

Is It Reasonable to Treat All Calcified Stenotic Aortic Valves With a Valved Stent?

Results From a Human Anatomic Study in Adults

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Objectives	This study was designed to study the behavior of a stent deployed inside human stenotic aortic valves.
Background	Endovascular valved stent (VS) implantation is a promising new therapy for patients with severe calcific aortic stenosis (AS). The precise characteristics of stent deployment in humans have been poorly studied so far.
Methods	Thirty-five patients with severe AS were included in the study. Sixteen patients (46%) had bicuspid aortic valves. A self-expandable stent specifically designed for VS implantation was deployed intraoperatively inside the aortic valve before surgical aortic valve replacement.
Results	In tricuspid aortic valves, the shape of stent deployment was circular, triangular, or elliptic in 68%, 21%, or 11%, respectively. Noncircular stent deployment was frequent in bicuspid aortic valves (the elliptic deployment being the rule [79%]), and stent underdeployment was constant. The incidence of gaps between the stent external surface and the aortic valve did not differ between tricuspid and bicuspid valves (58% vs. 43%; $p = 0.49$). Sharp calcific excrescences protruding inside the stent lumen were present in 3 cases (9%). Ex vivo study of a homemade VS confirmed that the regularity of the coaptation line of the leaflets was critically dependent on the presence or the absence of stent misdeployment.
Conclusions	Stent misdeployment was constant in bicuspid valves and occurred in one-third of cases of tricuspid valves. Premature failure of implanted VS (secondary to valve distortion or traumatic injury to the leaflets by calcific excrescences) might be an important concern in the future. (J Am Coll Cardiol 2008;51:579–84) © 2008 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most frequent valvular disease in Western countries, and its incidence is expected to increase with population aging. Until recently, surgical aortic valve replacement (AVR) was the only effective treatment for the most severe forms, providing relief of symptoms and an increase in life expectancy (1).

Recently, endovascular aortic valve implantation (AVI) has been proved to be feasible in AS, using either self- or balloon-expandable valved stents (VS) (2–4). Endovascular AVI was first performed in compassionate cases and then in high-risk surgical patients. However, AVI is not AVR, because the native aortic valve is preserved in the former and

removed in the latter. Preservation of the native valve during the endovascular procedure may be responsible, per se, for complications such as coronary obstruction or perivalvular leakage (2–4).

Recourse to percutaneous AVI is expected to increase in the future. However, the actual clinical experience remains limited, and many problems need to be solved. Aside from coronary obstruction and perivalvular leakage, conservation of the native aortic valve may lead to other, still unknown complications. Whether their occurrence depends on the anatomic type of the aortic valve, that is, bicuspid or tricuspid, is also unanswered.

In an attempt to elucidate these 2 questions, a human anatomic study was undertaken in patients scheduled for nonemergent surgical AVR.

Materials and Methods

During a 5-month period, 35 patients (15 men; median age 71.5 years, range 40 to 90 years) with severe AS and scheduled for AVR were included in the study. Median preoperative aortic valve area was 0.7 cm^2 (range 0.3 to 1 cm^2),

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Abbreviations and Acronyms

- AS** = aortic stenosis
- AVI** = aortic valve implantation
- AVR** = aortic valve replacement
- VS** = valved stent

and mean systolic transaortic valve gradient (median) was 43 mm Hg (range 10 to 92 mm Hg). Main pre-operative clinical and echocardiographic data are reported in Tables 1 and 2. The study was approved by the local institutional review board, and all patients gave their informed consent.

A braided nitinol self-expandable stent from Laboratoires Perouse (Ivry-le-Temple, France) was used for intraoperative aortic valve “stenting.” The stent was designed specifically for endovascular valve replacement (5). Its diameter at rest was 26 mm and was calibrated to develop a radial force of around 1 kg when deployed in a 20-mm diameter orifice. The stent was compressed by traction on a suture placed around it and then was manually loaded into a 5-ml syringe with a cut distal extremity used for stent delivery.

During surgery, after cardioplegic arrest of the heart, the ascending aorta was opened and the aortic valve exposed. The distal extremity of the syringe was positioned inside the exposed aortic valve. The stent was delivered under visual control inside the aortic valve by slowly pushing the piston of the syringe. Then, the final stent deployment was carefully analyzed. The shape of the deployed stent was noticed, and a special attention was given to the presence of any gaps between the stent external surface and the leaflets’ inner surface. These gaps are likely to be the anatomical cause of the periprosthetic leaks observed in patients after percutaneous AVI. The gaps were checked with an oblique hook the same way perivalvular dehiscence after prosthetic valve replacement is looked for. Once the analysis was achieved, the stent was retrieved with a surgical forceps, and the AVR was performed. The aortic valve “stenting” lasted no more than 2 min.

To analyze the impact of stent deployment on valve geometry, a homemade pericardial VS was constructed.

Table 1 Preoperative Clinical Characteristics and Postoperative Outcome of the Study Population

Baseline Characteristics	n (%) or Median (Range)
Age (yrs)	71.5 (40–90)
Gender (M/F)	15 (43)/20 (57)
Systemic hypertension	20 (57)
Diabetes mellitus	5 (14)
Coronary artery disease	14 (40)
Renal failure requiring hemodialysis	1 (3)
Post-operative outcome	
30-day mortality	1 (3)
Low cardiac output syndrome	3 (9)
Reoperation for bleeding	1 (3)
Myocardial infarction	0
Stroke	0
Reoperation for bleeding	1 (3)
Mediastinitis	1 (3)

Table 2 Pre-Operative Echocardiographic Data of the Study Population

	n (%) or Median (Range)
Aortic valve area (cm ²)	0.7 (0.3–1)
Mean aortic gradient (mm Hg)	43 (10–92)
Aortic annulus diameter (mm)	19 (17–22)
Ejection fraction (%)	65 (20–87)
Ejection fraction \leq 30%	2 (6)
Left ventricular end-diastolic diameter (mm)	51 (36–65)
Septal thickness (mm)	12 (9–16)

This valve was calibrated for implantation inside a circular orifice with a 20-mm diameter and was also implanted in a triangular (equilateral) or an elliptic (0.73 eccentricity) orifice with a circumference identical to that of the circular orifice. Implantation was also performed in a 17-mm circular orifice to mimic the behavior of an oversized VS. The influence of annular calcifications located close to a VS commissure was also studied; this was mimicked by the presence of a bulging inside a circular orifice.

Data are expressed as median (range) for continuous variables and as percentage for categorical variables. Comparisons between categorical variables were performed with the Fischer exact test. A p value <0.05 was considered significant.

Results

Bicuspidy was present in 16 patients (46%). Stent delivery was impossible in 2 patients (6%) who had severely stenotic bicuspid valves.

After deployment, the aortic cross section of the stent could be basically categorized into 3 aspects that were grossly circular, elliptic, or triangular (Fig. 1). The stent deployment was highly dependent on valve anatomy (Table 3). The circular deployment was observed in 15 patients (45%), significantly more frequently in tricuspid than in bicuspid valves (68% [n = 13] vs. 14% [n = 2]; p = 0.004). The triangular aspect, usually mild, was seen mainly in tricuspid valves (n = 4; 21% of tricuspid valves). This aspect reflected the calcified leaflets’ rigidity, preventing them from being sufficiently bent and correctly applied against the stent’s external surface. The elliptic aspect was common in bicuspid valves (n = 11; 79% of bicuspid valves).

In tricuspid valves, the median deployed stent’s external diameter was 19 mm (range 17 to 20 mm) for the 13 cases with a circular stent deployment. The median aortic annulus diameter (as determined from the preoperative transthoracic echocardiographic measurement) was 18 mm (range 17 to 21 mm). Underdeployment (arbitrarily defined as a \geq 3 mm difference between the aortic annulus and the stent external diameter) was absent.

In bicuspid valves, the external diameter of the circularly deployed stent and of the aortic annulus were 18 and 21 mm in case 1 and 17 and 21 mm in case 2, respectively. Underdeployment was present in both cases.

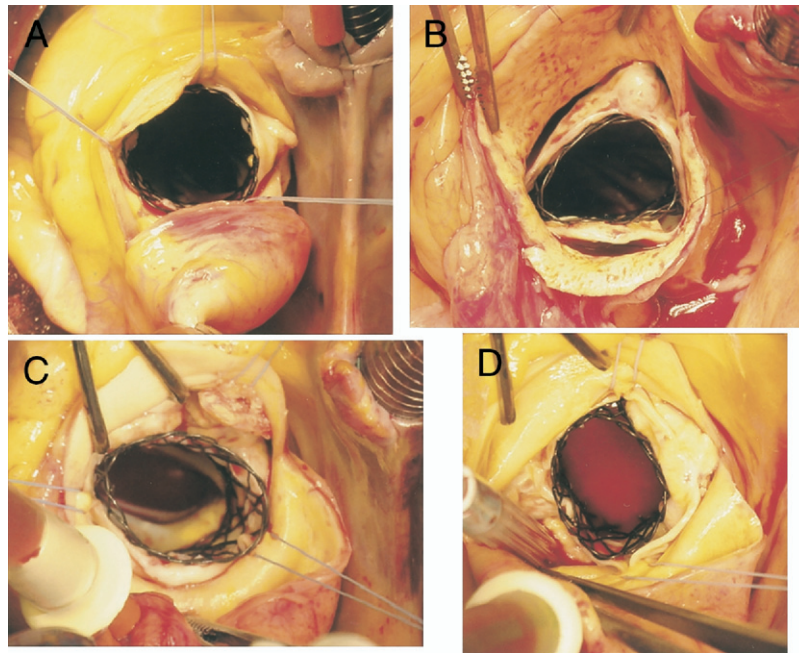


Figure 1 Different Shapes of Stent Deployment Encountered

Circular (A), triangular (B), and elliptic (C and D). Note the round calcifications crossing the stent frame.

A gap between the stent external surface and the inner surface of the aortic valve was identified in 17 patients (49%). These gaps were located exclusively at the level of the commissures. Their incidence was not dependent on the valve pathology (58% [n = 11] in tricuspid vs. 43% [n = 6] in bicuspid valves; p = 0.49). However, the presence of a periprosthetic gap depended on the shape of stent deployment (Fig. 2). The highest rate (100%) was observed with the triangular shape and the lowest with the circular one (33%). In tricuspid valves, the gaps involved 1, 2, or 3 commissures in 7 (37%), 4 (21%), and 0 cases, respectively.

The aortic leaflets' ventricular surface was always irregular, and calcifications almost constantly crossed the stent frame. These calcifications were usually small, round, and smooth (Fig. 1). In some cases (n = 3; 9%), however, these calcifications were particularly sharp, protruding into the stent lumen (Fig. 3).

The anchorage of the present stent to the surrounding tissue was judged firm by surgeons, and its removal was impossible without partial recompression. Aortic valve replacement was performed with a bioprosthetic or a mechanical valve in 31 (89%) and 4 (11%) patients, respectively.

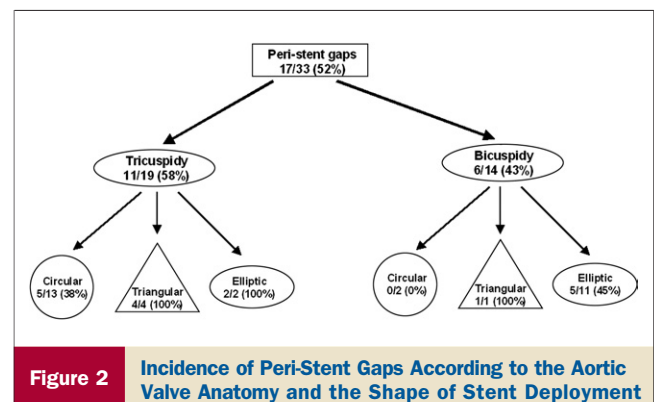
Table 3 Stent Shape After Deployment According to Aortic Valve Pathology

Stent Shape	Tricuspidy (n = 19)	Bicuspidy (n = 14)
Circular, n (%)	13 (68)	2 (14)
Elliptic, n (%)	2 (11)	11 (79)
Triangular, n (%)	4 (21)	1 (7)

After implantation of the homemade VS inside a circular 20-mm orifice, the coaptation line of the leaflets was regular and symmetric, reproducing the “Mercedes sign” (Fig. 4). In all other circumstances (undersized circular orifice, elliptic or triangular orifice, asymmetric circular orifice), the coaptation line was disorganized, reflecting leaflet distortion (Figs. 4 and 5). The severity of valve distortion markedly depended on the location of the commissures inside the triangular orifice (Fig. 6).

Discussion

Endovascular AVI has recently been proved feasible in AS using either self- or balloon-expandable VS (2-4). This promising new therapy might be beneficial to a great number of patients at high surgical risk or even patients for



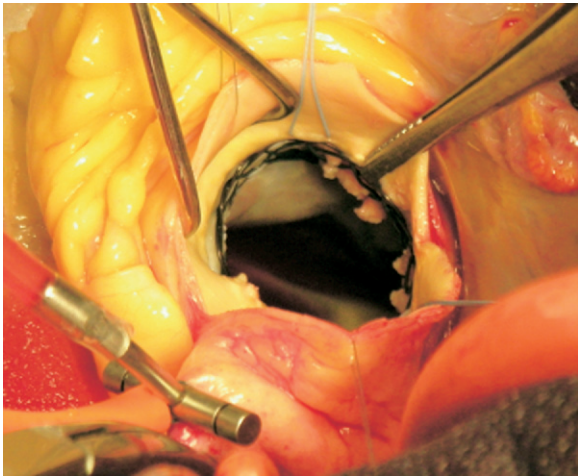


Figure 3 Sharp Calcific Excrescences Crossing the Stent Frame, Protruding Inside the Aortic Lumen

whom surgery is denied. The few clinical series currently available have pointed out several procedure-related complications, such as valve migration, coronary obstruction, or perivalvular leak (2–4).

Concerns have been raised regarding the potential traumatic injury to the pericardial leaflets of the current VS

during the crimping or loading process into the delivery catheter. For some models, VS deployment requires balloon dilation. The friction of the pericardial leaflets against the stent frame during deployment may also alter their structure or their mechanical properties, with potential negative effects on long-term durability (3). Mid-term or long-term follow-up are still lacking, hence the impact of these potentially deleterious processes on VS durability remains unknown.

The results of the present study suggest that durability of the VS implanted inside a stenotic aortic valve might also be altered through other mechanisms. In 9% of the cases, sharp calcific excrescences protruded inside the stent lumen. Repeated contact with a pericardial (or a polymeric) leaflet during the aperture-closure cycle of the valve may lead to leaflet perforation and valve dysfunction. Such lesions have been described by surgeons during bioprosthetic valve replacement when suture knots were left too long (6). Only sufficiently covered VS might be protected from the potentially harmful effect of these excrescences when the calcific aortic valve is left in place.

The major finding of this study was the high incidence of stent misdeployment (100% in bicuspid valves; one-third in tricuspid valves). For optimal functioning, VS requires an adequately sized cylindrical deployment of the stent part supporting the leaflets. Any stent misdeployment may lead

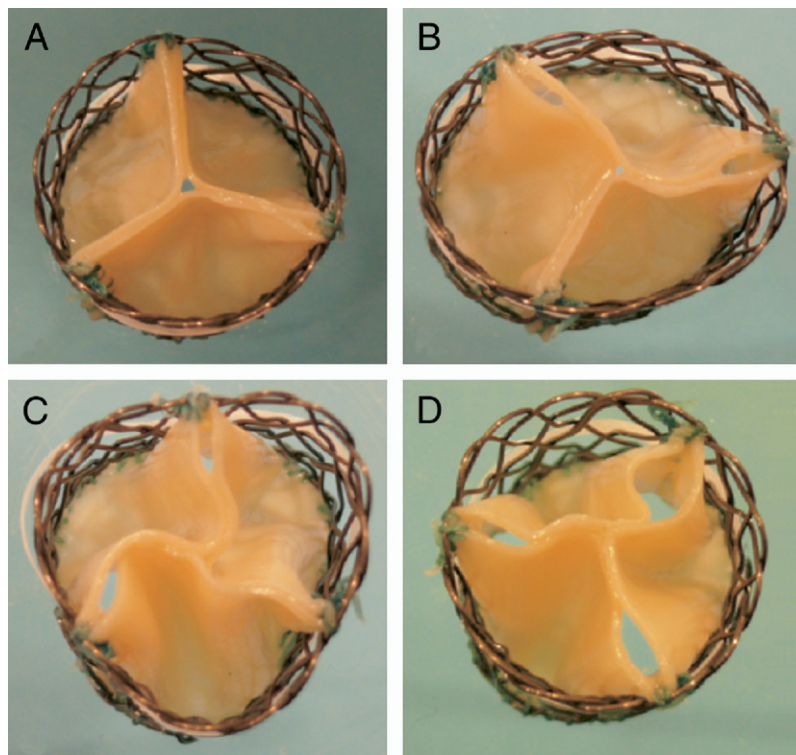


Figure 4 Influence of Size or Shape of the Orifice on the Valved Stent Deployment

No leaflet distortion was present with the valved stent (VS) deployed inside the circular orifice with a 25-mm diameter (A). Conversely, distortion occurred after deployment of the VS in an elliptical (B), a triangular (C), or an undersized circular orifice (D).

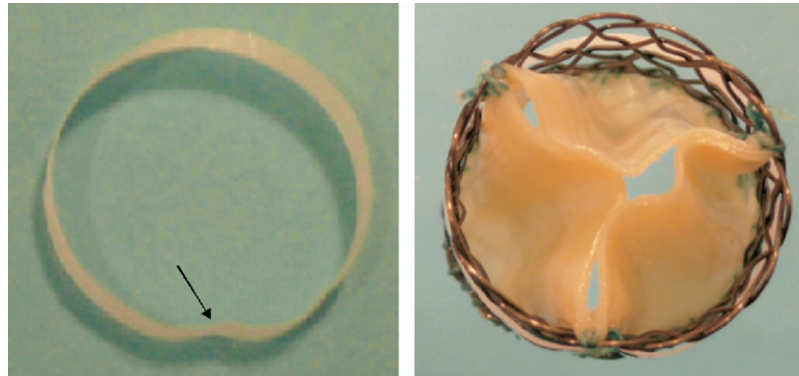


Figure 5 Leaflet Distortion in the Presence of Annular Calcification Close to One Commissure of the Deployed Valved Stent

Calcification, mimicked by an irregularity (**left, arrow**) inside the circular orifice, leading to valve distortion (**right**).

to valve distortion (Figs. 4 to 6). Valve distortion increases stress on 1 or more leaflets, especially at the level of the commissures, resulting in premature failure by leaflet tear or fibrosis, as demonstrated in an animal study (7).

Valve distortion may also occur despite circular stent deployment (Fig. 4). Such a situation may theoretically be observed with oversized VS implantation. Oversizing has been proposed by others (4,8) to reduce the incidence of periprosthetic leak. If the aortic valve and/or annulus do not strictly accommodate the oversized VS, valve distortion may occur because of excess of pericardial tissue relatively to the stent orifice area.

Calcific bicuspidy is a frequent condition in severe AS, with a 50% incidence in surgical series (9). Patients with a bicuspid aortic valve are usually younger with, therefore, a better post-operative long-term survival. Stent misdeployment in bicuspid valves was 100% in this anatomic study. Underdeployment was constant owing to the limited valve opening of bicuspid aortic valves. Furthermore, noncircular deployment of the stent was the rule (86%), increasing VS

distortion attributable to stent underdeployment. Based on these data, a high rate of patient–VS mismatches and of VS premature failure secondary to valve distortion would therefore be expected. Because of the negative effect of patient–prosthesis mismatch on midterm survival (10), the current procedural risk of endovascular VS implantation, and the potentially increased perioperative risk of a subsequent surgical AVR, we believe that endovascular VS implantation should not be recommended in patients with calcific bicuspid AS.

Aortic valve regurgitation was the most prevalent valvular complication reported following endovascular aortic VR (2–4). The AVR was paravalvular in origin, and its severity may be partially reduced by balloon redilation in balloon-expandable VS (4, 9). With self-expandable VS, their incidence might decrease with time (3). The present anatomic study confirmed the high incidence (58% in tricuspid valves) of peri-stent dehiscence, which was comparable to the echocardiographic incidence (52%) in the series of Grube *et al.* (3). Leaks were always located at the level of commissures.

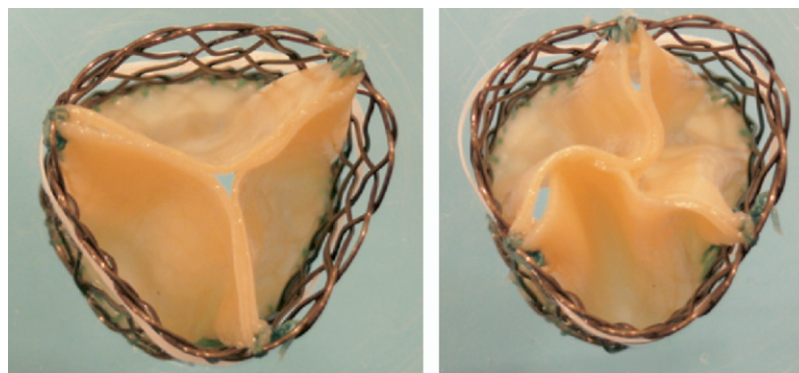


Figure 6 Valve Distortion Secondary to the Valved Stent Deployment Inside a Triangular Orifice

The severity of valve distortion was clearly dependent on positioning of the valved stent commissures inside the orifice (less severe in the **left panel** than in the **right panel**).

Aortic leaflets present rough ventricular surfaces in calcific AS. Round calcifications are almost constant and multiple on this side (Fig. 1). Despite their small size, they may have 2 consequences. First, their protrusion through the stent frame may provide a better VS anchorage. Subsequent stent migration would therefore be impossible without a spontaneous in vivo stent recompression, an eventuality rather unlikely to occur with self-expandable stents. Second, round calcifications may favor the occurrence of valve distortion (Fig. 5) or even periprosthetic leak. This may happen when part of the stent frame lies on the top of a rather large calcification, creating a gap between the external stent surface and the leaflets' internal surface. Technically speaking, this phenomenon may occur with any type of stent but is less likely with braided stents, whose frame can better accommodate this situation (as reflected by the local deformation of the stent frame in Fig. 1). These 2 potential consequences are partly speculative and require further evaluation.

The present study relied on the use of a self-expandable stent. In tricuspid aortic valve stenosis, its radial force was sufficient to achieve an adequate circular deployment in many cases (68%) and a firm anchorage in all cases. We do not believe that the use of a stiffer stent would have resulted in better expansion in bicuspid aortic valves. In these valves, because of the calcifications, the excursion of at least 1 leaflet (usually the leaflet with the raphe) (Fig. 1) is severely restricted, even with the surgeon's forceps. This restriction has also previously been shown in earlier studies demonstrating the poor results of valvuloplasty in bicuspid AS (11). However, it is possible that a better expansion might be observed in tricuspid valves (this is the subject of an ongoing study), but the risk of coronary obstruction might increase with such stiffer stents.

It is also possible that balloon valvuloplasty before aortic stenting (as is the case in clinical practice before VS implantation) may reduce the prevalence of noncircular stent deployment by "fragmentation" of the leaflet's calcifications. Fragmentation might improve the pliability of the aortic valve leaflets and, therefore, favor the circular deployment of the stent.

Rare postmortem cases have been discussed (2,4), but no systematic anatomic studies from cadaveric or autopsy series and no radiographic studies of VS deployment have been published so far. Such studies are required to corroborate or invalidate the present data, especially if the procedure is intended to be applied to a larger group of patients.

In conclusion, this first human anatomical study of intraoperative aortic valve stenting in patients with AS suggested that percutaneously implanted VS might show premature failure through 2 previously unrecognized mechanisms: injury to the leaflets by calcific excrescences and

valve distortion secondary to stent misdeployment. Owing to the relatively high incidence of these unrecognized mechanisms, physicians should wait for the mid- and long-term results of the procedure in high-risk patients before extending the indication to less risky surgical patients. The present study also has shown that stent misdeployment (and consequently valve distortion) was constant in bicuspid, suggesting that percutaneous AVI may have less favorable results in bicuspid than in tricuspid AS.

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REFERENCES

1. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol* 2006;48:e1–148.
2. Cribier A, Eltchaninoff H, Tron C, 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.
3. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the Corevalve self-expanding valve prosthesis in high-risk patients with aortic valve disease. The Siegburg first-in-man study. *Circulation* 2006;114:1616–24.
4. Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842–50.
5. Van Nooten G, Ozaki S, Herijgers P, Segers P, Verdonck P, Flameng W. Distortion of the stentless porcine valve induces accelerated leaflet fibrosis and calcification in juvenile sheep. *J Heart Valve Dis* 1999;8:34–41.
6. Zegdi R, Khabbaz Z, Borenstein N, Fabiani JN. A repositionable valved stent for endovascular treatment of deteriorated bioprostheses. *J Am Coll Cardiol* 2006;48:1365–8.
7. Garcia-Valentin A, Castellà M, Josa M, Mulet R. Bioprosthetic leaflet perforation due to repetitive trauma by overknotted sutures. *Eur J Cardiothorac Surg* 2006;29:106.
8. Walther T, Falk V, Borger MA, et al. Minimally invasive transapical beating heart aortic valve implantation—proof of concept. *Eur J Cardiothorac Surg* 2007;31:9–15.
9. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;111:920–5.
10. Tasca G, Mahgna Z, Perotti S, et al. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. *Circulation* 2006;113:570–6.
11. Isner JM, Salem DN, Desnoyer MR, et al. Treatment of calcific aortic stenosis by balloon valvuloplasty. *Am J Cardiol* 1987;59:313–7.