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Development of a risk score based on aortic calcification to predict one-year mortality after Transcatheter Aortic Valve Implantation

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Abstract

Objectives: To develop a new scoring system based on thoracic aortic calcification (TAC) to predict one-year cardiovascular and all-cause mortality.

Background: A calcified aorta is often associated with poor prognosis after transcatheter aortic valve implantation (TAVI). A risk score encompassing aortic calcification may be valuable in identifying poor TAVI responders.

Methods: The C₄CAPRI multicenter study included a training cohort (1425 patients treated by TAVI between 2010 and 2014) and a contemporary test cohort (311 patients treated in 2015). TAC was measured by computed tomography pre-TAVI. CAPRI risk scores were based on the linear predictors of Cox models including TAC in addition to comorbidities and demographic, atherosclerotic disease and cardiac function factors. CAPRI scores were constructed and tested in 2 independent cohorts.

Results: Cardiovascular and all-cause mortality at one year was 13.0% and 17.9% respectively in the training cohort and 8.2% and 11.8% in the test cohort. The inclusion of TAC in the model improved prediction: 1 cm³ increase in TAC was associated with a 6% increase in cardiovascular mortality and a 4% increase in all-cause mortality. The predicted and observed survival probabilities were highly correlated (slopes > 0.9 for both cardiovascular and all-cause mortality). The model's predictive power was fair [AUC 68% (95% CI: [64 – 72])] for both cardiovascular and all-cause mortality. The model performed similarly in the training and test cohorts.

Conclusions: The CAPRI score, which combines the TAC variable with classical prognostic factors, is predictive of one-year cardiovascular and all-cause mortality. Its predictive performance was confirmed in an independent contemporary cohort. CAPRI scores are highly relevant to current practice and strengthen the evidence-base for decision-making in valvular interventions. Its routine use may help prevent futile procedures.

Key words: TAVI, aortic stiffness, risk stratification, outcome, mortality

Abbreviations

AS: Aortic stenosis

AUC: Area under the ROC curve

C₄CAPRI: (4 Cities for assessing CALcification PRognostic Impact

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CT: Computed tomography

GFR: Glomerular filtration rate estimated by the Cockcroft formula

HF: Heart failure

IDI: Integrated discrimination improvement

HR: Hazard ratio

LVEF: Left ventricular ejection fraction

ROC: Receiver-operating characteristic

TAC: Thoracic aortic calcification

TAVI: Transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) represents the standard of care for relieving aortic stenosis (AS) in high risk patients; it is also preferred in symptomatic intermediate risk patients according to the latest European Society guidelines (1). Although TAVI efficiently normalizes the gradient across the aortic valve, approximately 25% of high-risk patients die within the first year following the procedure (2). Because of the competing risk of non-cardiovascular mortality or heart failure (HF) the true benefit of TAVI is difficult to estimate. Whereas perioperative mortality accounts for a minor part of overall deaths and is diminishing with technical refinement (3) most of this residual risk remains high. This points to a need to better identify potentially poor TAVI responders who would not benefit from the procedure. Lack of benefit may be defined as death and/or absence of functional improvement during a relatively short-term period after the procedure (6 months to 1 year)(4). Within this time frame, it is likely that adverse outcomes are mainly driven by factors present before the TAVI procedure. Among various candidates (4), predictors of left ventricular function improvement are probably highly important but remain insufficiently characterized. Vascular after-load deserves scrutiny as it becomes preeminent after AS relief (5): our group recently established the prognostic significance of aortic calcifications assessed manually by computed tomography (CT), on the outcomes after TAVI. In particular, ascending aortic calcification was predictive of HF (6) and total aortic calcification burden was predictive of cardiac mortality (7). This prognostic implication may also concern non cardiovascular mortality (8,9).

The C₄CAPRI study (4 Cities for assessing Calcification Prognostic Impact, NCT02935491) aimed at developing a score based on aortic calcification burden combined with classical predictors, to predict one-year cardiovascular and all-cause mortality after TAVI.

Methods

This was a multicenter study performed in 4 high volume French centers. Two different cohorts were considered: a “training cohort” used to develop the risk scores and a "test cohort" in which the predictive value of the model was tested.

PATIENTS

All patients undergoing TAVI for severe AS during the study period were part of the FRANCE 2 (2,10) and of the FRANCE TAVI registries (11). The training cohort encompassed all patients treated by TAVI for severe AS at Clermont-Ferrand University Hospital, Lyon Croix-Rousse University Hospital, Institut Cardiovasculaire Paris Sud, and Rouen University Hospital between January 2010 and December 2014. The test cohort comprised all patients implanted from January to December 2015 at the Lyon and Paris centers, reflecting the most recent practices available.

Patients were included in the analysis if a pre-operative CT-scan was available and thoracic aortic calcification (TAC) was assessed.

The C₄CAPRI study was approved by the Ethical Committee (Comité de Protection des Personnes SUD-EST IV, L16-56) and by the Commission Informatique et Liberté (CNIL N° 16-065). All patients provided written informed consent to anonymous processing of their data.

CALCIFICATION ANALYSIS

CT acquisition was performed on CT scanners with at least a 4cm z-coverage: Brilliance 64 and iCT (Philips, Best, Netherlands); Discovery CT750 HD (GEMS, Waukesha, USA). For each examination, the whole thoracic aorta was studied. CTs were performed after an intra-venous injection of iodine-based contrast agent, with electrocardiogram gating, tube voltage ranging from 100 to 140 kV and adapted mAs. Reconstruction parameters for axial slices ranged from

0.625 to 0.8. All images were anonymized, transferred to a core lab and analyzed by 3 operators, blinded to outcomes data.

Calcifications were extracted using a semi-automated dedicated software based on an open source environment available at https://www.creatis.insa-lyon.fr/site7/fr/creatools_accueil. The rater first delineates the ascending, horizontal, and descending thoracic aorta by placing at least 3 points (**Figure 1**). The main axis of the aorta was calculated using a third-order b-spline. An adjustable tube embedding the whole aorta was created and an initial threshold set at 550 UH was applied in the tube in order to detect calcifications. This threshold could be adapted to improve the performance of the algorithm. The results of the segmentation were visually asserted and each calcification was manually adjusted (by addition or subtraction) and validated by the user. A connectivity algorithm, based on graph theory, was subsequently applied in order to segment each calcification. The algorithm is a simple recursive function initialized in the center of each calcification after thresholding. For each pixel, the 28 neighboring pixels were checked and the algorithm was re-run for each pixel if their value was above the threshold. For each patient, TAC was calculated from the aortic sinus to the aortic hiatus as previously described (7); valvular calcifications were excluded.

Inter- and intra-observer reproducibility, assessed in a subset of randomly selected patients from the training cohort (N= 50 and 75, respectively), was high with intra-class correlation coefficients estimated respectively at 0.997 (95% confidence interval (CI): [0.994 – 0.998]) and 0.997 (95% CI: [0.996 – 0.998]).

PROCEDURES

Two TAVI systems were mainly used: a self-expandable prosthesis (Medtronic CoreValve ReValving System, Medtronic, Minneapolis, Minnesota) and a balloon expandable prosthesis

(Edwards SAPIEN valve, Edwards Lifesciences, Irvine, California); various routes (transfemoral, transapical, subclavian) and types of anesthesia were used in the different centers. The variables collected have been described elsewhere (6,10) and encompass demographics, cardiovascular history, biological variables, and echocardiographic variables.

OUTCOMES

The primary end point was cardiovascular death at 1 year. Secondary endpoint was all-cause mortality at 1 year. Vital status was obtained by telephone contact with patients, their relatives, carers or physicians, and by on-site planned visits. Follow-up was censored at 1 year following TAVI. Cardiovascular deaths were adjudicated by 2 experienced cardiologists blinded to patient characteristics and TAC. Cardiovascular deaths were defined according to the VARC-2 criteria (12). 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.

CONSTRUCTION OF CAPRI RISK SCORE

The characteristics of the cohorts were described using the absolute and relative frequencies for the qualitative characteristics and the mean and the standard deviation for the quantitative characteristics. TAC was considered as a three-class variable defined according to the tertiles for the analysis using the Kaplan Meier method, and as a continuous variable in the model used to build the risk score. In addition to the continuous TAC, the risk score was constructed from known prognostic mortality factors according to the literature (2,10,13-15) and expert opinion, split into 3 groups: 1) demographic and comorbidities, 2) atherosclerotic disease, 3) cardiac function (see **Online Methods** for details). Non redundant factors were selected in each group after estimating correlations between factors by Spearman coefficient, tetrachoric or polychoric

coefficients, according to the nature of the factors. Cox regression models were used to quantify the effects of the retained factors on mortality hazard. The prediction improvement linked to the added factors was tested using the likelihood ratio test as recommended (16), and quantified using the integrated discrimination improvement (IDI) index (17). The calibration of the final model was estimated by plotting observed survival probabilities against deciles of prediction and its discriminative performance, by using the cumulative/dynamic area under the ROC curve (AUC). The bootstrap method was used to quantify and correct the optimism of the estimated AUCs. The risk scores of mortality were computed using the linear combination of the factors included in the Cox model weighted by the regression coefficients. The same strategy of analysis was applied to cardiovascular and all-cause mortality.

The predictive performance of the risk scores was evaluated on the independent test cohort by assessing its calibration and estimating the AUC.

To illustrate the impact of the risk scores on the identification of potentially futile TAVI, futility thresholds corresponding to the expected 1-year mortality (between 15% and 25% for cardiovascular mortality and between 25% and 35% for all-cause mortality) of a medically treated population (18), were estimated in the training cohort. These thresholds were used in the test cohort to give an estimate of potentially futile TAVI, i.e., those patients in whom the mortality probability after TAVI would be equal to or greater than that without intervention (see **Online Methods** for details).

The analysis was performed using the statistical software SAS[®] version 9.3, and the R software, version 3.3.1.

Results

CHARACTERISTICS OF PATIENTS AND PROCEDURES

The flow of patients is shown in **Figure 2**. The characteristics of the training and of the test cohorts were similar concerning risk profile, route for TAVI, type of prosthesis, echocardiographic parameters, and TAC (**Table 1, Online Table 1**). There were no substantial differences to the excluded patients (**Online Table 2**). The rate of procedural success was high and a marked decrease of transaortic gradient accompanied by a small increase of left ventricular ejection fraction (LVEF) was observed (**Online Table 1**).

In the training cohort, 237 deaths were observed during the first year following TAVI, 170 of which were from cardiovascular causes. The one-year cardiovascular and all-cause mortalities in the training cohort were estimated at 13.0% (95% CI: [11.2; 14.8]) and 17.9% (95% CI: [15.9; 19.1]), respectively. In the test cohort, 30 deaths, 21 from cardiovascular causes, were observed. Cardiovascular and all-cause mortalities in this group were thus 8.2% (95% CI: [4.7; 11.6]) and 11.8% (95% CI: [7.7; 15.7]).

CORRELATION BETWEEN FACTORS BELONGING TO THE SAME GROUP AND TAC

For all three groups of risk factors, the correlations with TAC were low (**Figure 3; Online Figure 1**). The highest correlation was between TAC and peripheral vascular disease or coronary disease, with coefficients estimated at 0.17.

PREDICTIVE POWER OF TAC FOR CARDIOVASCULAR AND ALL-CAUSE MORTALITY

The survival curves of the 3 classes of TAC were significantly different for cardiovascular and all-cause mortality, respectively (**Online figure 2**), with a survival much lower for the patients with a TAC above the second tertile in comparison with the two other classes of TAC.

Among demographic variables and comorbidities, age, gender, glomerular filtration rate (GFR) and chronic obstructive pulmonary disease (COPD) were included in the Cox model. The inclusion significantly improved the prediction of cardiovascular and all-cause mortality

compared with the model without covariates ($p=0.002$, $p<0.0001$ respectively). Inclusion of the atherosclerotic disease factors (coronary artery disease, history of stroke or transient ischemic attack, or history of peripheral vascular disease) did not significantly improve the predictive power of the model ($p=0.75$ for cardiovascular and $p=0.16$ for all-cause mortality). Addition of factors linked to cardiac function (LVEF, pulmonary pressure, mean gradient, dyspnea (NYHA), mitral regurgitation) to the 2 previous groups improved significantly the prediction of cardiovascular and all-cause mortality ($p=0.0001$, $p<0.00001$ respectively).

Adding TAC to the other factors improved significantly the prediction of cardiovascular and all-cause mortality ($p<0.01$ and $p=0.04$ respectively). An increase of 1 cm^3 , was associated with a 6% increase in cardiovascular mortality (hazard ratio (HR): 1.06, 95% CI: [1.01; 1.10]) (**Table 2**) and a 4% increase in all-cause mortality (HR: 1.04, 95% CI: [1.00; 1.08]) (**Table 3**).

CALIBRATION AND DISCRIMINATION OF THE FINAL MODEL

The calibration of the model including the three groups of factors and the TAC was good for cardiovascular (**Online Figure 3A**) and all-cause mortality (**Online Figure 3B**). Slopes were 0.90 for cardiovascular and 0.95 for all-cause mortality, respectively. The IDI index measuring the improvement of the discrimination ability of the model by adding the TAC was significant, estimated at 0.006 (95% CI: [0.000; 0.025]) for cardiovascular mortality and at 0.004 (95% CI: [0.000; 0.018]) for all-cause mortality (**Online Figure 4A and 4B**). The AUC for cardiovascular mortality was 68% (95% CI: [64; 72]); that for all-cause mortality was 68% (95% CI: [64; 72]). The optimism of the AUC of the final models was low, estimated at 0.04% for cardiovascular mortality and 0.07% for all-cause mortality.

In comparison, the Euroscore performed less well for cardiovascular and all-cause mortality, with AUCs estimated at 56% (95% CI [52; 60]) and 57% (95% CI: [53; 61]), respectively.

Interestingly, adding TAC to the Euroscore was also able to improve its discrimination ability with an estimated IDI at 0.007 (95% CI: [0.001; 0.021]) for cardiovascular mortality and at 0.006 (95% CI: [0; 0.018]) for all-cause mortality (**Online Figure 4C and 4D**). The AUCs of TAC combined with Euroscore were estimated at 59% (95% CI [55; 62]) and 58% (95% CI [54; 62]), respectively.

RISK SCORES AND THRESHOLDS

Tables 2 and 3 present the coefficients of the risk scores constructed on the training cohort for predicting cardiovascular and all-cause mortality, respectively. **Figure 4** presents the components of the risk scores and the correspondence between risk scores and predicted mortality in the training cohort. The threshold of risk score corresponding to a predicted cardiovascular mortality of 20% was estimated at 0.7 (**Online Table 3**). The associated sensitivity and specificity were estimated at 33.4% and 87.5% respectively. The threshold of risk score corresponding to a predicted all-cause mortality of 30% was estimated at 0.78. The associated sensitivity and specificity were estimated at 27.8% and 90.8% respectively.

PREDICTIVE PERFORMANCE OF THE RISK SCORES ON THE TEST COHORT

The calibration of the risk scores on the test cohort was good (**Online Figure 3C and 3D**) with slopes estimated at 0.92 and 0.95 for cardiovascular and all-cause mortality, respectively. The AUCs were estimated at 66% (95% CI: [65; 67]) and 67% (95% CI: [65; 67]) for cardiovascular and all-cause mortality, respectively. For patients with a risk score above the 20% mortality threshold, cardiovascular mortality probability at one year was estimated at 29.6%, compared with 6% for patients with a risk score below or equal to the threshold. For all-cause mortality, the one-year probability of death in patients with a risk score above the 30% threshold was estimated at 50%, vs. 8.5% in patients with a risk score under or equal to the threshold. This corresponds to

112 and 77 out of 1000 patients respectively in whom TAVI would potentially be futile. The stringency of the criteria may be varied as illustrated in **Figure 5**.

Discussion

The CAPRI score is a newly developed, dedicated score encompassing an original and meaningful variable – TAC – in addition to classical variables representative of comorbidities, atherosclerotic and cardiac factors. A 1 cm³ increase in TAC predicted a 6% increase in cardiovascular mortality and a 4% increase in all-cause mortality. The CAPRI score has a good discriminative ability for one-year cardiovascular and all-cause mortality after TAVI.

THE CAPRI SCORE COMPONENTS AND PERFORMANCE

The identification of patients in whom non-modifiable factors will predispose to adverse outcomes post-TAVI is of utmost importance, both for ethical and economical reasons. The CAPRI score performs well when predicting cardiovascular and all-cause mortality. The validation process strictly followed recommendations (19) and represents the most ambitious attempt so far to develop a risk model for TAVI candidates. Since prediction models tend to perform better on the data from which they were constructed than on new data, strategies of bootstrapping were used for internal validation in order to limit the optimism bias. External validation was also used as a confirmatory step to assess the predictive performance of the scores. The CAPRI score included 3 groups of meaningful factors: demographic and comorbidities, atherosclerotic disease, and cardiac function (**Figure 4**). The components of these 3 groups have been largely found to have an important prognostic value among patients undergoing TAVI albeit differences exist according to different settings (4). Although comorbidities and cardiac function were mostly strongly associated with mortality, the inclusion of other factors makes the scores less dependent on the training cohort and more extendable to

other settings (19). The model is based on preprocedural factors only and can therefore be used prospectively to inform clinical decision-making. Importantly, the score is based on contemporary practice and not on cohorts from earlier trials (15,20), which is relevant with respect to the continuing extension of indications for TAVI.

Based on our previous analyses (6,7), we added TAC to the predictive variables. We used continuous TAC because categorization of a continuous variable is usually associated with a loss of power and inaccurate estimation of the effect of the covariate (21,22). TAC increased significantly the predictive ability of the model as shown by the likelihood test (16) and further highlighted by the IDI index(17). TAC appeared poorly correlated with other markers of atherosclerosis or risk factors in keeping with the Multi-Ethnic Study of Atherosclerosis (23). This suggests that TAC, a surrogate of aortic stiffening and vascular aging, may predict future HF after TAVI, in keeping with our previous reports (6,7). Only thoracic aortic calcification was assessed, as our previous study showed that most of the prognostic information was embedded there (7), and also because not all centers performed whole aorta CT-scan. TAC is precisely computable, highly reproducible, and may also encompass some aspect of frailty including fragility fracture (8), muscle loss (24) and cerebrovascular events (9). As frailty is complex to assess with no unequivocal definition (25), this additional facet of TAC may be interesting. The score was well calibrated for cardiovascular and all-cause mortality in both cohorts and its prognostic discriminative performance was also good. A score with a good calibration means that the model has a good ability to predict risk of poor outcome with the intervention. The CAPRI score appears highly relevant for objective decision making in individual patients. While no formal decision threshold can be proposed, we tried to estimate a meaningful threshold corresponding to the probability of one-year death with medical treatment. In a cohort

comparable to C₄CAPRI, the probability of dying was 23.7% which could increase to >35 % in the presence of symptoms (18). As in our study, most deaths were attributable to cardiovascular causes. In our cohort, CAPRI scores predicted a one-year cardiovascular and all-cause mortality risk after TAVI similar to or greater than that without the intervention in a substantial number of patients (Figure 5). For example, CAPRI scores above 0.70 and 0.78 for cardiovascular and all-cause mortality, respectively, indicate a 50% risk of all-cause death, and a 30% risk of cardiovascular death within the first year after TAVI, markedly higher than the estimated risk without intervention. On top of other markers (frailty or cognitive function), such a level of risk may represent an important argument against further proceeding with TAVI. Thus, the CAPRI score represents an objective way for the Heart Team to improve patient selection, and for the patient to make an informed decision.

OTHER RISK SCORES

Many scores are dedicated to peri-operative mortality prediction, e.g. the surgical scores Euroscore, Euroscore II, or the STS score. Their discriminative ability for one-year mortality is poor (13) in keeping with our study. The same applies to the France 2 score which has also been proposed to predict early post-TAVI mortality (14). The PARTNER and the TARIS scores have been proposed to predict mid-term all-cause deaths (26). These scores mainly represent various combinations of the same variables collected in registries or study cohorts. Despite the addition of some specific variables of functional and cognitive capacity, the discrimination of the PARTNER score remains moderate (20), much lower than the CAPRI score. The addition of “frailty syndrome” to the other risk factors appears not to improve 1-year predictions of the score (15). Importantly, these previous scores are based on extreme-risk and high-risk patients for standard aortic valve surgery; thus, their performance in lower-risk patients remains unknown. In

this respect, the CAPRI score is currently the only score which has been validated in lower risk patients (test cohort).

LIMITATIONS

The training cohort comprised patients treated between 2010 and 2014 and may not be representative of today's populations and technologies. It is conceivable that technological refinement and inclusion of patients with lower risk profiles may improve outcome further in the future. In this respect it is notable that the mortality rate in the test cohort, treated in 2015, was dramatically lower than in the training cohort. However, the CAPRI scores had very similar performance (AUC) in these more recently treated patients. The outcomes assessed in the C₄CAPRI multicenter study were limited to cardiovascular and all-cause mortality; its usefulness in predicting other relevant outcomes such as residual HF and quality of life is untested. The score would need to be prospectively evaluated for its power to predict functional improvement and/or persisting HF.

The model might have been improved by the inclusion of frailty-associated variables, e.g. daily life activities. However, such markers were not available in the C₄CAPRI cohorts and their prognostic impact remains to be determined.

CONCLUSIONS

Objective, evidence-based decision-making is critical to avoid futile interventions to make optimal use of finite medical resources. The current study proposes a new specific TAVI-risk score based on pathophysiological variables. The inclusion of TAC, an independent unbiased variable, markedly increased the predictive power of the score. The implementation of a TAC-based score into daily practice is facilitated by the fact that CT-scans are systematically

performed before TAVI. This study also emphasizes the critical role of aortic biomechanics in determining outcomes after TAVI.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A substantial number of patients exhibit a poor outcome despite TAVI; they should be identified. Thoracic aortic calcification (TAC) is associated with mortality after TAVI.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The CAPRI score, which encompasses TAC combined with classical prognostic factors, has a good ability to predict 1-year cardiovascular and all-cause mortality. Calculation of CAPRI scores should be part of the initial work-up for a more personalized evaluation of the patients who are candidates for a TAVI procedure.

TRANSLATIONAL OUTLOOK: The impact of aortic biomechanics and vascular aging on the outcome after TAVI are important but overlooked. Additional research is warranted in this field.

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Figure legends

Figure 1: Example of aortic calcification measurement: (A) thoracic aortic segmentation (red spheres are used to delineate the ascending, horizontal, and descending thoracic aorta); (B) calcification selection (blue and orange are for valvular and thoracic aortic calcifications, respectively); (C) arrows indicate the level of the corresponding cross sectional image

Figure 2: Study Flowchart

Figure 3: Correlations between the factors linked to atherosclerotic disease and thoracic aortic calcifications (TAC). The size and the color of the circles are indicative of the direction and the strength of the correlation respectively (legend on the right)

Figure 4: Components of the CAPRI score and correspondence between values of risk score and predicted mortality probability in the training cohort. GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TAC, thoracic aortic calcification.

Figure 5: Impact of CAPRI score to identify potentially futile TAVI. Mortality estimations for patients of the test cohort with a CAPRI score below or above a threshold corresponding to a predicted mortality of 15%, 20% or 25% for the cardiovascular mortality (Panel A) and of 20%, 25% or 30% for the all-cause mortality (Panel B), and expected numbers of avoided transcatheter aortic valve replacement (TAVI) per 1000 patients. The thresholds correspond to the expected mortality in a similar population treated medically (i.e not receiving TAVI), based on the literature.

Table 1. Description of demographic characteristics, comorbidities and disease characteristics of the patients included in the C₄CAPRI training and test cohorts

Characteristics	N	Training Cohort	N	Test Cohort
Age (years)	1425	83.4 ± 7.1	311	83.3 ± 7.4
Male n (%)	1425	730 (51.2)	311	152 (48.9)
BMI (kg/m ²)*	1402	31.5 ± 7.8	304	32.0 ± 9.0
Logistic Euroscore (%)	1407	17.5 ± 10.4	297	17.0 ± 11.6
NYHA class III/IV n (%)	1387	868 (62.6)	294	174 (59.2)
GFR (ml/min/1.73 m ²)*	1415	50.5 ± 22.9	306	52.1 ± 23.8
<i>Clinical History – n (%)</i>				
Previous CABG	1193	144 (12.1)	298	24 (8.1)
Previous PTCA	1406	379 (27)	398	74 (23.8)
Peripheral vascular disease	1421	316 (22.2)	305	63 (20.7)
Stroke or TIA	1421	129 (9.1)	305	27 (8.9)
COPD	1420	267 (18.8)	305	50 (16.4)
Diabetes	1425	366 (25.7)	306	86 (28.1)
Atrial fibrillation	1407	454 (32.3)	297	76 (25.6)
Permanent pacemaker	1198	155 (12.9)	305	46 (15.1)
<i>Echocardiographic findings</i>				
Mean gradient (mmHg)*	1396	47.1 ± 16.3	287	48.3 ± 16.5
LVEF (%)*	1412	56 ± 14	286	54.9 ± 14.9
Moderate/severe MR n (%)	1371	17 (1.2)	278	7 (2.5)

Pulmonary pressure (mmHg)*	1286	44 ± 14	280	43 ± 13
<i>Coronary status n (%)</i>				
Number of diseased vessels	1423		310	
None		781 (54.9)		196 (63)
1		330 (23.2)		70 (23)
2		180 (12.6)		25 (8)
3		132 (9.3)		19 (6)
TAC (cm ³)*	1420	3.3 ± 3.2	311	3.1 ± 3.2

BMI, body mass index; GFR, glomerular filtration rate; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TAC, thoracic aortic calcification.

*mean ± sd

Table 2. Hazard ratios and corresponding coefficients of the risk score estimated in the training cohort using a Cox model for predicting one year cardiovascular mortality

	Hazard ratio	95% CI	p-value	Coefficient
Demographic factors and comorbidities				
Age (years)	1.03	0.998; 1.06	0.07	0.026
Male	1.05	0.74; 1.49	0.77	0.051
GFR level*	1.32	1.05; 1.66	0.02	0.277
COPD	1.27	0.79; 1.87	0.24	0.236
Atherosclerotic disease factors				
Coronary artery disease	0.89	0.64; 1.25	0.50	-0.116
Peripheral vascular disease	0.92	0.61; 1.38	0.69	-0.084
Previous Stroke or TIA	1.34	0.81; 2.23	0.26	0.294
Cardiac function factors				
LVEF (%)	0.99	0.98; 1.003	0.16	-0.008
Pulmonary pressure (mmHg/10)	1.13	1.02; 1.26	0.02	0.126
Unknown pulmonary pressure	1.68	0.74; 3.80	0.21	0.519
Mean gradient (mmHg)	0.99	0.98; 1.001	0.07	-0.010
Dyspnea **	1.61	1.23; 2.10	<0.01	0.475
Mitral regurgitation level***	0.87	0.79; 1.09	0.23	-0.136
TAC (cm ³)	1.06	1.02; 1.11	<0.01	0.059

CI, confidence interval; GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack, LVEF, left ventricular ejection fraction; TAC, thoracic aortic calcification.

*GFR in four ordinal levels, i.e. 1: $<15 \text{ mL/min/1.73 m}^2$; 2: $[15 - 30[$; 3: $[30 - 60[$; 4: $[60 - 90[$; 5: $\geq 90 \text{ mL/min/1.73 m}^2$

** dyspnea in 2 ordinal levels, i.e 0: NYHA 1,2; 1: NYHA 3,4

***Mitral regurgitation in five ordinal levels, i.e. 0: absence; 1: light; 2: moderate; 3: important; 4: severe.

Table 3. Hazard ratios and corresponding coefficients of the risk score estimated in the training cohort using a Cox model for predicting one year all-cause mortality

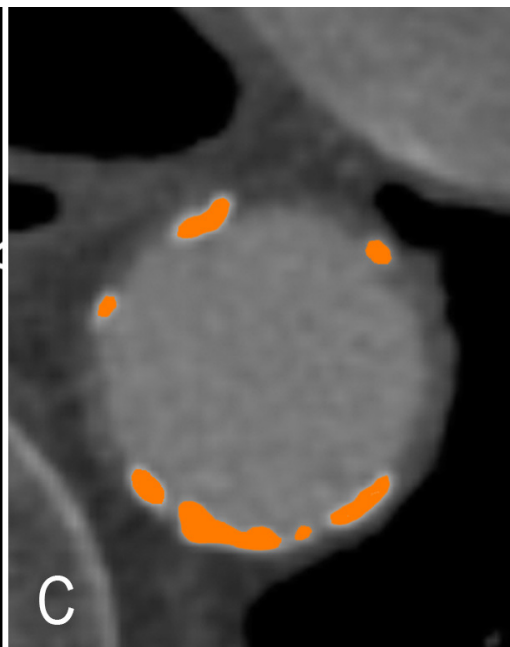
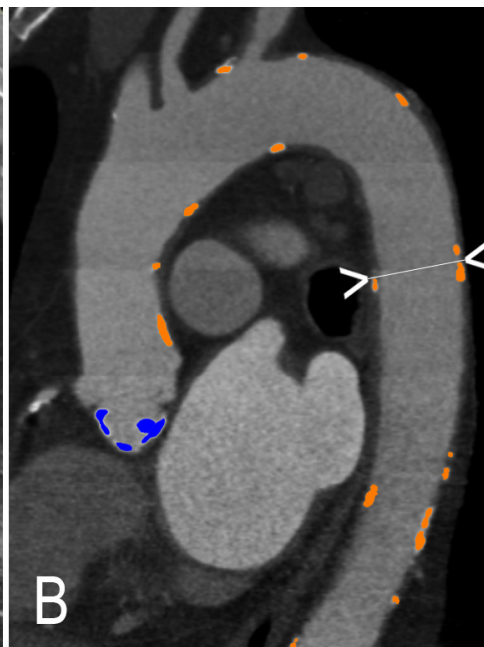
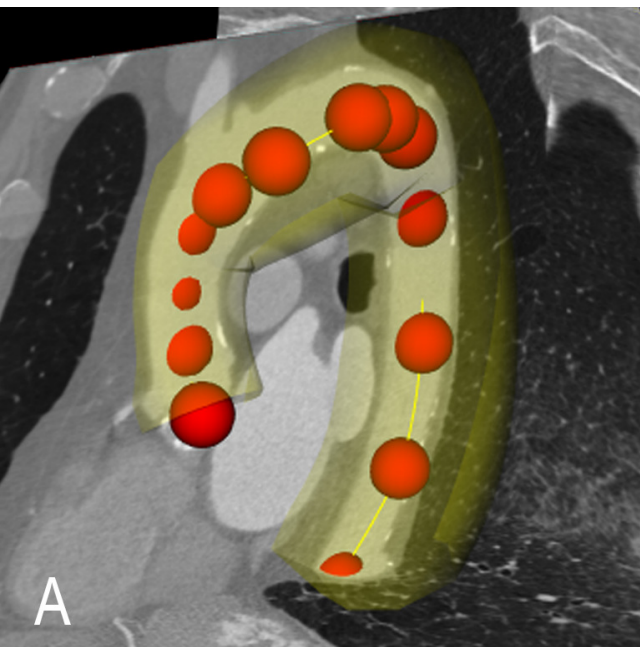
	Hazard ratio	95% CI	p-value	Coefficient
Demographic factors and comorbidities				
Age (years)	1.03	1.002; 1.05	0.03	0.026
Male	1.12	0.84; 1.50	0.44	0.114
GFR level*	1.40	1.16; 1.70	<0.01	0.333
COPD	1.21	0.87; 1.68	0.26	0.190
Atherosclerotic disease factors				
Coronary artery disease	1.07	0.81; 1.41	0.65	0.064
Peripheral vascular disease	1.31	0.96; 1.79	0.09	0.269
Previous Stroke or TIA	1.14	0.73; 1.79	0.55	0.135
Cardiac function factors				
LVEF (%)	0.99	0.98; 1.00	0.06	-0.010
Pulmonary pressure (mmHg/10)	1.15	1.05; 1.26	<0.01	0.140
Unknown pulmonary pressure	2.36	1.22; 4.55	0.01	0.858
Mean gradient (mmHg)	0.99	0.98; 1.002	0.11	-0.007
Dyspnea**	1.54	1.23; 1.94	<0.01	0.435
Mitral regurgitation level***	0.93	0.78; 1.12	0.43	-0.076
TAC (cm ³)	1.04	1.002; 1.08	0.04	0.040

CI, confidence interval; GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack, LVEF, left ventricular ejection fraction; TAC, thoracic aortic calcification.

*GFR in four ordinal levels, i.e. 1: <15 mL/min/1.73 m²; 2: [15 – 30[; 3: [30 – 60[; 4: [60 – 90[; 5: ≥ 90 mL/min/1.73 m²

** dyspnea in 2 ordinal levels, i.e 0: NYHA 1,2; 1: NYHA 3,4

***Mitral regurgitation in five ordinal levels, i.e. 0: absence; 1: light; 2: moderate; 3: important; 4: severe.



C₄CAPRI Training Cohort
TAVR 2010-2014
N=1897

Unavailable CT-scan
N=234

Truncated Aorta
N=189

Low quality CT-scan
N=49

TAVR included
N=1425

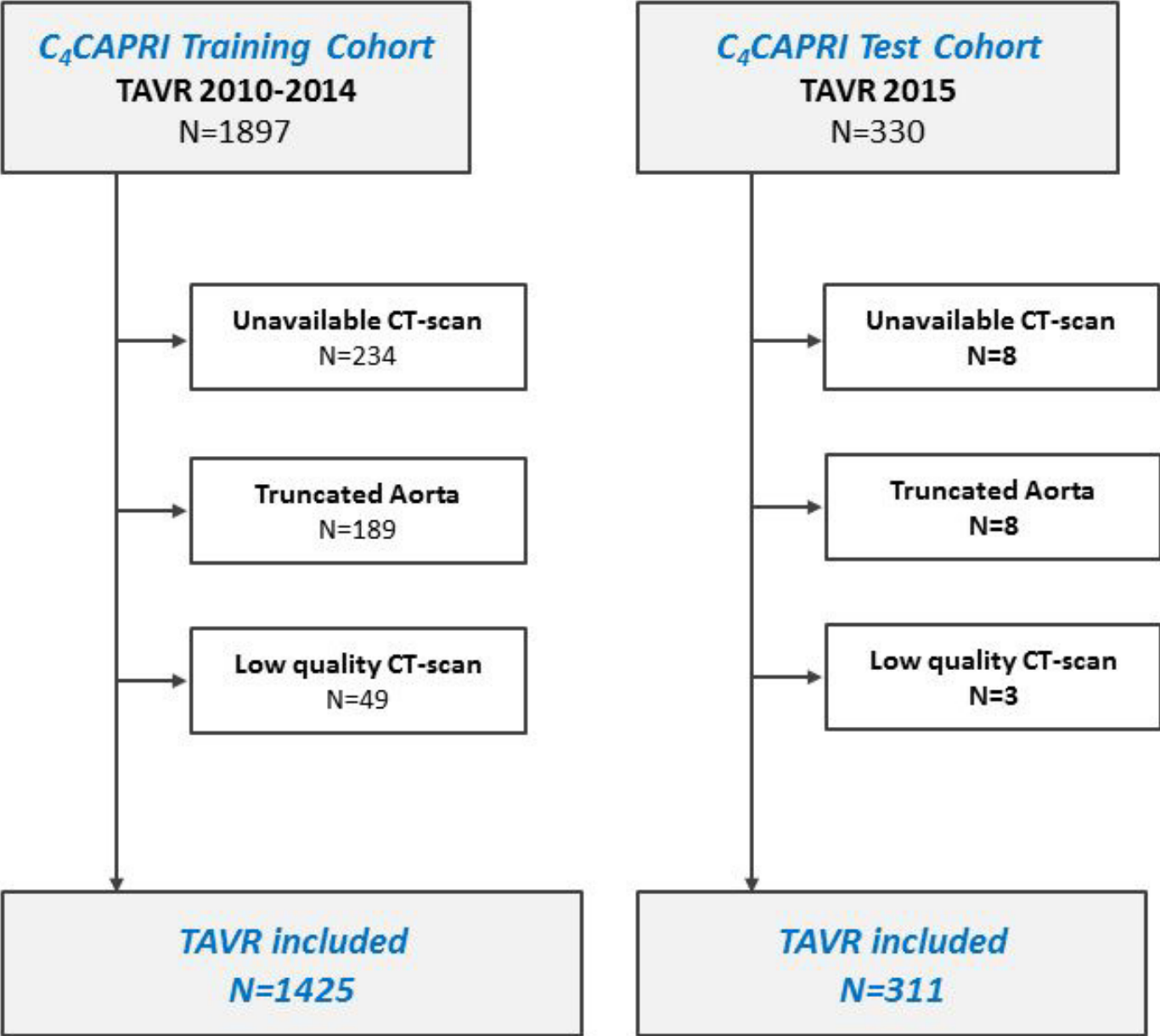
C₄CAPRI Test Cohort
TAVR 2015
N=330

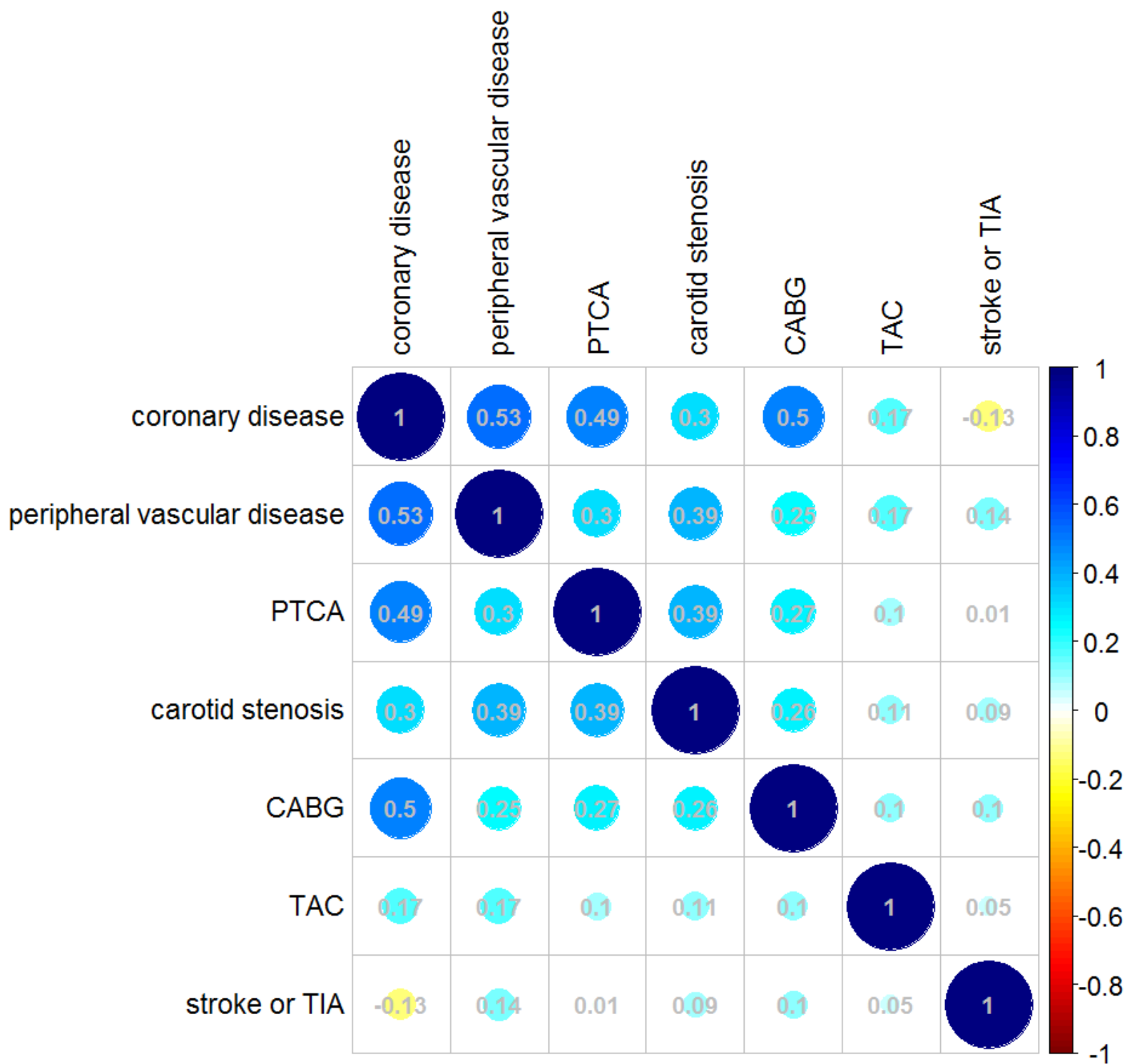
Unavailable CT-scan
N=8

Truncated Aorta
N=8

Low quality CT-scan
N=3

TAVR included
N=311





CAPRI score



Age

Male

eGFR level

COPD



Coronary disease

Peripheral vascular disease

Previous Stroke or TIA



LVEF

Pulmonary pressure

Mean aortic gradient

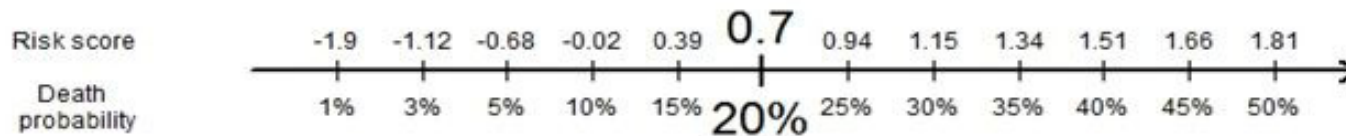
NYHA class

Mitral regurgitation level

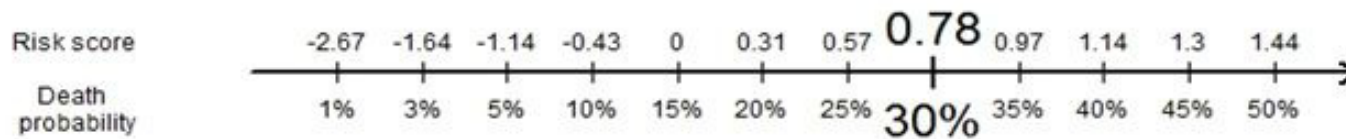


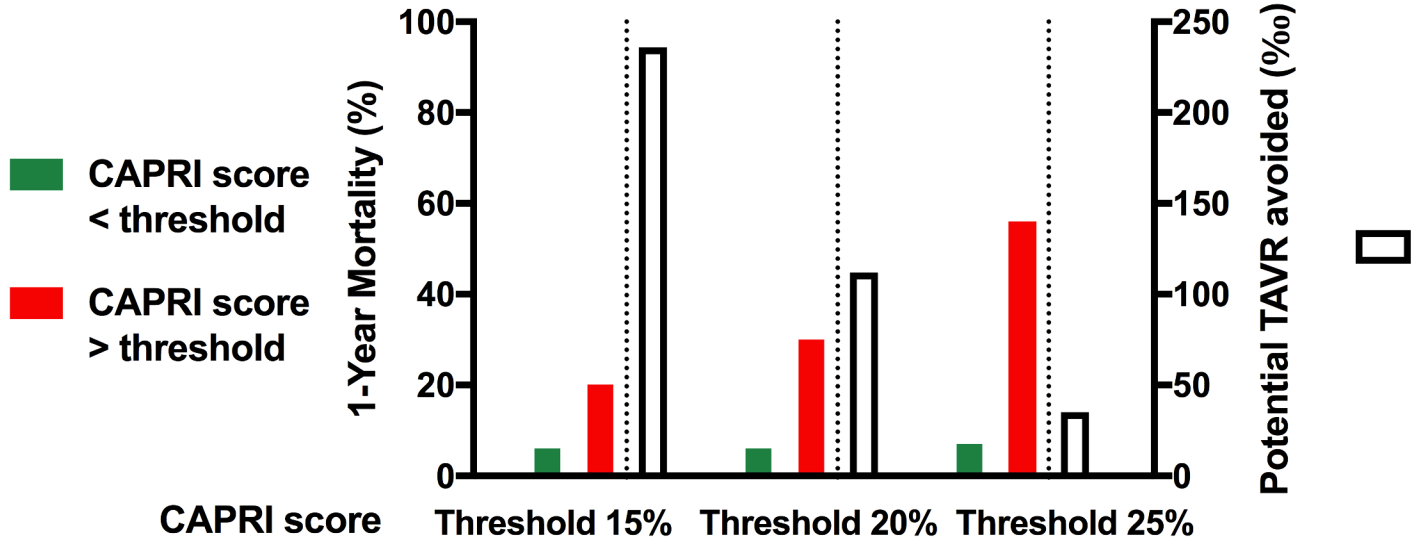
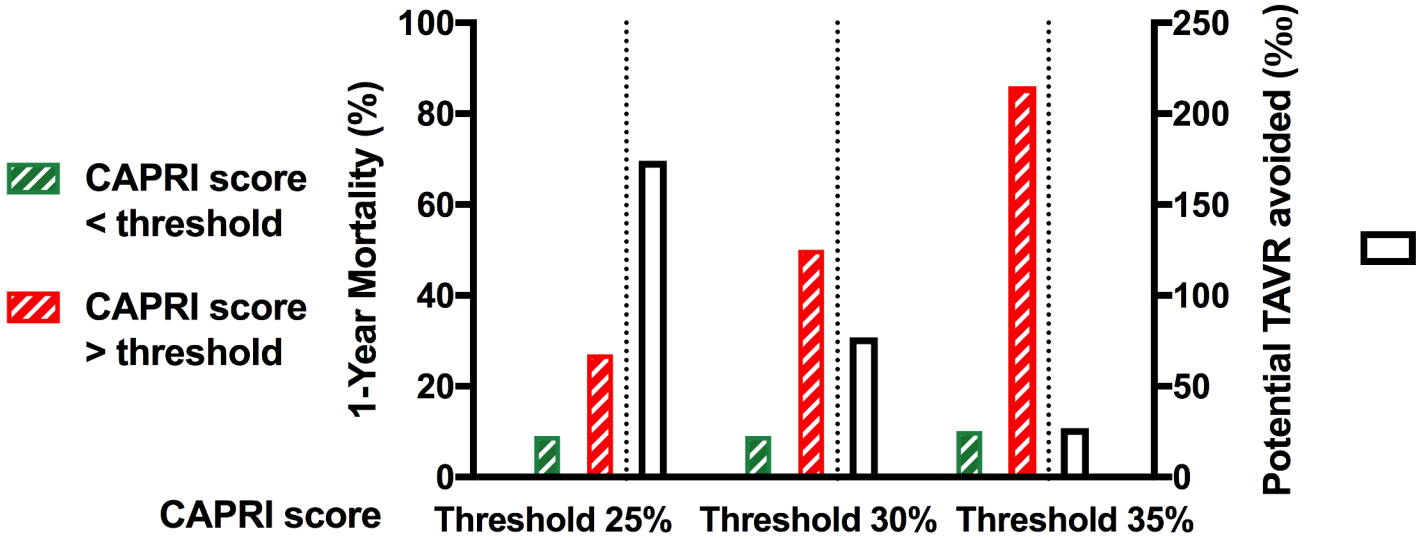
TAC

Cardiovascular mortality



All-cause mortality



A**Cardiovascular Mortality****B****All-Cause Mortality**

Online Methods

DEFINITION OF VARIABLES COLLECTED

Variables	Definitions
Diabetes	History of diabetes or ongoing treatment
Chronic obstructive pulmonary disease (COPD)	Chronic use of bronchodilators or corticosteroids for respiratory causes
Glomerular filtration rate (GFR)	Estimated with the Cockcroft formula and expressed in four ordinal levels, i.e. 1: <15 mL/min/1.73 m ² ; 2: [15 – 30[; 3: [30 – 60[; 4: [60 – 90[; 5: ≥ 90 mL/min/1.73 m ²
Atrial fibrillation	Atrial fibrillation documented on pre-TAVI EKG
Carotid stenosis	Carotid stenosis >50%
Peripheral vascular disease (PVD)	Intermittent claudication, >50% diameter stenosis or occlusion of a carotid artery, previous or planned intervention of the aorta, lower limb arteries or carotid arteries. Previous amputation for arterial causes
Stroke or transient ischemic attack (TIA)	History of stroke or TIA
Percutaneous transluminal coronary angioplasty (PTCA)	History of PTCA
Coronary artery bypass graft (CABG)	History of CABG
Pacemaker	Presence of a pacemaker before the TAVI procedure
Acute pulmonary edema	History of acute pulmonary edema
Dyspnea	Defined according to New York Heart Association (NYHA) class and expressed as a dichotomic variable, i.e. 0: NYHA 1,2; 1: NYHA 3,4
Right cardiac failure	Signs of right cardiac failure pre-TAVI
Left cardiac failure	Signs of left cardiac failure pre-TAVI
Coronary artery disease (CAD)	Assessed by pre-TAVI coronary angiogram and expressed as a dichotomic variable: 0 = no significant lesion of LAD, CX, and RCA; 1 = at least one diseased vessel defined as stenosis >50% on LAD and/or Cx and/or RCA
Left ventricular ejection fraction (LVEF)	Assessed by TTE using the Simpson method
Pulmonary pressure	Estimated by TTE and expressed as a continuous variable. If not measurable, categorized as “Unknown pulmonary pressure”

Mitral regurgitation	Assessed by TTE and expressed in five ordinal levels: 0 = absence; 1 = mild; 2 = moderate; 3 = important; 4: severe
Mean gradient	Mean aortic gradient assessed by TTE

CONSTRUCTION OF THE CAPRI RISK SCORE

In addition to the continuous TAC, the risk score was constructed from known prognostic mortality factors according to the literature (1-5) and expert opinion.

Components considered for building the score:

- 1) demographic factors and comorbidities: age, gender, body mass index, GFR, history of diabetes, COPD
- 2) factors linked to atherosclerotic disease: carotid stenosis, history of stroke or transient ischemic attack, history of CABG or PTCA, history of PVD, CAD
- 3) factors linked to cardiac function (history of acute pulmonary edema, dyspnea (NYHA), right or left cardiac failure, AF, permanent pacemaker, LVEF, pulmonary pressure, mean gradient, mitral regurgitation.

In order to select meaningful non-redundant factors in each group, within-group correlation between factors as well as correlation between factors and TAC was estimated using the Spearman coefficient for quantitative factors, and tetrachoric or polychoric coefficients for binary and ordinal factors, respectively. Non-redundant factors with <5% of missing data were included, except for pulmonary pressure. For patients in whom the measurement of pulmonary pressure was technically not possible, a category of unknown pulmonary pressure was added to the model.

Cox regression models were used to quantify the effects of the retained factors on mortality hazard. Four Cox models were constructed, the first including the retained demographic

factors and comorbidities, the second including the first model and retained factors linked to atherosclerotic disease, the third including the second model and the retained factors linked to cardiac function, and the fourth including the third model and TAC. The likelihood ratio test was used to compare the embedded models and to test the prediction improvement linked to the added factors as recommended (6). To further highlight the discrimination improvement related to the addition of TAC in the model of prediction, the integrated discrimination improvement (IDI) index was calculated. The IDI index quantifies the mean distance between the risk difference due to the addition of TAC in patients with the event and the risk difference in patients without the event (7). The calibration of the final model was assessed by plotting the observed survival probability for groups of patients with similar predicted survival according to the deciles of prediction. The discriminative performance of the final model was quantified using the cumulative/dynamic area under the ROC curve (AUC) estimated with the semi-parametric method proposed by Song and Zhou (8). The bootstrap method (9) was used to quantify and correct the optimism of the estimated AUCs. The risk scores of mortality were computed using a linear combination of the factors included in the Cox model (i.e. those of the retained factors of the three groups and TAC) weighted by the regression coefficients. The same analysis was applied to cardiovascular and all-cause mortality. The predictive performance of the risk scores was assessed for the independent test cohort by plotting observed survival probabilities against deciles of prediction and by estimating the AUC and 95% CI for discrimination assessment.

To illustrate the impact of the risk scores in identifying potentially futile TAVR, futility thresholds corresponding to the expected 1-year mortality of the same population treated medically (between 15% and 25% for cardiovascular mortality and between 25% and 35% for all-cause mortality) (10), were estimated in the training cohort by cross validation using a bootstrap method with thresholds corresponding to the mean of the estimations obtained on

1000 bootstrap samples. The sensitivities and specificities associated with these thresholds were also estimated. The thresholds estimated for the training cohort were used on the test cohort in order to quantify the mortality probability of patients with a prediction score below the thresholds using the Kaplan Meier method, and the proportion of patients with a prediction score above the thresholds. This allows for estimating potentially futile TAVR, i.e. those patients in whom the mortality probability after TAVR would be equal to or greater than that without intervention.

Online Results

Online Table 1. Procedural and performance characteristics of TAVR in the C₄CAPRI training and test cohorts

Characteristics	N	Training cohort	N	Test cohort
TAVR route n (%)	1421		305	
Transfemoral		1005 (71)		249 (82)
Apical		325 (23)		30 (10)
Other		91 (6)		26 (8)
<i>Devices</i>				
Implanted valve type n (%)	1223		309	
Edwards		891 (73)		211 (68)
Corevalve		326 (26.5)		93 (30)
Other		6 (0.5)		5 (2)

Implanted valve size n (%)	1407		306	
23		330 (23)		86 (28)
26		624 (44)		115 (38)
29		373 (27)		90 (29)
31		80 (6)		15 (5)
Successful implantation n (%)	1421	1395 (98.2)	311	308 (99)

Post-procedure echocardiographic findings

Mean gradient (mmHg) mean \pm SD	1298	9.5 \pm 4.7	253	11.1 \pm 6.6
LVEF (%) mean \pm SD	1255	58 \pm 13	249	56.7 \pm 13
Moderate/severe AR n (%)	1383	18 (1.3)	260	1 (0.4)

TAVR, transcatheter aortic valve replacement; LVEF, left ventricular ejection fraction; AR, aortic regurgitation

Online Table 2. Demographic characteristics, comorbidities and disease characteristics of the training cohort and of patients excluded from the training cohort, respectively

Characteristics	N	Included patients	N	Excluded patients
Age (years)	1425	83.4 ± 7.1	472	83.7 ± 6.7
Male sex n (%)	1425	730 (51.2)	472	215 (45.6)
BMI (kg/m ²)*	1402	31.5 ± 7.8	463	31.8 ± 6.1
Logistic Euroscore (%)	1407	17.5 ± 10.4	461	18.7 ± 11.2
NYHA class III/IV n (%)	1387	868 (62.6)	456	336 (73.7)
GFR (mL/min/1.73 m ²)*	1415	50.5 ± 22.9	466	47.3 ± 21.5
<i>Clinical History n° (%)</i>				
Previous CABG	1193	144 (12.1)	430	49 (11.4)
Previous PTCA	1406	379 (27)	466	129 (27.7)
Peripheral vascular disease	1421	316 (22.2)	469	110 (23.5)
Stroke or TIA	1421	129 (9.1)	469	46 (9.8)
COPD	1420	267 (18.8)	469	115 (24.5)
Diabetes	1425	366 (25.7)	472	144 (30.5)
Atrial fibrillation	1407	454 (32.3)	459	140 (30.5)
Permanent pacemaker	1198	155 (12.9)	427	63 (14.8)
<i>Echocardiographic findings</i>				
Mean gradient (mmHg)*	1396	47.1 ± 16.3	454	46.1 ± 15.4

LVEF (%)*	1412	56 ± 14	458	56.8 ± 14.5
Moderate/severe MR n (%)	1371	17 (1.2)	454	14 (3.1)
Pulmonary pressure (mmHg)*	1286	44 ± 14	403	44.2 ± 15.1

Coronary status

Number of diseased vessels	1423		467	
None		781 (54.9)		293 (62.7)
1		330 (23.2)		110 (23.6)
2		180 (12.6)		36 (7.7)
3		132 (9.3)		28 (6.0)

TAC (cm ³)*	1420	3.3 ± 3.2	472	NA
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BMI, body mass index; GFR, glomerular filtration rate; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TAC, thoracic aortic calcifications.

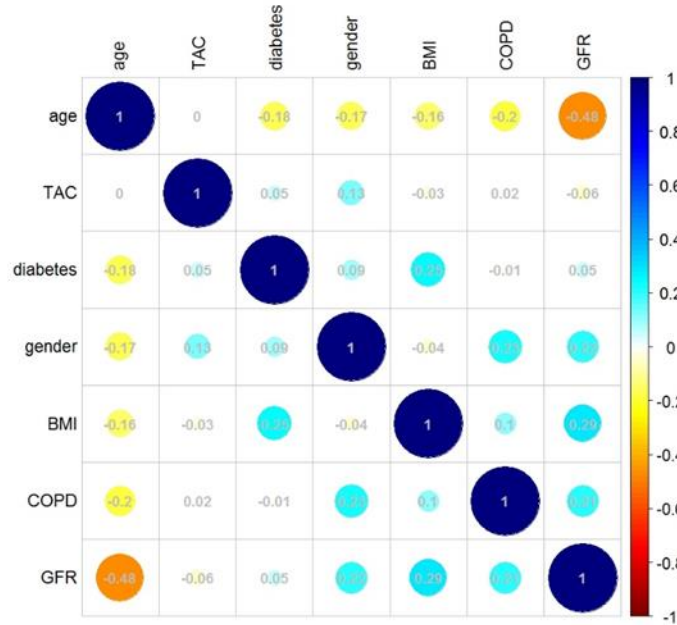
*mean ± sd

Online Table 3: Cross-validated risk scores thresholds corresponding to several predicted mortalities at one year and their associated sensitivity and specificity in the training cohort

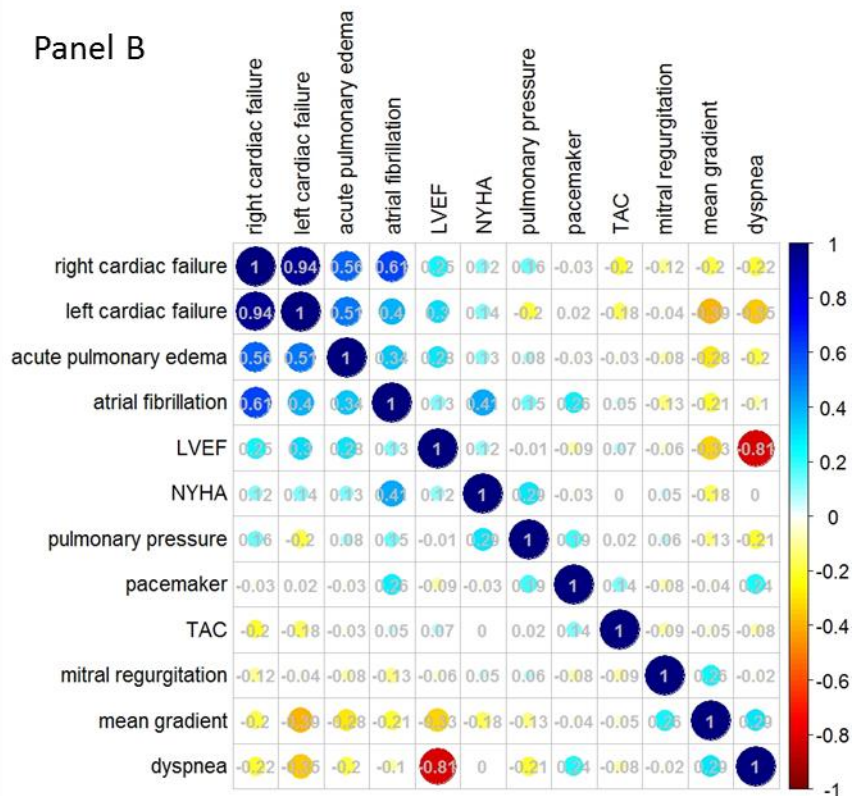
Probability	Threshold	Sensitivity %	Specificity %
Cardiovascular mortality			
15%	0.39	51.7	74.7
20%	0.70	33.4	87.5
25%	0.94	21.4	93.7
All-cause mortality			
25%	0.57	39.6	84.0
30%	0.78	27.8	90.8
35%	0.97	19.1	94.8

Online Figure 1: Correlation between variables belonging to each group (Panel A, comorbidities; Panel B, cardiac function) and thoracic aortic calcification (TAC). The size and color of the circles represent the direction and the strength of the correlations.

Panel A

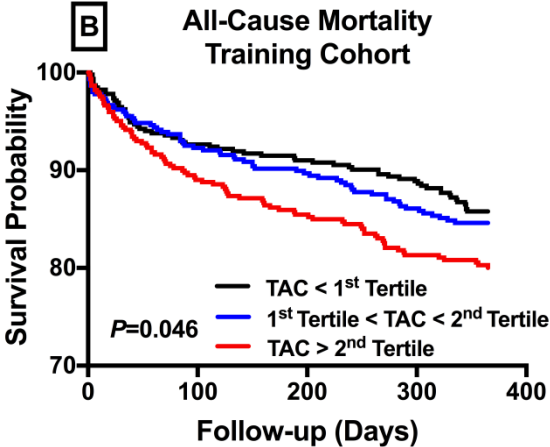
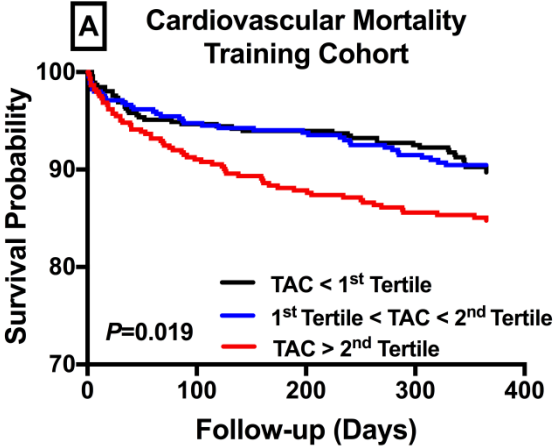


Panel B

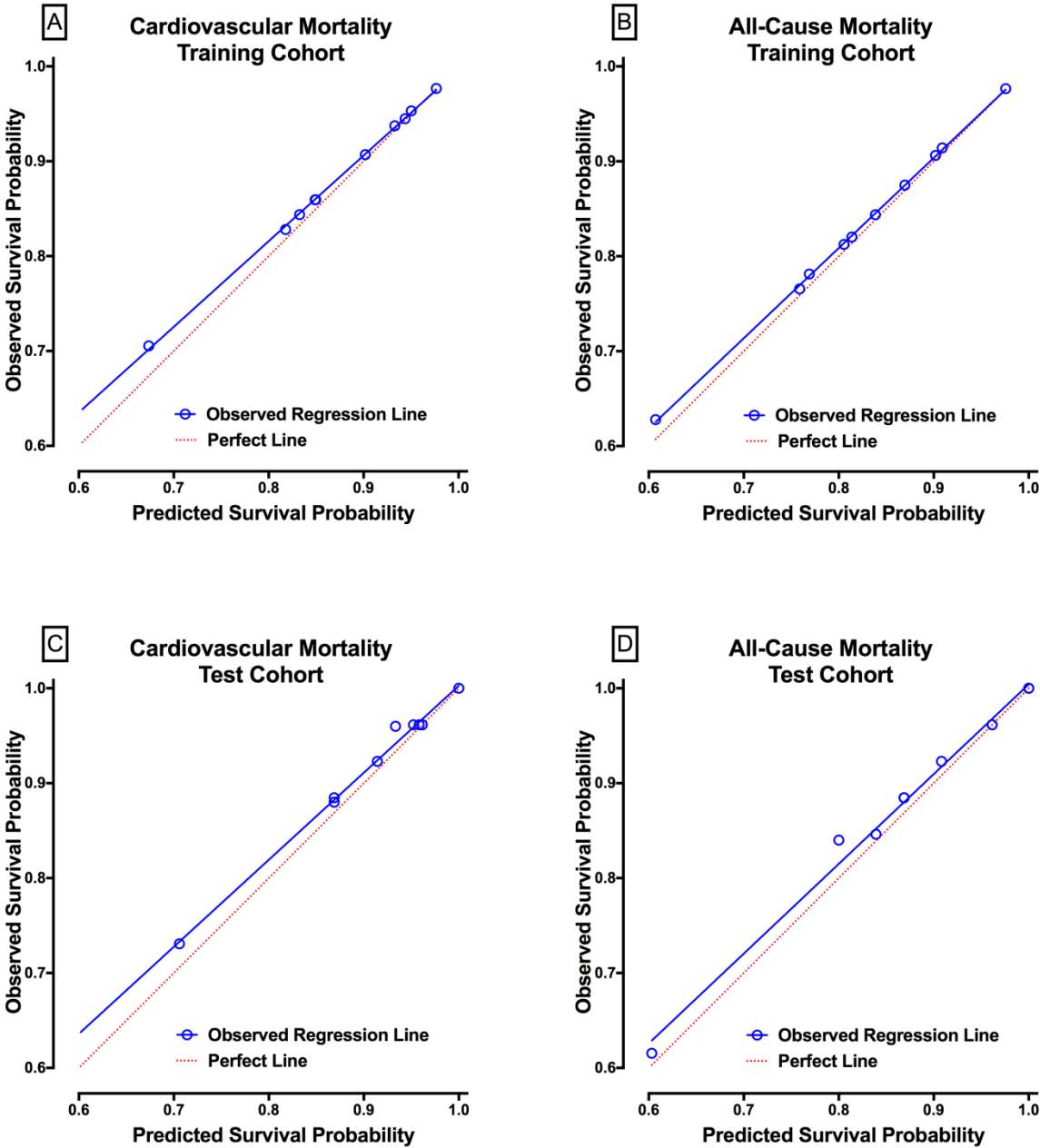


BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; TAC, thoracic aortic calcification.

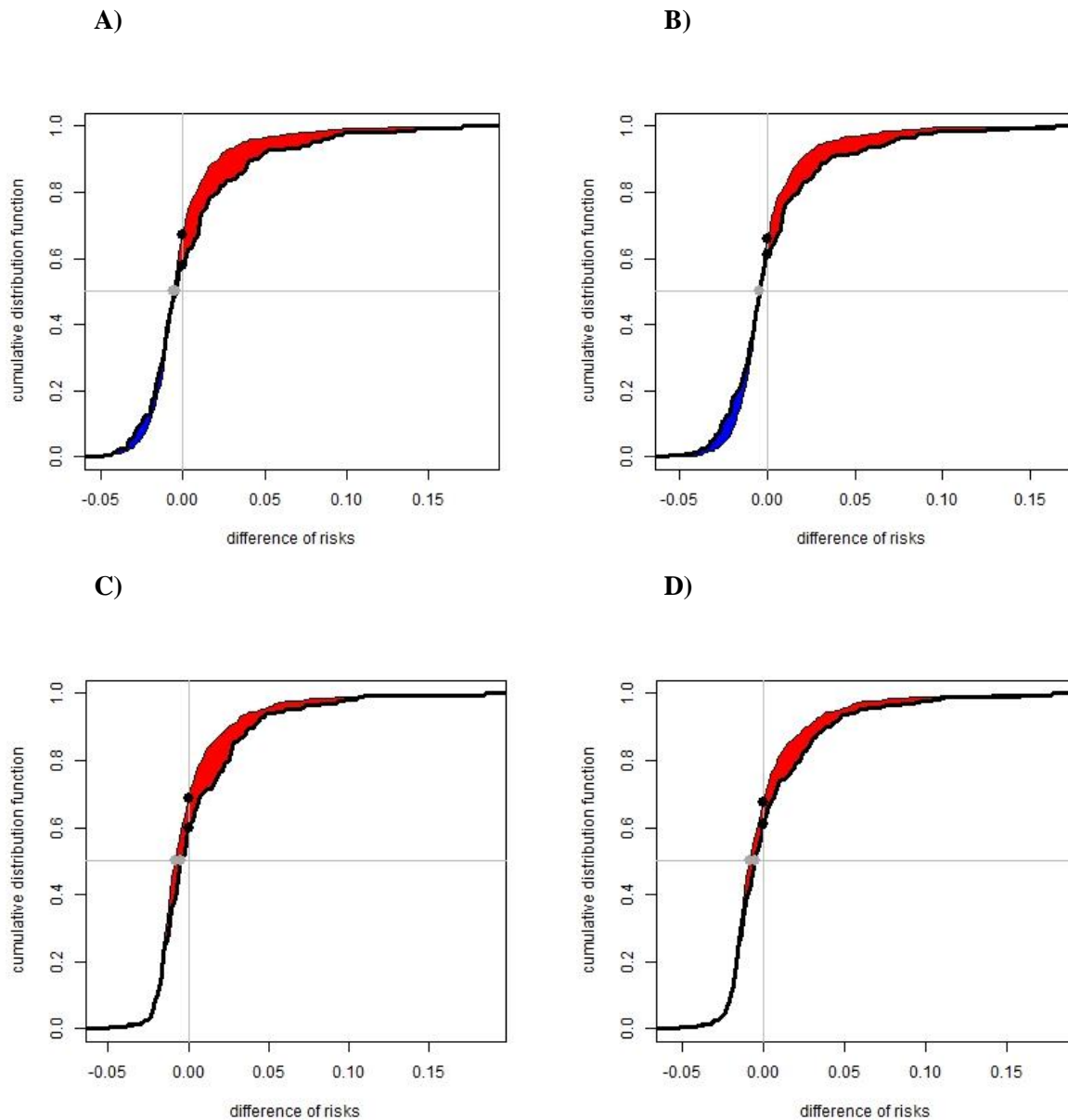
Online Figure 2: Survival curves according to TAC stratified into tertiles



Online Figure 3: Calibration of the final Cox models including the 3 groups of factors and the thoracic aortic calcifications (TAC) for predicting cardiovascular mortality and all-cause mortality on the training cohort (Panels A and B) and on the test cohort (Panels C and D).



Online Figure 4: Distribution of difference in predicted risk between the models with and without thoracic aortic calcification (TAC) in patients who experienced an event (thick line) and in patients without the event (thin line). Red areas correspond to predictive gain and blue areas to predictive loss. The integrated discrimination improvement index (IDI) represents the difference between the red and blue areas. Discrimination improvement with TAC is shown for the CAPRI score on A) cardiovascular mortality and B) all-cause death. Discrimination improvement with TAC for the Euroscore is shown for C) cardiovascular mortality and D) all-cause death.



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