only one procedural failure (8%) seen by Bruschi et al.[22] in his series of 12 patients, during a retrograde direct aortic access implantation of a Medtronic CoreValve. Investigators noticed bleeding from the ascending aorta, clinical and echocardiographic signs of cardiac tamponade immediately after an 18-Fr introducer was inserted. A median sternotomy was immediately performed with direct patch suturing of a right ventricular laceration. After acquiring hemostasis, the investigators decided to perform a femoral-approach TAVI. Despite successful implantation the patient died on the same day from an abdominal aortic aneurysm rupture. Finally, the largest study on 137 patients who had both the SAPIEN and CoreValve implanted demonstrated a procedural success in 99% of the patients. However, Bleiziffer, Eltchaninoff, and Bosmans did not delineate the details of their failures, including the approach or the specific valve type. The latter two likely due to the nature of harvesting a large national registry.

Assessment of Safety

Table 2 demonstrates 30-day major cardiovascular and cerebral adverse events following TAVI across all studies[17-26,50,51]. The range of these adverse events was as following: 30-day mortality (0%-18%); major ventricular tachyarrhythmia (0%–6%); supraventricular tachyarrhythmia (0%-31%); bradyarrhythmia requiring permanent pacemaker insertion (0%-25%); myocardial infarction (0%-15%); cardiac tamponade (0%-11%); cerebrovascular accident (0%-6%); conversion to surgery (0%-8%); cardiogenic shock/insufficiency requiring IABP placement (0%-17%); vascular complication (0%-17%); moderate to major paravalvular leak (0%-35%); valve-in-valve procedure (0%-6%); aortic dissection/perforation/rupture (1%-8%); and blood transfusion >2 units (9%-53%). The mean procedure duration varied from 106 to 174 minutes. The mean ICU stay ranged from 18 to 20 hours. The overall 30-day MACCE ranged from 2% to 35%, while survival at 6 months was between 59% and 93%. Only two specific studies generated survival curves out to 1 year (70-72%)[17,50], and one out to 2 years (66%), and 3 years (58%).[17]

TABLE 2. Procedural and 30-d clinical outcomes following transcatheter aortic valve implantation

Study	n	Death at 30 d, n (%)	Major tachyarrhythmia, n (%)	Pacemaker insertion, n (%)	Myocardial infarction, n (%)	Cardiac tamponade, n (%)	Cerebrovascular accident, n (%)	Conversion to surgery, n (%)	IABP Implantation, n (%)	Valve thrombosis, n (%)
Ye[17]	71	12 (17)	0	6 (9)	-	-	1 (1)	1 (1)	-	0
Zierer[18]	26	4 (15)	5 (19)*	-	-	-	0	2 (8)	2 (8)	1 (4)
Al-Attar[19]	18	3 (17)	1 (6)	1 (6)	-	2(11)	-		3 (17)	-
Walter[20]	59	8 (14)	18 (31)*	-	-	-	2 (3)	4 (7)	-	-
Svensson[21]	40	7 (18)	-	-	6 (15)	-	2 (5)	2 (5)	-	0
Bleiziffer[22]	137	17 (12)	0	27 (20)	-	-	7 (5)	1 (1)	-	-
Modine[23]	17	2 (12)	0	-	0	0	0	0	-	-
Petronio[24]	54	0	-	10 (19)	0	0	1 (2)	0	-	0
Bruschi[25]	12	1 (8)	0	3 (25)	-	-	-	0	-	-
Bapat[26]	108	9 (8)	-	-	0	0	6 (6)	-	-	-
Eltchaninoff[58]	83	13 (16)	-	7 (8)	0	1 (1)	2 (2)	-	-	-
Bosmans[51]	96	11 (11)	-	7 (7)	-	-	5 (5)	-	-	-

SD, standard deviation; *Supraventricular arrhythmia; *IABP*, Intra Aortic Balloon Pump; *au*, units; *MACCE*, Major adverse cardiovascular and cerebral events

TABLE 2. Continued

Vascular complications, n (%)	Paravalvular leak >2+, n (%)	Valve-in-valve procedure, n (%)	Aortic dissection/ perforation, n (%)	Multiple organ failure, n (%)	Transfusion >2 un, n (%)	Procedural duration, min ± SD	ICU stay, median hrs	MACCE, n (%)	Survival at 6 mo, n (%)	Survival at 1 yr, n (%)
2 (3)	4 (5)	-	1 (1)	2 (3)	-	-	-	-	74 ± 5	72 ± 6
2 (8)	6 (23)	-	1 (4)	2 (8)	-	152 ± 87	18	-	-	-
2 (11)	-	1 (6)	-	-	-	-	-	-	-	-
-	3 (5)	-	-	-	-	148 ± 92	20	-	76 ± 6	-
-	14(35)	-	-	1 (3)	-	-	-	14 (35)	59 ± 4	-
16 (12)	0	-	-	-	-	-	-	-	77	-
-	0	1 (6)	1 (6)	-	9 (53)	-	-	-	-	-
0	-	0	-	-	5 (9)	106 ± 29	-	1 (2)	93 ± 4	-
2 (17)	0	-	1 (8)	-	-	174 ± 63	-	-	-	-
3 (3)	1 (1)	-	-	-	-	-	-	-	-	-
5 (6)	-	-	0	-	-	-	-	-	-	-
-	-	1 (1)	-	2 (2)	-	-	-	-	77	71

Assessment of Efficacy

The efficacy of TAVI was assessed based on echocardiographic findings (Table 3)[17,18,20-25,50,51]. Two studies did not report echocardiographic measurements in order to evaluate for objective improvement in technical valvular function[19,26]. The remaining 10 studies all demonstrated significant improvement in hemodynamic performance ($P < .05$) when preprocedural values were compared to postprocedural echocardiography measurements. Mean aortic valve area increased from 0.5-0.7 cm^2 to 1.4-1.7 cm^2, mean pressure gradient decreased from 40-56 cm^2 to 6-12 cm^2, left ventricular ejection fraction ranged from 47-56% before and 54- 61% after TAVI.

TABLE 3. Echocardiographic measurements & clinical outcomes following TAVI

Study	n	Mean aortic valve area before TAVI (cm^2) ± SD	Mean aortic valve area after TAVI (cm^2) ± SD	Peak pressure gradient before TAVI (cm^2) ± SD	Peak pressure gradient after TAVI (cm^2) ± SD	Mean pressure gradient before TAVI (cm^2) ± SD	Mean pressure gradient after TAVI (cm^2) ± SD	LV ejection fraction before TAVI (%) ± SD	LV ejection fraction after TAVI (%) ± SD	NYHA functional class at baseline	NYHA functional class after TAVI	Death at 6 mo, n (%)
Ye[17]	71	0.6 ± 0.2	1.4 ± 0.3	-	-	44 ± 16	10 ± 4	56 ± 13	61 ± 7	3.3 ± 0.8	1.7 ± 0.8	-
Zierer[18]	26	0.6 ± 0.1	-	-	-	-	6 ± 2	-	-	3.5 ± 0.4	-	-
Al-Attar[19]	18	-	-	-	-	-	-	-	-	3.3 ± 0.7	-	-
Walter[20]	59	0.5 ± 0.2	-	-	18 ± 11	-	9 ± 6	47 ± 16	-	3.4 ± 0.5	-	13 (22)
Svensson[21]	40	0.6 ± 0.1	1.6 ± 0.4	65 ± 15	15 ± 5	40 ± 10	8 ± 3	52 ± 15	55 ± 19	3.3 ± 0.5	2.3 ± 0.8	13 (33)
Bleiziffer[22]	137	-	1.6 ± 0.4	-	-	-	12 ± 4	-	-	3.1 ± 0.3	1.7 ± 0.6	-
Modine[23]	17	0.6 ± 0.3	1.4 ± 0.4	-	-	47 ± 13	8 ± 4	52 ± 14	-	-	-	-
Petronio[24]	54	-	-	85	17	51	10	-	-	-	-	3 (9)
Bruschi[25]	12	0.7 ± 0.2	-	97 ± 19	-	56 ± 11	10 ± 4	54 ± 14	54 ± 9	-	1.2 ± 0.4	1 (8)
Bapat[26]	108	-	-	-	-	-	-	49 ± 13	-	-	-	30 (27)
Eltchaninoff[50]	83	0.7 ± 0.2	1.7 ± 0.5	-	-	46 ± 16	11 ± 5	51 ± 14	55 ± 13	-	-	-
Bosmans[51]	96	0.6 ± 0.2	-	-	-	49 ± 16	8	55 ± 14	58	-	-	-

TAVI, Transcatheter aortic valve implantation; *NYHA*, New York Heart Association; *SD*, standard deviation; *LV*, left ventricular

Assessment of Durability

At 1-month follow-up, the study patients had on average improved their NYHA functional class at least by 1 grade, limited only by their previous medical conditions.[17,21-25] These outcomes were followed out to 3 months, 6 months[21,22,24] and 12 months, 24 months[17,25] establishing a stable improvement in functional class. Follow-up echocardiographic measurements were available in 7 studies at 1 month,[17,20-25] 5 studies at 6 months,[17,21-22,25] 2 studies at 18 months,[17,25] and 1 study at 36 months.[17] According to these findings, there was no significant functional valvular deterioration upon echocardiography during the assessment period. Death rate at 6 months post-procedure ranged from 8% to 33%[20,21,24-26].

Ye and colleagues[17] reported that of the surviving 59 patients, ten patients died of non-valve-related complications, including cancer (1), lung diseases (COPD and/or pneumonia/sepsis in 4 patients), myocardial infarction (1), multiple organ failure (2), gastrointestinal bleed (1), and multiple factors/organ failure (1 patient). Another large multicenter trial[20] reported five additional deaths that were non-valve-related at a mean follow-up of 110 ± 77 days. Causes of death included respiratory and renal failure (2), heart failure (1), sepsis (1), and

unclear in 1 patient. Svensson and colleagues[21] also had similar findings at late follow-up in which 6 additional patients died of non-cardiac and non-procedure-related deaths. Petronio et al. [24] identified only 3 more deaths at 6 months (reasons unknown). One study also found at a mean follow-up of 14 ± 7 months, that there was only one additional death from pneumonia at 41 days post procedure.[25] Bapat and colleagues[26] also reported long-term mortality data, in which there were 19 additional deaths out of the surviving 84 patients in the transapical group at a mean follow-up of 384 ± 314 days. In the transaortic group, there were 2 deaths in the remaining 15 patients at a mean follow-up of 162 ± 154 days.

Svensson and associates[21] reported on a Food and Drug Administration-approved feasibility study involving 40 patients that underwent Edwards SAPIEN TAVI. This was the initial published study reporting on quality-of-life data. Quality-of-life scores improved from preoperatively (SF-12 Physical 28.7, SD 6.1; Mental 48.1, SD 11.5) to postoperatively at 6 months (SF-12 Physical 35.2, SD 7.4; Mental 50.4, SD 11.7). The physical improvement was significant (p=0.002). Another study that incorporated quality-of-life evaluation collected a self-assessed general health state on a scale of 0-100%.[22]

Preoperatively the patients rated themselves at 55±17%, this improved to 68±16% at 30 days postoperative ($p<0.001$).

DISCUSSION

Patients requiring cardiac surgery in the U.S. have steadily become older and more complicated with significant comorbidities. Calcified aortic stenosis continues to be the most common valvular disorder affecting this aging population. Although medical therapy has failed to change the course of the disease, especially once symptoms or left ventricular dysfunction manifest, surgical AVR remains the gold standard for definitive treatment[3]. However, surgical intervention includes the risks and morbidity associated with cardiopulmonary bypass and median sternotomy. Frail and elderly patients with poor functional status and severe AS are often excluded from surgical AVR due to potentially high operative risks. Consequently, the less invasive nature of TAVI is believed to offer a safer treatment option for this select group of patients[9].

Currently, no published literature has utilized randomized controlled trials to compare TAVI with conservative medical treatment, balloon valvuloplasty, or surgical AVR. However, multiple large clinical centers and combined registries with large patient experience with TAVI have begun to demonstrate promising results with improved quality of life[21]. The ongoing U.S. PARTNER trial

(Placement of AoRTic TraNscathetER Valve) compares TAVI versus surgical AVR in patients at high surgical risk and TAVI versus medical treatment or balloon aortic valvuloplasty in patients at extreme surgical risk. Although large centers enrolled in this massive nationwide study have already released extremely promising data, there is still a select subgroup that was initially precluded. Yet, vasculopathy causing access and deployment obstacles involve a large proportion of the high to extreme risk population undergoing surgical AVR.

The limitations and risks of employing TAVI utilizing alternative approaches in patients who lack adequate femoral artery access is still largely unknown. Patients with significant peripheral vascular disease have a greater risk of stroke and death either after conventional primary AVR and in reoperative valve replacements[38]. This increased risk causes inherent negative bias in patients with poor access that are chosen for non-traditional access. Furthermore vasculopathic patients requiring transapical TAVI using a mini left anterior thoracotomy may also be at increased risk due to the invasive nature. In many situations, the exact benefit of approaching with alternative access because of a porcelain aorta or a stenotic subclavian

artery creates an intrinsic difficulty of comparing outcomes in this subset of patients with symptomatic aortic stenosis.

The present systematic review based on the available observational series regarding TAVI deployed via non-traditional access demonstrated the following key points. First, in view of the feasibility and safety results of TAVI, the procedure success rate ranged from 90% to 100%, demonstrating a definite feasibility of the procedure[21,24]. The safety profile of this device remains unclear due to variability, as 30-day mortality (0%-18%), 30-day MACCE (range 2%-35%), and 6-month survival (59%-93%) were relatively low compared to previous studies documenting this high to extreme risk subgroup[21,24]. However, Ye and colleagues[17] demonstrated survival at 1, 2, and 3 years of 72%, 66%, and 58% with the most definitive and long-term dataset following patients that had transapical TAVI, which is the longest standing non-traditional access. In a report by Kojodjojo and associates, 62 patients who were declined by surgeons for conventional AVR had approximate survivals of 50%, 25%, and 10% at 1, 2, and 3 years[39]. However the limitation of these purely observational studies is that they are a not fair comparison to open surgical valve replacement, balloon valvuloplasty, or medical optimization.

Without randomized trials, it is not clear whether the high interventional mortality risk associated with TAVI is lower than the risk associated with conventional surgery. The procedural and short-term outcomes appeared to be improving in more recent studies with accumulating numbers of patients. In earlier reports, Cribier and colleagues[9] reported a procedural success rate as low as 82%. However the majority of studies included in this systematic review demonstrated procedural success rates of 100%[17-19,23,24,26]. Ye et. al described that their data indicated that the initial learning curve significantly influenced early mortality (33.3% in the first 15 patients versus 12.5% in the remainder of the patients)[17]. Although the learning curve may not change long term mortality (>2 years), the major obstacles are device technology, procedural skills, and decision making involving case selection, as well as decision making in the management of complications. At the current stage of experience, the number of patients required to regard a specialized center well-trained is not certain. However, the consensus amongst these studies describes that this procedure requires a highly trained team with the expertise and infrastructure to optimize safety for both staff and patients. Therefore, concentration of the services at centers with

experience is likely to increase quality of care for these patients.

Second, the short-term efficacy based on echocardiography measurements and NYHA functional class for patients, irrespective of the procedural approach used, seems to be encouraging. NYHA functional class was clinically lower by an entire unit from one month[17,21,22,25] to up to 36 months postoperatively[17]. After successful insertion, patients demonstrated remarkable improved quality of life, decreased gradients, improved orifice area, and return to a better functional performance[21,22]. Bleiziffer and colleagues demonstrated an improvement of NYHA class with their population (class III and IV 100%) preoperatively to less than 20% at 30 days and six months postoperatively[22]. These outcomes were also correlated to a statistically significant improvement in a self-assessment of general health state from 55% to 68% on a scale of 0-100%. Based on the data, TAVI seems to be not only feasible, but also efficacious. For this emerging intervention to be successful, it is imperative for more studies to evaluate quality of life objectively, follow patients long-term, and establish good data on the durability of this technology.

Based on the limited data available, echocardiographic measurements up to 12-months of follow-up did not demonstrate

significant functional deterioration. The current iteration of the Edwards SAPIEN valve has been in a pulse duplicator to 400 million cycles, approximately equal to 10.4 years. Clinically, after 500 valve insertions, there have been no late leaflet failures[21]. In fact these valves are based on the conventionally inserted bioprosthetic valves. In patients over 70 years of age, these valves used in open surgical AVR have demonstrated Kaplan-Meier freedom from reoperation due to valve failure of 93% at 12 years and 70% at 20 years[40,41]. However, TAVI long-term follow-up data is not available and the durability of these prostheses will probably be revealed by the PARTNER trial itself. Many studies have not only demonstrated significant improvements in hemodynamic performance, however they have also begun to measure the impact on patients' quality of life. Assessment of the long-term durability will require a minimum of 5-10 years of follow-up. Given the limited life expectancy of patients currently considered for TAVI, this may not be practical. Establishing data demonstrating continued improvement in functional status after TAVI will most likely be the most important clinical endpoint after one year.

Currently, the PARTNER trial is restricted to elderly patients considered to be at very high risk for conventional surgical AVR. In

the absence of published guidelines, the Society of Thoracic Surgeons, the American Association for Thoracic Surgery, and the Society for Cardiovascular Angiography and Interventions published a consensus statement recommending strict evaluation of patients undergoing TAVI[42]. Recent literature acknowledges that multidisciplinary teams should enroll patients at "high surgical risk" or "nonsurgical" candidates with AS. The eligibility of patients for TAVI was poorly defined in 4 studies[17,19,23,25]. However, the majority of investigators determined inclusion based on clinical assessment supplemented with predictive risk scores obtained from the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS). Another position paper released in 2008, directly addressed the difficulties of surgical mortality risk prediction and indication for TAVI by the European Association of Cardio-Thoracic Surgery, European Society of Cardiology, and the European Association of Percutaneous Cardiovascular Intervention. Clinical judgment was determined to be a better predictor than risk scores for the evaluation of surgical risk[43].

The validity of these tools for estimating the surgical risk incurred by high-risk patients has also been criticized. Although they

provide an objective estimation and quantifiable value of operative mortality risk they do not capture all relevant variable and are known to have limitations in this particular group of patients[44,45]. The majority of investigators have used logistic EuroSCORE as an objective preoperative risk stratification approach with TAVI. Although this is critical to compare clinical results of each different approaches, it is well known that EuroSCORE severely overestimates operative risk in high-risk patients[44,46,47,48]. Clinicians must be cautious in estimating operative risk from models that were not intended for this specific use. Furthermore, the definition of "high surgical risk" is difficult to delineate with consistency amongst investigators. There is a definite need for the development of a new scoring system for this exceptional patient population.

CONCLUSIONS AND FUTURE DIRECTIONS

Although the feasibility of TAVI has been demonstrated, there is a lack of comparative studies and the data on long-term efficacy and durability in non-femoral delivery of TAVI in the current literature. The relatively unproven nature and inherent risks of this new therapy mandate a formal team approach to patient selection with randomized controlled trials and rigorous follow-up to show whether different techniques for access are superior to conventional approaches. Before further convincing evidence becomes available, there is a definite need for further investigation in implantation technique, device positioning, as well as these devices themselves. However many of the basic questions of durability, safety, and efficacy compared to open surgical AVR will be demonstrated in time by the high-risk surgical arm of the current FDA-approved PARTNER trial. Meanwhile, decision on eligibility and approach must be individualized and assessed by a multidisciplinary team of cardiologists, cardiac surgeons, and cardiac anesthesiologists. One of the main challenges in the future will be the determination of clear indications with accurate risk stratification for surgical and interventional treatment of aortic stenosis. It is likely that progressive development of technology, familiarity with

techniques, and better understanding of appropriate criteria for patient selection will continue to refine the approaches for TAVI and its clinical implications.

REFERENCES

1. Task Force. Guidelines for the management of patients with valvular heart disease: Executive summary. *Circulation.* 1998;98;1949-84.
2. Carabello BA, Paulus W. Aortic stenosis. Lancet. 2009;372:956-66.
3. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. *Circulation.* 1982;66:1105-10.
4. Otto CM, Mickel MC, Kennedy JW, Alderman EL, Bashore TM, Block PC, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation.* 1994;89:642-50.
5. Lieberman EB, Bashore TM, Hermiller JB, Wilson JS, Pieper KS, Keeler GP, et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol.* 1995;26:1552-8.
6. Cribier A, Savin T, BerlandJ, Rocha P, Mechmeche R, Saoudi N, et al. Percutaneous transluminal balloon valvuloplasty of adult aortic stenosis: report of 92 cases. *J Am Coll Cardiol.* 1987;9:381-6.
7. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.
8. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation.* 2002; 106:3006-8.
9. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Sebagh L, Bash A et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol.* 2004;43: 698-703.
10. Thomas M, Shymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation.* 2010;122:62-69.
11. Wendler O, Wlather T, Nataf P, Rubino P, Schroefel H, Thielmann M, Treede H, Thomas M. Trans-apical aortic valve implantation: univariate and multivariate analyses of the early results from the SOURCE registry. *Eur J Cardiothorac Surg.* 2010:38:199-27.
12. Piazza N, Grube E, Gerckens U, Heijer den P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, 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. *EuroIntervention.* 2008;4:242-49.
13. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, et al & PARTNER Trial Investigators. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;36:1597-1607.

14. Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation.* 2006;113:842-50.
15. Marcheix B, Lamarche Y, Berry C, Asgar A, Laborde JC, Basmadjian A, et al. Surgical aspects of endovascular retrograde implantation of the aortic CoreValve bioprosthesis in high-risk older patients with severe symptomatic aortic stenosis. *J Thorac Cardiovasc Surg.* 2007;134:1150-6.
16. Walther T, Dewey T, Borger M, Kempfert J, Linke A, Becht R, Falk V, Schuler G, Mohr F, Mack M. Transapical aortic valve implantation: Step by step. *Ann Thorac Surg.* 2009;87:276-83.
17. Ye J, Cheung A, Lichtenstein SV, Nietlispach F, Albugami S, Masson, JB, Thompson CR, et al. Transapical transcatheter aortic valve implantation: Follow-up to 3 years. *J Thorac Cardiovasc Surg.* 2010;139:1107-13.
18. Zierer A, Wimmer-Greinecker G, Martens S, Moritz A, Doss M. The transpaical approach for aortic valve implantation. *J Thorac Cardiovasc Surg.* 2008;136:948-53.
19. Al-Attar N, Ghodbane W, Himbert D, Rau C, Raffoul R, Messika-Zeitoun D, Brochet E, Vahanian A, Nataf P. Unexpected complications of transapical aortic valve implantation. *Ann Thorac Surg.* 2009;88:90-4.
20. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, et al. Transapical minimally invasive aortic valve implantation: Multicenter experience. *Circulation.* 2007;116:I-240-5.
21. Svensson LG, Dewey T, Kapadia S, Roselli EE, Stewart A, Williams M, et al. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. *Ann Thorac Surg.* 2008;86:46-55.
22. Bleiziffer S, Ruge H, Mazzitelli D, Screiber C, Hutter A, Laborde JC, Bauernschmitt R, Lange R. Results of percutaneous and transapcial transcatheter aortic valve implantation performed by a surgical team. *Eur J Cardiothorac Surg.* 2009;35:615-21.
23. Modine T, Obadia J, Choukroun E, Rioufoul G, Sudre A, Laborde JC, Leprince P. Transcutaneous aortic valve implantation using the axillary/subcalvian access: Feasibility and early clinical outcomes. *J Thorac Cardiovasc Surg.* 2011;141:487-91.
24. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, Ramondo A, Ussia GP, Ettori F, Poli A, Brambilla N, Saia F, De Marco F, Colombo A. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv.* 2010;3:259-66.
25. Bruschi G, De Marco F, Fratto P, Oreglia J, Colombo P, Botta L, Klugmann S, Martinelli L. Alternative approaches for trans-catheter self-expanding aortic bioprosthetic valves implantation: single-center experience. *Eur J Cardiothorac Surg.* 2011;39:151-8.
26. Bapat V, Khawaja M, Attia R, Narayana A, Wilson K, Macgillivray K, Young C, Hancock J, Redwood S, Thomas M. Transaortic transcatheter aortic valve implantation using Edwards SAPIEN valve: A novel approach. *Catheter Cardiovasc Interv.* 2011:Epub ahead of print.

27. Karavolias G, Georgiadou P, Houri M, Sbarouni E, Thomopoulou S, Tsiapras D, Smirli A, Balanika M, Boudris V. Percutaneous aortic valve implantation of the Medtronic CoreValve self-expanding valve prosthesis via left subclavian artery access: The first case report in Greece. *Hellenic J Cardiol.* 2010;51:362-7.
28. Fraccaro C, Napodano M, Tarantini G, Gasparetto V, Gerosa G, Bianco R, Bonato R, Pittarello D, Isabella G, et al. Expanding the eligibility for Transcatheter aortic valve implantation: The trans-subclavian retrograde approach using the III generation CoreValve revalving system. *J Am Coll Cardiol Intv.* 2009;2:828-33.
29. Vavuranakis M, Vrachatis D, Toutouzas K, Economopoulos G, Kalogeras K, Stefanadis C. Successful percutaneous aortic valve implantation via a stenotic left subclavian artery access. *Heart Vessels.* 2010;25:359-62.
30. Mandegar MH, Nazeri I, Abdi S, Roshanali F. Successful transcatheter aortic valve implantation through ascending aorta and total revascularization using Edwards SAPIEN transcatheter heart valve system. *Ann Thorac Surg.* 2011;92:2262-3.
31. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: A novel approach for the truly "no-access option" patients. *Catheter Cardiovasc Interv.* 2010;75:1129-36.
32. Etienne PY, Papadatos S, Khoury EE, Pieters D, Price J, Glineur D. Transaortic transcatheter aortic valve implantation with the Edwards sapien valve: Feasibility, technical considerations, and clinical advantages. *Ann Thorac Surg.* 2011;92:746-8.
33. Astor BC, Kaczmarek RG, Hefflin B, Daley WR. Mortality after aortic valve replacement: Results from a nationally representative database. *Ann Thorac Surg.* 2000;70:1939-45.
34. Fish DR. Percutaneous heart valve replacement: Enthusiasm tempered. *Circulation.* 2004;110:1876-8.
35. NHS Centre for Reviews and Dissemination. Undertaking systemic reviews of re- search on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report 4. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.
36. Higgins JPT, Green S, (editors). *Cochrane handbook for systematic reviews of interventions. Version 5.0.0 [updated February 2008]*: The Cochrane Collaboration; 2008. Available from: www.cochrane-handbook.org
37. Agency for Healthcare Research and Quality. *Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment: number 47.* Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2002.
38. Svensson LG. *Aortic valve stenosis and regurgitation: an overview of management.* J Cardiovasc Surg. 2008;49:297-303.
39. Kojodjojo P, Gohil N, Barker D, Youssefi P, Salukhe TV, Choong A, et al. *Outcomes of elderly patients aged 80 and over with symptomatic, severe aortic stenosis: impact of patient's choice of refusing aortic valve replacement on survival.* QJM. 2008;101:567-73.

40. Banbury MK, Cosgrove DM 3rd, Thomas JD, et al. *Hemodynamic stability during 17 years of the Carpentier-Edwards aortic pericardial bioprosthesis.* Ann Thorac Surg. 2002;73:1460-5.
41. Svensson LG, Blackstone EH, Cosgrove DM 3rd. *Surgical options in young adults with aortic valve disease.* Curr Probl Cardiol. 2003;28:417-80.
42. Vassiliades TA Jr, Block PC, Cohn LH, Adams DH, Borer JS, Feldman T, et al. *The clinical development of percutaneous heart valve technology.* J Thorac Cardiovasc Surg. 2005;129:970-6.
43. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B, Cribier A, et al. *Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC) in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI).* Eur Heart J. 2008;29:1463-70.
44. Osswalkd BR, Gegouskov V, Badowski-Zyla D, et al. *Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement.* Eur Heart J. 2009;30:74-80.
45. Dewey, TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. *Reliability of risk algorithms in predicting early and late operative outcomes in high risk patients undergoing aortic valve replacement.* J Thorac Cardiovas Surg. 2008;135:180-7.
46. Brown ML, Schaff HV, Sarano ME, Li Z, Sundt TM, Dearani JA, et al. *Is the European System for Cardiac Operative Risk Evaluation model valid for estimating the operative risk of patients considered for percutaneous aortic valve replacement?* J Thorac Cardiovasc Surg. 2008;136:566-71.
47. Grossi EA, Schwartz CF, Yu P, Jorde UP, Crooke GA, Grau JB, et al. *High-risk aortic valve replacement: are the outcomes as bad as predicted?* Ann Thorac Surg. 2008;85:102-7.
48. Bhatti F, Grayson AD, Grotte G, Fabri BM, Au J, Jones M, et al. *The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk?* Heart. 2006;92:1817-20.
49. Taramasso M, Cioni M, Giacomini A, et al. *Emerging approaches of transcatheter valve repair/insertion*. Cardiol Res Pract. 2010; pii: 540749.
50. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, et al., on behalf of the FRANCE Registry Investigators. *Transcatheter aortic valve implantation: early results of the FRANCE (French Aortic National CoreValve and Edwards) registry.* Eur Heart J. 2011;32:191-7.
51. Bosmans J, Kefer J, Bruyne B, Herijgers P, Dubois C, et al., for the Belgian TAVI Registry Participants. *Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry*. Interact CardioVasc Thorac Surg 2011;12:762-7.