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: 1 approved, 1 approved with reservations]

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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

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Approval Status

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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.

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Any reports and responses or comments on the article can be found at the end of the article.

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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)⁵. 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 surgery⁷, with more than 10 million patients potentially suffering these complications annually worldwide⁴⁻⁷.

Troponin is the only available biomarker which helps to identify and manage MINS patients, providing rapid, specific and sensitive detection⁴⁻⁷. 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 surgery⁸. Typically, hs-cTnT monitoring is determined only in the post-operative period⁴, and despite the fact that some studies have determined hs-cTnT within 30 days before surgery⁶, 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 surgery^{9,10}. However, little is known about the economic consequences of troponin monitoring¹¹, 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 mechanisms^{14,15}. Theoretically, myocardial injury may originate from four main distinct mechanisms: coronary plaque rupture^{13,14}, a myocardial oxygen supply-demand mismatch^{15,16}, non-ischemic cardiac disorders such as 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*¹⁹.

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%)^{4,7}, 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,

Table 1. Eligibility criteria.

Inclusion criteria	<ul style="list-style-type: none"> • Age ≥ 65 years • Age < 65 years and documented cardiovascular disease* • Renal insufficiency (estimated glomerular filtration rate < 60 ml/min/m²)
Exclusion criteria	<ul style="list-style-type: none"> • Non cardiac surgery that does not require an overnight hospital admission or that only receives infiltrative (i.e. local) or topical anaesthesia • Dementia or mental diseases • Decline to participate

*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.

Time Period	Baseline	Surgery assessment	Post-surgery assessment	Hospital discharge	1-month follow-up	1-year follow-up
Eligibility Assessment	x					
Informed Consent	x					
Demographics	x					
Medical History	x					
Vitals signs	x	x	x			
Laboratory tests (haemoglobin, creatinine)	x	x	x	x		
Surgery Details		x				
Troponin*	x		x			
Current relevant medication**	x			x	x	x
Re-surgery				x	x	x
Re-hospitalization					x	x

*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 measurements ordered by clinicians. We will also register the number 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 fibrillation, stroke or pulmonary embolism). The main independent variables will be: age, sex, type of surgery, troponin measurement, cardiac risk index, history of coronary artery disease, cardiac arrest, congestive heart failure, peripheral vascular disease, stroke, transient ischemic attack, chronic renal failure, deep venous thrombosis or pulmonary embolism, diabetes, hypertension, 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 (relationships between variables), for prevalence and/or incidence we will calculate the corresponding 95% confidence intervals. We will explore univariate associations of independent variables 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 logistic regression model to explore which factors are associated to MACE. The variables entered into the multivariate model will be those that showed statistically significant association 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 alternatives: 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 developed 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 data²⁰ and the available research literature, searching in MEDLINE, PubMed, and PMC in our literature search. We will use the following search terms: perioperative medicine, high-sensitivity Troponin T monitoring, Perioperative 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 data²¹ 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%²². 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 $\geq 50\%$ stenosis); or extensive obstructive disease ($\geq 50\%$ stenosis in two coronary arteries including the proximal left anterior descending artery, $\geq 50\%$ stenosis in three coronary arteries, or $\geq 50\%$ 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 3. Definition of cases and controls for cardiac imaging sub-study.

Cases MINS/MI group	<u>MINS group</u> : patients with hs-cTnT value higher than 50% of preoperative level, without symptoms, without ECG changes related to ischemia, neither new wall abnormalities in the postoperative echocardiogram. <u>MI group</u> : patients with perioperative myocardial infarction according to the current definition
Controls	Patients from hs-cTnT monitoring program without MINS or MI

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 surgery⁵. Therefore, failure to monitor troponin measurements after noncardiac surgery will result in missing more than 80% of MINS events^{4,5}. In order to prevent missing of this prognostically relevant event and based on recommendations of some guidelines^{9,10}, 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^{4,5}; 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 surgery⁸. 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 missing⁶. On the other hand, nearly half of adults undergoing non-cardiac surgery exceed the 99th percentile of ≥ 14 ng/ post-surgery²³, and mild elevations of hs-cTnT are common in men and elderly non-MI

patients²⁴, hence, optimal cut-off levels could differ across populations. We identified a single study showing 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)²⁵. 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^{9,10}.

We identified two studies that analysed the cost-effectiveness of troponin monitoring^{11,12}. The first study, conducted in USA, included patients aged ≥ 65 years undergoing open abdominal aortic aneurysm (AAA) repair¹¹. 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 MINS¹². 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 prognostic 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 index²⁶. 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 involved²⁷.

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 hs-cTnT 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: Rationale and design of Perioperative Myocardial Ischemia (PMI): a protocol for troponin monitoring, prognostic thresholds, economic analysis and further insights into pathophysiology for non-cardiac surgery patients. <https://doi.org/10.17605/OSF.IO/GBV4U19>.

Reporting guidelines

Open Science Framework: SPIRIT checklist for “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”. <https://doi.org/10.17605/OSF.IO/GBV4U19>.

Grant information

This work was supported by the Fundació La Marató de TV3 (grant number: 20150110). PAC is supported by a Miguel Servet investigator contract from the Instituto de Salud Carlos III (CPII15/0034).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

Ekaterine Popova is a doctoral candidate at the Paediatrics, Obstetrics and Gynaecology and Preventive Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain. Catalonia, Spain: Iberoamerican Cochrane Centre. Biomedical Research Institute Sant Pau (IIB Sant Pau) working group: Francisco Rene Acosta, Raúl Aguilar Lopez and M^a Trinidad Muñoz Gallarin.

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Sebastiano Gili

Invasive Cardiology Department, Centro Cardiologico Monzino, IRCCS, Milan, Italy

Popova and colleagues present the rationale and design for a prospective study aiming to assess the clinical implications and cost-effectiveness of a structured program for the monitoring of pre- and post-operative troponin values in patients undergoing high-risk surgery. The main aim of the study is to evaluate the incidence of myocardial injury after non-cardiac surgery (MINS) and to explore its pathophysiology.

The presented protocol is of interest and the implementation of the study will be able to provide useful clinical information. There are some issues however that need to be discussed:

- Please provide definitions for documented cardiovascular disease in patients < 65 years old, in particular for coronary artery disease, peripheral artery disease and chronic heart failure.
- Post-surgical troponin elevation management is substantially left to the clinical decision and judgement of the cardiologist in charge of evaluating the patient. This could introduce some inconsistencies in the treatment of patients, the authors should consider to provide broad guidelines in this sense.
- C-statistic and ROC curve analysis will be performed on a relatively low number of expected events (about 150 expected MINS) and no internal or external validations is contemplated in the study protocol.
- Cost-effectiveness analysis: it is not clear how the comparator for this analysis, and in particular for the assessment of QALY, will be adopted for this analysis.
- The authors should clarify how they consider a simple score such as the Lee score, with well-known limitations, will be able to provide adequate matching in terms of cardiovascular risk and history in patients undergoing imaging studies.
- Given that the study is centered in the assessment of clinical implications of MINS, please discuss why the authors opted to include also overt post-operative MI in the imaging

analysis.

- Please discuss how incidental findings of subclinical coronary artery disease will be managed in the patients included in the imaging substudy, in particular in those without MINS/MI.

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: acute coronary syndromes, coronary artery disease, interventional cardiology, post-pci myocardial injury

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 June 2019

<https://doi.org/10.5256/f1000research.20805.r49799>

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Christian Puelacher

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²

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The presented protocol seems very promising to help understand the clinical applicability of perioperative hs-cTnT Screening after non-cardiac surgery in high-risk patients in routine practise. The follow-up data on adherence of medication prescribed for MINS will be very interesting. The concept to do a cost-benefit analysis seems very promising as well. Also the CTA and MRI study is ambitious and could yield very interesting results.

It is important to note, that the study protocol was submitted in 05/2019 as the study nears completion (start according to the protocol was in 2016). Therefore, alterations to the original study protocol are possible, I would invite the authors to comment on any changes done especially concerning the endpoint or procedures.

Some additional details could be considered:

1. The definition of MINS at the moment is to a part arbitrary as there is currently no agreed upon definition. There are however aspects to consider:
 - a) Previous studies were done, which used different cut-offs than that proposed by the study group. Importantly the VISION study identified possible cut-offs and the BASEL-PMI studies used a prospective cut-off. In both studies an absolute delta cut-off was used/found, which is in line with the agreed upon criteria for the definition of acute myocardial infarction. Using absolute delta cut-offs could enhance the protocol by creating a more readily usable flowchart (e.g. one cut-off for change to preoperative baseline) and allow for better comparison. Please consider doing a sensitivity analysis with aligned criteria.
 - b) Using MINS as the primary outcome poses a challenge in the flow-Chart, as MINS excludes other conditions leading to postoperative troponin elevations, e.g. sepsis, pulmonary embolism or tachyarrhythmia. Do the authors wish to use the same distinction or include all elevations (which seems sensible, as this is what the screening will uncover)? Please elaborate.
2. Prognostic Analysis: the combined MACE-endpoint consists of multiple endpoints, please extend the definition.
 - a) It is unclear to me why you ought to include unstable angina, as it is not expected that the coronary artery disease of the affected patients should worsen via surgery? This could introduce noise into this ambitious study
 - b) New atrial fibrillation will be difficult to assess using only one ECG at detection. Would you reconsider "onset of symptomatic AF or AF needing treatment"?
 - c) Why is "cardiovascular death" not part of the combined endpoint?
 - d) The use of a binary logistic model instead of a Cox proportional hazards model or a time-dependent analysis is unclear to me. As a certain amount of loss-to-followup is nearly unavoidable, and there is a competing endpoint all-cause death or (in case of cv-death being part of the endpoint) non-cardiovascular death, the Cox-model would offer benefits.

3. When evaluating potential threshold for the prognostic ability of hs-cTnT/MINS, I would recommend a methodology similar to that of the VISION study, which was done in a very thorough manner.
4. Substudy: Could you provide details on the matching procedure done for the substudy? Is this propensity score matching?
5. Cost-benefit analysis: in light of no clear MINS-Definition to date, I invite the authors to do sensitivity analyses using different assumptions for the definition of MINS.

The provided ideas are simply comments, the authors shall feel free to use any recommendations, especially as the study was already conducted according to the methods.
I congratulate the research group for such an undertaking.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: Research funding by the Swiss Heart Foundation and Roche Diagnostics to our research group

Reviewer Expertise: Clinical Research, perioperative cardiology, no Sound experience for economic analyses

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Jul 2019

Ekaterine Popova

Dear Dr. Puelacher,

Thank you very much for substantial revision and useful comments and suggestions. However, at this moment only one peer reviewer report has been received, so we can not submit a final revised version until additional comments have been received from another reviewer.

Please see our responses below.

Christian Puelacher

Department of Cardiology, University Hospital of Basel, University of Basel, Basel, Switzerland

The presented protocol seems very promising to help understand the clinical applicability of perioperative hs-cTnT screening after non-cardiac surgery in high-risk patients in routine practice. The follow-up data on adherence of medication prescribed for MINS will be very interesting. The concept to do a cost-benefit analysis seems very promising as well. Also the CTA and MRI study is ambitious and could yield very interesting results.

It is important to note, that the study protocol was submitted in 05/2019 as the study nears completion (start according to the protocol was in 2016). Therefore, alterations to the original study protocol are possible; I would invite the authors to comment on any changes done especially concerning the endpoint or procedures.

Reply: there have been no major changes in the protocol except for the inclusion of a new center to increase the recruitment for the sub-study 3 (ACE-CARD), and a modification in the MACCE definition. We have included a sentence in the protocol to reflect this in the manuscript (section "Current status of the trial", line 3). It reads as follows:

"Since the start of the study in 2016 there have been two modifications in the original protocol; one new center (Hospital Vall d'Hebron) joined the ACE-CARD substudy and the MACCE definition was modified, excluding unstable angina.

The reason for including a new center was the low recruitment rate. The MACCE definition was modified to according to the European perioperative clinical outcome (EPCO) definition statement (Jamer Ib, 2015)."

Ref.: Jamer Ib, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions. Eur J Anesthesiol 2015;32: 88-105.

Some additional details could be considered:

1. The definition of MINS at the moment is to a part arbitrary as there is currently no agreed upon definition. There are however aspects to consider:a) Previous studies were done, which used different cut-offs than that proposed by the study group. Importantly the VISION study identified possible cut-offs and the BASEL-PMI studies used a prospective cut-off. In both studies an absolute delta cut-off was used/found, which is in line with the agreed upon criteria for the definition of acute myocardial infarction. Using absolute delta cut-offs could enhance the protocol by creating a more readily usable flowchart (e.g. one cut-off for change to preoperative baseline) and allow for better comparison. Please consider doing a sensitivity analysis with aligned criteria.

Reply: thank you for the suggestion. We will perform sensitivity analysis considering absolute delta cut-offs instead of relative changes.

The section now reads:

"We will assess the agreement between diagnostic findings in the MINS population and the control group using Cohen's kappa coefficient. We will conduct sensitivity analysis using absolute delta cut-offs to define MINS in accordance to previous studies (Devereaux PJ, 2012; Puelacher C, 2018). For the significance level we will use a 5% ($\alpha = 0.05$) bilateral approach."

Ref.: Devereaux PJ, Chan MT, et al. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012; 307(21):2295–304.

Ref.: Puelacher C, Lurati Buse G, Seeberger D, BASEL-PMI Investigators. Perioperative Myocardial Injury after Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation. 2018 Mar 20; 137(12):1221-1232. doi: 10.1161/CIRCULATIONAHA.

- b) Using MINS as the primary outcome poses a challenge in the flowChart, as MINS excludes other conditions leading to postoperative troponin elevations, e.g. sepsis, pulmonary embolism or tachyarrhythmia. Do the authors wish to use the same distinction or include all elevations (which seems sensible, as this is what the screening will uncover)? Please elaborate.

Reply: we considered the definition of MINS (VISION study), as an elevated troponin measurement that occurs between surgery and the first 30 days after surgery, judged as resulting from myocardial ischemia (i.e., no evidence of a non-ischemic etiology such as pulmonary embolism, atrial fibrillation or sepsis). This definition includes patients with MI and patients with troponin elevation due to ischemic causes that don't fulfill criteria of conventional myocardial infarction (Thygesen K 2018).

Ref.: Thygesen K, Alpert JS, Jaffe AS, et.al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Glob Heart. 2018 Aug 23. pii: S2211-8160(18)30138-8. doi: 10.1016/j.gheart.2018.08.004.

1. Prognostic Analysis: the combined MACE-endpoint consists of multiple endpoints, please extend the definition.

Reply: we have modified the MACCE definition according the European perioperative clinical outcome (EPCO) definitions statement (Jamer Ib, 2015). Please, see Appendix 1.

- a) It is unclear to me why you ought to include unstable angina, as it is not expected that the coronary artery disease of the affected patients should worsen via surgery? This could introduce noise into this ambitious study

Reply: unstable angina should not have been included in the composite. We have modified accordingly.

- b) New atrial fibrillation will be difficult to assess using only one ECG at detection. Would you reconsider "onset of symptomatic AF or AF needing treatment"?

Reply: we have modified the terminology to address this concern. We are now using “new clinically important atrial fibrillation” instead of “new atrial fibrillation.”

- c) Why is "cardiovascular death" not part of the combined endpoint?

Reply: we consider all-cause death as the primary outcome. It is a more patient important outcome than the outcomes included in the composite, and we prefer to keep it separate. Nevertheless, we will report both vascular and non-vascular death.

- d) The use of a binary logistic model instead of a Cox proportional hazards model or a time-dependent analysis is unclear to me. As a certain amount of loss-to-follow up is nearly unavoidable, and there is a competing endpoint all-cause death or (in case of cv-death being part of the endpoint) non-cardiovascular death, the Cox-model would offer benefits.

Reply: we agree about using a Cox model instead of logistic regression. We will analyze time-to-death and time-to-MACCE using proportional hazard models. We will explore factors associated with death and MACCE by including clinically relevant variables into the multivariate models. We will obtain a final MACCE risk model following a backward elimination strategy. We will assess the proportional hazard assumption of all factors included in the analysis using Schoenfeld residuals plots. We will adjust for overoptimism in model performance by bootstrap validation. We will assess the overall discriminatory ability of the model using the C-statistic. We will evaluate model calibration using calibration plots, and we will compute the calibration slopes.

1. When evaluating potential threshold for the prognostic ability of hs-cTnT/MINS, I would recommend a methodology similar to that of the VISION study, which was done in a very thorough manner.

Reply: we will use two methodologies, including the one you suggest despite it is more related to the determination of the hs-cTnT cut-off point in the context of a multivariate predictive model. Our goal is to identify "univariate" cut-off points. We have also included a new reference (Mazumdar 2003), section “Statistical analysis”, line 20.

The section now reads:

“Finally, from receiver-operator characteristic (ROC) curve analysis, we will univariately estimate the best pre and post hs-cTnT cut-off values to predict 30 days and 1 year after surgery mortality and MACCE. We will select the cut-off that maximizes Youden’s index, and secondary cut off values to achieve sensitivities of 80, 85, 90, and 95%. For the predictive modeling, we will also explore what pre and post-surgery hs-cTnT threshold values will be better predictors to be used in the predictive multivariate models, for 30 days and 1 year after surgery mortality and MACCE. For this, we will use an iterative process based on Mazumdar et al methodology (Mazumdar 2003). In short, we will cross-validate different hs-cTnT thresholds and select the optimal cut-off based on log-likelihood tests of the predictor within the multivariate model.”

Ref.: Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. Stat Med. 2003; 22(4):559–71.

1. Substudy: Could you provide details on the matching procedure done for the substudy? Is this propensity score matching?

Reply: patients in the ACE-CARD substudy will be simple matched by sex, age (within five years of an interval), type of surgery, and Revised Cardiac Risk Index (Lee Criteria).

1. Cost-benefit analysis: in light of no clear MINS-Definition to date, I invite the authors to do sensitivity analyses using different assumptions for the definition of MINS.

Reply: thank you for the suggestion. We will conduct a sensitivity analysis using several definitions of MINS. We would like to clarify that we plan to conduct a cost-effectiveness analysis and not a cost-benefit analysis.

The provided ideas are simply comments; the authors shall feel free to use any recommendations, especially as the study was already conducted according to the methods.

I congratulate the research group for such an undertaking.

Appendix 1.

MACCE (Major Adverse Cardiac and Cerebrovascular Events) is defined as one or more of the following:

1. Myocardial injury after noncardiac surgery (MINS):

1.1. Myocardial infarction MI (3rd universal definition):The diagnosis of MI requires at least one of the followings: Detection of a rise and/or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the followings: a) signs or symptoms of ischemia (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); b) new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation ≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression ≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads; c) new left bundle branch block (LBBB); d) development of pathological Q waves present in any two contiguous leads that are ≥ 30 milliseconds; d) new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or e) identification of an intracoronary thrombus by angiography or autopsy.

1.2. Myocardial injury after noncardiac surgery (MINS) not meeting 3rd universal definition of MI:For MINS diagnosis following criterion is required: detection of a rise or fall of Troponin with at least one value above the 99th percentile of the upper reference limit (URL) AND 50% higher than the previous troponin measurement (before surgery), related to the preceding event that is judged as resulting from myocardial ischemia (i.e., no evidence of a non-ischemic etiology causing the troponin elevation such as pulmonary embolism or sepsis) AND does not fulfil the myocardial infarction definition above.

2. **Non-fatal cardiac arrest**, defined as an absence of cardiac rhythm or presence of chaotic rhythm requiring any component of basic or advanced cardiac life support.
3. **Congestive heart failure**, The definition of new congestive heart failure requires a clinical sign (i.e. at least one of the followings: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and a radiographic finding

(i.e., at least one of the followings: vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

4. **New clinically important atrial fibrillation**, is defined as important atrial fibrillation, documented with ECG evidence of atrial flutter, atrial fibrillation, or second- or third-degree atrioventricular conduction block, and results in angina, congestive heart failure, symptomatic hypotension, or requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
5. **Stroke**, is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death

Competing Interests: No competing interests were disclosed.

Comments on this article

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Reader Comment 11 Feb 2020

Joseph Alpert

This is a reasonable study with a solidly thought out protocol. The ms is well written and easy to understand. The study is important. I would accept it as written. Joseph Alpert

Competing Interests: No competing interests. JSA

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