Prognostic value of a comprehensive geriatric assessment for predicting one-year mortality in presumably frail patient with symptomatic aortic stenosis

Type
Research paper

Keywords
frailty, aortic stenosis, TAVI, comprehensive geriatric assessment

Abstract

Introduction
Despite of suffering a severe aortic stenosis, some patients are denied from either surgical or Transcatheter Aortic Valve implantation (TAVI) therapy because of a frail condition. We aim to identify whether a comprehensive geriatric assessment (CGA) might be useful to predict prognosis of presumably frail patients with severe aortic stenosis.

Material and methods
Between March 2011 and July 2016, 818 patients were consecutively and prospectively enrolled. 161 had a CGA and were considered for analysis. Considering combined CGA and Heart team recommendations, 102 TAVI were performed (TAVI group) and 59 patients constituted the no TAVI group. Primary endpoint was all-cause mortality at one year.

Results
There was no difference between the TAVI and the no TAVI groups considering morphometric data, cardiovascular risk factors or symptoms. The no TAVI group had higher surgical risk (logistic EuroSCORE1 33.4±17.8 vs. 22.7±14.9; p<0.001) and more moderate renal insufficiency (82% vs. 57%; p=0.001). One-year mortality was 16% in the TAVI group and 46% in the no TAVI group (p<0.001). Multivariate analysis revealed history of pulmonary edema, moderate renal failure, and not having a TAVI, to relate to 1-year mortality. There was an interaction of the Five-Times-Sit-to-Stand-Test (FTSST) upon the effect of TAVI on mortality (p=0.049), as FTSST was the only predictor for 1-year mortality in the no TAVI group (HR:0.18 95%CI 0.04–0.76; p=0.019).

Conclusions
One-year mortality was higher in geriatric-assessed frail patient who did not undergo TAVI. FTSST, which assesses patients' mobility, was the only prognostic marker for 1-year mortality, on top of usual medical parameters.
Prognostic value of a comprehensive geriatric assessment for predicting one-year mortality in presumably frail patient with symptomatic aortic stenosis

Running title: Comprehensive geriatric assessment in frail TAVI patients

Conflict of interest: the authors have no conflict of interest to disclose

Keywords: Aortic stenosis, TAVI, comprehensive geriatric assessment, frailty
Abstract

**Background**: Despite of suffering a severe aortic stenosis, some patients are denied from either surgical or Transcatheter Aortic Valve Implantation (TAVI) therapy because of a frail condition. We aim to identify whether a comprehensive geriatric assessment (CGA) might be useful to predict prognosis of presumably frail patients with severe aortic stenosis.

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**Conclusion**: One-year mortality was higher in geriatric-assessed frail patient who did not undergo TAVI. FTSST, which assesses patients’ mobility, was the only prognostic marker for 1-year mortality, on top of usual medical parameters.
Introduction

In developed western countries, aortic stenosis is the most common valvular heart disease in individuals over 65 years of age (1). Surgical aortic valve replacement (SAVR) is the first-line therapy for symptomatic patients, improving prognosis and quality of life (2)(3). Transcatheter aortic valve implantation (TAVI) may be performed among patients according to either a high surgical risk, a technical contraindication to surgery or a general poor condition named frailty (4)(5).

Frailty is a clinical syndrome combining decrease in physiological reserve and stress tolerance (6)(7) that can be assessed implicitly, while a comprehensive geriatric assessment (CGA) helps to globally assess medical and social issues of older adults based on a set of clinical scores, questionnaires and biological tests (8).

Heart Team and geriatric evaluation units will assess every patient denied from the surgical therapy because of frailty to determine whether TAVI remains appropriate (9)(10).

The aim of the study was to identify whether CGA might be useful to precise 1-year prognosis of presumably frail patients, whatever the management of aortic stenosis.

METHODS

Study population

A total of eight hundred eighteen patients considered for TAVI were prospectively and consecutively enrolled between March 2011 and July 2016.

Inclusion criteria were a symptomatic severe aortic stenosis and being denied for a SAVR by a heart team because of either a technical barrier (for instance porcelain aorta, chest deformation, or history of chest radiotherapy), a high preoperative risk as assessed by the
EuroSCORE (a risk model for the prediction of mortality after heart surgery), or because of an Heart Team-assessed general poor condition to undergo thoracic surgery named frailty. One hundred sixty-one patients presenting a general frail condition raised concerns about the direct individual benefits to perform TAVI; they necessitated a CGA before final decision from the Heart team and constituted the study population. The Heart team included an interventional cardiologist, a non-interventional cardiologist, a heart surgeon and an anesthesiologist; and took every CGA’s data into account to determine the most appropriate care.

Local ethical committee approved the research protocol (#2017/45) and the study was conducted in accordance with the declaration of Helsinki and local regulatory requirements.

**Data collection**

All data related to demographic, morphometric, echocardiographic parameters, and medical history were prospectively collected. Pulmonary hypertension was defined as a systolic pulmonary artery pressure of more than 35 mmHg, moderate renal insufficiency by a creatinine clearance of less than 60 ml/min, respiratory insufficiency by the daily use of bronchodilator or inhaled corticosteroid, and history of pulmonary edema by at least two acute episodes during the last twelve months (11).

The CGA was performed by the geriatric evaluation unit during hospitalization to appreciate medical and social issues related to older adults. The main items were: an evaluation of polypharmacy based on the number of therapeutic classes used per day and the use of psychoactive drugs, memory by the learning and recall categories of the Mini-Mental State Examination (Short MMSE) (12) and the clock-drawing test (CDT) score(13), pain was assessed by verbal rating scale (14), nutrition by the short form of the Mini Nutritional
Assessment (MNA) (15) and by the Body Mass Index (BMI), independency by Iso-Resource Group (GIR) (16) and Instrumental Activities of daily living (IADL) (17), and the mobility by the Five-Time-Sit-to-Stand test (FTSST) which was considered as positive if accomplished without assistance and/or without use of upper extremity support (18).

Follow-up and outcomes
Follow-up was completed for all patients for at least one year with a median of 456 [153; 815] days. It has been performed by immediate feedback from consultants and by phone interview of general practitioner.
The primary endpoint was all-cause mortality at one year.

Statistical analysis
All statistical tests were performed using SPSS 20.0 software (for Windows, SPSS, Inc, Chicago, Illinois). Quantitative variables were expressed as mean ± standard deviations, unless stated otherwise, and qualitative variables as numbers and percentages. Comparisons of quantitative variables were conducted by means of unpaired Student’s t-test. Comparisons of qualitative variables were performed using chi-squared or Fisher tests, when appropriate. Cox regression models were applied for the purpose of explaining 1-year all-cause mortality. Multivariate analysis included common medical data, aortic stenosis parameters, and CGA results. Only significant univariate correlates ($p<0.05$) were included into the multivariate Cox models. Specific interactions were tested between TAVI and NYHA score, FTSST, moderate renal failure and respiratory failure. Then, multivariate Cox regression models were performed separately on the TAVI and the no TAVI groups.
Proportional-hazard assumptions were tested by analysis of the Schoenfeld residuals.
Statistical significance was set at $p<0.05$. 
RESULTS

Baseline characteristics

Study population

CGA patients were older (85.9±4.6 vs 82.8±7.1 years old, p<0.001), with higher logistic EuroSCORE (29.5±17.5 vs 19.5± 12.6, p<0.001), lower LV ejection fraction (53.5±13.7 vs 58.7±12.2%, p<0.001) compared to patients who did not necessitate CGA prior to TAVI. CGA patients presented more history of atrial fibrillation (51 vs 32%, p<0.001), but similar rates of history of diabetes, peripheral artery disease, stroke, renal failure, coronary artery disease, and symptoms related to aortic stenosis.

Out of 161 CGA patients, 102 patients were only medically treated (no TAVI group) and 59 patients underwent a TAVI (TAVI group) (Figure 1). In the TAVI group, 14 patients had CoreValve (Medtronic, Santa Ana, CA, USA) prosthesis and 45 had Edwards Sapien, Sapien 3 or Sapien XT prosthesis (Edwards Lifesciences, Irvine, CA, USA). Forty-four (74%) patients had a transfemoral, 6 (10%) a transapical and 9 (16%) another approach. The TAVI was a success in 57 cases (96.6%) with no relevant procedural complications.

Mean age was 85.9±4.6 years (85.5±5.1 vs. 86.1±4.3; p=0.40) and mean body mass index was 26±5 kg/cm² (26.5±5 vs. 25.7±5.1; p=0.36).

The no TAVI group had higher surgical risk score (logistic EuroSCORE 1: 33.4±17.8 vs. 22.7± 14.9; p<0.001) and higher rates of moderate renal insufficiency (82% vs. 57%; p=0.001).

No TAVI and TAVI patients presented similar rates of New York Heart Association (NYHA) functional class III or IV (71% in TAVI group vs. 56% in no TAVI group; p=0.06), history of pulmonary edema (35% vs. 36%; p=0.88), so as similar left ventricular ejection fraction and transvalvular mean pressure gradient. However, there was more pulmonary hypertension in the TAVI group (61% vs. 50%; p=0.013) (Table 1).
Geriatrics characteristics

There was no difference regarding history of falls, number of therapeutic classes used per day, use of psychoactive drugs, social isolation and needs for home care workers support.

The no TAVI group presented more memory impairment with a lower short MMSE and CDT score (respectively 36% of MMSE3>5 vs. 57%; \( p=0.013\) and 1.4±2.1 points vs. 2.7±2.4; \( p=0.025\)). Moreover, the no TAVI group was more dependent with a significantly lower GIR score than the TAVI group (3.6±0.9 vs. 4.2±0.9; \( p<0.001\)) (Table 2). FTSST was achieved in 18 % of the cohort (respectively 15% vs 25% for no TAVI and TAVI group, \( p= 0.20\)).

One-year mortality

One-year mortality was 16% (n=16) in the TAVI group and 46% (n=27) in the no TAVI group (\( p<0.001\)) (figure 2).

Independent one-year mortality correlates were: not having a TAVI performed (HR: 76.92 IC95% [3.47 – 1707]; \( p=0.006\)), moderate renal insufficiency (HR: 3.67, 95%CI [1.29 – 10.44]; \( p=0.015\)) and a history of pulmonary edema (HR: 2.15, 95%CI [1.15 – 3.99]; \( p=0.016\)). We found an interaction for the effect of TAVI on one-year mortality according to FTSST (\( p=0.049\)) (Table 3).

In the no TAVI group, multivariate Cox regression model performed revealed a success in FTSST to be the best predictor for 1-year mortality (HR: 0.18, 95%CI [0.04–0.76]; \( p=0.019\)).

There was also a trend towards history of pulmonary edema (HR: 1.81, 95%CI [0.97–3.37]; \( p=0.06\)) and a respiratory insufficiency (HR: 0.36, 95%CI [0.12–1.03]; \( p=0.06\)) (Table 4, figure 3).

In the TAVI group, multivariate Cox analysis did not find any CGA parameter to be related to 1-year prognosis. Respiratory insufficiency (HR: 40.9, 95%CI [6.52–257]; \( p<0.001\)) and
moderate renal insufficiency (HR: 11.95, 95%CI [1.57–90.90]; p=0.017) were the predictors of one-year mortality.

**DISCUSSION**

The main results of our study are: (1) TAVI was effectively associated to a reduced 1-year all-cause mortality in presumably frail older patients suffering from severe aortic stenosis, and (2) FTSSST was the best mortality predictor among the patients who did not undergo TAVI.

In the no TAVI group, one-year mortality was very high, which is consistent with previous literature (19)(20). Only a few recent studies reported long-term survival of untreated severe aortic stenosis, as the last dated palliative therapy was balloon aortic valvuloplasty (BAV) in the 90s, when 1-year mortality was around 43% without (21) and 36% with (22) BAV. On the other hand, one-year mortality in the TAVI group was 16%. Considering our patients of being presumed unsuitable to TAVI, it is noticeable that this rate was consistent with the 21.4-26% range reported by the largest national registries (11)(23). Beyond the TAVI procedure by itself, one-year mortality predictors were history of pulmonary edema or moderate renal failure, as previously reported by others (24)(25), but none of the CGA parameters (table 3).

In the no TAVI group, the FTSSST was the best predictor for one-year mortality. Poor mobility was already identified as a good predictor of poor outcomes and mortality in heart disease. For instance, the Gait Speed test – another measure of functional capacity - (26) is associated to both morbidity and mortality in older patients undergoing cardiac surgery (27). In the TAVI population, slowest walker and those unable to walk also presented higher mortality (28). While loss of mobility may be inherent to the cardiac condition itself, our
analysis showed the mobility assessment alone and not the usual cardiac markers to relate to mortality in the no TAVI group. This result suggests frail patients to suffer more from poor general mobility condition rather than cardiac condition. We should acknowledge that every single patient from our cohort presented surgical aortic stenosis with severe symptoms (table 1), potentially explaining the fact that usual cardiac markers were not discriminant – and FTSST might relate to worse prognosis in the general subset of older patients. The loss of mobility is also often related to weight loss and/or cachexia in older adults, yet mean BMI and MNA were substantially normal (25.7±5.1 kg/m² and 7.9±2.3, respectively), and did not relate to prognosis.

Our patients are representative of patients from the beginnings of the TAVI procedure, therefore very high-risk patients. In the new ESC recommendations (29), TAVI takes a greater part of the invasive treatment for symptomatic aortic stenosis. Indeed, TAVI will now be recommended from the age of 75, for patient with lowest surgical risk represented by a STS score ≥ 4% and a logistic EuroSCORE ≥ 10% (compared to 10% and 20% in 2012, respectively) (29). Consequently, as TAVI will be considered in a larger number of lower risk patients, common medical comorbidities will become less prevalent and might lack accuracy in assessing long-term benefits, providing room for objective geriatric criterias.

The clinical interest of our results stems in showing evidence that TAVI improved overall survival in presumably frail patients, provided that individual decision was approved by CGA and Heart team. More, even if the present method was not meant to better identify patients who will benefit from TAVI, we highlight the fact that investigating patients’ mobility might be a cornerstone in assessing further prognosis. Whether or not physical training should be encouraged in patients with loss of mobility remains to be investigated among patients with severe aortic stenosis.
Limitations

Several limitations should be considered, the first being inherent bias due to a retrospective and observational non-randomized study, with a limited sample size. Secondly, our study assessed a very high-risk population, with severe symptomatic aortic stenosis, which was representative of the beginning of the TAVI procedure. Third, while evidence report frail older patients with TAVI to exhibit higher mortality (30)(31), the proportion of TAVI patients was too low to allow studying the impact of CGA parameters on prognosis. Finally, other prognostic markers might be investigated. The Charlson comorbidity index is a validated measure of 1-year mortality risk and disease’s burden (32). Low serum vitamin D level in older adults has demonstrated to be associated with cardiovascular risk (33), dementia (34) and all-cause mortality (35).

CONCLUSION

Aortic valve replacement by a TAVI was associated with reduced 1-year mortality among presumed frail older patients with severe aortic stenosis. FTSST was an independent predictor of one-year mortality in patients with severe aortic stenosis who did not undergo valve replacement.


FIGURES

Figure 1. Flow Chart

- **818 patients enrolled**
  - denied from SAVR

- **657 patients**
  - treated by TAVI without CGA

- **161 patients**
  - CGA before treatment

- **102 patients**
  - medically treated
  - *no TAVI group*

- **59 patients**
  - treated by TAVI
  - *TAVI group*
Figure 2. Time-to-event curves for the primary end-point

1- year survival (%)
Figure 3. Time-to-event curves for the primary end-point according to the FTSST results among the no-TAVI patients

FTSST means Five-Time-Sit-to-Stand test

FTSST: Success without assistance or with upper extremity support.
Table 1. Patient characteristics at baseline, cardiovascular data

<table>
<thead>
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<th></th>
<th>TOTAL</th>
<th>TAVI</th>
<th>no TAVI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphometric characteristics</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Age, years</td>
<td>85.9±4.6</td>
<td>85.5±5.1</td>
<td>86.1±4.3</td>
<td>0.4</td>
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<tr>
<td>Weight, kg</td>
<td>67.4±14.4</td>
<td>69.5±14.7</td>
<td>66.2±14.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160.8±8.4</td>
<td>161.6±7.6</td>
<td>160.3±8.8</td>
<td>0.34</td>
</tr>
<tr>
<td>Body mass index, kg/cm²</td>
<td>26±5</td>
<td>26.5±5</td>
<td>25.7±5.1</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Surgical risk scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic EuroSCORE 1, %</td>
<td>29.5±17.5</td>
<td>22.7±14.9</td>
<td>33.4±17.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STS, %</td>
<td>8.8±6</td>
<td>6.7±4.7</td>
<td>9.8±6.3</td>
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<td><strong>Medical history</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>67 (42)</td>
<td>22 (38)</td>
<td>45 (44)</td>
<td>0.49</td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>34 (21)</td>
<td>16 (28)</td>
<td>18 (17)</td>
<td>0.12</td>
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<tr>
<td>Atrial fibrillation, n (%)</td>
<td>82 (51)</td>
<td>30 (52)</td>
<td>52 (50)</td>
<td>0.84</td>
</tr>
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<td>Anticoagulation therapy, n (%)</td>
<td>76 (47)</td>
<td>29 (50)</td>
<td>47 (46)</td>
<td>0.56</td>
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<tr>
<td>Balloon aortic valvuloplasty after CGA, n (%)</td>
<td>13 (8)</td>
<td>0 (0)</td>
<td>13 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory insufficiency, n (%)</td>
<td>25 (15)</td>
<td>6 (10)</td>
<td>19 (18)</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>31 (19)</td>
<td>12 (21)</td>
<td>19 (18)</td>
<td>0.71</td>
</tr>
<tr>
<td>Moderate renal insufficiency, n (%)</td>
<td>117 (73)</td>
<td>33 (57)</td>
<td>84 (82)</td>
<td>&lt;0.001</td>
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<td><strong>Cardiovascular risks factors</strong></td>
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</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>134 (84)</td>
<td>45 (78)</td>
<td>89 (87)</td>
<td>0.17</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>72 (45)</td>
<td>26 (45)</td>
<td>46 (45)</td>
<td>0.95</td>
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<tr>
<td>Smoking, n (%)</td>
<td>12 (7)</td>
<td>4 (7)</td>
<td>8 (7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>42 (26)</td>
<td>18 (31)</td>
<td>24 (23)</td>
<td>0.27</td>
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<td><strong>Aortic stenosis parameters</strong></td>
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<td>NYHA &gt; 2, n (%)</td>
<td>99 (62)</td>
<td>41 (71)</td>
<td>58 (56)</td>
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<tr>
<td>History of pulmonary edema, n (%)</td>
<td>57 (35)</td>
<td>20 (35)</td>
<td>37 (36)</td>
<td>0.88</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
<td>53.5±13.7</td>
<td>54±13.3</td>
<td>53.2±13.9</td>
<td>0.73</td>
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<tr>
<td>Mean pressure gradient, mmHg</td>
<td>48.6±15.2</td>
<td>49.2±13.9</td>
<td>48.3±15.9</td>
<td>0.72</td>
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<tr>
<td>Pulmonary hypertension, n (%)</td>
<td>83 (53)</td>
<td>33 (61)</td>
<td>50 (50)</td>
<td>0.013</td>
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<table>
<thead>
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<th>Table 2. Patient characteristics at baseline, geriatrics data</th>
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<td><strong>TOTAL</strong></td>
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<td><strong>General characteristics</strong></td>
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<td>Exhaustion, n (%)</td>
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<td>Isolation, n (%)</td>
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<td>Homecare workers, n (%)</td>
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<td><strong>Comprehensive geriatric assessment</strong></td>
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<td>Simple verbal scale (SVC)</td>
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<td>Five-times-sit-to-stand-test (FTSST), n (%)</td>
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<td>Geriatric depression scale (GDS) &gt; 4</td>
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<tr>
<td>Instrumental activities of daily living scale (IADL)</td>
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<td>Short Mini Mental State Examination (short MMSE) &gt; 5, n (%)</td>
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<tr>
<td>Mini Nutritional Assessment (MNA)</td>
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<td>Iso-resource group (GIR)</td>
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<td>Clock drawing test, au</td>
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TAVI means transcatheter aortic valve implantation
Table 3. One-year all-cause mortality, multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95%CI</th>
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<tr>
<td>No TAVI</td>
<td>76.92</td>
<td>3.47 - 1707</td>
<td>0.006</td>
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<tr>
<td>History of pulmonary edema</td>
<td>2.15</td>
<td>1.15 - 3.99</td>
<td>0.016</td>
</tr>
<tr>
<td>Moderate renal insufficiency</td>
<td>3.67</td>
<td>1.29 - 10.44</td>
<td>0.015</td>
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<tr>
<td>FTSST success</td>
<td>25.72</td>
<td>0.53 - 1248</td>
<td>0.10</td>
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<tr>
<td>Mini nutritional assessment</td>
<td>0.94</td>
<td>0.81 - 1.09</td>
<td>0.42</td>
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<td>Interaction between FTSST and no TAVI</td>
<td>0.01</td>
<td>0.01 - 0.1</td>
<td>0.049</td>
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CI means confidence interval, FTSST means Five-Time-Sit-to-Stand test, HR means Hazard Ratio, TAVI means transcatheter aortic valve implantation
Table 4. One-year mortality in no TAVI group, multivariate analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
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<tbody>
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<td>History of pulmonary edema</td>
<td>1.81</td>
<td>0.97 - 3.37</td>
<td>0.06</td>
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<tr>
<td>Moderate renal insufficiency</td>
<td>2.24</td>
<td>0.77 - 6.54</td>
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<td>FTSST success</td>
<td>0.18</td>
<td>0.04 - 0.76</td>
<td>0.019</td>
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<tr>
<td>Respiratory insufficiency</td>
<td>0.36</td>
<td>0.12 - 1.03</td>
<td>0.06</td>
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CI means confidence interval, FTSST means Five-Time-Sit-to-Stand test, HR means Hazard Ratio, TAVI means transcatheter aortic valve implantation
818 patients enrolled
denied from SAVR

657 patients
treated by TAVI
without CGA

161 patients
CGA before treatment

102 patients
medically treated
no TAVI group

59 patients
treated by TAVI
TAVI group

Figure 1
1-year survival (%)

TAVI

p=0.001

no TAVI

days

no. at risk

TAVI  59  52  48
noTAVI  102  58  43

Figure 2
Figure 3

1-year survival (%)

no. at risk

<table>
<thead>
<tr>
<th></th>
<th>FTSS</th>
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<tr>
<td>days</td>
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<tr>
<td>0</td>
<td>12</td>
<td>70</td>
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