Prevalence and Clinical Impact of Iron Deficiency in Patients With Severe Aortic Stenosis Referred for Transcatheter Aortic Valve Implantation

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Patients referred for transcatheter aortic valve implantation (TAVI) are typically elderly with several co-morbidities, which might limit prognosis despite successful procedural outcome. To date, the prevalence and clinical impact of iron deficiency (ID) in patients with severe aortic stenosis who underwent TAVI remains poorly defined. This study included 495 patients who underwent transfemoral TAVI for severe symptomatic aortic stenosis. ID was defined as ferritin <100 ng/ml or ferritin 100 to 300 ng/ml, when transferrin saturation was <20%. The primary end point of the study was a composite of all-cause mortality, unplanned readmission for worsening heart failure or red blood cell transfusions during the first year after TAVI, which occurred in 22% (109 of 495) of the population. ID was present in 54% (268 of 495) of the entire cohort and was associated with a higher rate of the primary end point (27.6% [74 of 268] vs 15.4% [35 of 227]; p = 0.001). After multivariable adjustment, the association of ID with the primary end point remained significant (hazard ratio 1.64, 95% confidence interval [1.08 to 2.48]; p = 0.019). In a subgroup of ferropenic patients (n = 56), treatment with intravenous iron before TAVI was feasible, resulting in a considerable improvement of ferritin, transferrin saturation and symptoms at 30-day follow-up. In conclusion, ID is common in TAVI patients and is associated with adverse clinical outcome after TAVI. Correction of ID with intravenous iron seems feasible in contemporary TAVI patients. Whether this reduces transfusion rates and impacts clinical outcome after TAVI remains to be investigated in future prospective trials. **(Am J Cardiol 2019;124:1442−1448)**

Patients referred for transcatheter aortic valve implantation (TAVI) are typically elderly with several co-morbidities, which might limit prognosis despite successful valve implantation. Previous studies have shown that anemia is highly prevalent in TAVI patients and negatively impacts on prognosis.[1−3] In a small cohort, iron deficiency (ID) was common in anemic patients who underwent TAVI with a similar impact on prognosis compared with other anemia etiologies.[3] Periprocedural anemia was related to an increased red blood cell (RBC) transfusion rate,[4] which in turn was associated with increased mortality[5] and an increased risk for acute kidney injury in TAVI patients, which further impacts short- and long-term mortality.[6] Therefore, a conservative use of transfusions is demanded and strategies to reduce transfusion rates need to be further investigated. The administration of erythropoietin before TAVI failed to reduce the rate of RBC transfusions after TAVI, which might be due to ID.[7] In the present study, we investigated the prevalence and clinical impact of ID in patients with severe symptomatic aortic stenosis referred for transfemoral TAVI and further evaluated the feasibility of treating ID with intravenous iron.

Methods

This study included 495 patients with severe symptomatic aortic stenosis referred for transfemoral TAVI at the Department of Cardiovascular Diseases, Deutsches Herzzentrum München, Munich Germany between October 2015 and October 2017. Each patient was discussed by a multidisciplinary heart team and found eligible for transfemoral TAVI. All patients provided written informed consent.

ID was defined as ferritin <100 ng/ml or ferritin 100 to 300 ng/ml, when transferrin saturation (TSAT) was <20%.[8] The primary end point of this study was a composite of all-cause mortality, unplanned readmission for worsening heart failure, or any RBC transfusions during the first year after TAVI. In addition, all-cause mortality, readmission for worsening heart failure, and RBC transfusions were analyzed separately. Data collection involved demographic

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information, procedural data, as well as clinical and echocardiographic assessment. Adverse events were recorded throughout the follow-up period up to 12 months after TAVI. All clinical end points, procedural data, and in-hospital complications were categorized according to the updated Valve Academic Research Consortium criteria.[9] Patients were censored at last event-free contact. One-year follow-up was complete for 95.9% of all patients.

A subgroup of unselected ferropenic patients (n = 56), received 1.000 mg ferric carboxymaltose (Ferinject, Vifor Pharma, Glattbrugg, Switzerland) within 14 days before TAVI. The impact of intravenous iron administration on parameters of iron metabolism as well as symptoms according to New York Heart Association (NYHA) functional class was investigated at 30-day follow-up.

Categorical variables are expressed as frequencies and proportions and were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range and compared using Student *t* test or Mann-Whitney *U* test, respectively. For dichotomous analysis, 2 groups of patients, with and without ID, were created. Event rates of the combined primary end point as well as individual components (all-cause mortality, readmission for worsening heart failure and RBC transfusions) were calculated as crude rates.

Cox proportional hazard regression analysis was performed to determine factors associated with the primary end point. Due to the limited number of events, multivariable risk regression models were constraint to a limited number of significant and clinically relevant variables in univariate analyses to avoid model overfitting. These variables were logistic Euro (European System for Cardiac Operative Risk Evaluation)-SCORE I, NYHA class III/IV, atrial fibrillation, pulmonary hypertension, defined as pulmonary artery pressure (PAP) >60 mm Hg, mitral regurgitation grade III/IV, creatinine clearance, and ID. Because of significant collinearity with ID, hemoglobin values were not included in the model. Hazard ratios with their corresponding 95% confidence intervals were computed. Event rates were estimated using the Kaplan-Meier method. Group comparisons were performed using the log-rank test.

A 2-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using R (Version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics (Version 24.0 for Macintosh, IBM Corp., Armonk, New York).

Results

In total, 495 patients who underwent TAVI due to severe aortic stenosis were included in this analysis (Figure 1). Demographic data and baseline characteristics are shown in Table 1. Median age was 80 years [interquartile range 77 to 84] and 46% (229 of 495) were female. The population was a contemporary cohort of patients with a median logistic EuroSCORE I of 14.2% [8.4 to 23.9]. ID was present in 54% (268 of 495) of all patients. Baseline characteristics according to the presence of ID are displayed in Table 1. Patients with ID had an overall worse clinical risk profile. Median ferritin (80 ng/ml [47 to 116] vs 236 ng/ml [158 to 373]; p <0.001) and TSAT values (17.7% [13.6 to 22.4] vs 28.1% [23.8 to 35.0]; p <0.001) were lower in ferropenic patients compared with patients without ID.

Procedural data and in-hospital outcome are provided in Table 2. The combined primary end point occurred in 22% (109 of 495) of the population during the first year after TAVI. The individual components, that is, all-cause mortality, readmission for worsening heart failure, and any RBC transfusions, occurred in 8.1% (40 of 495), 6.9% (34 of 495), and 10.5% (52 of 495), respectively. Patients with ID had a significantly higher rate of the primary end point compared with those without (27.6% [74 of 268] vs 15.4% [35 of 227]; p = 0.001). This was driven by both, elevated mortality (10.4% (28 of 268) vs 5.3% (12 of 227); p = 0.036) and transfusion (13.8% (37 of 268) vs 6.6% (15 of 227); p = 0.009) rates. Cardiovascular mortality was present in 4.8% of the entire cohort (24 of 495). Patients with ID had a higher rate

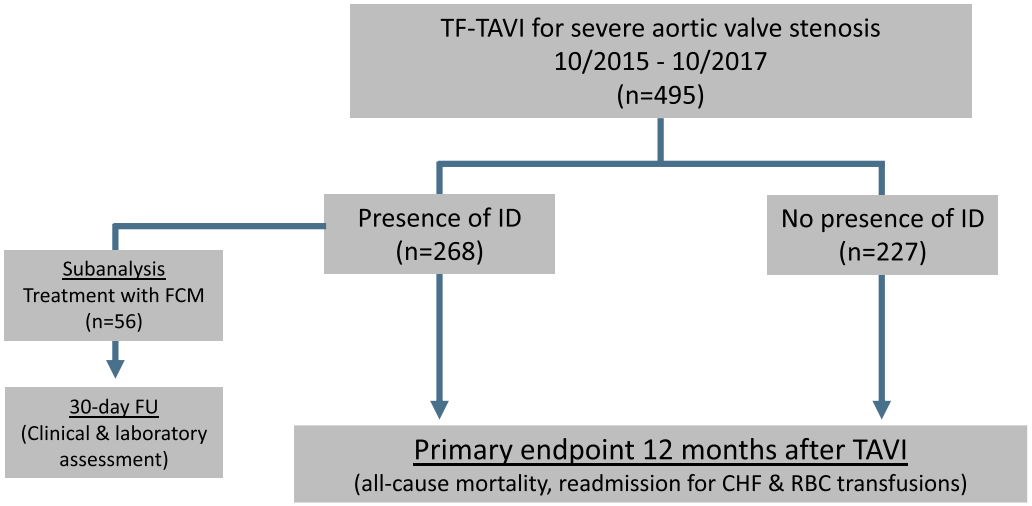

Figure 1. Study flowchart. CHF = chronic heart failure, FCM = ferric carboxymaltose, FU = follow-up, ID = iron deficiency, TF-TAVI = transfemoral transcatheter aortic valve implantation.

Table 1
Baseline characteristics according to iron deficiency

Variable	Iron deficiency		p value
	No (n = 227)	Yes (n = 268)	
Age (years)	80.0 [76.0;84.0]	81.0 [77.0;84.0]	0.208
Women	80 (35.2%)	149 (55.6%)	<0.001
Body Mass Index (kg/m^2)	25.9 [23.4;29.4]	25.9 [23.6;29.1]	0.961
Logistic EuroSCORE I (%)	12.1 [7.0;22.3]	15.8 [9.6;24.8]	0.008
New York Heart Association class III/IV	142 (62.6%)	190 (70.9%)	0.049
Arterial hypertension	210 (92.5%)	246 (91.8%)	0.767
Hypercholesterolemia	180 (79.3%)	217 (81.0%)	0.641
Diabetes mellitus	46 (20.3%)	85 (31.7%)	0.004
Coronary artery disease	176 (77.5%)	198 (73.9%)	0.346
Previous myocardial infarction	32 (14.1%)	33 (12.3%)	0.558
Previous coronary artery bypass grafting	29 (12.8%)	30 (11.2%)	0.588
Previous stroke	25 (11.0%)	32 (11.9%)	0.747
Previous malignancy	47 (20.7%)	64 (23.9%)	0.399
Previous pacemaker	29 (12.8%)	37 (13.8%)	0.737
Chronic obstructive pulmonary disease	33 (14.5%)	43 (16.0%)	0.643
Atrial fibrillation	69 (30.4%)	127 (47.4%)	<0.001
Left ventricular ejection fraction ≤35%	17 (7.5%)	24 (9.0%)	0.555
Mitral regurgitation grade III/IV	8 (3.5%)	23 (8.6%)	0.021
Pulmonary artery pressure >60 mm Hg	16 (7.0%)	43 (16.0%)	0.002
Mean transaortic gradient (mm Hg)	45.0 [38.0;52.0]	41.0 [34.0;50.3]	0.010
Baseline hemoglobin (g/dl)	13.4 [12.3;14.3]	12.5 [11.1;13.4]	<0.001
Creatinine clearance (ml/min)	56.0 [43.0;70.0]	49.0 [39.0;62.0]	0.007
C-reactive protein (mg/L)	2.0 [1.0;4.9]	2.6 [1.1;7.4]	0.064
Medication at discharge			
Dual antiplatelet therapy, n (%)	150/226 (66.4)	135/265 (50.9)	0.001
Oral anticoagulation with Vitamin K Antagonists, n (%)	33/226 (14.6)	58/265 (21.9)	0.038
Oral anticoagulation with Novel Oral Anticoagulants, n (%)	43/226 (19.0)	72/265 (27.2)	0.034
Triple therapy, n (%)	17/226 (7.5)	32/265 (12.1)	0.093

Table 2
Procedural characteristics according to iron deficiency

Variable	Iron deficiency		
	No (n = 227)	Yes (n = 268)	
Device success	198 (87.2%)	233 (86.9%)	0.925
Procedural success	223 (98.2%)	263 (98.1%)	0.932
Procedural time (min)	47.0 [40.0;57.0]	47.0 [39.3;57.0]	0.789
Fluoroscopy time (min)	11.2 [8.6;14.0]	10.6 [8.3;13.9]	0.191
Contrast (ml)	119 ± 46	115 ± 33	0.441
Major vascular complication	34 (15.0%)	32 (11.9%)	0.322
Life-threatening or major bleedings	39 (17.2%)	42 (15.7%)	0.651
Major stroke	2 (0.9%)	2 (0.7%)	0.867
Renal failure	4 (1.8%)	5 (1.9%)	0.932
New pacemaker implantation	11 (4.8%)	14 (5.2%)	0.848
Days in hospital	4.7 ± 2.0	4.6 ± 3.2	0.832
Days on intensive care unit	1.5 ± 1.3	1.2 ± 0.7	0.031

of cardiovascular mortality compared with those without (6.3% (17 of 268) vs 3.1% (7 of 227); p = 0.092). Kaplan-Meier cumulative incidence of the primary end point according to the presence of ID is depicted in Figure 2. After multivariable adjustment, the association of ID with the primary end point remained significant (hazard ratio 1.64, 95% confidence intervals [1.08 to 2.48]; p = 0.019; Table 3).

A subgroup of unselected patients with ID (n = 56) was treated with intravenous iron (ferric carboxymaltose; Ferinject) before TAVI. Treatment with intravenous iron improved median ferritin (from 63 ng/ml [29 to 91] to 264 ng/ml [124 to 416]) and TSAT values (from 15.1% [10.7 to 19.3] to 25.6% [18.9 to 32.6]) from baseline to 30-day follow-up (Figure 3). Consequently, the rate of ID declined from 100% (56 of 56) at baseline to 23% (13 of 56) at 30-day follow-up. Moreover, patients were more symptomatic according to NYHA functional class at baseline compared with 30-day follow-up (Figure 4). The rate of the combined primary end point was 25% (14 of 56).

Discussion

The present study investigates the prevalence and clinical impact of ID in patients with severe symptomatic aortic stenosis referred for transfemoral TAVI. The results can be summarized as follows: ID is common in contemporary TAVI patients with a prevalence of 54% and is associated with an unfavorable baseline risk profile. It seems to be independently associated with a higher rate of RBC transfusions and all-cause mortality after TAVI. In a subgroup of unselected patients, treatment of ID with intravenous iron before TAVI was feasible and led to improved ferritin and TSAT values as well as symptoms at 30-day follow-up.

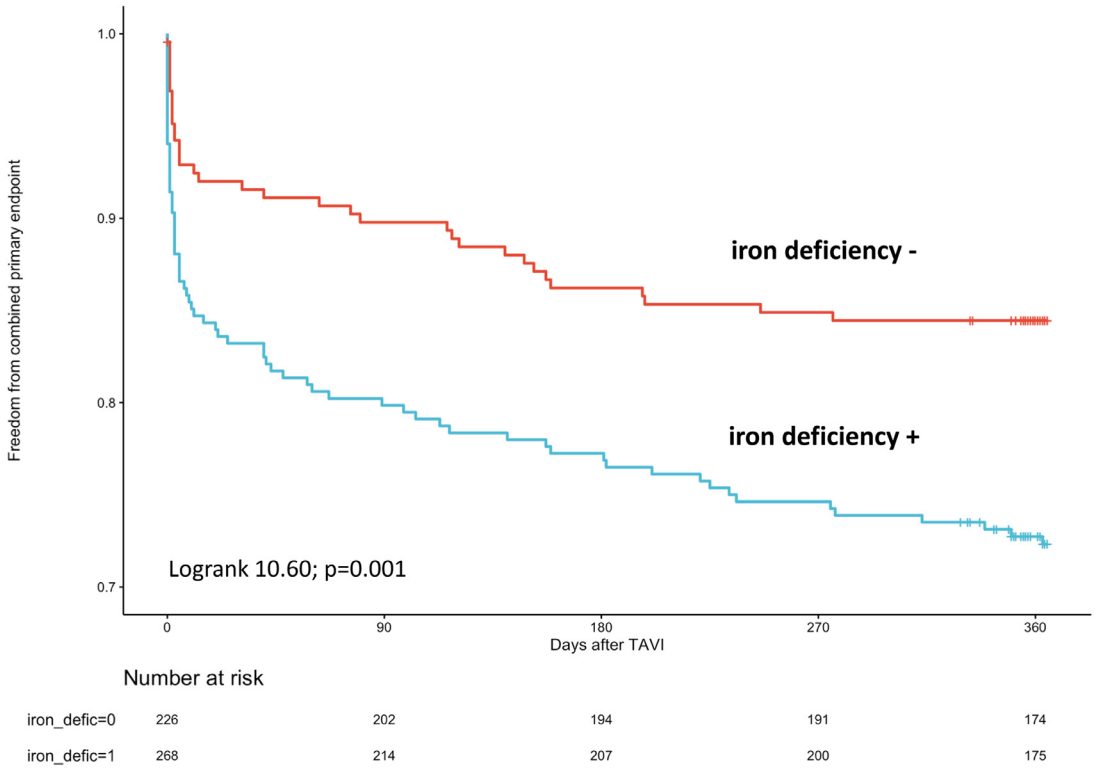

Figure 2. Kaplan-Meier event rates according to iron status.
Kaplan-Meier estimates for the primary end point with differences tested using log-rank test.

Table 3
Multivariable analysis to assess independent predictors of the primary end point

	Hazard ratio	95% confidence interval		p value
Log. EuroSCORE I	1.02	1.00	1.03	0.020
New York Heart Association class III/IV	1.46	0.91	2.34	0.117
Atrial fibrillation	1.14	0.77	1.68	0.521
Pulmonary hypertension	1.04	0.61	1.78	0.875
Mitral regurgitation grade III/IV	1.20	0.62	2.30	0.590
Creatinine clearance	0.99	0.97	1.00	0.011
Iron deficiency	1.64	1.08	2.48	0.019

According to current guidelines, TAVI is the recommended treatment option in patients with high-operative risk and should be considered as an alternative to conventional aortic valve replacement (SAVR) in patients with an intermediate-risk profile.[10] Despite a general trend to treat lower risk patients, current TAVI patients are typically elderly with several co-morbidities, which might impact on prognosis after an initially successful TAVI procedure.[11–14] Among other baseline risk factors, anemia is a common co-morbidity with a prevalence of almost 50% with a profound adverse impact on functional capacity and short- as well as midterm clinical outcome after TAVI.[1,3] Although, data regarding different etiologies remain scarce, ID seems to be common in anemic TAVI patients with a similar impact on prognosis compared with other anemia etiologies.[3]

So far, the optimal treatment strategy in anemic patients who underwent TAVI is unknown. Blood transfusions are performed in a considerable number of TAVI patients,[4] although they have already been linked to an increased rate of adverse clinical events including an impaired short- and long-term outcome.[6,15,16]

In cardiac surgery, preoperative administration of erythropoietin is currently recommended to reduce perioperative transfusion rates based on results from randomized controlled trials.[17–19] In TAVI patients, this strategy failed to reduce transfusion rates in the randomized EPICURE trial.[7] Thus, additional studies are required to investigate alternative treatment strategies. ID represents a potentially reversible cause of anemia and its diagnostic work-up might be of clinical relevance before TAVI given the available treatment options.

In chronic heart failure, ID has already been linked to disease progression and elevated mortality rates.[20,21] Treatment of ID with intravenous iron has demonstrated encouraging effects with an improvement of symptoms, functional capacity and health-related quality of life,[8,20,22–24] and a

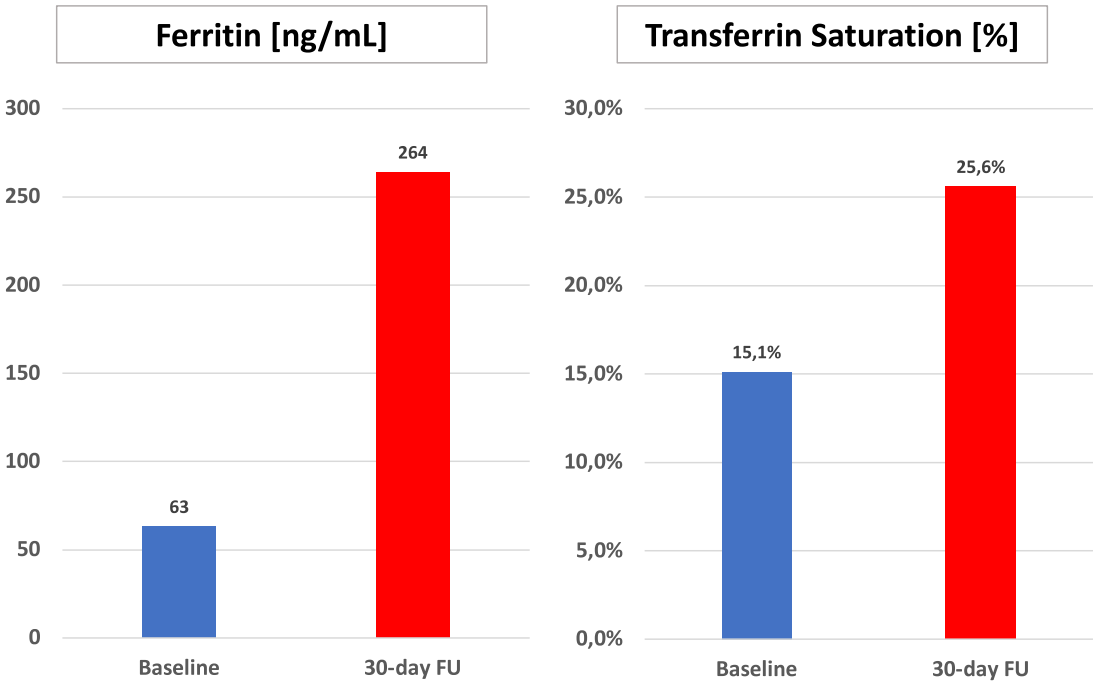

Figure 3. Changes in ferritin and TSAT values from baseline to 30-day follow-up in a subgroup of ferropenic patients treated with intravenous iron before TAVI.

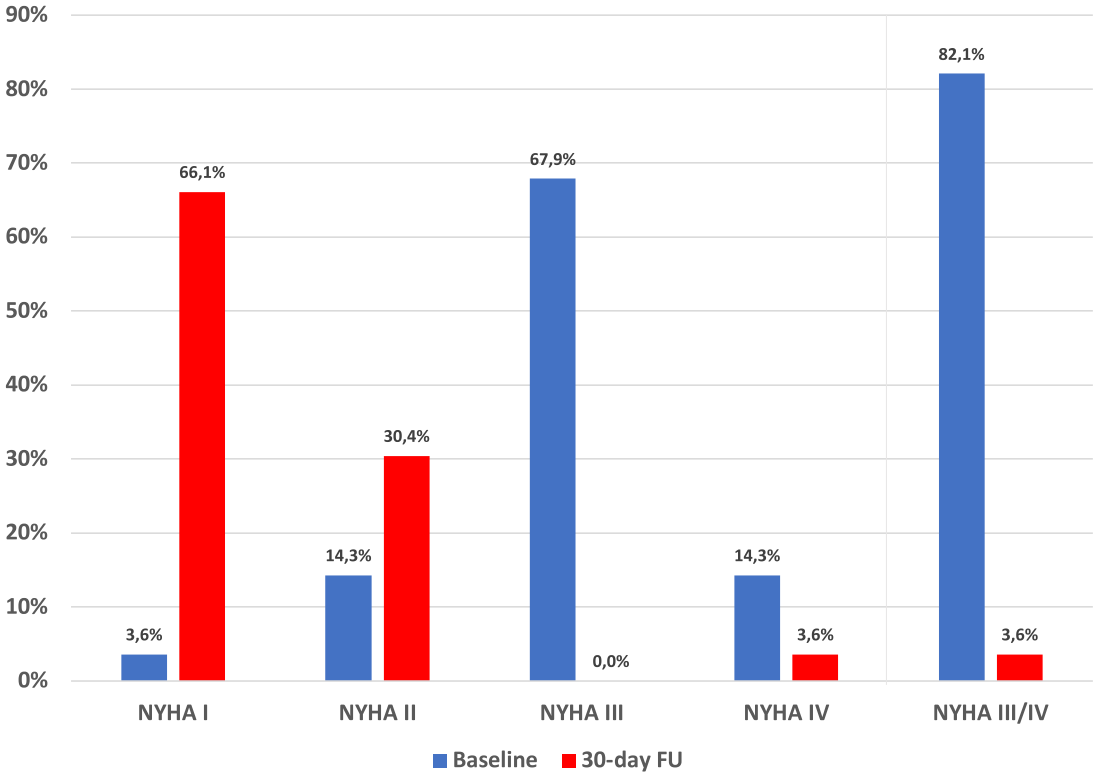

Figure 4. Changes in NYHA functional class from baseline to 30-day follow-up after TAVI in a subgroup of ferropenic patients treated with intravenous iron before TAVI.

reduction of adverse events including rehospitalizations for worsening heart failure,[21,22] and is therefore recommended in current heart failure guidelines.[25]

The present study is the first to investigate the prevalence and clinical impact of ID in patients referred for TAVI. ID is a common co-morbidity with a prevalence of 54% and is further associated with a higher rate of RBC transfusions and all-cause mortality after TAVI.

Given the encouraging effects from heart failure patients regarding treatment of ID, feasibility of treatment with

intravenous iron was investigated in contemporary TAVI patients. Our study demonstrates in a small subgroup of patients (n = 56), that treatment of ID with a singular administration of intravenous iron in patients with severe aortic stenosis before TAVI led to successful correction of ID in 3 quarters of our patients at 30-day follow-up. Additionally, the number of patients with symptomatic heart failure NYHA class III/IV at 30-day follow-up was considerably low with 3.6%.

Whether this correction of ID positively impacts clinical outcome needs to be further investigated in future prospective, randomized trials. In particular, it should be investigated whether ID is just a bystander indicating frailty or whether correction of ID before TAVI actually reduces the rate of periprocedural RBC transfusions, improves functional capacity and symptoms, and reduces mortality rates after TAVI. Additionally, the optimal timing of iron administration before TAVI needs to be specified.

This is an observational study from a single, high-volume center. Outcome of patients who underwent TAVI is complex and multifactorial. Thus, additional clinical and procedural factors may have been unrecognized in this analysis. Although not the scope of this study, the reasons for ID were not systematically investigated; nevertheless the etiology is likely multifactorial including nutritional deficiency, chronic disease states, hematological disorders and minor bleeding events in this cohort of patients.

In conclusion, ID is a common co-morbidity in contemporary TAVI patients and is associated with adverse clinical outcome after TAVI. Correction of ID with intravenous iron seems feasible in a subgroup of patients. Whether this impacts clinical outcome after TAVI remains to be investigated in future prospective trials.

Disclosures

AMK is a proctor for Edwards Lifesciences. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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