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Comparison of Early and Long-Term Outcomes After Trans-Catheter Aortic Valve Implantation in Patients with New York Heart Association Functional Class IV to those in Class III and Less

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Running title: TAVI and advanced functional status

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ABSTRACT

Our aim was to investigate the impact of a baseline New York Heart Association (NYHA) class IV on clinical outcomes of a large real-world population undergoing TAVI. The primary end-points were all-cause mortality, cardiovascular mortality and re-hospitalization, evaluated at the longest available follow-up and by means of a 3-month Landmark analysis. The secondary end-points were: change in NYHA class, left ventricular ejection fraction, pulmonary pressure and mitral

regurgitation. Out 2,467 patients, 271 (11%) had a NYHA functional class IV at the admission. The latter had higher STS score (9.2% vs. 5.5%; p<0.001) compared to NYHA ≤III patients, owing to more comorbidities (prior myocardial infarction, severe chronic kidney disease, atrial fibrillation, left ventricular dysfunction, significant mitral regurgitation, pulmonary hypertension). Device success was similar between the two groups (93.7% vs. 94.5%; p=0.583). At a median follow-up of 15 months (IQR 4-36 months) a lower freedom from primary end-points was observed among NYHA IV vs. NYHA ≤III group (survival from all-cause death: 52% vs. 58.4%; p=0.002; survival from cardiovascular death: 72.5% vs. 76.5%; p=0.091; freedom from re-hospitalization: 81.5% vs. 85.4%; p=0.038). However, after adjustment for baseline imbalance, NYHA IV did not influence the relative risk of long-term primary end-points. A 3-month Landmark analysis showed that NYHA IV independently predicted 3-month all-cause and cardiovascular mortality (HR: 1.77; 95% CI [1.10-2.83]; p=0.018 and HR: 1.64; 95% CI [1.03-2.59]; p=0.036, respectively). Instead, after 3-month follow-up NYHA IV did not affect the risk of primary end-points. A significant improvement of the secondary end-points was noted in both NYHA IV and NYHA ≤III groups.
In conclusion, the presence of NYHA class IV in TAVI candidates was associated to a significant increased risk of mortality within 3 months. Patients with baseline NYHA IV who survived at 3 months had a long-term outcome comparable to that of other subjects. Left ventricular systolic function, pulmonary pressure and mitral insufficiency significantly improved after TAVI regardless of the presence of NYHA class IV.

Key words: NYHA class IV, TAVI, mortality, re-hospitalization

Introduction

Transcatheter aortic valve implantation (TAVI) is by now a well-established therapy for patients with severe and symptomatic aortic stenosis at intermediate, high or prohibitive surgical risk[1-6]. Non-randomized data showed safety and efficacy of TAVI also in patients with severe pure aortic regurgitation and failed surgical bioprosthesis who cannot deal with redo[7-9]. TAVI has been shown to improve survival, quality of life and functional status. In particular, a significant reduction of

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New York Heart Association (NYHA) class at early and long-term follow-up has been previously and consistently reported in TAVI recipients[10,11].

However, limited evidence is available on prognostic significance of a baseline advanced functional NYHA class [12,13] and specific data on the presence of NYHA class IV at the admission in TAVI candidates are lacking. We sought to explore the impact of a baseline NYHA functional class IV on clinical outcomes of a large real-world population undergoing first and second generation of Medtronic self-expanding bioprosthesis implantation.

Methods

Between June 2007 and September 2017, all consecutive patients undergoing TAVI with either Medtronic CoreValve or Evolut R system were prospectively included in the Italian ClinicalService® Project (Clinical Trial Registration NCT01007474). This is an ongoing nation-based clinical data repository and medical care project aimed at describing and improving the use of implantable devices in Italian clinical practice already described elsewhere[14]. The project was approved by each site's Institutional Review Board or Medical Director and conforms to the principles outlined in the Declaration of Helsinki. Each patient provided an informed consent for data collection and analysis.

According to the current recommendations, eligibility for TAVI was established at each centre based on the consensus of a local multidisciplinary team (including cardiologists, cardiac surgeons and anaesthesiologists) that took into account the individual calculated risk of surgery, comorbidity or conditions not included into the scores, patient's frailty and the technical feasibility of TAVI. Clinical and echocardiographic follow-up were performed at 30 days, 1 year and then yearly with visits or telephone contacts according to each centre's clinical practice.

For the purpose of the current analysis, all consecutive patients whose baseline NYHA class was available were included. The study population was divided in two groups according to the presence of NYHA class IV or NYHA class ≤III at the admission. NYHA class IV was defined as the

presence of dyspnoea even at rest and inability to carry on any physical activity without discomfort and worsening of symptoms.

The primary endpoints, defined according to the VARC-2 recommendations, were: all-cause death, cardiovascular death and re-hospitalization due to valve-related symptoms or heart failure[15]. These endpoints have been stratified by the presence of NYHA class IV at the admission and evaluated at longest follow-up and by means of a Landmarks analysis with a cut-off of 3 months. The 3-month cut-off was assessed by visual estimation of the Kaplan Meier plots, identifying the point where the two curves started to get parallels.

The secondary end-points were the change in NYHA class after TAVI and the variations over time (baseline, discharge, 30-day and 1-year) of echocardiographic parameters (i.e. ejection fraction, pulmonary pressure and mitral regurgitation) in NYHA IV versus NYHA ≤III groups.

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are reported as count and percentage. Comparisons between groups have been performed using Wilcoxon's Test for continuous variables, while comparisons of categorical variables have been performed by means of Chi-square test or Fisher exact test for extreme proportions, as appropriate. To compare variables over time, a repeated measure model or the McNemar test have been performed, as appropriate.

The analyses of time-to-the-first event for the primary endpoints were described by means of Kaplan-Meier curves and long-rank test after testing proportional hazard hypothesis. A Landmark analysis for mortality and cardiovascular mortality at 3 months was performed, showing Kaplan Meier curves and survival probabilities. Baseline variables differently distributed at an alpha level of 0.10 (age, BMI, hypertension, prior MI, haemoglobin, severe chronic kidney disease, history of atrial fibrillation, significant aortic regurgitation, significant mitral regurgitation, ejection fraction and severe pulmonary hypertension) were entered in a stepwise Cox regression model in order to calculate the adjusted relative risk of primary endpoints. Each result was expressed as hazard ratio (HR) and corresponding 95% confidence interval (CI). Statistical tests were based on a two-sided

significance level of 0.05. The SAS software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses.

Results

Among 2,467 patients included in the present study, 271 subjects (11%) had a NYHA functional class IV at the admission.

Baseline characteristics according to the presence of NYHA class IV are reported in **Table 1.** Compared to patients presenting a NYHA class ≤III, those with NYHA class IV at the admission were more likely to have prior myocardial infarction, severe chronic kidney disease, history of atrial fibrillation, left ventricular dysfunction, significant mitral regurgitation and severe pulmonary hypertension. Moreover, NYHA IV population more frequently underwent TAVI due to pure aortic regurgitation or surgical bioprosthesis degeneration compared to NYHA ≤III group. As expected, NYHA IV patients had higher calculated surgical risk scores.

Procedural data stratified by the presence of NYHA class IV at the admission are shown in **Table 2.** Femoral approach was less common among patients with NYHA IV vs. NYHA≤ III. General anaesthesia was more frequently used in NYHA IV compared with NYHA ≤ III patients with consequently longer procedural time, but similar fluoroscopy time and contrast amount. Predilation was less frequently performed in NYHA IV vs. NYHA ≤ III group, whereas postdilation was more commonly carried out among NYHA IV patients. Device success was similar between the two groups.

In hospital all-cause and cardiovascular mortality were significantly higher in NYHA IV group compared with NYHA ≤ III patients (7.7% vs. 3.4%; p<0.001 and 5.9% vs. 3.3%; p=0.028 respectively). No differences were observed between the two groups with respect to bleeding events, vascular complications, AKI occurrence, need for new pacemaker and paravalvular leak rate at the discharge. Hospital length was significantly higher in NYHA IV as compared to the control group **(Table 3).**

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At 30 day follow-up an increased all-cause mortality rate was observed in NYHA IV vs. NYHA ≤ III group (8.9% vs. 5%; p=0.008). No differences were noted between the two groups with respect to cardiovascular mortality, stroke/TIA, myocardial infarction, re-hospitalization, need for new pacemaker and significant paravalvular leak **(Table 3).**

After a median follow up of 15 months (IQR 4-36 months) a significant lower survival free from all-cause death was noted among patients with NYHA IV as compared to NYHA ≤ III group (52% vs. 58.4%; p=0.002) **(Figure 1A).** A statistically non-significant trend towards a lower cardiovascular survival rate was observed in NYHA IV patients compared with the control group (72.5% vs. 76.5%; p=0.091) **(Figure 1B).** Survival free from re-hospitalization was significantly lower in NYHA IV patients as compared to NYHA ≤ III group (81.5% vs. 85.4%; p=0.038) **(Figure 1C).**

After adjustment for the baseline imbalance, the presence of NYHA class IV at the admission did not modify the relative risk of long-term all-cause death (HR: 1.07; 95%CI [0.78-1.48]; p=0.670), cardiovascular mortality (HR 0.97; 95%CI [0.62-1.53]; p=0.909) and re-hospitalization (HR 0.97; 95% CI [0.53 – 1.80]; p=0.940).

Within 3 months after TAVI, significantly lower rates of survival free from all-cause death (83.3% vs. 91.3%; p<0.001), cardiovascular mortality (89.6% vs. 93.6%; p=0.016) and re-hospitalization (93.9% vs. 96.6%; p=0.038) were observed in patients with NYHA IV at the admission as compared to patients with baseline NYHA class ≤ III **(Figure 2A, 2B and 2C).** Baseline NYHA class IV was associated with an increased adjusted relative risk of all-cause death (HR: 1.77; 95% CI [1.10-2.83]; p=0.018) and cardiovascular death (HR: 1.64; 95% CI [1.03-2.59]; p=0.036) within 3-month follow-up. However, the adjusted relative risk of re-hospitalization within 3-month is not affected by the presence of NYHA class IV at the baseline (HR: 1.33; 95% CI [0.67-2.64]; p=0.415).

Since 3-month time-point survival free from all-cause death, cardiovascular death and re-hospitalization did not differ between the two groups (NYHA IV vs. NYHA ≤ III group: 62.4% vs.

63.9%; p=0.430; 80.9% vs. 81.7%;p=0.960; 86.7% vs. 88.4%; p=0.280, respectively) **(Figure 2D, 2E and 2F)** and the adjusted risk of primary endpoints was not affected by baseline functional status (all-cause death: HR: 0.86; 95%CI [0.58-1.26]; p=0.440; cardiovascular death: HR: 0.63; 95% CI [0.33 - 1.19];p=0.157; re-hospitalization: HR: 0.78; 95% CI [0.40 - 1.51]; p=0.461).

NYHA class significantly improved during the follow-up in the overall population (P<0.001). Among patients with NYHA IV at the baseline, only 4.7% had persistence of NYHA IV at 30 days and none had NYHA IV at 1-year.

Mean left ventricular ejection fraction significantly increased from baseline up to 1-year follow-up in both NYHA IV and ≤III groups (both p<0.001) with values that were significantly lower in NYHA IV vs. NYHA ≤III group at baseline (45±14% vs. 52±12%; p<0.001), discharge (47±12% vs. 53±10%; p<0.001) and 30-day (49±12% vs. 54±10%; p<0.001), but reaching similarity at 1-year follow-up (53±12% vs. 56±9%; p=0.166) **(Figure 3A).**

Mean systolic pulmonary pressure and mitral regurgitation also significantly improved from baseline to discharge (both p <0.001), 30-day (both p <0.001) and 1-year (both p <0.001) follow-up in both groups **(Figure 3B and 3C).** Pulmonary pressure level was comparable in NYHA IV and NYHA ≤III groups since discharge up to 1-year time-point (discharge: 40± 12 mmHg vs. 38± 12 mmHg; p=0.095 – 30-day: 40± 13 mmHg vs. 38± 10 mmHg; p=0.166 – 1-year: 39± 13 vs. 38± 10 mmHg; p=0.516) **(Figure 3B).** Also mitral regurgitation degree was similar in NYHA IV and ≤III populations at discharge (p=0.138), 30-day (p=0.138) and 1-year (p=0.874) follow-up **(Figure 3C).**

Discussion

The main findings of the present study can be summarized as follows: i) NYHA class IV at the admission was independently associated to an increased risk of all-cause and cardiovascular mortality within 3 months after TAVI; ii) Patients with baseline NYHA IV who survived at 3-month follow-up had a long-term prognosis comparable to that of patients with NYHA class ≤III; iii) Left ventricle systolic function, systolic pulmonary pressure and mitral regurgitation significantly improve after TAVI regardless of baseline NYHA IV class.

Previous studies including TAVI populations often reported NYHA functional classes III and IV as a single entity. In PARTNER cohorts more than 90% of high- or extreme-risk patients and almost 80% of intermediate-risk patients had NYHA class III or IV at the admission. In European and American registries the rate of advanced NYHA class (III or IV) ranges from 75% to 91%[10,16]. An advanced functional status (NYHA III or IV) has been previously reported as predictor of adverse prognosis at early and mid-term follow-up after TAVI[12,13].

However, patients with severe aortic valve disease and NYHA class IV are highly different from others. They suffer from symptoms at rest and are definitely more clinically compromised than those with NYHA class ≤III. They are not electively admitted for TAVI but due to acute heart failure or pulmonary edema, often as first and dramatic manifestation of their aortic valve disease, sometimes requiring a definitive intervention to allow discharge.

The incidence of baseline NYHA class IV in our population (11%) is consistent with that reported in previous studies that separately showed baseline NYHA class IV data (5% to 20%)[4,6,12,13,17]. Nevertheless, current evidence regarding the prognostic role of baseline NYHA class IV on clinical outcome after TAVI is very limited and specific considerations on the presence of symptoms at rest in patients with severe aortic valve disease undergoing TAVI are lacking.

In our population, the higher mortality and re-hospitalization rate at long-term follow-up in NYHA IV compared with NYHA ≤III group was owed to the presence of more comorbidity. A high-risk profile (STS >8%) was observed in almost two-third of NYHA IV population due to a higher incidence of prior myocardial infarction, atrial fibrillation, severe chronic kidney disease, significant mitral regurgitation, left ventricular dysfunction and severe pulmonary hypertension. Indeed, after adjustment for these baseline imbalances, NYHA class IV did not influence the risk of long-term adverse events.

Nevertheless, a Landmark analysis showed that survival free from primary end-points at 3-month was lower in NYHA IV vs. NYHA ≤III within 3-month follow-up. NYHA IV resulted as independent predictor of 3-month all-cause and cardiovascular mortality increasing the relative risk

of 77% and 64%, respectively. Therefore, in TAVI candidates, the presence of symptoms at rest, may affect early-term prognosis. This result is expectable given that, as mentioned above, patients in NYHA class IV are basically admitted due to acute heart failure rather than for elective TAVI. Importantly, patients with NYHA class IV who undergo TAVI and survive at 3-month follow-up have a clinical outcome comparable to that of subjects with NYHA ≤III class.

Roughly one half of patients with severe aortic stenosis do not report symptoms[18]. Effort symptoms are difficult to be assessed in elderly populations with aortic disease because of a common inclination to restrict daily activities in order to avoid symptoms rather than complain about their difficult conditions. Often, these patients reach our attention when advanced and no longer self-controllable symptoms (at rest – NYHA IV) occur. American and European guidelines[19,20] state that asymptomatic patients with severe aortic stenosis should be followed with a watchful waiting strategy unless of left ventricular dysfunction, abnormal exercise stress test, very severe aortic stenosis, rapid progression of the disease, severe pulmonary hypertension or high level of neurohormones. However, these observations are based on non-randomized trials including surgery candidates. Similarly, our efforts should be pointed towards an early identification of symptoms in TAVI candidates, avoiding development of NYHA class IV and offering to these patients an early treatment that might improve early-term survival. The ongoing Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients With AsYmptomatic Severe Aortic Stenosis (EARLY TAVR) study (NCT03042104) will definitely shed light on this interesting issue.

Previous evidence consistently reported early and persistent improvement of left ventricular systolic function, pulmonary hypertension and mitral insufficiency in patients with severe aortic stenosis undergoing TAVI owed to afterload abolition[21-25]. We confirm these findings in a more complex population, including patients with bioprosthesis degeneration and pure aortic regurgitation, and regardless of baseline NYHA class IV. Indeed, left ventricular ejection fraction, systolic pulmonary pressure and mitral regurgitation degree, which are worse in NYHA IV vs. ≤III group at baseline, significantly improve up to 1-year follow-up in both groups.

Of note, pulmonary pressure level and mitral regurgitation degree of NYHA IV patients reached values similar to that of NYHA ≤III subjects at discharge. Whereas left ventricular ejection fraction progressively improved in NYHA IV group reaching levels comparable to NYHA ≤III patients at 1-year follow-up. A slower recovery of left ventricular systolic function in a particularly compromised population could be reasonable.

Our study has several main limitations. First, the non-randomized design and the consequent presence of possible confounding factors that could have influenced our results; however, the inclusion of consecutive patients and the statistical adjustment for baseline imbalance should have minimized potential selection bias. Second, the absence of an independent monitoring with external adjudication of the events might limit the strength of the present analysis. Third, echocardiographic data have not been analysed by an independent core laboratory, but by dedicated and highly experienced physicians at each centre. Fourth, data on left ventricular diastolic function, which has been previously shown to be associated with NYHA improvement after TAVI[26], are missing.

In conclusion, in TAVI candidates, a NYHA class IV at the admission was associated to an almost 80% increased risk of all-cause mortality and to a more than 60% increased risk of cardiovascular mortality within 3 months after the procedure compared to NYHA ≤III. However, after this time-point, the mortality risk was comparable between patients with baseline NYHA IV and NYHA ≤III class. A significant improvement of left ventricular systolic function, pulmonary pressure and mitral regurgitation after TAVI was observed regardless of NYHA IV class at the admission.

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Figure Legend

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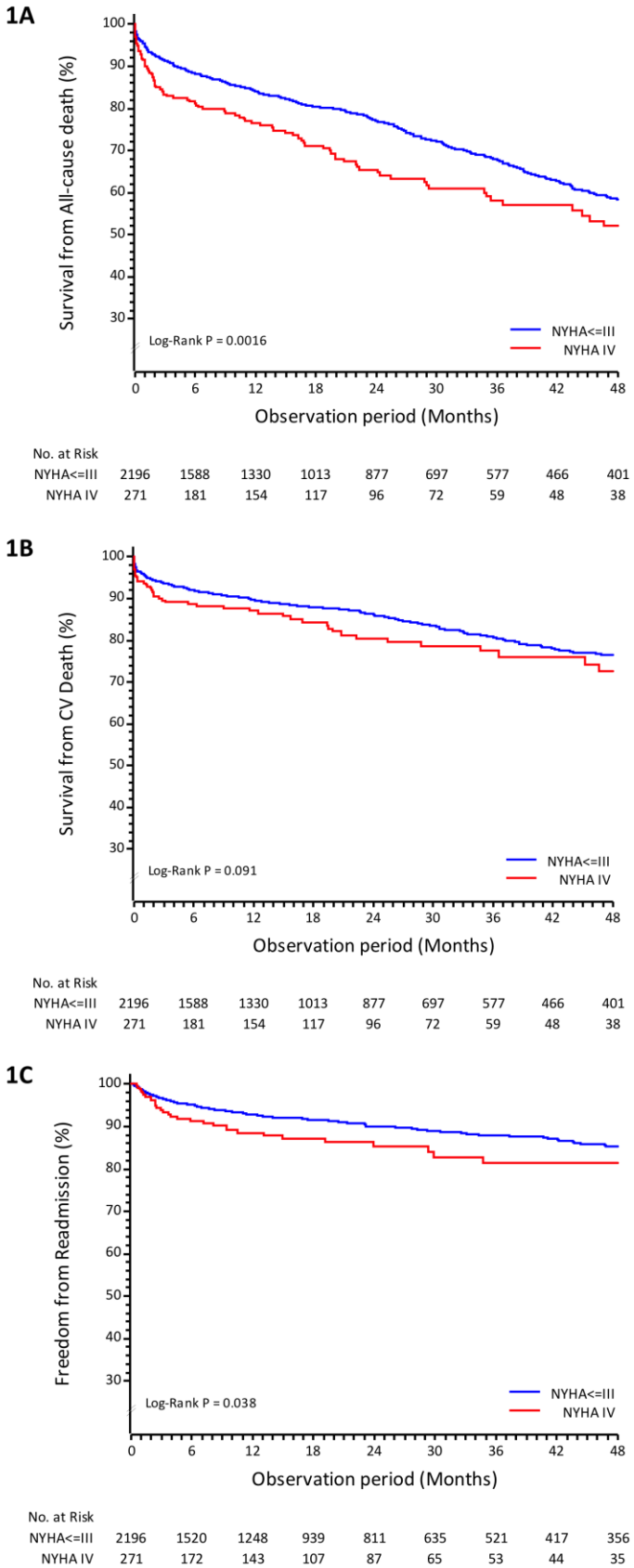
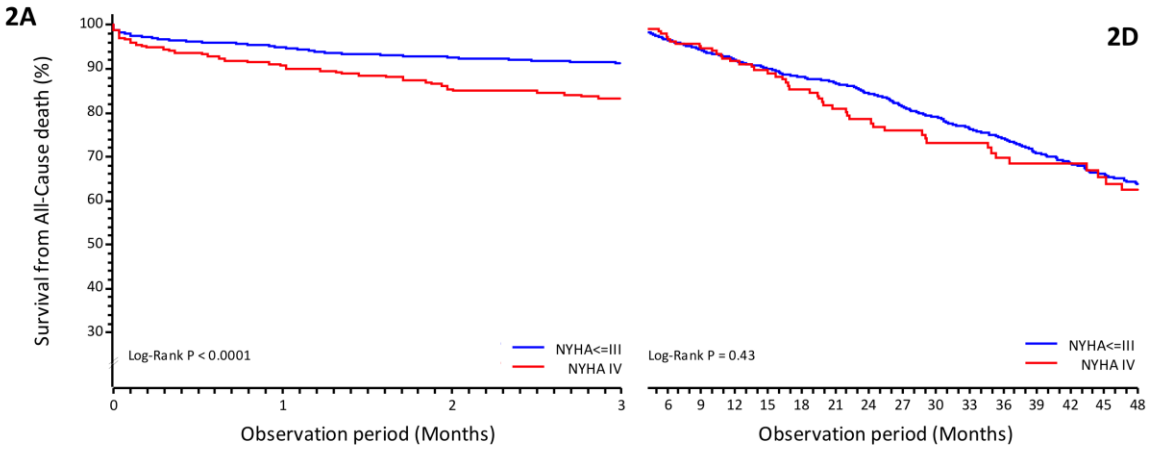
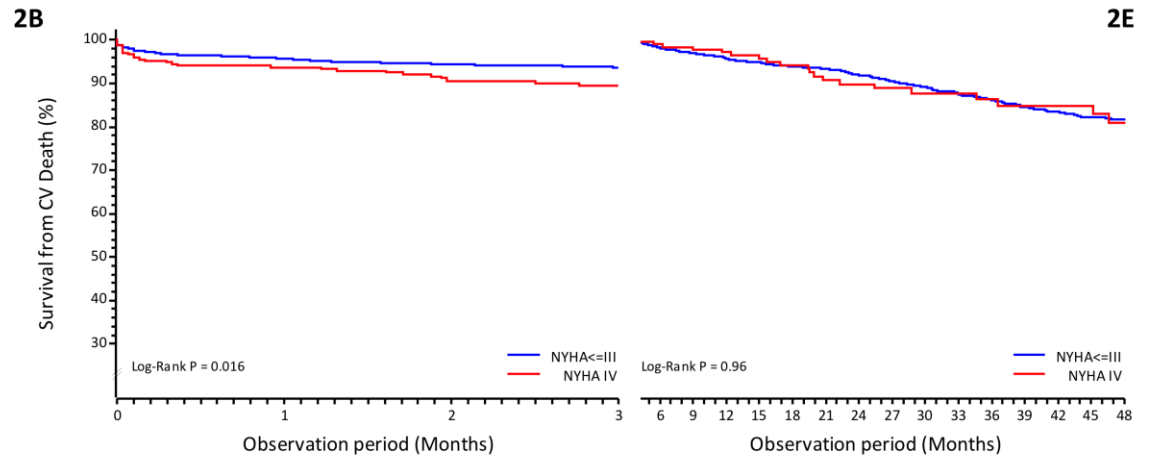


Figure 1. Kaplan Meyer curves of all-cause death (a), cardiovascular death (b) and readmission (c) up to 4-year follow-up according to the presence of NYHA class IV vs. ≤III at the admission.

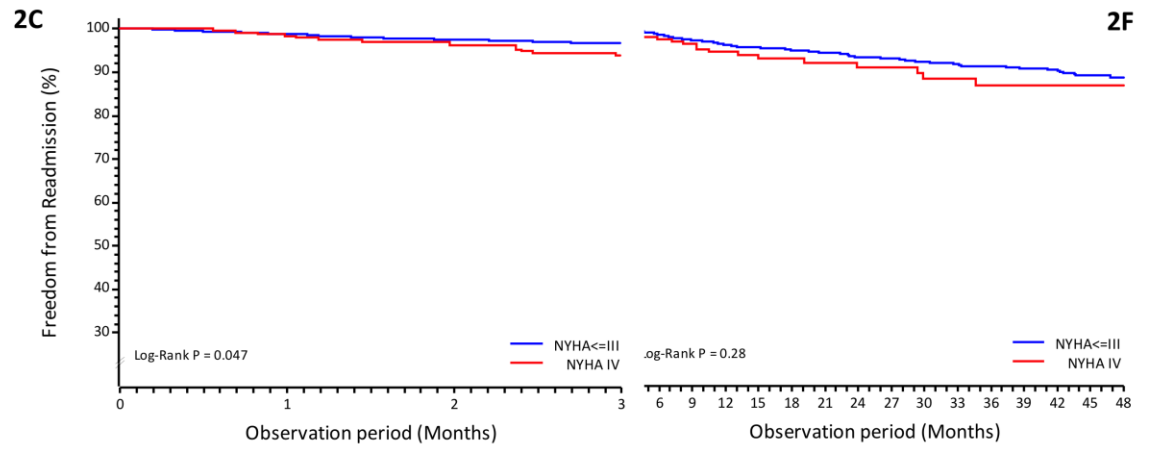
CV=cardiovascular; NYHA=New York Heart Association



No. at Risk																								
NYHA I II III	2196	2032	1842	1756	1588	1477	1330	1091	1013	953	877	754	697	645	577	505	466	436	401					
NYHA IV	271	242	219	200	181	168	154	124	117	104	96	83	72	68	59	49	48	43	38					



No. at Risk																								
NYHA<=III	2196	2032	1842	1756	1588	1477	1330	1091	1013	953	877	754	697	645	577	505	466	436	401					
NYHA IV	271	242	219	200	181	168	154	124	117	104	96	83	72	68	59	49	48	43	38					



No. at Risk																								
NYHA<=III	2196	2010	1801	1705	1520	1401	1248	1015	939	885	811	692	635	583	521	454	417	389	356					
NYHA IV	271	238	214	194	172	158	143	114	107	94	87	76	65	62	53	45	44	39	35					

Figure 2. Landmark analyses of all-cause death, cardiovascular death and readmission during the first 3 months after the procedure (a, b and c) and from 3-month to 4-year (d, e and f) according to the presence of NYHA class IV vs. ≤III at the admission.

CV=cardiovascular; NYHA=New York Heart Association

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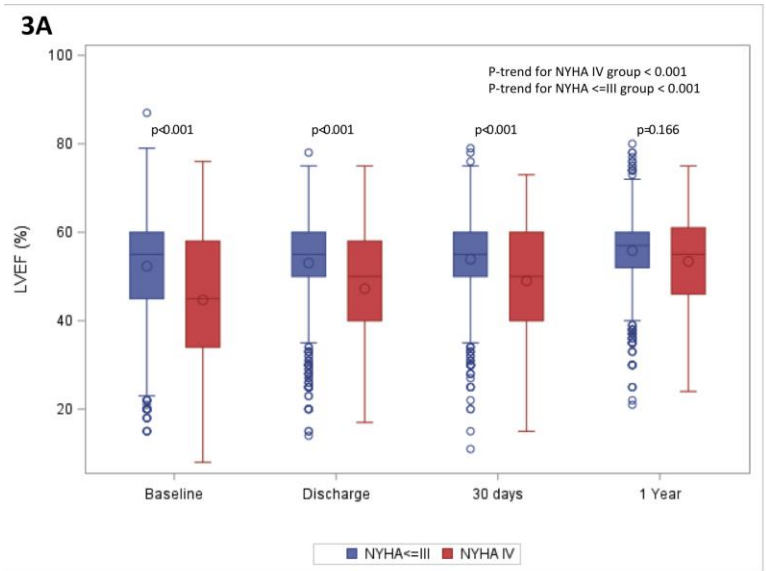
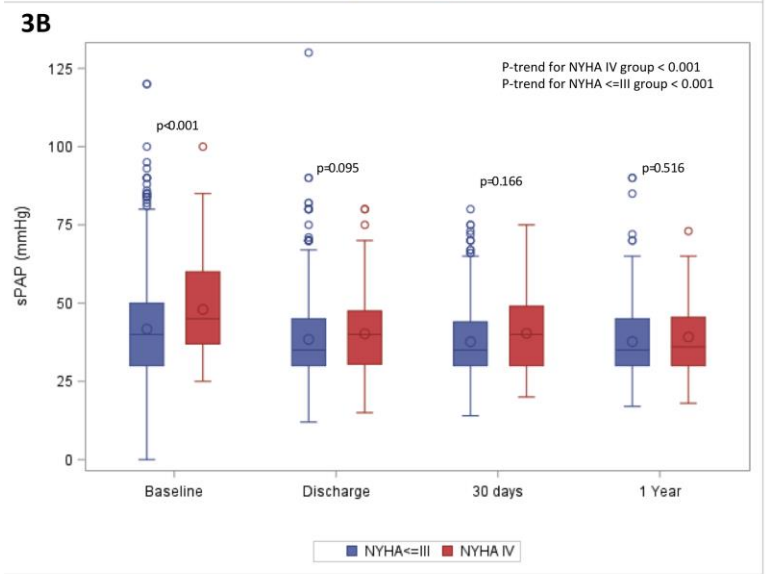

3A
P-trend for NYHA IV group < 0.001
P-trend for NYHA <=III group < 0.001
p<0.001
p<0.001
p<0.001
p=0.166
LVEF (%)
100
80
60
40
20
Baseline
Discharge
30 days
1 Year
NYHA<=III
NYHA IV


3B
P-trend for NYHA IV group < 0.001
P-trend for NYHA <=III group < 0.001
p<0.001
p=0.095
p=0.166
p=0.516
sPAP (mmHg)
125
100
75
50
25
0
Baseline
Discharge
30 days
1 Year
NYHA<=III
NYHA IV

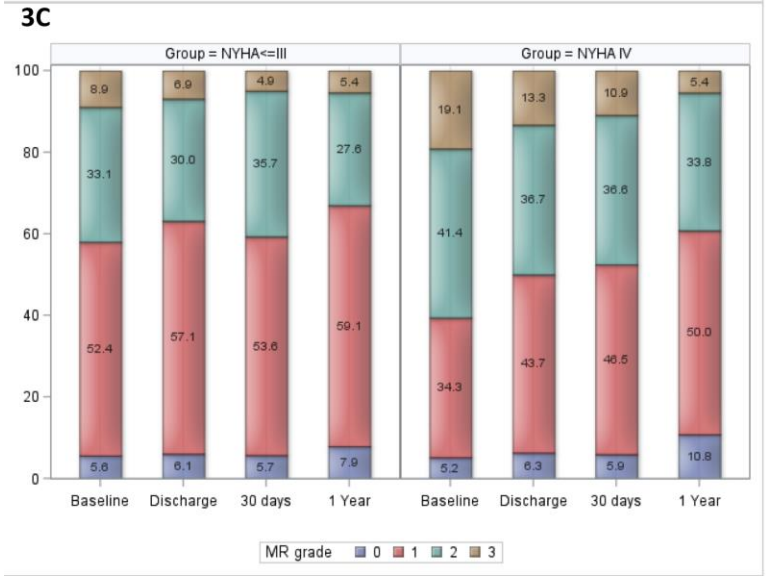

3C
Group = NYHA<=III
Group = NYHA IV
100
80
60
40
20
0
8.9
33.1
52.4
5.6
6.9
30.0
57.1
6.1
4.9
35.7
53.6
5.7
5.4
27.6
59.1
7.9
19.1
41.4
34.3
5.2
13.3
36.7
43.7
6.3
10.9
36.6
46.5
5.9
5.4
33.8
50.0
10.8
Baseline
Discharge
30 days
1 Year
Baseline
Discharge
30 days
1 Year
MR grade 0 1 2 3

Figure 3. Change in left ventricular ejection fraction (a), systolic pulmonary artery pressure (b) and mitral regurgitation (c) at baseline, discharge, 30-day and 1-year follow-up according to the presence of NYHA class IV vs. ≤III at the admission.

LVEF= left ventricular ejection fraction; MR=mitral regurgitation; NYHA= New York Heart Association; SPAP= systolic pulmonary artery pressure

Table 1. Baseline characteristics

Variable	**NYHA IV (n=271)**	**NYHA ≤ III (n=2,196)**
Age (years)	81 ± 9	82 ± 6
Men	125 (46%)	942 (43%)
Body mass index (kg/m^2)	25 ± 5	26 ± 5
STS score	13.1 ± 12.0	7.7 ± 7.5
<4%	29 (13%)	530 (31%)
4-8%	64 (29%)	695 (40%)
>8%	125 (57%)	502 (29%)
Haemoglobin (g/dl)	11.6 ± 1.7	11.8 ± 1.6
Creatinine clearance <30mL/min	95 (36%)	418 (20%)
Hypertension	210 (78%)	1813 (83%)
Diabetes mellitus	89 (33%)	629 (29%)
Prior stroke or transient ischaemic attack	32 (16%)	230 (16%)
Prior myocardial infarction	62 (23%)	346 (16%)
Chronic obstructive pulmonary disease	58 (21%)	436 (20%)
Peripheral vascular disease	69 (25%)	488 (22%)
History of atrial fibrillation	80 (29%)	411 (19%)
Pure aortic regurgitation	17 (6.3%)	36 (1.7%)

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Table 2. Procedural features

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Surgical aortic bioprosthesis failure	21 (7.8%)	76 (3.5%)
Baseline mean gradient (mmHg)	45.0 ± 16.4	50.8 ± 15.4
Significant aortic regurgitation (≥2+)	125 (50%)	611 (31%)
Significant mitral regurgitation (≥2+)	152 (61%)	852 (42%)
Left ventricular ejection fraction (%)	44.7 ± 14.3	52.3 ± 11.7
Left ventricular end diastolic volume (mL)	117.5 ± 51.2	106.6 ± 45.8
Left ventricular end systolic volume (mL)	71.1 ± 43.8	53.8 ± 34.0
Systolic pulmonary pressure >60 mmHg	48 (21%)	168 (9.2%)

Categorical variables are reported as n (%); continuous variables are reported as mean ± SD

Table 3. Acute outcomes

Variable	NYHA IV (n=271)	NYHA ≤ III (n=2,196)	P-value
General anaesthesia	81 (30%)	453 (21%)	0.001
Femoral access	220 (81%)	1882 (86%)	0.042
Evolut R device	66 (24%)	413 (19%)	0.051
Prosthesis size (mm)			0.004
23	12 (4.4%)	110 (5%)	
26	98 (36%)	975 (45%)	
29	125 (46%)	921 (42%)	
31	34 (12%)	151 (6.9%)	
34	2 (0.7%)	26 (1.2%)	
Predilation	153 (59%)	1437 (73%)	<0.001
Postdilation	88 (33%)	532 (26%)	0.007
Device success	254 (94%)	2076 (94%)	0.583
Procedural success	258 (95%)	2110 (96%)	0.486
Procedural time (min)	113.4 ± 49.8	105.7 ± 51.4	0.012
Fluoroscopy time (min)	23.3 ± 13.1	23.8 ± 13.4	0.336
Contrast media (ml)	175.6 ± 158.8	176.1 ± 99.9	0.155

Categorical variables are reported as n (%); continuous variables are reported as mean ± SD

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New permanent pacemaker implantation	52 (25%)	398 (21%)
Acute kidney injury stage 1	38 (17%)	261 (15%)
Acute kidney injury stage 2 or 3	1 (0.4%)	7 (0.5%)
Major bleeding	19 (7.2%)	131 (6.2%)
Life-threatening bleeding	6 (2.3%)	39 (1.8%)
Vascular complications	36 (13%)	320 (15%)
Paravalvular leak ≥2+	39 (15%)	298 (15%)
Hospital length (days from procedure to discharge)	19.5 ± 0.8	10.1 ± 1.8
30-day		
All-cause death	24 (8.9%)	110 (5%)
Cardiovascular death	17 (6.3%)	91 (4.1%)
Re-hospitalization	3 (1.1%)	25 (1.1%)
Myocardial infarction	3 (1.1%)	24 (1.1%)
Stroke or transient ischaemic attack	8 (3%)	57 (2.6%)
New permanent pacemaker implantation	59 (29%)	508 (27%)
Paravalvular leak ≥2+	17 (15%)	131 (13%)

Categorical variables are reported as n (%); continuous variables are reported as mean ± SD

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