The prognostic value of frontal QRS-T angle in patients undergoing transcatheter aortic valve implantation

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A R T I C L E   I N F O

Introduction

Transcatheter aortic valve implantation (TAVI) is the optimal treatment modality in suitable patients with severe symptomatic aortic stenosis [1]. It seems to have a broader usage for moderate to high risk patients due to an increase in success rates besides a decrease in complications [2]. Despite the increasing importance and usage of the procedure, risk stratification in patients undergoing TAVI is of great interest. Thus, new prognostic markers of TAVI procedure are still challenging.

The frontal QRS-T angle (fQRSTa) is defined as the absolute difference between ventricular depolarization (QRS) axis and repolarization (T) axis [3]. It is a novel marker of ventricular depolarization and repolarization heterogeneity and also reflects ventricular electrical instability. In previous studies, it was shown that QRSTa >90° was found to be related with the severity of cardiac diseases and sudden cardiac death [4,5]. Although abnormal QRSTa predicts total mortality in general population [6] and in patients with congestive heart failure [7] or coronary artery disease [8], the impact of fQRSTa on survival rates in patients undergoing TAVI has not been studied yet. In this study, we aimed to investigate the prognostic value of fQRSTa in patients with severe symptomatic aortic stenosis undergoing TAVI.

Materials and methods

Study population

The study was conducted at a single tertiary care center. We tried to recruit the maximum number of patients into the study from 2010 to 2018. A total of 321 patients were screened and 32 patients were excluded from the study. A total of 289 consecutive patients who underwent TAVI due to severe symptomatic aortic stenosis were included. Asymptomatic patients and patients with complete and incomplete right or left bundle brunch block or pathological Q wave on surface electrocardiography (ECG), tip I or III antiarrhythmic usage, history of cardiac pacemaker implantation, history of myocardial infarction and severe non-revascularized coronary artery lesions (left main coronary artery >50% or other coronary arteries >70% stenosis) were excluded from the study. In this cohort study, patient and data collections were obtained retrospectively and follow-up visits were done prospectively. Demographic, clinical, electrocardiographic and echocardiographic evaluations were recorded before TAVI from all subjects. Then, patients were divided into two groups as patients with narrow fQRSTa (≤90°) and wide fQRSTa (>90°).The study was approved by the local Ethic Committee.

Electrocardiography

A 12-lead surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250, Tokyo, Japan) with a 25 mm/s paper speed and a voltage of 10 mm/s, was obtained in supine position before TAVI was performed. Patients having complete and incomplete right or left bundle brunch block or pathological Q wave on a 12 lead ECG were excluded from the study. Measurements were evaluated by two different cardiologists who were blinded to the patient data. The frontal QRSTa was calculated as the absolute value of the difference between the frontal plane QRS and T axes. If such a difference was >180°, QRSTa was adjusted to the minimal angle as 360° minus the absolute value of the difference between the frontal plane QRS and T axes [3].

Transcatheter aortic valve implantation

Transthoracic and transesophageal echocardiography were performed for each patient to determine valve morphology and disease severity as well as cardiac functions and calcification of aortic valve. And also, multislice computed tomography was used to evaluate aortic valve, aortic annulus and the aorta anatomy besides the peripheral vascular anatomy and coronary ostium-annulus distance. Then, each patient was evaluated by our heart team to assess suitability for TAVI. In all patients, a retrograde transfemoral technique was used and the procedure was performed under general anesthesia. The procedure was performed by using the balloon-expandable Edwards Sapien XT valve (Edwards Lifesciences, Irvine, CA, USA), the self-expandable Medtronic

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CoreValve (Medtronic Inc., Minneapolis, MN, USA), Evolut R (Medtronic Inc., Minneapolis, MN, USA) and Portico (St. Jude Medical, St Paul, MN, USA) valves and mechanically expanded Lotus valve (BostonScientific, MA, USA). After the TAVI procedure, dual antiplatelet therapy including 100 mg acetylsalicylic acid plus 75 mg clopidogrel was administrated to all subjects for 6 months.

Clinical follow-up

To evaluate the impact of fQRSTa on mortality in patients with severe aortic stenosis undergoing TAVI, patient's follow-up visits were done at hospital admission for suitable patients within last 6 months and telephone follow-up visits were done for others who did not attend a follow-up visit. Perioperative and postoperative clinical evaluation and time of death were recorded from all subjects.

Statistical analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0 released 2012, IBM Corp., Armonk, New York, USA). Data was expressed as "n (%)" for categorical variables. Pearson chi-square and Fisher exact tests were performed for categorical variables. After fitness to normal distribution was analyzed with the Kolmogorov-Simirnov test, data was expressed as "median (minimum-maximum)" for variables without a normal distribution. Mann-Whitney U test was used for comparing quantitative variables without a normal distribution. Spearman correlation analysis was performed for correlations between continuous variables without a normal distribution. Univariate and multivariate logistic regression analyses were used to determine the independent predictors of mortality after TAVI procedure. A p-value <0.05 was considered statistically significant.

Results

Baseline demographic, clinical, electrocardiographic and echocardiographic variables of whole study group were demonstrated in Table 1. One hundred twenty (120) patients with narrow fQRSTa (≤90°) were consisted of group 1 and one hundred sixty-nine (169) patients with wide fQRSTa (>90°) were consisted of group 2. There were no significant differences in age, gender, smoking status, diabetes mellitus, coronary artery disease, body mass index, chronic obstructive pulmonary disease, hypertension, dyslipidemia, peripheral arterial disease, previous cerebrovascular disease, atrial fibrillation, creatinine, hemoglobin, leukocyte and thrombocyte levels, valve types (balloon expandable, self expandable or mechanically expandable), valve size, the Society of Thoracic Surgeons (STS) score, ejection fraction (EF), aortic valve area, maximum aortic gradient, mean aortic gradient, postoperative discharging time and cardiac pacemaker implantation between two groups. The median value of fQRSTa was 40 (1–86) in group 1 and 145 (91–179) in group 2, respectively.

There was no statistical significant difference in the duration of follow–up time between groups. However, in-hospital mortality [5% (6) vs 17.2% (29), $p = 0.002$] was significantly higher in patients with wide fQRSTa. In-hospital mortality was 5% in patients with narrow fQRSTa (2 patients died due to heart failure, 1 patient due to stroke, 1 patient due to acute pericardial tamponade linked to shock and 2 patients due to malign arrhythmia). However, it was 17.2% in patients with wide fQRSTa (2 patients died from multi-organ failure, 11 patients due to heart failure, 7 patients due to arrhythmia and 9 patients due to peri-procedural complications such as major stroke). While long term mortality rate in whole study group was 30.1%, it was significantly higher in patients with wide fQRSTa [11.7% (14) vs 43.2% (73), $p < 0.001$] (Table 1). Additionally, Spearman correlation analysis revealed a negative correlation between fQRSTa and left ventricle EF ($r = -0.158$, $p = 0.007$) (Fig. 1).

Table 1
Baseline demographic, clinical, electrocardiographic and echocardiographic variables of whole study group.

	Narrow fQRSTa (≤90°) (n = 120)	Wide fQRSTa (>90°) (n = 169)	p
Age	80 (52–95)	80 (55–99)	0.563
Gender (female), % (n)	64.2 (77)	59.8 (101)	0.448
Coronary artery disease, % (n)	65.0 (78)	60.9 (103)	0.483
Smoking, % (n)	24.2 (29)	27.2 (46)	0.560
Body mass index (kg/m²)	26.6 (20.0–32.7)	27.4 (19.0–32,9)	0.486
COPD, % (n)	65.0 (78)	55.6 (94)	0.109
Diabetes mellitus, % (n)	40.8 (49)	39.6 (67)	0.839
Hypertension, % (n)	72.5 (87)	71.6 (121)	0.866
Dyslipidemia, % (n)	26.7 (32)	29.0 (49)	0.664
Peripheral arterial disease, % (n)	34.2 (41)	32.5 (55)	0.773
Previous cerebrovascular disease, % (n)	1.7 (2)	3.6 (6)	0.281
Atrial fibrillation, % (n)	15.0 (18)	21.9 (37)	0.141
Creatinine (mg/dl)	0.99 (0.13–2.75)	1.0 (0.12–6.65)	0.182
Hemoglobin (g/dl)	11.4 (7.1–15.3)	11.3 (7.37–17.2)	0.949
Leukocytes × 10³/mm³	7.79 (2.9–19.2)	7.8 (3.5–19.0)	0.542
Thrombocyte × 10³/mm³	224 (98–397)	232 (127–496)	0.184
Valve type, % (n)			
Balloon expandable	71.7 (86)	71.0 (120)	0.082
Self expandable	23.3 (28)	17.2 (29)	
Mechanically expanded	5.0 (6)	11.8 (20)	
Valve size, % (n)			
23 mm	29.2 (35)	21.9 (37)	0.562
25 mm	6.7 (8)	6.5 (11)	
26 mm	31.7 (38)	31.4 (53)	
27 mm	8.3 (10)	8.3 (14)	
29 mm	24.2 (29)	32.0 (54)	
The society of thoracic surgeons (STS) score	9.94 (4.36–34.03)	10.0 (4.1–25.0)	0.395
Ejection fraction (%)	60 (25–65)	60 (15–70)	0.314
Aortic valve area (cm²)	0.7 (0.36–0.99)	0.7 (0.40–0.99)	0.857
Maximum aortic gradient (mmHg)	76.5 (45–164)	79.0 (57–164)	0.760
Mean aortic gradient (mmHg)	46 (40–89)	47 (40–96)	0.507
Postoperative discharging time (days)	7 (2–42)	7 (2–23)	0.458
Cardiac pacemaker implantation, % (n)	13.3 (16)	16.6 (28)	0.451
In-hospital mortality, % (n)	5 (6)	17.2 (29)	**0.002**
In-hospital mortality time (days)	4 (1–28)	2 (1–27)	0.292
Follow-up time (months)	24 (0–100)	28 (0–99)	0.668
Total mortality, % (n)	11.7 (14)	43.2 (73)	**<0.001**

(COPD: chronic obstructive pulmonary disease, fQRSTa: frontal QRS-T angle).
Bold numbers mean the results have statistical significance with p<0.005.

In multivariate logistic regression analysis, STS score (OR:1.119, CI:1.044–1.199, $p = 0.002$), postoperative pacemaker implantation (OR:3.576, CI:1.428–8.952, $p = 0.007$), and fQRSTa (OR:1.015, CI:1.009–1.020, $p < 0.001$) were found to be independent predictors of long term mortality in patients with severe aortic stenosis undergoing TAVI (Table 2). Additionally, fQRSTa was the only independent predictor of in-hospital mortality (OR:1.012, CI:1.004–1.019, $p = 0.002$) (Table 3). A Kaplan-Meier survival analysis also revealed that long term survival was found to be significantly decreased in patients with wide fQRSTa (Log Rang $p < 0.001$) (Fig. 2).

Discussion

In our study, to the best of our knowledge, associations of fQRSTa and in-hospital and long term mortality was demonstrated first time in patients with severe symptomatic aortic valve stenosis undergoing TAVI. Additionally, wide fQRSTa was found to be an independent predictor of mortality in patients who underwent TAVI. Higher postoperative pacemaker implantation rate and STS score were also
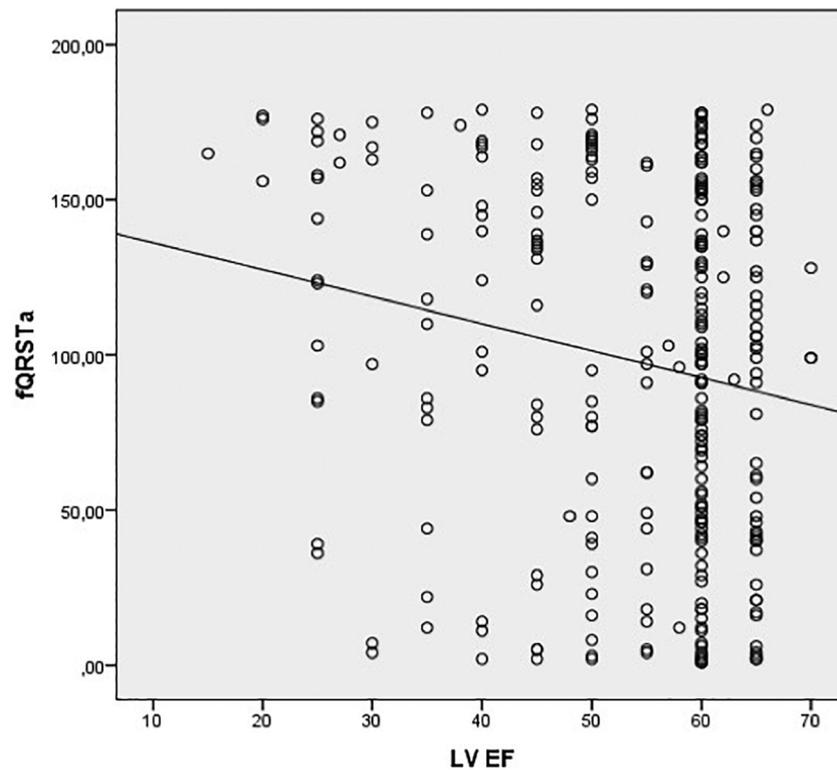
Fig. 1. The correlation between fQRSTa and left ventricle EF. A negative correlation between fQRSTa and left ventricle EF was shown. (EF: ejection fraction, fQRSTa: frontal QRS-T angle).

independent predictors of long term mortality. A negative correlation between left ventricle EF and fQRSTa was demonstrated before performing TAVI.

The fQRSTa is defined as the absolute difference between ventricular depolarization and repolarization axis [3] and it is associated with adverse cardiovascular events such as sudden cardiac death and higher cardiovascular and total mortality in several populations. Especially, it was demonstrated that QRST angle >90° was related with sudden

cardiac death [9]. In the DEFINITE trail, a wider fQRSTa >90° was found to be a predictor of adverse outcomes including cardiac arrest and death in patients with non-ischemic cardiomyopathy [10]. Wide QRSTa is a predictor of mortality in asymptomatic population without cardiovascular disease [11], in elderly patients [12], in patients with acute coronary syndrome [13] and congestive heart failure [7]. However, to the best of our knowledge, the prognostic value of fQRSTa has not been studied yet in patients with aortic stenosis.

Table 2
Univariate and multivariate logistic regression analyses showing independent predictors of long term mortality in patients undergoing TAVI.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% C.I. (Lower-Upper)	p	Odds ratio	95% C.I. (Lower-Upper)	p
Age	1.019	0.985–1.053	0.284			
Gender	1.570	0.942–2.618	0.084			
Body mass index	1.031	0.958–1.109	0.418			
Smoking	1.507	0.825–2.753	0.182			
Coronary artery disease	1.110	0.662–1.861	0.693			
COPD	0.696	0.413–1.173	0.174			
Diabetes mellitus	0.709	0.426–1.179	0.185			
Hyperlipidemia	0.693	0.402–1.197	0.189			
Hypertension	1.442	0.835–2.490	0.189			
Peripheral arterial disease	1.153	0.672–1.977	0.605			
Cerebrovascular disease	3.087	0.374–25.479	0.295			
Atrial fibrillation	**0.476**	**0.260–0.872**	**0.016**	0.574	0.294–1.119	0.103
Creatinine	1.401	0.974–2.015	0.069			
Leukocytes	0.989	0.890–1.098	0.830			
Thrombocyte	0.999	0.995–1.002	0.450			
Hemoglobin	0.957	0.824–1.111	0.565			
Ejection fraction	0.986	0.966–1.006	0.174			
STS score	**1.114**	**1.042–1.190**	**0.001**	**1.119**	**1.044–1.199**	**0.002**
Postoperative discharging time	1.010	0.959–1.063	0.707			
Postoperative pacemaker implantation	**2.563**	**1.094–6.001**	**0.030**	**3.576**	**1.428–8.952**	**0.007**
Valve type	1.150	0.609–2.170	0.666			
Valve size	0.969	0.867–1.082	0.574			
fQRSTa	**1.013**	**1.008–1.019**	**<0.001**	**1.015**	**1.009–1.020**	**<0.001**

(COPD: chronic obstructive pulmonary disease, fQRSTa: frontal QRS-T angle, STS: The society of thoracic surgeons).
Bold numbers mean the results have statistical significance with p<0.005.

**Table 3**
Logistic regression analysis showing independent predictors of in-hospital mortality in patients undergoing TAVI.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% C.I. (Lower-Upper)	p	Odds ratio	95% C.I. (Lower-Upper)	p
Age	0.979	0.937–1.024	0.359			
Gender	1.079	0.524–2.221	0.836			
Body mass index	1.040	0.938–1.153	0.450			
Smoking	1.803	0.717–4.530	0.210			
Coronary artery disease	1.298	0.634–2.658	0.475			
COPD	0.468	0.211–1.039	0.062			
Diabetes mellitus	0.520	0.255–1.060	0.072			
Hyperlipidemia	0.897	0.418–1.924	0.780			
Hypertension	1.399	0.660–2.964	0.381			
Peripheral arterial disease	0.821	0.394–1.711	0.599			
Cerebrovascular disease	229,844,016	0.000	0.999			
Atrial fibrillation	0.639	0.281–1.454	0.286			
Creatinine	0.908	0.507–1.628	0.747			
Leukocytes	0.987	0.851–1.145	0.864			
Thrombocyte	1.003	0.998–1.008	0.225			
Hemoglobin	0.830	0.667–1.033	0.095			
Ejection fraction	0.980	0.954–1.007	0.146			
STS score	1.058	0.980–1.142	0.147			
Postoperative pacemaker implantation	269,245,905	0.000	0.997			
Valve type	1.182	0.502–2.783	0.702			
Valve size	1.057	0.904–1.236	0.485			
QRSTa	**1.012**	**1.004–1.019**	**0.002**	1.012	1.004–1.019	0.002

(COPD: chronic obstructive pulmonary disease, fQRSTa: frontal QRS-T angle, STS: The society of thoracic surgeons).
Bold numbers mean the results have statistical significance with p<0.005.

Aortic valve stenosis is the most common degenerative valvular heart disease in developing countries [14]. In patients with aortic stenosis, myocardial hypertrophy occurs due to increased left ventricular afterload. This compensatory mechanism causes elevated systolic wall stress and impaired coronary blood flow results in left ventricular electrical heterogeneity [15–17]. And it results in abnormal ventricular repolarization. As for fQRSTa, it plays an important role to detect mentioned abnormal depolarization and repolarization before overt ECG changes [18]. While ventricular depolarization and repolarization axis are in similar direction under normal hemodynamic conditions [18], chronic severe degenerative aortic stenosis can result in wide fQRSTa due to several mentioned mechanisms above [9]. Thus, patients having abnormal ventricular repolarization, reflected by wide fQRSTa, can be under high risk even if valve disease is treated. In our study, we showed that wide fQRSTa is related with poor prognosis in aortic stenosis patients after percutaneous treatment of valve disease. It means,
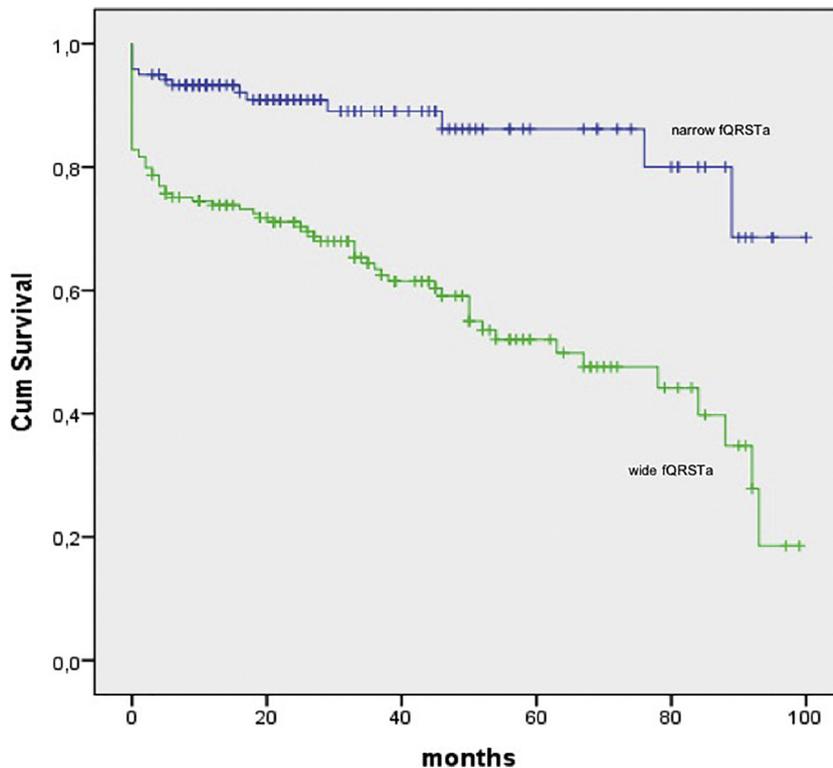
Fig. 2. Kaplan-Meier survival curves for narrow and wide fQRSTa groups. A Kaplan-Meier survival analysis revealed that long term survival was found to be significantly decreased in patients with wide fQRSTa (Log Rang p < 0.001). (fQRSTa: frontal QRS-T angle).

patients having myocardial heterogeneity before the intervention can be under increased risk of short and long term adverse cardiac events. It can also be used for patient selection.

TAVI is the common accepted treatment modality in patients with severe symptomatic aortic stenosis under intermediate to high surgical risk. However, conventional surgical risk scores are insufficient to predict prognosis after TAVI. Because of this, new prognostic markers of TAVI procedure are still challenging. In the Placement of Aortic Transcatheter Valve (PARTNER) trial, the rate of mortality within first year after TAVI was as high as 24.7% [19]. This means some patients may be unsuitable to benefit from the procedure. In a review of thirty-one studies, with a total of 13,857 patients were evaluated and 83%, 75%, 65%, 48%, and 28% of the patients were still alive at 1, 2, 3, 5, and 7 years after TAVI, respectively [20]. In our study, total mortality rate was 30,1% in whole study group during follow-up time. The predictors of mortality in patients undergoing TAVI were evaluated in several studies. In the German Transcatheter Aortic Valve Implantation Registry Study including 1444 patients, female gender, renal failure, residual aortic regurgitation, atrial fibrillation, prior mitral regurgitation, advanced age, prior myocardial infarction, diabetes mellitus, low gradient aortic stenosis, urgent or surgical TAVI procedure, prior decompensation and frailty were predictors for 5-year mortality [21]. In the UK Transcatheter Aortic Valve Implantation Registry from 870 participants, renal dysfunction, atrial fibrillation, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) ≥18.5, respiratory dysfunction, and ventricular dysfunction (left ventricular ejection fraction <30%) were found as independent predictors of mortality with 3 and 5-year survival rates of 61.2% and 45.5%, respectively [22]. In our study, STS score, postoperative cardiac pacemaker implantation and wide fQRSTa were independent predictors of long term mortality after TAVI. It was revealed that total mortality rate was 11.7% in patients with narrow fQRSTa and 43.2% in patients with wide fQRSTa. While atrial fibrillation was associated with mortality, it was not an independent predictor of mortality, in our study. Although left ventricular dysfunction is known as a mortality predictor, we did not find an association between EF and mortality. It may be explained by insufficient number of patients with reduced EF in our study. However, we demonstrated that left ventricle EF was found to be negatively correlated with fQRSTa. It can be explained by the relationship between ventricular heterogeneity and myocardial dysfunction. This could be one of the most important reasons for wide fQRSTa to be linked to adverse cardiac events. Furthermore, preoperative damaged ventricle, reflected by wide fQRSTa, can be related with postoperative complications linked to increased mortality. Additionally, wide fQRSTa related arrhythmias could be the other underlying mechanism of increased mortality rates. In the light of foregoing data, fQRSTa seems to have a prognostic value on short and long term mortality in severe aortic stenosis patients undergoing TAVI. However, large scaled studies are needed for future investigations.

Conclusion

In our study, it was revealed that wide fQRSTa is a predictor of adverse cardiac outcomes in patients with aortic stenosis undergoing TAVI. And, it can also be used for risk prediction before the procedure.

Limitations

The major limitation of the study was relatively small sample size due to the single-center experience design of the study. Secondly, some patients did not attend hospital follow-up visits. Because of this, we are unsure about the certain reasons of mortality in long term follow-up. Lack of the data about fQRSTa linked adverse outcomes such as ventricular arrhythmic events and incomplete left ventricle re-modeling after TAVI were also the other main limitation.

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