Clinical Significance of Electrocardiographic Markers of Myocardial Damage prior to Aortic Valve Replacement Running Title: ECG Strain, bundle branch block and aortic valve stenosis

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ABBREVIATIONS LIST

AS: Aortic Stenosis

AVR: Aortic Valve Replacement

ECG: Electrocardiogram

GLS: Global Longitudinal Strain

IBS: Integrated backscatter

LVH: Left Ventricular Hypertrophy

LVEF: Left Ventricular Ejection Fraction

NYHA: New York Heart Association

INTRODUCTION

Aortic valve replacement (AVR) is the only treatment that proved efficacy to reduce morbi-mortality in symptomatic patients with severe aortic stenosis (AS) (1,2). Nevertheless, one third of the patients remain symptomatic (3–5) or does not improve their functional capacities after surgery (6,7). This lack of improvement is believed to reflect accumulating myocardial damage, secondary to the long-standing pressure overload. In AS, the chronic increased afterload is known to induce compensatory left ventricular hypertrophy (LVH), to maintain normal wall stress and cardiac function, and progressive myocardial fibrosis, both associated with adverse outcomes after AVR (8–10). Recent findings regarding cardiac fibrosis and imaging have not been translated into daily practice since cardiac magnetic resonance imaging (MRI) is hardly accessible and speckle-tracking strain in transthoracic echocardiography (TTE) is not feasible in a substantial proportion of patients with AS due to poor echogenicity or atrial fibrillation. Unlike these imaging modalities, electrocardiogram (ECG) is a reliable and widespread tool to quickly assess the markers of a pathological myocardium. In line, a particular electrographic pattern called ECG strain has been described as a specific marker of mid-wall myocardial fibrosis on late gadolinium enhancement and T1 mapping cardiac MRI (11). This pattern has been associated with an increased risk of cardiovascular mortality and morbidity in asymptomatic severe AS (11,12) and after isolated surgical AVR (13). The fifth of patients with severe AS and presenting pre-operative intraventricular conduction abnormalities, i.e. left or right bundle branch block (LBBB or RBBB), were excluded in studies exploring the ECG strain pattern. To date, there is no large prospective study exploring the long-term prognostic impact of ECG markers of myocardial damage (i.e. intraventricular conduction abnormalities and ECG strain) after surgical or transcatheter AVR for severe AS. We hypothesized patients with pre-operative ECG markers

of ventricular myocardial damage to be at high risk of post-AVR cardiovascular complications irrespective of other prognostic factors.

METHODS

Study population and design

From April 2008 to October 2017, we prospectively studied consecutive patients with severe AS referred to our Heart Valve Clinic (CHU Lille) for an AVR (14,15). The operative technique (surgical or transcatheter) was based on current guidelines and left to the discretion of the Heart Team. Patients with another significant valvular disease, ventricular paced rhythm, a medical history of previous cardiac surgery or congenital heart disease were excluded. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Transthoracic echocardiography

A comprehensive pre-operative TTE including assessment of the aortic valve, was performed before AVR according to current guidelines (16) using state-of-the-art echocardiographic ultrasound systems (Vivid 7, Vivid E9 or Vivid E95, GE Healthcare, Little Chalfont, UK). From 2014, ultrasonic myocardial tissue characterization for the LV was implemented in routine: 2D speckle-tracking with systolic deformation analysis and integrated backscatter (IBS) were performed. IBS was obtained by placing region of interest in the mid-myocardium of anterior septum in parasternal long-axis view. IBS was then calibrated by subtracting pericardial IBS intensity as previously descried. (17)

Electrocardiogram

A standard pre-operative 12-lead ECG was recorded at 25 mm/s and 1 mV/cm for all participants. ECG interpretation was performed and adjudicated by several observers (AC, SN, FP, FJ, SM, HR, SO, CS, MW, AC, ALM, BB & DM) blinded to clinical and outcome

data. LVH was defined by a Romhilt-Estes score ≥ (5 points) or a Sokolow-Lyon index > 3.5 mV (18) and the ECG strain was defined as ≥0.1mV concave downsloping ST-segment depression with asymmetrical T-wave inversion in the lateral leads (I, aVL, V5, V6) as previously described. (19)

Baseline conduction abnormalities (left bundle branch block (LBBB), right bundle branch block (RBBB) were also recorded and defined in accordance with the American Heart Association recommendations (20). Our population was divided in 3 groups according to the following ECG patterns: group 1 = no ECG strain pattern, group 2 = ECG strain pattern, group 3 = baseline conduction abnormalities.

Follow-up

Patients were followed-up by direct patient interview and clinical examination, telephone calls with the physicians, patients or next of kin, or review of the autopsy records and death certificates. The following cardiac major events (ME) were recorded: cardiovascular deaths, cardiac hospitalizations for acute heart failure and stroke (21). All-cause mortality was also recorded. Any event was adjudicated by two independent investigators blinded to the index clinical and echocardiographic data.

Statistical analysis

Based on previous literature, we hypothesized that a third of AS patients would display hallmark of cardiac damage, a rate of ME at 5 years of 25% in patients without ECG strain and a rate of 35% in patients with hallmark of myocardial damage/fibrosis (8-22). This hypothesis implied that we had to analyse outcomes in at least 918 patients to obtain a statistical power of 90% and a probability of a type I error of 0.05 as previously described (23). Continuous variables were tested for normality with Shapiro test, and were given as mean±SD. Categorical variables were given as percentages of individuals. Patients were separated in three groups according to pre-operative ECG patterns. One-way ANOVA

analysis of variance was used for comparison of the three groups with Bonferroni post hoc t-test. Time-related clinical events were plotted with Kaplan-Meier curves according to ECG strain and conduction abnormalities definition and compared with log-rank tests. Cox proportional-hazards regression stepwise model was used to determine whether ECG strain and conduction abnormalities were associated with ME after adjusting for potential confounding variables. Variables with a value of $p<0.10$ on univariable analysis were incorporated into the multivariable model. A p value <0.05 was considered statistically significant. Unless specified, statistics were performed using MedCalc v16.4 (Olstead, Belgium).

RESULTS

Pre-operative ECG markers of ventricular myocardial damage in severe symptomatic AS.

A total of 1122 consecutive patients referred for AVR were included. Mean age was 73±11 years. The population was made of 56% of male, one fourth had diabetes and the large majority (91%) was symptomatic (New York Heart Association (NYHA) class ≥ 2). The mean LV ejection fraction (EF) was 59±10% and 78% underwent surgical aortic valve replacement (SAVR). ECG strain pattern was found in 236 patients (21%) and conduction abnormalities in 152 patients (13.5%). Characteristics of the population according to pre-operative ECG patterns are summarized in Table 1. A study flow chart is given in Supplemental Figure 1.

Patients with ECG fibrosis/damage hallmarks were older, more frequently men, with more severe symptoms (NYHA stage), with more advanced myocardial disease as reflected by higher LV mass index (LVMi), larger left atrium area together with lower LVEF, global longitudinal strain global (GLS) (respectively -14.8±4.6 and -13.8±4.1 vs. -16.6±4.4%, p=0.003) and IBS (respectively -21.3±11.0 and -21.4±11.0 vs. -28.6±7.9 dB, p=0.02) (Figures 1 & Supplemental Figure 2). Accordingly, patients with ECG strain displayed a higher prevalence of ECG LVH assessed by Romhilt-Estes score (72 vs. 20%, p<0.0001) or Sokolow-Lyon index (19 vs. 3%, p<0.0001). Atrial fibrillation and concomitant coronary artery bypass graft surgery were respectively present in 10% and 20% of the population with a similar prevalence in the 3 groups.

Prognostic impact of pre-operative ECG markers of ventricular myocardial damage.

The mean follow-up was 4.4±1.5 years. ME occurred in 212 patients (18.9%) with 113 cardiovascular deaths (10%), 89 cardiac hospitalizations for acute heart failure (8.0%) and 54 strokes (4.8%). All-cause deaths occurred in 257 patients (23.0%).

Both pre-operative ECG strain and conduction abnormalities were significantly associated with increase occurrence of ME in comparison with patients free from ECG strain, respectively (HR (95% confidence interval, CI): 1.56 (1.13-2.14), p=0.006, and 1.47 (1.02-2.13), p=0.04 (Figure 2A). While conduction abnormalities were significantly associated with both cardiovascular death and all-cause mortality, HR (95% CI) respectively: 2.31 (1.49-3.6), p=0.0002 and 1.49 (1.08-2.07), p=0.015, ECG strain was not (HR (95% CI) respectively: 1.27 (0.79-2.04), p=0.29 and 1.10 (0.85-1.58), p=0.34) (Figures 2B, 2C and Supplemental Figure 3).

On Cox univariable analysis, the occurrence of ME at 1500 days was significantly associated with old age, diabetes, hypertension, stroke, NYHA class, low pre-operative LVEF and mean aortic gradient, atrial fibrillation and the two ECG hallmarks of LV myocardial damage (Table 2). After multivariable adjustment using Cox regression analysis with stepwise selection of variables, old age, diabetes, high NYHA class, low LVEF and the presence of ECG strain were independently associated with long-term occurrence of ME (p=0.44 and Chi-squared=7.98 by Hosmer-Lemeshow test). ECG strain was predictive of ME independently of the type of AVR (HR: 1.40 (1.02-1.92); p=0.03). Intra-ventricular conduction abnormalities were not retained in the model.

DISCUSSION

Exploring the clinical impact of pre-operative ECG markers of ventricular myocardial damage in a large cohort of patients with severe AS undergoing AVR, we demonstrated that ECG strain and conduction abnormalities were frequent, i.e. respectively in 21% and 13.5% of patients. This was consistent with previous studies reporting prevalence of 14 to 31% of this ECG features. (11–13). Importantly, both ECG strain and conduction abnormalities were associated with long-term cardiac major events with conduction abnormalities also associated with all-cause and cardiovascular deaths. The presence of pre-operative ECG strain was independently associated with long-term occurrence of ME together the commonly reported factors of poor prognosis after AVR, i.e. old age, diabetes, high NYHA class and low LVEF (22-25).

To date, AVR is recommended in patients with severe AS and symptoms or with a LVEF < 50% (1,2). However, recent studies by Lancellotti et al. (22) and Tribouilloy et al. (23) demonstrated that patients with a LVEF respectively < 60% and < 55% are associated with an increased morbi-mortality even after AVR, suggesting that early (surgical or transcatheter) AVR should be considered to avoid irreversible myocardial damages. There is therefore a growing interest in studying the myocardial consequences of this valvular heart disease. We proposed here the simple ECG as an easy but efficient tool to improve multi-parametric risk stratification of patients prior to AVR, and thus refining the optimal timing of AVR by focusing on the myocardial repercussion of AS.

Although its physiopathology remains debated, previous studies showed that ECG strain is associated with an advanced hypertrophic response to AS with mid-wall fibrosis (12). Accordingly, we showed that patients with ECG hallmarks of myocardial damage were older, more frequently men, with more severe symptoms, lower LVEF, higher LVMi and larger left

atrium area. Moreover, in line with studies identifying GLS and IBS as tools to detect increased myocardial fibrosis (17, 23), these 2 parameters exploring the LV were significantly depressed in AS patients with BBB or ECG strain pattern.

In addition of being a marker of a more advanced disease, ECG strain was independently associated with poor outcomes, corroborating recent findings by Magne et al. (13).

Based on our findings, multiparametric stratification of patients with severe AS prior to AVR should integrate hallmarks of ventricular myocardial damage. BBB or ECG strain pattern should encourage consideration for early intervention at the time of low peri-operative morbi-mortality associated with both surgical and trans-catheter AVR.

Limitations

Assessment of myocardial fibrosis was restricted to TTE parameters since cardiac magnetic resonance (MRI) was not used routinely in our hospital in this population. The relative prognostic insights of MRI hallmarks of ventricle damage on top of the widely available ECG and TTE should be tested in future studies. We sought to investigate preoperative ECG markers, and not postoperative results of AVR (surgical or transcatheter), in order to help the preoperative multiparametric staging of cardiac damage to guide AVR. Accordingly, we decided not to include peri-operative and post-operative characteristics in the survival model.

Clinical Perspectives

ECG is a reliable and widespread tool to easily identify a subgroup of patients with extensive anatomical and functional cardiac damage secondary to AS that translate into higher incidence of cardiac events after AVR. It should help the multiparametric staging of cardiac damage to guide AVR.

CONCLUSION

BBB or ECG strain are observed in a third of AS patients referred for AVR. These ECG markers of myocardial damage identify a subgroup of patients with extensive anatomical and functional cardiac damage secondary to AS that translate into higher incidence of cardiac events after AVR.

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FIGURE LEGENDS

Figures 1. Ultrasonic myocardial characterization. Comparison of a) Global Longitudinal Strain and b) Integrated backscatter according to pre-operative ECG in the patients included since 2014. p-value by post-hoc t-test with Bonferroni correction. Mean ± SD.

Figures 2. Kaplan-Meier Survival Curves. Long-Term prognostic impact of pre-operative ECG markers of ventricular myocardial damage. Event-free survival from A) Major Events (cardiovascular death, stroke, or acute heart failure), B) Cardiovascular Deaths and C) All-Cause Deaths according to pre-operative ECG. P-value by log-rank test.

Supplemental Figure 1. Flow Chart

Supplemental Figure 2. Representative ultrasonic myocardial characterization and post-AVR outcomes according to pre-operative ECG. Patients with ECG strain or conduction abnormalities displayed lower SLG and IBS. ECG Strain was associated with the onset of ME and conduction abnormalities with the onset of ME, cardiovascular and all cause deaths

Supplemental Figure 3. Kaplan-Meier Survival Curves. Long-Term prognostic impact of pre-operative ECG markers of ventricular myocardial damage. Event-free survival from A) Acute heart failure, B) Stroke. P-value by log-rank test.

Table 1: Patients' characteristics according to pre-operative ECG (n=1122)

	All population (n=1122)	No ECG Strain (n=734)	ECG Strain (n=236)	Conduction abnormalities (n=152)	p-value
Pre-operative data					
Age (years)	72.9 ± 10.7	72.8 ± 10.7	71.1 ± 11.2	76.5 ± 9.3*#	**<0.001**
Gender Male n (%)	628 (56.0)	384 (51.5)	161 (68.2)	83 (54.6)	**0.0001**
BMI (kg/m^2)					
Smoker n (%)	234 (20.9)	144 (19.6)	65 (27.5)	25 (16.4)	**0.009**
Diabetes mellitus n (%)	306 (27.3)	203 (27.7)	68 (28.8)	35 (23.0)	0.42
Hypertension n (%)	729 (65.0)	481 (65.5)	151 (64.0)	97 (63.8)	0.86
Stroke n (%)	83 (7.4)	45 (6.1)	22 (9.3)	16 (10.5)	0.08
PAD n (%)	108 (9.6)	71 (9.7	23 (9.8)	14 (9.2)	0.85
CAD n (%)	229 (20.4)	140 (19.1)	62 (26.3)	27 (17.8)	0.38
NYHA n (%)					**0.0008**
1	97 (8.6)	72 (9.8)	17 (7.2)	8 (5.3)	
2	631 (56.2)	419 (57.1)	130 (55.1)	82 (53.9)	
3	317 (28.3)	211 (28.7)	59 (25.0)	47 (30.9)	
4	77 (6.9)	32 (4.4)	30 (12.7)	15 (9.9)	
TTE data					
LVEF (%)	59.1 ± 9.6	60.3 ± 8.4	56.2 ± 12.1*	58.8 ± 9.9*	**<0.001**
Max aortic velocity (m/s)	4.40 ± 0.68	4.4 ± 0.6	4.5 ± 0.8	4.3 ± 0.6	0.07
Mean gradient (mmHg)	50.6 ± 13.3	50.7 ± 12.3	52.6 ± 15.7 *	50.1 ± 13.5	**0.035**
LVMi (g/m²)	117.9 ± 33.0	111.7 ± 29.8	130.8 ± 36.4 *	127.9 ± 33.4 *	**<0.001**
LA surface (cm²)	25.8 ± 7.9	24.9 ± 8.0	27.1 ± 8.2 *	28.2 ± 5.7 *	**0.004**
ECG data					
Atrial Fibrillation n (%)	118 (10.5)	84 (11.4)	18 (7.6)	16 (10.5)	0.25
LVH Romhlit-Estes n (%)	319 (28.4)	149 (20.3)	170 (72.0)	--	**<0.0001**
LVH Sokolow-Lyon n (%)	69 (6.1)	25 (3.4)	44 (18.6)	--	**<0.0001**
Operative data					
SAVR n (%)	848 (78.3)	549 (74.8)	163 (69.1)	106 (69.7)	**0.0019**
Concomitant CABG n (%)	219 (19.5)	148 (20.2)	47 (19.9)	24 (15.8)	0.51

BMI: Body Mass Index; CAD: Coronary Artery Disease; LA: Left Atrium; LVEF: Left Ventricular Ejection Fraction; LVH: Left Ventricular Hypertrophy; LVMi: Left Ventricle Mass index; NYHA: New York Heart Association; PAD: Peripheral Artery Disease; SAVR: Surgical Aortic Valve Replacement

P-value by one-way anova analysis of variance with Bonferroni post hoc paired t-test

* for $p<0.05$ by post-hoc t-test vs no ECG strain; # for $p<0.05$ by post-hoc t-test vs ECG strain

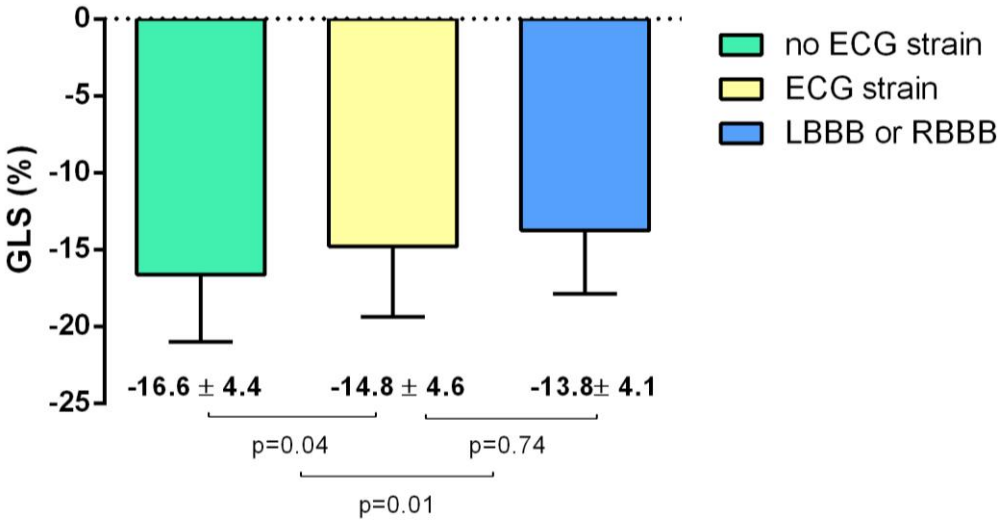
Table 2: Univariable and multivariable Cox analyses to assess determinants of ME after AVR

	Univariable analysis			Multivariable analysis		
	p-value	HR (95% CI)	β±SE	p-value	HR (95% CI)	β±SE
Age (years)	**<0.0001**		**0.04±0.008**	**0.008**		**0.02±0.008**
Gender n (%)	0.38	1.13 (0.86-1.49)				
BMI (kg/m^2)	0.43		0.01±0.01			
Smoker n (%)	0.73	1.06 (0.76-1.48)				
Diabetes mellitus n (%)	**0.001**	**1.61 (1.21-2.13)**		**0.0006**	**1.65 (1.24-2.20)**	
Hypertension n (%)	**0.04**	**1.37 (1.02-1 .83)**		--	--	--
Stroke n (%)	**0.05**	**1.57 (1.00-2.47)**		--	--	--
NYHA n (%)	**<0.0001**	**1.77 (1.48-2.13)**		**0.037**	**1.23 (1.01-1.50)**	
LVEF (%)	**<0.0001**		**-0.03±0.007**	--		--
Mean aortic gradient (mmHg)	**0.01**		**-0.01±0.006**	--	--	
LVMi (g/m²)	0.12		0.004±0.002			
Atrial Fibrillation n (%)	**0.0001**	**1.87 (1.45-2.95)**		**0.02**	**1.54 (1.07-2.23)**	
LVH Romhilt-Estes n (%)	0.22	1.21 (0.89-1.65)				
LVH Solow-Lyon n (%)	0.23	0.72 (0.53-1.16)				
ECG signs of fibrosis n (%)						
ECG Strain	**0.006**	**1.56 (1.13-2.14)**		**0.03**	**1.40 (1.02-1.92)**	
Conduction abnormalities	**0.04**	**1.47 (1.01-2.13)**		--	--	--
SAVR n (%)	**< 0.0001**	**0,29 (0,22-0,38)**		**< 0.0001**	**0,44 (0,31-0,62)**	

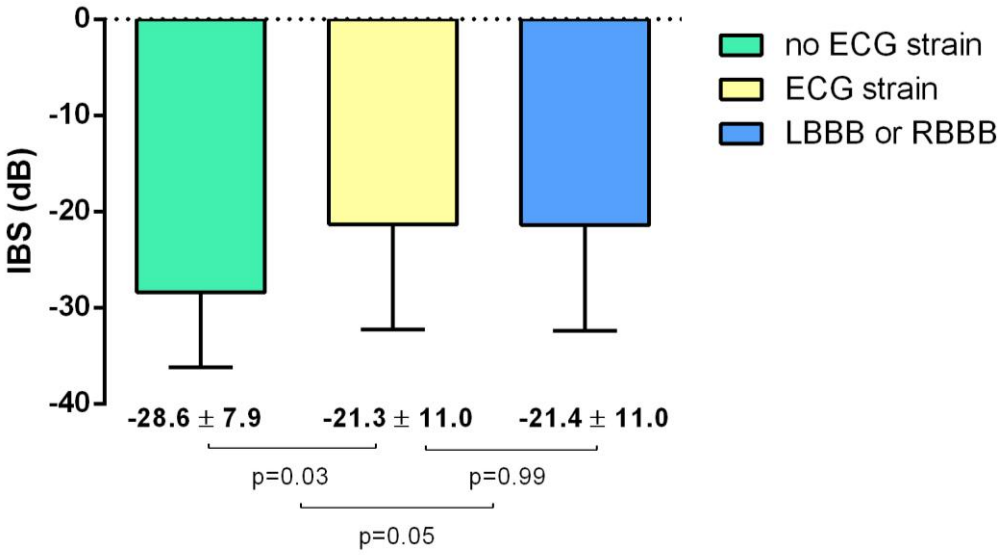
BMI: Body Mass Index; CAD: Coronary Artery Disease; LA: Left Atrium; LVEF: Left Ventricular Ejection Fraction; LVH: Left Ventricular Hypertrophy; LVMi: Left Ventricle Mass index; NYHA: New York Heart Association; PAD: Peripheral Artery Disease; SAVR: Surgical Aortic Valve Replacement

Figures 1. Ultrasonic myocardial characterization. Comparison of A. Global longitudinal strain and B. Integrated backscatter according to pre-operative ECG in the patients included since 2014. p-value by post-hoc t-test with Bonferroni correction. Mean +/- SD

A. Global longitudinal strain according to pre-operative ECG

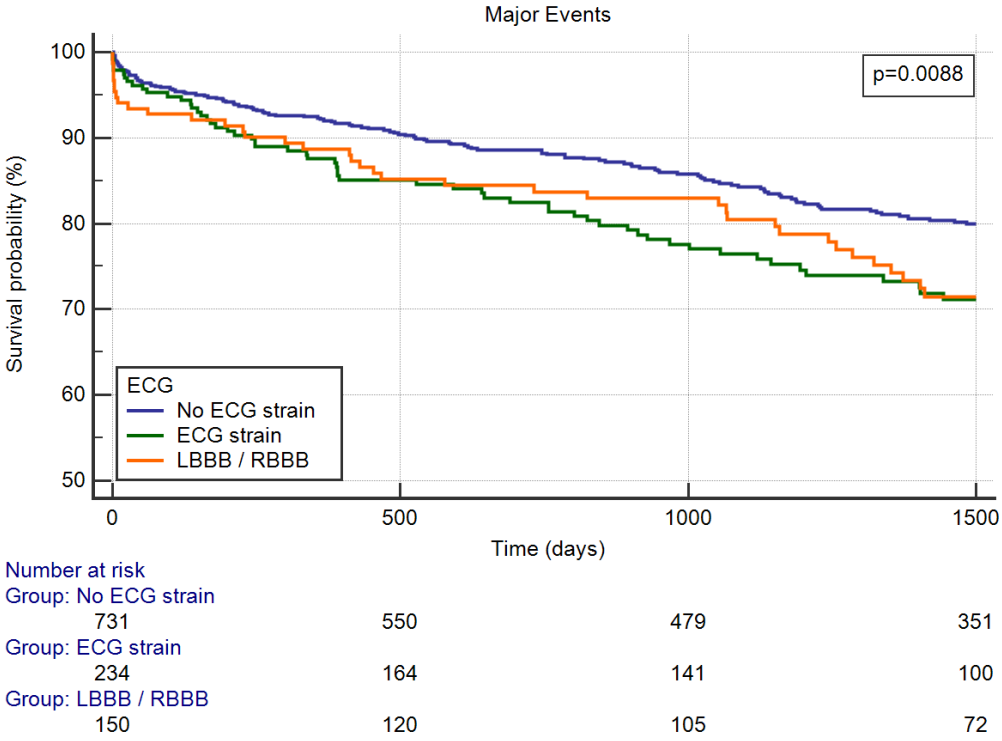


B. Integrated backscatter according to pre-operative ECG

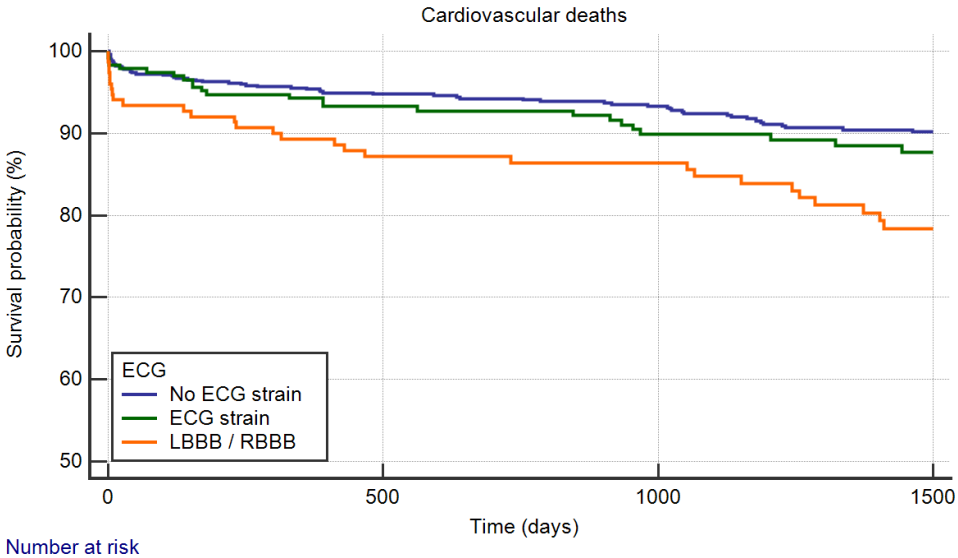


Figures 2. Kaplan-Meier Survival Curves. Long-Term prognostic impact of pre-operative ECG markers of ventricular myocardial damage. Event-free survival from A) Major Events (cardiovascular death, stroke or acute heart failure), B) Cardiovascular Deaths and C) All Cause Deaths, according to pre-operative ECG. P-value by log-rank test.

2A.



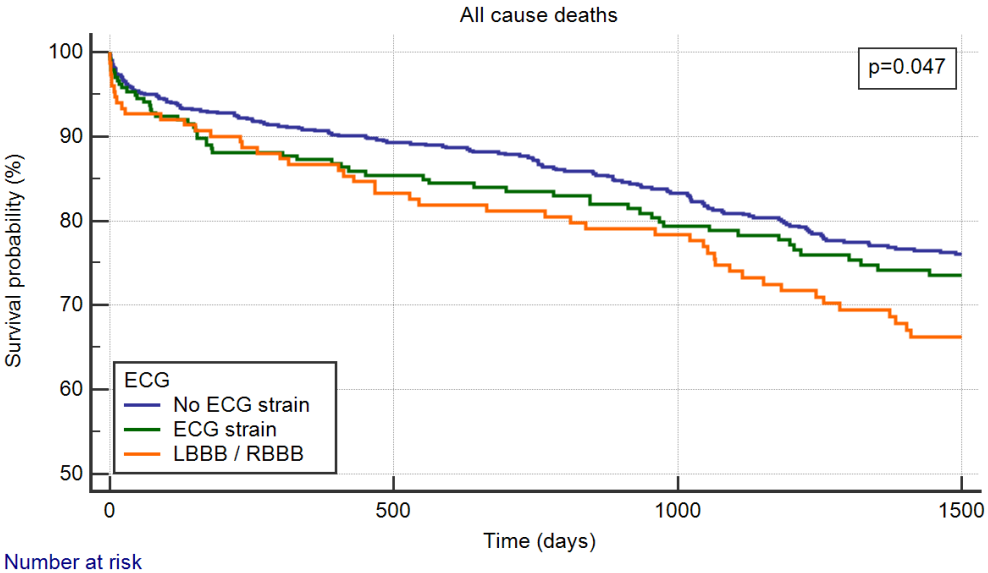
2B.



Number at risk

Group: No ECG strain			
730	564	502	368
Group: ECG strain			
234	176	156	115
Group: LBBB / RBBB			
149	122	109	78

2C.



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