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ORIGINAL RESEARCH

Electrocardiographic Strain Pattern Is a Major Determinant of Rehospitalization for Heart Failure After Transcatheter Aortic Valve Replacement

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BACKGROUND: Electrocardiographic strain pattern (ESP) has recently been associated with increased adverse outcome in aortic stenosis and after surgical aortic valve replacement. Our study sought to determine the impact and incremental value of ESP pattern in predicting adverse outcome after transcatheter aortic valve replacement.

METHODS AND RESULTS: A total of 585 patients with severe aortic stenosis (mean age, 83±7 years; men, 39.8%) were enrolled for transcatheter aortic valve replacement from November 2012 to May 2018. ESP was defined as ≥1-mm concave downsloping ST-segment depression and asymmetrical T-wave inversion in the lateral leads. The primary end points of the study were all-cause mortality, rehospitalization for heart failure, myocardial infarction, and stroke. A total of 178 (30.4%) patients were excluded because of left bundle-branch block (n=103) or right bundle-branch block (n=75). Among the 407 remaining patients, 106 had ESP (26.04%). At a median follow-up of 20.00 months (11.70–29.42 months), no impact of electric strain on overall and cardiac death could be established. By contrast, incidence of rehospitalization for heart failure was significantly higher (33/106 [31.1%] versus 33/301 [11%]; $P<0.001$) in patients with ESP. By multivariate analyses, ESP remained a strong predictor of rehospitalization for heart failure (hazard ratio, 2.75 [95% CI, 1.61–4.67]; $P<0.001$).

CONCLUSIONS: In patients with aortic stenosis who were eligible for transcatheter aortic valve replacement, ESP is frequent and associated with an increased risk of postinterventional heart failure regardless of preoperative left ventricular hypertrophy. ESP represents an easy, objective, reliable, and low-cost tool to identify patients who may benefit from intensified postinterventional follow-up.

Key Words: aortic stenosis ■ heart failure ■ transcutaneous aortic valve implantation

Transcatheter aortic valve replacement (TAVR) has become the method of choice for patients with severe aortic valve stenosis in selected high- and intermediate-risk patients for cardiac surgery. Today's issue relies in identifying patients with a predictable poor outcome despite technically successful TAVR. Therefore, risk models, blood biomarkers, and echocardiographic markers have been extensively studied to improve risk stratification and identify specific subgroups at higher risks. The extent and nature of heterogeneity in the population with aortic stenosis (AS) rely mainly on valve-related factors, symptoms, and comorbidities. Myocardial response to pressure overload includes left ventricular hypertrophy (LVH) and myocardial fibrosis, both associated with adverse outcomes.[1–6]

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CLINICAL PERSPECTIVE

What Is New?

- Incremental value of electrocardiographic strain pattern in predicting rehospitalization for heart failure in patients with symptomatic severe aortic stenosis who underwent transcatheter aortic valve replacement was determined.

What Are the Clinical Implications?

- Electrocardiographic strain pattern helps to identify patients with a high risk for post–transcatheter aortic valve replacement acute heart failure.
- Patients with electrocardiographic strain pattern may benefit from an extended and intensified postinterventional follow-up.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
ESP	electrocardiographic strain pattern
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TTE	transthoracic echocardiography

An electrocardiographic pattern of LVH and strain has recently been associated with midwall myocardial fibrosis,[1,2] increased risk of cardiovascular morbidity, and mortality in asymptomatic AS and in those undergoing surgical aortic valve replacement (SAVR).[2–6] However, the relation of electrocardiographic left ventricular (LV) strain and cardiovascular outcomes in patients who underwent TAVR is sparse. Therefore, the present study aimed to (1) better characterize the prevalence of electrocardiographic strain pattern (ESP) in patients undergoing TAVR, (2) evaluate potential predictors, and (3) assess the impact of ESP on survival and the risk of adverse events among patients with severe AS undergoing TAVR.

METHODS

The data that support the findings of this study are available from the corresponding author on request.

Patients

A total of 585 patients with severe AS, according to current guideline classification,[7] and high or intermediate surgical risk, according to logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), who underwent TAVR between November 2012 and May 2018 at our institution (Nouvel Hôpital Civil, Strasbourg University, Strasbourg, France) were enrolled. Patients with baseline left bundle-branch block, right bundle-branch block, or ventricular paced rhythm were excluded from further analysis. The study protocol was approved by the Commission Nationale de l'Informatique et des Libertés committee (ethical code No. 911262). All patients gave written informed consent.

Electrocardiographic Analysis

A resting 12-lead ECG (scale, 10 mm=1 mV; speed, 25 mm/s) was acquired in all subjects the day before TAVR procedure and 1 month after the procedure. Electrocardiographic interpretation was performed by 2 independent and experienced clinicians, blinded to the patients' clinical details.

ESP was defined as ≥1-mm concave down-sloping ST-segment depression and asymmetrical T-wave inversion in the lateral leads (I, aVL, V5, and V6), as previously described.[8]

Exclusion criteria from further analysis were complete left bundle-branch block, right bundle-branch block, or ventricular paced rhythm. Heart rate, QT, corrected QT, PR, and QRS intervals were calculated. Validated electrocardiographic criteria of LVH were measured. This included the following: (1) the voltage of R wave in lead aVL, (2) the Sokolow-Lyon Index, which was defined as the amplitude of leads SV1+RV5 or RV6 (whichever is larger), and (3) the Cornell voltage criteria, which were measured as the amplitude of R wave in lead aVL+S wave in lead V3. The electrical LVH was assessed by Cornell voltage criteria (S in V3+R in aVL >28 mm for men or S in V3+R in aVL >20 mm for women) or Sokolow-Lyon criteria ≥35 mm.

Collection of Data and Outcomes

All baseline preoperative clinical data, risk factors, comorbidities, and follow-up variables were recorded and entered into a secure, ethics-approved database. Clinical end points, including mortality, stroke, bleeding, access-related complications, and conduction disturbances, were assessed according to the definitions provided by the Valve Academic Research Consortium-2. All patients underwent echocardiography before TAVR and at 30 days of follow-up. Echocardiographic LVH was defined according to current standard and recommendations (LV mass index >115 g/m^2 for men or >95 g/m^2 for women).[9] Significant paravalvular aortic regurgitation at 30 days was defined by transthoracic echocardiography (TTE) as a circumferential extent of regurgitation >10% (Valve Academic Research Consortium-2). All clinical events were adjudicated by an events validation committee.

All patients were contacted by telephone and questioned by a standardized questionnaire about their health status, symptoms, medications, and the occurrence of adverse events. In case of no response, data were obtained from family physician telephone contacts or hospital records.

The co–primary end points of the study were the overall all-cause mortality after TAVR, cardiovascular death (defined as death resulting from myocardial infarction, sudden cardiac death, heart failure [HF], stroke, or other cardiovascular causes), rehospitalization for heart failure (defined as any event requiring the administration of intravenous therapy), and myocardial infarction and stroke, assessed separately and by a composite end point (major adverse cardiac event).

The secondary end points were echocardiographic data at 1-month follow-up (prosthetic valve function and LV parameters), pacemaker implantation at 1 month, and postprocedural bleeding.

Statistical Analysis

Quantitative variables were described by group of ESP and expressed as mean±SD. Categorical variables were expressed as numbers and percentages. Categorical variables were compared with χ^2 tests or Fisher exact tests. Continuous variables were compared with the use of parametric (ANOVA) or nonparametric Mann-Whitney tests, as appropriate. To determine predictors of rehospitalization for HF, regression analysis was performed. Variables with $P<0.05$ in univariate analysis were entered into a stepwise ascending multivariate analysis. Survival and rehospitalization data were calculated from the time of the TAVR to the date of last follow-up available. The impact of ESP and echocardiographic LVH on both survival and rehospitalization for cardiac decompensation after TAVR was assessed using both univariate and multivariate Cox hazard model. Variables with a univariate $P<0.05$ were considered for subsequent multivariate models. Results are presented as hazard ratios (HRs) with 95% CIs. Proportional hazards assumption has been tested and was valid for the variables of interest. $P<0.05$ was considered significant. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL).

Intraobserver and interobserver variability was analyzed in 10% of the total cohort (n=41) by 2 independent observers blinded to the strain results. Variability of the different ESPs was calculated by intraclass correlation coefficient and showed excellent reproducibility (intraclass correlation coefficient >0.80).

RESULTS

Demographics

Among the 585 eligible patients undergoing TAVR, 178 (30.4%) were excluded from analyses because of the presence of right bundle-branch block (n=75), left bundle-branch block, or ventricular paced rhythm (n=103) (Figure 1). Patients with ventricular paced rhythm were included in the left bundle-branch block group. Of the 407 patients included in this study, ESP (Figure 2) was documented in 106 (26.04%). Patients with ESP were more likely to have a history of myocardial infarction, coronary artery bypass grafting, and diabetes mellitus and lower body mass index. HF was more frequently recorded at admission, with a more frequent Killip 4 status. Lower LV ejection fraction (LVEF), increased LV

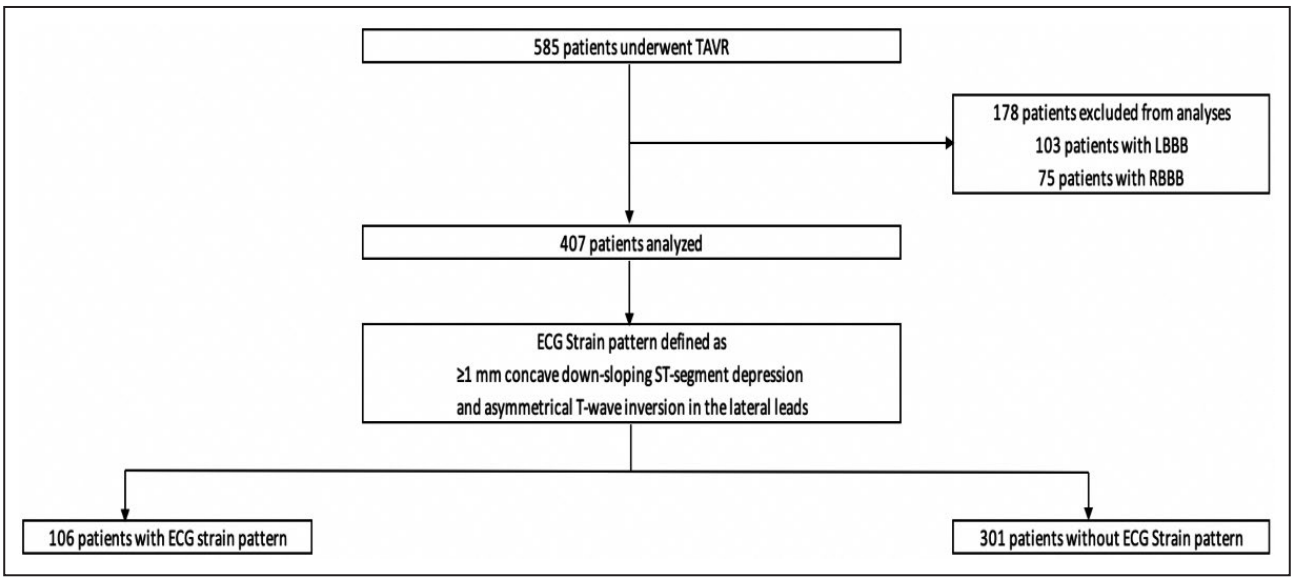

Figure 1. Flowchart of the study.
LBBB indicates left bundle-branch block; RBBB, right bundle-branch block; and TAVR, transcatheter aortic valve replacement.

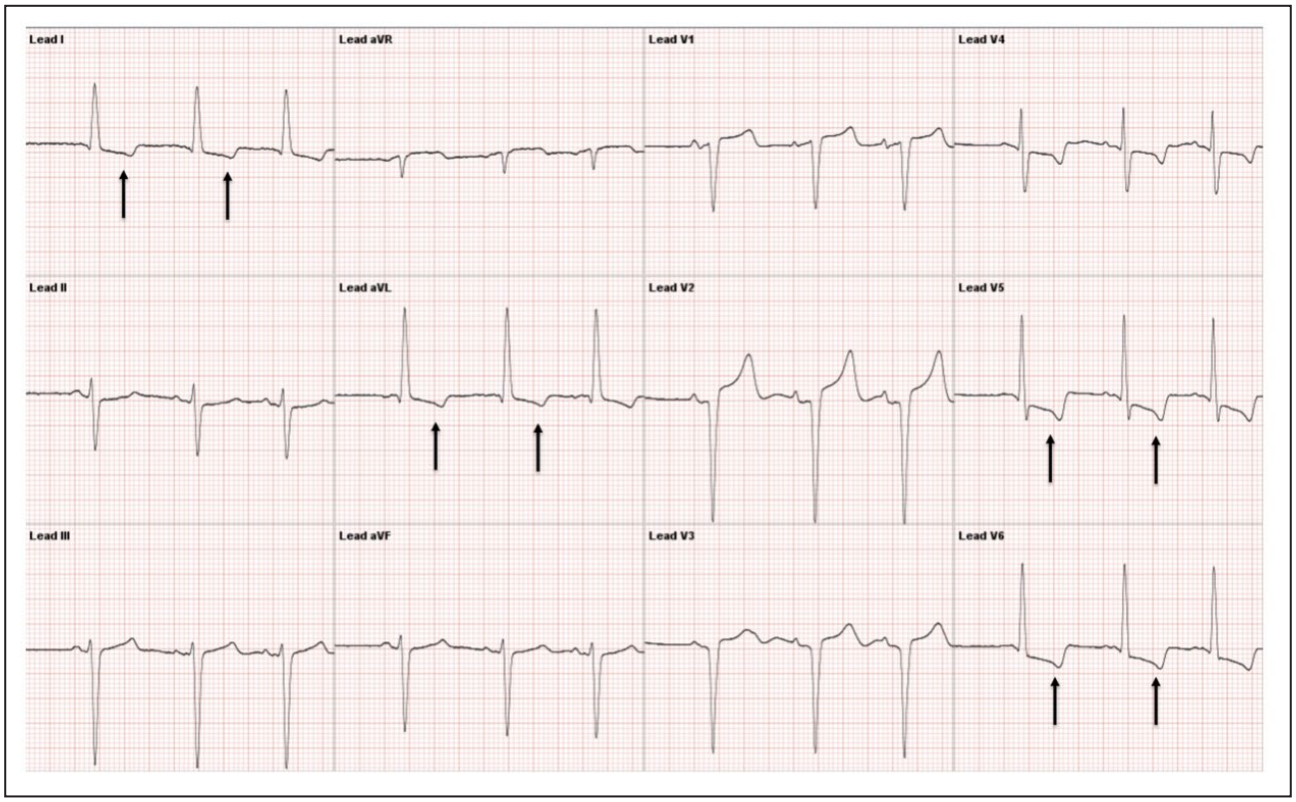

Figure 2. Electrocardiographic strain pattern (black arrows) in a patient with severe aortic stenosis admitted for transcatheter aortic valve replacement.

mass, adverse LV remodeling (assessed by increased left ventricular end-diastolic diameter and left ventricular end-systolic diameter), and greater transvalvular aortic gradient at baseline were more frequently recorded among patients with ESP. Consistent with an increasing severity of AS, smaller aortic valve area was evidenced in patients with ESP. Both electrocardiographic criteria of increased LV mass (Cornell voltage criteria or Sokolow-Lyon index) and echocardiographic LVH were more frequently evidenced in patients with ESP.

Increased intraventricular conduction time (based on the mean QRS duration) and atrioventricular conduction time (based on mean PR interval duration) were observed in the group with ESP. Baseline characteristics, stratified by the presence or absence of ESP, are summarized in Table 1. Procedural management together with discharge antithrombotic medications are displayed in Table 2 and did not differ between the 2 subsets of patients. There was no significant difference between the 2 groups at baseline and for post-TAVR biological parameters (Table 3).

Prognostic Impact of ESP

The impact of ESP on primary and secondary end points is given in Table 4. At a median follow-up of 20.00 months (11.70–29.42 months), death from any cause and cardiac death did not differ significantly between groups (Figure 3). There was no statistically significant difference for myocardial infarction, stroke, and HF events at 1-month follow-up. Major adverse cardiac events at 1 month, assessed by a composite of death from any cause and/or stroke and/or hospitalization for HF and/or myocardial infarction, showed similar incidence. By contrast, rehospitalization for HF was significantly higher in patients with ESP (33/106 [31.1%] versus 33/301 [11%]; $P<0.001$) (Table 4 and Figure 4).

Paravalvular aortic regurgitation, assessed by either TTE or with prolonged ADP closure time (a primary hemostasis point-of-care test validated to identify the presence of paravalvular aortic regurgitation[10]), postprocedural bleeding, pacemaker implantation at 1 month, and echocardiographic remodeling, assessed by left ventricular end-diastolic diameter and left ventricular end-systolic diameter at 30-day follow-up, were not significantly different among the 2 groups. However, LVEF after 1-month follow-up remained lower in patients with ESP.

Prognostic Impact of Electrocardiographic Strain Resolution

Of the original cohort of 106 ESP-positive participants at baseline, there were 73 patients (68.9%) with further electrocardiographic data available at 1-month follow-up

Table 1. Baseline Characteristics, According to ESP Status

Characteristics	Whole Population (n=407)	ESP (n=106)	No ESP (n=301)	*P* Value
Clinical parameters				
Age, y	83.0±7.5	81.6±8.9	83.5±6.8	0.022
Male sex, n (%)	162 (39.8)	44 (41.5)	118 (39.2)	0.38
Logistic EuroSCORE, %	17.2±12.5	18.5±12.4	16.8±12.6	0.24
BMI, kg/m^2	27.5±6.3	26.3±4.5	27.9±6.8	0.020
Killip class on admission, n (%)				
II	179 (44.0)	40 (37.7)	139 (46.2)	0.08
III	195 (47.9)	51 (48.1)	144 (47.8)	0.53
IV	33 (8.1)	15 (14.2)	18 (6.0)	0.009
History of myocardial infarction, n (%)	49 (12.0)	19 (17.9)	30 (10)	0.030
History of PCI, n (%)	126 (31.0)	39 (36.8)	87 (28.9)	0.13
CABG, n (%)	37 (9.1)	19 (17.9)	18 (6.0)	<0.001
PAD, n (%)	119 (29.2)	33 (31.1)	86 (28.6)	0.62
AF history, n (%)	161 (39.6)	34 (32.1)	127 (42.2)	0.042
Chronic kidney disease (creatinine level >150 µmol/L), n (%)	73 (17.9)	22 (20.8)	51 (16.9)	0.23
Stroke history, n (%)	61 (15.0)	20 (18.9)	41 (13.6)	0.13
Chronic obstructive pulmonary disease, n (%)	59 (14.5)	12 (11.3)	47 (15.6)	0.18
Current smoking, n (%)	11 (2.7)	4 (38)	7 (2.3)	0.31
Hypertension, n (%)	324 (79.8)	87 (82.9)	237 (78.7)	0.22
Diabetes mellitus, n (%)	134 (33.0)	45 (42.9)	89 (29.6)	0.009
Insulin-requiring diabetes mellitus, n (%)	38 (9.4)	17 (16.2)	21 (7.0)	0.006
Dyslipidemia, n (%)	224 (55.2)	64 (61.0)	160 (53.2)	0.10
Prehospital antithrombotic management, n (%)				
Single APT	219 (53.9)	69 (65.1)	150 (50)	0.005
Dual APT	84 (20.6)	27 (25.5)	57 (18.9)	0.10
Anticoagulant therapy	148 (36.4)	34 (32.1)	114 (37.9)	0.17
Echocardiography				
LVEF, %	56.7±12.3	51.8±15.0	58.4±10.7	<0.001
Echocardiography-based LV hypertrophy, n (%)	251 (76.5)	78 (87.6)	173 (72.4)	0.002
LV mass, g/m^2	126.9±32.7	135.9±33.4	123.6±31.9	0.002
Interventricular septum thickness, mm	12.3±2.5	12.4±2.6	12.3±2.5	0.72
LV posterior wall thickness, mm	11.1±2.2	11.3±2.6	11.0±2.0	0.36
LVEDD, mm	49.2±7.0	50.4±7.6	48.7±6.7	0.042
LVESD, mm	33.2±8.8	35.8±10.0	32.3±8.1	<0.001
Mean aortic pressure gradient, mm Hg	49±12.9	52.3±15.2	47.9±11.8	0.003
AVAi, cm^2/m^2	0.41±0.10	0.39±0.11	0.41±0.10	0.025
Systolic PAP, mm Hg	40.1±13.3	42.2±12.8	39.4±13.4	0.08
ECG				
Sinus rhythm, n (%)	309 (75.9)	82 (77.4)	227 (75.4)	0.40
AF, n (%)	98 (24.1)	24 (22.6)	74 (24.6)	0.40
Heart rate, bpm	73±13	73±13	73±13	0.55
PR interval in sinus rhythm, ms	186.6±40.2	195.8±45.1	183.3±37.9	0.015
QRS, ms	102±13	105±12	100±12	<0.001
QT interval, ms	416±40	427±42	412±39	0.002
Corrected QT interval, ms	455±36	463±39	452±34	0.004

(*Continued*)

Table 1. Continued

Characteristics	Whole Population (n=407)	ESP (n=106)	No ESP (n=301)	*P* Value
R wave in lead aVL, mV	7.1±4.4	9.1±5.7	6.4±3.7	<0.001
S wave in lead V3, mV	10.5±5.4	12.4±6.3	9.9±4.9	<0.001
Cornell voltage criteria, mV	17.7±7.2	21.5±7.9	16.3±6.4	<0.001
Sokolow-Lyon index, mV	21.7±8.9	28.2±9.4	19.4±7.5	<0.001
LVH by Cornell voltage criteria, n (%)	84 (20.6)	41 (38.7)	43 (14.3)	<0.001
LVH by Sokolow-Lyon index, n (%)	36 (8.8)	25 (23.6)	11 (3.7)	<0.001
LVH by Sokolow-Lyon index or Cornell criteria, n (%)	103 (25.3)	53 (50)	50 (48.5)	<0.001
LVH by Sokolow-Lyon index and Cornell criteria, n (%)	17 (4.2)	13 (76.5)	4 (23.5)	<0.001

Data are presented as mean±SD or number (percentage). Echocardiographic LVH was defined according to current standard and recommendations (LV mass index >115 g/m^2 for men or >95 g/m^2 for women). AF indicates atrial fibrillation; APT, antiplatelet therapy; AVAi, indexed aortic valvular area; BMI, body mass index; bpm, beats per minute; CABG, coronary artery bypass grafting; Cornell criteria for LVH, S in V3+R in aVL >28 mm (men) and S in V3+R in aVL >20 mm (women); Cornell voltage criteria, R wave in lead aVL+S wave in lead V3; ESP, electrocardiographic strain pattern; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVH, LV hypertrophy; PAD, peripheral artery disease; PAP, pulmonary artery pressure; and PCI, percutaneous coronary intervention.

(available electrocardiographic data included data from those without conduction abnormalities or ventricular paced rhythm). Persistent electrocardiographic strain was evidenced in 41 patients (56.2%), and strain regression was evidenced in 32 patients (43.8%). Baseline characteristics, echocardiographic data, and biological parameters were not significantly different among ESP^{persistent}/ESP^{resolution} patients. Predictive factors of strain resolution were studied among the 73 patients. In this small subset of patients, no significant predictor of ESP resolution could be established. Rehospitalization for HF was 29.3% in ESP^{persistent} patients and 25% in ESP^{resolution} patients (Table S1).

Predictors of HF Rehospitalization Following TAVR

By univariate Cox analysis, body mass index, insulin-requiring diabetes mellitus, mean transprosthetic pressure gradient at 1-month follow-up, post-TAVR pacemaker, and ESP strain pattern (HR, 2.62 [95% CI, 1.61–4.28]; *P*=0.001) were significant predictors of rehospitalization for HF (Table 5).

In multivariate analysis, body mass index, insulin-requiring diabetes mellitus, mean prosthetic pressure gradient at 1-month follow-up, pacemaker implantation after TAVR, and ESP remained strong independent factors, associated with rehospitalization for HF after TAVR. More important, no significant impact on LVH, assessed by either electrocardiographic or TTE criteria, and rehospitalization for HF could be demonstrated (Figures 5 and 6).

DISCUSSION

The current report, drawn from a cohort of 407 patients with AS, aimed to specifically assess the occurrence and prognostic impact of ESP in patients undergoing TAVR. The salient results of the present study are as follows: (1) ESP was evidenced in a sizeable proportion of patients with AS (26.04%), (2) ESP was associated with increased echocardiographic AS severity (mean aortic gradient, aortic valve area, altered LVEF, and Killip class at admission) and increased conduction disturbances, (3) ESP was not associated with an increased mortality rate at 1-year follow-up, and (4) ESP was a strong independent predictor of HF recurrence after TAVR regardless of LVH.

Prevalence of ESP in AS

In line with the present work, several reports have emphasized the high frequency and dismal prognosis of ESP in patients with AS. The incidence of ESP in our population (26.04%) was similar to those previously reported and ranging from 12% to 31%.[2–5,11] Previous report by Guinot et al[3] recorded similar rate of ESP (28%) among 390 patients with AS referred for isolated SAVR. Despite similar ESP incidence in this study, patients were younger (74±10 years), had a lower risk profile (EuroSCORE II, 2.1%±1.5%), and had a 4-fold increased risk of long-term mortality among patients with ESP. Electrocardiographic strain was recently observed in 21% of 1122 patients referred for aortic valve replacement (either surgical or transcatheter).[12]

Impact of Electrocardiographic Strain on Outcome and Predictors of HF After TAVR

ESP has been extensively associated with the presence and severity of anatomic LVH[8,13] and associated with adverse clinical course and poor prognosis, including enhanced mortality.[2–6,11] First considered as a precious adaptive mechanism to increased

Table 2. Procedural Characteristics, According to ESP Status

Characteristics	Whole Population (n=407)	ESP (n=106)	No ESP (n=301)	*P* Value
Approach, n (%)				
Transfemoral	369 (90.9)	93 (88.6)	276 (91.7)	0.22
Transcarotid	37 (9.1)	12 (11.4)	25 (8.3)	0.33
Balloon aortic valvuloplasty	24 (5.9)	12 (11.3)	12 (4.0)	0.008
Valve, n (%)				
Sapien	247 (60.7)	61 (57.5)	186 (61.8)	0.26
Corevalve	160 (39.3)	45 (42.5)	115 (38.2)	0.49
Size, mm				
23	126 (31)	27 (25.5)	99 (32.9)	0.10
26	140 (34.4)	38 (35.8)	102 (33.9)	0.40
29	126 (31.0)	37 (34.9)	89 (29.6)	0.18
31	10 (2.5)	3 (2.8)	7 (2.3)	0.51
34	5 (1.2)	1 (0.9)	4 (1.3)	0.61
Postdilatation	40 (9.8)	10 (9.4)	30 (10)	0.52
Discharge antithrombotic medication, n (%)				
Aspirin	395 (97.1)	102 (96.2)	293 (97.3)	0.38
Clopidogrel	242 (59.5)	60 (56.6)	182 (60.5)	0.28
Dual APT	242 (59.5)	61 (57.5)	181 (60.1)	0.36
Anticoagulant therapy	171 (42.0)	42 (39.6)	129 (42.9)	0.32

APT indicates antiplatelet therapy; and ESP, electrocardiographic strain pattern.

overload, the development of LVH in AS leads to adverse ventricular remodeling, myocardial fibrosis, and oncosis, which further drive LV decompensation. The mechanisms leading to ESP with ST- and T-wave abnormalities in patients with AS are more likely to result from subendocardial ischemia. LV ESP is presumably the electrocardiographic translation of chronic myocardial oxygen imbalance, resuming

Table 3. Biological Parameters, According to ESP Status

Parameter	Whole Population (n=407)	ESP (n=106)	No ESP (n=301)	*P* Value
Hb, g/dL				
Baseline	12.2±1.7	12.3±1.6	12.1±1.7	0.38
Post-TAVR, day 1	10.7±1.8	10.9±1.6	10.6±1.8	0.19
Platelets, $\times 10^9$/L				
Baseline	226±74	226±67	226±76	0.98
Post-TAVR, day 1	178±59	174±53	179±61	0.46
WCC, $\times 10^9$/L				
Baseline	7.5±2.8	7.4±1.9	7.6±3.0	0.53
Post-TAVR, day 1	8.9±3.2	9.0±3.2	8.9±3.3	0.80
CT-ADP				
Baseline	196±76	205±77	193±75	0.17
Post-TAVR, day 1	149±78	154±79	148±79	0.46
Creatinine level, µmol/L				
Baseline	115.8±74.6	118.0±68.2	115.0±76.8	0.72
eGFR, mL/min per 1.73 m^2				
Baseline	54.8±21.1	53.3±20.0	55.3±21.5	0.41

Data are presented as mean±SD. CT-ADP indicates closure time ADP; eGFR, estimated glomerular filtration rate; ESP, electrocardiographic strain pattern; Hb, hemoglobin level; TAVR, transcatheter aortic valve replacement; and WCC, white blood cell count.

Table 4. Impact of ESP on Primary and Secondary End Points

Variable	Whole Population (n=407)	ESP (n=106)	No ESP (n=301)	*P* Value
Primary end points, n (%)				
Death from any cause	83 (20.4)	22 (20.8)	61 (20.3)	0.51
Death from any cause <1 mo	5 (1.2)	1 (0.9)	4 (1.3)	0.61
Death from any cause 1 mo–1 y	28 (6.9)	4 (3.8)	24 (8)	0.10
Death from any cause >1 y	50 (12.3)	16 (15.1)	34 (11.3)	0.20
Cardiovascular death	36 (8.8)	9 (8.5)	27 (9.0)	0.53
Noncardiovascular death	47 (11.5)	13 (12.3)	34 (11.3)	0.46
Myocardial infarction	8 (2)	2 (1.9)	6 (2)	0.65
Stroke <1 mo	19 (4.7)	7 (6.6)	12 (4)	0.20
Rehospitalization for heart failure <1 mo	5 (1.2)	1 (0.9)	4 (1.3)	0.61
MACE <1 mo	24 (5.9)	7 (6.6)	17 (5.6)	0.44
Rehospitalization for heart failure	66 (16.2)	33 (31.1)	33 (11)	<0.001
Secondary end points, n (%)				
Bleeding				
Postprocedural bleeding	122 (30.0)	29 (27.4)	93 (30.9)	0.29
Major and life-threatening bleeding	67 (16.5)	19 (17.9)	48 (15.9)	0.37
Major bleeding	47 (11.5)	12 (11.3)	35 (11.6)	0.55
Life-threatening bleeding	20 (4.9)	7 (6.6)	13 (4.3)	0.24
Bleeding requiring red blood cell transfusion >2 U	79 (19.4)	17 (16)	62 (20.6)	0.19
Minor bleeding	55 (13.5)	10 (9.4)	45 (15)	0.10
Pacemaker implantation <1 mo	71 (17.5)	19 (17.9)	53 (17.4)	0.50
Echocardiography, at 1-mo follow-up				
LVEDD, mm	50.2±6.8	51.1±7.6	49.8±6.5	0.09
LVESD, mm	32.7±8.2	33.7±9.7	32.3±7.5	0.13
Vmax, cm/s	215.6±52.7	217.3±54.3	215±52.2	0.70
Prosthetic gradient, mm Hg	10.7±5.6	11.0±5.8	10.6±5.5	0.52
LVEF, %	58.5±11.4	56.6±11.7	59.2±11.2	0.049
Gain LVEF, %	0.94±6.4	0.45±6.7	1.1±6.4	0.37
Systolic PAP, mm Hg	36.7±10.5	35.9±10.3	37.0±10.5	0.35
Immediate PVR, n (%)	53 (13.1)	14 (13.5)	39 (13.0)	0.51
PVR at 1-mo follow-up, n (%)				
Traces	148 (37.4)	38 (36.5)	110 (37.7)	0.47
PVR 1/4	77 (19.4)	18 (17.3)	59 (20.2)	0.31
PVR 2/4	36 (9.1)	14 (13.5)	22 (7.5)	0.06
PVR 3/4	13 (3.3)	1 (1)	12 (4.1)	0.10
PVR 4/4	3 (0.8)	2 (1.9)	1 (0.3)	0.17
PVR >1/4	52 (13.1)	17 (16.3)	35 (12.0)	0.17

Data are presented as mean±SD or number (percentage). ESP indicates electrocardiographic strain pattern; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MACE, major adverse cardiac event (death from any cause and/or stroke and/or rehospitalization for heart failure and/or myocardial infarction); PAP, pulmonary artery pressure; PVR, paravalvular regurgitation; and Vmax, peak aortic jet velocity.

from altered coronary perfusion by increased myocardial oxygen demand attributable to excessive LV mass (myocyte hypertrophy and the addition of new myocytes in response to wall stress and pressure overload) and adverse LV geometric change, function, and fibrosis in response to AS.[14]

In our report, ESP is a powerful marker of AS severity and heart failure after TAVR, with the ability to identify an "at-risk population" who may benefit from more aggressive medical management. The strong associations of ESP with AS severity, reduced LVEF, and LVH are key elements to explain the poor prognosis observed after

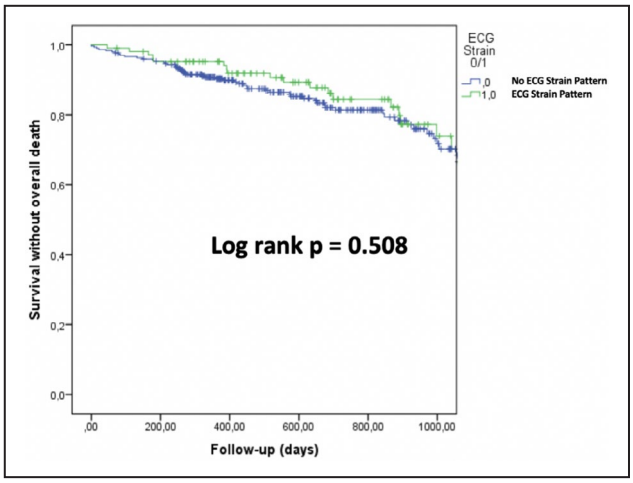

Figure 3. Kaplan-Meier curve for overall survival, according to baseline electrocardiographic strain pattern status.

TAVR. ESP is likely to reflect a more advanced stage of LV fibrosis in response to increased pressure overload or myocardial ischemia.[2,5] Recently, ESP in AS has been strongly associated with midwall fibrosis.[2,6] Myocardial fibrosis is now well established as a hallmark pathological feature of LV decompensation in AS; yet, it is not routinely assessed in clinical practice. Indeed, myocardial biopsy and histological analysis are still considered the gold standard assessments of myocardial fibrosis but face limitations inherent to their invasive features. On the other hand, cardiac magnetic resonance enables a comprehensive and noninvasive assessment of fibrosis across the entire myocardium but faces lack of availability in clinical practice. Although LV electrocardiographic strain and LVH share similar pathways and features,[8,13] HF recurrence in our study was only associated with ESP and independently from LVH (assessed by either TTE or ECG criteria). This finding strongly reinforces the view that ESP, besides its recognized association with myocardial hypertrophy, constitutes a surrogate marker of LV fibrosis. ESP may therefore represent an easy, reliable, low-cost, and powerful electrocardiographic tool in the day use practice for all physicians involved in TAVR.

LV Remodeling After TAVR

Preoperative myocardial fibrosis and remodeling, including LVH, are known to impact outcomes after aortic valve replacement. ESP has been associated with increased mortality in surgical cohorts,[3,12] but such association was not evidenced in our population undergoing TAVR.

Although major trials, such as PARTNER (Placement of Aortic Transcatheter Valves) and US CoreValve trials, showed early similar hemodynamic response and LV remodeling after both procedures, controversies still persist on differences in cardiac remodeling between SAVR and TAVR. In real-life nonrandomized studies, TAVR may result in a better hemodynamic response and, therefore, a more favorable LV remodeling than after SAVR for the first few years of follow-up.[15]

These findings are relevant with the report by Kim et al,[16] with a hemodynamic comparability of SAVR and TAVR, a higher incidence of prosthesis-patient mismatch in SAVR and a higher incidence of paravalvular leak in TAVR.

Focusing on LVH and fibrosis, a first hint challenging a possible plastic and regressive human myocardial interstitial fibrosis in AS was given by Treibel et al.[17] In this cardiac magnetic resonance imaging study, post-SAVR focal fibrosis did not resolve, but diffuse fibrosis and myocardial cellular hypertrophy regressed. The authors suggested that diffuse fibrosis may be plastic, measurable by cardiac magnetic resonance imaging, and a potential therapeutic target. In a substudy of the NOTION (Nordic Aortic Valve Intervention) trial, a randomized trial comparing TAVR with SAVR in patients aged >70 years, Ngo et al[18] showed that patients undergoing SAVR had a larger LV mass regression at 1 year compared with patients undergoing TAVR. These results have to be interpreted with caution as patients undergoing TAVR generally experience more paravalvular aortic regurgitation and increased pacemaker implantations.

To conclude, it seems that in real life, TAVR is naturally assigned to those with higher comorbidities that affect LV remodeling. Other coexistent conditions, such as age, sex, renal failure, concomitant coronary artery disease, and mitral valve disease, may also be important factors in explaining differences in outcomes.

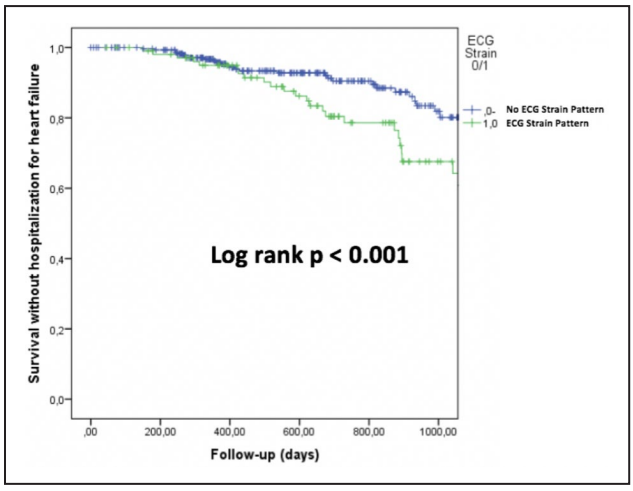

Figure 4. Kaplan-Meier survival estimates for heart failure rehospitalization after transcatheter aortic valve replacement, according to baseline electrocardiographic strain pattern status.

Table 5. Univariate and Multivariate Cox Regression for the HF Recurrence After TAVR

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Baseline clinical parameters				
Age	0.96 (0.95–1.02)	0.35		
Sex (male)	0.64 (0.38–1.08)	0.97		
BMI	1.04 (1.01–1.08)	0.023	1.04 (1.01–1.08)	0.022
Logistic EuroSCORE	1.00 (0.98–1.02)	0.96		
Hypertension	1.66 (0.76–3.64)	0.21		
Current smoking	0.63 (0.09–4.57)	0.65		
Diabetes mellitus	1.44 (0.89–2.35)	0.14		
Insulin-requiring diabetes mellitus	2.16 (1.02–4.57)	0.044	2.47 (1.09–5.59)	0.030
Dyslipidemia	1.49 (0.91–2.45)	0.12		
History of myocardial infarction	1.12 (0.59–2.15)	0.73		
History of PCI	0.81 (0.47–1.38)	0.44		
CABG	1.19 (0.57–2.49)	0.65		
PAD	0.98 (0.58–1.65)	0.94		
Stroke history	0.71 (0.36–1.41)	0.33		
AF history	1.55 (0.95–2.51)	0.08		
Chronic obstructive pulmonary disease	0.93 (0.47–1.82)	0.83		
Chronic kidney disease (creatinine level >150 µmol/L)	1.51 (0.88–2.58)	0.14		
Baseline creatinine level	1.00 (1.00–1.00)	0.41		
Baseline eGFR	0.99 (0.98–1.00)	0.21		
Baseline echocardiographic parameters				
Baseline LVEF	0.96 (0.16–5.82)	0.96		
Baseline LVEF <40%	0.86 (0.39–1.89)	0.71		
Baseline LVEDD	0.99 (0.95–1.04)	0.65		
Baseline mean aortic gradient	1.00 (0.99–1.02)	0.77		
Baseline AVAi	0.25 (0.03–2.36)	0.22		
Interventricular septum thickness	1.10 (0.97–1.24)	0.14		
LV mass	1.00 (0.99–1.01)	0.66		
Echocardiography-based LV hypertrophy	1.56 (0.70–3.46)	0.28		
Baseline electrocardiographic parameters				
Heart rate	1.01 (0.993–1.03)	0.22		
Electrocardiographic strain	2.62 (1.607–4.28)	<0.001	2.75 (1.61–4.67)	<0.001
LVH by Sokolow-Lyon index	1.24 (0.611–2.50)	0.55		
LVH by Cornell voltage criteria	1.26 (0.726–2.19)	0.41		
LVH by Sokolow-Lyon index and Cornell criteria	1.57 (0.678–3.65)	0.29		
LVH by Sokolow-Lyon index or Cornell criteria	1.18 (0.70–2.00)	0.54		
Procedural and postprocedural parameters				
Balloon postdilatation	1.18 (0.58–2.40)	0.64		
Post-TAVR pacemaker implantation	2.20 (1.30–3.73)	0.003	2.27 (1.28–4.02)	0.005
Post-TAVR–CT-ADP	1.00 (1.00–1.01)	0.13		
Echocardiography at 1-month of follow-up				
Paravalvular regurgitation ≥1/4 at 1 mo of follow-up	1.04 (0.55–1.94)	0.91		
LVEF at 1-mo of follow-up	0.20 (0.03–1.25)	0.09		
LVEF at 1-mo of follow-up <40%	1.31 (0.56–3.06)	0.53		

(*Continued*)

Table 5. Continued

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
LVEDD at 1-mo of follow-up	0.98 (0.94–1.01)	0.19		
LVESD at 1-mo of follow-up	0.98 (0.95–1.01)	0.20		
Mean prosthetic gradient at 1-mo of follow-up	1.06 (1.02–1.10)	0.004	1.05 (1.01–1.09)	0.013

AF indicates atrial fibrillation; AVAi, indexed aortic valvular area; BMI, body mass index; CABG, coronary artery bypass grafting; CT-ADP, closure time ADP; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVH, LV hypertrophy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and TAVR, transcatheter aortic valve replacement.

Pacemaker Implantation

Significant increased atrioventricular and intraventricular conduction times at baseline in patients with ESP reinforced the view of increased adverse cellular remodeling and interstitial and fibroblast replacement.[19] The hypothesis of atrioventricular and intraventricular conduction disturbance in AS attributable to myocardial fibrosis has previously been described by Prihadi et al.[5] Myocardial fibrosis is known to predispose to arrhythmia by impairing electrical conduction, encouraging the development of reentry circuits, and increasing ventricular refractoriness and myocyte excitability.[20–22] Despite this noxious impact of fibrosis on conduction disturbances, it did not translate into an increased rate of pacemaker implantation in patients with ESP. Patients with pacemaker implantation after TAVR were nonetheless at higher risk of postprocedural rehospitalization for HF.

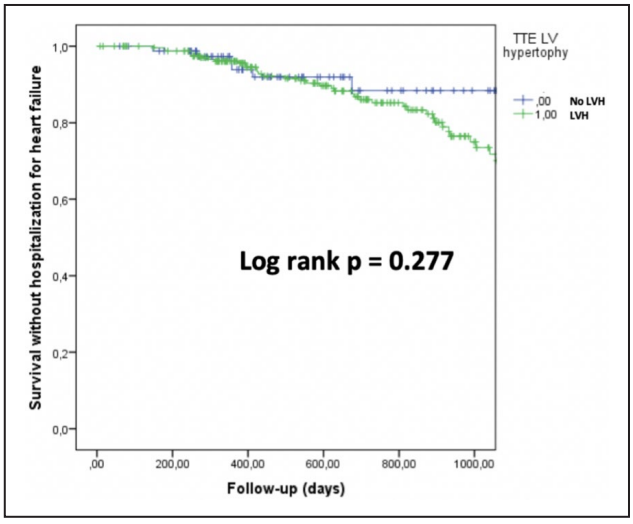

Figure 5. Kaplan-Meier survival estimates for heart failure rehospitalization after transcatheter aortic valve replacement, according to the presence of baseline echocardiographic left ventricular hypertrophy (LVH). Echocardiographic LVH was defined according to current standard and recommendations (left ventricular [LV] mass index >115 g/m^2 for men or >95 g/m^2 for women). TTE indicates transthoracic echocardiography.

Bioprosthetic Aortic Valve Function at 1 Month

The extent of myocardial fibrosis in AS is closely related to hemodynamic markers of myocardial performance, such as LV end-diastolic pressure, LVEF, and mean aortic gradient. In our experience, patients with higher mean prosthetic gradients at 1-month follow-up were more often readmitted for HF. By contrast, no impact of LVEF impairment could be evidenced. Reversibility of LVH and diffuse fibrosis but not focal fibrosis after aortic valve replacement have been recently demonstrated.[8,17] A causality dilemma may arise in this setting of LV fibrosis and residual aortic gradient. On one hand, disturbance of LV function is unlikely to be only related to TAVR, which itself results in myocardial mass regression and improvement of overall cardiac function. More likely, LVEF impairment reflects the long-term deleterious effect of fixed myocardial fibrosis with altered diastolic function and increased LV end-diastolic pressure. On the other hand, remaining with higher postprocedural aortic prosthetic gradients leads to increased LV pressure overload and may attenuate the beneficial reversing of cardiac fibrosis, as nicely assessed by Everett et al.[8] Challenging this paradigm of fibrosis reversibility, Al-Hijji et al showed no difference on mortality rates between patients with and those without ESP resolution on postdischarge ECG after TAVR.[11] Discharge, midterm, and long-term ESP reversibility may be of particular interest in future reports to further assess the long-term prognostic of patients undergoing TAVR.

Electrocardiographic Strain: A Surrogate Marker of LV Fibrosis and Target to Treat?

Previous studies have underlined that both ESP and LVH were independently associated with increased risk of new-onset HF and mortality in patients with AS.[3,4] By contrast, in our experience, no impact of LVH, assessed by either electrocardiographic criteria (Sokolow or Cornell) or TTE on HF recurrence, could be established. More important, in this population undergoing TAVR, ESP remained a strong predictor of rehospitalization for HF, independently of LVH. Among

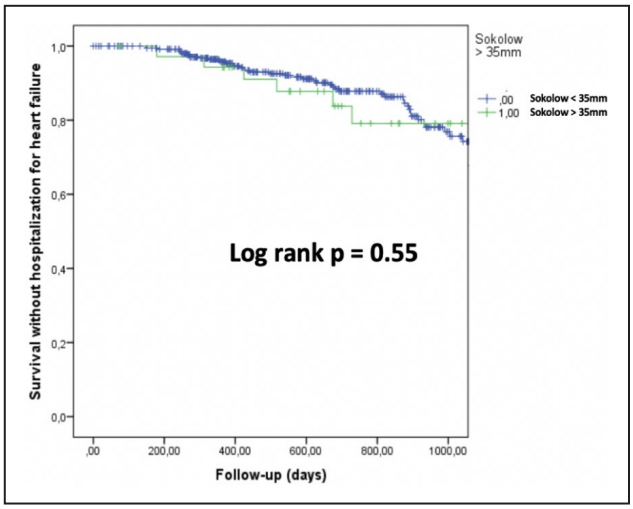

Figure 6. Kaplan-Meier survival estimates for heart failure rehospitalization after transcatheter aortic valve replacement, according to the presence of baseline electrocardiographic Sokolow-Lyon left ventricular hypertrophy (LVH) criteria.
Sokolow-Lyon index: Sum of S wave in V1 and R wave in V5 or V6. LVH according to Sokolow-Lyon index is defined as a sum ≥35 mm.

various explanations, we could not exclude that ESP represents an integrated marker of LVH, but mainly myocardial fibrosis. According to this paradigm, LVH could at least in part regress after TAVR, whereas no significant changes in fibrosis (and ESP) would occur. Accordingly, it is important to soften our statement about the role of ESP given that ESP, body mass index, insulin-requiring diabetes mellitus, pacemaker implantation, and mean prosthetic gradient at 1-month follow-up were all identified as independent predictors of HF recurrence.

ESP, a surrogate marker of cardiac fibrosis, may be of particular interest for early detection of LV decompensation, improved risk assessment, and further guidance on the timing of valve intervention in patients undergoing TAVR. Futures applications, such as artificial intelligence and machine learning, applied to ECG interpretation in AS, may help the multiparametric staging of cardiac damage in AS before TAVR.

Study Limitations

Several limitations should be taken into account in the interpretation of the data: (1) The ≥1-mm concave down-sloping ST-segment depression and asymmetrical T-wave inversion in the lateral leads are not specific to strain pattern, and potential providers of lateral subendocardial ischemia (eg, coronary artery disease and more specifically circumflex artery lesion and impaired coronary microvascular function) could influence the interpretation of our results. However, pre-TAVR coronarography angiography was performed in all patients, and significant obstructive coronary artery disease was usually treated by percutaneous coronary intervention and stenting. (2) B-type natriuretic peptide value was not systematically recorded before TAVR. (3) Time course of electrocardiographic changes after TAVR was not studied. (4) Other determinants of afterload (eg, impedance) were not investigated. (5) Because of the overwhelming predominance of White individuals in our cohort, the generalization of the results to other ethnicities should be cautiously considered. (6) Several difficulties have to be acknowledged with hospitalization alone as a criterion when referring to HF. Indeed, hospitalization threshold may differ across institutions, access variability to HF care programs, and variability in practice patterns for prescribing intravenous diuretics, vasodilators, or inotropes. (7) Finally, the methods of the study, with a single center and a retrospective design, should be considered.

CONCLUSIONS

ESP in patients with AS who are eligible for TAVR is frequent and associated with an increased risk of postinterventional HF. These findings strongly reinforce that baseline ESP constitutes an easy, reliable, low-cost, and powerful electrocardiographic tool in the day use practice and may help in guiding the time of intervention in patients with AS with high or intermediate surgical risk. The incremental value of this electrocardiographic pattern in the post-TAVR risk assessment needs further studies as it may help physicians in tailoring follow-up and improving post-TAVR clinical follow-up.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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Supplemental Material

Table S1. Impact of ECG strain pattern resolution and persistence one month after the TAVR procedure

	ESP resolution at one-month (n = 32)	Persistent ESP at one-month (n = 41)	
Overall mortality	**3 (9.4%)**	**10 (24.4%)**	**0.10**
Cardiac death	**1 (3.1%)**	**4 (9.8%)**	**0.27**
Heart Failure	**8 (25%)**	**12 (29.3%)**	**0.69**
PM implantation	**2 (6.3%)**	**5 (12.2%)**	**0.39**

ESP= ECG strain pattern; PM = Pacemaker