EuPreCHO Appendix 02 - Endpoint definitions

1. Definition of major pathologies in TTE

The endpoint will be a composite of major pathologies in preoperative TTE that may be reasonably expected to change perioperative management, including moderate-severe left ventricular systolic dysfunction [1], severe (Grade II or more) left ventricular diastolic dysfunction [2], severe right ventricular dysfunction and/or pulmonary hypertension [3], and severe left-sided valvulopathy [4, 5].

Detailed definitions are reported in the tables below.

Major Pathology	Defining criteria
Moderate-severe left ventricular systolic dyfunction	- decreased contractility (LVEF ≤40% [6, 7] by Simpson's method or eyeballing) or based on corresponding qualitative statement in TTE report (e.g. "severe reduction"); and/or - any new (or previously undocumented) regional wall motion abnormalities (RWMA) on visual or myocardial strain analysis in conjunction with at least mildly reduced LVEF (41-49%) [1, 6, 7]
Significant (Grade II or more) LV diastolic dysfunction with evidence of increased LV filling presssures	- E/A ≥2 [8] OR -E/A ≤0.8 + E>50cm/sec AND at least ≥ 2 additional criteria (Average E/e' ratio >14, peak TR velocity >2,8 m/sec, LA volume index >34 mL/m2) [8] OR -E/A >0.8 to <2 AND at least ≥ 2 additional criteria (Average E/e' ratio >14, peak TR velocity >2,8 m/sec, LA volume index >34 mL/m2) [8] or based on corresponding diagnosis in TTE report
Significant RV dysfunction	-RV failure phenotype defined as a dilated (RV:LV>0.6) and increased CVP (>8mmHg) or a dilated IVC with no or small respiratory variations during spontaneous breathing - Chronic cor pulmonale defined as a hypertrophic right ventricle with increased SPAP - Acute cor pulmonale defined as a dilated RV (RV:LV>0.6) and paradoxical septal motion, OR - RV dysfunction phenotype (defined as any one or more of tricuspid annular plane systolic excursion (TAPSE) <17mm, RV fractional area change <35%, RV free-wall strain, peak systolic (S') velocity of tricuspid

	annulus (<9.5 cm/s) measured with tissue Doppler, RV free wall strain > -20%) [3, 9] AND at least one sign of RV failure or increased SPAP [3] or based on corresponding diagnosis in TTE report *Significant pulmonary hypertension* is defined as peak tricuspid regurgitant velocity >2.8m/sec + additional echocardiographic signs of RV dysfunction [3] or based on corresponding diagnosis in TTE report
Severe left-sided valvulopathies	1) clinically significant mitral stenosis [4, 5], 2) severe mitral regurgitation [5] 3) severe aortic stenosis [5], 4) severe aortic valve regurgitation [4, 5] According to diagnostic criteria below, or based on obvious anatomical abnormalities with colour Doppler suggesting major changes in flow [10], or based on corresponding diagnosis in TTE report

NOTE: if quantitative measures are not reported but the TTE report includes qualitative descriptions, the endpoint will be adjudicated based on the use of "severe", "major", "markedly", or corresponding wording when referring to the various pathologies. Examples: restrictive LV filling pattern indicating markedly elevated LAP; Grade III (marked elevation in filling pressure) [2], "clinically relevant mitral stenosis" [5]….

1.1. Criteria for clinically significant mitral stenosis (moderate-severe):

- mitral valve area ≤1.5 cm2 [5]

1.2. Criteria for severe mitral regurgitation [5]:

	Primary mitral regurgitation	Secondary mitral regurgitation
Qualitative		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic/dense/triangular	Holosystolic/dense/triangular
Semiquantitative		
Vena contracta width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (2D PISA, mm^2)	≥40 mm^2	≥40 mm^2 (may be ≥30 mm^2 if elliptical regurgitant orifice area)
Regurgitant volume (mL/beat)	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
Regurgitant fraction (%)	≥50%	≥50%
Structural		
Left ventricle	Dilated (ESD ≥40 mm)	Dilated
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m^2)	Dilated

1.3. Criteria for severe aortic stenosis [5]:

- High-gradient aortic stenosis mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s and valve area ≤1.0 cm2 (or ≤0.6 cm2/m2);
- High-flow, low-gradient aortic stenosis with mean gradient <40mmHg and SVi>35ml/m2 (https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Aortic-valve-stenosis-evaluation-and-management-of-patients-with-discordant-grading)
- Low-flow, low-gradient aortic stenosis with reduced ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm2, LVEF<50%, SVi ≤35 mL/m2);
- Low-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm2, LVEF ≥50%, SVi ≤35 mL/m2) and exclusion of other explanation for findings

1.4 Criteria for severe aortic regurgitation

Qualitative	
Valve morphology	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet area[a]	Large in central jets, variable in eccentric jets
CW signal of regurgitant jet	Dense
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)
Semiquantitative	
Vena contracta width (mm)	>6
Pressure half-time[b] (ms)	<200
Quantitative	
EROA (mm^2)	≥30
Regurgitant volume (mL/beat)	≥60
Enlargement of cardiac chambers	LV dilatation

2. Definition of components of perioperative management

Intensified perioperative management will be defined as one or more of the following:

- discussion in preoperative multidisciplinary board and derived decisions (e.g. technique? modifications, cancellations, postponing of scheduled procedure),
- changes in cardiovascular medication,
- cardiological workup (cardiac MRI, CCT, stress-imaging, coronary angiography, PCI, valvuloplasty or TAVI),

- invasive or advanced intraoperative haemodynamic monitoring (arterial line, central venous line, pulmonary arterial catheter, intraoperative TEE, PiCCO (Pulse index Continuous Cardiac Output) or other devices for cardiac output estimation
- goal-directed haemodynamic management (as per locally implemented protocol),
- anaesthesia technique,
- planned ICU/IMC admission or planned extended PACU stay
- postoperative troponin monitoring

3. Definition of disability free survival and other clinical endpoints

3.1. Disability-free survival at 30 days

Disability will be assessed using the WHODAS 2 questionnaire. The WHO assigns significant disability in presence of a WHODAS score of 25% [16, 17]. For calculation of the 12-item WHODAS score, the ordinal categories of Likert scale for each item will be assigned numerical values (none=0 to extreme=4) for a total maximal score of 48 and transformed into the percentage of maximal disability score as published [18].

3.2. Secondary endpoint at 30 days

Endpoint	**Definition**
All-cause mortality	Death of any cause
Major adverse cardiac events	Composite of cardiac death, myocardial infarction, cardiac arrest, coronary revascularization [11], and acute heart failure or decompensated chronic heart failure.
Cardiac Death	Death with a vascular cause and including death after a myocardial infarction, cardiac arrest, and cardiac revascularisation procedure [11].
Myocardial infarction	According to the 4th universal definition [12]: The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a **rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following**: • Symptoms of myocardial ischaemia; • New ischaemic ECG changes;

	• Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; • Identification of a coronary thrombus by angiography or autopsy Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for MI. <u>For coronary artery procedure- related MI the following applies:</u> Coronary procedure-related MI ≤ 48 hours after the index procedure is defined by an elevation of cTn values > 5 times after PCI and > 10 times after CABG of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following: • New ischaemic ECG changes (this criterion is related to MI after PCI only); • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. Isolated development of new pathological Q waves meets the criteria after PCI or CABG if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG. Other types of procedure-related MI include stent thrombosis and in-stent restenosis that meet the criteria above.

	Post-mortem demonstration of a procedure-related thrombus meets the MI criteria. NOTE: a systematic troponin screening after surgery is not mandated in the study.
Acute heart failure or decompensation of chronic heart failure	***Inhospital:*** signs of congestion and/or of peripheral hypoperfusion considered of cardiac origin by attending physician and severe enough to trigger initiation or intensification of treatment or documented physician´s diagnosis in the medical charts. ***After discharge***: onset of symptoms and/or signs of HF (signs of congestion and/or of peripheral hypoperfusion), severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit Signs of congestion include: peripheral oedema, dyspnoea with orthopnoea, respiratory failure (hypoxaemia-hypercapnia), tachypnoea and increased work of breathing, elevated jugular venous pressure, respiratory rales/crackles, crepitations, vascular redistribution/interstitial/alveolar pulmonary edema in chest x-ray. Signs of hypoperfusion include: cold sweaty extremities, oliguria, mental confusion, dizziness, narrow pulse pressure, biochemical manifestations of hypoperfusion (elevated serum creatinine, metabolic acidosis and elevated serum lactate) [6]
Nonfatal cardiac arrest	Successful resuscitation from documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation [11] or documented physician´s diagnosis of nonfatal cardiac arrest in the clinical records.
Coronary revascularization	Percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery [11]
Complication Clavien-Dindo Class [13] NOTE: all classes are collected, only class ≥ 3 represent an endpoint	*Grade I* Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and

	physiotherapy. This grade also includes wound infections opened at the bedside. *Grade II* Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. *Grade III* Requiring surgical, endoscopic or radiological intervention III a: intervention not under general anesthesia III b: intervention under general anesthesia *Grade IV* Life-threatening complicationrequiring intermediate care/intensive care unit-management IV a: single organ dysfunction (including dialysis) IVb: multi organ dysfunction *Grade V* Death
ICU/IMC (re)admission	Unplanned postoperative admission to ICU/IMC (first admission or unplanned admission after discharge from planned ICU/IMC admission)
Length of ICU/IMC stay	Reported in days. In case of readmission the cumulative stay in ICU will be considered.
Days-alive-and-out-of-hospital (DAOH)	DAOH at X days (DAOHx) is calculated from the day of the index procedure as: X- length of stay of index hospitalization (in days) – length of stay of any subsequent readmissions in days (including planned readmissions). If a patient died during the follow-up time X, his DAOHX will be set at 0 independent of any time spent at home [14]

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