Impact of left ventricular function and transaortic gradient on outcomes from transcatheter aortic valve implantation: data from the UK TAVI Registry

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Abstract

Aims: Aortic valve surgery in the presence of reduced ejection fraction (EF) or low transaortic gradient is associated with adverse outcome. Low gradient (LG) may be associated with reduced EF, known as low EF-low gradient (LEF-LG), or "paradoxically" low with normal EF (P-LG). Our aim was to investigate the impact of EF and transaortic gradient on outcome following transcatheter aortic valve implantation (TAVI).

Methods and results: We retrospectively analysed the UK TAVI Registry from 2007 to 2011 (n=2,535 consecutive patients, mean age 81.3±7.5, logistic EuroSCORE 21.8±14). Thirty-day mortality was 7.8%, low EF (<50%) was present in 39%, low gradient (<64 mmHg) was present in 27%, LEF-LG in 15% and P-LG in 12% of patients, respectively. LEF-LG patients had the highest risk profile vs. the other groups (EuroSCORE 30±16 vs. 20±12, p<0.001). Neither EF nor gradient impacted on procedural outcome or 30-day mortality. Mortality at two years was significantly higher in LEF-LG patients (34.7%), whereas, in patients with low EF/high gradient (27.8%) or normal EF/low gradient (23%), mortality was not significantly different from that of normal EF/high gradient (23%) patients. LEF-LG independently predicted reduced survival, HR 1.7 (1.4-2.1).

Conclusions: Neither low EF nor low gradient affected procedural success or 30-day mortality. Long-term survival was reduced in LEF-LG patients but not in those with low EF and high gradient or P-LG with normal EF.

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Abbreviations

AR   aortic regurgitation
AVOA   aortic valve orifice area
EF   ejection fraction
LEF-LG low ejection fraction-low gradient
LG   low gradient
P-LG   paradoxical low gradient (in the presence of normal ejection fraction)
SAVR   surgical aortic valve replacement
TAVI   transcatheter aortic valve implantation

Introduction

Symptomatic aortic stenosis may justify treatment with surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI)[1,2]. Severe aortic stenosis is defined as a transvalvular velocity >4 m/s (equating to a peak pressure drop of 64 mmHg) and an aortic valve orifice area (AVOA) of <1 cm^2 (or valve index <0.6 cm^2/m^2)[3,4].

Discordant echocardiographic measures, where the AVOA is <1 cm^2 but the peak velocity is <4 m/s, may be seen in the context of reduced left ventricular ejection fraction (EF), known as low EF-low gradient (LEF-LG) aortic stenosis. A further subset of patients have AVOA <1 cm^2, peak velocity <4 m/s but with normal ejection fraction and low transaortic gradients. This phenomenon has been termed "paradoxical" low flow-low gradient aortic stenosis (P-LG), and is often due to a reduced stroke volume (<35 ml/m^2)[5,6].

Incorrect evaluation of patients with low gradient aortic stenosis may lead either to failure to offer effective treatment, or to inappropriate treatment that may be harmful. Transvalvar velocities are dependent on cardiac contractility, stroke volume and peripheral vascular resistance, factors that are not incorporated into standard evaluation[7]. Several authors have demonstrated inherent inconsistencies within the diagnostic echocardiographic criteria that may lead to discrepant data[4,8]. There is historical evidence of patients with low gradient aortic stenosis deemed non-severe who, on re-evaluation with adjustment for variations of transaortic flow, have a high prevalence of truly severe aortic stenosis[5,7-10].

The outcome of SAVR in patients with symptomatic severe aortic stenosis is generally better than the outcome with medical therapy. Operable patients with severe aortic stenosis in the context of reduced EF[11,12], LEF-LG[13-16], and P-LG with or without low stroke volume[5,17] all derive benefit from SAVR. However, surgery in these higher risk groups is associated with a higher morbidity and mortality than in patients with normal EF and normal transaortic gradients.

TAVI may be offered to patients who are deemed inoperable or high risk for conventional aortic valve surgery[1,2,18]. The impact of TAVI on outcome in patients with low gradient aortic stenosis has been less well described than following SAVR, although preliminary data suggest favourable outcomes[19-21]. The increasing use of TAVI for high-risk patients therefore justifies further evaluation of selection and outcome. We used the UK TAVI database to explore these factors. The specific aims were to determine the early and intermediate outcome of TAVI in patients with depressed ejection fraction, to report the prevalence and impact of low gradient aortic stenosis (LEF-LG and P-LG) on early and intermediate outcome and, finally, to explore the interrelationship of ejection fraction, AVOA, and valve gradient on survival after TAVI.

Methods

UK TAVI REGISTRY

All TAVI procedures in the UK are prospectively recorded in the UK TAVI Registry, as previously described[22]. Patient selection for TAVI was at the discretion of the Heart Team in each centre but conformed to a standard process with clinical evaluation, angiography and echocardiography performed in all patients prior to decision on treatment made by a multidisciplinary Heart Team.

Standard definitions were used for baseline clinical parameters and these data were uploaded to the central cardiac audit database. Procedural outcome and complications were self-reported according to the definitions outlined in the national data set and published previously[22].

All-cause mortality was tracked by linkage, using each patient's NHS number, with the Office of National Statistics. All deaths in England and Wales are registered with this national body and consequently mortality data are highly robust. The recorded cause of death was not available.

UK centres have adopted transfemoral as the default access, with other access routes (transapical, trans-subclavian and transaortic) used according to local expertise and valve device. The following technologies were available: Medtronic CoreValve (Medtronic, Minneapolis, MN, USA) from 2007, Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA) (transfemoral 2007, transapical from 2008).

CLASSIFICATION OF AORTIC STENOSIS

The echocardiographic evaluation of the aortic valve recorded in the UK TAVI database is limited to aortic valve orifice area (AVOA) derived from the continuity equation, and peak pressure gradient (PPG) derived from the modified Bernoulli equation; these data were self-reported by the treating centres. Body mass index and gender were recorded, and aortic valve index was calculated according to the Mosteller formula. Left ventricular function was defined as normal (EF >50%), moderately impaired (EF 30-49%), or severely impaired (EF <30%).

Patients in whom the dominant valve pathology was aortic regurgitation were excluded from these analyses. Patients with aortic valve orifice area >1 cm and peak pressure gradient <64 mmHg in the presence of normal ejection fraction were excluded since these subjects did not fulfil accepted criteria for severe aortic stenosis[3,4]. Patients receiving "valve in valve" TAVI for stenotic surgical prosthesis were not excluded.

Low gradient aortic stenosis was defined as AVOA <1.0 cm^2 with a peak pressure gradient <64 mmHg (equivalent to peak velocity <4 m/s). LEF-LG was defined as peak pressure <64 mmHg with

EF <50%. P-LG aortic stenosis was defined as peak pressure drop <64 mmHg with normal ejection fraction (>50%).

Stroke volume (by measurement of pulsed wave Doppler in the left ventricular outflow tract) is not reported.

STATISTICAL ANALYSIS

The impact of ejection fraction on survival was examined in binary fashion (normal vs. impaired, and severely impaired vs. others). The impact of gradient on survival was examined in binary fashion (low gradient <64 mmHg vs. high gradient >64 mmHg). Categorical variables were analysed with a two-sample test of equality of proportions using Koopman's method. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and informally using quantile-quantile plots. Normally distributed variables were compared using unpaired t-tests, as were skewed variables after transformation. To control for multiple confounders, a Cox regression model was developed. Potential confounders were selected according to clinical importance using components of the logistic EuroSCORE (LES) model, namely age, gender, chronic lung disease, peripheral vascular disease, prior myocardial infarction, stroke, critical status, previous cardiac surgery, vascular access for TAVI, successful valve implantation, and severity of AR (by echocardiography) post procedure. It was not possible to use the LES variable itself because ejection fraction, which is one of its components, was used as a covariate in the regression models. The treating hospital was used as a fixed effect in the regression models to account for clustering within hospitals. To account for missing data, multiple imputation by chained equations was performed, using 20 completed data sets. Survival plots are presented as unadjusted actuarial survival.

Results

A total of 2,490 implants were recorded in 2,591 procedures. Sixteen cases were repeat procedures in patients who had previously had TAVI or attempted TAVI. In 36 patients aortic regurgitation was the dominant pathology and aortic valve area was >1.5 cm^2. In 19 patients the echocardiographic criteria submitted did not conform to accepted values of severe aortic stenosis (PPG was <64 mmHg, AVOA was <1 cm^2 and EF normal), and these patients were excluded from the analyses. This left a study sample of 2,456 implants in 2,535 procedures.

Completeness of data was as follows: 99% demographics, 96.5% risk factors, and 94% procedural variables. Logistic EuroSCORE and serum creatinine were skewed variables and were log transformed. Mortality tracking was achieved in 100%. Median follow-up was 492 days (range 0-1,981). A total of 741 patients lived beyond two years of follow-up; 630 patients died within two years.

PATIENT CHARACTERISTICS

Baseline data are presented on the basis of valve gradient and subsets of low gradient AS (P-LG vs. LEF-LG) **(Table 1)**. The mean age was 81.3±7.5; logistic EuroSCORE was 21.8±14. Overall procedural success was achieved in 96.8% of patients; unadjusted 30-day mortality was 7.8%. Left ventricular impairment was present in 39.6% and was severe in 9.2% of cases. The prevalence of low gradient severe aortic stenosis was 27.8%; LEF-LG was present in 15% and P-LG in 12% of cases. Low gradient patients were younger, taller and heavier than normal gradient patients, and were more likely to have reduced ejection fraction. Low gradient patients were significantly more likely to be male, to have a higher logistic EuroSCORE, to have pre-existing diabetes, and to be clinically unstable at the time of valve implantation.

Reduced ejection fraction was associated with male sex (47% male vs. 31% female), diabetes (27% vs. 19%), previous myocardial infarction (34% vs. 16%), and prior cardiac surgery (39% vs. 28%), all p<0.05. The differences observed with gender and ejection fraction meant that P-LG patients were significantly more likely to be female. The AVA/valve index was greater in low-flow patients, and this effect was driven primarily by the P-LG cohort.

OUTCOMES
LEFT VENTRICULAR IMPAIRMENT

Procedural outcome and complication were unaffected by the presence of reduced ejection fraction **(Table 2)**. Unadjusted 30-day mortality was not significantly affected by the presence of reduced EF (6.4% mortality for normal EF, 10% for moderately impaired EF, and 9% for severely impaired EF; p=0.39). Late mortality was increased in patients with reduced EF (one-year 25% vs. 17%, p<0.05, two-year 30% vs. 22%, p<0.05). There was no difference between one-year and two-year mortality rates in patients with moderately impaired EF or severely impaired EF. After adjustment, ejection fraction impacted significantly on survival at final follow-up (median 492 days; range 0-1,981), the hazard ratio (HR) for any reduction in ejection fraction being 1.41 (1.2-1.7) and for severe reduction in ejection fraction being 1.6 (1.3-2.1). However, the adverse effect of LV dysfunction was limited to patients with both low EF and low gradient (HR 1.7 [1.4-2.1]). The presence of low EF with high transaortic gradient (LEF-HG) suggested an intermediate adverse effect that did not meet statistical significance (HR 1.08 [0.67-1.79]) **(Figure 1)**.

LOW AND HIGH GRADIENT AS

Low gradient aortic stenosis was present in 27.3% of cases. Procedural success, rate of complication and unadjusted survival were unaffected by low gradient **(Table 3)**. After adjustment, survival at final follow-up was worse for low gradient aortic stenosis (HR 1.3 [1.11-1.57]).

SUBTYPES OF LOW GRADIENT AS

The prevalence of LEF-LG was 15% and of P-LG was 12%. Both the unadjusted and adjusted survival rates of patients with LEF-LG were worse than of patients with high-flow aortic stenosis (34.7% vs. 23.2% at two years). In contrast, the outcomes for P-LG patients matched those of high-flow patients both before and after adjustment **(Figure 2)**.

**Table 1. Baseline characteristics of all patients, divided by gradient.**

	All N=2,535	High gradient N=1,812	Low gradient N=678	Diff.	95% CI	p¶	P-LG N=292	LEF-LG N=386	Diff.	95% CI	p¶
Age (yrs)	81.3 (7.5)	81.7 (7.1)	80.7 (8.2)	1.0	(0.4 , 1.7)	<0.001	82.1 (0.6)	79.5 (0.4)	2.5	(1.3, 3.7)	<0.001
Creatinine* (mmol/L)	102	101	106	−5	(−8, −2)	NA	101	114	−13	(−19, −8)	NA
Height (m)	1.64 (0.1)	1.64 (0.10)	1.66 (0.10)	−0.02	(−0.030, −0.012)	<0.001	1.64 (0.10)	1.68 (0.10)	−0.04	(−0.05, −0.02)	<0.001
Weight (kg)	73.1 (0.3)	72.6 (0.4)	74.2 (0.6)	−1.6	(−3.0, −0.1)	<0.05	73.0 (1.01)	75.1 (0.80)	−2.0	(−4.6, 0.5)	0.11
Peak velocity gradient (mmHg)	80.0 (0.5)	90.8 (0.5)	51.0 (0.5)	39.7	(38.5, 41.1)	<0.001	54.3 (0.6)	48.5 (0.6)	5.8	(4.0, 7.6)	<0.001
Logistic EuroSCORE*	18.1	17.1	21.0	−3.8	(−4.7, −2.4)	NA	16.1	26.8	−10.7	(−12.2, −8.1)	NA
Body mass index (kg/m²)	26.9 (0.1)	26.9 (0.1)	26.7 (0.2)	0.2	(−0.3, 0.6)	0.52	27.0 (0.33)	26.5 (0.24)	0.53	(−0.29, 1.33)	0.20
Pulmonary hypertension	333 (15.0%)	251 (15.5%)	82 (13.8%)	1.8%	(−6.9%, 10.5%)	0.70	26 (10.1%)	56 (16.5%)	−6.5%	(−21.6%, 8.6%)	0.44
Chronic lung disease	683 (28.0%)	495 (28.0%)	188 (28.1%)	−0.1	(−7.6%, 7.4%)	0.97	67 (23.6%)	121 (31.5%)	−7.9%	(−21.0%, 5.1%)	0.25
Peripheral vascular disease	684 (28.2%)	486 (27.7%)	198 (29.5%)	−1.7%	(−9.2%, 5.8%)	0.65	80 (26.9%)	118 (31.6%)	−4.7%	(−17.5%, 8.1%)	0.48
Renal replacement therapy or creatinine >200 mmol/L	124 (5.2%)	74 (4.2%)	50 (7.7%)	−3.5%	(−12.1%, 5.2%)	0.41	12 (4.3%)	38 (10.2%)	−5.9%	(−20.9%, 0.0%)	0.53
Male sex	1,331 (53.5%)	913 (50.4%)	418 (61.6%)	−11.2%	(−16.9%, −5.6%)	<0.001	150 (51.4%)	268 (69.7%)	−18.3%	(−28.0%, −8.6%)	<0.001
Previous myocardial infarction	568 (22.9%)	368 (20.3%)	200 (29.7%)	−9.3%	(−16.9%, −1.8%)	<0.05	59 (20.4%)	141 (36.6%)	−16.2%	(−29.2%, −3.1%)	<0.05
Diabetes	554 (22.4%)	372 (20.6%)	182 (27.0%)	−6.4%	(−14.0%, 1.3%)	0.092	62 (21.4%)	120 (31.2%)	−9.7%	(−22.9%, 3.4%)	0.17
Prior cardiac surgery	804 (32.4%)	542 (30.0%)	262 (38.8%)	−8.8%	(−15.8%, −1.8%)	<0.05	98 (33.7%)	164 (42.6%)	−8.9%	(−21.0%, 3.1%)	0.15
Femoral access	1,680 (67.5%)	1,243 (68.6%)	437 (64.5%)	4.1%	(−1.1%, 9.3%)	0.12	175 (60.0%)	262 (67.9%)	−7.9%	(−17.1%, 1.3%)	0.09
Subclavian access	138 (5.5%)	94 (5.2%)	44 (6.5%)	−1.3%	(−9.9%, 7.3%)	0.76	21 (7.2%)	23 (6.0%)	1.2%	(−13.5%, 15.9%)	0.87
Apical access	567 (22.8%)	401 (22.1%)	166 (24.5%)	−2.4%	(−10.0%, 5.3%)	0.54	87 (29.8%)	79 (20.5%)	9.3%	(−3.8%, 22.4%)	0.17
Other access	105 (4.2%)	74 (4.1%)	31 (4.6%)	−0.5%	(−9.1%, 8.1%)	0.91	9 (3.1%)	22 (5.7%)	−2.6%	(−17.5%, 12.3%)	0.76
SAPIEN	1,279 (51.4%)	920 (50.8%)	359 (53.0%)	−2.2%	(−8.3%, 3.9%)	0.48	168 (57.5%)	191 (49.5%)	8.1%	(−2.2%, 18.3%)	0.13
CoreValve	1,198 (48.1%)	889 (49.1%)	309 (45.8%)	3.3%	(−3.2%, 9.8%)	0.32	121 (41.4%)	188 (48.5%)	−7.3%	(−18.6%, 4.0%)	0.21
Other/mixed	13 (0.5%)	3 (0.2%)	10 (1.5%)	−1.3%	(−10.4%, 7.8%)	0.86	3 (1.0%)	7 (1.8%)	0.8%	(−15.8%, 14.3%)	0.93
Normal LV (EF >50%)	1,490 (60.4%)	1,203 (67.0%)	287 (42.6%)	24.4%	(18.1%, 30.1%)	<0.001	287 (100%)	0 (0%)	N/A	N/A	N/A
Impaired LV (EF 35-50%)	749 (30.3%)	507 (28.2%)	242 (36.0%)	−7.8%	(−15.0%, 0.6%)	<0.05	0 (0%)	242 (62.7%)	N/A	N/A	N/A
Severe LVSI (EF <35%)	230 (9.2%)	86 (4.8%)	144 (21.4)	−16.6%	(−24.7%, −8.5%)	<0.001	0 (0%)	144 (37.3%)	N/A	N/A	N/A
Aortic valve index (cm²)	0.36 (0.01)	0.34 (0.01)	0.38 (0.01)	−0.04	(−0.05, −0.03)	<0.001	0.40 (0.01)	0.38 (0.01)	0.02	(0.01, 0.04)	<0.01

* median; ¶ not adjusted for multiple testing. Baseline characteristics of all patients, divided by gradient and subtype of low gradient aortic stenosis (low ejection fraction low gradient [LEF-LG] and paradoxical low gradient [P-LG]).
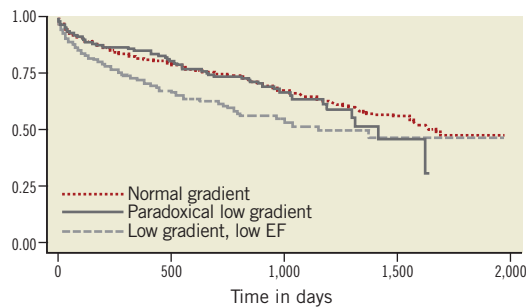
Figure 1. *Survival curve by baseline gradient (high gradient vs. low ejection fraction-low gradient [LEF-LG] vs. paradoxical low gradient [P-LG]).*
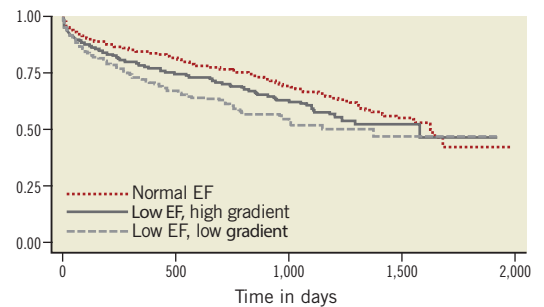
Figure 2. *Survival curve by EF and gradient (normal EF vs. low ejection fraction-low gradient [LEF-LG] vs. low ejection fraction-high gradient [LEF-HG]).*

Table 2. Procedural outcome and complication by baseline ejection fraction.

	All	EF >50%	EF <50%	Diff.	95% CI	p	EF >50%	EF <30%	Diff.	95% CI	p
30-day mortality	195 (7.8%)	97 (6.4%)	98 (9.8%)	–3.4%	(–11.0%, 4.3%)	0.39	97 (6.4%)	21 (9.0%)	–2.6%	(15.7%, 10.6%)	0.68
1-year mortality	502 (20.0%)	251 (16.6%)	251 (25.2%)	–8.6%	(–15.6%, –1.5%)	<0.05	251 (16.6%)	62 (26.5%)	–9.9%	(–21.8%, 2.0%)	0.07
2-year mortality	627 (25.0%)	325 (21.5%)	302 (30.3%)	–8.8%	(15.6%, –2.0%)	<0.05	325 (21.5%)	75 (32.1%)	–10.6%	(–22.0%, 0.9%)	0.05
Stroke	62 (2.5%)	42 (2.8%)	20 (2.0%)	0.8%	(–7.2%, 8.7%)	0.87	42 (2.8%)	2 (0.9%)	1.9%	(–11.8%, 15.6%)	0.87
Myocardial infarction	18 (0.7%)	10 (0.7%)	8 (0.8%)	–0.2%	(–8.1%, 7.8%)	0.97	10 (0.7%)	0 (0.0%)	0.7%	N/A	N/A
Aortic regurgitation ≥moderate	285 (11.4%)	157 (10.4%)	128 (12.9%)	–2.5%	(–10.0%, 5.0%)	0.52	157 (10.4%)	31 (13.3%)	–2.9%	(–15.7%, 10.0%)	0.64
Vascular complication	79 (3.1%)	46 (3.0%)	33 (3.3%)	–0.3%	(–8.2%, 7.6%)	0.94	46 (3.0%)	7 (2.99%)	0%	(–13.6%, 13.6%)	0.99
Blood transfusion	540 (21.7%)	316 (21.1%)	224 (22.8%)	–1.7%	(–8.8%, 5.4%)	0.65	316 (21.0%)	49 (21.1%)	–0.1%	(–12.3%, 12.2%)	0.99
New renal replacement therapy	115 (4.6%)	67 (4.5%)	48 (4.9%)	–0.4%	(–8.3%, 7.4%)	0.92	67 (4.5%)	16 (6.9%)	–2.4%	(–15.8%, 10.9%)	0.69
Permanent pacemaker	282 (11.3%)	171 (11.4%)	111 (11.2%)	0.2%	(–7.4%, 7.7%)	0.97	171 (11.4%)	30 (12.9%)	–1.5%	(–14.5%, 11.4%)	0.81

Discussion

The findings of this study indicate that both impairment of left ventricular function and low gradient aortic stenosis are common in patients undergoing TAVI, affecting 39.6% and 27% of patients in the UK TAVI Registry, respectively. The interaction of ejection fraction and transaortic gradient has a complex relationship with outcome and risk.

EFFECT OF EJECTION FRACTION

Left ventricular dysfunction by any measure or severity of ejection fraction had no significant effect on procedural success and short-term outcome. Beyond the procedure, low EF is associated with significant attrition. In our study, low EF with high gradient was associated with a more favourable outcome, and this may reflect preservation of cardiac reserve and better EF recovery following TAVI, an effect that has been reported previously[23]. Real-world data from Canada[24], France[25] and now the UK have failed to show an adverse impact of left ventricular dysfunction on procedural success or short-term outcome. Only the German TAVI registry has found increased procedural risk with reduced ejection fraction, an effect possibly driven by a different definition of normal EF

(>40%)[26]. The hypothesis generated by these data is that the safety of the TAVI procedure is not influenced by the presence of underlying left ventricular dysfunction. This is in contrast to the literature on surgical aortic valve replacement, where low EF patients are exposed to higher earlier mortality than patients with normal EF. One question is whether TAVI should be a default strategy in patients with reduced EF and/or reduced transaortic gradients. The theoretical benefits of TAVI in high-risk patients with reduced EF include the avoidance of cardiopulmonary bypass and prolonged ventilation, minimisation of patient-prosthesis mismatch, and more rapid recovery of ventricular function than is associated with aortic valve surgery[19,21,23,27-29]. Comparison of outcome between non-randomised samples of patients treated by surgery and TAVI is challenging due to substantial variation in baseline characteristics. The 30-day mortality of patients with low EF in the UK TAVI population is 9.8%: this compares well to the published surgical outcomes ranging between 9 and 18%[16,30,31]. The one-year mortality of patients with reduced EF receiving TAVI in the UK is 25%, for LEF-LG 28.8% and P-LG 16%. The equivalent outcomes at one year of patients treated by SAVR for reduced EF range between

Table 3. Procedural outcome by baseline gradient and subtype of low gradient aortic stenosis.

	All N=2,535	High gradient N=1,812	Low gradient N=678	Diff.	95% CI	p	P-LG N=292	LEF-LG N=386	Diff.	95% CI	p
Procedural success	2,396 (96.3%)	1,737 (96.0%)	659 (97.2%)	–1.2%	(–2.8%, 0.0%)	0.15	284 (97.2%)	375 (97.2%)	0.1%	(–2.4%, 2.6%)	0.93
30-day mortality	191 (7.8%)	134 (7.4%)	57 (8.4%)	–1.0%	(–9.4%, 7.3%)	0.80	19 (6.5%)	38 (9.8%)	–3.3%	(–17.9%, 11.3%)	0.69
1-year mortality	497 (20.0%)	340 (18.8%)	157 (23.2%)	–4.4%	(–12.2%, 3.4%)	0.26	46 (15.8%)	111 (28.8%)	–13.0%	(–26.5%, 0.5%)	0.09
2-year mortality	620 (24.9%)	420 (23.2%)	200 (29.5%)	–6.3%	(–13.8%, 1.2%)	0.09	66 (22.6%)	134 (34.7%)	–12.1%	(–25.0%, 0.8%)	0.08
Stroke	61 (2.5%)	45 (2.5%)	16 (2.4%)	0.1%	(–8.6%, 8.8%)	0.98	9 (2.9%)	7 (1.8%)	1.3%	(–11.7%, 14.2%)	0.84
Myocardial infarction	18 (0.7%)	14 (0.8%)	4 (0.6%)	0.2%	(–8.7%, 9.0%)	0.97	3 (1.0%)	1 (0.3%)	0.7%	(–14.4%, 15.9%)	0.94
AR ≥ moderate	292 (11.8%)	221 (12.2%)	71 (10.5%)	1.7%	(–6.6%, 10.0%)	0.69	25 (8.6%)	46 (12.0%)	–3.4%	(–17.8%, 11.1%)	0.60
Vascular complication	78 (3.11%)	61 (3.4%)	17 (2.5%)	0.9%	(–7.8%, 9.6%)	0.86	5 (1.7%)	12 (3.1%)	–1.4%	(–16.4%, 13.6%)	0.87
Blood transfusion	541 (22.0%)	398 (22.2%)	143 (21.4%)	0.8%	(–7.1%, 8.6%)	0.85	59 (19.2%)	85 (22.2%)	–3.0%	(–16.4%, 10.4%)	0.67
New renal replacement therapy	114 (4.6%)	76 (4.2%)	38 (5.7%)	–1.5%	(–10.1%, 7.2%)	0.73	11 (3.8%)	27 (7.1%)	–3.3%	(–18.2%, 11.6%)	0.70
Permanent pacemaker	283 (11.5%)	209 (11.6%)	74 (11.0%)	0.6%	(–7.7, 9.0%)	0.88	27 (9.3%)	47 (12.3%)	–2.9%	(–17.4%, 11.5%)	0.70

15 and 22%[16,30-32]. The Euro Heart Survey confirmed that a significant proportion of patients with important aortic valve disease were either never considered for SAVR, or were felt to be inoperable due to age, reduced EF and frailty[33]. Furthermore, the surgical outcomes in the trials cited above are based on patients who were on average 10-15 years younger than the patients in the UK TAVI database and with substantially lower baseline logistic EuroSCORE. Therefore, the current evidence base suggests that procedural safety may favour TAVI over surgery in some patients with reduced EF.

EFFECT OF GRADIENT ON OUTCOMES

Low gradient aortic stenosis was present in 27% of patients, a level consistent with previous reports[5,8,30]. The presence of low gradient did not affect procedural outcomes. The low gradient group was itself split with about half (15% overall) LEF-LG and the rest (12% overall) P-LG aortic stenosis.

As in other studies, the P-LG patients were older and more often female[34], and in this series more likely to be treated with non-femoral access. Despite these more adverse baseline characteristics, the P-LG patients had outcomes no worse than normal EF and high gradient patients following TAVI.

GRADIENT AND FLOW

The present study has no data on transaortic flow (measured by pulsed wave Doppler in the left ventricular outflow tract): therefore, we are unable to define low-flow physiology. Recently, retrospective analyses of the PARTNER data by Herrmann et al and of the Canadian registry by Le Ven et al have highlighted the importance of low transaortic flow, defined as a stroke volume <35 mL/m^2, in determining outcome following SAVR and TAVI[35,36]. Low-flow and low gradient are not the same, but are often associated. The prevalence of low-flow was similar in these papers (55% & 52.3%, respectively), as was the proportion of patients with low-flow with reduced ejection fraction LEF-LG (12% & 15%, respectively).

We can speculate that many of the UK TAVI Registry patients defined as P-LG also had low-flow. Consistent with this assertion is the fact that the proportion of patients in the UK TAVI Registry with P-LG is similar to that of PLF-LG (with normal EF) reported in PARTNER and the Canadian registry (12% in UK TAVI vs. 14% & 9%, respectively) and of LEF-LG (15% in UK TAVI vs. 12% & 15%, respectively).

The impact of aortic stenosis in the context of P-LG or PLF-LG (with normal EF) appears important. A single study on initially asymptomatic patients reported a one-year mortality <5% with an annualised SAVR rate of 13.8%[34], but three other studies suggest a less benign natural history of PLF-LG aortic stenosis, with a one-year mortality in the absence of SAVR greater than 15%[5,17,30]. Subgroup analysis of the PARTNER data suggested a superior survival of PLF-LG patients treated by SAVR or TAVI compared to medical management.

Despite the difficulties of comparing trials, it is clear that aortic stenosis with PLF physiology or P-LG is associated with significant harm in the presence of symptoms, and that these patients are

offered SAVR less often[17,30]. TAVI in these patients seems to perform well: in our study these patients had outcomes matching those of patients with high gradients, while in PARTNER the patients had survival superior to those treated with medical therapy.

The LEF-LG patients have significant attrition beyond the initial procedure, and this finding is consistent with all recent studies. This increase in all-cause mortality is presumably driven by the presence of irreversibly reduced ejection fraction. The combination of reduced EF and low gradient was associated with the worst outcome, survival at one year being 71% and at two years being 65%. Despite this attrition, the 65% two-year survival rate is comparable to surgical outcomes which vary between a 55-80% two-year survival rate following surgery, and <25% survival rate with conservative management[12,13,15].

Although ejection fraction appears to dominate long-term outcome, we found evidence that patients with a high gradient in the presence of reduced EF had good outcomes. This presumably reflects adequate cardiac reserve that can be reversed by successful valve intervention.

The present data show acceptable outcomes for TAVI in patients with low EF, low gradient, or both. The combination of low gradient and low EF identified a high-risk population. The phenomena of paradoxical low gradient with normal ejection fraction or high gradient in the presence of reduced ejection fraction did not significantly impact on survival following TAVI, although the survival for LEF-HG was intermediate between normal EF and LEF-LG when plotted with actuarial curves. The 30-day mortality for patients with low gradient, low EF, or both compares well to published outcomes for surgery and, although attrition beyond the TAVI procedure is considerable, the survival is comparable to that of SAVR in published series.

Study limitations

The limitations of the UK TAVI data set have already been partially described in the text. Outcomes are based on all-cause mortality with no discrimination between cardiac and non-cardiac death. The absence of measures of stroke volume, left ventricular dimensions and aortic valve impedance prevent categorisation of low-flow physiology. Furthermore, data from important investigations performed by the treating centres such as stress echo, transoesophageal imaging, cross-sectional imaging and invasive evaluation were not available for analysis. Finally, there is a lack of a control group, such as a group with moderate aortic stenosis or severe aortic stenosis treated conservatively or with SAVR.

Conclusions

Low gradient and low EF were commonly seen in the UK TAVI Registry population. In contrast to the existing literature on SAVR, procedural outcome and 30-day mortality were not significantly affected by reduced EF or low gradient.

Late mortality was increased with the combination of low EF and low gradient, but not in those patients with low EF and high gradient, or in those with paradoxical low gradient AS with normal EF.

Impact on daily practice

Management of aortic stenosis with reduced ejection fraction (EF) or low transaortic gradient can be challenging. Surgical valve replacement is associated with increased morbidity and mortality. In the UK TAVI Registry, the prevalence of reduced EF was 39.6% and low gradient 27.3%. Low gradient was associated with reduced EF in 15% and was paradoxically low with normal EF in 12%. Short-term outcome after TAVI was unaffected by reduced EF or low gradient. Patients with normal EF had the best long-term outcome, even if the transaortic gradient was low. Paradoxical low gradient was associated with smaller, female patients and may be associated with reduced stroke volume. Patients with reduced EF had the worst long-term mortality although a subset of patients with low EF and high transaortic gradient had good outcome. Heart Teams should be reassured that the procedural success of TAVI is unaffected by low gradient or reduced EF.

Conflict of interest statement

C. Malkin is a consultant for Boston Scientific. M. Thomas is a consultant and proctor for Edwards Lifesciences. N. Moat is a consultant to Medtronic, and has received honoraria from Edwards Lifesciences and Abbott. D. Blackman is a consultant and proctor for Medtronic, and a proctor for Boston Scientific. O. Wendler is a consultant and proctor for Edwards Lifesciences. M. Monaghan is a consultant for Edwards Lifesciences. The other authors have no conflicts of interest to declare.

References

1. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370:1790-8.

2. 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; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-98.

3. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists, Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr , Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B.

ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2006;48:e1-148.

4. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-96.

5. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation.* 2007;115:2856-64.

6. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1-23; quiz 101-2.

7. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J.* 2008;29:1043-8.

8. 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;31:281-9.

9. Cramariuc D, Cioffi G, Rieck AE, Devereux RB, Staal EM, Ray S, Wachtell K, Gerdts E. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. *JACC Cardiovasc Imaging.* 2009;2:390-9.

10. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, Pibarot P. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. *J Am Coll Cardiol.* 2005;46:291-8.

11. Clavel MA, Fuchs C, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler-Klein J, Beanlands RS, Mathieu P, Magne J, Pibarot P. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS Study. *Circulation.* 2008;118:S234-42.

12. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR. Survival after aortic valve replacement for severe aortic stenosis with low

transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol.* 2002;39:1356-63.

13. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, Petit-Eisenmann H, Gori M, Jobic Y, Bauer F, Chauvel C, Leguerrier A, Tribouilloy C. Aortic valve replacement for low-flow/low-gradient aortic stenosis: operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol.* 2008;51:1466-72.

14. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Guéret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation.* 2003;108:319-24.

15. Tribouilloy C, Lèvy F, Rusinaru D, Guèret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Quéré JP, Monin JL. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol.* 2009;53:1865-73.

16. Vaquette B, Corbineau H, Laurent M, Lelong B, Langanay T, de Place C, Froger-Bompas C, Leclercq C, Daubert C, Leguerrier A. Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. *Heart.* 2005;91:1324-9.

17. 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;60:1259-67.

18. 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; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-607.

19. Clavel MA, Webb JG, Rodes-Cabau J, Masson JB, Dumont E, De Larochelliere R, 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;122:1928-36.

20. Ewe SH, Ajmone Marsan N, 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;160:1113-20.

21. Zhao Y, Lindqvist P, Nilsson J, Holmgren A, Naslund U, Henein MY. Trans-catheter aortic valve implantation--early recovery of left and preservation of right ventricular function. *Interact Cardiovasc Thorac Surg.* 2011;12:35-9.

22. 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;58:2130-8.

23. O'Sullivan CJ, Stortecky S, Heg D, Pilgrim T, Hosek N, Buellesfeld L, Khattab AA, Nietlispach F, Moschovitis A, Zanchin T, Meier B, Windecker S, Wenaweser P. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J.* 2013;34: 3437-50.

24. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. 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.

25. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med.* 2012;366:1705-15.

26. 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; German Transcatheter Aortic Valve Interventions Registry Investigators. Transcatheter aortic valve implantation in patients with low-flow, low-gradient aortic stenosis. *JACC Cardiovasc Interv.* 2012;5:552-9.

27. Kempny A, Diller GP, Kaleschke G, Orwat S, Funke A, Schmidt R, Kerckhoff G, Ghezelbash F, Rukosujew A, Reinecke H, Scheld HH, Baumgartner H. Impact of transcatheter aortic valve implantation or surgical aortic valve replacement on right ventricular function. *Heart.* 2012;98:1299-304.

28. 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;61:2514-21.

29. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ, Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J.* 2012;33:1518-29.

30. Pai RG, Varadarajan P, Razzouk A. Survival benefit of aortic valve replacement in patients with severe aortic stenosis with low ejection fraction and low gradient with normal ejection fraction. *Ann Thorac Surg.* 2008;86:1781-9.

31. Halkos ME, Chen EP, Sarin EL, Kilgo P, Thourani VH, Lattouf OM, Vega JD, Morris CD, Vassiliades T, Cooper WA, Guyton RA, Puskas JD. Aortic valve replacement for aortic stenosis in patients with left ventricular dysfunction. *Ann Thorac Surg.* 2009;88:746-51.

32. Ding WH, Lam YY, Duncan A, Li W, Lim E, Kaya MG, Chung R, Pepper JR, Henein MY. Predictors of survival after aortic valve replacement in patients with low-flow and high-gradient aortic stenosis. *Eur J Heart Fail.* 2009;11:897-902.

33. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Bärwolf C, Boersma E, Ravaud P, Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J.* 2005;26:2714-20.

34. Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, Chambers JB, Egstrup K, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Rossebø A, Pedersen TR, Skjærpe T, Willenheimer R, Wachtell K, Neumann FJ, Gohlke-Bärwolf C. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. *Circulation.* 2011;123:887-95.

35. 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;127:2316-26.

36. 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, Rodés-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;62:782-8.