STUDY PROTOCOL

Rationale and design of perioperative myocardial ischemia: a protocol for troponin monitoring, prognostic thresholds, economic analysis and further insights into pathophysiology for non-cardiac surgery patients [version 1; peer review: awaiting peer review]

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Abstract

Introduction: Worldwide, near 200 million adults undergo major non-cardiac surgery each year, and 10 million of them are estimated to suffer a myocardial injury after non-cardiac surgery (MINS), defined as an elevated high sensitive troponin T (hs-cTnT) in the first 3 days after surgery. Troponin levels need to be monitored in order to diagnose MINS, high sensitive cardiac Troponin T (hs-cTnT) assays being currently the most frequently used. Perioperative hs-cTnT screening could lead to care decisions that can potentially improve clinical outcomes. However, many of the clinical and economic implications of perioperative hs-cTnT monitoring remain unclear, and need to be elucidated.

Methods and analysis: Prospective cohort that will include patients with high cardiovascular risk undergoing major non-cardiac surgery, expected to require at least an overnight hospital admission. Three determinations of
hs-cTnT in each patient (before surgery, at 48, and 72 hours after surgery) will be obtained. We will determine the incidence and prognosis of MINS, and calculate prognostically relevant thresholds for pre- and post-operative hs-cTnT. We will also conduct a cost-effectiveness analysis of hs-cTnT screening, compared with usual care. Finally, using computed tomography angiography (CTA) and cardiac magnetic resonance imaging (MRI), we aim to elucidate further the pathophysiology of MINS.

Ethics and dissemination: Our center had Ethics approval before including patients. Written informed consent is required for all patients before inclusion. The study will evaluate the feasibility and impact of implementing an hs-cTnT monitoring program at a tertiary hospital, as well as its cost-effectiveness, determine pre and postoperative thresholds of hs-cTnT and finally, evaluate potential mechanisms involved in perioperative ischemic events. The dissemination plan includes publishing the results in a policy-influencing journal, conference presentations, engagement of influential medical organizations, and taking published results to real practice.

Keywords
Myocardial Ischemia, PMI, MINS, hs-cTnT, cost-effectiveness, CT-angiography, MRI.
Strengths and limitations of this study

- Our study will evaluate the feasibility and impact of implementing a high sensitive cardiac Troponin T (hs-cTnT) monitoring program in patients undergoing non-cardiac surgery, and will inform preoperative and post-operative prognostically relevant thresholds.

- The study will also determine the cost-effectiveness of hs-cTnT monitoring compared with usual care.

- Our cardiac imaging sub-study is the first case-control cohort application of non-invasive advance imaging diagnostic tools, computed tomography angiography (CTA), and cardiac magnetic resonance imaging (MRI) with the objective to better understand the pathophysiology of myocardial injury after non-cardiac surgery (MINS).

- During the implementation of hs-cTnT monitoring, some troponin measurements and, in consequence, some of MINS events may be missed in patients who do not experience ischemic symptoms.

- Due to the case-control design of the cardiac imaging sub-study, there might be difficulties to include healthy controls, as they might be reluctant to undergo further diagnostic testing.

Introduction

Surgery and cardiovascular complications

Worldwide, annually over 200 million adults undergo major non-cardiac surgery1 and this number is growing continuously. Despite preoperative screening, technical improvement and early detection during clinical screening, perioperative myocardial injury (PMI) remains the first cause of morbidity and mortality within 30 days of surgery2. Available evidence indicates that patients undergoing non-cardiac surgery with only elevated cardiac markers reflecting cardiac injury, such as troponin, have a very poor prognosis3. However, most of these patients do not experience ischemic symptoms, and do not fulfill criteria for conventional clinical diagnosis of myocardial infarction (MI).

The clinical profile and short-term prognosis of patients undergoing non-cardiac surgery, was described in one of the largest multicentre international cohorts (VISION study)4, suggesting a new entity called myocardial injury after non-cardiac surgery (MINS)5, defined as troponin T elevation (>0.03 ng/ml) in the first 3 days post-surgery. The definition of MINS is broader than the definition of MI as it also includes other prognostically relevant PMIs due to ischemia, but does not include PMIs due to non-ischemic causes (e.g. pulmonary embolism, sepsis, or cardioversion)4. Another recent prospective diagnostic study confirmed that despite early detection during routine clinical screening, PMI is associated with substantial short- and long-term mortality6. Therefore MINS, usually undetected by the absence of ischemic symptoms, is the most common major cardiovascular complication after non-cardiac surgery6, with more than 10 million patients potentially suffering these complications annually worldwide7,8.

Troponin is the only available biomarker which helps to identify and manage MINS patients, providing rapid, specific and sensitive detection9,10. Routine monitoring for perioperative cardiac biomarkers, with the most frequently used high-sensitive cardiac Troponin T (hs-cTnT) assay, leads to recognize most of MINS and may improve prognosis. Preoperative hs-cTnT concentrations are also associated with postoperative MI and long-term mortality after non-cardiac surgery11. Typically, hs-cTnT monitoring is determined only in the post-operative period1, and despite the fact that some studies have determined hs-cTnT within 30 days before surgery12, a preoperative threshold has not yet been established.

In order to prevent missing this prognostically relevant event, nowadays guidelines recommend monitoring perioperative troponin in high-risk patients undergoing major non-cardiac surgery11,12. However, little is known about the economic consequences of troponin monitoring12, therefore economic evaluations of troponin monitoring compared to usual care, are needed. The implementation of postoperative troponin monitoring seems cost-effectively, particularly in patients at high risk for MINS12.

Finally, despite a lot of recent interest mechanisms underlying MINS remain unclear13. There is laboratory, autopsy, imaging, and clinical evidence suggesting that coronary artery thrombosis may be one of the main pathophysiological mechanisms14,15. Theoretically, myocardial injury may originate from four main distinct mechanisms: coronary plaque rupture14,15, a myocardial oxygen supply-demand mismatch16, non-ischemic cardiac disorders such an atrial fibrillation episode17, or a non-cardiac cause as pulmonary embolism18. Minimally invasive diagnostic tools such as computed tomography angiography (CTA), together with cardiac magnetic resonance imaging (MRI), could help understand underlying mechanisms of MINS, and potentially improve the management and prognosis of these patients.

Given the above, we will evaluate the feasibility and impact of the implementation of routine hs-cTnT monitoring for the detection of prognostically relevant myocardial injury, determine hs-cTnT thresholds that could best predict short and long-term prognosis, conduct a full cost-effectiveness analysis, and further elucidate the pathophysiological mechanisms of MINS in high-risk patients undergoing major non-cardiac surgery.

Methods

The study is divided in three sub-studies.

1) Hs-cTnT screening programme implementation and clinical evaluation

Objectives

- To implement a hs-cTnT monitoring program in high-risk non-cardiac surgical patients

- To determine the incidence and prognosis of MINS detected by a monitoring program

- To determine which cut-off points of hs-cTnT better discriminate patients with death and/or MACE (myocardial...
infarction, unstable angina, congestive heart failure, new atrial fibrillation, stroke or pulmonary embolism) events (at 30 days and at 1 year) from those without.

**Design**

Prospective cohort.

**Study population**

We will include adults ≥65 years or <65 years with documented cardiovascular disease (history of coronary artery disease, chronic heart failure, stroke and peripheral vascular disease), undergoing a major non-cardiac surgery (intraperitoneal, intrathoracic, major vascular, major orthopaedic, emergency) and expected to require at least an overnight hospital admission, that meets inclusion criteria, and no exclusion criteria (Table 1).

**Patient recruitment**

Research personal will screen all surgical patients daily, both scheduled and emergency, to identify eligible patients. Potentially eligible patients will be approached to obtain informed consent after surgery and before hospital discharge. Template informed consent forms to be used are available as *Extended data*.

**Procedures**

We will measure hs-cTnT using a Roche Cobas e601 analyser (limit of detection 5.0 ng/L, 99th percentile 14 ng/L, 10% coefficient of variation at 13 ng/L) at three predefined time points: preoperatively (during the preoperative visit or just before surgery), and at 48 h and 72 h after surgery. If a rise and/or fall of hs-cTnT with at least one value above the 99th percentile upper reference (14 ng/L) is detected, a cardiologist will perform a clinical evaluation for possible MINS related symptoms, and a 12-lead electrocardiogram (ECG). If the post-surgery ECG has no changes, compared with ECG before surgery, we will conduct an echocardiography. In all included patients the cardiologist will conduct a structured clinical evaluation that will include the revision of current relevant medication (ASA and other antiplatelet, ACE inhibitors, statins, beta-blockers, anticoagulants). Cardiologists will discuss all treatment decisions derived from this visit and will discuss with treating surgeons (see Figure 1).

A Coordination Committee will carry out periodic meetings to develop and assess the optimal implementation of the hs-cTnT monitoring strategy. Throughout the study we will have periodic meetings with, surgeons, anaesthesiologists, cardiologists, internists, and biochemistry personnel to explore barriers and perceptions about the monitoring program implementation. Alternatively, in case of detecting difficulties the Committee will propose potential solutions or alternative strategies. The Committee will include surgeons from the main surgical departments (orthopaedic, vascular, general, thoracic, plastic, otorhinolaryngology, and neurosurgery), anaesthesiologists, internists, and clinical epidemiologists.

To improve compliance with the screening program, we will aim to implement electronic solutions as much as possible, including the adaptation of electronic preoperative requests templates. For post-operative hs-cTnT measurements at 48 h and 72 h after surgery, we will involve corresponding treating surgical departments, and aim to implement automatically alerts on the electronic health records, as well as for cardiologist consultations. While these strategies are implemented, study personal will guarantee the optimal compliance of all circuits during the study period. Gradually the goal is that the monitoring program is run without the need of additional study personal, and that it is embedded within clinical routine.

**Follow-up**

We will follow-up all recruited patients during hospitalization, at 1 month and at 1 year after the date of surgery. The 1-month and 1-year follow-up visits will be performed by telephone. If the patients (or relatives) indicate that they have experienced any of the main outcomes, we will obtain the relevant source documents (Table 2).

**Sample size**

We estimated the sample size considering our experience with previous perioperative studies in our hospital (Hospital de la Santa Creu i Sant Pau) and a pilot study. In the hospital, approximately 80–100 patients per month (up to 1,000 patients per year) undergo major non-cardiac surgery. We therefore expect to recruit approximately 60–65 patients per month and a total of approximately 1,500 patients over a two-year period. From an estimated incidence of death (1–2%)\(^{1,2}\), and of major adverse cardiac events (MACE) (myocardial infarction, unstable angina, congestive heart failure, new atrial fibrillation, stroke or pulmonary embolism) (8–10%), we expect to observe 15–30 deaths and approximately 120–150 MACE composite events. We also expect to observe a 10% incidence of MINS (150 cases). This sample size will allow as estimating incidence of MINS.

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**Table 1. Eligibility criteria.**

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<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Age ≥65 years</td>
<td>Non cardiac surgery that does not require an overnight hospital admission or that only receives infiltrative (i.e. local) or topical anaesthesia</td>
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<tr>
<td>Age &lt;65 years and documented cardiovascular disease*</td>
<td>Dementia or mental diseases</td>
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<td>Renal insufficiency (estimated glomerular filtration rate &lt;60 ml/min/m(^2))</td>
<td>Decline to participate</td>
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*History of coronary artery disease, chronic heart failure, stroke, or peripheral vascular disease.
**Figure 1.** The high-sensitive troponin T (hs-cTnT) monitoring program flow chart.

**Table 2.** Study procedure and follow-up schedule.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Baseline</th>
<th>Surgery assessment</th>
<th>Post-surgery assessment</th>
<th>Hospital discharge</th>
<th>1-month follow-up</th>
<th>1-year follow-up</th>
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<tr>
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<td>Informed Consent</td>
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<td>Demographics</td>
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<td>Medical History</td>
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<td>Vitals signs</td>
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<td>Laboratory tests (haemoglobin, creatinine)</td>
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<td>Current relevant medication**</td>
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<td>Re-surgery</td>
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<tr>
<td>Re-hospitalization</td>
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*High-sensitive cardiac Troponin T before surgery and at 48 and 72 hours after surgery.

**ASA and other antiplatelet, ACE inhibitors, statins, beta-blockers, and anticoagulants.
death and MACE events with a precision greater than 1.5% for
the corresponding 95% confidence intervals.

Data collection methods and data management
We will obtain all data about hospital management (baseline,
operative, and hospital discharge), and after discharge at one
month and one year. We will collect the number of hs-cTnT mea-
surements ordered by clinicians. We will also register the num-
ber of performed structured cardiologist visits. We will register
occurrence of MINS, MACE, death and changes of medication
during hospitalization, at 1 month and 1 year after surgery.
Study personnel will collect data on case report forms (CRFs)
and enter this information in a secure computerized database.
Patients will be identified using a unique numeric code, and all
patient data will be anonymized to ensure confidentiality. We
will conduct periodically (every quarter) data validity checks
ensuring data quality.

Variables
Our main dependent variables will be screening coverage, and
the incidence of MINS, death and MACE (myocardial infarction,
unstable angina, congestive heart failure, new atrial fibril-
lation, stroke or pulmonary embolism). The main independent
variables will be: age, sex, type of surgery, troponin measure-
ment, cardiac risk index, history of coronary artery disease
cardiac arrest, congestive heart failure, peripheral vascular dis-
ease, stroke, transient ischemic attack, chronic renal failure, deep
venous thrombosis or pulmonary embolism, diabetes, hyperten-
sion, current atrial fibrillation, and chronic obstructive pulmonary
disease.

Statistical analysis
We will describe variables according to their nature. We will
provide the percentage and the number of cases for categorical
variables. For quantitative variables, we will provide the mean
and standard deviation. In terms of inferential statistics (rela-
tionships between variables), for prevalence and/or incidence
we will calculate the corresponding 95% confidence intervals.
We will explore univariate associations of independent vari-
ables to main outcomes (death and MACE) using chi-square
test or Fisher’s exact test, and t-tests or non-parametric tests as
needed.

We will conduct multivariate analysis using a binary logis-
tic regression model to explore which factors are associated
to MACE. The variables entered into the multivariate model
will be those that showed statistically significant associa-
tion in the univariate approach, and those that are considered as
clinically relevant. We will obtain a final risk model following a
backward elimination strategy. We will assess goodness of fit
using the Hosmer-Lemeshow test, and a coefficient of calibration
using C statistic to estimate the area under the ROC curve.

Finally, from receiver-operator characteristic (ROC) curve
analysis, we will estimate the best pre and post hs-cTnT cut-off
values to predict 30 day and 1 year after surgery mortality and
MACE. We will select the cut-off that maximizes Youden’s
index, and select secondary cut off values to achieve sensitivities
of 80, 85, 90, and 95%. All tests will use a 5% (alpha =
0.05) significance level and will be two-tailed. We will use
SPSS V 25.0 for all the analysis.

2) Cost-effectiveness analysis
Objective
To evaluate the cost-effectiveness of a hs-cTnT monitoring
program for the detection of MINS, compared with current
practice (no screening).

Design and procedures
We will develop an economic model considering two alterna-
tives: the application of an hs-cTnT monitoring program for the
detection of MINS/MI versus current practice, based on the
application of standard treatments in the presence of ischemic
symptoms.

Our model will include the elaboration of a decision tree for
short-term analysis, with a follow-up of patients at 30 days,
and a Markov model for long-term analysis (lifetime). Both
analyses will be develop from the perspective of the Spanish
National Health System (SNS). In the long-term analysis, both
costs and effects will be discounted at an annual rate of 3%, as
recommended by the economic evaluation guides, and annual
Markov cycles will be used.

Data collection and data management
In terms of items of direct healthcare costs, valued in Euros
2018, we will consider the following:

- Monitoring costs: hs-cTnT tests costs, health professional’s
  fees, laboratory technician fees, and administrative costs of
  implementation of the hs-cTnT monitoring program.
- Diagnostic tests cost: health professionals (cardiologist,
nurse) fees, and consumables materials.
- Costs of treatment: hospitalizations, outpatient visits,
  and other hospital costs
- Follow-up patients cost: administrative costs

Given the perspective of the study, we will not include the non-health
care costs and indirect costs. The health effects will be expressed
as quality-adjusted life years (QALYs) in the lifetime study, and
by avoided events in short-term study. We will obtain patients’
utilities from local data and the available research literature,
searching in MEDLINE, PubMed, and PMC in our literature
search. We will use the following search terms: periopera-
tive medicine, high-sensitivity Troponin T monitoring, Periop-
erative Myocardial Ischemia, MINS, Troponin T cut-off point,
Troponin T monitoring cost-effectiveness, computed tomography
angiography (CTA), and cardiac magnetic resonance imaging (MRI).

Statistical analysis
We will estimate the incremental cost-effectiveness ratio
(ICER) and we will perform sensitivity analysis of the key
parameters. We will conduct a probabilistic sensitivity analysis to
develop an acceptability curve in the long-term. We will present
the results of the study separately; especially by temporal perspective, patient’s age (eg ≥65 years vs. <65 years) and MINS risk group (e.g. MINS vs. MI).

3) Cardiac imaging

Objective
To clarify the underlying mechanisms involved in MINS and PMI in high cardiovascular risk patients undergoing non-cardiac surgery.

Design
Nested case-control study.

Study population
Patients from sub-study 1 will also be included in this sub-study (see eligibility criteria in Table 1).

Sample size
Local pilot data shows an incidence of MINS of 10%, and a prevalence of significant coronary atherosclerosis identified by CTA in asymptomatic cardiovascular high-risk Mediterranean people of 18.9%. We will need 130 patients with MINS/MI and 130 matched controls (adjusting by sex, age within five years interval, type of surgery and Lee index), accepting an alpha risk of 0.05, a beta risk of 0.2 in a two-sided test, and a loss rate of patients of 10%. We will validate our assumptions for this calculation once half of the sample is recruited.

Procedures
Within the postoperative hospitalization period, we will approach eligible patients with the specific sub-study informed consent for the CTA and MRI exams. We will distinguish two groups of patients: cases and controls (Table 3).

We will perform CTA after 30 days of hospital discharge at Hospital de Sant Pau (Barcelona). Few days before the CTA, a cardiologist will treat patients with a beta-blocker (atenolol 25–50 mg or ivabradine 5–7.5 mg to achieve a heart rate of approximately ≤60 beats per minute). Expert evaluators (cardiologist or radiologist with level 3 training in interpretation of coronary computed tomography angiography), will read each angiogram using a 17-segment model of the coronary arteries, without knowledge of the clinical data. Each scan will be scored as normal (no evidence of coronary atherosclerosis); non-obstructive coronary artery disease (evidence of at least one coronary artery plaque with a <50% stenosis); obstructive coronary artery disease (at least one coronary artery plaque with a ≥50% stenosis); or extensive obstructive disease (≥50% stenosis in two coronary arteries including the proximal left anterior descending artery, ≥50% stenosis in three coronary arteries, or ≥50% stenosis in the left main coronary artery).

After each CTA, we will conduct a MRI exam for every patient to analyse the global and segmental cardiac contractility, an assessment of necrosis and myocardial viability by studying late gadolinium enhancement contrast, and a pharmacological stress test with adenosine in the cases of CTA with obstructive coronary artery disease. After a matching analyses for the principal confounding factors (age, sex, Lee index, and type of surgery), one control for each case will be selected to complete the same CTA and MRI studies.

With the available findings, after the two tests, complemented with clinical anamnesis and relevant ECG changes, MINS patients will be classified into one of the following categories:
- Plaque rupture
- Supply-demand mismatch
- Non-ischemic cardiac cause
- Non-cardiac cause

Data collection and data management
We will collect all perioperative clinical data. We will include the following variables: demographic (age and gender), therapeutic (previous medical treatment with aspirin, other antiplatelet agents, statins or beta-blockers), related diagnostic tests (sensitivity), risk factors (Lee index and type of surgery), comorbidities, and perioperative data.

Statistical analysis
We will describe variables according to their nature. We will obtain absolute and relative frequencies for categorical variables. We will provide the mean and standard deviation for quantitative variables. We will estimate the prevalence of each one of the proposed aetiologies along with their exact 95% confidence intervals in the MINS sub-cohort, and compare these prevalence to the ones observed in the non-MINS cohort. We will assess if there is an association between aetiology and MINS status using contingency tables of each aetiology in the two groups (MINS and non-MINS), along with chi-square test or Fisher’s exact tests for the evaluation of the statistical association. In case of any clearly distinct covariate disbalance, a multivariate approach

<table>
<thead>
<tr>
<th>Table 3. Definition of cases and controls for cardiac imaging sub-study.</th>
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<tr>
<td><strong>Cases</strong></td>
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<td><strong>Controls</strong></td>
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will be used. We will assess the agreement between diagnostic findings in the MINS population and control group using Cohen’s kappa coefficient. For the significance level we will use a 5% (alpha = 0.05) bilateral approach. We will use SPSS V 25.0 for all the analysis.

Study organization
The study is coordinated by the Hospital de la Santa Creu i Sant Pau (Barcelona), which is primarily responsible for the organization of the study, development, study database, ensuring data quality, ensuring monitoring, coordination of the sub-studies, and data analyses. This study is part of a research line of perioperative medicine, which explores strategies for diagnosis, prevention, treatment, and risk prediction that promotes better management of patients undergoing surgery. The research team of this study is a multidisciplinary group that combines clinical investigators from epidemiology, anesthesiology, cardiology and biochemical departments, with large experience in the perioperative medicine area. The study structure includes an Adjudication Committee, an Operations Committee, and Steering Committee. The Adjudication Committee composed of clinicians who have expertise in perioperative outcomes, adjudicates all important clinical events. The Steering Committee supervises the whole project, and Operations Committee is in charge of the day to running of the study. Each sub-study has one lead investigator, and the project has one principal investigator (PAC). Given that it is an observational cohort it was considered not necessary to have a monitoring committee.

Ethics and dissemination
The protocol has received approval and consent from the Ethics Committee of Clinical Research Institute of our centre. Research personnel or good clinical practice trained health care professionals will obtain written informed consent for each patient. All data will be stored on a central encrypted, high-security computer system and kept strictly confidential.

In the case-control sub-study that includes CTA and MRI explorations, we will be contracted a specific insurance for controls. In case of patients with MINS, the CTA and MRI tests are clinically justified.

Dissemination policy
The knowledge dissemination plan includes traditional modes of dissemination (i.e., publication in a policy-driving journal, national/international conference presentations), as well as engagement of influential medical organizations. Broader dissemination will be performed by the Biomedical Research Institute Sant Pau (IIB Sant Pau) public website, and Twitter account. Also dissemination will be conducted in the Spanish Association of Anesthesia and Cardiology, as well as in our international network of perioperative medicine

Current status of the trial
Approval and consent was received from the Ethics Committee of Clinical Research Institute of the Hospital de la Santa Creu i Sant Pau, for Protocol version: 1.1. Date: 2016-05-09. The study is currently in progress, having screened 1,900 patients, and recruited a total of 1,200 patients. Patient recruitment was initiated in 2016 and will end in 2019.

Discussion

Executive summary
We will evaluate feasibility and impact of the implementation of routine hs-cTnT monitoring for the detection of prognostically relevant myocardial injury. Our proposal will also aim to determine the hs-cTnT threshold that could best predict short and long-term prognosis. Given the scarce evidence regarding the economic aspects of troponin monitoring our cost-effectiveness analysis will provide new important knowledge in this area. Finally, by the application of the advance imaging techniques (CTA and MRI), this proposal will provide further insights in the identification of the mechanisms of MINS in high-risk patients undergoing major non-cardiac surgery.

Our study in the context of previous research

Troponin monitoring. Available evidence indicates that among patients undergoing noncardiac surgery, MINS is common (8%), one in ten patients suffering MINS will die within 30 days, and majority of these events can be only detected with hs-cTnT screening in the first 72 hours after surgery. Therefore, failure to monitor troponin measurements after noncardiac surgery will result in missing more than 80% of MINS events.

In order to prevent missing of this prognostically relevant event and based on recommendations of some guidelines, we will implement hs-cTnT screening programme within clinical routine. However, little is known about the feasibility and impact of hs-cTnT screening in real practice.

Our study will implement routine hs-cTnT screening program, and evaluate its feasibility and impact at a tertiary hospital. Routine screening for perioperative hs-cTnT will lead to recognize most of MINS, improve clinical outcomes, and can potentially reduce short and long-term mortality after major non-cardiac surgery. Differently to previous studies, in case of elevated hs-cTnT a cardiologist will conduct a structured evaluation. Our hypothesis is that patients with a prognostically relevant hs-cTnT peak will likely improve their 1-month and 1-year prognosis if they receive structured management, treatment, and adequate follow-up. Clinicians will be better informed about how to interpret hs-cTnT values, and policy makers will be better informed to decide (or not) to implement routine troponin monitoring in high cardiovascular risk patients.

Preoperative and postoperative hs-cTnT thresholds. In most of the previous studies hs-cTnT was obtained only after surgery; however, in our study hs-cTnT will also be measured before surgery. This will help to determine the relevant pre and post-operative thresholds. There are only a few studies that have measured hs-cTnT levels before the time of surgery. The cohort study within the VINO trial (n = 608), concluded that hs-cTnT concentrations before surgery were significantly associated with postoperative MI, and long-term mortality after non-cardiac surgery. We also identified a more recent cohort that measured hs-cTnT before surgery (within 30 days before surgery), where PMI was defined as an absolute increase in hs-cTnT of ≥14 ng/L above preoperative value, or between 2 postoperative values if the preoperative value was missing. On the other hand, nearly half of adults undergoing non-cardiac surgery exceed the 99th percentile of ≥14ng/ post-surgery, and mild elevations of hs-cTnT are common in men and elderly non-MI
The results of our cohort study showed cut-off values to differentiate acute MI from non-acute MI but in non-surgical elderly patients (>70 years old), being nearly four times the 99th percentile with hs-cTnT (54 ng/L). In contrast, the best cut-off value in younger patients was close to the 99th percentile for hs-cTnT (17 ng/L). Given the above, there is a need to determine optimal preoperative and post-operative prognostically relevant hs-cTnT thresholds in high cardiovascular risk patients undergoing major non-cardiac surgery.

**Economic consequences.** There are only few economic analyses studies evaluating the cost-effectiveness of hs-cTnT monitoring, including a broad spectrum of non-cardiac surgical procedures. Despite the lack of conclusive economic evidence, troponin monitoring is now recommended in some clinical guidelines.

We identified two studies that analysed the cost-effectiveness of troponin monitoring. The first study, conducted in USA, included patients aged ≥65 years undergoing open abdominal aortic aneurysm (AAA) repair. The authors concluded that postoperative Troponin I screening after AAA repair was cost-effective, with an incremental cost-effectiveness ratio of 2003 US$12,641 per QALY. The second study was recently conducted by VISION study investigators. This is a model-based cost-consequence analysis which compares the impact of routine troponin T monitoring versus standard care on the incidence of MINS. The model inputs were based on Canadian patients enrolled in VISION study. The costs associated with a troponin T monitoring program to detect MINS were moderate. The study concluded that implementation of troponin T monitoring seems appealing, particularly in patients at high risk for MINS, based on the estimated incremental cost per health gain. No cost-effectiveness analysis of hs-cTnT monitoring high-risk cardiovascular patients in major non-cardiac surgery patients (in comparison with usual care) is yet available. Our study will address this question in the Spanish setting using data from real clinical practice.

**MINS pathophysiology.** Understanding the pathophysiology of MINS is crucial to develop potential prophylactic and therapeutic interventions to improve the prognosis of patients undergoing non-cardiac surgery. However, angiographic, histological or imaging studies that provide an overview of the incidence of etiological mechanisms of MINS are currently not available. We identified a single study where CTA was used for screening of coronary artery disease before non-cardiac surgery, improving perioperative risk stratification with clinical tools as the Lee index. VISION study investigators have published a single prospective cohort study (Coronary CTA VISION) with 955 patients using CTA before non-cardiac surgery, concluding that myocardial infarction occurs across the spectrum of coronary artery disease, suggesting that there could be several pathophysiologic mechanisms involved.

Given the scarce available data better understanding of the pathophysiology of MINS is much needed. With non-invasive diagnostic tools, such as CTA and MRI our study could improve the understanding of the underlying mechanisms involved in MINS. This new knowledge could inform prophylactic and therapeutic interventions.

**Study limitations and strengths.** Our study has several limitations. During hs-cTnT monitoring implementation, some monitored troponin measurements may be missed, due to fast hospital discharge, no staff collaboration, haemolysis of the samples, etc. Also there may have missed some structured cardiologist visits, due to fast hospital discharge or coordination problems. Therefore, we may miss MINS events in patients who do not experience ischemic symptoms. Regarding the cost-effectiveness study, there may be variability in sample-associated costs and results. Finally, the cardiac imaging sub-study has a nested case-control design, where inclusion of healthy controls without any clinical justification for carrying out diagnostic tests may be difficult.

Our study has also several strengths. It is a rigorous proposal that will address several very relevant questions simultaneously. It will evaluate the feasibility and impact of implementing troponin monitoring program at a tertiary hospital, with large sample of adults who underwent noncardiac surgery. All patients will undergo troponin monitoring before and after surgery, using the same troponin assay. The study will also inform preoperative and post-operative prognostically relevant thresholds that likely will improve mortality and major cardiovascular events prediction. Our study will also determine the cost-effectiveness of troponin monitoring, and finally, the application of non-invasive advance imaging diagnostic tools (CTA and MRI), will contribute in the identification of the mechanisms involved in MINS.

**Implications for practice and research.** The results of our cohort study will offer high-quality evidence to guide practice, and will likely have major implications in the management and prognosis of this public health problem. Success of implementation of the hs-cTnT monitoring program will be good example for its implementation in other sites, in Spain and elsewhere. New knowledge about preoperative and post-operative prognostically relevant thresholds will improve the prediction of mortality, and major cardiovascular events.

Given the low cost of hs-cTnT and poor prognosis of patients with MINS, potential management, treatment and hs-cTnT monitoring is likely to be cost-effective for the national health system. Our economic evaluation study will throw light on the cost effectiveness of troponin monitoring compared to usual care, which will likely improve prognosis and unnecessary costs. Policy makers will be better informed to decide (or not), to implement troponin screening in high cardiovascular risk patients.

The understanding of the pathophysiology of MINS will help to develop new prophylactic and therapeutic measures to improve the prognosis of patients, and reduce unnecessary costs. Moreover, the results of this study can help scientists to shape...
research initiatives in the future, applying these techniques to detection of myocardial injury. The success of this study will allow bringing research results to daily practice, evaluate their implementation, and facilitate further nested research that will address important questions in the field. This study is potentially an example of knowledge transfer, taking published results to real practice, with the aim to influence patient important outcomes.

Data availability

Underlying data
No underlying data are associated with this article.

Extended data

Open Science Framework: SPIRIT checklist for “Rationale and insights into pathophysiology for non-cardiac surgery patients.”

Reporting guidelines

Open Science Framework: SPIRIT checklist for “Rationale and design of peripерative myocardial ischemia: a protocol for troponin monitoring, prognostic thresholds, economic analysis and further insights into pathophysiology for non-cardiac surgery patients.”

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