Re-evaluation of peri-operative cardiac risk (the MET REPAIR study)

Study protocol of a prospective, multicentre cohort study sponsored by the European Society of Anaesthesiology

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The number of surgical procedures carried out each year worldwide is estimated to exceed 310 million.\textsuperscript{1} Approximately one-third of these are major procedures in patients with increased cardiovascular risk.\textsuperscript{2} In adult in-patients undergoing non-cardiac surgery in Europe, overall in-hospital mortality was 4% but was more than 7% in patients with coronary artery disease or congestive heart failure.\textsuperscript{3} Furthermore, some 8% of patients undergoing non-cardiac surgery may be expected to suffer major adverse cardiac events (MACE) by the 30th postoperative day.\textsuperscript{4} Considering these impressive additional risks, guidelines on preoperative cardiac risk assessment of patients undergoing non-cardiac surgery are regularly issued by the European Society of Anaesthesiology (ESA)\textsuperscript{2,5} and the European Society of Cardiology (ESC)\textsuperscript{2} and the corresponding North American Societies.\textsuperscript{5,6} According to the two major guidelines, an estimation of maximal cardiovascular functional capacity expressed as metabolic equivalents (METs) is of great importance because maximal METs reflect maximal oxygen delivery.\textsuperscript{2,5} In the nonoperative setting, measured cardiovascular functional capacity expressed in METs has consistently been associated with poorer cardiovascular outcomes.\textsuperscript{7,8} Questionnaire-based MET estimation has performed well for predicting both measured METs,\textsuperscript{9} and long-term cardiovascular adverse events.\textsuperscript{10} For surgical patients, the data are much more limited. A recent systematic review addressing actually measured cardiopulmonary exercise tests and postoperative MACE retrieved 37 studies and 7852 patients undergoing mostly major abdominal surgery and abdominal aortic aneurysm repair.\textsuperscript{11} Although a meta-analytic approach could not be implemented, the vast majority of these studies detected a relevant association between cardiopulmonary exercise testing and general adverse events, including all-cause mortality, postoperative complications and length of hospital and ICU stay. However, most studies did not assess cardiovascular adverse events, the preferred outcome for a measure used to guide cardiac testing. In terms of linking measured and self-reported METs, we have been able to identify one interesting protocol.\textsuperscript{12} Preoperative cardiopulmonary exercise test measurements, self-assessment by the Duke Activity Status Index (DASI) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations will be determined in 1723 patients undergoing elective, major non-cardiac surgery. The authors will examine possible associations with all-cause, 30-day mortality or non-fatal myocardial infarction (MI). In addition to being of interest for linking measured and self-reported exercise tolerance, this protocol is...
also of interest because it accounts for preoperative measurements of NT-proBNP, a biomarker known to be prognostic of adverse events in non-cardiac surgery\textsuperscript{13} and recommended by very recent guidelines.\textsuperscript{6}

Clinical practicability and cost limit the use of actual exercise testing to higher risk patients capable of performing exercise testing. Consequently, METs are estimated using self-reported activity and reference values.\textsuperscript{14} Although a significant association between the DASI questionnaire and measured VO\textsubscript{2}max has been shown,\textsuperscript{15} the evidence regarding questionnaire-estimated METs and cardiac events after non-cardiac surgery is limited and inconclusive. Wiklund \textit{et al.}\textsuperscript{16} estimated the predictive value of METs for in-hospital cardiac complications in approximately 5900 patients undergoing in-hospital non-cardiac surgery: METs were not independently associated with cardiac events, potentially due to the inclusion of low cardiovascular risk procedures and patients (event rate of 1.6%). Smaller studies have shown conflicting data.\textsuperscript{17,18}

Despite scarce and inconclusive evidence, the ESA, the ESC and the American College of Cardiology/American Heart Association recommend using self-reported cardiovascular functional capacity in METs as a core question in preoperative cardiac risk assessment for patients undergoing higher risk non-cardiac surgery.\textsuperscript{2,3} Therefore, a prospective, large, simple study is urgently needed to re-evaluate self-reported METs for the non-cardiac, surgical population.

Currently, more than 122 centres in 26 countries are registered to participate in MET: rEevaluation for Peri-operative cArdIac Risk (MET-REPAIR). Any hospital in Europe is welcome to participate as a study centre. Non-European centres have been accepted upon request to the steering committee. Participating centres will be asked to enrol a minimum of 50 patients (up to 500) over a minimal recruitment period of 8 weeks, determined by the individual centre during the course of the project. The project will continue until June 2018 or until 15,000 patients have been recruited, whichever comes last.


**Study objectives**

The primary objective is to answer the question: ‘Are METs estimated by questionnaire predictive of perioperative major adverse cardiovascular events or cardiovascular mortality in patients undergoing higher-risk noncardiac surgery?’. If so, we will compare the optimal cut-off for METs estimated by questionnaire to the current, guideline-endorsed 4-MET cut-off.

We will also assess the ability of simple questions (e.g. the ability to climb two flights of stairs) to predict perioperative cardiovascular events or cardiovascular mortality.

Finally, in an optional sub-study for interested centres, we will examine the incremental predictive value of measuring NT-proBNP concentrations when added to clinical data and estimated METs. The rationale for this is to examine the value of self-reported exercise testing beyond NT-proBNP measurements.

**Inclusion/exclusion criteria**

Patients planned as in-patients after surgery will be included provided that they are either (first) 45 years of age or older and have a revised cardiac risk index at least 2 or American College of Surgeons National Surgical Quality Improvement Program Myocardial Infarction or Cardiac Arrest (NSQIP MICA) risk more than 1\%\textsuperscript{19} or (second) 65 years of age or older and scheduled for intermediate or high-risk procedures, as classified by the 2014 ESA guidelines.\textsuperscript{2} Exclusion criteria are planned out-patients, non-elective surgery and patients having suffered stroke within the last 7 days, acute coronary syndrome within the last 30 days, or congestive heart failure within the last 30 days. In addition, patients unable to perform ambulation due to congenital or long-standing illnesses/states will be excluded (e.g. paraplegia, polio etc.), but explicitly not patients undergoing orthopaedic surgery, joint arthroplasty etc.

**Outcomes**

The primary endpoint is the composite of intraoperative or postoperative in-hospital cardiovascular mortality, nonfatal cardiac arrest, acute MI, stroke or congestive heart failure requiring transfer to a higher unit of care or prolonging stay on ICU/intermediate care (≥24h).

Secondary endpoints include the single items of the primary composite endpoint, all-cause, in-hospital mortality, complications at least grade III in the Clavien–Dindo classification,\textsuperscript{20} length of hospital stay and length of ICU stay. Furthermore, in hospitals, routinely implementing perioperative troponin screening, myocardial injury after noncardiac surgery will be recorded. Finally, in centres participating in the post-discharge, 30-day follow-up, we will assess the primary, composite endpoint as well as all-cause mortality at 30 days.

**Data collection**

Eligible patients will be asked to complete a two-page questionnaire based on exercise tolerance. At discharge or at postoperative day 30 if hospital stay exceeds 30 days, occurrence of adverse in-hospital outcomes will be extracted from medical charts. In selected centres, discharged patients will be also contacted by phone or by mail for 30-day outcome assessment. These data will be augmented by relevant clinical data (e.g. cardiovascular history, type of surgery).
Statsitics
We will include 15,000 patients to observe 300 events, assuming a 2% incidence of our primary outcome. We will investigate a possible association between self-reported METs and in-hospital cardiovascular mortality and/or MACE by a multivariable hierarchical logistic regression model. The sample size allows adjusting the main analysis for the predetermined confounding variables: age, sex, ASA functional class, functional dependency in activities of daily living, estimated glomerular filtration rate, active cancer, diabetes mellitus, hypertension, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, peripheral vascular disease, stroke and level of surgical risk as classified by the 2014 ESA guidelines. Self-reported METs will be modelled continuously, dichotomised according to receiver operating characteristics (ROC) curves employing Youden’s J-statistic, and dichotomised based on the published cut-off at four METs.

Specifically, we will examine the independent prognostic value (adjusted odds ratio), compare model characteristics (Akaike information criterion, c-statistic) and assess risk re-stratification [net reassignment improvement (NRI)] for the basic model + MET cut-off based on the ROC optimum (main analysis 1) and also for basic model + the 4 MET cut-off endorsed by current guidelines (main analysis 2). For clinical practicability, the NRI of the MET cut-offs in addition to the revised cardiac risk index and the NSQIP MICA will be calculated.

In addition, we will compare model parameters of the basic logistic regression and alternative approaches to functional capacity estimation (e.g. ability to climb stairs).

In the NT-proBNP sub-study, we will compare model characteristics and the area under the ROC curves using the coefficients from the main analyses and adding NT-proBNP as a continuous variable, divided into quartiles and dichotomised according to ROC curves employing Youden’s J-statistic.

Dissemination policy and nested sub-studies
The writing group and the ‘MET-REPAIR Investigators’ will be authors of the publications derived from MET-REPAIR. There will be a note associated with the byline clearly stating that the individual names of the group authorship are elsewhere in the article and that those names are authors. The number of authors per centre is undisclosed to ensure authors are not named authors. The number of authors per centre is undisclosed to ensure the group is represented. The number of authors per centre is undisclosed to ensure the group is represented. The number of authors per centre is undisclosed to ensure the group is represented. The number of authors per centre is undisclosed to ensure the group is represented.

In summary, MET REPAIR will investigate the prognostic impact of self-reported functional capacity prior to noncardiac surgery, a clinically highly relevant question potentially affecting everyday decisions for any anaesthesiologist. This prospective cohort, sponsored by the ESA, aims to enrol 15,000 patients within the next year. A complete study protocol may be downloaded at http://www.esahq.org/research/clinical-trial-network/planned-trials/met-repair.

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References


