The appreciation of prosthetic heart valves

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PART II

Evaluation of prosthetic valves

Chapter 5

Regression to the mean and absence of left ventricular mass regression after aortic valve replacement

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Abstract

Objective:
Left ventricular (LV) mass regression after aortic valve replacement (AVR) for aortic stenosis is believed to be a favorable prognostic factor, but is absent in a quarter of patients. This study sought to find an explanation for the absence of echocardiographic LV mass regression after AVR in the PERIGON Pivotal trial.

Methods:
Clinical records and echocardiographic images from a prospective surgical AVR cohort of 683 patients were analyzed. The presence of LV mass regression from baseline was determined at each follow-up visit. To quantify the potential role of random measurement error of LV mass, sets of simulated data were generated with different degrees of random measurement error.

Results:
Patients without LV mass regression at 1 year had a lower LV mass at baseline compared to patients with LV mass regression (163±50g vs. 199±52g, p <0.001). There were no other relevant differences in patient characteristics and clinical outcomes between the two groups, including mortality after 1 year (HR: 1.44 [95% CI: 0.58-3.57]). When 25% of total variance in the simulated dataset was due to random measurement error, the proportion of patients without LV mass regression was similar to the PERIGON trial, respectively 30% and 27%.

Conclusions:
There were no plausible clinical explanations for the observed absence of LV mass regression, nor was it associated with inferior outcomes. Instead, this unexpected finding seems due to the regression to the mean of inflated random measurement error, resulting from raising linear dimensions to the third power for the calculation of LV mass.

Introduction

Aortic stenosis (AS) induces hypertrophic remodelling of the left ventricle (LV) to cope with the extra afterload. When left untreated, this leads to a cascade of diastolic and systolic LV dysfunction and ultimately death. Therefore, relieve of AS with aortic valve replacement (AVR) is recommended to reverse this remodelling process. As LV reverse remodelling of hypertrophy is accompanied by a decrease in mass, the degree of LV mass regression during the first year after AVR is believed to be an important prognostic factor of long-term outcomes (1).

Although MRI has demonstrated superior precision (2-4), echocardiography is the mainstay for the clinical assessment of LV mass regression (5). LV mass can be quickly calculated with two-dimensional trans-thoracic echocardiography (2D-TTE) using the American Society of Echocardiography (ASE) Cube formula (6,7), as this formula only requires measurement of the LV end-diastolic diameter, septal wall and posterior wall thickness. However, as these linear dimensions are raised to the third power, even minor random measurement error can create major differences in calculated LV mass (5).

Despite the expected and generally measured reduction in LV mass during the first year of follow-up, it has been reported that LV mass regression is absent in a quarter of patients (1,8,9). This study aims to establish whether the absence of LV mass regression reflects a true pathophysiologic process, or rather a statistical artefact resulting from regression to the mean of random measurement error.

Methods

Patient recruitment

The PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial is a prospective multicenter trial to evaluate the safety and effectiveness of the Avalus bioprosthetic valve (Medtronic, Minneapolis, Minn, USA) (10, 11). Patients with moderate or severe aortic stenosis or aortic regurgitation and an indication for aortic valve replacement with a bioprosthesis were eligible for enrolment. Some concomitant procedures were allowed as coronary artery bypass grafting and ascending aortic repair not requiring circulatory arrest. In total, 1115 patients were enrolled at 38 sites across Europe, Canada, and the United States between 2014 and 2017. The Medical Ethical Committee of the participating centres approved the study protocol, and all participants gave their written informed consent. For this analysis, only patients with pure aortic stenosis and available LV mass measurements at both baseline and 1 year were included.

Follow-up

Baseline evaluation included co-morbidities, New York Heart Association (NYHA) functional status, and Society of Thoracic Surgeons (STS) score. Patients underwent a baseline 2D-TTE. After implant, patients were scheduled for follow-up at hospital discharge (up to 30 days), 3 to 6 months, 1 year, and annually through 5 years. These visits included assessment of NYHA classification and TTE.

Echocardiography

All 2D-TTE exams were sent to an echo core lab (Cardiovascular Core Laboratories, MedStar Health Research Institute, Hyattsville, Md, USA) for central assessment of the following parameters: mean aortic gradient, effective orifice area, Doppler velocity index, LV ejection fraction, cardiac output, and LV mass. To obtain indexed effective orifice area (EOAi), body surface area was calculated with the DuBois formula at baseline. LV mass was determined according to the ASE Cube formula (6,7): LV mass (g) = $0.8\{1.04[(LVEDD + IVST + PWT)^3 - LVEDD^3] + 0.6$, where LVEDD is left ventricular end-diastolic diameter, IVST is interventricular septum end-diastolic thickness and PWT is posterior wall end-diastolic thickness. The change in LV mass was calculated by subtracting LV mass after 1 year from LV mass at baseline. Relative wall thickness was calculated as: (PWT*2)/LVEDD. Stroke volume was calculated as the LV outflow tract area multiplied by the pulsed-wave Doppler LV outflow tract velocity-time integral.

Statistical analysis

Patients were grouped based on the presence or absence of LV mass regression from baseline to 1 year post-operatively. Categorical patient characteristics were summarized as number and percentage, and continuous patient characteristics were summarized as mean ± standard deviation. The Chi-square test and independent t-test were used to compare categorical and continuous characteristics and outcomes between groups. To analyze the impact of LV mass regression at 1 year on subsequent survival, a landmark analysis was performed, starting at 1 year of follow-up, to assess cumulative survival from this time point onward (Kaplan-Meier method). To compare survival between the two groups, the log-rank test and Cox regression analysis were used.

In a subset of patients with complete LV mass measurements up to two years follow-up, the presence or absence LV mass regression compared to baseline assessment was verified at each visit. All statistical tests were 2-sided, and the analyses were performed using R version 3.4.4 (R Development Core Team, Vienna, Austria, 2018).

Random measurement error

To quantify the potential role of random measurement error on the observed absence of

LV mass regression, sets of simulated data of 1000 subjects were generated. This allowed us to vary the values of parameters that potentially give rise to the observed relation between LV mass and baseline and change of LV mass at 1 year and assess their relative contributions. The baseline values of LV mass were assumed to be normally distributed with a mean of 190 g and a standard deviation of approximately 50 g, which is the result of natural ('true') variation between individuals and of random measurement error. The contribution of random measurement error was expressed as a percentage of the total observed variance (square of the standard deviation). The values of the follow-up measurement of LV mass were supposed to depend on the baseline value of LV mass and subject to the same random measurement error. Also, follow-up measurements were expected to follow a normal distribution with an observed standard deviation of 50, of which the same predefined percentage was due to measurement error. Random measurement error was thought to be independent of LV mass values and of each other. The relative reduction of true LV mass was assumed to be 0% to 20%, i.e., an average reduction of 10% or 0.1 gram per gram of LV mass. For each subject, a percentage of reduction was sampled from an uniform distribution.

Results

Baseline characteristics

Supplementary Figure 1 illustrates the study flow chart for the selection of patients for this analysis. In total, 683 patients with pure aortic stenosis and change in LV mass were included. Mean age was 70.3 ± 8.3 years, 511 (75%) was male and mean LV mass at baseline was 189 ± 54 g. The baseline and procedural characteristics according to the presence of LV mass regression are presented in Table 1. An average decrease in LV mass was observed during the first year of -25 ± 43 g. LV mass regression was present in 496 (73%) patients. There were no significant differences in patient and procedural characteristics between patients with or without LV mass regression, including prevalent hypertension (73% vs. 75%, p = 0.55) or implanted valve size (23.5 ± 2 mm vs. 23.2 ± 2, p = 0.055). Only Body Mass Index (BMI) was significantly higher in patients with absent LV mass regression (29 ± 5 vs 30 ± 6, p = 0.027).

Table 1. Patient characteristics of the study population according to presence of left ventricular mass regression after one-year follow-up.

	Present LVMR (n = 496)	**Absent LVMR (n = 187)**	**p value**
Age (years)	70 ± 8	70 ± 8	0.92
Male	376 (76%)	135 (72%)	0.38
Body surface area (m^2)	1.98 ± 0.2	1.99 ± 0.2	0.62
BMI (kg/m^2)	29 ± 5	30 ± 6	0.027
NYHA class III/IV	208 (42%)	77 (41%)	0.93
STS risk of mortality (%)	1.93 ± 1.3	1.84 ± 1.2	0.37
Congestive heart failure	94 (19%)	33 (18%)	0.78
Coronary artery disease	223 (45%)	81 (43%)	0.77
Hypertension	361 (73%)	141 (75%)	0.55
Renal insufficiency	43 (9%)	17 (9%)	0.98
Diabetes	129 (26%)	53 (28%)	0.60
Paroxysmal or chronic AF	48 (10%)	19 (10%)	0.96
Total CPB (minutes)	106 ± 39	107 ± 41	0.87
Total ACC (minutes)	82 ± 32	80 ± 30	0.67
Concomitant CABG	176 (35%)	61 (33%)	0.54
Label Valve Size (mm)	23.5 ± 2	23.2 ± 2	0.055

Data are presented as mean (SD), or number of patients (%). ACC – aortic cross clamp; AF – atrial fibrillation; BMI – body mass index; CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass; LVMR – Left ventricular mass regression; NYHA – New York Heart Association; STS – Society of Thoracic Surgery.

Echocardiographic parameters

As shown in Figure 1 and Table 2, LV mass and each of the three components to calculate LV mass (LVEDD, IVST and PWT) were lower at baseline, but higher at 1 year in patients with absent LV mass regression. There were no significant differences in mean gradient, indexed effective orifice area or Doppler velocity index at discharge. At 1-year, hemodynamic parameters were significantly in favor of patients with LV mass regression (Supplementary Figure 2), however there were no significant differences at 6 months or two-year follow-up. Cardiac output, LVEF and stroke volume were consistent between the groups at baseline and throughout follow-up.

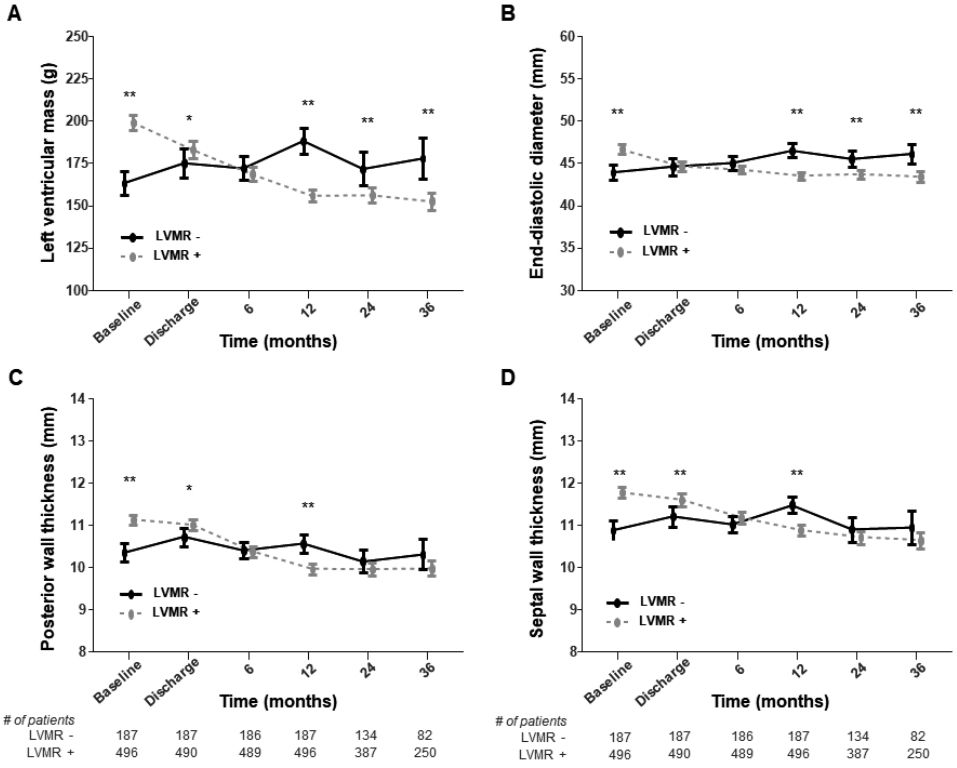


Figure 1. Changes in LV mass and its components according to presence of LV mass regression at one-year follow-up. LVMR + present left ventricular mass regression; LVMR - absent left ventricular mass regression; * $p < 0.05$; ** $p < 0.01$; LV mass (A); LV end-diastolic diameter (B); Posterior wall thickness (C); and septal wall thickness (D) over time in all patients.

In the subset of patients with complete LV mass measurements up to two years, 41 (43%) out of the 95 patients without LV mass regression from baseline to one-year follow-up, did have LV mass regression from baseline to two-year follow-up (Figure 2). Conversely, 33 (13%) out of 250 with LV mass regression, did not have LV mass regression from baseline to two-year follow-up. Only 162 (47%) patients were classified consistently as with or without LV mass regression at each follow-up visit.

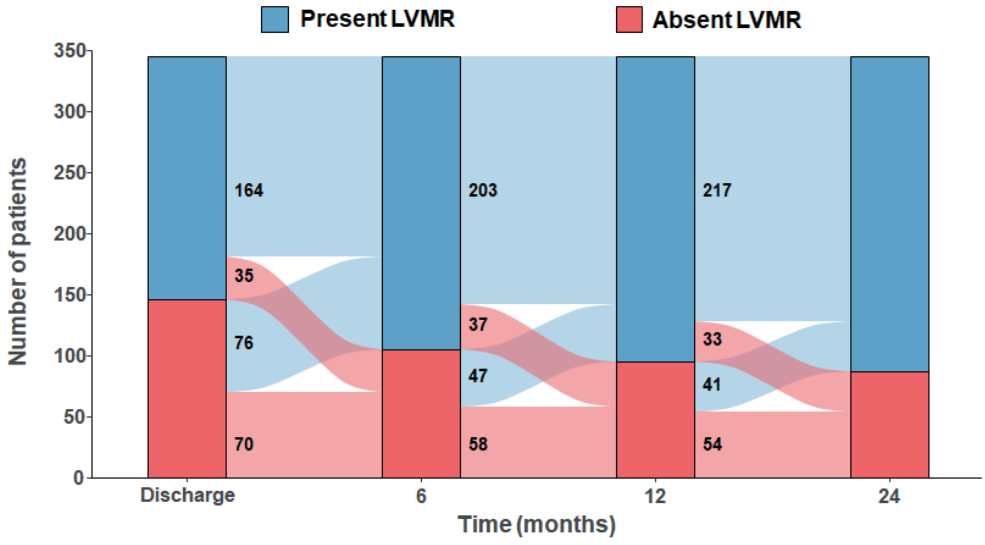


Figure 2. Consistency of present or absent LV mass regression compared to baseline assessment. LVMR – Left ventricular mass regression; In the subset of patients with complete LV mass measurements up to two years, 41 (43%) out of the 95 patients with absent LV mass regression from baseline to one-year follow-up, did have LV mass regression from baseline to two-year follow-up.

Table 2. Echocardiographic parameters according to presence of left ventricular mass regression after one-year follow-up.

	Baseline			Discharge			1 Year		
	Present LVMR (n = 496)	**Absent LVMR (n = 187)**	**p value**	**Present LVMR (n = 496)**	**Absent LVMR (n = 187)**	**p value**	**Present LVMR (n = 496)**	**Absent LVMR (n = 187)**	**p value**
LV mass (g)	199 ± 52	163 ± 49	<0.001	183 ± 50	175 ± 54	0.12	156 ± 40	188 ± 53	<0.001
LV mass index (g/m^2)	100 ± 23	82 ± 20	<0.001	93 ± 24	87 ± 23	0.012	79 ± 18	94 ± 21	<0.001
LV end-diastolic diameter (mm)	47 ± 6	44 ± 6	<0.001	45 ± 6	45 ± 6	0.98	43 ± 5	46 ± 6	<0.001
LV septal wall diameter (mm)	11.8 ± 1.5	10.9 ± 1.6	<0.001	11.6 ± 1.4	11.2 ± 1.5	0.007	10.9 ± 1.4	11.5 ± 1.3	<0.001
LV posterior wall diameter (mm)	11.1 ± 1.4	10.3 ± 1.5	<0.001	11 ± 1.3	10.7 ± 1.4	0.03	10 ± 1.4	10.6 ± 1.5	<0.001
Relative wall thickness	0.48 ± 0.08	0.48 ± 0.09	0.54	0.5 ± 0.08	0.49 ± 0.09	0.18	0.46 ± 0.09	0.46 ± 0.08	0.48
LV ejection fraction (%)	59 ± 10	60 ± 8	0.05	57 ± 10	59 ± 9	0.18	62 ± 8	62 ± 8	0.7
Stroke volume (ml)	77 ± 19	74 ± 17	0.086	66 ± 16	66 ± 17	0.99	73 ± 16	73 ± 16	0.72
Cardiac output (l/min)	5 ± 1.3	5 ± 1.2	0.77	5.1 ± 1.2	5 ± 1.3	0.53	4.6 ± 1	4.6 ± 1.1	0.85
Mean gradient (mmHg)	44.8 ± 16.3	41.7 ± 13.4	0.013	12.9 ± 4.5	13.2 ± 5.3	0.49	12.4 ± 4.3	13.7 ± 5.3	0.005
Doppler velocity index	0.25 ± 0.1	0.25 ± 0.06	0.61	0.49 ± 0.1	0.48 ± 0.1	0.58	0.46 ± 0.09	0.43 ± 0.09	0.005
Indexed EOA (cm/m^2)	0.41 ± 0.22	0.4 ± 0.11	0.21	0.8 ± 0.19	0.78 ± 0.22	0.24	0.76 ± 0.18	0.71 ± 0.16	0.002
Moderate and severe AR	62 (13%)	15 (8%)	0.13	1 (0%)	0 (0%)	1	4 (1%)	1 (1%)	1
Moderate and severe MR	14 (3%)	1 (1%)	0.13	3 (1%)	2 (1%)	0.91	21 (4%)	16 (9%)	0.041

Data are presented as mean ± SD or number of patients (%). AR – aortic regurgitation; EOA – effective orifice area; LV – left ventricular; LVMR – Left ventricular mass regression; MR – mitral regurgitation.

Clinical outcomes

The cumulative incidence of mortality and distribution of NYHA class over time is illustrated in Figure 3. At three-year follow-up, there were 14 (3%) and 7 (4%) deaths in the group of patients with and without LV mass regression, respectively. The absence of LV mass regression was not associated with all-cause mortality after the landmark of 1-year follow-up with an unadjusted hazard ratio of 1.44 [95% CI: 0.58-3.57]. The proportion of patients with NYHA III/IV at follow-up was similar between the two groups: 3% vs. 2%, 3% vs. 4% and 2 vs. 3% at 1,2 and 3 years, respectively.

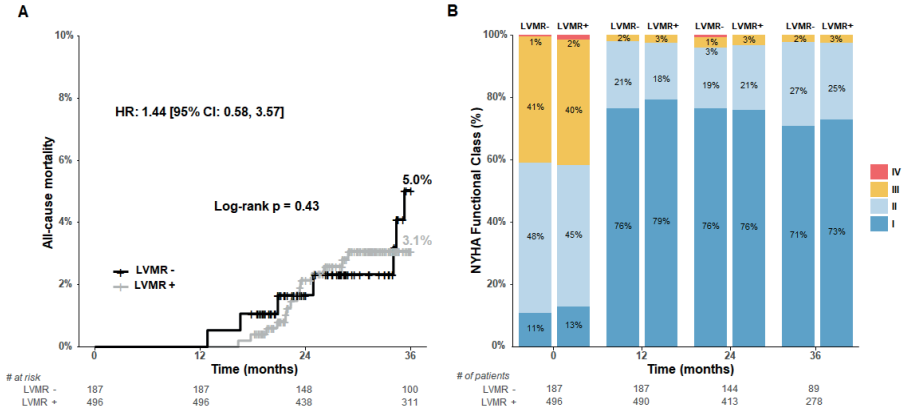


Figure 3. Clinical outcomes during follow-up according to presence of LV mass regression at one-year follow-up. LVMR + present left ventricular mass regression; LVMR - absent left ventricular mass regression; NYHA – New York Heart Association; No significant difference in all-cause mortality at 3-year follow-up (A); Similar distribution of NYHA class over time (B).

Impact of random measurement error

The impact of various degrees of random measurement error on the estimated relation between LV mass at baseline and the change in LV mass is shown in Figure 4. If no random measurement error is present (top left panel), the average regression from LV mass at baseline observed is 10% or 0.1 g per g LV mass at baseline. With an increasing percentage of random measurement error, the relation between LV mass at baseline and the change in LV mass becomes more negative because of regression to the mean. In Figure 5, the results are shown of the ensuing simulation together with the observed effect of LV mass at baseline on the change in LV mass in the PERIGON trial. In the simulated data set, 25% random measurement error resulted in an increased effect of LV mass at baseline on the change in LV mass (-0.10 vs -0.33 per g LV mass at baseline). The proportion of simulated patients with absent LV mass regression was 30%, versus 27% of the actual patients in the PERIGON trial.

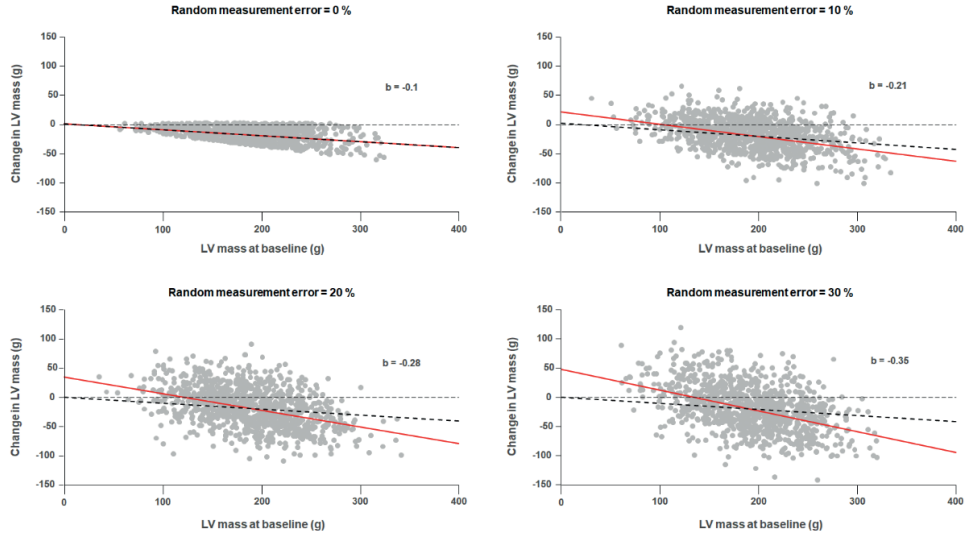


Figure 4. Impact of random measurement error on the relation between LV mass at baseline and change in LV mass. Each panel indicates the percentage of the observed variance in LV mass measurements that is due to random measurement error. The dashed black lines are regression lines in the absence of random measurement error and serve as a reference. The relative reduction of true LV mass was assumed to be 0% to 20%, i.e., an average reduction of 0.1 gram per gram LV mass. The red lines are the regression lines estimated in the presence of random measurement error (b = estimated regression coefficient). For each panel, 1000 observations were simulated (grey points represent simulated values).

Discussion

In line with previous work (1,12,13), we found a strong association between LV mass at baseline and degree of LV mass regression in the PERIGON trial. This finding can be interpreted as those patients with severe LV hypertrophy will benefit most of AVR. However, in 187 of 683 patients (27%) undergoing aortic valve replacement with a single type of bioprosthesis, no echocardiographic LV mass regression was observed during the first year of follow-up. We were unable to identify any clinical explanation for the absence of LV mass regression, and did not observe an association with inferior outcomes. Furthermore, low LV mass at baseline was not only associated with absence of LV mass regression, but even an observed increase of LV mass (Figure 5). It is hard to think of an etiologic cause; if patients with severe aortic stenosis did not develop LV hypertrophy, it is unlikely that they would rapidly develop this after surgery. The association between LV mass at baseline and degree of LV mass regression in this patient cohort, could well be explained by random measurement error, with the observed absence of LV mass regression being a consequence of regression to the mean. Absence of

echocardiographic LV mass regression does therefore not imply that reverse remodelling did not occur.

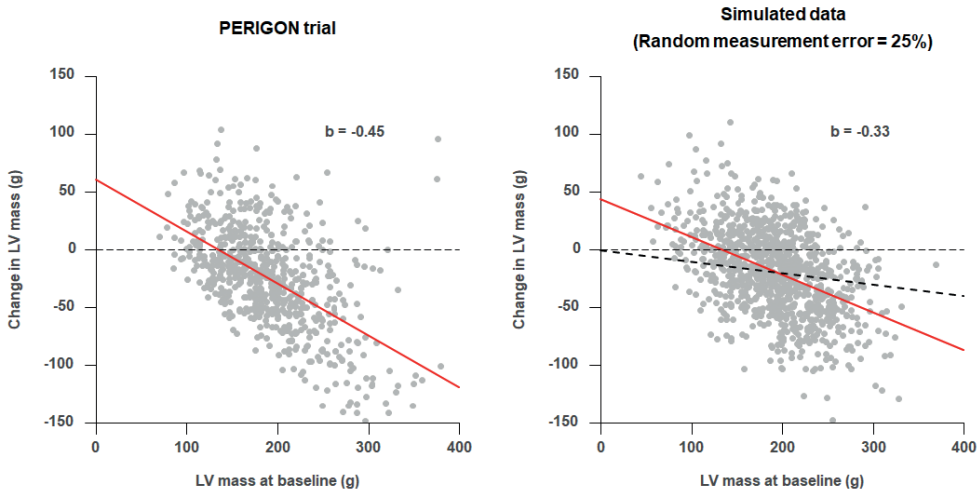


Figure 5. The relation of LV mass at baseline on the change of LV mass for simulated data and observed data from the PERIGON trial. The left panel displays the relation between LV mass at baseline and change in LV mass, as observed in the PERIGON Pivotal Trial. As represented by the red line, the slope for this relation was -0.45. In the right panel, 1000 observations were simulated (grey points represent simulated values) with a mean LV mass at baseline of 190 ± 50 g. The relative reduction of true LV mass was assumed to be 0% to 20%, i.e., an average reduction of 0.1g per gram LV mass (represented by the dashed black line). When 25% of the variance in LV mass measurements is due to random measurement error, a slope of -0.33 could be observed for the linear relation between LV mass at baseline and change in LV mass (red line).

As any measurement, determining LV mass is subject to some degree of random error. Random error refers to any non-systematic variation in the observed values around a true mean, either by random measurement error or random fluctuations in a patient (e.g. circadian blood pressure patterns) (14). When measurements are repeated in individual patients, random high measurements are likely to be followed by lower measurements, whereas random low measurements are more likely to be followed by higher measurements. This tendency for an extreme measurement to become less extreme when measured again is called regression to the mean (15). The larger the random error, the stronger the effect of regression to the mean will be (Figure 4).

This seems especially relevant for the calculation of LV mass with the standard ASE cube formula, as LV end-diastolic diameter, LV septal wall thickness and posterior wall thickness are all raised to the third power. This means that any random measurement error of these LV dimensions is also inflated by the power three. As a result, regression

to the mean of random measurement error can give a misleading impression about the effect of AVR on LV mass regression in individual patients. This includes the observed absence of LV mass regression, when true regression of LV mass is superseded by the regression to the mean effect in opposite direction (Figure 4).

Our simulated data were generated based on a simple model, which assumed measurement error to be random and not, for example, heteroscedastic or differential (16). Nevertheless, an almost identical relationship between LV mass at baseline and LV mass regression, as observed in the PERIGON trial, was generated with the contribution of 25% random measurement error to the total variance. Our hypothesis that the absence of LV mass regression is a statistical artefact is furthermore supported by the lack of major baseline and procedural differences between patients with and without LV mass regression. In addition, there was no difference in mortality and functional status after 1 year, which would be expected if the absence of LV mass regression was a true finding. Lastly, a substantial number of patients fluctuated between presence and absence of LV mass regression over consecutive follow-up visits (Figure 2).

Clinical implications

Our observations show that changes in LV mass observed with 2D-TTE, have inherent shortcomings and are therefore unsuitable to guide decision-making for the individual patient. The absence of LV mass regression does not necessarily convey that aortic valve replacement was ineffective. LV mass regression could still be used as an endpoint in randomized trials, as random measurement error is distributed evenly across treatment arms. However, interpretation of differences in LV mass regression will be hampered by the unclear effect size of LV mass regression on clinical outcomes. Further studies with accurate measurements of LV mass are required to establish whether there is any (predictive) clinical value of the extent of LV mass regression or that it generally leads to erroneous results. While no imaging modality is perfect, cardiac MRI may provide a superior alternative to 2D-TTE, as it has previously shown higher accuracy and reproducibility for the calculation of LV mass (2-4).

Limitations

The results from the simulated data sets combined with the lack of plausible clinical explanations provide a strong argument that regression to the mean of random measurement error explains the observed absence of LV mass regression in a quarter of patients. However, a shortcoming is the unavailability of repeated TTE measurements at the same time interval, to establish the exact between-study difference due to random measurement error. Therefore, this study is hypothesis-generating and requires further confirmation. Another limitation is that no tissue biopsies were performed to exclude

pathohistological myocardial changes. However, patient characteristics that could be associated with cardiac amyloidosis and fibrosis were evenly distributed between patients with and without absence of LV mass regression. In addition, we observed no difference in clinical outcomes between the two groups, which would be expected if cardiac amyloidosis or fibrosis was present.

Conclusions

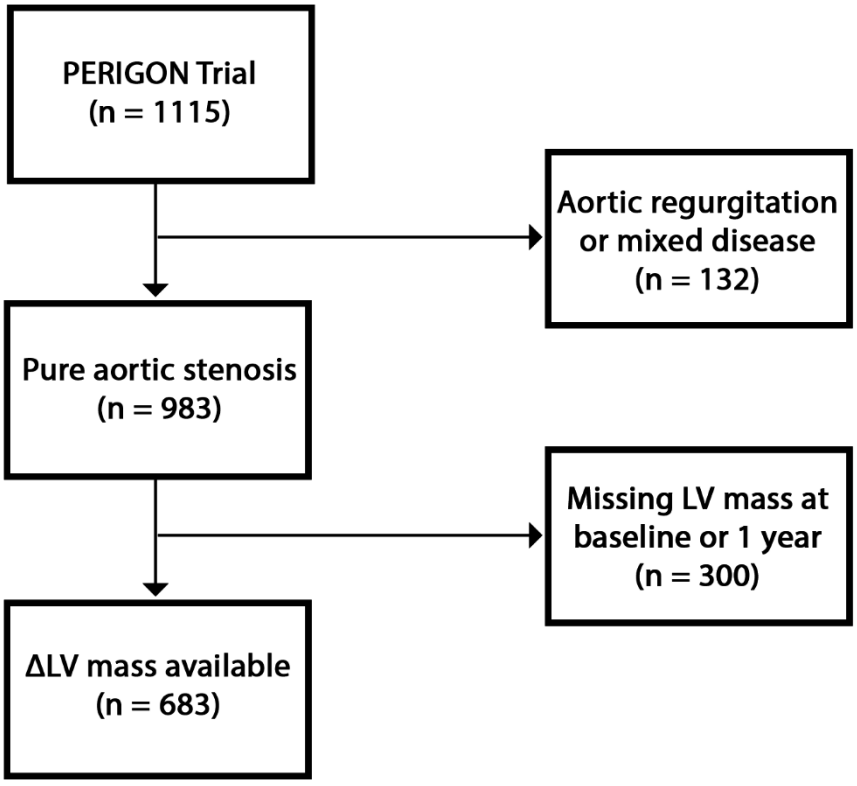
The absence of echocardiographic LV mass regression after AVR is likely explained by regression to the mean of random measurement error. This finding challenges the use of 2D-echocardiography to assess LV mass regression as an outcome measure of reverse remodeling after AVR.

References

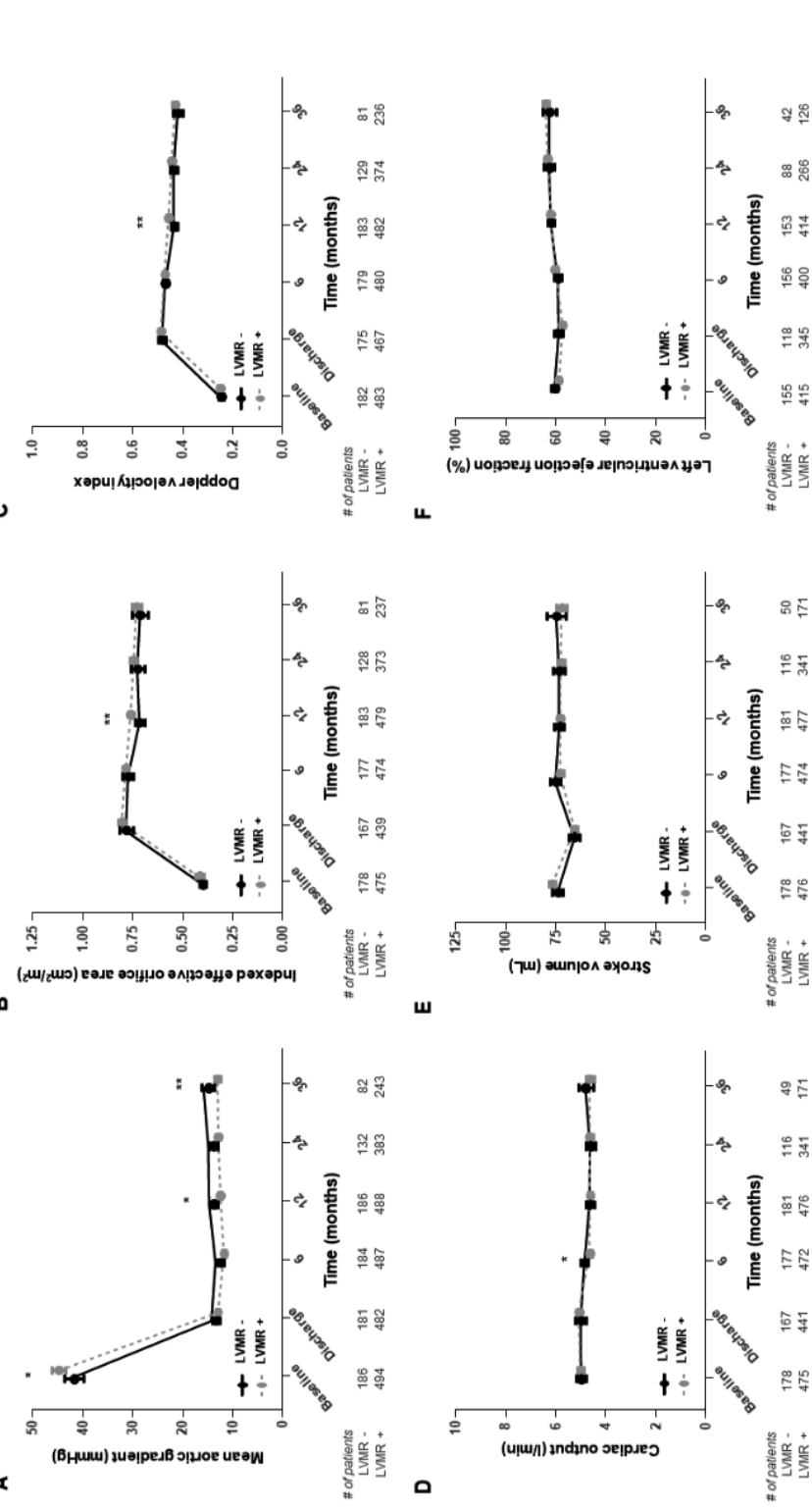
1. Chau KH, Douglas PS, Pibarot P, et al. Regression of Left Ventricular Mass After Transcatheter Aortic Valve Replacement: The PARTNER Trials and Registries. Journal of the American College of Cardiology. 2020;75:2446-2458.
2. Breitenbach I, Harringer W, Tsui S, et al. Magnetic resonance imaging versus echocardiography to ascertain the regression of left ventricular hypertrophy after bioprosthetic aortic valve replacement: Results of the REST study. The Journal of Thoracic and Cardiovascular Surgery. 2012;144:640-645.e641.
3. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. American Journal of Hypertension. 1995;8:221-228.
4. Myerson SG, Montgomery HE, World MJ, Pennell DJ. Left ventricular mass: reliability of M-mode and 2-dimensional echocardiographic formulas. Hypertension (Dallas, Tex. : 1979). 2002;40:673-678.
5. Kadkhodayan A, Lin G, Popma JJ, et al. A Paradox between LV Mass Regression and Hemodynamic Improvement after Surgical and Transcatheter Aortic Valve Replacement. Structural Heart. 2017;1:51-61.
6. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. The American Journal of Cardiology. 1986;57:450-458.
7. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.
8. Lessick J, Mutlak D, Markiewicz W, Reisner SA. Failure of Left Ventricular Hypertrophy to Regress after Surgery for Aortic Valve Stenosis. Echocardiography. 2002;19:359-366.
9. Vannan MA, Tridetti J, Lancellotti P. Intervention In Severe Aortic Stenosis: It May Be Time When the Left Ventricle Says So⋆. Journal of the American College of Cardiology. 2020;75:2459-2462.
10. Klautz RJM, Kappetein AP, Lange R, et al. Safety, effectiveness and haemodynamic performance of a new stented aortic valve bioprosthesis†. European Journal of Cardio-Thoracic Surgery. 2017;52:425-431.
11. Sabik JF, Rao V, Lange R, et al. One-year outcomes associated with a novel stented bovine pericardial aortic bioprosthesis. The Journal of Thoracic and Cardiovascular Surgery. 2018;156:1368-1377.e1365.
12. Gaudino M, Alessandrini F, Glieca F, et al. Survival after aortic valve replacement for aortic stenosis: does left ventricular mass regression have a clinical correlate? European Heart Journal. 2004;26:51-57.
13. Lim E, Ali A, Theodorou P, et al. Longitudinal study of the profile and predictors of left ventricular mass regression after stentless aortic valve replacement. 2008;85:2026-2029.
14. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. International Journal of Epidemiology. 2004;34:215-220.

15. Pocock SJ, Bakris G, Bhatt DL, Brar S, Fahy M, Gersh BJ. Regression to the Mean in SYMPLICITY HTN-3: Implications for Design and Reporting of Future Trials. Journal of the American College of Cardiology. 2016;68:2016-2025.
16. van Smeden M, Lash TL, Groenwold RHH. Reflection on modern methods: five myths about measurement error in epidemiological research. International Journal of Epidemiology. 2019.

Appendix



Supplementary Figure 1. Study flow chart. LV – left ventricular; ΔLV mass – change in LV mass during the first year of follow-up.



Supplementary Figure 2. Echocardiographic parameters of hemodynamic function during follow-up. LVMR + present left ventricular mass regression; LVMR - absent left ventricular mass regression; * $p < 0.05$; ** $p < 0.01$; Mean aortic gradient (A); Indexed effective orifice area (B); Doppler velocity index (C); Cardiac output (D); Stroke volume (E); and Left ventricular ejection fraction (F) over time in all patients