Original article

Clinical impact of acute kidney injury on short- and long-term outcomes after transcatheter aortic valve implantation with the CoreValve prosthesis

CrossMark

Antonio J. Muñoz-García (MD, PhD)*, Erika Muñoz-García (MD),
Manuel F. Jiménez-Navarro (MD, PhD), Antonio J. Domínguez-Franco (MD),
Juan H. Alonso-Briales (MD, PhD), José M. Hernández-García (MD, PhD),
Eduardo de Teresa-Galván (MD, PhD) RIC Investigators

Department of Cardiology, Instituto de Biomedicina de Málaga (IBIMA), Virgen de la Victoria Clinical University Hospital, Málaga, University of Málaga, Spain

ARTICLE INFO

ABSTRACT

Background: Acute kidney injury (AKI) after cardiac surgery is associated with increased mortality, but few data exist on the occurrence and clinical impact of AKI associated with transcatheter aortic valve implantation (TAVI). The objective of this study was to determine the incidence and prognosis of AKI after percutaneous implantation of the CoreValve® (Medtronic, Minneapolis, MN, USA) prosthesis.
Methods: A total of 357 patients with severe aortic stenosis and 9 patients with pure native aortic regurgitation were treated with the CoreValve prosthesis. AKI was defined according to Valve Academic Research Consortium criteria as the absolute increase in serum creatinine ≥ 0.3 mg/dl at 72 h post percutaneous procedure.
Results: AKI was identified in 58 patients (15.8%), none of whom required renal replacement therapy. In patients with AKI, the mortality at 30 days was 13.5% compared with 1.6% of patients without AKI, [odds ratio (OR) = 12.2 (95% CI 3.53–41.9); $p < 0.001$] and total mortality after a mean of 26.2 ± 17 months was 29.3% vs. 14.9% [OR = 2.36 (95% CI 1.23–4.51), $p = 0.008$]. In the multivariate analysis, AKI was an independent predictor of cumulative total mortality [hazard ratio = 2.151, (95% CI from 1.169 to 3.957), $p = 0.014$].
Conclusions: The deterioration of renal function in patients undergoing TAVI with the CoreValve prosthesis is a serious and frequent complication. The occurrence of AKI was associated with increased early mortality and was also a predictor of worse outcomes in follow-up.

© 2014 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

The incidence of acute kidney injury (AKI) is a serious complication in patients with severe aortic stenosis undergoing valve replacement surgery, with an incidence between 1% and 30%, depending on the definition used [1]. In addition, it is associated with high mortality [2]. AKI can occur in different clinical scenarios, such as transcatheter aortic valve implantation (TAVI), which has become an alternative therapeutic option for patients with severe aortic stenosis considered at high surgical risk [3,4]. Some studies suggest that TAVI is an effective and safe method to treat kidney transplant recipients who have aortic stenosis, and it is associated with lower morbidity and mortality compared to conventional open-heart surgery [5]. However, few data exist on the impact of AKI on clinical outcome.

The objective of this study was to determine the occurrence and prognosis of AKI on short- and long-term outcomes after percutaneous implantation of the CoreValve® (Medtronic, Minneapolis, MN, USA) aortic valve prosthesis in patients with aortic stenosis who are considered at high surgical risk.

Materials and methods

Between April 2008 and December 2013, 363 patients with symptomatic aortic valve stenosis and 9 patients with pure native aortic valve regurgitation who were considered high-risk or

* Corresponding author at: Department of Cardiology Hospital Clínico Universitario Virgen de la Victoria, Campus de Teatinos s/n, 29010 Málaga, Spain. Tel.: +34 952300525; fax: +34 952300525.
 E-mail address: ajmunozgarcia@secardiologia.es (A.J. Muñoz-García).

non-surgical candidates underwent implantation with the Cor-eValve prosthesis. AKI was defined according to the Valve Academic Research Consortium (VARC) criteria [6], as the absolute increase in serum creatinine ≥ 0.3 mg/dl or an increase of over 50% at 72 h post-procedure.

From our analysis, we excluded two patients with preoperative renal replacement therapy and four patients who died during procedure due to left ventricular perforation, iatrogenic dissection of left main coronary artery, electromechanical dissociation, or cardiogenic shock prior to prosthesis implantation.

All patients underwent a systematic determination of serum creatinine and an estimated glomerular filtration rate (eGFR) calculation based on the simplified modification of diet in renal disease (MDRD) formula 24 h prior to procedure, 72 h after TAVI, and at 6 months following the procedure.

Chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2, equivalent to CKD stage ≥ 3 according to the Kidney Disease Outcome Quality Initiative [7].

We routinely used a prophylactic treatment with N-acetylcys-teine, and patients with preprocedural CKD received intravenous hydration before the procedure, for the prevention of contrast-induced nephropathy. The contrast medium used in all TAVI procedures was iodixanol 320 mg of iodine/ml (Visipaque, GE Healthcare, Cork, Ireland), which is a non-ionic, iso-osmolar, dimetric type of contrast medium.

Statistical analysis

The data are expressed as the mean $\pm$ standard deviation for continuous variables and as the absolute number and percentage for categorical variables. A basic descriptive analysis and a survival analysis were performed with the Kaplan–Meier method. Qualitative variables were compared using the χ^2 or Fisher's test, and the Student t test was used for continuous variables according to their distribution. A stepwise logistic regression analysis including significant variables in the univariate analysis was used to determine independent predictors of AKI. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). A multivariate analysis was made with Cox regression analysis to identify the variables related with late mortality and performed stepwise to show the association of the various risk factors more clearly. This model included those variables that were significant ($p < 0.05$) in the univariate analysis. Results are presented as a hazard ratio (HR) with 95% CI. Significance was set at $p < 0.05$. The data were analyzed with SPSS version 15.0 (Chicago, IL, USA).

Results

AKI was identified in 58 patients (15.8%), none of whom required renal replacement therapy. After implantation there was a slight improvement in renal function, baseline serum creatinine decreased from 1.29 ± 0.5 mg/dl to 1.20 ± 0.5 mg/dl ($p = 0.001$), eGFR increased from 48.9 ± 20 mL/min/1.73 m^2 to 52.7 ± 22 mL/min/1.73 m^2 ($p = 0.001$) and remained stable at 6 months following procedure (creatinine 1.21 ± 0.4 mg/dl and eGFR 50.25 ± 19 mL/min/1.73 m^2). There were no differences in the amount of contrast medium received (176 ± 64 cm^3 for patients with AKI vs. 169 ± 67 cm^3 for patients without AKI, $p = 0.470$). The serum creatinine improved in patients with CKD, slightly decreasing from 1.96 ± 0.4 mg/dl to 1.74 ± 0.5 mg/dl, $p = 0.001$, with an increase in eGFR from 32.6 ± 13 mL/min/1.73 m^2 to 37.2 ± 17 mL/min/1.73 m^2. The factors associated with the development of AKI are shown in Table 1 and the only independent predictors for AKI after TAVI were prior stroke [OR 2.42, (95% CI 1.175–4.985), $p = 0.017$] and the presence of pure native aortic regurgitation [OR 4.642 (95% CI 1.106–19.49), $p = 0.036$].

Table 1

Baseline and periprocedural characteristics of patients undergoing TAVI, according to the occurrence of post-procedural AKI.

	Without AKI $N = 308$	AKI $N = 58$	p value
Age (years)	79.2 ± 6.4	79.9 ± 4.5	0.444
Sex (male)	122 (39.6%)	28 (48.3%)	0.218
Cardiovascular risk factor			
Hypertension	254 (82.5%)	47 (84%)	0.793
Diabetes mellitus	133 (43.2%)	17 (29.3%)	0.058
Hyperlipidemia	160 (51.9%)	29 (50%)	0.785
Smoker	73 (23.7%)	14 (24.1%)	0.943
Coronary artery disease	121 (39.3%)	26 (44.8%)	0.430
Acute myocardial infarction	52 (16.9%)	7 (12.1%)	0.360
CABG	25 (8.1%)	7 (12.1%)	0.328
PCI	87 (28.2%)	16 (27.6%)	0.918
Frailty, n (%)	49 (15.9%)	5 (8.6%)	0.151
Charlson index, mean $\pm$ SD	3.4 ± 1.8	3.6 ± 2	0.517
Logistic EuroSCORE (%)	18 ± 11	18.3 ± 14	0.849
I. Karnofsky, mean $\pm$ SD	60.2 ± 19	62.7 ± 19	0.364
Prior stroke	36 (11.7%)	16 (27.6%)	0.001
Porcelain aorta	23 (7.5%)	5 (8.6%)	0.762
Extracardiac arteriopathy	49 (16%)	12 (20.7%)	0.376
NYHA class functional III–IV	270 (87.7%)	49 (84.5%)	0.126
COPD	109 (35.4%)	20 (34.5%)	0.894
Pure native aortic regurgitation	5 (1.6%)	4 (6.9%)	0.017
Pre-procedural creatinine (mg/dl)	1.28 ± 0.4	1.29 ± 0.9	0.928
Glomerular filtration rate	49.01 ± 21	48.3 ± 19.1	0.822
Chronic kidney disease stage	68 (22.1%)	14 (24.1%)	0.730
Echocardiographic parameters			
LVEF (%), mean $\pm$ SD	60.2 ± 15	61.7 ± 13.4	0.479
LVEF < 40%	55 (17.9%)	8 (13.8%)	0.452
Moderate or severe MR	67 (21.7%)	8 (13.7%)	0.239
Moderate or severe AR	116 (37.3%)	20 (34.5%)	0.868
Pulmonary hypertension	58 (20%)	8 (13.7%)	0.752
Treatment			
Diuretics	281 (91.2%)	55 (94.8%)	0.360
Calcium antagonist	49 (15.9%)	9 (15.5%)	0.940
Beta-blockers	136 (44.3%)	28 (48.3%)	0.577
ACE inhibitors	180 (58.6%)	38 (65.5%)	0.327
Digoxin	33 (10.7%)	4 (6.9%)	0.373
Procedure			
Time of procedure (minutes)	101.5 ± 36	109 ± 44	0.130
Access site			
Trans-femoral	277 (89.9%)	49 (84.5%)	
Trans-subclavian	30 (9.7%)	8 (13.8%)	0.342
Direct trans-aortic	1 (0.3%)	1 (1.7%)	
General anesthesia	26 (8.4%)	6 (10.3%)	0.638
Pre-dilatation	253 (84.3%)	47 (81%)	0.840
Prosthesis			
23 mm	4 (1.3%)	1 (1.8%)	
26 mm	186 (60.4%)	26 (45.6%)	0.128
29 mm	107 (34.7%)	29 (50.9%)	
31 mm	11 (3.6%)	1 (1.8%)	
Post-dilatation	83 (26.9%)	17 (29.3%)	0.711
Valve in valve	14 (4.5%)	5 (8.8%)	0.187
AR post-TAVI $\geq 2+$ Sellers	73 (23.8%)	19 (32.8%)	0.028
New onset LBBB	100 (46.7%)	19 (51.4%)	0.607
Required pacemaker implantation	71 (24.9%)	20 (37.7%)	0.053
Red blood cell transfusion	95 (32.4%)	19 (35.2%)	0.691

TAVI, transcatheter aortic valve implantation; AKI, acute kidney injury; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AR, aortic regurgitation; ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; LBBB, Left Bundle Branch Block.

In patients with AKI, mortality at 30 days was 13.8% compared with 1.3% of patients without AKI, $p = 0.001$; total mortality after a mean of 26.2 ± 17 months was 29.3% in patients with AKI compared with 14.9% in those without AKI, $p = 0.008$.
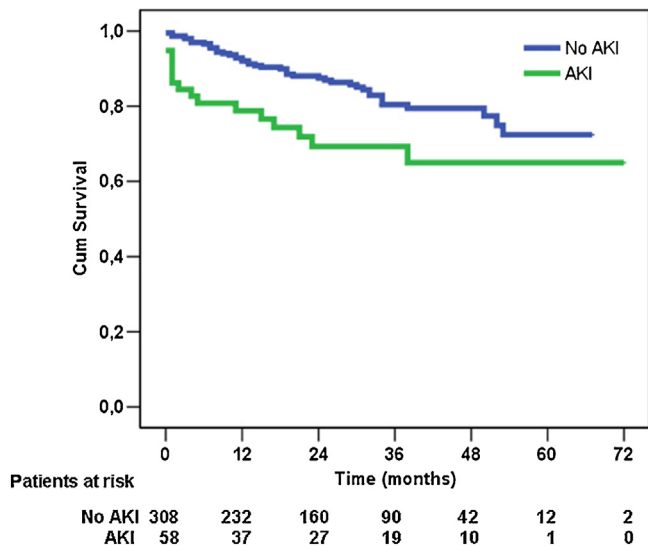
Fig. 1. Comparative analysis between survival in patients with and without AKI after transcatheter aortic valve implantation (using Kaplan–Meier survival curves), log-rank test = 7.89; $p < 0.005$. AKI, acute kidney injury; Cum, cumulative.

Survival at 12 and 24 months was 92.8% and 87.4% respectively in patients without AKI compared with 78.8% and 69.3% in patients with AKI (Fig. 1).

In the multivariate analysis, AKI was an independent predictor of cumulative total mortality (Table 2).

Discussion

In the present study, we show that the AKI group had higher mortality at 30 days compared with the group without AKI and also that AKI was a strong independent predictor of late mortality.

In our study, AKI, based on VARC definition, occurred in 15.8% of patients undergoing TAVI, which is similar to percentages reported by other series [8–10], but in our series no patient required renal replacement therapy.

Khawaja et al. [11] reported that the incidence of AKI in a series of 248 patients was 35.9%, with 10% requiring dialysis. This different incidence reported is probably due to the different baseline characteristics of the patients: 18.1% of patients were in stage 4 or 5 of CKD and there are important differences based on the approaches used to implant the prosthesis (43.1% trans-femoral, 41.5% trans-apical, and 15.3% trans-aortic), compared with our study (89.1% trans-femoral, 10.3% trans-subclavian, and 0.5% trans-aortic). Recently, Saia et al. [12] reported similar results: the incidence of AKI was 41.7% and there were differences according to the approaches used, so the trans-apical access might have contributed to the higher rate of AKI in these studies.

Nevertheless, the mechanisms of renal damage after TAVI are probably multifactorial, and the predictive factors of renal injury

after TAVI have not been well defined; some studies identify hypertension and chronic obstructive pulmonary disease as significant risk factors for AKI [8]. In our series only prior stroke was associated with the development of AKI and it is likely that these patients had more peripheral arterial disease, with a higher risk of embolization of atheromatous plaques, than patients with pure native aortic regurgitation; it is possible that the critical clinical state of these patients pre-procedure influenced the renal perfusion. The need for red blood cell transfusion is a well-recognized predictor of AKI after TAVI and following cardiac surgery in most series [8,9]. However, this was not confirmed in our study; it is possible that the effect of blood transfusion on the development of AKI depends on the number of units used. In the present study this was 1.8 ± 2 units compared with 3.6 ± 4.3 units in the series where blood transfusion was a predictor of AKI [8].

An interesting finding of this study was that the number of patients with aortic regurgitation AR post-TAVI > 2+ Sellers was higher in the AKI group than in the group without AKI. In addition, pure native aortic valve regurgitation is associated with an increased risk of developing AKI after TAVI. This is an important finding because AR is a strong independent predictor of mortality in the TAVI population in most series [13–15]. Acute AR could be associated with a negative impact on left ventricular function, due to a lack of left ventricular dilatation that leads to a rapid rise of end-diastolic pressure relative to regurgitant volume and a low forward stroke volume, influencing renal perfusion. This increase in end-diastolic pressure related to backward volume is even greater in patients with aortic stenosis due to the presence of diastolic dysfunction.

Another possible mechanism contributing to the development of AKI is contrast nephropathy; however, we found that the amount of contrast medium was not associated with AKI after TAVI, probably due to prophylactic administration of oral acetylcysteine as well as careful management of fluids, particularly in older patients with high preoperative serum creatinine, and the use of iso-osmolar contrast media in all our patients undergoing TAVI. Nevertheless, several previous investigations have identified that a ratio of contrast media × serum creatinine/body weight over 2.7 is associated with an increased risk of AKI after TAVI; therefore, the contrast dose should be adjusted [16].

Compared with other percutaneous procedures, a TAVI carries an inherent risk of hemodynamic changes during procedure and an increased risk of complications, such as vascular complications, requiring red blood cell transfusion or residual paravalvular aortic regurgitation, all of which may potentially increase the risk of AKI. In the present study, when we analyzed the predictors of AKI in the multivariate analysis, predictors were prior stroke and pure aortic valve regurgitation. Thus, the risk of AKI after TAVI depends primarily on patient clinical characteristics and, perhaps, on procedure.

In order to prevent the occurrence of AKI, good screening and appropriate patient selection are crucial, TAVI patients should receive optimal hydration and total amount of contrast media should be minimized, and the presence of aortic debris should be assessed to avoid distal embolization [17].

Interestingly, there was a slight additional improvement in renal function among most CKD patients, and it appears probable that improvement in cardiac performance after TAVI leads to an enhancement in renal function.

The results of the present study show that patients who presented with AKI had a higher mortality at 30 days after TAVI and confirm AKI as an independent predictor of late mortality in long-term follow-up. Bagur et al. [8] reported that AKI was an independent predictor of in-hospital mortality after TAVI, which is consistent with our data. Webb et al. [18] and the Italian registry demonstrated that CKD was an important independent predictor

Table 2
Multivariate and Cox regression analyses: independent factors of total mortality in long-term follow-up after TAVI.

	HR	CI 95%	p
Acute kidney injury	2.151	1.169–3.957	0.014
Stroke after TAVI	5.644	1.988–16.02	0.001
Coronary artery disease	2.473	1.453–4.209	0.001
Karnofsky index	0.975	0.961–0.988	0.001

TAVI, transcatheter aortic valve implantation; HR, hazard ratio; CI, confidence interval.

of mortality between 30 days and 1 year [13]. These results highlight the important effect of renal function on the clinical outcome of patients undergoing TAVI.

This study has some limitations: this was a single-center study with inclusion criteria censored by a multidisciplinary team. The results may therefore be influenced by the effects of possible confounders and bias in the study design and selection. Results were based on a single determination of serum creatinine and eGFR at 72 h following procedure, whereas it has recently been recommended that timing for diagnosis of AKI be extended from 72 h to 7 days. The role of an adjusted contrast dose was not analyzed and dosage appears to be associated with contrast-induced nephropathy.

Conclusions

The deterioration of renal function in patients undergoing TAVI with the CoreValve prosthesis is a serious and frequent complication. The occurrence of AKI was associated with increased early mortality and was also a predictor of worse outcomes in long-term follow-up.

Disclosures

Dr José M. Hernández and Dr Juan H. Alonso are physician proctors for Medtronic Inc. None of the other authors has conflicts of interest to report.

References

[1] Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006;1:19–32.
[2] Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343–8.
[3] Leon MB, Craig R, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Gyton RA, Pichard AD, Bavaria JE, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. N Eng J Med 2010;363:1597–607.
[4] Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Matucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080–90.
[5] Fox H, Büttner S, Hemmann K, Asbe-Vollkopf A, Doss M, Beiras-Fernandez A, Moritz A, Zeiher AM, Scheuermann E, Geiger H, Fichtlscherer S, Hauser IA, Lehmann R. Transcatheter aortic valve implantation improves outcome compared to open–heart surgery in kidney transplant recipients requiring aortic valve replacement. J Cardiol 2013;61:423–7.
[6] Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–17.
[7] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(Suppl. 1):S1–266.
[8] Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson JB, Gutiérrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodés-Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2010;31:865–74.
[9] Elhmidi Y, Bleiziffer S, Piazza N, Hutter A, Opitz A, Hettich I, Kornek M, Ruge H, Brockmann G, Mazzitelli D, Lange R. Incidence and predictors of acute kidney injury in patients undergoing transcatheter aortic valve implantation. Am Heart J 2011;161:735–9.
[10] Nuis RJ, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2011;77:881–9.
[11] Khawaja MZ, Thomas M, Joshi A, Asrress KN, Wilson K, Bolter K, Young CP, Hancock J, Bapat V, Redwood S. The effects of VARC-defined acute kidney injury after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. Eurointervention 2012;8:563–70.
[12] Saia F, Ciuca C, Taglieri N, Marrozzini C, Savini C, Bordoni B, Dall'ara G, Moretti C, Pilato E, Martìn-Suàrez S, Petridis FD, Di Bartolomeo R, Branzi A, Marzocchi A. Acute kidney injury following transcatheter aortic valve implantation: incidence, predictors and clinical outcome. Int J Cardiol 2013;168:1034–40.
[13] 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, et al. 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.
[14] Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Bouvier E, Farge A, Donzeau-Gouge P, Cormier B, Morice MC. Impact of post-procedural aortic regurgitation on mortality after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2012;5:1247–56.
[15] Gotzmann M, Korten M, Bojara W, Lindstaedt M, Rahlmann P, Mugge A, Ewers A. Long-term outcome of patients with moderate and severe prosthetic aortic valve regurgitation after transcatheter aortic valve implantation. Am J Cardiol 2012;110:1500–6.
[16] Yamamoto M, Hayashida K, Mouillet G, Chevalier B, Meguro K, Watanabe Y, Dubois-Rande JL, Morice MC, Lefevre T, Teiger E. Renal function based contrast dosing predicts acute kidney injury following transcatheter aortic valve implantation. J Am Coll Cardiol Interv 2013;6:479–86.
[17] Arai T, Lefèvre T. Who is the right patient for TAVI. J Cardiol 2014;63:178–81.
[18] Webb JG, Altwegg L, Boone RH, Cheung A, Ye J, Lichtenstein S, Lee M, Masson JB, Thompson C, Moss R, Carere R, Munt B, Nietlispach F, Humphries K. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation 2009;119:3009–16.