European Heart Journal (2014) **35**, 2627–2638
doi:10.1093/eurheartj/ehu256

REVIEW

Clinical update

Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation

Jeroen J. Bax[1]*, Victoria Delgado[1], Vinayak Bapat[2], Helmut Baumgartner[3], Jean P. Collet[4], Raimund Erbel[5], Christian Hamm[6], Arie P. Kappetein[7], Jonathon Leipsic[8], Martin B. Leon[9], Philip MacCarthy[10], Nicolo Piazza[11,12], Philippe Pibarot[13], William C. Roberts[14], Josep Rodés-Cabau[15], Patrick W. Serruys[7], Martyn Thomas[2], Alec Vahanian[16], John Webb[8], Jose Luis Zamorano[17], and Stephan Windecker[18]

[1]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2 2300 RC, Leiden, The Netherlands; [2]Department of Cardiology and Cardiothoracic Surgery, St Thomas' Hospital, London, UK; [3]Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany; [4]Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [5]Department of Cardiology, West-German Heart Center Essen, University Duisburg Essen, Essen, Germany; [6]Department of Cardiology, Kerckhoff-Klinik, Bad Nauheim, Germany; [7]Erasmus Medical Center, Rotterdam, The Netherlands; [8]St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [9]Columbia University Medical Center, Center for Interventional Vascular Therapy, New York Presbyterian Hospital, New York, USA; [10]Cardiovascular Department, King's College Hospital, London, UK; [11]Interventional Cardiology, McGill University Health Center, Montreal, Canada; [12]Cardiovascular Surgery, German Heart Center Munich, Bavaria, Germany; [13]Quebec Heart and Lung Institute, Québec, Canada; [14]Baylor Heart and Vascular Institute and the Departments of Internal Medicine (Division of Cardiology) and Pathology, Baylor University Medical Center, Dallas, TX, USA; [15]Department of Cardiology, Laval University, Quebec, Canada; [16]Bichat Hospital, University Paris VII, Paris, France; [17]Cardiac Imaging Department, University Hospital Ramon y Cajal, Madrid, Spain; and [18]Department of Cardiology, Bern University Hospital, Bern, Switzerland

Received 16 April 2014; revised 13 May 2014; accepted 2 June 2014; online publish-ahead-of-print 25 July 2014

An exponential increase in the use of transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis has been witnessed over the recent years. The current article reviews different areas of uncertainty related to patient selection. The use and limitations of risk scores are addressed, followed by an extensive discussion on the value of three-dimensional imaging for prosthesis sizing and the assessment of complex valve anatomy such as degenerated bicuspid valves. The uncertainty about valvular stenosis severity in patients with a mismatch between the transvalvular gradient and the aortic valve area, and how integrated use of echocardiography and computed tomographic imaging may help, is also addressed. Finally, patients referred for TAVI may have concomitant mitral regurgitation and/or coronary artery disease and the management of these patients is discussed.

Keywords Transcatheter aortic valve implantation • Aortic stenosis • Imaging • Patient selection • Mitral regurgitation • Coronary artery disease

Introduction

In 2002, transcatheter aortic valve implantation (TAVI) was introduced as an alternative treatment in patients with severe aortic valve stenosis (AS).[1] Since then several transcatheter valve prostheses have received CE approval including the balloon-expandable Edwards SAPIEN valve prostheses (Edwards SAPIEN; Edwards Lifesciences, Irvine, CA, USA) and its recent device iterations (SAPIEN XT, SAPIEN 3) available for transfemoral and transapical access, the self-expandable CoreValve system (Medtronic, Inc., Minneapolis, MN, USA), the transfemoral

* Corresponding author. Tel: +31 715202020, Fax: +31 715266809, Email: j.j.bax@lumc.nl

self-expanding Portico valve (St Jude Medical. St Paul, MN, USA), the Direct Flow prosthesis (Direct Flow Medical, Inc., Santa Rosa, CA, USA), the Lotus valve (Boston Scientific Corporation, Natick, MA, USA), and the transapical Symetic Acurate (Symetis SA, Ecublens, Switzerland), JenaValve (JenaValve, Munich, Germany), and Medtronic Engager (Medtronic, Inc., Minneapolis, MN, USA).[2] Over the years, a rapid development in prosthetic valves has been witnessed, with the introduction of various prosthetic designs and sizes.[3] The crossing profile of the delivery sheaths has been improved and the sizes have been reduced. These developments have significantly improved procedural success rates and outcome, with a reduction in complications.

It is estimated that >100 000 TAVIs have been performed between 2002 and 2013. It has also become evident that many areas of uncertainty exist around TAVI, which are addressed in the current reviews.[4,5] In the first part, issues around patient selection are discussed, such as the need for improved risk scores, and the value of sophisticated, three-dimensional non-invasive imaging for prosthesis sizing. Uncertainty also exists on optimal visualization of native valve anatomy in bicuspid valves, and the quantification of stenosis severity in low-flow low-gradient AS. Another issue of controversy is the outcome after TAVI in patients with pre-existent left ventricular (LV) dysfunction. Finally, concomitant mitral regurgitation (MR) and coronary artery disease (CAD) are frequently encountered and the need and timing for therapeutic intervention is unclear as well as their impact on prognosis.

The available literature on these issues will be reviewed and the specific areas, where conclusive data are lacking will be summarized. Part 2 will focus on procedural issues and outcomes.[5]

Risk scores for patient

The decision of surgical aortic valve replacement (SAVR) or TAVI in symptomatic severe AS depends on the presence of contraindications for SAVR or a high-surgical risk.[6,7] Two risk scores are used to calculate the risk of cardiac surgery (including SAVR): the Society of Thoracic Surgeons-Predicted Risk of Mortality score (STS-PROM) and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) model (additive and logistic).[8,9] When the STS-PROM score exceeds 10% or when the logistic EuroSCORE is ≥20%, referral for TAVI should be considered.[6,7] These risk scores, however, were developed and validated in the standard surgical risk populations and predict short-term mortality (hospital or 30-day) after cardiac surgery. Both scoring systems have, therefore, important deficiencies especially in a heterogeneous high-risk patient population such as TAVI candidates. Moreover, they are inadequate to predict the long-term outcome or procedural complications. The EuroSCORE II has recently been developed from data of 22 381 patients undergoing cardiac surgery and validated in a subset of 5553 patients.[10] Variables such as impaired mobility, New York Heart Association (NYHA) functional class and diabetes were incorporated into the new risk score.[10] This score appears to have superior discriminatory power for predicting 30-day mortality over the original logistic EuroSCORE.[11]

The reasons for suboptimal performance of the scores are diverse. The development cohort of patients from whom a score was derived is usually very different from the patients to whom it is applied. Also, changes in surgical techniques, peri-operative care, patients' characteristics, and differences in hospitals and even surgeons or interventionalists may further explain the modest performance of the scores. Finally, risk scores are usually developed through the standard statistical approaches, not taking into account risk factor interactions or procedure-specific weightings.

The application of risk scores for referral to TAVI is also limited, since conventional cardiovascular risk factors (i.e. peripheral vascular disease, diabetes) are included in the scores, but specific risk factors for TAVI are not included, such as frailty, porcelain aorta, vessel tortuosity, chest wall malformation, or chest radiation. In addition, risk predictions should be based on standardized definitions such as the Valve Academic Research Consortium (VARC) criteria.[12]

The EuroSCORE II showed better discriminatory power for predicting 30-day mortality after TAVI, when compared with the logistic EuroSCORE and STS-PROM in a cohort of 350 TAVI patients (areas under the curve 0.70, 0.61, and 0.59, respectively).[13] Recently, based on data from the FRANCE-2 registry, a risk score has been proposed which includes a specific procedural variable in the calculation: the TAVI access site (transfemoral vs. non-transfemoral).[14] However, the discrimination of this risk score was still modest (area under the curve 0.59), indicating the limitations of the score to reliably individualize risk.

Accordingly, the unmet needs currently include improvements in risk scores to better individualize patient risk in the populations considered for TAVI. The open questions are (i) how to improve discrimination between low- and high-surgical risk (including SAVR), (ii) how to identify patients who should be referred for TAVI, and (iii) how to predict procedural risk and outcome in TAVI candidates.

It may be difficult (if not impossible) to develop the specific scores that answer these questions, since this concerns a complex patient group, in whom individualized decision-making may be preferred to ensure that every patient receives the optimal therapy. In addition to scores, discussion on individual patient management should take place in the 'Heart Team' including cardiologists with specific interest on valvular heart disease, transcatheter interventions and cardiac imaging, cardiothoracic surgeons, anaesthesiologists, and other specialists such as geriatricians.[6,7]

Imaging to guide prosthesis sizing

Aortic valve annulus sizing is crucial for accurate selection of prosthesis size. Three-dimensional imaging modalities are superior to two-dimensional (2D) techniques to assess the elliptical geometry and to accurately measure the dimensions of the aortic annulus.[15,16] Compared with 2D TEE, 3D imaging modalities may modify sizing in up to 40% of patients.[17]

In daily clinical practice, the technique of choice for aortic annulus sizing is multi-detector row computed tomography (MDCT) which provides high spatial resolution data that can be easily post-processed using dedicated TAVI workstation packages.[18] Magnetic resonance imaging provides an alternative technique for aortic annulus sizing, but is infrequently used in clinical practice. During the procedure, 3D TEE can also be used for aortic annulus sizing, and current ultrasound systems include dedicated platforms that permit live measurements of 3D data. From 3D TEE and MDCT different measurements can be derived which have been associated with paravalvular aortic regurgitation (AR) (*Table 1* and *Figure 1*).[19–24]

Table 1 Three-dimensional aortic annulus measurements proposed for transcatheter aortic valve size selection

Dimension	Three-dimensional measurement approach	Effects on paravalvular AR
Minimum diameter	Shortest diameter measured in the cross-sectional view of the aortic annulus	Increased risk of paravalvular AR and valve migration due to prosthesis undersizing[22]
Maximum diameter	Largest diameter measured in the cross-sectional view of the aortic annulus	Risk of paravalvular AR is minimized compared with minimum diameter,[22] but increased risk of annulus rupture if prosthesis is oversized by ≥20%[23,24]
Mean diameter	(maximum diameter + minimum diameter)/2	Risk of paravalvular AR is reduced when compared with using minimum diameter[20,22]
Perimeter	Planimetered perimeter of the aortic annulus in the cross-sectional view of the aortic annulus	Risk of paravalvular AR is minimized compared with minimum diameter[22]
Area	Planimetered area of the aortic annulus in the cross-sectional view of the aortic annulus	Integration of area measured with MDCT led to a reduction in paravalvular AR in a prospective multicentre observational study[19]

AR, aortic regurgitation; MDCT, multi-detector computed tomography; TAVI, transcatheter aortic valve implantation; TEE, transoesophageal echocardiography.

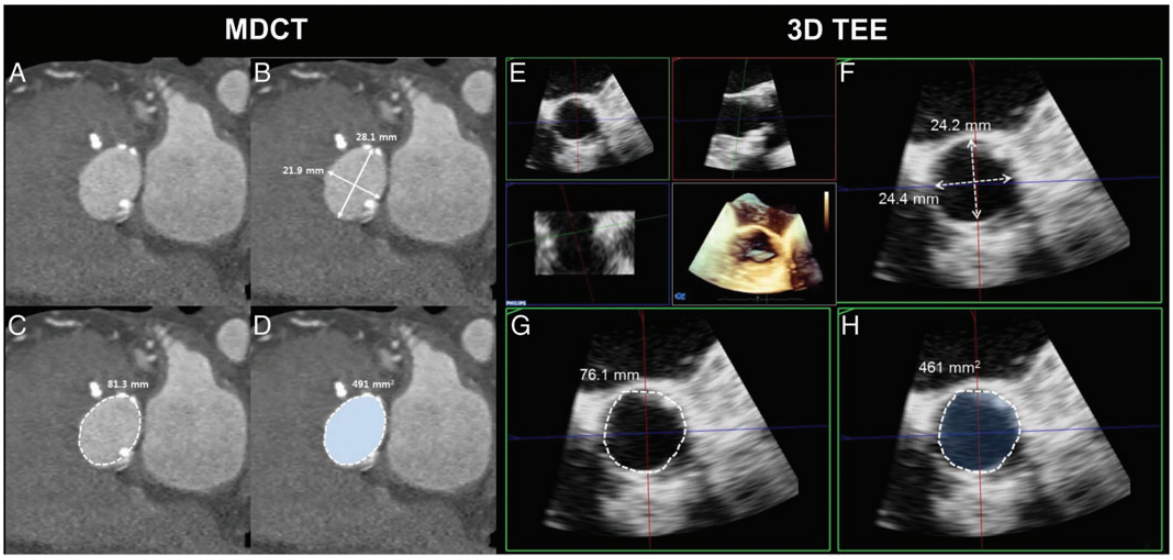

Figure 1 Aortic valve annulus measurement. Double oblique transverse reconstructions of the aortic annulus on multi-detector row computed tomography in an 84 year-old man with severe aortic stenosis (*A*). Routine measurements performed on multi-detector row computed tomography include the minimum and maximum diameters (*B*) as well as the perimeter (*C*) and the area (*D*). Similarly, three-dimensional transoesophageal echocardiography can be post-processed to obtain the cross-sectional view of the aortic annulus and the minimum and maximum diameters, and the perimeter and area can be measured (*E*). The multi-planar reformation planes are aligned across the aortic annulus displaying the double oblique transverse view where the minimum and maximum diameters (*F*), perimeter (*G*), and area (*H*) can be measured.

Selection of prosthesis size based only on minimum or maximum diameters may result in both significant under- and oversizing, respectively, due to their inability to characterize the non-circular geometry of the annulus.[22] The consequences of an undersized prosthesis include significant paravalvular AR or increased risk of prosthesis migration while an oversized prosthesis increases the risk of annulus rupture. Subsequent studies have used the perimeter or area measurements to reduce the risk of these complications.[20,22] Wilson *et al.*[22] showed that the difference between the MDCT perimeter or area measurements and the nominal prosthesis perimeter or area, predicted the presence of significant paravalvular AR (area under curve 0.80 and 0.71, respectively). Implantation of a prosthesis with a nominal area <10% greater than the MDCT annulus area was associated with an increased risk of significant paravalvular AR.[22] In contrast, a relative oversizing ≥20% was associated with an increased risk of aortic annulus rupture.[23,24] Recently, a prospective study recommended between 5 and 10% of prosthesis oversizing (nominal prosthesis area/MDCT annulus area) for Edwards SAPIEN valves to ensure appropriate apposition of the prosthetic frame into the aortic annulus and maximize annular sealing by the prosthesis. If >15–20% of oversizing was anticipated, intentional underexpansion of the selected prosthesis was recommended by underfilling the balloon 10% in order to minimize the risk of annulus rupture (*Table 2*).[19] Of importance, prosthesis oversizing

Table 2 Proposed sizing chart for the Edwards SAPIEN valve and the CoreValve system based on multi-detector row computed tomography measurements

	Edwards SAPIEN/SAPIEN XT prosthesis size			
	20-mm	**23-mm**	**26-mm**	**29-mm**
Diameter (mean), mm	17.3–20.3	20.3–23.3	23.3–26.3	26.3–29.3
Area, cm^2	2.41–3.20[a]	3.20–4.15[b]	4.15–5.30[c]	5.30–6.62[d]
Perimeter, mm	55.6–65.4	65.4–75.2	75.2–85.0	85.0–94.8
	Edwards SAPIEN 3			
	—	**23-mm**	**26-mm**	**29-mm**
Area, cm^2	—	3.38–4.30	4.30–5.46	5.40–6.80
Area-derived diameter, mm	—	20.7–23.4	23.4–26.4	26.2–29.5
	CoreValve system			
	23-mm	**26-mm**	**29-mm**	**31-mm**
Diameter (mean), mm	18–20	20–23	23–27	26–29
Area, cm^2	2.54–3.14	3.14–4.15	4.15–5.72	5.31–6.60
Perimeter, mm	56.5–62.8	62.8–72.3	72.3–84.8	81.6–91.1

[a]Consider balloon underfilling from 2.4 to 2.7 cm^2.
[b]Consider balloon underfilling from 3.20 to 3.50 cm^2.
[c]Consider balloon underfilling from 4.20 to 4.45 cm^2.
[d]Consider balloon underfilling from 5.35 to 5.60 cm^2.

based on diameter or perimeter is not equivalent to prosthesis oversizing based on the area: a 10–20% oversizing based on perimeter may correspond to 30–40% oversizing based on the area with consequent increased risk of annulus rupture. Similarly, several studies have shown that aortic annulus sizing with 3D TEE reduced the incidence of paravalvular AR after TAVI when compared with 2D TEE measurements.[15,21,25] The main advantages of 3D TEE are that it can be performed during the procedure and does not involve radiation or ionized contrast agents which may impact on the renal function. However, this technique is operator dependent which may lead to some variability in aortic annulus sizing.

While advanced 3D imaging modalities have allowed for a better understanding of annulus geometry and sizing, the optimal measurement for sizing and degree of annulus oversizing by perimeter or area to reduce paravalvular AR while minimizing the risks of annular rupture remain still debated. Of note, sizing of valve prosthesis depends on the individual design of each prosthesis and the recent advent of devices with sealing cuffs to mitigate AR may further reduce the risk of aortic regurgitation without the need of aggressive oversizing.

Bicuspid aortic valve: prevalence, diagnosis, and implications for transcatheter aortic valve implantation

It has been estimated that 1% of the worldwide population has a congenitally bicuspid aortic valve (BAV). A recent necropsy study of 218 unoperated patients >20 years of age with congenitally malformed aortic valves (unicuspid or bicuspid) showed that the valve had functioned abnormally in 75% of patients, with AS being the most frequent dysfunction (87%).[26]

The frequency of the operatively-excised stenotic unicuspid and BAVs has also been studied (*Figure 2*). Among 219 men aged 71–80 years who underwent SAVR between 1993 and 2004 at a single centre, there were 4 unicuspid, 94 bicuspid and 119 tricuspid valves, whereas of the 138 women aged 71–80 years there were 1 unicuspid, 55 bicuspid, and 79 tricuspid valves.[27] Interestingly, in 1.4% of patients the anatomy of the aortic valve could not be determined.

Diagnosis of bicuspid anatomy with 2D echocardiography can be challenging. In 100 patients (mean age 70 years) with isolated AS who underwent SAVR, the prevalence of congenitally malformed valves was 51% and in 14 patients, 2D echocardiography could not diagnose the anatomy of the aortic valve [with 10 (71%) having congenitally malformed valves].[28] Magnetic resonance imaging and MDCT provide a higher spatial resolution data and have demonstrated improved accuracy to identify BAV.[29,30] In 50 patients with AS (34% BAV) undergoing SAVR, the accuracy of MDCT to diagnose the aortic valve anatomy was superior to 2D echocardiography (98 vs. 66%, respectively).[30] This may be related to the better visualization of the valvular pathology despite the presence of heavy calcifications as observed in operatively excised bicuspid stenotic valves.[31]

Based on this evidence, there may be a significant proportion of patients with severely stenotic BAV who could be candidates for TAVI. However, BAV has been considered a less favourable

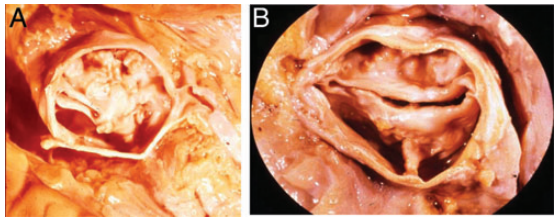

Figure 2 Unicuspid and bicuspid aortic valve. Unicuspid unicommissural aortic valve (*A*). The lumen is eccentrically located and one true commissure is present. Congenitally bicuspid aortic valve with the two cusps located anterior and posterior with a raphe in the anterior cusp (*B*).

anatomy for transcatheter valve deployment and function and accordingly several trials, including the Placement of AoRTic TraNscathetER valves (PARTNER) trials, have excluded patients with this anatomy.[32,33] Recently, published series have demonstrated that TAVI is a feasible and safe procedure in patients with severe AS and BAV.[34–36] In the USA, Transcatheter Valve Therapy registry, 2% of the patients had BAVs.[37] Among 229 patients undergoing preprocedural MDCT, 9.2% patients had a BAV.[34] Compared with patients with tricuspid aortic valves, the CoreValve system was more frequently used among patients with BAV (47.6 vs. 16.3%, $P = 0.002$). The procedural outcomes were comparable between patients with BAV and patients with tricuspid valves in terms of successful implantation (100 vs. 93%, $P = 0.37$), significant AR after TAVI (19 vs. 14.9%, $P = 0.54$) and 30-day combined safety endpoint (14.3 vs. 13.5%, $P = 1.00$).[34] Extent and amount of valve calcifications may also impact on the deployment of the transcatheter valves (*Figure 3*). Wijesinghe *et al.*[36] reported a circular deployment of the prosthesis in 11 patients with stenotic BAV undergoing TAVI with the Edwards SAPIEN valve, whereas others reported an elliptical deployment in 36 patients with stenotic BAV treated with the CoreValve system.[34,35] An elliptical deployment of the transcatheter valve may lead to valve dysfunction and significant paravalvular AR.

Finally, it is important to note that BAV anatomy may be associated with aortopathy (aneurysm of the ascending aorta or aortic coarctation) that should be evaluated prior to TAVI, since it is a contraindication.[32,38] In addition, left coronary artery dominance is more frequently observed among patients with BAV. The height and location of the coronary ostia may also be different in these patients and accurate assessment is crucial to anticipate potential complications such as coronary ostium occlusion by a bulky calcified cusp. Multi-detector row computed tomography may be an accurate and comprehensive imaging tool to select patients with severely stenosed BAV who are considered for TAVI.

Low-flow, low-gradient aortic stenosis: how to assess severity

The assessment of severity is an important step in the management of patients with AS. The clinical utility of measuring stenosis severity is three-fold: to ensure that AS is the cause of symptoms, to evaluate the prognosis, and to decide upon treatment.

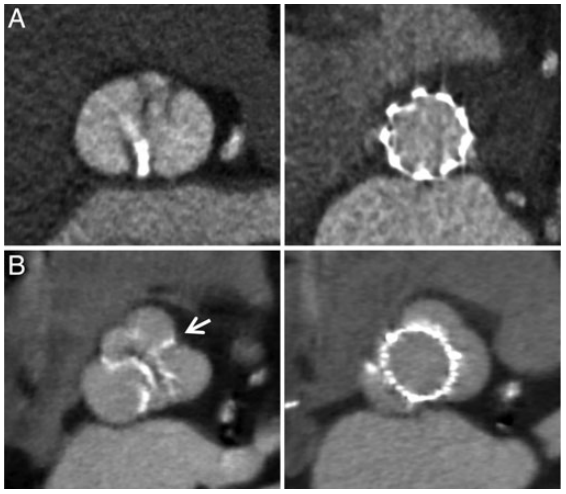

Figure 3 Transcatheter aortic valve implantation in the bicuspid aortic valve. (*A*) Example of a bicuspid aortic valve (without fusion raphe). This anatomical variant is clearly visualized with multidetector row computed tomography. This 82-year-old patient with symptomatic severe aortic stenosis underwent successful transcatheter aortic valve implantation. The multi-detector row computed tomography post-transcatheter aortic valve implantation shows circular deployment of the stent frame. (*B*) Example of a bicuspid aortic valve with fusion raphe between the left and the right coronary cusp. The multi-detector row computed tomography acquired during systole of 87-year-old patient shows the right and the left coronary cusps fused (arrow). After transcatheter aortic valve implantation, the multi-detector row computed tomography showed an ellipsoid deployment of the device.

Echocardiography is the reference method for evaluating AS severity, but accurate assessment is sometimes challenging. Severe AS with small AVA (<1.0 cm^2) and low transvalvular gradients is not uncommon in daily clinical practice. According to recent guidelines, severe AS is defined as an aortic valve area (AVA) <1 cm^2, a mean gradient >40 mmHg and maximum jet velocity >4 m/s.[6,7] However, many patients have discordant findings, mostly with small AVA, but with small gradients. In the PARTNER trials, with centralized echocardiographic evaluation of 951 patients with severe AS, 45% had a low transvalvular gradient.[39] This situation raises uncertainty as regard the severity of AS as well as the indication for intervention.

The entity of severe AS with a low transvalvular gradient has first been recognized in patients with reduced LV ejection fraction (LVEF).[40] In the PARTNER trials, 15% of patients with low LVEF had low-flow, low-gradient AS.[39] In such patients, a small valve area does not definitely confirm severe AS, since mild to moderately diseased valves may not open fully (secondary to the reduced LV function), resulting in a small valve area (pseudo-severe AS) which is not an indication for intervention. Low-dose dobutamine stress echocardiography may be helpful to distinguish severe AS from pseudo-severe AS. In severe AS, the valve area changes minimally during low-dose dobutamine echocardiography, but the gradient increases significantly (mean gradient >40 mmHg) (*Figure 4* and Supplementary material online, *Movie S1*).

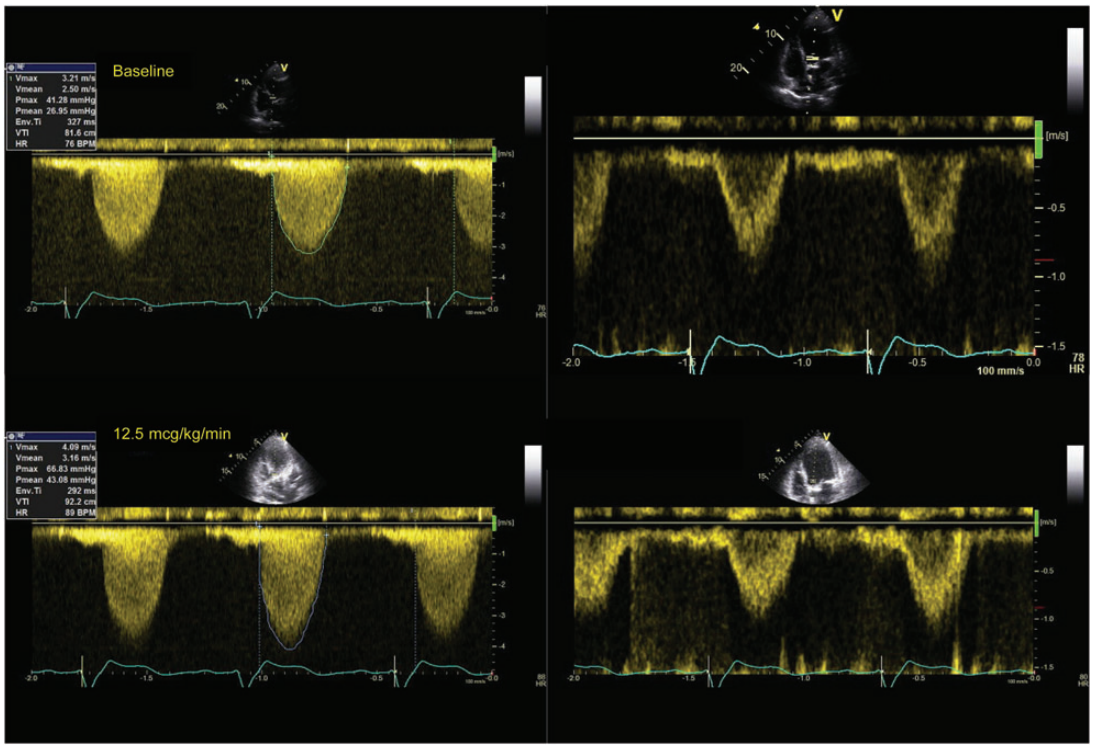

Figure 4 Low-dose dobutamine echocardiography in low-flow low-gradient severe aortic stenosis. Changes in transvalvular gradients and aortic valve area during staged dobutamine infusion: baseline and 12.5 μg/kg/min. During dobutamine infusion the mean gradient increased from 26 to 43 mmHg, the aortic valve area remained unchanged and stroke volume increased by 38%. This indicates that the patient had severe aortic stenosis with low-flow, low-gradient, low ejection fraction and presence of flow reserve (courtesy of Dr Eric Brochet). Env. Ti, envelope time; HR, heart rate; P_{max}, pressure maximum; P_{mean}, pressure mean; V_{max}, aortic maximum jet velocity; V_{mean}, mean jet velocity; VTI, velocity time integral.

More recently, the possibility of severe AS in patients with AVA <1.0 cm^2 and a mean gradient <40 mmHg, despite preserved LVEF, has been suggested, introducing the new entity of paradoxical low-flow (stroke volume index ≤ 35 mL/m^2), low-gradient AS.[41] In the PARTNER trials, 14% of the AS patients had normal LVEF, low-flow, and low-gradient.[39] The management of this subset of AS patients remains challenging.

When confronted with this entity the following steps should be taken: first, potential errors in the measurement of gradient, stroke volume index, AVA should be excluded. Secondly, to eliminate the confounding effect of small body size, calculation of the indexed AVA may be helpful. A value >0.6 cm^2/m^2 indicates moderate AS. Finally, establishing whether the global haemodynamic load is severely increased (i.e. valvulo-arterial impedance) may be of help.[42]

Corroborating methods are useful in cases where echocardiography is technically challenging or inconclusive because of discordant evaluation of severity. Particular attention has recently been given to the evaluation of the degree of valve calcification. Recent studies have emphasized the use of MDCT for the quantification of valvular calcification (*Figure 5*).[43,44] Aortic valve calcification load identifies severe AS accurately (sensitivity 86%, specificity >79%) in men (calcium score threshold ≥ 2065 a.u.) and in women (threshold ≥ 1275 a.u.).[43] Clavel *et al.*[43] applied these criteria to low-flow, low-gradient AS, and showed that at least half of the patients had severe AS irrespective of flow. Multi-detector row computed tomography has the advantage of being a reproducible technique which is flow-independent. Currently, MDCT and low-dose dobutamine echocardiography should not be considered as competitive but rather as complementary techniques (*Figure 6*).

Further studies comparing diagnostic strategies and outcome in patients with low-flow, low-gradient AS are needed to optimally identify and manage these patients. Alternatively, in patients in whom it is difficult to determine the precise AS severity, a symptomatic improvement after balloon valvuloplasty suggests the presence of a severe AS, and TAVI can be beneficial.[45]

Left ventricular systolic dysfunction and outcome

The prevalence of LV systolic dysfunction among patients with severe AS treated with TAVI ranges between 6 and 11%, considering a cut-off value of LVEF ≤ 30%, and between 27 and 46%, if LVEF is between 30 and 50%.[46–48] Left ventricular ejection fraction is an important prognostic factor and is included in current operative risk scores.[8–10] However, the association between LV systolic dysfunction and TAVI procedural risks remains controversial.[48–53] While some studies have shown an increased procedural risk among

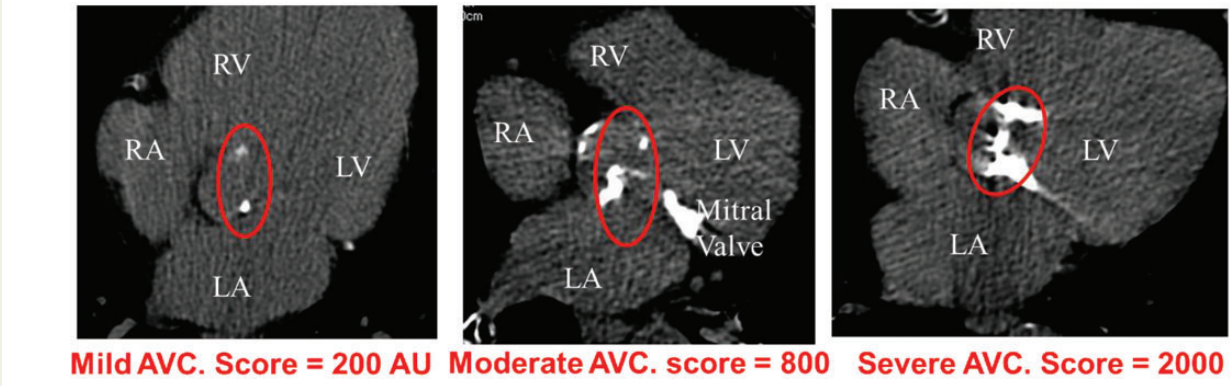

Figure 5 Aortic valve calcification assessment. Calcium scoring using multi-detector row computed tomography. This figure shows three different patients with mild, moderate, or severe aortic valve calcification. The units used are arbitrary units (courtesy of Dr David Messika–Zeitoun). AVC, aortic valve calcification; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

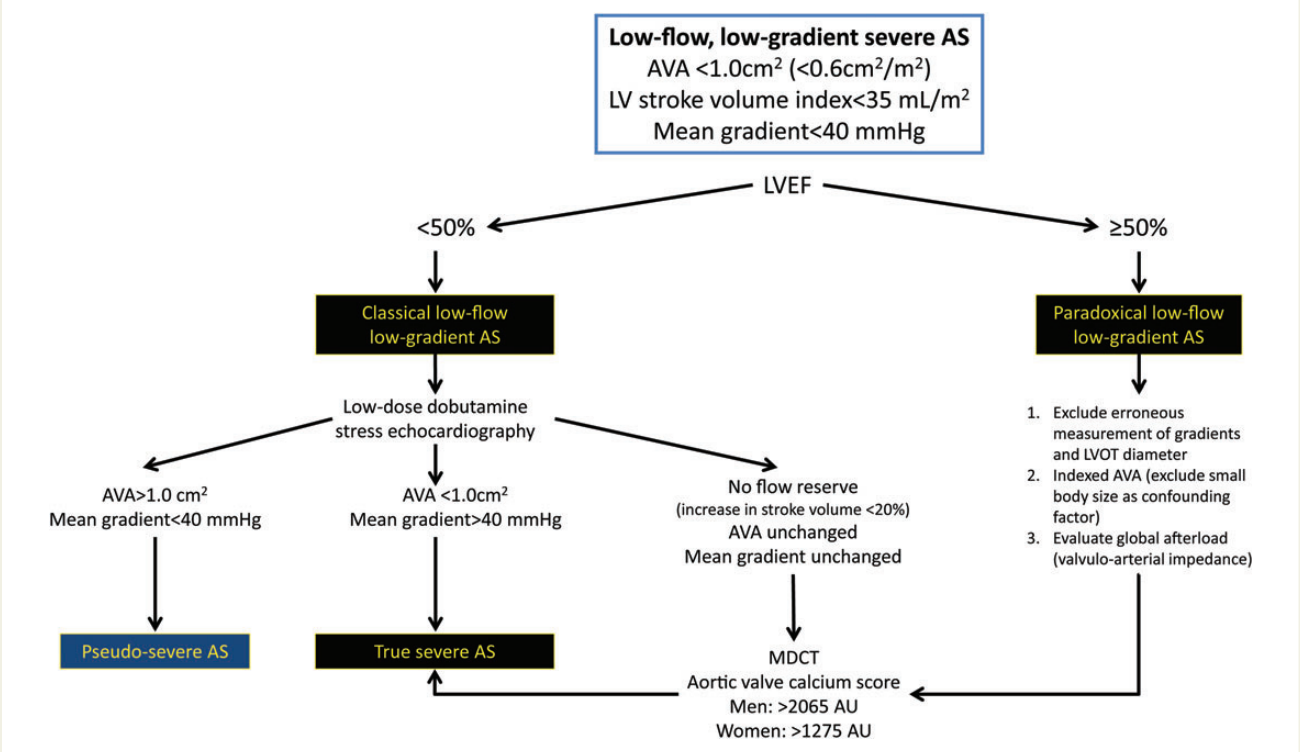

Figure 6 Evaluation of patients with low-flow, low-gradient severe aortic stenosis. AS, aortic stenosis; AU, arbitrary units; AVA, aortic valve area; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MDCT, multi-detector row computed tomography.

patients with low LVEF,[48,53] other series have not confirmed this association.[46,50,51] For example, in the Italian registry including 663 patients undergoing TAVI with the CoreValve system LVEF <40% was independently associated with early mortality.[53] In contrast, data from the Pilot European Sentinel registry, including 4571 patients with 5.7% having an LVEF <30%, did not demonstrate this association.[46] Furthermore, it has been suggested that LVEF may not reflect the extent of myocardial dysfunction in patients with severe AS and concentric LV hypertrophy, whereas stroke volume may be a more comprehensive parameter of the effects of increased afterload on the LV. The recent subanalysis of the PARTNER trial including all cohorts showed that only low-flow (stroke volume index ≤35 mL/m^2) was independently associated with 2-year mortality, whereas low-gradient and low LVEF were not associated.[39]

Importantly, TAVI has also been associated with significant improvement in LVEF at follow-up.[54–59] The majority of series has shown a significant improvement in LVEF early after TAVI (before hospital discharge) which is generally followed by a gradual and sustained improvement at the 1-year follow-up.[54,55,57–59] This improvement in LVEF is associated with a significant and durable improvement in symptoms, functional class and quality of life.[33,48,58,60]

The degree of LVEF improvement is highly variable and depends on several factors. Compared with SAVR, LVEF improves more after TAVI.[55,57] In the randomized PARTNER cohort A trial, LVEF improved earlier with TAVI, although there was no difference between groups at 2 years.[49] It has been suggested that a greater improvement in LV function might be expected with TAVI since this is a less invasive procedure that may minimize myocardial injury and transcatheter aortic valves have superior haemodynamic performance.[61] Other factors associated with changes in LVEF after TAVI include a lower mean aortic valve gradient and a higher baseline LVEF, previous permanent pacemaker, new-onset of a left bundle branch block and pacemaker implantation after TAVI.[62,63] Transcatheter aortic valve implantation access (transfemoral vs. transapical) has been also associated with LVEF improvement in univariate analysis. Elmariah *et al.*[56] showed that transfemoral access was an unadjusted predictor of LVEF improvement, whereas transapical access was not.

Based on this evidence, it seems that TAVI can be performed in patients with LV dysfunction with a modest risk and is associated with marked symptomatic and survival benefit. Important questions for the future include: How can we reduce the risk of TAVI in patients with severe LV dysfunction (LVEF <20%)? How can we predict whether LV function will improve?

Concomitant mitral regurgitation: prevalence, pathophysiology, and impact on outcome

Mild MR is very common in patients with severe AS, being reported in 60–90%, but has in general raised little concern.[64] However, even moderate MR has been reported in up to 74%[65] although other authors reported only 13–17%.[66,67] This variation may be (partially) due to differences in the methodology of MR grading. The high driving pressure in severe AS may easily lead to overestimation of MR severity when using colour flow mapping. Nevertheless, it has to be recognized that the study reporting the highest prevalence used vena contracta width—a less pressure-dependent measure of MR severity—for quantification.[65] Reported prevalence of moderate or severe MR in patients eventually undergoing TAVI ranged between 19 and 33% (*Figure 7*).[33,37,68–72]

Aetiology and pathophysiology

Concomitant MR may have different aetiologies which can have major impact on the response to aortic valve replacement and long-term outcome. Mitral regurgitation is considered functional (secondary MR) in the absence of structural pathology of the mitral valve. In patients with additional CAD, cardiomyopathy or atrial fibrillation with left atrial enlargement, and annulus dilation, functional

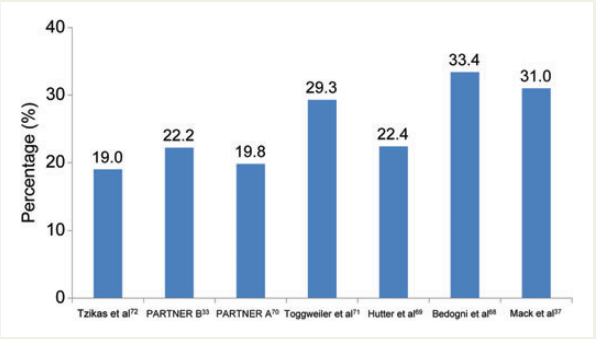

Figure 7 Prevalence of moderate/severe mitral regurgitation in patients undergoing transcatheter aortic valve implantation.

MR may not only be a consequence of AS but may also relate to such concomitant cardiac disease. Annulus calcification is frequently present and it is difficult to decide how much it contributes to the presence of MR and whether to consider MR functional or at least partially structural. Less common, 'degenerative MR' (prolaps/flail) may co-exist as well as post-rheumatic MR or MR after infective endocarditis. Hekimian *et al.*[73] reported in 187 patients referred for TAVI that 32% had functional and 68% organic MR. *Figure 8* summarizes pathophysiological considerations.[64] Left ventricular remodelling and increase in LV pressure caused by AS may generate MR or aggravate co-existing MR of other causes. Mitral regurgitation by itself or by promotion of atrial fibrillation may decrease functional capacity. On the other hand, MR can precipitate diagnostic challenges by reducing forward stroke volume resulting in low-flow, low-gradient AS, or by impeding detection of subclinical myocardial dysfunction due to relative increase in LVEF.[64]

Improvement of mitral regurgitation after transcatheter aortic valve implantation

In 451 patients undergoing TAVI with balloon-expandable Edwards SAPIEN prostheses, 319 had mild or no MR, 89 had moderate, and 43 severe MR.[71] One year after TAVI, among patients with moderate MR at baseline, 58% improved ≥1 grade, 17% remained unchanged and 1% worsened to severe while the remaining 24% of patients had died. Among patients with severe MR at baseline, 49% improved ≥1 grade and 16% remained unchanged at the 1-year follow-up (35% had died). Data from the PARTNER trial cohort A indicated no difference in MR improvement following TAVI vs. SAVR.[49]

Varying results have been reported for the CoreValve system. In 58 patients undergoing TAVI with this device (16 with ≥ mild MR), De Chiara *et al.*[74] found no change in MR in 55%, reduction in 12%, and worsening in 33% of their study population. Similarly, among 79 patients treated with the CoreValve system, Tzikas *et al.*[72] reported improvement in MR severity in 25%, but worsening in 22% and new MR in 42%. Worsening of MR was suspected to be

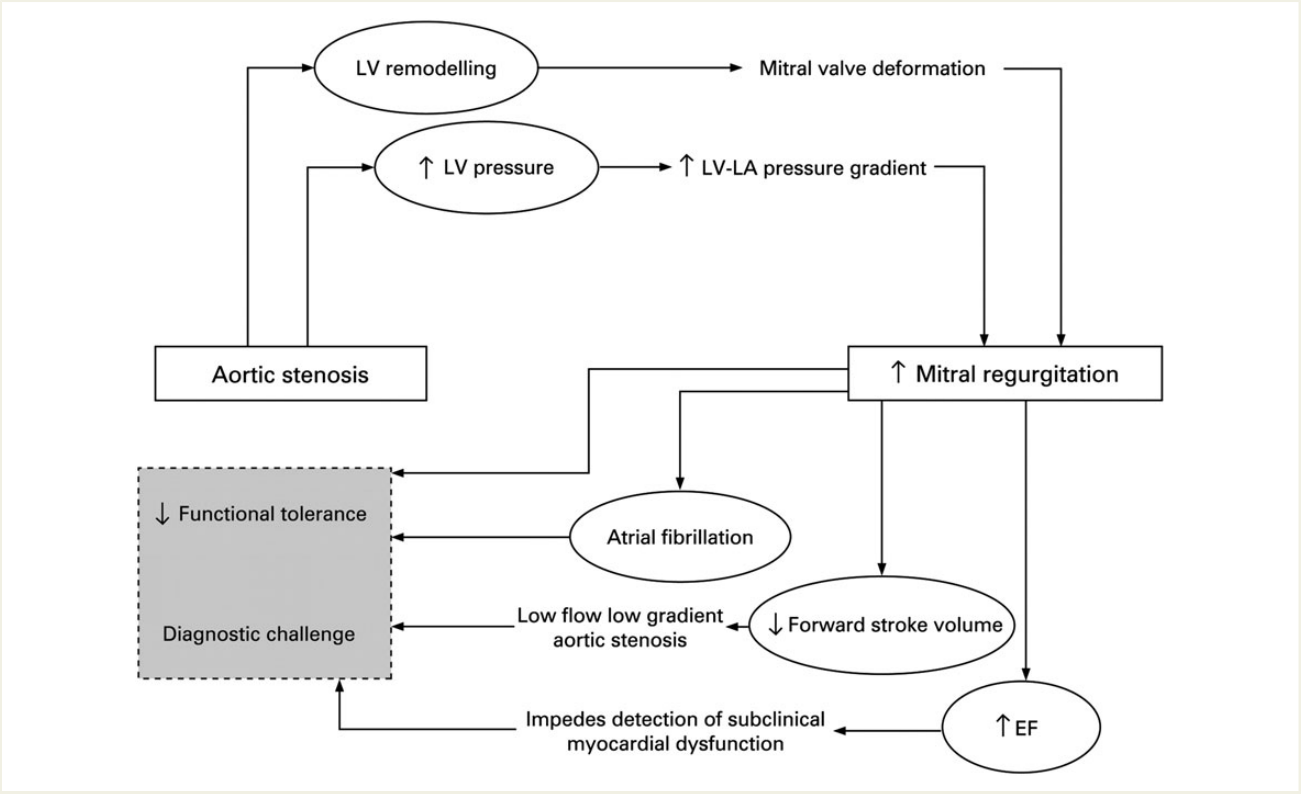

Figure 8 Pathophysiology of concomitant mitral regurgitation in aortic stenosis. See text for explanation (reproduced with permission from Unger *et al.*[64]). EF, ejection fraction; LA, left atrium; LV, left ventricle.

related to deep implantation of the prosthesis in the LV outflow tract.[72] Recent data from the CoreValve Italian registry ($n = 1007$ patients, 337 with ≥moderate MR) showed similar results as those with the Edwards SAPIEN valve: moderate MR improved in 35% and severe MR in 47%.[68]

Improvement of MR can be observed early and late after successful AS intervention (*Figure 9*). Possible mechanisms for the improvement of MR after successful AS intervention are the decrease in LV pressure overload and LV—left atrium gradient but also LV reverse remodelling due to afterload reduction and relieve of (intermittent) ischaemia after revascularization. While improvement caused by LV—left atrium gradient reduction is supposed to occur early, improvement due to LV reverse remodelling should take more time. Interestingly, most improvement in MR was observed within 7 days early after TAVI,[73] with little change between Day 7 and 1 month after TAVI, although LV reverse remodelling was observed at 1 month. Similarly, in the PARTNER trial MR predominantly improved acutely after TAVI.[49]

How to predict improvement in MR after TAVI remains challenging. In patients undergoing TAVI, the baseline mean transvalvular gradient ≥40 mmHg, functional MR, the absence of pulmonary hypertension, and the absence of atrial fibrillation were independently associated with improvement in MR at 1 year.[71] In addition, improvement in MR after balloon valvuloplasty as bridge to TAVI in patients with severe AS and very high risk could suggest a sustained reduction in MR after TAVI.[75]

Impact of mitral regurgitation on outcome after transcatheter aortic valve implantation

After TAVI, patients with moderate or severe MR were reported to have a higher 30-day mortality but similar survival after 1 month.[71] D'Onofrio *et al.*[76] found a trend towards higher hospital mortality in patients with more than mild MR. Hutter *et al.*[69] could not identify moderate or severe MR as an independent predictor of mortality while in the CoreValve Italian registry 30-day and 1-year mortality were significantly increased.[68] In all studies, the MR group had a significantly worse baseline risk profile. Nevertheless, both groups experienced a significant reduction in NYHA functional class, being in class I or II in >90%. In the PARTNER trial,[49] MR at baseline was a predictor of mortality in the group with SAVR but not in the TAVI group although this observation must be interpreted with caution. Moderate MR was present in 17.4% of patients with TAVI and 18.8% in those undergoing SAVR.

Clinically, the most important remaining questions are:

(i) How to identify patients in whom MR will not improve after intervention remains insufficiently solved.
(ii) Whether concomitant moderate/severe MR is an independent predictor of worse outcome after intervention remains controversial.
(iii) Whether intervention on concomitant MR at the time of AVR can improve outcome remains to be shown. The fact that

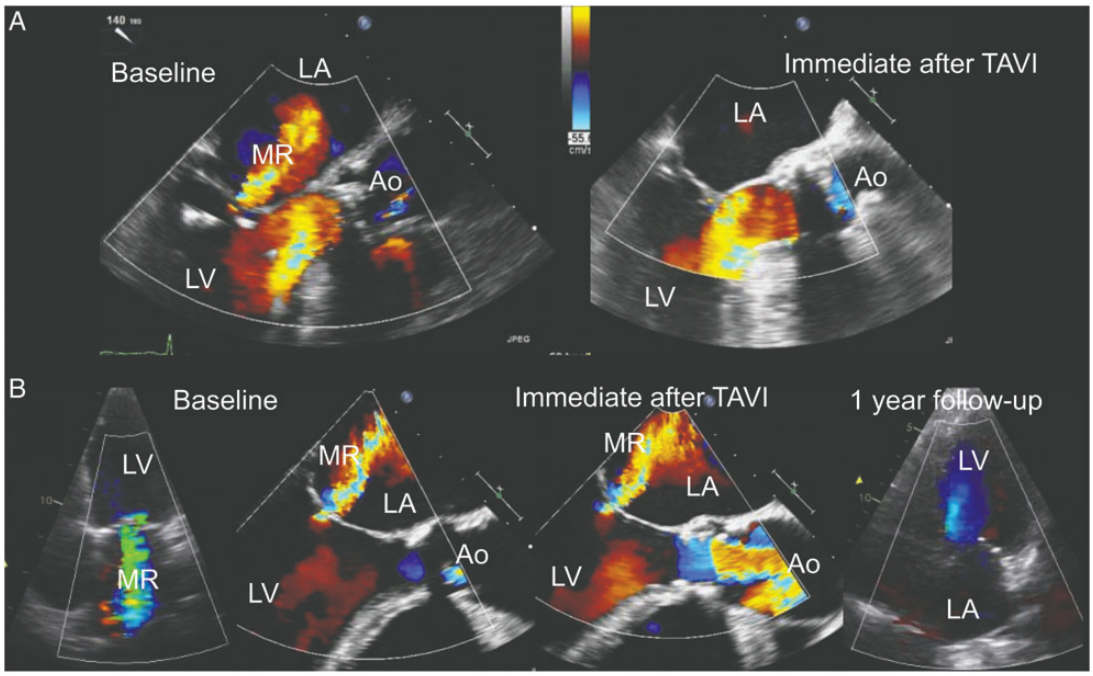

Figure 9 Mitral regurgitation improvement early and late after transcatheter aortic valve implantation. (*A*) Colour-Doppler transoesophageal echocardiography performed during transcatheter aortic valve implantation shows moderate mitral regurgitation in a patient with severe aortic stenosis. Immediately after transcatheter valve deployment, mitral regurgitation resolved. (*B*) Colour-Doppler transthoracic echocardiography showing moderate mitral regurgitation in a patient undergoing transcatheter aortic valve implantation. Periprocedural colour-Doppler transthoracic echocardiography shows unchanged moderate mitral regurgitation after valve deployment. However, at the 1-year follow-up, mitral regurgitation reduced significantly.

additional mitral valve surgery markedly increases the risk of surgery, particularly in the elderly when significant mitral annulus calcification is present, needs to be taken into account in this context.

(iv) Whether TAVI may offer a stepwise approach with either simultaneous or later transcatheter intervention on the mitral valve (when MR remains significant) requires further investigation.

Concomitant coronary artery disease

Concomitant CAD has been reported in >60% of octogenarians undergoing SAVR[77,78] and in 40 to 75% of high-risk patients undergoing TAVI.[79] A meta-analysis of seven observational studies reported no sizeable impact of CAD on mortality in patients undergoing TAVI, but results have to be interpreted with caution due to the inclusion of heterogeneous populations, with advanced age and absence of the long-term follow-up.[80] A detailed analysis of the impact of CAD on prognosis among patients undergoing TAVI originates from a study of 445 patients quantifying CAD using the SYNTAX score.[81] Coronary artery disease was present in 65% of patients and categorized as a low SYNTAX score (0–22) in 47% and as high in 18%. At the 1-year follow-up, patients with a high SYNTAX score had an increased risk of cardiovascular mortality, stroke, and myocardial infarction compared with those with a low SYNTAX score or no CAD (no CAD: 13%, low SYNTAX score: 16%, high SYNTAX score: 30%; $P = 0.02$).[81]

According to European Society of Cardiology/American College of Cardiology/American Heart Association (ESC/ACC/AHA) guidelines on valvular heart disease, all the patients considered for TAVI should undergo diagnostic coronary angiography as part of the routine evaluation to determine the presence and extent of CAD as well as treatment allocation (Class IC).[6,7]

Revascularization by percutaneous coronary intervention (PCI) among patients with severe AS undergoing TAVI has been shown feasible and safe in observational studies.[82–84] In contrast to coronary artery bypass grafting (CABG) at the time of SAVR, PCI among patients undergoing TAVI appears to confer no excess short-term risk of death, myocardial infarction, and stroke compared with isolated TAVI.[82–87] However, the impact of revascularization by PCI on a long-term prognosis and need for revascularization among patients undergoing TAVI is not established. The selection of lesions treated by PCI is usually based on clinical presentation and angiography since functional methods of ischaemia detection have not been validated among patients with severe AS. Some centres are comprehensive and attempt to treat any lesion with a diameter stenosis >50%,[82] whereas others limit treatment to proximal lesions with a diameter stenosis >70%.[84] An even more conservative strategy relies on a clinical follow-up after TAVI to re-assess the

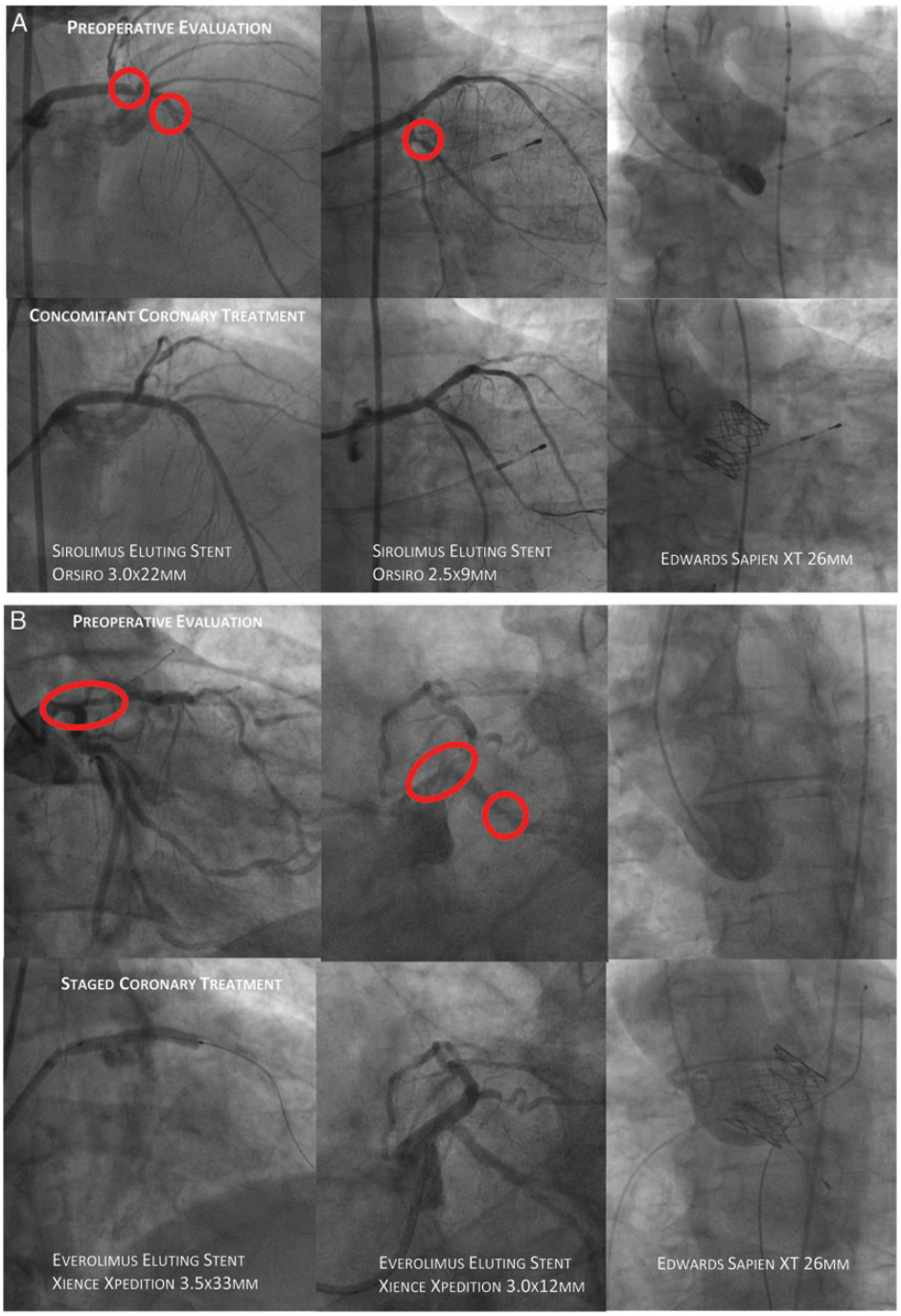

Figure 10 Coronary artery disease in patients undergoing transcatheter aortic valve implantation. (*A*) An 88-year-old man with symptomatic severe aortic stenosis (AVA 0.6 cm^2, mean gradient 35 mmHg) and two vessel coronary artery disease (SYNTAX Score 18) with two serial lesions in the left anterior descending coronary artery and the ostium of the first marginal branch of the left circumflex coronary artery. The STS score was 18% and a logistic EuroSCORE 53%. The patient was accepted for transcatheter aortic valve implantation and concomitant percutaneous coronary intervention. The procedure was performed sequentially. First, the serial left anterior descending coronary artery lesions were treated with a single drug-eluting stent and treatment of the ostial first marginal branch. Second, a 26 mm Edwards SAPIEN XT prosthesis was implanted. (*B*) An 86 year-old man with symptomatic severe aortic stenosis (AVA 0.7 cm^2, mean gradient 37 mmHg), normal left ventricular ejection fraction and significant coronary artery disease with a distal left main and proximal lesion of the LAD coronary artery. Risk score assessment revealed a logistic EuroSCORE of 15.9%, a STS score of 8.2%, and a SYNTAX Score of 23. The patient was accepted for transcatheter aortic valve implantation and staged percutaneous coronary intervention. First, the patient underwent successful percutaneous coronary intervention of the left main and left anterior descending coronary artery lesion by implantation of a drug-eluting stent. Second, the patient underwent transcatheter aortic valve implantation with implantation of a 29 mm Edwards SAPIEN XT prosthesis at the 6-week follow-up.

necessity of coronary intervention depending on symptoms. Of note, revascularization was less likely to be complete among patients undergoing PCI and TAVI with a high SYNTAX score (>22) compared with a low SYNTAX score.[81] However, completeness of revascularization did not impact clinical outcomes in 124 TAVI patients with significant CAD who underwent staged or concomitant PCI in 32% of cases according to a Heart Team decision.[87] In this context, revascularization by means of PCI is not only influenced by the complexity of underlying CAD but also by procedural considerations including the amount of contrast agent particularly among patients with renal failure, duration of the procedure, and leading clinical problem (CAD vs. AS). Another related issue is whether PCI is performed during the same session as TAVI (either before or after TAVI) or staged. While it appears reasonable to perform PCI during the same session as TAVI thereby limiting the number of procedures and access sites, circumstances such as complexity and duration of PCI as well as contrast agent exposure may favour a staged approach (*Figure 10*). Indeed, the flexibility in terms of the timing of PCI relative to the TAVI intervention should be perceived as an advantage in the overall patient management. ACTIVATION (ISRCTN75836930),[88] a prospective trial of 310 patients with CAD and severe AS undergoing TAVI randomly assigned to PCI or medical treatment currently recruits patients and will assess the primary endpoint of all-cause mortality and re-hospitalization at 1 year. Moreover, two randomized clinical trials comparing TAVI and SAVR in intermediate-risk patients (SURTAVI: NCT01586910 and PARTNER II: NCT01314313) also include patients with significant CAD who may undergo CABG in case of SAVR or PCI in case of TAVI as advised by the Heart Team.[89,90] These studies will advance our understanding of the percutaneous when compared with a surgical treatment strategy of patients with combined AS and CAD.

Conclusion

The use of TAVI in patients with severe AS who are not eligible or have high risk for SAVR has increased exponentially over the recent years. In the current article, various areas of uncertainty related to the selection of patients for TAVI were discussed. First, the current risk scores are suboptimal in identifying patients at high risk for SAVR, and improved patient selection for TAVI is needed (and should also take into account improved prediction of outcome after TAVI).

Non-invasive imaging with contemporary techniques is important in patient selection. Adequate assessment of the aortic annulus is important for prosthesis sizing, and 3D techniques such as MDCT have shown that undersizing may lead to AR after TAVI, whereas oversizing may cause annular rupture. Precise definition of valve anatomy is particularly important in bicuspid valves, which often have more extensive calcifications, and MDCT appears the technique of choice. Besides valvular anatomy, the assessment of stenosis severity can also be challenging. Not infrequent, a mismatch between the transvalvular gradient and the AVA is encountered: these patients typically have small AVA with a low gradient. In patients with LV dysfunction, low-dose dobutamine echocardiography may help to differentiate between a true (fixed) stenosis and a pseudo-stenosis (not opening of the valve) due to LV dysfunction. The mismatch between the gradient and the AVA can also be noted in patients with normal LV function, and in these patients a calcium score (derived from CT) may identify patients with a true stenosis.

It has also been recognized that LV function is important for outcome after TAVI, but prediction of reversibility of LV dysfunction after TAVI remains difficult.

Moderate-to-severe MR can be present in up to 33% of patients with severe AS treated with TAVI. Improvement in MR has been shown acutely after TAVI and may be related to the reduction in LV pressure overload; late improvement in MR after TAVI has also been reported and may be related to the LV reverse remodelling with reduction in mitral annular dimensions. Conversely, MR may also persist after TAVI. From the currently available studies, it appears that prediction of improvement is difficult. Moreover, the prognostic value of persistence of MR after TAVI is unclear.

Finally, concomitant CAD is reported in 40–75% of patients referred for TAVI, and the precise management is unclear: should revascularization be performed prior to TAVI? Different studies comparing different strategies are planned and will provide further information on this topic.

In part 2 of this review,[5] areas of uncertainty on procedural issues and outcomes will be discussed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: N.P. is proctor and consultant for Medtronic, P.M. is proctor for Edwards Lifesciences, J.W. disclosed consultant fees from Edwards Lifesciences, V.D. disclosed consulting fees from Medtronic and St. Jude Medical, speaking fees from Abbott Vascular. A.P.K. is member of the steering committee of the SURTAVI trial, P.P. has research contract with Edwards Lifesciences and V-Wave Ltd., C.H. is advisor to Medtronic and received speaker fees from Abbott Vascular and Edwards Lifesciences, M.T. is advisor to Edwards Lifesciences, A.V. received speakers fees from Edwards Lifesciences, H.B. received speaker and consultant fees for Edwards Lifesciences, Direct Flow Medical, Abbott Vascular and Actelion, J.R-C. received consulting fees from Edwards Lifesciences and St. Jude Medical, V.B. is consultant for Edwards, Medtronic and St. Jude Medical. J.P.C. received research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération Française de Cardiologie et Société Française de Cardiologie. The remaining authors have nothing to disclose. The Department of Cardiology of the Leiden University Medical Center received research grants from Medtornic, Boston Scientific and Biotronik. The Department of Cardiac Imaging of the University Hospital Ramon y Cajal received research grants from Philips Healthcare, Siemens and Toshiba. The Department of Cardiology of the Bern University Hospital received research grants from Biotronik and Edwards Lifesciences.

References

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;**106**:3006–3008.

2. Mack MJ, Holmes DR, Webb J, Cribier A, Kodali SK, Williams MR, Leon MB. Patient selection for transcatheter aortic valve replacement. *J Am Coll Cardiol* 2013;**62**: S1–10.
3. Bourantas CV, Van Mieghem NM, Soliman O, Campos CA, Iqbal J, Serruys PW. Transcatheter aortic valve update 2013. *Euro Intervention* 2013;**9**(Suppl):S84–S90.
4. Bax JJ, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R, Hamm C, Kappetein AP, Leipsic J, Leon MB, MacCarthy P, Piazza N, Pibarot P, Roberts WC, Rodés-Cabau J, Serruys PW, Thomas M, Vahanian A, Webb J, Zamorano JL, Windecker S. Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu256.
5. Bax JJ, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R, Hamm C, Kappetein AP, Leipsic J, Leon MB, MacCarthy P, Piazza N, Pibarot P, Roberts WC, Rodés-Cabau J, Serruys PW, Thomas M, Vahanian A, Webb J, Zamorano JL, Windecker S. Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu257.
6. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De BM, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Popescu BA, Von SL, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**: 2451–2496.
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC Guideline 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. *Circulation* 2014;**129**:e521–e643.
8. STS National Database Risk Calculator. **http://www.sts.org/sections/stsnationaldatabase/riskcalculator** (December 2013).
9. Roques F, Nashef SA, Michel P, Gauducheau E, de VC, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999;**15**:816–822.
10. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;**41**:734–744.
11. Barili F, Pacini D, Capo A, Ardemagni E, Pellicciari G, Zanobini M, Grossi C, Shahin KM, Alamanni F, Di Bartolomeo R, Parolari A. Reliability of new scores in predicting perioperative mortality after isolated aortic valve surgery: a comparison with the society of thoracic surgeons score and logistic EuroSCORE. *Ann Thorac Surg* 2013;**95**:1539–1544.
12. Kappetein AP, Head SJ, Genereux P, Piazza N, Van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;**60**:1438–1454.
13. Stahli BE, Tasnady H, Luscher TF, Gebhard C, Mikulicic F, Erhart L, Buhler I, Landmesser U, Altwegg L, Wischnewsky MB, Grunenfelder J, Falk V, Corti R, Maier W. Early and late mortality in patients undergoing transcatheter aortic valve implantation: comparison of the novel EuroScore II with established risk scores. *Cardiology* 2013;**126**:15–23.
14. Iung B, Laouenan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Laskar M, Vahanian A, Gilard M. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart* 2014;**100**:1016–1023.
15. Altiok E, Koos R, Schroder J, Brehmer K, Hamada S, Becker M, Mahnken AH, Almalla M, Dohmen G, Autschbach R, Marx N, Hoffmann R. Comparison of two-dimensional and three-dimensional imaging techniques for measurement of aortic annulus diameters before transcatheter aortic valve implantation. *Heart* 2011;**97**: 1578–1584.
16. Koos R, Altiok E, Mahnken AH, Neizel M, Dohmen G, Marx N, Kuhl H, Hoffmann R. Evaluation of aortic root for definition of prosthesis size by magnetic resonance imaging and cardiac computed tomography: implications for transcatheter aortic valve implantation. *Int J Cardiol* 2012;**158**:353–358.
17. Messika-Zeitoun D, Serfaty JM, Brochet E, Ducrocq G, Lepage L, Detaint D, Hyafil F, Himbert D, Pasi N, Laissy JP, Iung B, Vahanian A. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. *J Am Coll Cardiol* 2010;**55**:186–194.
18. Delgado V, Ng AC, Schuijf JD, van der Kley F, Shanks M, Tops LF, van de Veire NR, de Roos A, Kroft LJ, Schalij MJ, Bax JJ. Automated assessment of the aortic root dimensions with multidetector row computed tomography. *Ann Thorac Surg* 2011;**91**: 716–723.
19. Binder RK, Webb JG, Willson AB, Urena M, Hansson NC, Norgaard BL, Pibarot P, Barbanti M, Larose E, Freeman M, Dumont E, Thompson C, Wheeler M, Moss RR, Yang TH, Pasian S, Hague CJ, Nguyen G, Raju R, Toggweiler S, Min JK, Wood DA, Rodes-Cabau J, Leipsic J. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. *J Am Coll Cardiol* 2013;**62**:431–438.
20. Jilaihawi H, Kashif M, Fontana G, Furugen A, Shiota T, Friede G, Makhija R, Doctor N, Leon MB, Makkar RR. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* 2012; **59**:1275–1286.
21. Jilaihawi H, Doctor N, Kashif M, Chakravarty T, Rafique A, Makar M, Furugen A, Nakamura M, Mirocha J, Gheorghiu M, Stegic J, Okuyama K, Sullivan DJ, Siegel R, Min JK, Gurudevan SV, Fontana GP, Cheng W, Friede G, Shiota T, Makkar RR. Aortic annular sizing for transcatheter aortic valve replacement using cross-sectional 3-dimensional transesophageal echocardiography. *J Am Coll Cardiol* 2013; **61**:908–916.
22. Willson AB, Webb JG, LaBounty TM, Achenbach S, Moss R, Wheeler M, Thompson C, Min JK, Gurvitch R, Norgaard BL, Hague CJ, Toggweiler S, Binder R, Freeman M, Poulter R, Poulsen S, Wood DA, Leipsic J. Three-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol* 2012;**59**:1287–1294.
23. Barbanti M, Yang TH, Rodes CJ, Tamburino C, Wood DA, Jilaihawi H, Blanke P, Makkar RR, Latib A, Colombo A, Tarantini G, Raju R, Binder RK, Nguyen G, Freeman M, Ribeiro HB, Kapadia S, Min J, Feuchtner G, Gurtvich R, Alqoofi F, Pelletier M, Ussia GP, Napodano M, de Brito FSJ, Kodali S, Norgaard BL, Hansson NC, Pache G, Canovas SJ, Zhang H, Leon MB, Webb JG, Leipsic J. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation* 2013;**128**: 244–253.
24. Blanke P, Reinohl J, Schlensak C, Siepe M, Pache G, Euringer W, Geibel-Zehender A, Bode C, Langer M, Beyersdorf F, Zehender M. Prosthesis oversizing in balloon-expandable transcatheter aortic valve implantation is associated with contained rupture of the aortic root. *Circ Cardiovasc Interv* 2012;**5**:540–548.
25. Ng AC, Delgado V, van der Kley F, Shanks M, van de Veire N, Bertini M, Nucifora G, Van Bommel RJ, Tops LF, de Weger A, Tavilla G, de Roos A, Kroft LJ, Leung DY, Schuijf J, Schalij MJ, Bax JJ. Comparison of aortic root dimensions and geometries before and after transcatheter aortic valve implantation by 2- and 3-dimensional transesophageal echocardiography and multislice computed tomography. *Circ Cardiovasc Imaging* 2010;**3**:94–102.
26. Roberts WC, Vowels TJ, Ko JM. Natural history of adults with congenitally malformed aortic valves (unicuspid or bicuspid). *Medicine (Baltimore)* 2012;**91**:287–308.
27. 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**:920–925.
28. Ayad RF, Grayburn PA, Ko JM, Filardo G, Roberts WC. Accuracy of two-dimensional echocardiography in determining aortic valve structure in patients >50 years of age having aortic valve replacement for aortic stenosis. *Am J Cardiol* 2011;**108**: 1589–1599.
29. Buchner S, Hulsmann M, Poschenrieder F, Hamer OW, Fellner C, Kobuch R, Feuerbach S, Riegger GA, Djavidani B, Luchner A, Debl K. Variable phenotypes of bicuspid aortic valve disease: classification by cardiovascular magnetic resonance. *Heart* 2010;**96**:1233–1240.
30. Tanaka R, Yoshioka K, Niinuma H, Ohsawa S, Okabayashi H, Ehara S. Diagnostic value of cardiac CT in the evaluation of bicuspid aortic stenosis: comparison with echocardiography and operative findings. *AJR Am J Roentgenol* 2010;**195**:895–899.
31. Roberts WC, Ko JM. Weights of operatively-excised stenotic unicuspid, bicuspid, and tricuspid aortic valves and their relation to age, sex, body mass index, and presence or absence of concomitant coronary artery bypass grafting. *Am J Cardiol* 2003; **92**:1057–1065.
32. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012;**59**:1200–1254.

33. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
34. Hayashida K, Bouvier E, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Watanabe Y, Farge A, Donzeau-Gouge P, Cormier B, Morice MC. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. *Circ Cardiovasc Interv* 2013;**6**:284–291.
35. Himbert D, Pontnau F, Messika-Zeitoun D, Descoutures F, Detaint D, Cueff C, Sordi M, Laissy JP, Alkhoder S, Brochet E, Iung B, Depoix JP, Nataf P, Vahanian A. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. *Am J Cardiol* 2012;**110**:877–883.
36. Wijesinghe N, Ye J, Rodes-Cabau J, Cheung A, Velianou JL, Natarajan MK, Dumont E, Nietlispach F, Gurvitch R, Wood DA, Tay E, Webb JG. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv* 2010;**3**:1122–1125.
37. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;**310**:2069–2077.
38. Roberts WC, Vowels TJ, Ko JM, Filardo G, Hebeler RF Jr, Henry AC, Matter GJ, Hamman BL. Comparison of the structure of the aortic valve and ascending aorta in adults having aortic valve replacement for aortic stenosis versus for pure aortic regurgitation and resection of the ascending aorta for aneurysm. *Circulation* 2011; **123**:896–903.
39. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation* 2013;**127**:2316–2326.
40. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003;**108**:319–324.
41. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2012;**60**:1259–1267.
42. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J* 2010;**31**:281–289.
43. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal S, Malouf J, Araoz P, Michelena H, Cueff C, Larose E, Capoulade R, Vahanian A, Enriquez-Sarano M. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler-Echocardiographic and Computed Tomographic Study. *J Am Coll Cardiol* 2013;**62**:2329–2338.
44. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, Duval X, Iung B, Enriquez-Sarano M, Vahanian A, Messika-Zeitoun D. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart* 2011;**97**:721–726.
45. Eltchaninoff H, Durand E, Borz B, Furuta A, Bejar K, Canville A, Farhat A, Fraccaro C, Godin M, Tron C, Sakhuja R, Cribier A. Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: acute and long-term outcomes. *Am Heart J* 2014;**167**:235–240.
46. Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P, Wenaweser P, Zembala M, Nickenig G, Alegria BE, Snow T, Iung B, Zamorano P, Schuler G, Corti R, Alfieri O, Prendergast B, Ludman P, Windecker S, Sabate M, Gilard M, Witowski A, Danenberg H, Schroeder E, Romeo F, Macaya C, Derumeaux G, Maggioni A, Tavazzi L. The 2011–12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. *EuroIntervention* 2013;**8**:1362–1371.
47. Hamm CW, Mollmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, Cremer J, Kuck KH, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Bohm M, Heusch G, Funkat AK, Meinertz T, Neumann T, Papoutsis K, Schneider S, Welz A, Mohr FW. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014;**35**:1588–1598.
48. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;**58**:2130–2138.
49. Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Gopalakrishnan D, Keane MG, Anwaruddin S, Wang Z, Bilsker M, Lindman BR, Herrmann HC, Kodali SK, Makkar R, Thourani VH, Svensson LG, Akin JJ, Anderson WN, Leon MB, Douglas PS. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (placement of aortic transcatheter valves). *J Am Coll Cardiol* 2013;**61**:2514–2521.
50. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695.
51. Lauten A, Zahn R, Horack M, Sievert H, Linke A, Ferrari M, Harnath A, Grube E, Gerckens U, Kuck KH, Sack S, Senges J, Figulla HR. Transcatheter aortic valve implantation in patients with low-flow, low-gradient aortic stenosis. *JACC Cardiovasc Interv* 2012;**5**:552–559.
52. Le Ven F, Freeman M, Webb J, Clavel MA, Wheeler M, Dumont E, Thompson C, De Larochellière R, Moss R, Doyle D, Ribeiro HB, Urena M, Nombela-Franco L, Rodes-Cabau J, Pibarot P. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol* 2013;**62**: 782–788.
53. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;**123**:299–308.
54. Bauer F, Lemercier M, Zajarias A, Tron C, Eltchaninoff H, Cribier A. Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis: the Cribier-Edwards/Edwards-Sapien valve experience. *J Am Soc Echocardiogr* 2010;**23**:370–376.
55. Clavel MA, Webb JG, Rodes-Cabau J, Masson JB, Dumont E, De LR, Doyle D, Bergeron S, Baumgartner H, Burwash IG, Dumesnil JG, Mundigler G, Moss R, Kempny A, Bagur R, Bergler-Klein J, Gurvitch R, Mathieu P, Pibarot P. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation* 2010;**122**:1928–1936.
56. Elmariah S, Palacios IF, McAndrew T, Hueter I, Inglessis I, Baker JN, Kodali S, Leon MB, Svensson L, Pibarot P, Douglas PS, Fearon WF, Kirtane AJ, Maniar HS, Passeri JJ. Outcomes of Transcatheter and Surgical Aortic Valve Replacement in High-Risk Patients With Aortic Stenosis and Left Ventricular Dysfunction: Results From the Placement of Aortic Transcatheter Valves (PARTNER) Trial (Cohort A). *Circ Cardiovasc Interv* 2013;**6**:604–614.
57. Ewe SH, Ajmone MN, Pepi M, Delgado V, Tamborini G, Muratori M, Ng AC, van der Kley F, de Weger A, Schalij MJ, Fusari M, Biglioli P, Bax JJ. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. *Am Heart J* 2010;**160**: 1113–1120.
58. Fraccaro C, Al-Lamee R, Tarantini G, Maisano F, Napodano M, Montorfano M, Frigo AC, Iliceto S, Gerosa G, Isabella G, Colombo A. Transcatheter aortic valve implantation in patients with severe left ventricular dysfunction: immediate and mid-term results, a multicenter study. *Circ Cardiovasc Interv* 2012;**5**:253–260.
59. Pilgrim T, Wenaweser P, Meuli F, Huber C, Stortecky S, Seiler C, Zbinden S, Meier B, Carrel T, Windecker S. Clinical outcome of high-risk patients with severe aortic stenosis and reduced left ventricular ejection fraction undergoing medical treatment or TAVI. *PLoS One* 2011;**6**:e27556.
60. Gotzmann M, Rahlmann P, Hehnen T, Muller P, Lindstaedt M, Mugge A, Ewers A. Heart failure in severe aortic valve stenosis: prognostic impact of left ventricular ejection fraction and mean gradient on outcome after transcatheter aortic valve implantation. *Eur J Heart Fail* 2012;**14**:1155–1162.
61. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De LR, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodes-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol* 2009;**53**:1883–1891.
62. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodes-Cabau J, Szeto WY, Jilaihawi H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J* 2014;**35**:1599–1607.
63. Biner S, Michowitz Y, Leshem-Rubinow E, Topilsky Y, Ben-Assa E, Shimiaie J, Banai S, Keren G, Steinvil A, Finkelstein A. Hemodynamic impact and outcome of permanent pacemaker implantation following transcatheter aortic valve implantation. *Am J Cardiol* 2014;**113**:132–137.
64. Unger P, Dedobbeleer C, Van CG, Plein D, Cosyns B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. *Heart* 2010;**96**: 9–14.

65. Waisbren EC, Stevens LM, Avery EG, Picard MH, Vlahakes GJ, Agnihotri AK. Changes in mitral regurgitation after replacement of the stenotic aortic valve. *Ann Thorac Surg* 2008;**86**:56–62.
66. Barreiro CJ, Patel ND, Fitton TP, Williams JA, Bonde PN, Chan V, Alejo DE, Gott VL, Baumgartner WA. Aortic valve replacement and concomitant mitral valve regurgitation in the elderly: impact on survival and functional outcome. *Circulation* 2005; **112**:I443–I447.
67. Ruel M, Kapila V, Price J, Kulik A, Burwash IG, Mesana TG. Natural history and predictors of outcome in patients with concomitant functional mitral regurgitation at the time of aortic valve replacement. *Circulation* 2006;**114**:I541–I546.
68. Bedogni F, Latib A, De MF, Agnifili M, Oreglia J, Pizzocri S, Latini RA, Lanotte S, Petronio AS, De CM, Ettori F, Fiorina C, Poli A, Cirri S, De SS, Ramondo A, Tarantini G, Marzocchi A, Fiorilli R, Klugmann S, Ussia GP, Tamburino C, Maisano F, Brambilla N, Colombo A, Testa L. Interplay between mitral regurgitation and transcatheter aortic valve replacement with the CoreValve Revalving System: a multicenter registry. *Circulation* 2013;**128**:2145–2153.
69. Hutter A, Bleiziffer S, Richter V, Opitz A, Hettich I, Mazzitelli D, Ruge H, Lange R. Transcatheter aortic valve implantation in patients with concomitant mitral and tricuspid regurgitation. *Ann Thorac Surg* 2013;**95**:77–84.
70. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
71. Toggweiler S, Boone RH, Rodes-Cabau J, Humphries KH, Lee M, Nombela-Franco L, Bagur R, Willson AB, Binder RK, Gurvitch R, Grewal J, Moss R, Munt B, Thompson CR, Freeman M, Ye J, Cheung A, Dumont E, Wood DA, Webb JG. Transcatheter aortic valve replacement: outcomes of patients with moderate or severe mitral regurgitation. *J Am Coll Cardiol* 2012;**59**:2068–2074.
72. Tzikas A, Piazza N, van Dalen BM, Schultz C, Geleijnse ML, van Geuns RJ, Galema TW, Nuis RJ, Otten A, Gutierrez-Chico JL, Serruys PW, de Jaegere PP. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;**75**:43–49.
73. Hekimian G, Detaint D, Messika-Zeitoun D, Attias D, Iung B, Himbert D, Brochet E, Vahanian A. Mitral regurgitation in patients referred for transcatheter aortic valve implantation using the Edwards Sapien prosthesis: mechanisms and early postprocedural changes. *J Am Soc Echocardiogr* 2012;**25**:160–165.
74. De Chiara B, Moreo A, De Marco F, Musca F, Oreglia J, Lobiati E, Bruschi G, Belli O, Mauri F, Klugmann S. Influence of CoreValve ReValving System implantation on mitral valve function: an echocardiographic study in selected patients. *Catheter Cardiovasc Interv* 2011;**78**:638–644.
75. Saia F, Marrozzini C, Ciuca C, Guastaroba P, Taglieri N, Palmerini T, Bordoni B, Moretti C, Dall'ara G, Branzi A, Marzocchi A. Emerging indications, in-hospital and long-term outcome of balloon aortic valvuloplasty in the transcatheter aortic valve implantation era. *EuroIntervention* 2013;**8**:1388–1397.
76. D'Onofrio A, Gasparetto V, Napodano M, Bianco R, Tarantini G, Renier V, Isabella G, Gerosa G. Impact of preoperative mitral valve regurgitation on outcomes after transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2012;**41**:1271–1276.
77. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000;**35**:747–756.
78. Roberts WC, Ko JM, Garner WL, Filardo G, Henry AC, Hebeler RF Jr, Matter GJ, Hamman BL. Valve structure and survival in octogenarians having aortic valve replacement for aortic stenosis (+/− aortic regurgitation) with versus without coronary artery bypass grafting at a single US medical center (1993 to 2005). *Am J Cardiol* 2007;**100**:489–495.
79. Goel SS, Ige M, Tuzcu EM, Ellis SG, Stewart WJ, Svensson LG, Lytle BW, Kapadia SR. Severe aortic stenosis and coronary artery disease--implications for management in the transcatheter aortic valve replacement era: a comprehensive review. *J Am Coll Cardiol* 2013;**62**:1–10.
80. D'Ascenzo F, Conrotto F, Giordana F, Moretti C, D'Amico M, Salizzoni S, Omede P, La Torre M, Thomas M, Khawaja Z, Hildick-Smith D, Ussia G, Barbanti M, Tamburino C, Webb J, Schnabel RB, Seiffert M, Wilde S, Treede H, Gasparetto V, Napodano M, Tarantini G, Presbitero P, Mennuni M, Rossi ML, Gasparini M, Biondi ZG, Lupo M, Rinaldi M, Gaita F, Marra S. Mid-term prognostic value of coronary artery disease in patients undergoing transcatheter aortic valve implantation: a meta-analysis of adjusted observational results. *Int J Cardiol* 2013;**168**:2528–2532.
81. Stefanini GG, Stortecky S, Cao D, Rat-Wirtzler J, O'Sullivan CJ, Gloekler S, Buellesfeld L, Khattab AA, Nietlispach F, Pilgrim T, Huber C, Carrel T, Meier B, Juni P, Wenaweser P, Windecker S. Coronary artery disease severity and aortic stenosis: clinical outcomes according to Syntax-score in patients undergoing transcatheter aortic valve implantation. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu074.
82. Abdel-Wahab M, Mostafa AE, Geist V, Stocker B, Gordian K, Merten C, Richardt D, Toelg R, Richardt G. Comparison of outcomes in patients having isolated transcatheter aortic valve implantation versus combined with preprocedural percutaneous coronary intervention. *Am J Cardiol* 2012;**109**:581–586.
83. Goel SS, Agarwal S, Tuzcu EM, Ellis SG, Svensson LG, Zaman T, Bajaj N, Joseph L, Patel NS, Aksoy O, Stewart WJ, Griffin BP, Kapadia SR. Percutaneous coronary intervention in patients with severe aortic stenosis: implications for transcatheter aortic valve replacement. *Circulation* 2012;**125**:1005–1013.
84. Wenaweser P, Pilgrim T, Guerios E, Stortecky S, Huber C, Khattab AA, Kadner A, Buellesfeld L, Gloekler S, Meier B, Carrel T, Windecker S. Impact of coronary artery disease and percutaneous coronary intervention on outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention* 2011;**7**:541–548.
85. Conradi L, Seiffert M, Franzen O, Baldus S, Schirmer J, Meinertz T, Reichenspurner H, Treede H. First experience with transcatheter aortic valve implantation and concomitant percutaneous coronary intervention. *Clin Res Cardiol* 2011;**100**:311–316.
86. Pasic M, Dreysse S, Unbehaun A, Buz S, Drews T, Klein C, D'Ancona G, Hetzer R. Combined elective percutaneous coronary intervention and transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg* 2012;**14**:463–468.
87. Van Mieghem NM, van der Boon RM, Faqiri E, Diletti R, Schultz C, van Geuns RJ, Serruys PW, Kappetein AP, van Domburg RT, de Jaegere PP. Complete revascularization is not a prerequisite for success in current transcatheter aortic valve implantation practice. *JACC Cardiovasc Interv* 2013;**6**:867–875.
88. Thomas M. PercutAneous Coronary inTerventIon prior to transcatheter aortic VAlve implantaTION: a randomised controlled trial (ACTIVATION). **http://www.controlled-trials.com/ISRCTN75836930/** (December 2013).
89. 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). **http://www.clinicaltrials.gov/ct2/show/NCT01586910?term=SURTAVI&rank=1** (December 2013).
90. The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves. **http://www.clinicaltrials.gov/ct2/show/NCT01314313?term=NCT01314313&rank=** (December 2013).