EuPreCHO - Appendix 01 – Protocol Synopsis

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Project Title:	EuPreCHO: European study on perioperative management and outcome following Preoperative Transthoracic Echocardiography in noncardiac surgery patients.
Short Title :	EuPreCHO
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Protocol Version and Date:	Version 1.0 Date 17MAY2024
Project design:	International, prospective case control study
Background and Rationale:	In August 2022 the European Society of Cardiology (ESC) published updated guidelines including recommendations on preoperative transthoracic echocardiography (TTE). The update resulted in broadened criteria for preoperative TTE. The impact of preoperative TTE on outcome is controversial and underlying evidence was mostly derived from administrative databases. There is also a knowledge gap in terms of what changes in perioperative management are derived from TTE information in current daily practice and what their impact on outcome may be. Further, a secondary analysis in a large international cohort suggests that the criteria used in the ESC guidelines to recommend TTE may not be efficient.

Objective(s):	**Main objective:** EuPreCHO aims at answering the following 3 research questions (RQ) in patients undergoing intermediate and high-risk noncardiac surgery : 1. what factors enhance the prediction of major pathologies in preoperative TTE? 2. does the perioperative management of patients evaluated with vs without preoperative TTE differ in current clinical practice? 3. does the outcome of patients evaluated with vs without preoperative TTE differ in current clinical practice? **Secondary objectives:** To evaluatee if NTproBNP information compared to troponin information contributes to the prediction of major pathologies detected on preoperative TTE.
Outcomes(s):	**RQ1:** major pathologies in TTE consisting in • Moderate-severe left ventricular systolic dysfunction • Significant (Grade II or more) LV diastolic dysfunction with evidence of increased LV filling pressures • Significant right ventricular dysfunction • Severe left-sided valvulopathies **RQ2**: Primary endpoint will be intensified perioperative management 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), , • optimization of cardiovascular medication, • cardiac workup • invasive or advanced intraoperative haemodynamic monitoring • goal-directed haemodynamic management • anaesthesia technique • planned ICU/IMC admission or planned extended PACU stay. **RQ3**: Primary endpoint will be disability- free survival at 30 days (12-item WHODAS questionnaire). Secondary endpoints will be 30-day all-cause mortality, 30-day composite of all-cause death and myocardial infarction, 30-day major adverse cardiac events (cardiac death, myocardial infarction, cardiac arrest, coronary revascularization, acute heart failure/ decompensation of chronic heart failure), days-alive-and-out-of-hospital (DAOH) at 30 days, and in-hospital complications with Clavien-Dindo Class ≥3. Tertiary endpoints are ICU/IMC (re)-admission and length of ICU/IMC stay.

Inclusion / Exclusion criteria:	*Inclusion criteria* are inpatients planned for elective, inhospital, intermediate or high-risk noncardiac surgery procedures AND either aged ≥65 years or with ≥2 cardiovascular risk factors or with known cardiovascular disease. 'Exposed' will be patients in whom TTE was performed within 3 months before surgery. 'Non-exposed' will be patients in whom TTE was NOT performed. *Exclusion criteria* are under 18 years, day surgery, urgent/emergency procedures, current ICU patient, cardiac surgery within the last month prior to the index noncardiac procedure, unwilling or unable to provide informed consent, unable to complete the WHODAS questionnaire (literacy or language barrier), previous enrollment in EuPreCHO (in case of repeated surgery)
Project assessments:	Baseline: 12-item WHODAS questionnaire and troponin measurement (where applicable + NTproBNP); extraction of relevant clinical data (history of illness, planned operation, etc.) from medical charts; extraction of TTE findings from clinically indicated TTE. At discharge: extraction of relevant clinical data (ICU admission, in-hospital complications, length of stay, etc.) from medical charts At day 30 after surgery: follow-up by mail or by phone for outcome assessment (12-item WHODAS questionnaire and the collection of information on postoperative events)
Number of Participants:	5500 exposed (TTE within 3 months before surgery) and 2750 non-exposed. *Of note, the 2:1 exposed-to-non-exposed ratio was chosen to reduce the burden for centres both in terms of data collection and in terms of preoperative biomarkers to be measured, while maintaining the power for the modelling to improve prediction of major pathologies in TTE.*
Project Duration, schedule:	Follow-up duration is 30 days.
Statistical Considerations:	RQ1: multivariable logistic regression with predefined covariates; RQ2: multilevel logistic regression with predefined variables. As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for TTE using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust). RQ3: multilevel logistic regression with predefined variables. In sensitivity analyses, clinical factors will be substituted by clinical risk scores (RCRI, NSQIP MICA, AUB-HAS2 Cardiovascular Risk Index). As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for TTE using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust). For DAOH, due to the expected non-normal distribution, a quantile regression will be conducted.

Risk-Benefit statement:	The study is observational, i.e., it will collect pseudonymised data from preoperative TTE that are requested upon clinical decision of the attending clinicians (i.e. TTE is **NOT** study-mandated) and record information on the resulting perioperative management. Therefore, routine clinical management will not be affected. Study assessments consist of answering the WHODAS questionnaire and one preoperative blood sample (5 mL). Data handling will comply with the General Data Protection Regulation (GDPR) (EU) 2016/679. As such the risk associated with the study appears minimal. The benefit for future noncardiac surgery patients appears relevant as the data collected may contribute to more targeted, preoperative TTE therefore reducing potentially unnecessary testing and reducing procrastination of surgical procedures potentially resulting from "clogged" echo labs. On the other hand, the study will potentially identify risk groups where more targeted TTE will reduce the chance of missing relevant findings.