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# **Role for Vascular Factors in Long-term Outcomes after Transcatheter Aortic Valve Implantation**

## **Running title: TAVI and outcomes**

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## Abstract

Despite major technological advances, one-year morbi-mortality after transcatheter aortic valve implantation (TAVI) is still high. Further outcome improvements may be obtained provided proper identification of prognostic factors. A change of prognostic value over time should be the hallmark of an outcome-implicated factor. In 1425 patients after TAVI, the examined prognostic factors were: demographic factors and comorbidities (age, male sex, glomerular filtration rate, and chronic obstructive pulmonary disease), cardiac function (left ventricular ejection fraction, pulmonary pressure, aortic gradient, dyspnea, and mitral regurgitation), and vascular factors (coronary artery disease, peripheral vascular disease (PVD), previous stroke, and thoracic aortic calcium --TAC-- as assessed by CT-scan). Cox models were used to analyze cardiovascular and all-cause mortalities over 3 years of follow-up. The time-dependent effects of the factors were analyzed using the distribution of Schoenfeld residuals. During the study period, 375 (26.3%) deaths occurred of whom 248 (17.4%) from cardiovascular causes. Only two factors associated with cardiovascular or all-cause mortality showed significant changes over time: dyspnea and PVD. The effect of dyspnea on cardiovascular mortality decreased over time (first- and third-year hazard ratios [95% confidence intervals]: 1.47 [1.10;1.96] and 0.94 [0.55;1.63], respectively), whereas the effect of PVD increased (first- and third-year hazard ratios: 0.87 [0.56;1.35] and 2.58 [1.25;5.33], respectively). TAC had a stable effect. In conclusion, the detrimental effects of vascular factors remained stable (TAC) or increased (PVD) over time. These factors should be targeted by specific measures to improve post-TAVI outcomes.

**Keywords:** Transcatheter aortic valve implantation, vascular disease, vascular compliance, risk factors.

## **Introduction**

In Europe and North America, aortic stenosis (AS) is the most common valvular disease requiring intervention <sup>1,2</sup>. With time, transcatheter aortic valve implantation (TAVI) has become the standard of care for severe AS in symptomatic patients at high surgical risk and is now also accepted in intermediate-risk symptomatic patients <sup>3</sup>. Yet, post-TAVI mortality is still high: around 20% at one year <sup>4</sup>. Identifying prognostic factors of late cardiovascular mortality is critical to design strategies able to improve post-TAVI long-term progression. Yet, identifying prognostic factors involved in aortic stenosis from simple risk markers is not easy. We raised the hypothesis that finding stability or change of factor prognostic values over time allows identifying those involved in the disease course. The aim of the present study was to determine the change over three years of the prognostic effects of three categories of predictors (comorbidities, cardiac, and vascular) on cardiovascular and all-cause mortality. Among the vascular predictors, a special attention was paid to thoracic aortic calcium (TAC) burden assessed by CT scan because it would be a significant predictor of short- <sup>5</sup> and long-term mortality<sup>6</sup>.

## **Methods**

C<sub>4</sub>CAPRI is a multicentric cohort that includes all patients treated by TAVI between 2010 and 2014 at three French university hospitals (Clermont-Ferrand, Lyon Croix-Rousse, and Rouen) and at Institut Cardiovasculaire Paris Sud (details in ref. <sup>5</sup>). One inclusion criterion was the availability of a preoperative CT scanner that allows TAC measurement. The study was approved by the Local Ethical Committee and by the Commission Nationale

Informatique et Liberté. All patients provided written informed consents to anonymous processing of their data.

Chronic kidney disease (CKD) was assessed by Cockcroft's estimated glomerular filtration rate (eGFR) expressed in five ordinal levels: 1:  $\geq 90$ ; 2: [60–90]; 3: [30–60]; 4: [15–30]; and 5:  $< 15$  mL/min/1.73 m<sup>2</sup>. Chronic obstructive pulmonary disease (COPD) was defined as chronic use of bronchodilators or corticosteroids for respiratory problems. Dyspnea was expressed according to the four levels of the NYHA functional classes. Preoperative left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography according to Simpson's method. Preoperative pulmonary pressure was expressed in mm Hg. A categorical variable was built to identify patients with unassessable pulmonary pressure. Preoperative aortic mean gradient was measured by Doppler and expressed in mm Hg. Preoperative mitral regurgitation level was graded according to the European guidelines<sup>7</sup> and expressed in five ordinal levels: 0: absence; 1: light; 2: mild; 3: moderate; and 4: severe. Peripheral vascular disease (PVD) was defined as intermittent claudication;  $> 50\%$  diameter stenosis or occlusion of a carotid artery; previous or planned intervention on the aorta, the lower limb arteries, or the carotid arteries; and previous amputation for arterial causes. Stroke or transient ischemic attack (TIA) was defined as history of stroke or TIA. Coronary artery disease was assessed by coronary angiography and expressed in two levels: 0: no lesion; 1: presence of at least one lesion inducing  $\geq 50\%$  luminal reduction. TAC was assessed by CT-scan and expressed in cm<sup>3</sup><sup>5</sup>. TAC included calcification of the aortic root, ascending aorta, arch, and descending aorta above the diaphragm.

The primary and secondary endpoints were respectively cardiovascular mortality and all-cause mortality at three years after TAVI. The vital status was obtained by phone contact with patients, relatives, caregivers, or physicians or by on-site planned visits. The cause of

death was classified as cardiac or non-cardiac by two different cardiologists blind to the patients' data according to the Valve Academic Research Consortium-2 (VARC2) consensus document <sup>8</sup>.

Quantitative variables were summarized as means  $\pm$  standard deviations (SD). Qualitative variables were summarized as frequencies (counts) and percentages. A univariable Cox model was fit to quantify the effect of each factor. Multivariable Cox models were built to model cardiovascular mortality rate and all-cause mortality rate according to the following known prognostic factors of long-term mortality after TAVI: demographic factors and comorbidities (age, male sex, eGFR, and COPD), cardiac function factors (LVEF, pulmonary pressure and unassessable pulmonary pressure, aortic mean gradient, dyspnea, and mitral regurgitation), and vascular factors (coronary artery disease, peripheral vascular disease, previous stroke or TIA, and TAC). All quantitative factors were considered as continuous variables. The linearity of each effect was assessed by checking its functional form. The change over three years of the effect of a prognostic factor was determined by analyzing the distribution of its scaled Schoenfeld residuals against time. At each failure time, Schoenfeld residuals correspond to the difference between the value of the covariate in patients experiencing the failure and the mean value of this covariate in at-risk patients <sup>9</sup>. A random distribution of the scaled residuals over time is in favor of a stable effect of the covariate. An increasing or decreasing pattern of the scaled residuals suggests a time-dependent effect of the covariate. This dependency was quantified and tested using the correlation coefficient of Pearson. For each covariate, the hazard ratios at one, two, and three years of follow-up were estimated with their 95% confidence intervals by adding an interaction term between that covariate and each year of follow-up in the Cox model. A time-dependent effect was considered statistically significant whenever it was associated with a p-value  $\leq 0.1$ . Statistical

analyses used R software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

Patients' characteristics at baseline are shown in Supplementary Table 1. The transfemoral approach was predominant (n=1005; 71%). The most frequently implanted valves were Edwards SAPIEN (n=891; 73%) and Medtronic CoreValve (n=326; 26.5%). Eighteen patients (1.3%) showed postoperative aortic regurgitation at discharge. The baseline pulmonary pressure was unassessable in 139 patients (9.8%). Over the first three years after TAVI, 375 deaths occurred (26.3%) of whom 248 from cardiovascular causes. Cardiac deaths as defined by the VARC-2 criteria represented 66% of all deaths.

Age, eGFR level, LVEF, pulmonary pressure, and dyspnea were significantly associated with both cardiovascular and all-cause mortality. The presence of PVD was significantly associated only with all-cause mortality. A 1-cm<sup>3</sup> increase in TAC was significantly associated with cardiovascular mortality (HR: 1.06; 95% CI: [1.03;1.10]) and all-cause mortality (1.05 [1.02;1.08]) (Supplementary Table 1).

In multivariable analysis, age and eGFR level were found significantly associated with cardiovascular and all-cause mortality, whereas COPD was significantly associated only with all-cause mortality (Table 1). Dyspnea and high pulmonary pressures were significantly associated with increases in cardiovascular and all-cause mortality. However, high preoperative mean gradients were associated with low mortality rates (Table 1). PVD was significantly associated with all-cause mortality, whereas TAC was significantly associated with both cardiovascular and all-cause mortality (Table 1).

The effects of demographic factors and comorbidities on cardiovascular mortality were not significantly time-dependent (Table 2). Among cardiac function factors, the deleterious prognostic effect of dyspnea decreased significantly over time (Table 2, Figure 1). Among vascular factors, the deleterious effect of PVD increased significantly over time (Table 2, Figure 1), whereas the deleterious effects of TAC was not significantly time-dependent (Table 2, Supplementary Figure 1). The effect of peripheral PVD was not found statistically significant during the first year of follow-up (adjusted HR estimated at 0.87 [0.56;1.35]; however, it increased over time to reach an adjusted HR estimated at 2.58 [1.25;5.33] during the third year of follow-up (Table 3). The adjusted HRs estimated for TAC over the three years of follow-up had close values.

The effects of demographic factors and comorbidities on all-cause mortality were not significantly time-dependent (Table 2, Figure 1). Concerning the cardiac function factors, the changes over time of the effects of dyspnea on all-cause mortality were similar to those found for cardiovascular mortality, whereas the deleterious effect of PVD did not increase significantly over time (Table 2, Figure 1).

## **Discussion**

TAVI has been a major breakthrough in AS management. Yet, the high post-operative mortality rates <sup>4</sup> requires a thorough identification of factors of poor outcome. The present analysis (changes in factor prognostic effects after TAVI) showed that PVD was the only factor whose prognostic value increased over time: its HR with cardiovascular mortality increased three times over three years. The prognostic value of most other prognostic factors, including TAC, remained stable. This suggests strongly that vascular factors are involved in late cardiovascular death after TAVI.



The long-term outcome after TAVI depends obviously on prosthesis-related and patient-related factors. Among the latter, the present study emphasized the prognostic value of TAC on late mortality. This agrees with a similar result obtained in a small group of patients<sup>6</sup>. History of PVD seemed to have also a strong prognostic factor but its prognostic value on cardiovascular mortality increased over time. These facts bring internal consistency regarding the prognostic effects of vascular factors, suggest that a longer exposure to these factors increases cardiovascular mortality, and support the hypothesis that vascular factors are involved in cardiovascular mortality after TAVI. It has been previously shown that medial calcifications (especially of the ascending thoracic aorta)<sup>10</sup> increase aortic stiffness<sup>6</sup>, increase then left ventricular after-load and remodeling and increase therefore the rate of cardiovascular events<sup>6</sup>. Late post-TAVI cardiovascular mortality may be at least partly explained by this impact on the left ventricle. Another explanation would be an increased risk related to diffuse atherosclerosis but, here, coronary artery disease and previous stroke or TIA were not significantly associated with poor post-TAVI outcome. Anyway, the present results confirm the previously suggested important role of the vascular status in post-TAVI mortality<sup>11</sup>.

Concerning the prognostic value of cardiac factors, the effect of dyspnea decreased over time; this may reflect a selection of patients with severe heart failure before intervention who died rapidly after TAVI. In accordance with previous reports on the poor prognostic effect of low-gradient AS, the aortic mean gradient had here a “protective effect” against late mortality<sup>12</sup>. This suggests that TAVI that relieves AS, solves also the valvular problem. The prognostic effects of LVEF on post-TAVI outcome are still controversial (18,19 vs 20). Here, LVEF was not found significantly associated with late cardiovascular mortality. Also, the prognostic value of MR level is still uncertain<sup>16</sup>. Here, preoperative moderate-to-severe MR was not associated with late mortality after TAVI. Finally, pulmonary hypertension had a

strong prognostic value on cardiovascular and all-cause mortality that did not decrease with time. This is consistent with previous results despite distinct interpretations related to the type of pulmonary hypertension<sup>17</sup>. As expected, age, COPD, and eGFR level were found strongly associated with long-term cardiovascular and all-cause mortality<sup>18–22</sup>; their prognostic values remained generally stable over time, which is consistent with their contribution to late post-TAVI outcome.

The late outcome after TAVI was found linked with vascular factors. These factors may thus be targets for new treatment strategies. Interestingly AS, aortic calcifications, and the presence of peripheral vascular disease share the same histopathological mechanisms; i.e., atherosclerosis, inflammation, hemodynamic factors and, active calcification<sup>23</sup>. Renin-angiotensin system (RAS) blockade has positive effects on major clinical outcomes, including survival of patients with AS or undergoing conventional surgery<sup>24</sup>; this may be mediated, at least partly, by the vascular benefit that optimizes ventricular-arterial coupling. Recently, post-TAVI RAS blockade was found associated with increased left ventricle mass index regression, reduced all-cause mortality<sup>25</sup>, and a trend towards decreased heart failure exacerbations during the first year after TAVI<sup>26</sup>. The results of a recently launched prospective randomized controlled trial<sup>27</sup> may corroborate the benefit of RAS blockade after TAVI.

First, the patients included 2010 to 2014 may not be similar to currently treated patients because of constant changes in the recommendations and recent studies on TAVI indications. Second, because of different CT-scan acquisition protocols between centers, it was impossible to investigate abdominal aortic calcifications (already shown to be strongly predictive of cardiovascular mortality after TAVI)<sup>6</sup>. Aortic thoracic calcifications are more related to aortic stiffening than abdominal calcifications whereas the latter are more related to

atherosclerotic load; having both conditions would allow differentiating the underlying mechanisms; atherosclerosis-related stiffness would lead to vascular damage and impact post-TAVI outcomes.

In conclusion, vascular factors exert probably detrimental effects on late cardiovascular mortality after TAVI. They are thus promising targets for treatment strategies aimed at decreasing post-TAVI mortality.

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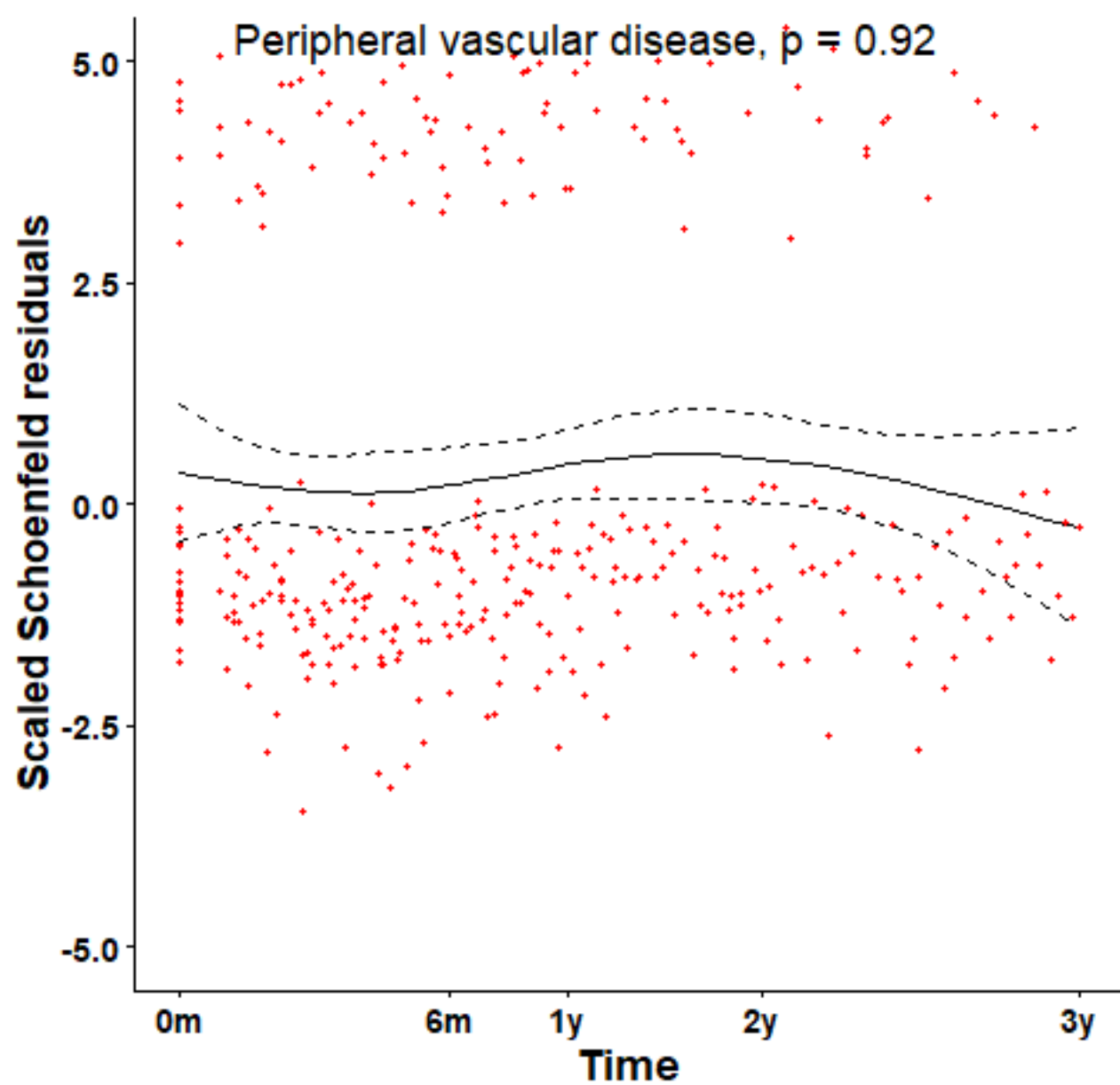
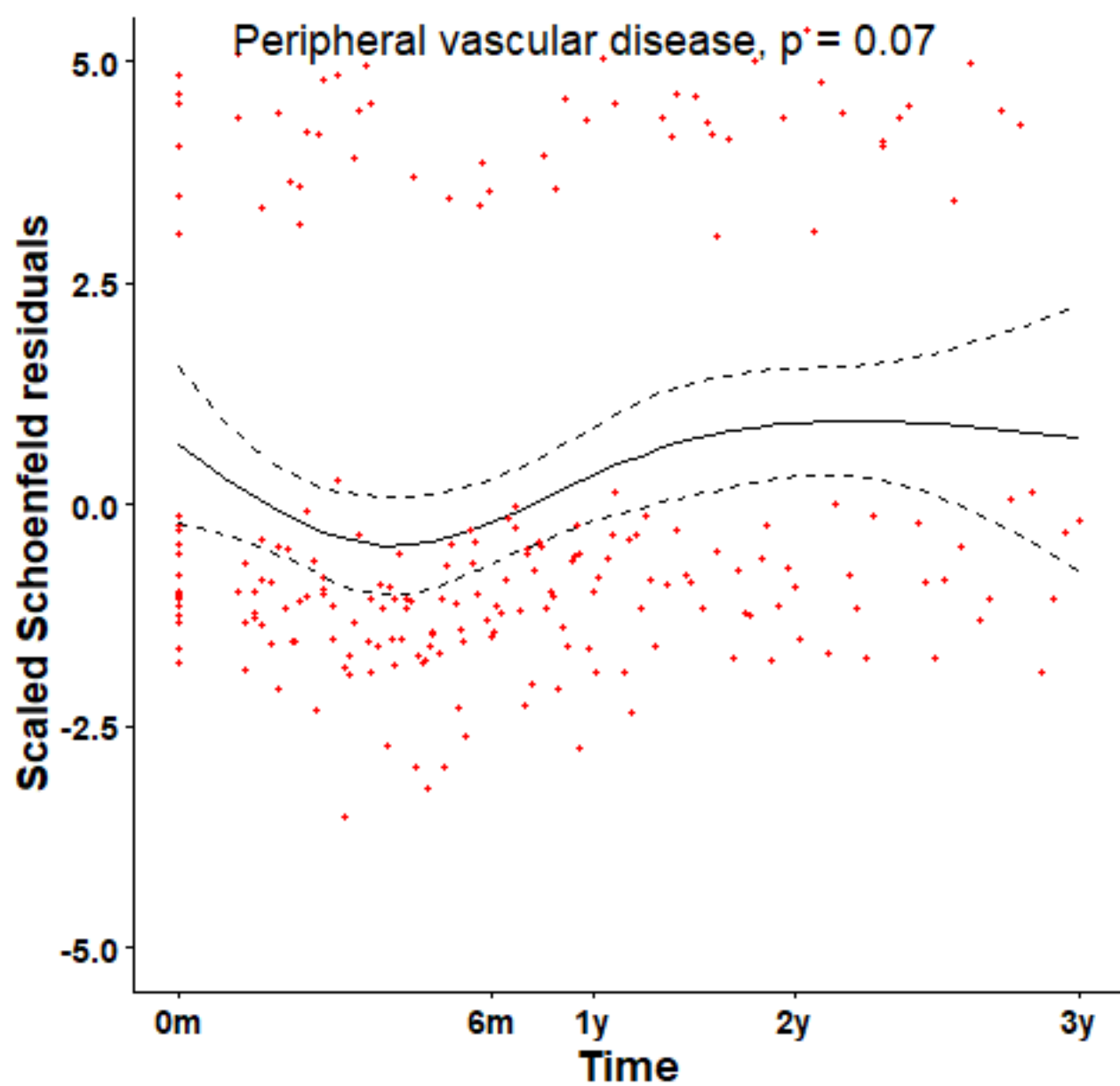
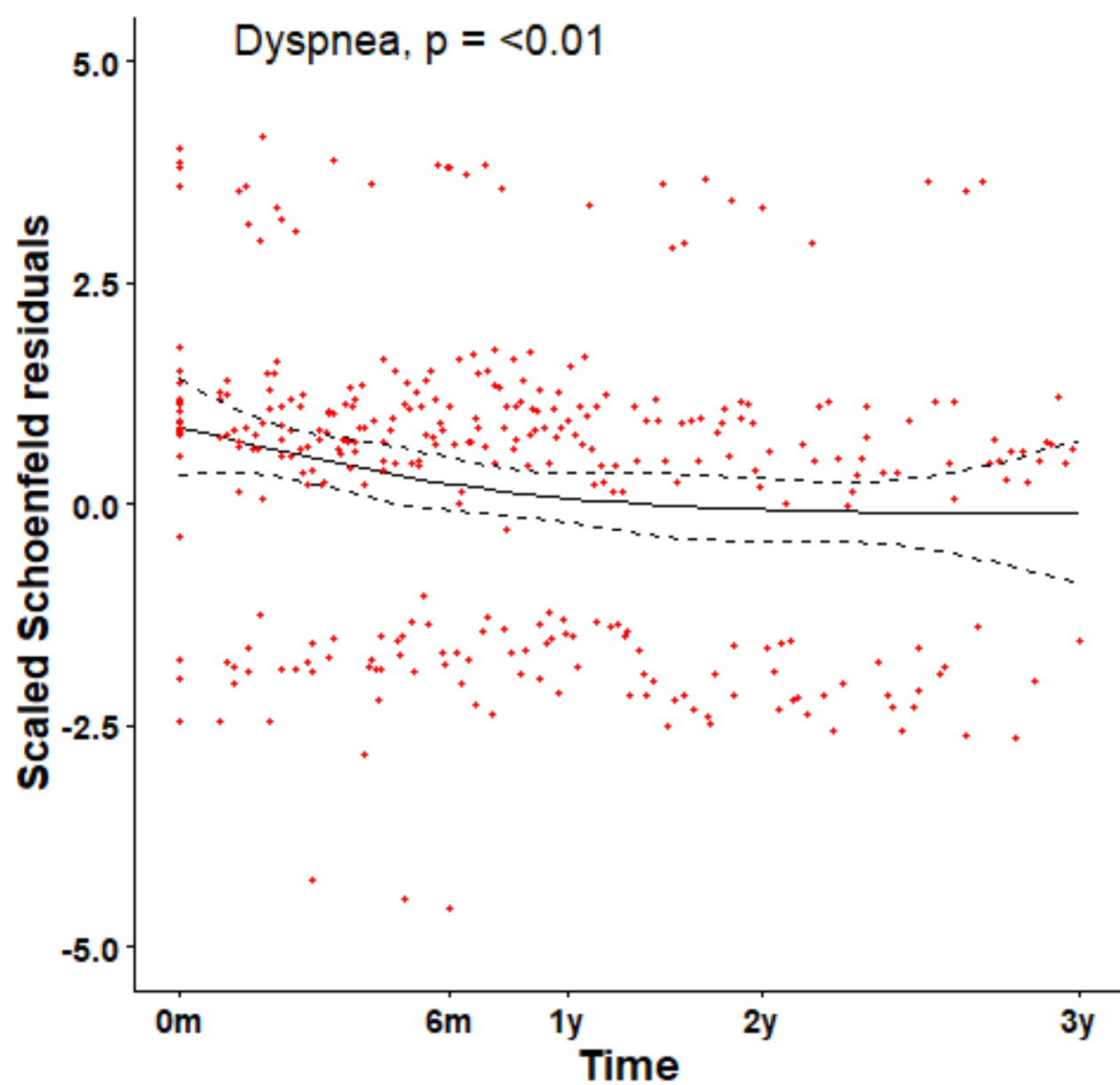
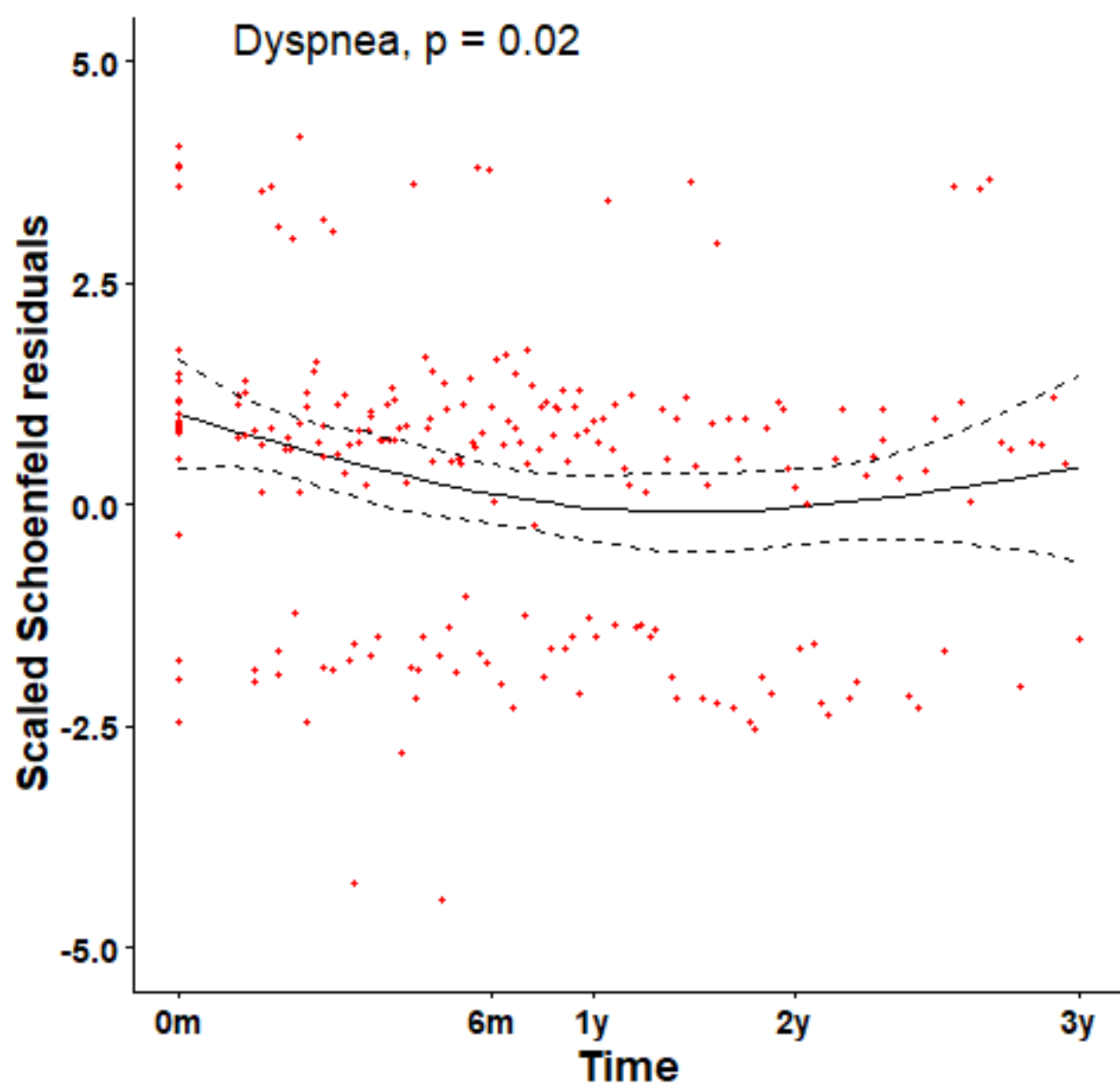
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### **Legends for Figure**

**Figure 1.** Plots of scaled Schoenfeld residuals against time of prognostic factors whose effects on mortality change significantly with time, dyspnea and peripheral vascular disease. (Left panels: cardiovascular mortality; right panels: all-cause mortality).

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**Table 1.** Effects of potential prognostic factors on cardiovascular and all-cause mortality: results of the multivariable Cox Model

Factors	3-year cardiovascular mortality		3-year all-cause mortality	
	Adjusted HR [95% CI]	p	Adjusted HR [95% CI]	p
Age (years)	1.03[1.01;1.05]	0.02	1.03[1.01;1.05]	<0.01
Men	1.03[0.77;1.36]	0.86	1.06[0.84;1.34]	0.61
eGFR level*	1.27[1.05;1.53]	0.01	1.28[1.10;1.49]	<0.01
Chronic obstructive pulmonary disease	1.30[0.95;1.79]	0.10	1.29[1.00;1.68]	0.05
Left ventricle ejection function (%)	0.99[0.98;1.00]	0.15	0.99[0.98;1.00]	0.04
Pulmonary pressure (10 mm Hg)	1.10[1.01;1.21]	0.04	1.10[1.02;1.19]	0.01
Unknown pulmonary pressure	1.64[0.85;3.14]	0.14	1.85[1.10;3.09]	0.02
Preoperative aortic mean gradient (10 mm Hg)	0.92[0.84;1.00]	0.06	0.91[0.85;0.98]	0.01
Dyspnea †	1.37[1.10;1.71]	<0.01	1.29[1.08;1.54]	<0.01
Preoperative MR level ‡	0.95[0.76;1.15]	0.59	0.98[0.84;1.14]	0.75
Coronary artery disease	0.93[0.71;1.23]	0.61	1.00[0.80;1.24]	0.97
Peripheral vascular disease	1.25[0.91;1.71]	0.17	1.34[1.04;1.72]	0.03
Previous stroke or TIA	1.09[0.70;1.71]	0.69	0.92[0.63;1.36]	0.68
Total aortic calcification volume (cm <sup>3</sup> )	1.06[1.02;1.10]	<0.01	1.04[1.01;1.08]	<0.01

eGFR, Cockcroft's estimated glomerular filtration rate; MR, mitral regurgitation; TIA, transient ischemic attack

\* eGFR in five ordinal levels: 1:  $\geq 90$ ; 2: [60–90]; 3: [30–60]; 4: [15–30]; and 5:  $<15$  mL/min/1.73 m<sup>2</sup>

† Dyspnea in the four ordinal levels of NYHA.

‡ Mitral regurgitation in five ordinal levels: 0: absence; 1: light; 2: mild; 3: moderate; and 4: severe.

**Table 2.** Stability of the effects of the prognostic factors on cardiovascular and all-cause mortality: estimates of the correlations between the scaled Schoenfeld residuals and time

Factors	3-year cardiovascular mortality		3-year all-cause mortality	
	Correlation coefficient of Pearson	P	Correlation coefficient of Pearson	P
Age (years)	-0.01	0.92	-0.001	0.98
Men	-0.02	0.81	-0.03	0.58
eGFR level*	-0.04	0.53	-0.08	0.14
Chronic obstructive pulmonary disease	-0.04	0.58	0.02	0.76
Left ventricle ejection function (%)	0.06	0.41	0.04	0.47
Pulmonary pressure (mm Hg)	-0.01	0.90	-0.05	0.30
Unknown pulmonary pressure	0.01	0.93	-0.04	0.49
Aortic mean Gradient (mm Hg)	-0.05	0.44	-0.06	0.25
Dyspnea †	-0.16	0.02	-0.16	<0.01
Preoperative MR level ‡	0.06	0.37	0.04	0.46
Coronary artery disease	-0.01	0.92	-0.06	0.31
Peripheral vascular disease	0.12	0.07	0.01	0.92
Previous stroke or TIA	-0.07	0.32	-0.06	0.23
Total aortic calcification volume (cm <sup>3</sup> )	0.03	0.68	0.03	0.57

eGFR, Cockcroft's estimated glomerular filtration rate; MR, mitral regurgitation; TIA, transient ischemic attack

\*eGFR in 5 ordinal levels: 1:  $\geq 90$ ; 2: [60–90]; 3: [30–60]; 4: [15–30]; 5: <15 mL/min/1.73 m<sup>2</sup>

† Dyspnea in 4 ordinal levels of NYHA

‡ Mitral regurgitation in 5 ordinal levels: 0: absence; 1: light; 2: mild; 3: moderate; 4: severe

**Table 3.** Estimates of the hazard ratios for each year of follow-up of factors whose effects on mortality change significantly with time

Factor	Cardiovascular mortality			All-cause mortality		
	First year	Second year	Third year	First year	Second year	Third year
Dyspnea	1.47 [1.10;1.96]	0.99 [0.60;1.62]	0.94 [0.55;1.63]	1.45 [1.14;1.84]	1.19 [0.80;1.77]	0.75 [0.51;1.11]
Peripheral vascular disease	0.87 [0.56;1.35]	1.78 [0.90;3.52]	2.58 [1.25;5.32]	1.33 [0.96;1.84]	1.37 [0.76;2.46]	1.29 [0.71;2.36]
TAC (cm <sup>3</sup> )	1.06 [1.01;1.11]	1.07 [0.98;1.16]	1.09 [0.99;1.21]	1.04 [1.00;1.08]	1.02 [0.94;1.10]	1.07 [0.99;1.16]

Values are Adjusted HR [95% CI]; Dyspnea in four ordinal levels of NYHA; TAC, thoracic aortic calcification volume; cm<sup>3</sup>, cubic centimeter.