Incidence, Prognostic Impact, and Predictive Factors of Readmission for Heart Failure After Transcatheter Aortic Valve Replacement

Eric Durand, Maxime Doutriaux, Nicolas Bettinger, Christophe Tron, Charles Fauvel, Fabrice Bauer, Jean-Nicolas Dacher, Najime Bouhzam, Pierre-Yves Litzler, Alain Cribier, et al.

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 23, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jcin.2017.09.010

Incidence, Prognostic Impact, and Predictive Factors of Readmission for Heart Failure After Transcatheter Aortic Valve Replacement

Eric Durand, MD, PhD,[a] Maxime Doutriaux, MD,[a] Nicolas Bettinger, MD,[a] Christophe Tron, MD,[a] Charles Fauvel, MS,[a] Fabrice Bauer, MD, PhD,[a] Jean-Nicolas Dacher, MD, PhD,[b] Najime Bouhzam, MD,[a] Pierre-Yves Litzler, MD,[c] Alain Cribier, MD,[a] Hélène Eltchaninoff, MD[a]

ABSTRACT

OBJECTIVES The aim of this study was to assess the incidence, prognostic impact, and predictive factors of readmission for congestive heart failure (CHF) in patients with severe aortic stenosis treated by transcatheter aortic valve replacement (TAVR).

BACKGROUND TAVR is indicated in patients with severe symptomatic aortic stenosis in whom surgery is considered high risk or is contraindicated. Readmission for CHF after TAVR remains a challenge, and data on prognostic and predictive factors are lacking.

METHODS All patients who underwent TAVR from January 2010 to December 2014 were included. Follow-up was achieved for at least 1 year and included clinical and echocardiographic data. Readmission for CHF was analyzed retrospectively.

RESULTS This study included 546 patients, 534 (97.8%) of whom were implanted with balloon-expandable valves preferentially via the transfemoral approach in 87.8% of cases. After 1 year, 285 patients (52.2%) had been readmitted at least once, 132 (24.1%) for CHF. Patients readmitted for CHF had an increased risk for death ($p < 0.0001$) and cardiac death ($p < 0.0001$) compared with those not readmitted for CHF. On multivariate analysis, aortic mean gradient (hazard ratio [HR]: 0.88; 95% confidence interval [CI]: 0.79 to 0.99; $p = 0.03$), post-procedural blood transfusion (HR: 2.27; 95% CI: 1.13 to 5.56; $p = 0.009$), severe post-procedural pulmonary hypertension (HR: 1.04; 95% CI: 1.00 to 1.07; $p < 0.0001$), and left atrial diameter (HR: 1.47; 95% CI: 1.08 to 2.01; $p = 0.02$) were independently associated with CHF readmission at 1 year.

CONCLUSIONS Readmission for CHF after TAVR was frequent and was strongly associated with 1-year mortality. Low gradient, persistent pulmonary hypertension, left atrial dilatation, and transfusions were predictive of readmission for CHF. (J Am Coll Cardiol Intv 2017;10:2426–36) © 2017 by the American College of Cardiology Foundation.

Since the first-in-human transcatheter aortic valve replacement (TAVR) by Cribier et al. (1) in 2002, management of severe symptomatic aortic stenosis (AS) has substantially evolved. Indeed, TAVR has been shown to reduce mortality compared with medical therapy in inoperable patients and to be noninferior to surgery in high-risk patients (2,3). More recently, TAVR with a balloon-expandable valve has been shown to be noninferior to surgery in intermediate-risk patients in the randomized

From the [a]Department of Cardiology, Normandie Université, UNIROUEN, Rouen University Hospital, INSERM U1096, Rouen, France; [b]Department of Radiology, Normandie Université, UNIROUEN, Rouen University Hospital, INSERM U1096, Rouen, France; and the [c]Department of Cardiac Surgery, Normandie Université, UNIROUEN, Rouen University Hospital, INSERM U1096, Rouen, France. Dr. Cribier is a consultant and proctor for Edwards Lifesciences. Dr. Eltchaninoff has received lecture fees from and is a proctor for Edwards Lifesciences. Dr. Durand has received lecture fees from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to contents of this paper to disclose.

Manuscript received June 29, 2017; revised manuscript received September 5, 2017, accepted September 13, 2017.

PARTNER (Placement of Aortic Transcatheter Valves) 2 trial and superior to surgery in the propensity-matched PARTNER 2S3i trial (4,5). Fostered by refinements in device technology, careful selection, and reduction in complications, readmission after TAVR remains a substantial issue, affecting 17.9% to 43.9% of patients at 1 year, as demonstrated in previous reports (6,7). Readmission after an index hospitalization may be related to noncardiac causes, including a patient's comorbidities, and cardiac causes. Congestive heart failure (CHF) seems to be 1 of the major cardiac causes, and as data on prognostic impact and predictive factors associated with CHF are lacking, it remains a challenge to detect populations at risk and prevent acute heart failure episodes leading to readmission.

SEE PAGE 2437

We sought to assess the incidence, prognostic impact, and predictive factors of readmission for CHF in a population of patients with severe AS treated by TAVR.

METHODS

STUDY PROTOCOL. This was a single-center study including all patients who had undergone TAVR at our university hospital between January 1, 2010, and December 31, 2014. Patients who died during TAVR or during initial hospitalization were not included. Data were retrieved from a dedicated in-hospital database prospectively maintained since 2002. According to current guidelines, only patients with severe symptomatic AS and life expectancy >1 year were eligible. TAVR indication was decided by the local heart team, and patients included were contraindicated or at high risk for surgery.

Patients received SAPIEN balloon-expandable valves (Edwards Lifesciences, Irvine, California) (the SAPIEN XT from 2010 to June 2014 and the SAPIEN 3 from July 2014 to December 2014) and self-expanding CoreValve devices (Medtronic, Minneapolis, Minnesota), as previously described (8,9). In-hospital and follow-up data were entered into a dedicated database. Clinical outcomes were defined according to Valve Academic Research Consortium 2 criteria (10). All patients provided written informed consent form before the procedure.

FOLLOW-UP. Clinical follow-up was carried out during pre-scheduled outpatient clinic visits or by telephone contact at 1 and 12 months post-TAVR and yearly thereafter. Records from referring cardiologists, general practitioners, and other hospitals were consulted whenever necessary for further information. Complete information on readmission during follow-up was obtained in 99.6% of patients (2 patients were lost to follow-up). The mean length of follow-up was 27.2 ± 0.7 months.

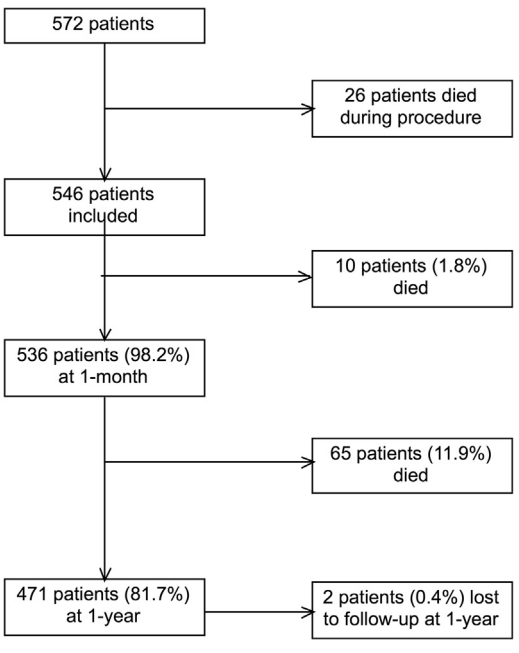
HOSPITAL READMISSION. Readmission was defined as a patient's being admitted to a hospital ward or an intensive care unit. Visits to the emergency department or admission to a daycare hospital were excluded from the present analysis. Reasons for readmission and in-hospital death were recorded after a detailed review of medical records. Readmission for CHF was defined by clinical and or radiological signs of cardiac heart failure and/or an increased N-terminal pro-brain natriuretic peptide level. Cutoffs used were >450, >900, and >1,800 pg/ml, respectively, in patients <50, 50 to 75, and >75 years of age, as previously described (11).

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared using the Student *t* test or the Mann-Whitney rank sum test, as

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
CHF = congestive heart failure
CI = confidence interval
HR = hazard ratio
LVEF = left ventricular ejection fraction
TAVR = transcatheter aortic valve replacement

FIGURE 1 Study Flowchart



Among the 572 patients treated with transcatheter aortic valve replacement from 2010 to 2014, 546 were included in the study; 26 patients (4.5%) died during the procedure or initial hospitalization. During the follow-up period, 10 patients died at 1 month and 65 patients at 1 year.

TABLE 1 Baseline Characteristics

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
Age, yrs	83.9 ± 7.3	84.1 ± 5.8	83.9 ± 7.8	0.72
Male	255 (46.7)	57 (43.2)	198 (47.8)	0.37
Hypertension	413 (75.8)	96 (72.7)	317 (76.8)	0.35
Diabetes	159 (29.2)	44 (33.3)	115 (27.8)	0.23
Dyslipidemia	327 (60.0)	73 (55.7)	254 (61.4)	0.26
Myocardial infarction	62 (11.5)	16 (12.2)	46 (11.2)	0.75
Coronary angioplasty	125 (23.0)	31 (23.7)	94 (22.8)	0.91
CABG	54 (9.9)	15 (11.4)	39 (9.5)	0.51
Atrial fibrillation	208 (38.4)	57 (43.5)	151 (36.7)	0.18
Pacemaker	70 (12.9)	20 (15.3)	50 (12.1)	0.37
Aortic valvuloplasty	82 (15.1)	29 (22.3)	53 (12.9)	0.01
Peripheral artery disease	72 (13.3)	19 (14.5)	53 (12.9)	0.66
Porcelain aorta	20 (3.7)	7 (5.3)	13 (3.2)	0.28
Stroke	35 (6.4)	6 (4.6)	29 (7.0)	0.41
COPD	99 (18.2)	23 (17.6)	76 (18.4)	0.90
Thoracic irradiation	25 (4.6)	7 (5.3)	18 (4.4)	0.63
Cancer	98 (18.1)	30 (23.1)	68 (16.5)	0.12
Frailty	129 (23.6)	32 (24.2)	99 (23.9)	0.92
NYHA functional class ≥III	387 (72.6)	103 (80.5)	284 (70.1)	0.02
Clinical presentation				
CHF before TAVR	252 (46.5)	76 (58.5)	176 (42.7)	0.002
Left HF before TAVR	175 (33.7)	48 (37.8)	127 (32.4)	0.28
Right HF before TAVR	190 (36.6)	54 (42.5)	136 (34.7)	0.11
Logistic EuroSCORE, %	15.6 ± 10.9	16.5 ± 11.8	15.2 ± 10.5	0.26
Medications				
Loop diuretic agents	317 (59.4)	88 (66.7)	229 (57.0)	0.05
MR antagonists	40 (7.5)	10 (7.6)	30 (7.5)	1.00
ACE inhibitors	208 (39.0)	56 (42.4)	152 (37.8)	0.36
Beta-blockers	226 (42.3)	56 (42.4)	170 (42.3)	1.00
Anticoagulant agents	148 (27.8)	39 (29.5)	109 (27.3)	0.65
Electrocardiography				
Heart rate, beats/min	76.8 ± 15.9	75.2 ± 15.3	77.3 ± 16.0	0.27
Sinus rhythm	382 (70.9)	80 (62.5)	302 (73.5)	0.02
Atrial fibrillation	151 (28.1)	45 (35.4)	106 (25.9)	0.04
Right bundle branch block	65 (12.1)	14 (10.9)	51 (12.4)	0.76
Left bundle branch block	73 (13.6)	18 (14.2)	55 (13.4)	0.88
Laboratory tests				
Creatinine, μmol/l	111.6 ± 57.1	118.4 ± 57.6	109.5 ± 56.9	0.12
Hemoglobin, g/dl	12.3 ± 1.5	11.9 ± 1.6	12.4 ± 1.5	0.04
CRP, mg/L	8.2 ± 14.3	7.3 ± 11.3	8.5 ± 15.1	0.39
NT-proBNP, pg/ml	5,316.56 ± 911.5	5,761.0 ± 926.0	5,166.6 ± 907.6	0.56

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HF = heart failure; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; TAVR = transcatheter aortic valve replacement.

appropriate. Categorical variables were compared using the chi-square or Fisher exact test. Patients were divided into 2 groups on the basis of the presence or absence of readmission for CHF. Survival outcome was determined using Kaplan-Meier methodology and compared using the log-rank test. A Cox regression was also performed to evaluate the impact of the number of readmissions for CHF (as a time-varying covariate) on death and cardiac death. Stepwise Cox multivariate regression analyses were performed to assess the predictive factors of readmission for CHF after TAVR. The model was built on the basis of a univariate association between the variable of $p = 0.05$ and an elimination of $p = 0.10$.

TABLE 2 Baseline Echocardiographic Data

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
LVEDD, mm	51.4 ± 8.5	51.9 ± 8.5	51.3 ± 8.6	0.50
LVESD, mm	34.3 ± 9.3	34.8 ± 9.1	34.1 ± 9.4	0.48
IVS, mm	11.9 ± 2.2	11.6 ± 2.1	12.0 ± 2.3	0.11
PWT, mm	11.1 ± 2.1	11.0 ± 1.9	11.2 ± 2.2	0.27
LVEF, %	59.6 ± 14.8	57.8 ± 14.8	60.2 ± 14.8	0.11
LVEF <30%	26 (4.9)	8 (6.2)	18 (4.4)	0.48
LA diameter, mm	43.0 ± 7.8	44.5 ± 7.9	42.5 ± 7.8	0.68
LVOT VTI, cm	21.0 ± 6.4	20.5 ± 6.7	21.1 ± 6.4	0.37
Mitral regurgitation				
Grades 2–4	157 (28.8)	51 (38.6)	106 (25.7)	0.006
Aortic regurgitation				
Absence	154 (28.3)	33 (25.2)	121 (29.2)	0.44
Grades 3 and 4	21 (3.9)	5 (3.8)	16 (3.9)	1.00
Aortic mean gradient, mm Hg	46.7 ± 16.7	43.4 ± 15.8	47.8 ± 16.9	0.009
Aortic valve area, cm^2	0.69 ± 0.22	0.68 ± 0.20	0.69 ± 0.22	0.65
SVI, ml/m^2	37.8 ± 14.9	37.7 ± 13.3	37.8 ± 15.4	0.95
SVI <35 ml/m^2	248 (45.4)	63 (47.7)	185 (44.7)	0.71
PASP, mmHg	43.7 ± 14.5	48.1 ± 16.7	42.2 ± 13.4	<0.0001
PASP >60 mm Hg	57 (14.6)	21 (20.8)	36 (12.4)	0.05

Values are mean ± SD or n (%).

CHF = congestive heart failure; IVS = interventricular septum; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVOT = left ventricular outflow tract; PASP = pulmonary artery systolic pressure; PWT = posterior wall thickness; SVI = stroke volume index; VTI = velocity-time integral.

TABLE 3 Hospital Outcomes

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
Stroke				
Major	8 (1.5)	0	8 (1.9)	0.21
Minor	4 (0.7)	0	4 (1.0)	0.58
TIA	2 (0.4)	0	2 (0.5)	1.00
Bleeding				
Life threatening	35 (6.4)	15 (11.5)	20 (4.8)	0.01
Major	65 (11.9)	20 (15.4)	45 (10.8)	0.16
Minor	42 (7.7)	10 (7.7)	32 (7.7)	1.00
Transfusion	106 (19.4)	39 (30.0)	67 (16.2)	0.001
Acute kidney injury				0.08
Grade 3	7 (1.3)	1 (0.8)	6 (1.4)	
Grade 2	3 (0.5)	1 (0.8)	2 (0.5)	
Grade 1	76 (13.8)	27 (20.5)	49 (11.7)	
Vascular complication				
Major	79 (14.6)	23 (17.8)	56 (13.6)	0.25
Minor	52 (9.6)	13 (10.1)	39 (9.4)	0.86
Myocardial infarction	6 (1.1)	4 (3.1)	2 (0.5)	0.03
Pacemaker	42 (7.7)	7 (5.7)	35 (8.5)	0.44
ICU length of stay, days	2.3 ± 2.3	2.6 ± 2.5	2.2 ± 2.2	0.07
Hospitalization length of stay, days	6.8 ± 12.5	7.7 ± 7.8	6.6 ± 13.7	0.39
Early discharge (<72 h)	207 (37.9)	31 (24.0)	176 (42.8)	<0.0001

Values are n (%) or mean ± SD.

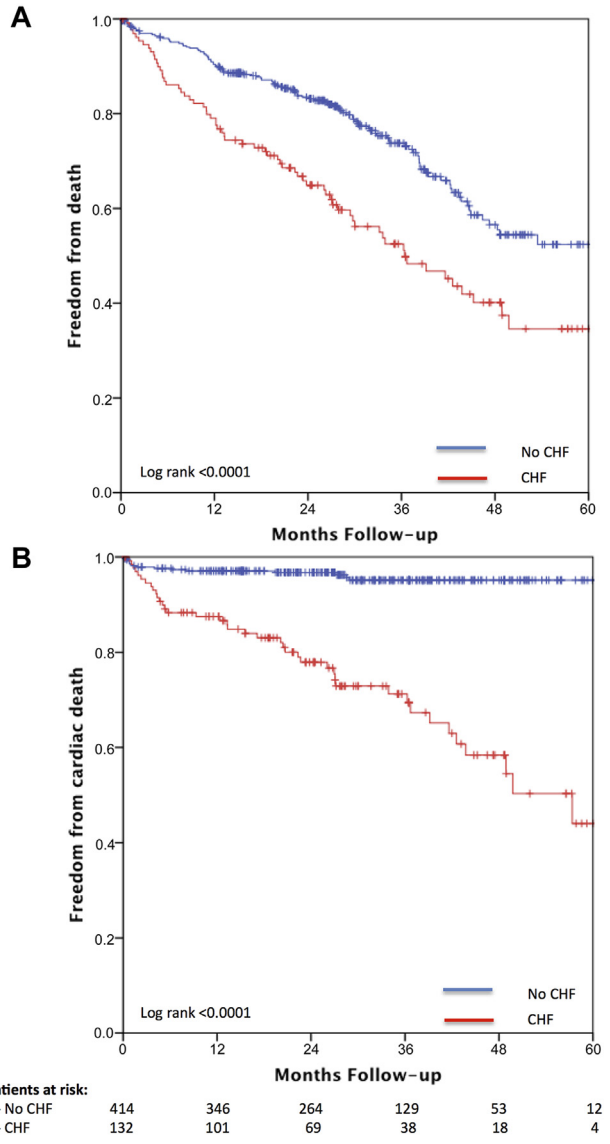
CHF = congestive heart failure; ICU = intensive care unit; TIA = transient ischemic attack.

TABLE 4 Hospitalization Laboratory Results

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
Troponin peak, ng/l	267.8 ± 721.48	372.0 ± 1,241.3	235.5 ± 450.1	0.07
Creatinine peak, µmol/l	121.0 ± 81.5	136.2 ± 82.9	116.2 ± 80.6	0.02
Hemoglobin nadir, g/dl	10.4 ± 1.7	10.1 ± 1.8	10.5 ± 1.7	0.01
NT-proBNP peak, ng/l	4,273.9 ± 748.5	5,829.1 ± 1,104.7	3,810.4 ± 597.5	0.02
CRP peak, mg/l	50.0 ± 52.2	55.7 ± 60.2	48.2 ± 49.1	0.16

Values are mean ± SD.
Abbreviations as in Table 1.

FIGURE 2 Impact of Congestive Heart Failure Readmission on Survival



Kaplan-Meier curves of freedom from death **(A)** and cardiac death **(B)** in patients readmitted for congestive heart failure (CHF) **(red)** and those not readmitted for CHF **(blue)**.

All statistical tests were 2 sided. Differences were considered statistically significant at a p value of ≤0.05. All data were analyzed using SPSS version 17.0 (IBM, Armonk, New York).

RESULTS

Among the 572 patients who underwent TAVR from 2010 to 2014, 546 were included in the study; 26 patients (4.5%) died during the procedure or initial hospitalization (Figure 1).

The main baseline and procedural characteristics and in-hospital complications are shown in Tables 1 to 3. The characteristics are presented in the overall population according to whether patients were readmitted for CHF. The mean age was 83.9 ± 7.3 years, and 53.3% were women. The mean logistic European System for Cardiac Operative Risk Evaluation score was 15.6 ± 10.9%. The majority of patients had dyspnea equal to or more than New York Heart Association functional class III (72.6%), and nearly one-half of patients (n = 252 [46.5%]) had been hospitalized for acute heart failure (Table 1).

Mean aortic valve area was 0.69 ± 0.22 cm^2, mean aortic gradient was 46.7 ± 16.7 mm Hg, mean left ventricular ejection fraction (LVEF) was 59.6 ± 14.8%, and 26 patients (4.9%) had LVEFs ≤30%. Fifty-seven patients (14.6%) had severe pulmonary hypertension (pulmonary artery systolic pressure >60 mm Hg), and mean pulmonary artery systolic pressure was 43.7 ± 14.5 mm Hg (Table 2). Four hundred eighty-two patients (87.8%) underwent implantation using a transfemoral approach, with local anesthesia and conscious sedation in all cases. Sixty-four patients (11.7%) not eligible for a transfemoral approach underwent implantation using a transapical approach. The majority of patients received SAPIEN XT (n = 482 [88.3%]) or SAPIEN 3 (n = 52 [9.5%]) valves. Other patients received CoreValve devices (n = 12 [2.2%]). Twenty-one patients (3.8%) underwent valve-in-valve procedures for degenerative bioprostheses. The mean length of stay in the intensive care unit was 2.3 ± 2.3 days, and the mean total length of hospitalization was 6.8 ± 12.5 days. Early discharge (within 72 h) was achieved in 207 patients (37.9%). Complications occurring and laboratory results during initial hospitalization are shown in Tables 3 and 4, respectively.

INCIDENCE OF READMISSION FOR CHF. In the year following the TAVR procedure, 285 patients (52.2%) were readmitted at least once, 132 (24.1%) for CHF. Among patients readmitted for CHF, 84 (63.6%) had a

single readmission, and 48 (36.4%) had multiple readmissions (n = 21 [15.9%] twice, n = 20 [15.1%] 3 times, n = 5 [3.8%] 4 times, and n = 2 [1.5%] 5 times or more).

PROGNOSTIC IMPACT OF READMISSION FOR CHF. Results are shown in Figures 2 to 4. Overall 1-month and 1-year mortality of the studied population was 1.8% and 13.7%, respectively. Including patient deaths during the hospital phase, 30-day mortality was 6.3%. During a mean follow-up period of 27.2 months, the overall mortality rate was 31.5%.

We evaluated the impact of 1-year readmissions for CHF after TAVR on death and cardiac death. Patients readmitted for CHF had an increased risk for death ($p < 0.0001$) (Figure 2A) and cardiac death ($p < 0.0001$) (Figure 2B) compared with those not readmitted for CHF. Cardiac deaths accounted for 71.9% of total mortality in patients readmitted for CHF compared with only 18.6% in patients not readmitted for CHF. We also evaluated the impact of the number of readmissions on total and cardiac death in Figures 3 and 4. Patients with multiple readmissions for CHF had significantly higher total mortality ($p < 0.0001$) (Figure 3A) and cardiac mortality ($p < 0.0001$) (Figure 3B). Figures 4A and 4B show that total and cardiac mortality increased with the number of readmissions, respectively.

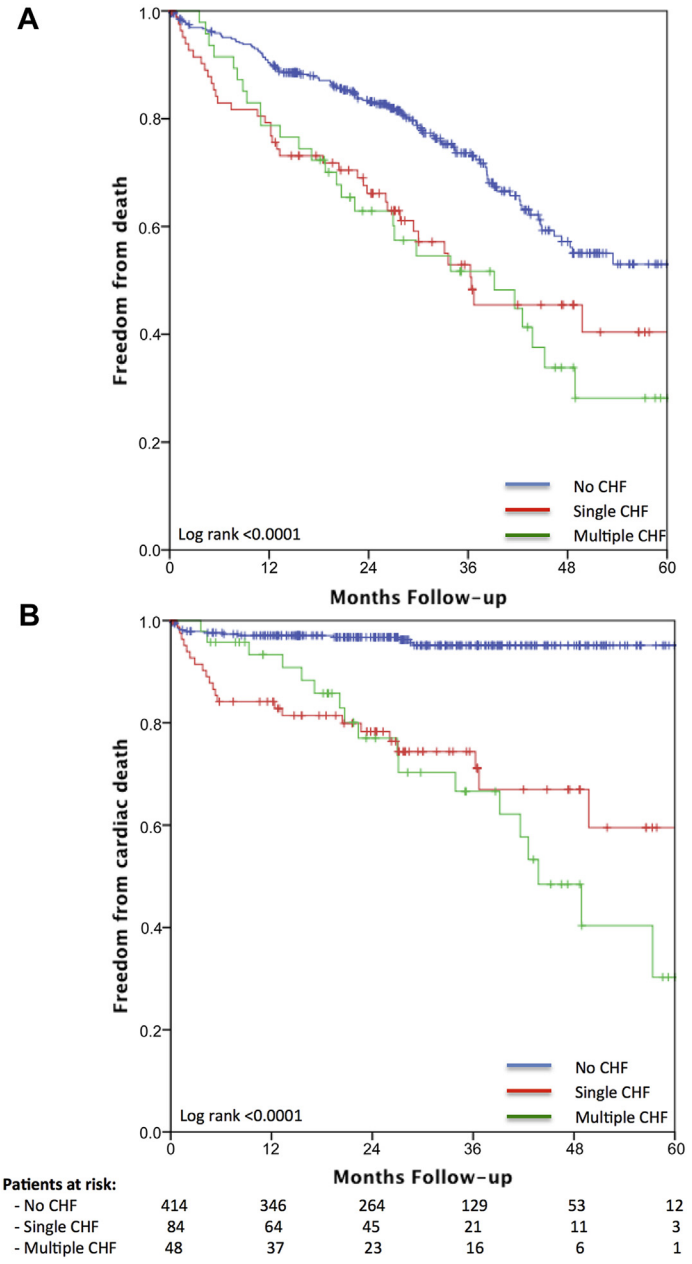
PREDICTORS OF READMISSION FOR CHF. Tables 1 to 3 compare baseline and procedural characteristics and in-hospital complications of the study population according to readmission for CHF. One-month and 1-year data of echocardiographic follow-up and medical therapy are presented in Tables 5 and 6, respectively. Univariate and multivariate analysis of predictors of readmission for CHF are shown in Table 7.

Patients readmitted for CHF were more likely to have medical histories of balloon aortic valvuloplasty, higher New York Heart Association functional classification, heart failure before TAVR, loop diuretic therapy, atrial fibrillation, and anemia (Table 1). Patients readmitted for CHF were more likely to have significant mitral regurgitation, pulmonary hypertension, and lower mean aortic gradient before TAVR (Table 2).

Procedural characteristics were similar in both groups. However, patients with CHF following TAVR had more major bleeding, transfusions, vascular complications, and myocardial infarction. They were also less likely to be discharged early (Table 3).

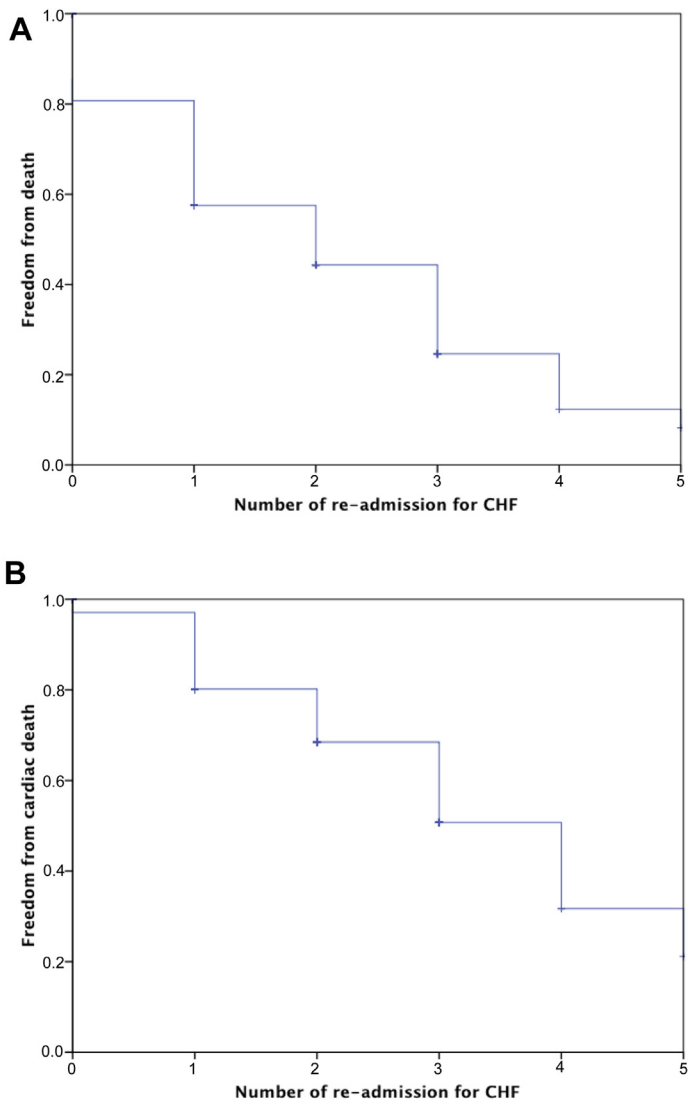
Post-procedural echocardiographic follow-up showed that patients readmitted for CHF had higher left ventricular end-diastolic and end-systolic diameters and pulmonary artery systolic pressure. Patients readmitted for CHF had lower LVEF and had more frequently significant paravalvular aortic and mitral regurgitation. Left atrial diameter at 1 year was also increased (Table 5). Regarding drugs, patients readmitted for CHF were more likely to be

FIGURE 3 Impact of No, Single, and Multiple Readmissions for Congestive Heart Failure on Survival



Kaplan-Meier curves of freedom from death **(A)** and cardiac death **(B)** in patients with no **(blue)**, single **(red)**, and multiple **(green)** readmissions for congestive heart failure (CHF).

FIGURE 4 Impact of the Number of Readmissions for Congestive Heart Failure on Death and Cardiac Death



The impact of the number of readmissions on death **(A)** and cardiac death **(B)** was evaluated by Cox regression. CHF = congestive heart failure.

treated with loop diuretic agents, beta-blockers, and anticoagulant agents (Table 6).

By multivariate analysis, aortic mean gradient (hazard ratio [HR]: 0.88; 95% confidence interval [CI]: 0.79 to 0.99; p = 0.03), post-procedural blood transfusion (HR: 2.27; 95% CI: 1.13 to 5.56; p = 0.009), severe post-procedural pulmonary hypertension (HR: 1.04; 95% CI: 1.00 to 1.07; p < 0.0001), and left atrial diameter (HR: 1.47; 95% CI: 1.08 to 2.01; p = 0.02) were independently associated with readmission for CHF at 1 year (Table 7).

DISCUSSION

In this study, with prospectively entered data from a single high-volume center expert in TAVR, including 546 TAVR patients, we assessed the incidence, prognostic impact, and predictive factors of readmission for CHF following TAVR. The main findings of the present study are as follows: 1) in the year following TAVR, about one-quarter of patients were readmitted for CHF; 2) the mortality rate was high and significantly higher in the group of patients readmitted for CHF and increased with the number of readmissions; 3) factors independently associated with CHF readmission were low aortic mean gradient before TAVR, post-procedural blood transfusion, severe persistent post-procedural pulmonary hypertension, and left atrial dilatation.

INCIDENCE OF READMISSION FOR CHF. As shown in previous reports, readmission after an index hospitalization is common, involving a high rate of patients treated by TAVR. Previous studies have reported the incidence of early (within 30 days) and late readmission following TAVR (6,7,12–15). The rate of early readmission varied from 4.0% to 17.9%. A higher rate of early readmission was reported in patients who underwent TAVR with a transapical approach (6,7,13). A single study by Nombela-Franco et al. (6) reported the incidence of readmission up to 1 year after TAVR and showed that TAVR was involved in 43.9% of all-cause readmissions. Among this population, 58.9% were admitted for noncardiac causes, mainly because of pre-existing comorbidities, and 41.1% for cardiac causes, mainly CHF (23.3%). These results are consistent with those of our study, with 1-year total readmission rate and for CHF of 52.2% and 24.1%, respectively.

PROGNOSTIC IMPACT OF READMISSION FOR CHF. In our study, we assessed the prognostic impact of readmission for CHF. To our knowledge, this is the first study reporting the impact of readmission for CHF on mortality after TAVR. Among patients who were discharged from the hospital, the mortality rate was 1.9% at 1 month, 13.7% at 1 year, and 31.4% after a mean follow-up duration of 27.2 ± 0.7 months. Readmission for CHF after TAVR was strongly associated with a higher mortality rate at 1 year (24.2% vs. 10.4%, p < 0.0001) and at the end of the follow-up (50.0% vs. 25.6%, p < 0.0001). Cardiovascular deaths accounted for 71.9% of total mortality in patients readmitted for CHF compared with only 18.6% in patients not readmitted for CHF. Nombela-Franco et al. (6) previously assessed the impact of early

readmission (within 30 days), regardless of cause or etiology, on mortality with a mean follow-up duration close to that of our study. They also reported that mortality rate at 2 years was significantly increased in patients readmitted within 30 days after TAVR compared with those not readmitted (30.2% vs. 19.2%, p = 0.002). These results confirm that readmission after TAVR is common in about 50% of all cases in the year after the procedure. Approximately 30% to 50% of readmissions are of cardiac origin related to CHF and have a major prognostic impact on mortality.

PREDICTIVE FACTORS FOR CHF. Finally, we assessed predictive factors of readmission for CHF after TAVR. By multivariate analysis, 4 independent factors were identified (low aortic mean gradient before TAVR, post-procedural blood transfusion, severe persistent post-procedural pulmonary hypertension, and left atrial dilatation). In contrast, LVEF before TAVR and paravalvular aortic regurgitation were not predictive. The impact of aortic valve gradient and LVEF on outcomes of TAVR was recently reported in a large series of patients (n = 11,292) (16). During the first year of follow-up after TAVR, patients with left ventricular dysfunction and low aortic valve gradients (<40 mm Hg) had higher rates of death and recurrent CHF. However, after adjustment, only low aortic valve gradient was associated with higher mortality (HR: 1.21; 95% CI: 1.11 to 1.32; p < 0.001) and higher rates of CHF (HR: 1.52; 95% CI: 1.36 to 1.69; p < 0.001), whereas the effect of LVEF was no longer significant. Previous studies have demonstrated that patients with low-flow, low-gradient AS have evidence of myocardial fibrosis, a finding that has been linked to abnormal left ventricular remodeling and reduced compliance and filling of the left ventricle as well as to poorer clinical outcomes in patients with severe AS (17,18). In contrast, the prognostic impact of pulmonary hypertension on outcomes after TAVR has also been reported (19–21). All studies showed that pulmonary hypertension before TAVR was frequent and increased mortality after TAVR. Furthermore, patients with persistent severe pulmonary hypertension had a worse prognosis than those with a decrease in pulmonary artery systolic pressure lower than 60 mm Hg (2-year mortality rate 50.0% vs. 18.6%, p = 0.001) (21). Usually, patients with pre-capillary or combined pulmonary hypertension have more frequently persistent pulmonary hypertension after TAVR (20). One can easily understand that these patients, despite treatment for AS, might be readmitted for CHF. Classification of pulmonary hypertension, by right heart catheterization, as post-capillary or pre-capillary or combined, could therefore help the heart team choose the best option to treat and monitor these patients. We also observed that hemorrhagic complications and transfusions are predictive of readmission for CHF. We and others previously evaluated the impact of bleeding and transfusions on outcomes after TAVR (22). Post-procedural transfusions were frequent (35.2%) and increased 30-day and 1-year mortality (22). The negative impact of blood transfusions could be explained by different hypotheses: anemia is known to be predictive of CHF, and overload due to transfusion may worsen pre-existing cardiac disease. Chronic anemia leading to

TABLE 5 Echocardiographic Follow-Up

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
1-month follow-up				
LVEDD, mm	51.9 ± 11.8	54.1 ± 13.6	51.1 ± 10.9	0.02
LVESD, mm	33.1 ± 9.0	34.8 ± 9.6	32.4 ± 8.8	0.02
IVS, mm	11.6 ± 2.3	11.6 ± 2.4	11.6 ± 2.2	0.96
PWT, mm	10.9 ± 1.9	10.9 ± 1.9	10.9 ± 1.9	0.75
LVEF, %	60.2 ± 11.9	58.0 ± 12.8	61.0 ± 11.6	0.02
LVEF <30%	9 (1.6)	5 (4.2)	4 (1.1)	0.05
LA diameter, mm	45.1 ± 8.7	46.4 ± 8.5	44.6 ± 8.7	0.11
LVOT VTI, cm	24.8 ± 6.8	23.7 ± 5.8	25.2 ± 7.1	0.09
Mitral regurgitation				
Grades 2–4	109 (19.1)	36 (27.2)	73 (16.7)	0.009
Aortic regurgitation				
Grade >2	111 (21.5)	38 (29.0)	73 (18.9)	0.02
Grade 3 or 4	8 (1.5)	6 (4.5)	2 (0.5)	0.001
Aortic mean gradient, mm Hg	10.0 ± 3.8	9.7 ± 4.1	10.2 ± 3.7	0.24
Aortic valve area, cm^2	1.82 ± 0.37	1.81 ± 0.38	1.83 ± 0.36	0.62
PASP, mm Hg	40.4 ± 13.3	45.9 ± 15.8	38.3 ± 11.6	<0.0001
PASP >60 mm Hg	35 (6.1)	18 (18.0)	17 (6.3)	0.001
1-yr follow-up				
LVEDD, mm	50.0 ± 8.1	51.7 ± 9.1	49.5 ± 7.7	0.03
LVESD, mm	32.3 ± 7.5	33.4 ± 7.1	31.9 ± 7.9	0.16
IVS, mm	11.3 ± 2.3	10.9 ± 2.1	11.4 ± 2.4	0.11
PWT, mm	10.7 ± 1.9	10.5 ± 1.8	10.8 ± 2.0	0.22
LVEF, %	61.3 ± 10.7	58.4 ± 12.1	62.1 ± 10.1	0.004
LVEF <30%	4 (1.0)	2 (1.5)	2 (2.2)	0.23
LA diameter, mm	44.5 ± 7.7	48.4 ± 7.9	43.1 ± 7.2	<0.0001
LVOT VTI, cm	24.8 ± 7.2	24.2 ± 7.2	25.0 ± 7.0	0.46
Aortic regurgitation				
Grade >2	96 (20.9)	33 (31.7)	63 (17.7)	0.004
Grade 3 or 4	4 (1.0)	3 (2.3)	1 (0.2)	0.04
Aortic mean gradient, mm Hg	10.8 ± 4.8	10.7 ± 5.5	10.8 ± 4.6	0.84
Aortic valve area, cm^2	1.77 ± 0.35	1.75 ± 0.38	1.77 ± 0.33	0.55
PASP, mm Hg	40.4 ± 13.1	47.0 ± 15.1	38.0 ± 11.4	<0.0001
PASP >60 mm Hg	24 (9.1)	13 (18.3)	11 (5.7)	0.003

Values are mean ± SD or n (%).
Abbreviations as in Table 2.

TABLE 6 Medical Therapy at Follow-Up

	Overall Population (n = 546)	Readmission for CHF (n = 132)	No Readmission for CHF (n = 414)	p Value
1 month				
Loop diuretic agents	219 (42.4)	70 (53.4)	149 (38.6)	0.002
MR antagonists	22 (4.3)	9 (6.9)	13 (3.4)	0.13
ACE inhibitors	119 (23.0)	28 (21.4)	91 (23.6)	0.63
Beta-blockers	159 (30.8)	49 (37.4)	110 (28.5)	0.06
Anticoagulant agents	115 (22.2)	31 (23.7)	84 (21.8)	0.71
1 yr				
Loop diuretic agents	144 (31.7)	53 (51.0)	91 (26.0)	<0.0001
MR antagonists	16 (3.5)	7 (6.7)	9 (2.6)	0.06
ACE inhibitors	70 (15.4)	20 (19.2)	50 (14.3)	0.22
Beta-blockers	116 (25.6)	38 (36.5)	78 (22.3)	0.005
Anticoagulant agents	78 (17.3)	30 (28.8)	48 (13.8)	0.001

Values are n (%).
Abbreviations as in Table 1.

transfusion during TAVR hospitalization could explain CHF readmission during the first year after the procedure. Finally, we found that persistent left atrial dilatation was also predictive of CHF after TAVR. Atrial dilatation is common in patients presenting with AS (23). TAVR is associated with significant recovery of left atrial structure and function, suggesting reverse cavity remodeling, and such functional recovery is determined primarily by the severity of pre-procedural valve stenosis (24). The persistence of atrial dilatation after TAVR could therefore be attributed either to over-delayed management of AS or to another associated uncorrected heart disease (mitral regurgitation, hypertension, and so on).

STUDY LIMITATIONS. Despite these interesting results, our study presents some limitations. First, as a retrospective analysis from a prospective register, our results should be considered hypothesis generating. Although we corrected for measured covariates in the multivariate model, unmeasured confounders may still persist, and a prospective study should be considered to confirm our findings.

Second, we lacked echocardiographic data regarding right ventricular dimension and function or tricuspid regurgitation presence and its severity, which could lead to a better understanding of mechanism.

Third, as this was a single-center study, our population was of moderate size, and results may be limited by lack of statistical power.

Finally, we observed that medical therapy in patients readmitted for CHF was suboptimal, as only one-half of the patients were treated with loop diuretic agents during follow-up. Further effort should be made to identify patients at risk for CHF

TABLE 7 Predictors of Readmission for Congestive Heart Failure

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Aortic valvuloplasty	1.94 (1.17-3.22)	0.01	3.03 (0.39-23.4)	0.29
CHF admission before TAVR	1.89 (1.26-2.81)	0.002	2.13 (0.42-11.1)	0.36
Loop diuretic agents before TAVR	1.51 (1.00-2.28)	0.05	4.80 (0.69-33.51)	0.07
Hemoglobin before TAVR	0.83 (0.73-0.94)	0.004	0.49 (0.19-1.23)	0.13
Atrial fibrillation	1.57 (1.03-2.41)	0.04	1.08 (0.51-2.26)	0.84
Aortic mean gradient	0.98 (0.97-0.99)	0.01	0.88 (0.79-0.99)	0.03
Transfusion post-TAVR	2.22 (1.40-3.51)	0.001	2.27 (1.13-5.56)	0.009
Creatine peak post-TAVR	1.00 (1.00-1.00)	0.04	1.02 (0.99-1.05)	0.07
NT-proBNP post-TAVR	1.00 (1.00-1.00)	0.03	1.00 (1.00-1.00)	0.15
Hemoglobin post-TAVR	0.86 (0.77-0.97)	0.01	0.77 (0.36-1.67)	0.08
MI post-TAVR	6.68 (1.21-36.9)	0.001	4.02 (0.35-43.3)	0.93
LVEDD post-TAVR	1.02 (1.00-1.04)	0.03	0.98 (0.84-1.14)	0.79
LVESD post-TAVR	1.03 (1.00-1.05)	0.02	0.94 (0.76-1.15)	0.54
LVEF <30% post-TAVR	3.77 (1.00-14.3)	0.04	1.02 (0.92-1.13)	0.74
MR grade >2 post-TAVR	1.80 (1.13-2.85)	0.01	6.71 (0.99-45.61)	0.06
AR grade >2 post-TAVR	1.75 (1.11-2.76)	0.016	1.38 (0.27-7.19)	0.29
PASP >60 mm Hg post-TAVR	3.25 (1.60-6.61)	0.001	1.04 (1.00-1.07)	<0.0001
LA diameter post-TAVR	1.10 (1.04-1.16)	<0.0001	1.47 (1.08-2.01)	0.02

AR = aortic regurgitation; CI = confidence interval; MI = myocardial infarction; MR = mitral regurgitation; other abbreviations as in Tables 1 and 2.

before TAVR and enhance post-discharge health care measures in this group of patients.

CONCLUSIONS

Given the high frequency and poor prognosis of readmission for CHF after TAVR, it is important to identify patients at risk (patients presenting with low gradient and/or pulmonary hypertension before TAVR) and avoid hemorrhagic complications requiring transfusions. Our results suggest that early management of patients at the onset of symptoms and careful selection before TAVR, including right catheterization (in combination with echocardiography and computed tomography), would identify a vulnerable group of patients with a higher risk for poorer outcomes in the coming months and/or reduce the incidence of readmission for CHF after TAVR. Future efforts should be made to identify and enhance post-discharge health care measures in this group of patients.

ACKNOWLEDGMENT The authors thank Nikki Sabourin-Gibbs for her help in editing the manuscript.

ADDRESS FOR CORRESPONDENCE: Dr. Eric Durand, Rouen University Hospital-Charles Nicolle, Department of Cardiology, 1 rue de Germont, 76031 Rouen Cedex, France. E-mail: eric.durand@chu-rouen.fr.

PERSPECTIVES

WHAT IS KNOWN? Previous studies have shown that readmission after TAVR, for whatever reason, is frequent and is associated with poorer clinical outcomes.

WHAT IS NEW? Our results, focusing on readmission for CHF after TAVR, suggest that readmission for CHF involved about one-quarter of patients and is associated with higher mortality. Patients with low gradient, left atrial dilatation, or pulmonary hypertension and those who receive transfusions during the procedure are at higher risk for CHF.

WHAT IS NEXT? Further effort should be made to identify patients at risk for CHF before TAVR and enhance post-discharge health care measures in this group of patients.

REFERENCES

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.

2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

3. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.

5. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218–25.

6. Nombela-Franco L, del Trigo M, Morrison-Polo G, et al. Incidence, causes, and predictors of early (≤30 days) and late unplanned hospital readmissions after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2015;8:1748–57.

7. Kolte D, Khera S, Sardar R, et al. Thirty-day readmissions after transcatheter aortic valve replacement in the United States insights from the nationwide readmissions database. Circ Cardiovasc Interv 2017;10:e004472.

8. Durand E, Borz B, Godin M, et al. Transfemoral aortic valve replacement with the Edwards SAPIEN and Edwards SAPIEN XT prosthesis using exclusively local anesthesia and fluoroscopic guidance: feasibility and 30-day outcomes. J Am Coll Cardiol Intv 2012;5:461–7.

9. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2012;9:15–29.

10. Kappetein AP, Head SJ, Genereux P, et al., Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

11. Kim HN, Januzzi JL. Natriuretic peptide testing in heart failure. Circulation 2011;123:2015–9.

12. Urena M, Webb JG, Eltchaninoff H, et al. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol 2015;65:437–48.

13. Vejpongsa P, Bhise V, Charitakis K, et al. Early readmissions after transcatheter and surgical aortic valve replacement. Catheter Cardiovasc Interv 2017. In press.

14. Durand E, Eltchaninoff H, Canville A, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. Am J Cardiol 2015;115:1116–22.

15. Serletis-Bizios A, Durand E, Cellier G, et al. A prospective analysis of early discharge after transfemoral transcatheter aortic valve implantation. Am J Cardiol 2016;118:866–72.

16. Baron SJ, Arnold SV, Herrmann HC, et al. Impact of ejection fraction and aortic valve gradient on outcomes of transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2349–58.

17. Herrmann S, Stork S, Niemann M, et al. Low gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J Am Coll Cardiol 2011;58:402–12.

18. Adda J, Mielot C, Giorgi R, et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 2012;5:27–35.

19. Luçon A, Oger E, Bedossa M, et al. Prognostic implications of pulmonary hypertension in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation: study from the FRANCE 2 registry. Circ Cardiovasc Interv 2014;7:240–7.

20. O'Sullivan CJ, Wenaweser P, Ceylan O, et al. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with

severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation. Insights from the new proposed pulmonary hypertension classification. Circ Cardiovasc Interv 2015;8:e002358.

21. Sinning JM, Hammerstingl C, Chin D, et al. Decrease of pulmonary hypertension impacts on prognosis after transcatheter aortic valve replacement. EuroIntervention 2014;9:1042–9.

22. Borz B, Durand E, Godin M, et al. Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis. Heart 2013;99:860–5.

23. Gotzmann M, Thiessen A, Lindstaedt M, Mugge A, Ewers A. Left atrial diameter, aortic mean gradient, and hemoglobin for risk stratification in patients undergoing transcatheter aortic valve implantation. Clin Cardiol 2013;4:228–34.

24. D'Ascenzi F, Cameli M, Henein M, et al. Left atrial remodelling in patients undergoing transcatheter aortic valve implantation: a speckle-tracking prospective, longitudinal study. Int J Cardiovasc Imaging 2013;29:1717–24.

KEY WORDS aortic stenosis, heart failure, TAVR