

## SUPPLEMENTAL MATERIALS

# Refined Staging Classification of Cardiac Damage Associated with Aortic Stenosis and Outcomes after Transcatheter Aortic Valve Intervention

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## **TABLE OF CONTENTS**

<b>SUPPLEMENTARY TABLE 1. DIFFERENCE BETWEEN THE ORIGINAL AND MODIFIED STAGING CLASSIFICATION OF CARDIAC DAMAGE .....</b>	<b>3</b>
<b>SUPPLEMENTARY TABLE 2. ECHOCARDIOGRAPHIC AND INVASIVE DATA ACCORDING TO STAGE OF CARDIAC DAMAGE .....</b>	<b>4</b>
<b>SUPPLEMENTARY TABLE 3. SENSITIVITY ANALYSIS: CLINICAL OUTCOMES AT 1 YEAR IN PATIENTS UNDERWENT TAVI AFTER SEPTEMBER 2012 .....</b>	<b>6</b>
<b>SUPPLEMENTARY TABLE 4. CLINICAL OUTCOMES AT 1 YEAR IN PATIENTS WHO WERE UNCATEGORIZED TO ANY OF THE SUB-GROUPS IN STAGE 4.....</b>	<b>7</b>
<b>SUPPLEMENTARY TABLE 5. CLINICAL OUTCOMES AT 1 YEAR ACCORDING TO THE REFINED CARDIAC STAGING SYSTEM (FIGURE 4) .....</b>	<b>8</b>

**Supplementary Table 1. Difference between the original and modified staging classification of cardiac damage**

<b>Original Staging System</b>	<b>Modified Staging System</b>
<b>Stage 1 (LV Damage)</b>	<b>Stage 1 (LV Damage)</b>
LV hypertrophy (LV mass index >115 g/m <sup>2</sup> Male, >95 g/m <sup>2</sup> Female)	LV hypertrophy (LV mass index >115 g/m <sup>2</sup> Male, >95 g/m <sup>2</sup> Female)
LV diastolic dysfunction (E/e' >14)	LV diastolic dysfunction (Grade ≥2* <sup>1</sup> )
LV systolic dysfunction (LVEF <50%)	Subclinical LV systolic dysfunction (LVEF<60%)
<b>Stage 2 (LA/Mitral valve Damage)</b>	<b>Stage 2 (LA/Mitral valve Damage)</b>
LA dilation (LAVi >34mL/m <sup>2</sup> )	LA dilation (LAVi >34mL/m <sup>2</sup> )
Mitral regurgitation ≥moderate	Mitral regurgitation ≥moderate
Atrial fibrillation	Atrial fibrillation
<b>Stage 3 (Pulmonary vasculature/Tricuspid valve Damage)</b>	<b>Stage 3 (Pulmonary vasculature/Tricuspid valve Damage)</b>
Pulmonary hypertension (Systolic PAP ≥60mmHg)	Pulmonary hypertension (Systolic PAP ≥60mmHg or Mean PAP≥25mmHg)
Tricuspid regurgitation ≥moderate	Tricuspid regurgitation ≥moderate
<b>Stage 4 (RV Damage)</b>	<b>Stage 4 (RV Damage/Low-flow state)</b>
Moderate to severe RV systolic dysfunction (visually assessed)	RV systolic dysfunction (quantitatively assessed)* <sup>2</sup>
	Moderate-to-severe low-flow (SVi <30ml/m <sup>2</sup> )
* LV diastolic dysfunction (grade ≥II) and RV dysfunction (quantitatively assessed) were defined in accordance with the guideline recommendations.	

LV = left ventricular; LVEF = left ventricular ejection fraction; LA = left atrial; PAP = pulmonary artery hypertension; RV = right ventricular; SVi = stroke volume index.

**Supplementary Table 2. Echocardiographic and Invasive data according to stage of cardiac damage**

	<b>Total population</b>	<b>Stage 0 or 1</b>	<b>Stage 2</b>	<b>Stage 3</b>	<b>Stage 4</b>	<b>p-value</b>
	N = 1156	N = 52	N = 105	N = 278	N = 721	
<b>LV systolic function</b>						
LVEF (%)	53.6 ± 15.1	60.5 ± 10.5	57.9 ± 12.5	57.7 ± 12.5	50.8 ± 15.9	<0.001
Stroke volume index (ml/m <sup>2</sup> )	29.1 ± 9.9	35.8 ± 8.1	36.6 ± 9.6	32.8 ± 8.0	25.9 ± 9.4	<0.001
<b>LV diastolic function</b>						
Average E/e' ratio	21.0 ± 11.3	16.5 ± 7.7	17.7 ± 9.2	21.6 ± 11.4	21.8 ± 11.8	0.007
TR velocity (m/s)	2.87 ± 0.58	2.51 ± 0.70	2.66 ± 0.55	2.98 ± 0.51	2.88 ± 0.59	<0.001
LA volume index (ml/m <sup>2</sup> )	43.5 ± 21.2	26.5 ± 5.3	46.5 ± 13.8	42.3 ± 15.9	44.9 ± 24.1	<0.001
LV mass index (g/m <sup>2</sup> )	143.6 ± 49.2	125.9 ± 45.5	152.0 ± 55.2	139.9 ± 42.4	145.4 ± 50.8	0.010
<b>RV function</b>						
TAPSE (mm)	19.2 ± 5.8	23.0 ± 4.4	23.5 ± 4.6	22.6 ± 4.5	16.9 ± 5.3	<0.001
DTI (S') velocity (cm/s)	11.9 ± 3.2	14.1 ± 4.0	13.3 ± 2.5	13.1 ± 2.53	11.0 ± 3.2	<0.001
FAC (%)	40.9 ± 10.7	44.4 ± 7.9	46.2 ± 9.2	44.6 ± 8.8	38.1 ± 11.0	<0.001
<b>Valvular abnormality</b>						
Mitral regurgitation moderate or severe	238 (21.0%)	0 (0.0%)	14 (13.3%)	48 (17.4%)	176 (25.0%)	<0.001

Tricuspid regurgitation moderate or severe	165 (14.5%)	0 (0.0%)	0 (0.0%)	39 (14.1%)	126 (17.9%)	<0.001
<b>Pulmonary artery pressure</b>						
Systolic PAP	49.6 ± 16.6	32.0 ± 6.8	35.4 ± 7.5	53.2 ± 14.1	51.7 ± 17.2	<0.001
Mean PAP	31.9 ± 11.8	18.3 ± 4.5	18.9 ± 3.8	33.9 ± 9.4	33.9 ± 12.1	<0.001
LV = left ventricular; LVEF = left ventricular ejection fraction; TR = tricuspid regurgitation; LA = left atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; DTI = doppler tissue imaging; FAC = fractional area change; PAP = pulmonary artery pressure.						

**Supplementary Table 3. Sensitivity analysis: clinical outcomes at 1 year in patients underwent TAVI after September 2012**

	<b>Stage 0</b>	<b>Stage 1</b>	<b>Stage 2</b>	<b>Stage 3</b>	<b>Stage 4</b>	<b>linear trend Hazard Ratio/Odds Ratio (95% CI)</b>	<b>p-value**</b>
	N = 14	N = 23	N = 66	N = 162	N = 447		
All-cause death (n, %)	1 (7.7)	1 (4.3)	7 (10.7)	16 (9.9)	69 (15.6)	1.36 (1.03-1.79)	0.030
Cardiovascular death (n, %)	0 (0.0)	0 (0.0)	5 (7.7)	7 (4.4)	47 (10.9)	1.72 (1.13-2.61)	0.011
The Kaplan-Meier estimated event rates and hazard ratios with 95% confidence intervals are provided.							
*p-values for a linear trend.							

**Supplementary Table 4. Clinical outcomes at 1 year in patients who were uncategorized to any of the sub-groups in Stage 4**

	<b>Un-subclassified (Stage 4)</b>
	N = 135
All-cause death (n, %)	17 (12.8)
Cardiovascular death (n, %)	9 (7.1)
Myocardial infarction (n, %)	0 (0.0)
Disabling stroke (n, %)	2 (1.6)
Major/life-threatening bleeding (n, %)	30 (22.5)

**Supplementary Table 5. Clinical outcomes at 1 year according to the refined cardiac staging system (Figure 4)**

	Early stage	Transitional Stage	Advanced Stage	Linear trend Hazard Ratio/Odds Ratio (95% CI)	p-value**
	N=52	N = 580	N = 552		
All-cause death (n, %)	2 (3.9)	58 (10.1)	122 (22.4)	2.41 (1.80-3.22)	<0.001
Cardiovascular death (n, %)	0 (0.0)	34 (6.0)	90 (16.9)	3.19 (2.18-4.67)	<0.001
NYHA III or IV (n, %)*	3/ 49 (6.1)	58/494 (11.7)	66/396 (16.7)	1.57 (1.12-2.19)	0.009

The Kaplan-Meier estimated event rates and hazard ratios with 95% confidence intervals are provided.

\*Numbers of patients with NYHA III or IV/numbers of patients assessed at 1 year and odds ratios with 95% confidence intervals are provided.

\*\*p-values for a linear trend.

Patients were hierarchically classified into the most advanced stage if at least one of the following criteria was met within that stage: advanced stage – RV dysfunction or severe pulmonary hypertension; transitional stage – low-flow state, mild or moderate pulmonary hypertension;  $\geq$ moderate tricuspid regurgitation, atrial fibrillation,  $\geq$ moderate mitral regurgitation, or LA dilatation; early stage – no cardiac damage, LVEF <60%, LV diastolic dysfunction  $\geq$ grade II, or LV hypertrophy (Figure 4).