unRaveling pErioperative MyocArdial lNjury (REMAIN)

Department of Anesthesiology

Erasmus MC, Rotterdam, The Netherlands

non-WMO-applicable research

Full title of protocol	unRaveling pErioperative MyocArdial INjury
Short title or Acronym	REMAIN
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Subsidising party	N.A.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

DRE	Digital Research Environment
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
GCP	Good Clinical Practice
IC	Informed Consent
KLEP	Klinische Epidemiologie
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming
WMO	Medical Research Involving Human Subjects Act, in Dutch: Wet Medisch- wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Myocardial injury is an independent predictor for poor outcome after non-cardiac surgery. The causes for myocardial injury can be multifactorial. Knowing what the exact cause for myocardial injury is, is often unclear or mixed pathophysiology exist. However, in clinical practice doctors have an opinion on the most likely cause.

Objective: The aim of this study is to gain insight into the etiology of myocardial injury after non cardiac surgery. Secondary we try to find what doctors think of the most logical explanation for myocardial injury, what phenotype is associated with the most likely cause, how this determines prognosis and what factors are associated with improved outcome.

Study design: Retrospective cohort study

Study population: Patients who underwent non-cardiac surgery in the Erasmus MC in the period 2017-2023.

Intervention: None

Main study parameters/endpoints: The primary endpoint is a description of the main etiologies found within patients with an elevated troponin T after non cardiac surgery.

Nature and extent of burden and risks associated with participation, benefit and group relatedness:
There will not be a significant burden to patients. This study will use existing data from patients that have been operated in the time period 2017-2023 in the Erasmus MC. There is no additional intervention required.

1. Introduction and rationale

Myocardial injury, a significant increase/or elevation of cardiac troponin after non-cardiac surgery, has proven to be a major contributor to perioperative mortality[1, 2]. It is estimated that myocardial injury contributes to 34-42% of all deaths following non-cardiac surgery within 30 days [3]. One major difference between non-surgical acute myocardial infarction and perioperative myocardial injury is that the vast majority of patients experiencing perioperative myocardial injury do not show any typical ischemic symptoms (chest pain and/or ischemic changes on the electrocardiogram). It is therefore difficult to diagnose myocardial injury, without knowing biomarker profiles. Due to the lack of typical symptoms, most patients with myocardial injury are currently not detected in routine clinical practice. Surprisingly, whether a patient fulfills the definition for acute myocardial infarction (i.e. has clinical symptoms, or ECG changes, or imaging evidence of new loss of viable myocardium), the prognosis is the same for all elevations, regardless of symptoms [3-5].

In the last decade, extensive efforts have been made to determine the etiology of myocardial injury, in order to discover a pathophysiology that is leading and may guide us to treatment options. One of the published definition is MINS (Myocardial Injury after Noncardiac Surgery) [4, 6-8]. This definition evaluates all elevations for any other cause that may be causing the elevation (i.e. sepsis, heart failure, tachyarrhythmias, renal failure, chronic elevations). If any of these other causes are unlikely, a diagnosis of MINS can be made; MINS therefore covers the spectrum of ischemic heart disease (acute coronary syndromes and type 2 ischemia). Unfortunately, it is not known which criteria are used to rule out other causes, the individual contribution on mortality of the other phenotypes or how often mixed etiologies are possible.

A second strategy has recently been published by another research group (Figure 1) [9]. Here an increase in troponin in the first steps is analyzed for a cause other than type 2 ischemia. If there is, treatment may be started appropriate to the most likely cause. Thus, by definition, if no other cause found likely, type 2 ischemia becomes the most logical cause. The prognosis varies greatly depending on what researchers found the most likely cause [9, 10]. These results call for an replication in our hospital, since we have been measuring myocardial injury for more than a decade. Furthermore, it is unclear anesthesiologists in different phases of training, agree with regard to the most likely cause of the myocardial injury. In this study we would like to search for more clarity regarding these questions, which are better elaborated below.

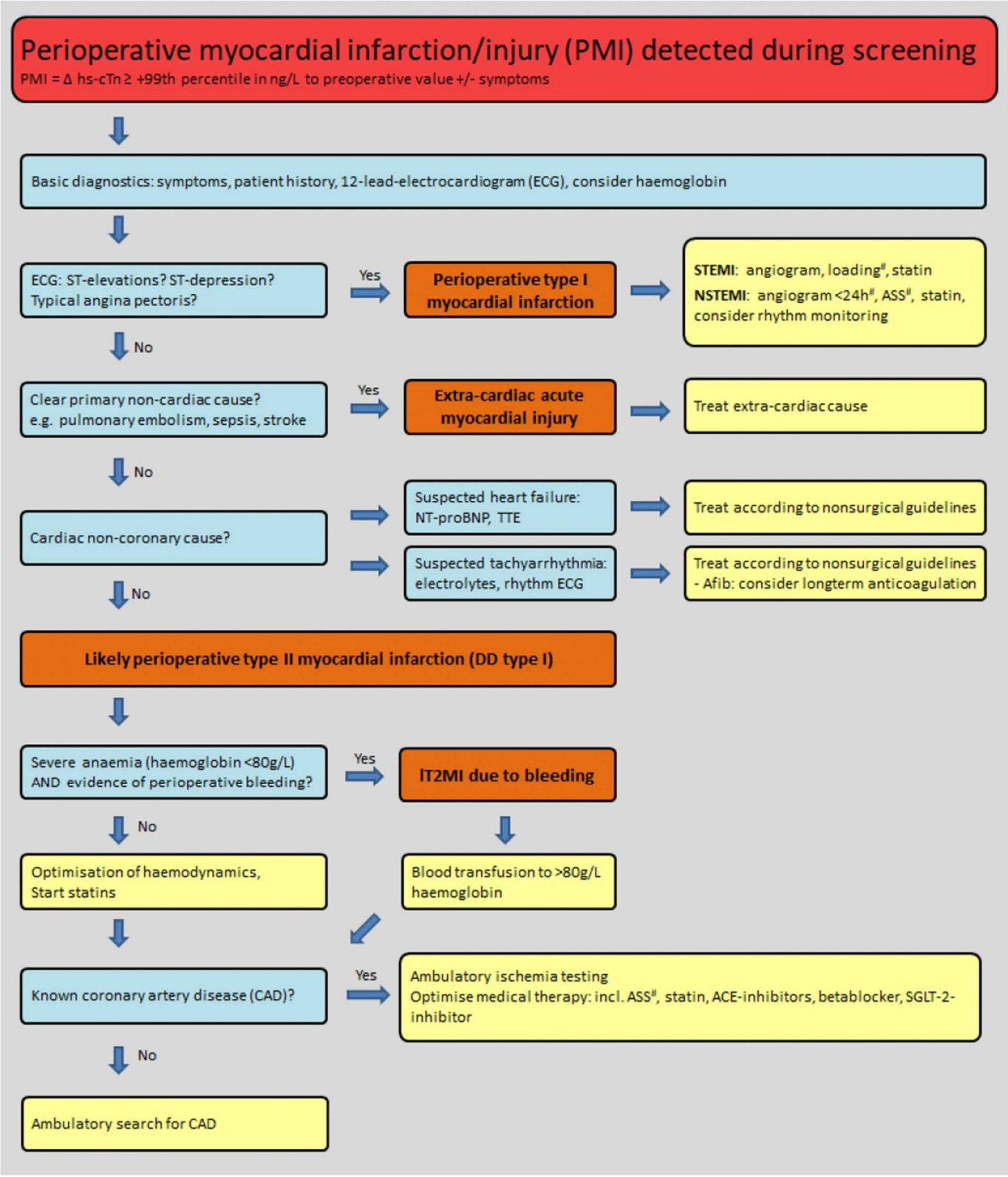

Figure 1: Evaluating scheme for patients with perioperative myocardial injury

2. Objective(s)

The aim of this study is multiple:

Primary aim:

- The primary aim is to determine the etiology of myocardial injury after non cardiac surgery.

Secondary aims:

- Do phenotypes, with regard to blood pressure, heart rate, of ST-segment analysis, differ between the different etiologies?
- How often do health care providers from different levels of training differ in opinion on the most likely diagnosis?
- What were clinical features present for selecting the most the likely etiology?

3. Study type

3.1 *Study type:*

X Retrospective
☐ Prospective
☐ Combination Retrospective/Prospective

3.2 Check all the applicable boxes:

X Medical records (re-use of data from healthcare, including AI) Case report
☐ Re-use data from research
X Evaluations of quality of healthcare (retrospective)
☐ Research with additional use of residual material from regular healthcare
☐ Research with re-use of human materials from research or existing biobank
☐ Research with human materials without biobank
☐ De novo biobank (human material obtained without burdensome or invasive procedures)
☐ Post marketing survey research with medical devices
☐ Phase IV research
☐ Healthcare evaluation research (prospective) Medical devices
☐ In Vitro Diagnostic Tests Other research, describe

4. Study population

4.1 *Population (base)*

The population to be studied consists of all non-cardiac surgical patients who underwent surgery at Erasmus MC in the period 2017-2023.

4.2 *Inclusion criteria*

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age > 18 year of age
- Undergoing non-cardiac surgery in the Erasmus MC, with (high-sensitive) Troponin T > 50 ng/L measured in any of the first three days after surgery.

4.3 *Exclusion criteria*

The following types of operations are excluded from the analysis:

- Re-operations within the study period.
- Daycare surgery

4.4 *Sample size calculation*

The sample size is based on convenience sampling of the cohort of routine postoperative troponin measurements in the Erasmus MC since 2017 (MEC-2017-062). A total of 100 patients per year with a (high-sensitive) Troponin T > 50 ng/L are estimated [11] which would result in roughly 700 patients.

4.5 (*Planned) start date*

Baseline and in hospital data extraction can be started as soon as approval by the ethics committee is given. We plan to start as soon as we receive permission to collect the necessary data. Expected start date is October 2023.

4.6 *(Planned) end data*

March 1st 2027

5. Methods

5.1 *Procedures*

The baseline population will consist of all patients who underwent a form of non-cardiac surgery, regardless of the type of anesthesia in the time period 2017-2023 in the Erasmus MC. For patients who have undergone multiple operations, only the first operation will be included for analysis. There are no restrictions to the type of anesthesia: local, locoregional and general

anesthesia will be included. The same applies for the type of surgery: emergency as well as elective surgery will be included. Baseline variables, medication use, type of surgery and perioperative hemodynamic and laboratory variables will be extracted from the hospital information system. Myocardial injury will be defined as a peak high-sensitive troponin T > 50 ng/L, measured on one of the first three postoperative days. One year mortality is registered, as well as major vascular events. This is in line with previous publications from our group. The adjudication strategy used for patients with myocardial injury will follow a similar pattern compared to scheme in Figure 1. For the adjudication process anesthesiologists in various forms of training (resident and attending) will be invited. The total panel will have a maximum of 6-10 members. Two members will receive a sample of patients to adjudicate. Together the entire panel will adjudicate all patients. In case of non-agreement between raters, a third rater will make a final decision. The goal to investigate the differences between the raters.

5.2 *Standard clinical care versus extra for research*

N.A.

5.3 *Please describe the burden and risks associated with participation, e.g. the amount and number of blood samples, biopsies, liquor, hair, urine, nails, saliva etc., the number of site visits, physical examinations or other tests, questionnaires or diaries that have to be filled out, physical and psychological discomfort associated with participation*

N.A.

5.4 *A risk-benefit analysis must be given, if applicable.*

N.A.

5.5 *Medical device(s)/In vitro diagnostic tests*

N.A.

6. Unexpected discoveries

6.1 Is there a chance of unexpected discoveries?

☐ Yes

X No

6.2 If yes, describe the procedures, who will be notified, how the subjects are notified.

N.A.

7. Exchange, sharing or transfer of data and/or human material and/or images outside Erasmus MC

N.A

8. Statistical analysis

8.1 Main study parameter/endpoint

The primary endpoint is a description of the main etiologies found within patients with an elevated troponin T after non cardiac surgery.

8.2 Secondary study parameters/endpoints

Differences in the adjudication process between different doctors will be assessed according to intraclass coeficients and Fleisch Kappa[12].

8.3 Other study parameters:

N.A.

9. Recruitment and consent

9.1 *Will the subjects be asked for informed consent?*

☐ Yes *(Upload Patient Information Letter and Informed Consent)*

☐ No, only anonymous data is used, i.e. the data can never be traced back to an individual subject

X No, this research will be performed under the exception consent

(Upload form Care for data Template, in Dutch: Formulier uitzondering toestemming)

☐ Other (e.g. partly, indirectly) *Please describe the situation.*

9.2 *If yes, please give a description of the recruitment and informed consent procedures.*

N.A.

9.3 *If no, exception consent: describe how it is safeguarded that subjects are excluded who have objected against the re-use of their data, human material, images.*
Since the primary endpoint is 1-year mortality, asking for informed consent is virtually impossible.

10. Handling and storage of data and images

10.1 *Describe how subject's privacy is protected. Describe how, when and by whom data is coded, and how the key table is safeguarded.*
All study patients will be given an anonymous study ID, untraceable to the patient.

Baseline and outcome data, hemodynamic and laboratory data will be entered in the Clint/DRE database of the Erasmus MC or directly extracted from the hospital information system and stored on the DRE. After the adjudication process has finished, all research data will be anonymized so that cannot be traced to individual persons and can only be viewed by authorized personnel. These persons are the principal investigators of this study, members of the health care inspection and members of the Medical Research Ethics Committee.

For this, a separate file containing the code for unblinding will be kept in the Erasmus MC environment and will only be accessible to those directly involved in the study.

10.2 *Describe how data is stored (i.e. which data management system/data capture system), who has access to the coded source data, how long data will be kept, which steps are taken to ensure data security, what happens with the data after the research has been completed.*

All collected data in this study will be stored in a secure environment inside the Erasmus MC and can only be accessed by those involved in data management and analysis for the study. The hemodynamic and laboratory data that will be extracted from the electronic medical record and will be stored in a secure environment in the DRE and are only accessible to study staff.

Both data sources will be stored for 15 years.

10.3 *Describe how images are stored, how the subject's privacy is protected, what happens with images after the research has been completed.*

N.A.

10.4 *Describe how approval of re-use of data and/or images is obtained.*

N.A.

11. Handling and storage of human material

N.A.

12. Amendments

N.A.

13. Publication

Do you have the intention to submit the study results in a manuscript for publication in a journal:

X Yes

☐ No, *please motivate*

14. References

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6. Biccard, B.M., et al., *Myocardial Injury After Noncardiac Surgery (MINS) in Vascular Surgical*

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15. Attachments

N.A.