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Tumor Marker Carbohydrate Antigen 125 Predicts Adverse Outcome After Transcatheter Aortic Valve Implantation

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Objectives This study sought to predict the value of tumor marker carbohydrate antigen 125 (CA125) before and after transcatheter aortic valve implantation (TAVI) for all-cause death and a composite endpoint of death, admission for heart failure, myocardial infarction, and stroke (major adverse cardiac events [MACE]).

Background Risk stratification after TAVI remains challenging. The use of biomarkers in this setting represents an unmet need.

Methods CA125 was measured in 228 patients before and after TAVI. The association with outcomes was assessed using parametric Cox regression and joint modeling for baseline and longitudinal analyses, respectively. CA125 was evaluated as logarithm transformation and dichotomized by its median value (M1 $\leq$15.7 U/ml vs. M2 $>$15.7 U/ml).

Results At a median follow-up of 183 days (interquartile range: 63 to 365) and 144 days (interquartile range: 56 to 365), 50 patients (22%) died and 75 patients (33%) experienced MACE. A 3-fold increase in the rates for death and MACE was observed in patients above the median (M2 vs. M1) of CA125 (5.2 vs. 1.6 per 10 person-years and 8.3 vs. 3.3 per 10 person-years, respectively; p for both $<$0.001). In a multivariable analysis adjusted for logistic EuroSCORE, New York Heart Association functional class III/IV, and device success, baseline values of CA125 (M2 vs. M1) independently predicted death (hazard ratio [HR]: 2.18; 95% confidence interval [CI]: 1.11 to 4.26; p = 0.023) and MACE (HR: 1.77; 95% CI: 1.05 to 2.98; p = 0.031). In the longitudinal analysis, lnCA125 as a time-varying exposure, was highly associated with both endpoints: HR: 1.47; 95% CI: 1.01 to 2.14; p = 0.043 and HR: 2.26; 95% CI: 1.28 to 3.98; p = 0.005, for death and MACE, respectively.

Conclusions Serum levels of CA125 before and after TAVI independently predict death and MACE. (J Am Coll Cardiol Intv 2013;6:487–96) © 2013 by the American College of Cardiology Foundation

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Transcatheter aortic valve implantation (TAVI) is increasingly used as a therapeutic option for patients with symptomatic aortic stenosis and elevated surgical risk. It has been shown to be superior to medical therapy in patients with prohibitive elevated risk (1) while being comparable to conventional surgical aortic valve replacement in high-risk patients (2).

Due to a high comorbid burden present in this population, the prediction of outcome after TAVI is very challenging. In this population, identifying the intrinsic role of the procedure on outcomes must be dissected from the effect of the associated comorbidities, progression of comorbid conditions and elevated age. Potentially, biomarkers may play an important role in this setting. The first studies on the prognostic usefulness of biomarkers in TAVI have relied on natriuretic peptides. However, these studies were conducted in a small series of patients and yielded conflicting results (3–5).

Tumor marker carbohydrate antigen 125 (CA125) is an emerging cardiac biomarker. In heart failure (HF), CA125 has shown to be elevated and is released by mesothelial cells as a response to serosal effusions and inflammation (6,7). It has been shown that CA125 is strongly related to HF severity and adverse outcomes in HF (8–10). Recently, in the setting of aortic stenosis, elevated levels of CA125 have also shown to be associated with disease severity and adverse outcomes (11). To date, however, there are no data on the prognostic value of CA125 after TAVI.

We hypothesized that CA125, as a baseline measurement, might be a useful prognostic biomarker in patients undergoing TAVI. Additionally, and more importantly, we hypothesized that changes in CA125 after TAVI might be strongly indicative of adverse outcomes following TAVI. As such, the aim of this study was 2-fold: 1) to evaluate the prognostic significance of pre-procedural values of CA125; and 2) to determine whether repeated measurements of CA125 after TAVI remain indicative of elevated risk.

Abbreviations and Acronyms

CI = confidence interval
HF = heart failure
HR = hazard ratio
JM = Joint Modeling
MACE = major adverse cardiac events
NT-proBNP = N-terminal pro–B-type natriuretic peptide
NYHA = New York Heart Association
TAVI = transcatheter aortic valve implantation

Methods

Patients and indications. We included 228 consecutive patients undergoing TAVI in our institution. TAVI was performed due to degenerative calcified native aortic stenosis in 211 cases (93%), degenerated bioprostheses in 13 cases (6%), and severe aortic regurgitation in 4 cases (2%). An interdisciplinary heart team discussed all cases, and consensus was reached regarding the best therapeutic strategy in each individual case. The local ethics committee approved the study protocol, and all patients provided written informed consent to participate in a clinical registry.

Description of the TAVI procedures. TAVI was performed either via the transfemoral approach (n = 137) using a balloon expandable (SAPIEN XT, Edwards Lifesciences, Irvine, California, n = 79) or a self-expandable prosthesis (CoreValve, Medtronic, Irvine, California, n = 58) or by the transapical approach (n = 89) using a balloon expandable prosthesis (SAPIEN XT, Edwards Lifesciences). In 2 cases, a different access route was used (subclavian and direct aortic). Access route was dichotomized as "transfemoral" versus "non-transfemoral." TAVI procedures were performed in the catheterization laboratory or the hybrid operating suite under general anesthesia. TAVI operators were unaware of CA125 values.

Laboratory analyses and CA125 measurement. CA125 was determined from routine blood samples using a chemiluminometric immunoassay (ADVIA Centaur, Siemens Healthcare, Erlangen, Germany) at least 24 h before TAVI and on follow-up visits. Blood samples were measured and analyzed immediately. The manufacturer's cutoff value for a pathological test result is >30 U/ml.

Follow-up and definition of outcomes. All data were prospectively collected. Two cardiologists and 3 trained nurses, unaware of CA125 values, were in charge of patients' follow-up. Scheduled visits took place on a 3-month basis during outpatients' clinic visits, telephone interviews with the patient or his/her family, or by reviewing the patient's hospital record. Patients were scheduled at the outpatient clinic (at least 1 to 3 and 6 to 12 months after TAVI) for clinical and echocardiographic examinations as well as blood sampling.

The endpoints of this study were all-cause death and major adverse cardiac events (MACE) defined as a composite of all-cause death, acute HF requiring admission, myocardial infarction, and stroke, whichever occurred first during follow-up. Procedure-related death, but not other procedural complications, were included into MACE. To adjudicate an event, consensus between the 2 cardiologists was required.

Thirty-day mortality was defined as death from any cause during the first 30 days after the procedure or as intrahospital death after the TAVI procedure. Procedural success was defined using the following criteria: successful vascular access, delivery, and deployment of the device with successful retrieval of the delivery system, correct position of the device in the proper anatomical location with adequate performance, and the patient leaving the operating theater alive. Device success and procedural complications were categorized using criteria defined by the Valve Academic Research Consortium (12). In short, device success was defined as procedural success with a correct position and function of the prosthesis (less than grade 2 residual aortic regurgitation) and only 1 valve implanted per patient (12).

Statistical analysis. Continuous variables were expressed as a mean ± SD or as the median (interquartile range) and using the unpaired Student *t* test or Mann-Whitney *U* test as appropriate. Discrete variables were compared with the chi-square test or Fisher exact test as appropriate. Outcome rates were depicted among the populations according to the median and manufacturer's cutoff value (30 U/ml) of CA125 using the Kaplan-Meier method and compared with the log-rank test.

BASELINE ANALYSIS. A multivariable time-to-event analysis was performed using a flexible parametric survival analysis (13). For this analysis, our primary exposure was CA125 continuous (transformed by its logarithm, lnCA125); however, we also tested for the prognostic effect of CA125, either dichotomized according to the median (M2 vs. M1) or according to the manufacturer's cutoff value (30 U/ml). Baseline covariates were chosen based on scientific knowledge, regardless of their p value in the univariate analysis. The final baseline model included logistic EuroSCORE, New York Heart Association (NYHA) functional class III/IV, and device success as covariates. The model's discrimination and calibration was assessed by the Harrell's C statistic and the Hosmer–Lemeshow test, respectively.

LONGITUDINAL ANALYSIS. In order to test whether longitudinal measures of CA125 better discriminate those patients with a higher likelihood of adverse outcomes, CA125 levels (and other relevant prognostic factors) were collected before TAVI (baseline) and every 3 months afterward until last time point of event-free follow-up or the date of death (or MACE). Apart from CA125, those prognostic factors that were missing during follow-up, and thus could not be used as time-varying variables, were included in the models using the respective baseline values. To account for the fact that our study includes a repeated-measures design with a survival endpoint, we used a Joint Modeling (JM) approach. This is a family of methods that has been developed to explicitly account for the dependence between the longitudinal change of a continuous exposure and event time data (14). The benefits of the joint modeling approach compared with the traditional Cox regression models is the fact that it accounts for the measurement error (i.e., biological variation) and the informative dropout in CA125, and that it can give more efficient results (i.e., smaller standard errors) by combining information from the longitudinal and survival outcomes (15). Joint models of this type combine a linear mixed effect that describes the longitudinal trajectory of a continuous exposure, with a proportional hazards model for the time-to-event. In the former model, covariates and random terms (random intercepts and random slopes) are selected using a likelihood-ratio test. In the latter model, the fitted exposure trajectory is related to the hazard for event through a parametric Cox analysis.

In order to determine how longitudinally updated values of CA125 relate with the hazard for death or MACE, we modeled its natural logarithm within a linear mixed regression framework that include random intercept and slopes (heretofore called the longitudinal submodel). N-terminal pro–B-type natriuretic peptide (NT-proBNP) (transformed by its natural logarithm) was added as a time-varying covariate. Time (in weeks) was included as a random effect and modeled with a polynomial of power −1. Sex, logistic EuroSCORE of 20%, and left ventricular ejection fraction (%) were included as time-constant covariates (with their respective baseline values).

In the survival approach (heretofore called the survival submodel), the predicted time-history of lnCA125 from the linear mixed model was related to the hazard for death or MACE through a time-varying parametric Cox. Here, the hazard function was modeled with restricted cubic splines. The final model included lnNT-proBNP as a time-varying covariate, whereas the logistic EuroSCORE, device success and NYHA functional class III/IV were included as time-constant covariates.

The survival estimates are presented as hazard ratios (HR) with the 95% confidence intervals (CI).

A 2-sided p value of <0.05 was considered statistically significant for all analyses. Baseline analyses were carried-out using Stata (StataCorp, Stata Statistical Software Release 12, College Station, Texas). The longitudinal analyses were performed with the statistical module JM (16) in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline clinical, echocardiographic, and laboratory characteristics of the entire study population are displayed in Table 1. TAVI was successfully performed in 221 patients (97%) with device success achieved in 196 cases (86%). Procedural mortality was 2% (5 of 228), and the overall 30-day mortality was 7% (15 of 228). The procedural data and complications are depicted in Table 2.

During a median follow-up of 183 days [interquartile range: 63 to 365], in total, 50 patients (22%) died. MACE occurred in 75 patients (33%: death [n = 42], admissions for acute heart failure [n = 28], stroke [n = 4], and myocardial infarction [n = 1]) during a median follow-up of 144 [56 to 365] days. The clinical, laboratory, and echocardiographic characteristics at baseline according to all-cause death and MACE are presented in Table 1.

Baseline CA125 and adverse outcome after TAVI. The clinical, laboratory, echocardiographic and procedural characteristics of the patients at baseline were stratified according to the median of CA125, and are presented in Tables 3 and 4. Median pre-procedural CA125 was higher in patients who died (28 U/ml [15 to 51] vs. 12 U/ml [8 to 29]; p = 0.001) and who experienced MACE (23 U/ml [9 to 28] vs. 14 U/ml [9 to 28]; p = 0.003).

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Table 1. Baseline Clinical and Echocardiographic Characteristics for the Entire Population and According to All-Cause Death and MACE

Variables	All Patients (N = 228)	All-Cause Death		p Value	MACE		p Value
		No (n = 178)	Yes (n = 50)		No (n = 153)	Yes (n = 75)	
Clinical characteristics							
Age, yrs	79 ± 6	79 ± 6	80 ± 6	0.087	79 ± 6	79 ± 6	0.793
Male	124 (54)	99 (56)	25 (50)	0.481	87 (57)	37 (49)	0.284
Logistic EuroSCORE	16 [9–23]	14 [9–21]	19 [11–26]	0.016	14 [8–21]	18 [11–26]	0.159
Access TF vs. non-TF	137/91	110/68	27/23	0.320	96/57	41/34	0.242
Body mass index, kg/m^2	27 ± 4	27 ± 4	26 ± 4	0.179	27 ± 4	27 ± 4	0.777
Diabetes	81 (36)	63 (35)	18 (36)	0.937	50 (33)	31 (41)	0.200
Hypertension	145 (64)	117 (66)	28 (56)	0.206	99 (65)	46 (61)	0.619
Hypercholesterolemia	57 (25)	43 (24)	14 (28)	0.579	37 (24)	20 (27)	0.684
Atrial fibrillation	79 (35)	55 (31)	24 (48)	0.025	47 (31)	32 (43)	0.075
Previous SAVR	13 (6)	9 (5)	4 (8)	0.428	8 (5)	5 (7)	0.660
Previous CABG	32 (14)	24 (14)	8 (16)	0.651	17 (11)	15 (20)	0.069
Previous CAD	87 (38)	66 (37)	21 (42)	0.527	55 (36)	32 (43)	0.326
Previous PCI	51 (22)	43 (24)	8 (16)	0.221	35 (23)	16 (21)	0.793
Previous malignoma	29 (13)	24 (14)	5 (10)	0.514	20 (13)	9 (12)	0.819
Previous MI	16 (7)	12 (7)	4 (8)	0.758	9 (6)	7 (9)	0.338
Previous stroke*	25 (11)	22 (12)	3 (6)	0.203	16 (11)	9 (12)	0.726
Renal failure†	66 (29)	43 (24)	23 (46)	0.003	36 (24)	30 (40)	0.010
COPD‡	36 (16)	22 (12)	14 (28)	0.007	20 (13)	16 (21)	0.108
Peripheral arteriopathy	41 (18)	31 (17)	10 (20)	0.674	29 (19)	12 (16)	0.585
Pacemaker	26 (11)	17 (10)	9 (18)	0.097	14 (9)	12 (16)	0.126
Previous dialysis	11 (5)	7 (4)	4 (8)	0.236	5 (3)	6 (8)	0.117
NYHA functional class III/IV	190 (83)	141 (79)	49 (98)	0.002	118 (77)	72 (96)	<0.001
Laboratory							
Hemoglobin, g/dl	12.2 ± 1.8	12.3 ± 1.8	11.9 ± 1.6	0.173	12.2 ± 1.8	12.2 ± 1.8	0.973
Creatinine, mg/dl	1.44 ± 0.9	1.35 ± 1.04	1.74 ± 1.36	0.033	1.28 ± 0.9	1.76 ± 0.2	0.008
CA125, U/ml	17 [9–40]	12 [8–29]	28 [15–51]	0.001	14 [9–28]	23 [13–52]	0.003
NT-proBNP, pg/ml	2,103 [748–5,381]	1,727 [616–4,384]	4,325 [1,450–8,806]	0.007	1,699 [566–4,148]	3,601 [1,352–8,681]	0.011
Echocardiography							
LVEF ≥50%	179 (79)	145 (82)	34 (68)	0.018	128 (84)	51 (68)	0.026
LVEF 40%–49%	35 (15)	21 (12)	14 (28)		18 (12)	17 (23)	
LVEF ≤40%	14 (6)	12 (7)	2 (4)		7 (5)	7 (9)	
Mean gradient, mm Hg	48 ± 17	49 ± 18	45 ± 12	0.098	50 ± 18	43 ± 14	0.003
Maximal gradient, mm Hg	80 ± 28	81 ± 30	76 ± 19	0.202	83 ± 29	73 ± 24	0.014
PAH§	24 (11)	13 (7)	11 (22)	0.006	13 (9)	11 (15)	0.151
Aortic valve area, cm^2	0.7 [0.6–0.8]	0.7 [0.6–0.8]	0.7 [0.6–0.9]	0.979	0.7 [0.6–0.8]	0.7 [0.6–0.9]	0.712

Values are mean ± SD, n (%), or median [interquartile range]. *Severely affecting ambulation or day-to-day functioning. †Serum creatinine >200 μmol/l. ‡On long-term use of bronchodilators or steroids. §Pulmonary artery pressure ≥60 mm Hg.

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TF = transfemoral.

An approximate 3-fold increase in the rate of death and MACE was observed in patients with elevated baseline CA125 (M2 = 5.2 vs. M1 = 1.6 per 10 persons-year and M2 = 8.3 vs. M1 = 3.3, respectively; p for both <0.001) and for CA125 >30 U/ml versus CA125 ≤30: 6.1 versus 2.3 per 10 persons-year and 9.5 versus 4.2 per 10 persons-year, respectively; p for both <0.001). These differences were consistent along the entire follow-up. Using the Kaplan-Meier method, the cumulative event rates for all-cause death and MACE are displayed in Figures 1 and 2 and in Online Figures 1 and 2.

In the multivariate analysis, after adjusting for the logistic EuroSCORE, NYHA functional class III/IV and device success, baseline CA125 (M2 vs. M1) remained independently associated with an increased risk of all-cause death (HR: 2.18; 95% CI: 1.11 to 4.26; p = 0.023) and MACE

Table 2. Intra- and Post-Procedural Data and Complications of the Entire Patient Population and According to All-Cause Death and MACE

Variables	All Patients (N = 228)	All-Cause Death			MACE		
		No (n = 178)	Yes (n = 50)	p Value	No (n = 153)	Yes (n = 75)	p Value
Procedural success	221 (97)	175 (98)	46 (92)	0.022	150 (98)	71 (95)	0.165
Device success	196 (86)	159 (89)	37 (74)	0.006	138 (90)	58 (77)	0.009
Myocardial infarction	3 (1)	1 (1)	2 (4)	0.059	1 (1)	2 (3)	0.210
Emergency sternotomy	6 (3)	4 (2)	2 (4)	0.494	4 (3)	2 (3)	0.982
Procedural time, min	64 [51–84]	62 [50–82]	70 [53–90]	0.250	60 [50–80]	70 [53–86]	0.051
Contrast, ml	88 [58–140]	87 [54–134]	101 [63–158]	0.414	80 [52–134]	100 [67–150]	0.062
Fluoroscopy, min	13 [9–17]	13 [9–17]	13 [10–21]	0.713	13 [9–17]	13 [9–21]	0.846
Major vascular complications	12 (5)	7 (4)	5 (10)	0.142	7 (5)	5 (7)	0.506
Life-threatening bleeding	20 (9)	14 (8)	6 (12)	0.361	14 (9)	6 (8)	0.773
Major bleeding	41 (18)	29 (16)	12 (24)	0.210	24 (16)	17 (23)	0.197
Major stroke	4 (2)	1 (1)	3 (6)	0.010	0 (0)	4 (5)	0.004
Minor stroke	1 (0.4)	0 (0)	1 (2)	0.059	0 (0)	1 (1)	0.329
Post-procedural AR (>1)	11 (5)	5 (3)	6 (12)	0.006	4 (3)	7 (10)	0.042
Rethoracotomy	8 (4)	3 (2)	5 (10)	0.005	3 (2)	5 (7)	0.070
Need for vaECMO	21 (9)	16 (9)	5 (10)	0.827	13 (9)	8 (11)	0.594
Prophylactic vaECMO	12 (5)	12 (7)	0 (0)	0.059	10 (7)	2 (3)	0.219
Emergency vaECMO	9 (4)	4 (2)	5 (10)	0.013	3 (2)	6 (8)	0.028
Need for acute dialysis	22 (10)	6 (3)	16 (32)	<0.001	3 (2)	19 (25)	<0.001
Need for pacemaker	32 (16)	23 (14)	9 (23)	0.210	22 (16)	10 (16)	0.973
Days on ICU	1 [1–2]	1 [1–1]	3 [1–5]	<0.001	1 [1–1]	1 [1–4]	<0.001
Days in hospital	9 [7–14]	9 [7–13]	13 [7–22]	0.037	9 [7–12]	11 [7–18]	0.098

Values are n (%) or median [interquartile range].

AR = aortic regurgitation; ICU = intensive care unit; MACE=major adverse cardiac events; vaECMO = vena-arterial extracorporeal membrane oxygenation.

(HR: 1.77; 95% CI: 1.05 to 2.98; p = 0.031). Risk estimates were borderline significant for CA125 >30 U/ml, and nonsignificant for lnCA125 (Table 5). The Harrell's C statistics of the multivariate models with and without CA125 (>median) were 0.724 versus 0.697 for all-cause death and 0.695 versus 0.678 for MACE.

In a sensitivity analysis, in which NT-proBNP (either as a continuous variable or dichotomized by its median) was forced into the final model, it was not associated with either endpoint (Table 5). In such analyses, however, the association of CA125 (M2 vs. M1) with the risk of all-cause death (HR: 2.20; 95% CI: 1.11 to 4.34; p = 0.023) and MACE (HR: 1.78; 95% CI: 1.05 to 3.01; p = 0.031) remained almost unaltered.

Longitudinal analyses. Including baseline measurements, available measurements of CA125 per patient ranged from 1 to 5 with a median of 2. Of the 228 patients undergoing TAVI, 69 (30%) had only 1 value (corresponding to baseline), mainly because of early deaths. In 29% of the patients (65 of 228), 2 values; in 22% (51 of 228), 3 values; in 13% (29 of 228), 4 values; and in 6% (14 of 228), 5 values were available.

The mean observed trajectory for lnCA125 showed no important fluctuations in patients with no events. In those with events, a steady increase in lnCA125 before the occurrence of death or MACE was observed (Figs. 3A and 3B, Online Figs. 3 and 4 for natural values of CA125). This indicates a positive association between longitudinal response and time to death/MACE. Moreover, these patients started the follow-up with higher values of lnCA125. Regression estimates from the JM-longitudinal submodel are presented in Table 6.

The output from the JM-survival submodel identified lnCA125 as a powerful and independent predictor of both endpoints (Table 6). After controlling for lnNT-proBNP (modeled as a time-varying covariate), and baseline values of the logistic EuroSCORE, NYHA functional class III/IV, and device success, we found that for each unit increase in lnCA125, there was a predicted 47% increase for the risk of death. For MACE, the predicted increase of risk was even greater (more than 2-fold) (see Table 6 for the estimates). Of note, the regression estimate for lnCA125 did not change significantly after eliminating the nonsignificant variables from the model (EuroSCORE and lnNT-proBNP).

Two additional sensitivity analyses were performed to evaluate the prognostic significance of CA125 (M2 vs. M1) and CA125 (>30 vs. ≤30 U/dl). Here, lnNT-proBNP was modeled as a time-varying exposure instead of lnCA125. In the first analysis, CA125 (M2 vs. M1), but not lnNT-proBNP, was independently related to the risk of death (HR:

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Table 3. Clinical and Echocardiographic Characteristics of the Entire Patient Population and According to Median CA125

Variables	CA125-M1 (n = 108)	CA125-M2 (n = 120)	p Value
Clinical characteristics			
Age, yrs	79 ± 5	80 ± 7	0.295
Male	51 (47)	73 (61)	0.039
Logistic EuroSCORE	11 [8–19]	18 [11–27]	<0.001
Access TF vs. non-TF	60/48 (56/44)	77/43 (64/43)	0.185
Body mass index, kg/m^2	27.3 ± 3.9	26.2 ± 4.0	0.059
Diabetes	38 (35)	43 (36)	0.919
Hypertension	80 (74)	65 (54)	0.002
Hypercholesterolemia	32 (30)	25 (21)	0.126
Atrial fibrillation	30 (28)	49 (41)	0.039
Previous SAVR	2 (2)	11 (9)	0.017
Previous CABG	17 (16)	15 (13)	0.482
Previous CAD	46 (43)	41 (34)	0.191
Previous PCI	31 (29)	20 (17)	0.029
Previous malignoma	19 (18)	10 (8)	0.036
Previous MI	7 (7)	9 (8)	0.764
Previous stroke*	13 (12)	12 (10)	0.623
Renal failure†	23 (21)	43 (36)	0.016
COPD‡	18 (17)	18 (15)	0.730
Peripheral arteriopathy	25 (23)	16 (13)	0.054
Pacemaker	14 (13)	12 (10)	0.482
Previous dialysis	3 (3)	8 (7)	0.171
NYHA functional class III/IV	74 (69)	116 (97)	<0.001
Laboratory			
Hemoglobin, g/dl	12.3 ± 1.8	12.1 ± 1.7	0.288
Creatinine, mg/dl	1.27 ± 0.92	1.59 ± 1.27	0.031
NT-proBNP, pg/ml	1,054 [455–2,450]	4,010 [1,575–9,191]	<0.001
Echocardiography			
LVEF ≥50%	98 (91)	81 (68)	<0.001
LVEF 40%–49%	8 (7)	27 (23)	
LVEF ≤40%	2 (2)	12 (10)	
Mean gradient, mm Hg	47 ± 17	49 ± 18	0.315
Maximal gradient, mm Hg	78 ± 28	82 ± 28	0.293
PAH§	4 (4)	20 (17)	0.004
Aortic valve area, cm^2	0.7 [0.7–0.9]	0.7 [0.6–0.8]	0.196

Values are mean ± SD, n (%), or median [interquartile range]. *Severely affecting ambulation or day-to-day functioning. †Serum creatinine >200 μmol/l. ‡On long-term use of bronchodilators or steroids. §Pulmonary artery pressure ≥60 mm Hg.

CA125-M1 = below the median; CA125-M2 = above the median; other abbreviations as in Table 1.

2.88; 95% CI: 1.43 to 5.80; p = 0.003) and MACE (HR: 2.02; 95% CI: 1.19 to 3.43; p = 0.010) (Online Table 1). In the second analysis, the estimates for CA125 (>30 vs. U/ml ≤30 U/ml) did not reach statistical significance for death (HR: 1.55; 95% CI: 0.83 to 2.90; p = 0.167), although it did for MACE (HR: 1.93; 95% CI: 1.16 to 3.19; p = 0.011). Values of CA125 >30 U/ml were associated with an almost 2-fold increase in MACE (HR: 1.93; 95% CI: 1.16 to 3.19; p = 0.011) (Online Table 2). In both analyses, lnNT-proBNP, either as a main time-varying exposure or as a time-varying covariate, was not significantly associated with either endpoint.

Discussion

The present study is the first, to our knowledge, to assess the prognostic value of CA125 in TAVI. It could be shown that first, CA125 (modeled as lnCA125) was a strong predictor of death or MACE in a longitudinal setting. Explicitly, using JM analysis, serial CA125 measurements after TAVI were significant predictors of both outcomes, even when modeled simultaneously with time-varying NT-proBNP, logistic EuroSCORE, baseline NYHA functional class III/IV, and device success. Second, patients with elevated baseline CA125 values (above the median) showed an independent increase of risk for all-cause death or MACE after TAVI.

Risk prediction in TAVI. Risk prediction in TAVI is an important research avenue aimed at the identification of those patients who might benefit most from close follow-up and/or additional monitoring after the procedure. However, this is a challenging goal, mainly because despite successful TAVI, patients still remain at high risk for adverse events due to an extremely high burden of comorbidity. This issue becomes evident by a relative high mortality rate during follow-up as has been reported from randomized trials (17) and registries (18)

Table 4. Intra- and Post-Procedural Data and Complications for the Entire Population and According to Median CA125

Variables	CA125-M1 (n = 108)	CA125-M2 (n = 120)	p Value
Procedural success	106 (98)	115 (96)	0.312
Device success	92 (85)	104 (87)	0.748
Myocardial infarction	1 (1)	2 (2)	0.624
Emergency sternotomy	2 (2)	4 (3)	0.485
Procedural time, min	64 [53–85]	63 [51–82]	0.964
Contrast administration, ml	85 [59–152]	90 [57–130]	0.685
Fluoroscopy, min	13 [9–19]	13 [9–17]	0.941
Major vascular complications	4 (4)	8 (7)	0.317
Life-threatening bleeding	10 (9)	10 (8)	0.805
Major bleeding	16 (15)	25 (21)	0.237
Major stroke	0 (0)	4 (3)	0.124
Minor stroke	0 (0)	1 (1)	0.342
Post-procedural regurgitation, >1	5 (5)	6 (5)	0.885
Rethoracotomy	2 (2)	6 (5)	0.197
Need for vaECMO	5 (5)	16 (13)	0.023
Prophylactic vaECMO	2 (2)	10 (8)	0.029
Emergency vaECMO	3 (3)	6 (5)	0.390
Need for acute dialysis	7 (7)	15 (13)	0.124
Need for permanent pacemaker	15 (16)	17 (16)	0.988
Days on intensive care unit	1 [1–2]	1 [1–2]	0.631
Days in hospital	9 [7–12]	9 [7–14]	0.701

Values are n (%) or median [interquartile range].

Abbreviations as in Tables 1 and 2.

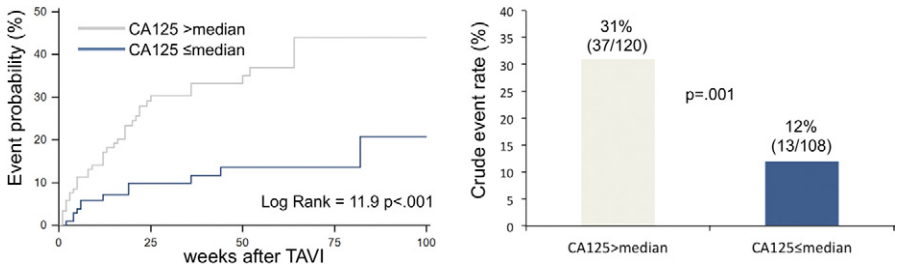

Figure 1. Cumulative and Crude Event Rate of All-Cause Death According to Elevated CA125

To the **left**, the cumulative rate of all-cause death is depicted with Kaplan-Meier method, whereas on the **right**, the crude death rates are shown. TAVI = transcatheter aortic valve implantation.

with a comparable rate of procedural and device success as in the present study. Thus, in TAVI, there is an unmet need to discover novel tools to improve the prediction of outcomes and to discriminate those patients who may benefit the most.

In this way, risk prediction using pre-procedural variables is the most appealing approach, since it bears the potential to determinate expected benefit from the procedure and therefore to allow a more rational treatment allocation. Several scores, such as the logistic EuroSCORE (19) or the STS score (20), have been proposed to summarize all prognostic factors. Biomarkers, in this setting, might be envisioned, not only as a tool for pre-procedural risk assessment, but also for monitoring treatment success after TAVI.

Biomarkers in TAVI. Natriuretic peptides show elevated values in aortic stenosis, correlate with disease severity, and have been used to predict symptom-free survival, prognosis, and post-operative outcome (21–23). As a consequence, these biomarkers were the first to be studied for risk prediction in the setting of TAVI (3–5). Nevertheless, these studies have been conducted in small populations and short-term follow-up, and have yielded conflicting results.

In our study, although lnNT-proBNP was associated with death and MACE, we did not find a prognostic value of NT-proBNP when modeled concomitantly with CA125 and other adjusting covariates. This was true for baseline values as well as in the JM analyses. These negative findings may be explained by the fact that NT-proBNP has a short half-life (24) and is therefore of limited use to assess long-term prognosis. Additionally, the high prevalence of old age and renal dysfunction in this population may also explain the limited use of this biomarker in this setting. Finally, a high correlation found between NT-proBNP and CA125 ($r = 0.49$) in the present study may also play a role.

Additionally, periprocedural elevations of cardiac necrosis markers (e.g., troponin or creatine kinase–myocardial band) have been associated with an increased mortality and a lesser degree of improvement of left ventricular ejection fraction (25). Because we did not perform routine troponin determination in our present study population, we cannot provide a comparison of CA125. Emerging evidence, however, allows us to speculate that most patients who meet the criteria for TAVI will have pre-procedural troponin determinations within normal limits.

Clinical role of CA125 following TAVI. CA125 is an emerging biomarker in HF and is released by mesothelial cells in response to the presence of serosal effusions and/or proin-

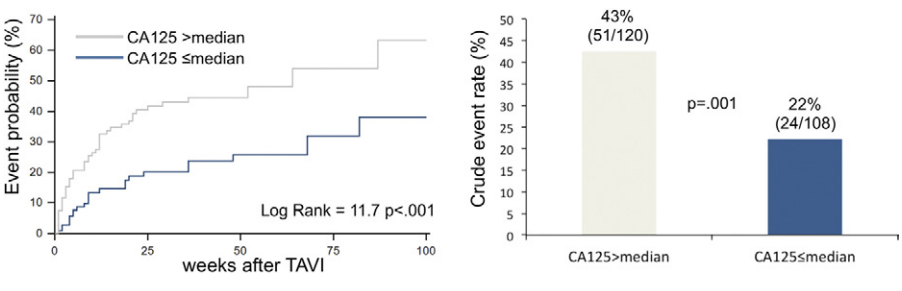

Figure 2. Cumulative and Crude Event Rate of MACE According to Elevated Levels of Pre-Procedural CA125

To the **left**, the cumulative rate of major adverse cardiac events (MACE) is depicted with Kaplan-Meier method, whereas on the **right**, the crude MACE rates are shown. TAVI = transcatheter aortic valve implantation.

Table 5. Pre-Procedural Estimates of the Association of CA125 and NT-proBNP and the Risk of All-Cause Death and MACE

	All-Cause Death			MACE		
Variables	HR (95% CI)	p Value	Harrell's C Statistic	HR (95% CI)	p Value	Harrell's C Statistic
lnCA125*	1.15 (0.89–1.50)	0.280	0.689	1.13 (0.91–1.41)	0.264	0.675
CA125 M2 vs. M1*	2.18 (1.11–4.26)	0.023	0.724	1.77 (1.05–2.98)	0.031	0.695
CA125 >30 U/ml*	1.74 (0.99–1.40)	0.063	0.695	1.53 (0.95–2.47)	0.078	0.676
lnNT-proBNP†	1.06 (0.84–1.34)	0.607	0.721	1.06 (0.85–1.28)	0.493	0.695
NT-proBNP >median†	1.11 (0.57–2.17)	0.758	0.723	1.10 (0.64–1.90)	0.726	0.693

Parametric Cox regression analysis was performed, with baseline hazard function modeled with 4 degrees of freedom restricted cubic splines. *Estimates adjusted by the logistic EuroSCORE, NYHA functional class III/IV and device success. †Estimates adjusted by the logistic EuroSCORE, NYHA functional class III/IV, device success, and CA125 above the median.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

flammatory cytokines (6). These 2 triggers of CA125 are pathophysiological mechanisms, which are profoundly related to the severity and progression of HF (26–28). Accordingly, previous studies have shown that CA125 is associated with disease severity and outcome in HF (8–10,29,30). Moreover, a recent study has shown that CA125 is also elevated in symptomatic severe aortic stenosis and correlates with symptom severity and outcomes (11).

In the present study, elevated CA125 levels before TAVI and during follow-up were associated with a higher rate of death and MACE. These effects were independent of established risk predictors, such as the logistic EuroSCORE, NYHA functional class III/IV, or device success. When compared with NT-proBNP, CA125 showed a clear superiority as a prognostic biomarker, perhaps due to its stability and longer half-life (around 7 to 12 days) (31).

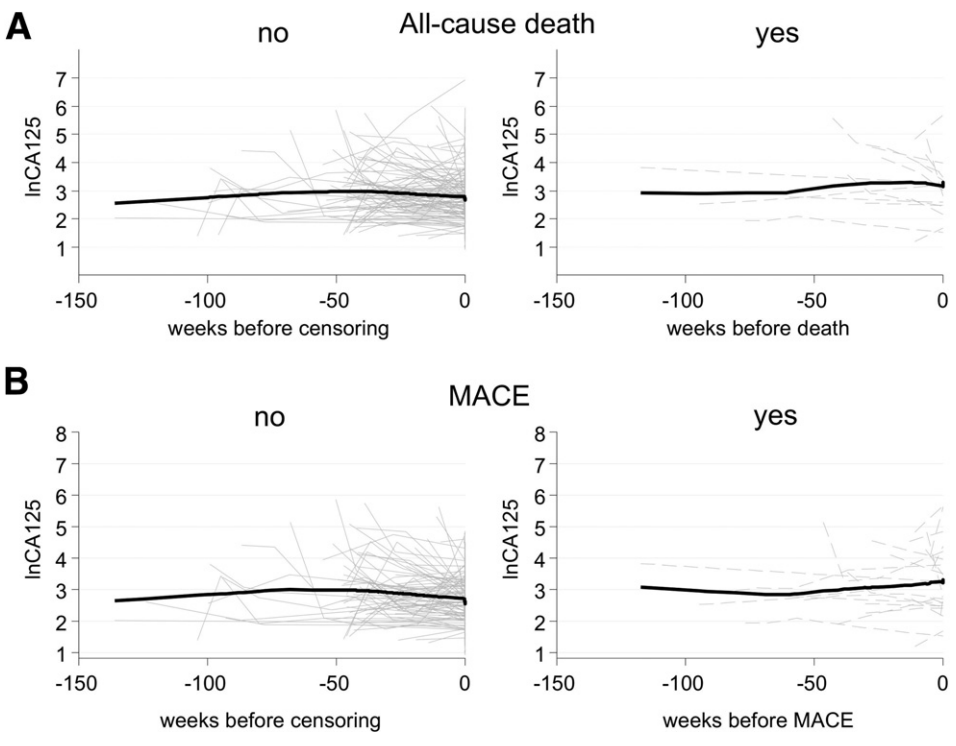

Figure 3. Subject-Specific Longitudinal Trajectories of LnCA125

Subject-specific longitudinal trajectories of LnCA125 for patients who were censored or reached an endpoint. **Solid lines** denote the fit of the loess smoother. Time scale is adjusted to each patient's survival time. **A and B** display the longitudinal trajectories across died/censoring or MACE/censoring status, respectively. In patients who were censored and did not reach an endpoint (censored = last contact alive and event-free), CA125 levels remain relatively stable with a slight decreasing tendency over time. By contrast, patients who experienced an event, lnCA125 levels show an elevation as they get closer to the event. MACE = major adverse cardiac events.

Table 6. Joint Model Regression Estimates

	All-Cause Death		MACE	
Longitudinal Submodel for lnCA125*	**β-Coefficient (95% CI)**	**p Value**	**β-Coefficient (95% CI)**	**p Value**
Intercept	1.456 (0.908 to 2.004)	0.000	0.807 (0.272 to 1.343)	0.003
lnNT-proBNP†	0.153 (0.092 to 0.213)	0.000	0.243 (0.185 to 0.301)	0.000
LVEF‡	−0.074 (090 to −0.057)	0.000	−0.030 (−0.045 to −0.015)	0.000
Sex	0.224 (0.007 to 0.441)	0.043	0.128 (−0.103 to 0.359)	0.276
Time, weeks†	−0.091 (−0.141 to −0.042)	0.000	−0.008 (−0.016 to 0.001)	0.068
Sex*time	0.045 (0.015 to 0.074)	0.003	0.004 (−0.001 to 0.009)	0.082
EuroSCORE20‡	−0.130 (−0.378 to 0.118)	0.304	0.082 (−0.173 to 0.337)	0.528
EuroSCORE20*time	0.033 (0.001 to 0.064)	0.042	0.005 (−0.001 to 0.010)	0.089
	All-Cause Death		**MACE**	
Survival Submodel§	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
lnCA125†	1.47 (1.01 to 2.14)	0.043	2.26 (1.28 to 3.98)	0.005
lnNT-proBNP†	1.06 (0.81 to 1.39)	0.659	0.95 (0.75 to 1.21)	0.691
EuroSCORE‡	1.48 (1.04 to 2.10)	0.028	1.15 (0.84 to 1.56)	0.380
Device success, 1 vs. 0‡‖	0.44 (0.22 to 0.86)	0.016	0.48 (0.26 to 0.86)	0.015
NYHA functional class III/IV‡	4.43 (1.36 to 14.44)	0.014	4.78 (1.46 to 15.62)	0.010

*Linear mixed regression analysis with time (in weeks) modeled with random intercept and slopes. †Time-varying. ‡Baseline variable. §Parametric Cox regression analysis, with baseline hazard function modeled with 4 degrees of freedom–restricted cubic splines. ‖Defined as procedural success with a correct position and function of the prosthesis (less than grade 2 residual aortic regurgitation) and only 1 valve implanted per patient.

EuroSCORE = the logistic EuroSCORE continuous; EuroSCORE20 = the logistic EuroSCORE dichotomized(>20%); lnCA125 = natural logarithm of CA125; lnNT-proBNP = natural logarithm of NT-proBNP; other abbreviations as in Tables 1 and 5.

Additionally, as a biomarker, CA125 possesses some more theoretical advantages. First, levels of this biomarker show a close relationship with HF severity and increased risk of death and subsequent readmission for acute HF (8–10,28). Second, it is widely available and less expensive than other biomarkers. Third, plasma levels do not seem to be relevantly influenced by age, renal function, or body mass index (8,9). Fourth, evidence from data in patients with acute HF supports the hypothesis that changes in CA125 over time are more likely due to changes in disease status than to biological variation (9,29). Moreover, with a half-life longer than 1 week, CA125 does not seem to be a marker with high short-term variability.

These properties advocate CA125 as the ideal biomarker to monitor the evolution of our elderly TAVI patients. Despite being a stable biomarker, CA125 has shown temporal trajectories that closely follow the functional status of the patient, and consequently, discriminates those patients at high risk for adverse outcomes (29).

Clinical implications. First, baseline CA125 values might be a useful tool for the determination of the optimal time point for TAVI. Those patients with elevated levels of CA125 may require a more aggressive treatment before the procedure. Perhaps the subgroup with persistently elevated levels of CA125 may not benefit at all from the procedure.

Second, our longitudinal results support the potential for the use of this biomarker for monitoring the clinical evolution after TAVI. Potentially, patients with rising levels of CA125 after TAVI may be regarded to be at high risk for events and consequently may require close clinical observation and/or intensified treatment. At this moment, however, it is unclear whether normalization of CA125 values by a more aggressive treatment before and/or after TAVI, will attenuate the elevated risk for adverse events. The answer to this question will require additional studies and, more importantly, clinical trials specifically designed to address this issue.

Strength and limitations. First, this is the first to evaluate the prognostic usefulness of CA125 in a novel setting (patients undergoing TAVI). Second, a novel statistical approach for modeling repeated measurements of CA125 is employed. This allowed us to monitor the follow-up of the patients after TAVI with more statistical precision than using baseline values of the biomarker alone.

An inherent limitation of the JM analysis, we were not able to explore a more flexible functional form of CA125. However, our previous experience with CA125 in acute HF supports the use of either linear or logarithmic transformation when related to the log hazard for all-cause mortality. Finally, some variables were missing during follow-up and were included in the longitudinal models with their baseline values.

Conclusions

This study demonstrated for the first time that CA125 is an excellent prognostic tool for monitoring the evolution of

patients undergoing TAVI. Elevated pre-procedural and the longitudinal evolution of CA125 levels predicted adverse outcomes after TAVI.

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Key Words: biomarker ■ CA125 ■ joint modeling ■ prognosis ■ transcatheter aortic valve implantation.

APPENDIX

For supplementary figures and tables, please see the online version of this paper.