

Significance of the CAPRI risk score to predict heart failure hospitalization post-TAVI: The CAPRI-HF study

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ABSTRACT

Background: Predictors of heart failure (HF) hospitalization after transcatheter aortic valve implantation (TAVI) are not well defined. CAPRI is a score for predicting 1-year post-TAVI cardiovascular and all-cause mortality. The aim of the present study is to assess the prognostic significance of the CAPRI score for HF hospitalization 1 year after TAVI.

Methods and results: CAPRI-HF is an ancillary study of the C4CAPRI trial, analyzing 409 consecutive patients treated by TAVI. The primary outcome was hospitalization for HF during the first year post-intervention. The prognostic value of the CAPRI score was assessed by multivariable analysis adjusted for diabetes, atrial fibrillation, vascular route, pacemaker implantation, post-TAVI aortic regurgitation, transfusion and pulmonary artery systolic pressure. A subanalysis focused on patients with low-gradient aortic stenosis (LGAS). At 1 year, HF hospitalization occurred in 78 (19.9%) patients. Patients with HF were more prone to have diabetes, atrial fibrillation, renal dysfunction, lower mean aortic gradient, higher logistic EuroSCORE and higher CAPRI score ($p < .05$ for all associations).

In the multivariable analysis, CAPRI score was the sole predictor of HF: hazard ratio (HR) for each 0.1 CAPRI score increase was 1.065, 95% confidence interval (CI) 1.021–1.110. This was confirmed when adjusted for EuroSCORE: HR 1.066, 95% CI 1.024–1.110. The predictive power of the CAPRI score increased for LGAS: HR 1.098, 95% CI 1.028–1.172.

Conclusions: CAPRI score helps predict HF post-TAVI. Including the score in the decision-making process may help selecting candidates for TAVI and identifying patients who need close monitoring post-procedure.

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1. Introduction

The number of transcatheter aortic valve implantation (TAVI) procedures is increasing due to the recent extension of indications

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to patients at lower risk [1]. However, a substantial number of patients do not benefit from the procedure and rates of early death and repeated readmissions for heart failure (HF) remain an issue [2,3]. Outcomes can be improved by improving patient selection to avoid futile interventions and by improving treatment strategies in those patients at high residual risk of HF [4].

Predictors of HF hospitalization after TAVI are not well defined. Few studies have tackled this issue [2] and no standardized score is available to predict HF after TAVI. We have recently developed the CAPRI score to predict 1-year post-TAVI cardiovascular and all-cause mortalities [5]. This dedicated score includes thoracic aortic

calcification (TAC) volume (assessed by CT scan) in addition to cardiac, vascular, and comorbid conditions. Our demonstration that TAC is predictive of mortality after TAVI independent of classical variables [6,7] has recently been confirmed by other groups [8].

We hypothesized that CAPRI score could also predict 1-year post-TAVI HF hospitalization since it encompasses several variables potentially involved in HF. Residual HF after TAVI is an even greater concern in low-gradient aortic stenosis (LGAS) patients [2]. There is a need for predictors in this population since classical cardiac and valvular parameters have failed to predict clinical outcomes after AS relief [9]. Because the CAPRI score includes TAC, a surrogate of aortic stiffness, it may be particularly relevant for LGAS which is often associated with high vascular load [10].

The aim of the present study was to assess the prognostic significance of the CAPRI score to predict HF hospitalization during the first year after TAVI in a consecutively treated population. We also tested the prognostic significance in a subset of patients with LGAS.

2. Methods

CAPRI-HF was an ancillary study of the C4CAPRI trial (4 Cities for assessing CAlcification PRognostic Impact NCT02935491), which was a multicenter study, performed in 4 high volume French centers [5].

2.1. Patients

The present study included 409 consecutive patients from 2 out of the 4 centers (Rouen and Lyon University hospitals), undergoing TAVI between 2010 and 2014 and for whom follow-up data on HF was available. The C4CAPRI cohort has been described elsewhere [5]. Patients were indicated for TAVI in the presence of severe AS when surgical aortic valve replacement was either contraindicated or deemed too high risk by the multidisciplinary Heart Team. To be included in the C4CAPRI cohort, patients had to have a pre-operative CT-scan for TAC assessment and CAPRI score calculation. For the main analysis patients were analyzed according to whether they had undergone HF hospitalization. For the subanalysis, LGAS was defined as a mean aortic gradient <40 mm Hg [11].

2.2. Outcomes

The primary outcome was HF requiring hospitalization during the first year after TAVI. Follow-up was censored at 1 year following TAVI. Patients deceased during the first year were not considered as having experienced the primary outcome unless a hospitalization for HF had been recorded. Data collection was performed through dedicated web-based case report forms in each center, which were merged for analysis. Range checks to identify extreme values and assessments of internal consistency were applied during upload.

2.3. Calculation of CAPRI score

The score has been described elsewhere [5]. Briefly, CAPRI score encompasses TAC burden assessed by CT scanner of the whole thoracic aorta as previously described [5]; cardiac (left ventricle ejection fraction (LVEF); mean aortic gradient, mitral regurgitation, pulmonary systolic artery pressure (PSAP), coronary artery disease), vascular (vascular disease), and comorbid (renal function, and chronic obstructive pulmonary disease) conditions. We adapted the score for cardiovascular mortality and for all-cause mortality by adjusting the coefficient of each variable for the specific outcome.

2.4. Statistical analysis

Variables are summarized as means \pm standard deviations, medians with interquartile ranges, or numbers and percentages, as appropriate. CAPRI score was considered as a categorical variable (tertiles) or a continuous variable as appropriate. For the purpose of this study (predicting HF hospitalization during the first year after TAVI), we used the cardiovascular mortality CAPRI score in the main analysis. The performance of the all-cause mortality CAPRI score was used in a sensitivity analysis (presented in the Supplementary materials).

The prognostic value of the CAPRI score was first assessed by building the cumulative incidence curves of HF hospitalization for the three groups defined according to the tertiles of CAPRI score, using the Aalen-Johansen estimator in order to take into account the competing risk corresponding to death. The three curves were compared using the Gray's test. The prognostic value of CAPRI score considered as a continuous variable was further quantified and tested in univariable and multivariable Cox regression analysis in order to estimate its cause-specific effect.

Several models were built according to the existent literature [2,3,12].

- Model 1 adjusted for Logistic EuroSCORE.
- Model 2 adjusted for significant differences in terms of baseline characteristics. (excluding variables included in the CAPRI score) between the groups of patients with and without HF hospitalization.
- Model 3 adjusted for vascular access, post TAVI aortic regurgitation, post TAVI PASP, post TAVI transfusion, and post TAVI pacemaker implantation.
- Model 4 adjusted for the variables in models 2 and 3.

The interaction between mean aortic gradient and CAPRI score was tested and found significant at $p < .05$. This justified the subanalysis in LGAS patients.

Further sensitivity analysis was performed after exclusion of patients who didn't have a transfemoral TAVI.

Finally, in order to assess the ability of the CAPRI score to predict recurring HF hospitalization ordinal multivariate regression analyses were performed at 3 levels; no HF (reference subgroup), 1 HF occurrence, ≥ 2 HF occurrences. A similar analysis was performed for the CAPRI score for all-cause death.

All analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA and R software, version 3.6.1). A p value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline data

Among the 409 patients, 14 peri-procedural deaths and 3 patients lost to follow-up were excluded. Thus, 392 patients were included in the study. 78 (19.9%) patients experienced at least one HF hospitalization. 60 (15.3%) patients died during the follow-up, respectively 28 (35.9%) patients of the 78 who experienced HF hospitalization and 32 (10.2%) patients of the 314 who didn't experience HF hospitalization, $p < .001$. Table 1 summarizes the characteristics of the cohort as well as according to the hospitalization of HF. On average, patients were 83.7 ± 7.3 years old, 183 (46.7%) were men, mean LVEF was $59.1 \pm 14.3\%$ and mean aortic gradient was 45.9 ± 15.6 mm Hg. TAVI was performed with femoral access in 339 (86.5%) patients. Patients with HF hospitalization were more prone to have diabetes, atrial fibrillation, renal dysfunction, lower mean aortic gradient, higher PSAP and higher logistic EuroSCORE ($p < .05$ for all associations). Though levels of TAC and several individual variables in the CAPRI score (LVEF, coronary artery disease, vascular disease, and chronic obstructive pulmonary disease) did not differ significantly between patients with HF and without HF, the CAPRI score was significantly higher in patients who experienced HF ($p < .05$).

Table S1 summarizes patients' characteristics according to mean aortic gradient. LGAS patients were more often women and had higher rates of diabetes atrial fibrillation, peripheral vascular disease or pacemaker use. The CAPRI score was higher in LGAS patients, $p < .001$; the same trend was noticed for the EUROSCORE, $p = .048$.

3.2. Prognostic power of the CAPRI score

At the 1-year follow-up, 78 (19.9%) patients recorded one or more HF hospitalizations. Fig. 1 displays the cumulative incidence curves according to the three groups defined according to the tertiles of CAPRI score for all patients and according to aortic gradient. CAPRI score ranges were -2.288 to -0.188 for group 1; -0.188 to 0.344 for group 2 and 0.344 to 1.685 for group 3. Higher CAPRI scores were associated with greater risk of HF hospitalization, $p < .001$ (Fig. 1). Analyzing subgroups according to mean aortic gradient, the same trend was found in LGAS patients, $p = .007$. In patients with mean aortic gradient ≥ 40 mm Hg, cumulative incidence curves did not differ significantly between the three groups ($p = .1$).

Table 2 summarizes univariate and multivariate Cox analyses in all patients and in LGAS patients. CAPRI score was predictive of HF hospitalization in all models. In the model adjusted for logistic

Table 1
Patient's baseline characteristics (CAPRI HF cohort).

	All	No hospitalization for HF	Hospitalization for HF	p
Number of patients	392	314	78	
Demographic characteristics				
Age (years) ^a	83.7 ± 7.3	83.7 ± 7.6	83.9 ± 6.3	0.79
Male sex n (%)	183 (46.7)	153 (48.7)	30 (38.5)	0.104
BMI (kg/m ²) ^a	26.4 ± 5.6	26.4 ± 5.6	26.5 ± 5.4	0.94
Clinical history				
Diabetes n (%)	110 (28.1)	80 (25.5)	30 (38.5)	0.022
Hypertension n (%)	296 (75.7)	237 (75.7)	59 (75.6)	0.989
Smoker n (%)	74 (18.9)	62 (19.8)	12 (15.4)	0.372
Dyslipidemia n (%)	221 (56.5)	180 (57.5)	41 (52.6)	0.431
Atrial fibrillation n (%)	157 (40.2)	115 (36.7)	42 (53.8)	0.006
CAD n (%)	143 (36.6)	120 (38.3)	23 (29.5)	0.146
PVD n (%)	59 (15.1)	43 (13.7)	16 (20.5)	0.132
Previous stroke or TIA n (%)	37 (9)	26 (8.3)	8 (10.3)	0.579
Pace maker n (%)	50 (12.8)	40 (12.7)	10 (12.8)	0.985
COPD n (%)	88 (22.4)	71 (22.6)	17 (21.8)	0.877
NYHA 3/4 n (%)	260 (66.5)	204 (65.2)	56 (71.8)	0.268
Pre-TAVI TTE parameters				
Mean LVEF % ^a	59.1 ± 14.3	59.8 ± 14.2	56.5 ± 14.6	0.069
Mean aortic gradient (mm Hg) ^a	45.9 ± 15.6	47.1 ± 15.4	40.9 ± 15.6	0.002
LGAS n (%)	132 (33.7)	94 (29.9)	38 (48.7)	0.002
Aortic valve area (cm ²) ^a	0.71 ± 0.22	0.71 ± 0.23	0.70 ± 0.19	0.806
Moderate/severe MR n (%)	8 (2)	4 (1.3)	4 (5.1)	0.032
PASP (mm Hg) ^a	42.7 ± 15	41.5 ± 14	47.7 ± 15	0.002
Aortic calcifications				
LogTAC (cm ³) ^a	0.327 ± 0.48	0.317 ± 0.48	0.365 ± 0.50	0.441
Renal function				
GFR (mL/min/1.73 m ²) ^a	51.1 ± 26	52.5 ± 27.2	45.3 ± 19.9	0.028
Risk scores				
Euroscore ^a	17.27 ± 9.7	16.76 ± 9.4	19.26 ± 10.4	0.041
CAPRI cardiovascular ^a	0.0593 ± 0.631	0.0042 ± 0.635	0.2811 ± 0.567	<0.001
CAPRI all causes ^a	0.024 ± 0.638	−0.0306 ± 0.649	0.2444 ± 0.5449	0.001
Procedural and peri-procedural data				
Femoral access n (%)	339 (86.5)	277 (88.2)	62 (79.5)	0.044
Balloon expendable valve n (%)	382 (97.4)	305 (97.1)	77 (98.7)	0.67
Blood transfusion n (%)	68 (17.3)	49 (15.6)	19 (24.4)	0.068
Aortic regurgitation >2 n (%)	11 (2.9)	9 (3)	2 (2.6)	0.882
PASP				0.283
≤60 n (%)	254 (64.8)	205 (65.3)	49 (62.8)	
Nonmes n (%)	117 (29.8)	95 (30.3)	22 (28.2)	
>60 n (%)	21 (5.4)	14 (4.5)	7 (9)	
New pacemaker implantation	52 (13.5)	41 (13.1)	11 (15.1)	0.657

HF, heart failure; BMI, body mass index; GFR, glomerular filtration rate; CAD, coronary artery disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; TTE, transthoracic echography; LVEF, left ventricular ejection fraction; LGAS, low gradient aortic stenosis; MR, mitral regurgitation; TAC, thoracic aortic calcifications, nonmes, non-measurable; PASP pulmonary artery systolic pressure.

^a Mean ± sd.

EuroSCORE, the CAPRI score considered as a continuous variable was the sole predictor of HF hospitalization. The hazard ratio (HR) for each 0.1 CAPRI score increase was 1.066, 95% confidence interval (CI) 1.024–1.062. In the adjusted multivariate Cox analysis only CAPRI score was predictive of HF: HR for each 0.1 CAPRI score increase 1.068, 95% CI 1.021–1.065. The results were similar in LGAS patients (Table 2).

When restricting the analysis to patients with transfemoral TAVI, results remained very similar (Table S2).

Similar results were obtained with the CAPRI score for all-cause death when performing the cox regression analysis (Supplementary data, Table S3).

4. Discussion

The present study demonstrates that the CAPRI score designed to predict one-year mortality after TAVI also predicts HF hospitalization. CAPRI score has been shown to be valuable for risk stratification before TAVI [5], and the present analysis indicates its utility in the follow-up of patients at risk of HF.

Despite procedural success, the risk of developing HF remains high after TAVI: HF hospitalization was experienced by 19.9% of

patients in the present study and by up to 40% in other studies [2,3]. HF reduces patients' wellbeing and prognosis, especially in older people like those typically treated with TAVI [2,3,13]. It is further associated with depression [14], lower quality of life [15], and increased mortality [2]. In the present study we again stress the association of HF and mortality. Improved identification of patients at high risk of HF would help focus management efforts on those patients post-TAVI who need the greatest vigilance, as well as reduce the risk of futile procedures.

Many factors are involved in HF [16] and some predictors have been identified in other studies, notably new pacemaker implantation [12] mitral regurgitation, low LVEF, atrial fibrillation, blood transfusion or renal insufficiency [2,3]. Some of these variables are part of the CAPRI score which includes cardiac, vascular and comorbid conditions, e.g., renal insufficiency, which is more prevalent in patients with HF and is an independent prognostic factor in diastolic and systolic dysfunction [17]. The CAPRI score is unique in that it includes TAC, a surrogate of aortic stiffness and consequently high afterload, and impaired myocardial perfusion. This suggests a pathophysiological role for TAC in HF, especially HF with preserved LVEF [18,19]. In the present cohort no significant difference of TAC was observed between HF and non-HF patients conversely to what

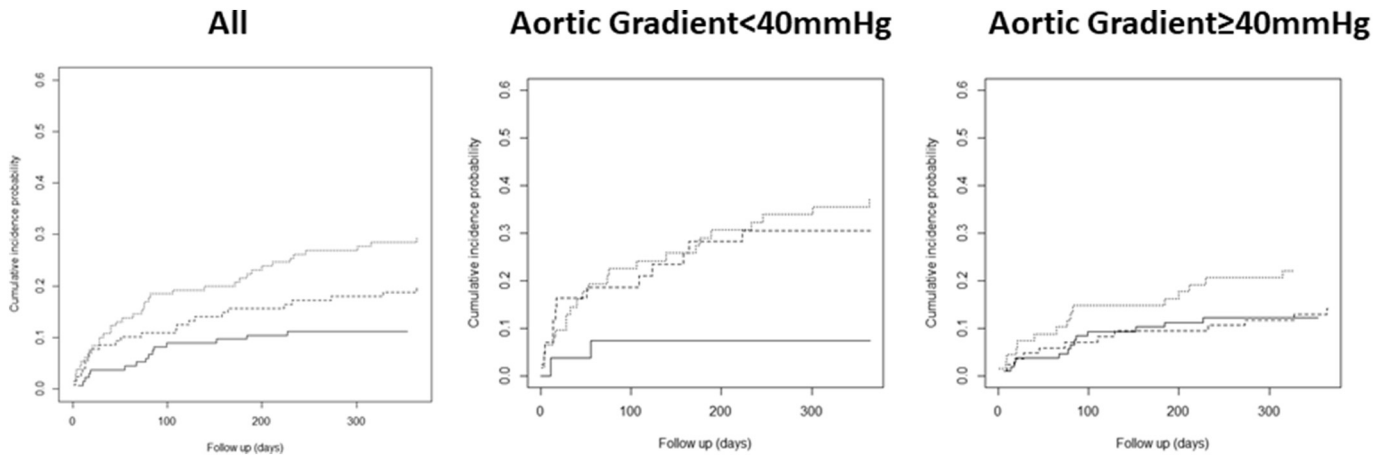


Fig. 1. Cumulative incidence curves according to the three groups defined according to groups defined on tertiles of CAPRI score for all patients and in subgroups according to mean aortic gradient.

has been previously observed with a longer follow-up of 1000 days. Yet, a greater proportion or heavily calcified patients (third tertile) are represented in the HF than in the non-HF subgroups (data not shown) [7]. Aortic stiffness has also been linked to HF [18] in other settings. Post-TAVI, high vascular load will continue to exert a detrimental effect on LV function [6,7,20] contributing to HF.

Other post TAVI parameters may promote HF such as PASP >60 mm Hg, aortic regurgitation, vascular access, or pacemaker implantation [2,3,12]. Yet taking these variables into account in the multivariate model did not reduce the prognostic value of the CAPRI score. In contrast, the EUROSCORE, which was developed for patients undergoing cardiac surgery and not calibrated on TAVI patients [21], did not predict HF, further confirming the value of the CAPRI score.

Predicting outcomes may be particularly important in LGAS patients since they are known to be at higher risk of morbidity and mortality than non-LGAS patients [7–9] and are more prone to suffer from HF after TAVI [2,3]. LGAS is a complex condition, in which the valvular impediment may be intertwined with other pathophysiological determinants such as systolic and diastolic dysfunction [22] and high vascular load [10]. This makes the prediction of outcomes based on classical parameters, mainly valvular criteria, extremely challenging [9]. Possibly because of the multifactorial pathophysiology, CAPRI score seems to be particularly adapted to predict HF after TAVI in LGAS patients.

4.1. Clinical implications

Calculation of CAPRI score may be a useful addition to the initial work-up for a more personalized evaluation of candidates for a TAVI procedure [23,24]. For some patients, TAVI can be a futile intervention even after procedural success. In patients with a high CAPRI score in whom TAVI is still considered necessary, close monitoring and intensification of medical treatment after the procedure may be indicated. This may be even truer in LGAS patients.

A high CAPRI score may be defined as higher than 0.7 as it corresponds to the mortality cut-off proposed in the pivotal trial [5] and as it also selects patients belonging to the tertile associated with the highest risk of HF.

5. Study limitations

HF hospitalization wasn't assessed in 2 of the 4 centers involved in the CAPRI study, however the number of patients included in the CAPRI HF study and the number of events allowed a robust analysis. The diagnosis of HF may be challenging [25]. However retaining only HF requiring hospitalization has certainly strengthened the robustness of the outcome. It has allowed us to check that the clinical judgment and the paraclinical tests were consistent with this diagnosis. Natriuretic peptides would have been interesting in this respect but unfortunately they were not available in this

Table 2

Relative risk of HF hospitalization in unadjusted and adjusted Cox regression models.

	Hospitalization for HF All N = 392		Hospitalization for HF LGAS N = 132	
	HR [95% CI]	p	HR [95% CI]	p
CAPRI score + 0.1 unit ^a	1.072 [1.032–1.112]	<0.001	1.084 [1.022–1.149]	0.007
CAPRI score + 0.1 unit ^b	1.066 [1.024–1.110]	0.002	1.080 [1.012–1.151]	0.020
CAPRI score + 0.1 unit ^c	1.060 [1.019–1.101]	0.003	1.085 [1.021–1.152]	0.008
CAPRI score + 0.1 unit ^d	1.072 [1.030–1.115]	0.001	1.097 [1.028–1.170]	0.005
CAPRI score + 0.1 unit ^e	1.065 [1.021–1.110]	0.003	1.098 [1.028–1.172]	0.005

HF, heart failure; HR, hazard ratio; CI, confidence interval; LGAS, low gradient aortic stenosis.

^a Unadjusted.

^b Model 1 adjusted for Euroscore.

^c Model 2 adjusted for pre-TAVI parameters: diabetes, atrial fibrillation.

^d Model 3 adjusted for post-TAVI parameters: vascular access (femoral Y/N), blood transfusion or severe vascular access leakage, aortic regurgitation >2, pulmonary systolic blood pressure (high, low, undefined), new pacemaker implantation.

^e Model 4 adjusted for both pre and post TAVI parameters: diabetes, atrial fibrillation, vascular access (femoral Yes, No), blood transfusion, aortic regurgitation >2, pulmonary artery systolic pressure (high, low, undefined), new pacemaker implantation.

cohort. Yet, in the particular setting of TAVI patients, the diagnostic value of NT-proBNP remains uncertain because of the numerous confounders that may alter its significance (left ventricular hypertrophy, atrial fibrillation, renal failure...) and because of the lack of unequivocal threshold [25]. A more precise classification of HF would have been valuable but this was not assessed. It would have been interesting to assess the stroke volume index in order to better categorize LGAS patients.

6. Conclusions

The CAPRI score is predictive of HF hospitalization after TAVI, including LGAS patients. Calculation of CAPRI scores may be valuable as part of the initial work-up for a more personalized evaluation of TAVI candidates. The score allows a better identification of poor responders to a TAVI procedure as well as of patients at high residual HF risk post-procedure.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.08.033>.

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