RESEARCH PROTOCOL

Troponin Elevation After Major noncardiac Surgery (TEAMS)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
ASA	**American Society of Anesthesiologists class**
BNP	**Brain natriuretic peptide**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRP	**C-reactive protein**
CV	**Curriculum Vitae**
ENIGMA II	**Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia**
ECG	**Electrocardiogram**
eGFR	**Estimated glomerular filtration rate**
GCP	**Good Clinical Practice**
GP	**General practitioner**
Hb	**Hemoglobin**
IC	**Informed Consent**
ICU	**Intensive care unit**
NITE	**Non-infarct troponin elevation**
NoCAE	**Noncardiac adverse event**
MACE	**Major adverse cardiovascular event**
MAPE	**Major adverse postoperative event**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MINS	**Myocardial injury after noncardiac surgery**
PMI	**Postoperative myocardial injury**
RCRI	**Revised Cardiac Risk Index**
(S)AE	**(Serious) Adverse Event**
SIRS	**Systemic inflammatory response syndrome**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
TTE	**Transthoracic echo**
UHNT	**University Health Network Toronto**
UMCU	**University Medical Center Utrecht**
VISION	**Vascular Events in Noncardiac Surgery Patients Cohort Evaluation**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WHODAS	**World Health Organisation Disability Assessment Score**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Patients undergoing major noncardiac surgery may experience major adverse postoperative events (MAPE), which lead to mortality and morbidity. Such complications are hard to diagnose, as typical symptoms are often not present in most often postoperative patients (e.g., chest pain may be masked by pain medication).

Routinely measuring cardiac troponins during the perioperative period is an accurate method to confirm diagnosis of postoperative myocardial injury (PMI). In patients aged > 60 years undergoing intermediate or high risk noncardiac surgery, PMI occurs in 15% of the patients. Approximately one third of them develops an often symptomless myocardial infarction. However, PMI is also associated with other cardiac and noncardiac pathologies including heart failure, arrhythmias, pulmonary embolism, sepsis and renal failure. Therefore, we consider PMI as either myocardial infarction or noninfarct troponin elevation (NITE). Currently, the etiology and long term effects of PMI on disability are unknown. Differentiation of patients with PMI in the appropriate disease entity will hopefully contribute to more suitable treatment and prevention of major complications.

The aim of this study is to investigate and compare the independent prognostic effects of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability. We will be diagnosing the differing PMI phenotypes using clinical evaluation and biomarkers.

Objective:

Primary objective

To investigate and compare the independent prognostic effects of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability in patients undergoing elective noncardiac surgery.

Secondary objectives

1. To investigate and compare the independent prognostic effect of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability free survival in patients undergoing elective noncardiac surgery.
2. To examine whether (combinations of) perioperatively measured biomarkers are associated with in-hospital MAPE in patients undergoing elective noncardiac surgery. MAPE are divided in different subtypes, including:
    a. MACE, which is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal ventricular fibrillation,

ventricular hemodynamic compromise, atrial fibrillation requiring cardioversion, pulmonary embolism and stroke.

b. Noncardiac MAPE including sepsis, renal failure, unexpected intensive care unit (ICU) admission and respiratory disorders.
c. All-cause mortality

3. To examine whether (combinations of) perioperatively measured biomarkers are associated with 6-month MACE and all-cause mortality in patients undergoing elective noncardiac surgery.
4. To assess the added value of the perioperatively measured biomarkers on top of the currently used Revised Cardiac Risk Index (RCRI) to predict MACE after noncardiac surgery.

Study design

This prospective observational cohort study includes patients, aged 60 years and older, undergoing elective intermediate or high risk noncardiac surgery under spinal or general anesthesia with an expected postoperative hospital admittance of at least 24h. All patients are required to visit the preanesthesia outpatient clinic for preoperative consultation. In addition to care as usual, extra blood samples will be taken preoperatively and postoperatively up to three days after surgery to determine the following biomarkers: high sensitive troponin, brain natriuretic protein, C-reactive protein, creatinine and hemoglobin. At postoperative day 2, extra to routine care noninvasive imaging (i.e. electrocardiography and transthoracic echography) will be performed. Preoperatively measured biomarkers are considered baseline measurements. Biomarker values will be blinded from treating physicians in case this particular biomarker was not measured in routine care. In-hospital MAPE will be monitored including cardiac events, respiratory failure, pulmonary embolism, sepsis, renal failure and mortality. In addition, patients will be asked to fill out the WHODAS 2.0 questionnaire preoperatively and 6 months after their surgery to assess disability. Their general practitioners (GPs) will be approached to determine whether MACE and/or mortality have occurred during the 6 months follow up after surgery.

Study population

Patients aged >60 years undergoing elective intermediate (e.g. hip replacement) or high risk (e.g. liver resection) noncardiac surgery under general or spinal anesthesia with a postoperative hospital stay of at least 24 hours are eligible for participation in this study. We aim to include 500 patients in this study. Approximately 1,200 patients undergo elective major noncardiac surgery each year in the UMC Utrecht. Taking into account nonparticipation and potential lower inclusion rates at the

beginning of the study, the estimated inclusion time is one year with six months follow-up resulting in a total study time of 18 months.

Main study parameters/endpoints:

Primary end points:

Disability is expressed in terms of the WHODAS 2.0 which is based on different functional domains, including cognition, mobility, self-care, getting along, life activities and participation.

Secondary endpoints:

- *Disability free survival* is defined as being alive with a WHODAS 2.0 score ≤ 25% and no increase of the preoperative score ≥ 25% at 6 months after surgery.
- *An in-hospital major adverse postoperative events (MAPE)*, which could be distinguished in:
    - *Major adverse cardiac event (MACE),* which is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal ventricular fibrillation, non-fatal ventricular hemodynamic compromise and atrial fibrillation requiring cardioversion.
    - *Noncardiac MAPE,* which is defined as a composite outcome consisting of respiratory disorders (including pneumonia and respiratory failure), pulmonary embolism, sepsis and/or systemic inflammatory response syndrome (SIRS), renal failure, reoperation and unplanned ICU admission.
- *In hospital all-cause mortality*
- *Length of hospital stay*
- *6-month MACE*
- *6-month all-cause mortality*

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

In addition to routine care, patients will be asked to fill out the WHODAS 2.0 before surgery and additional blood will be drawn (7 cc in total) before induction of anesthesia. Postoperatively, extra blood will be taken up to three days after surgery (7 cc in total each time) during routine blood draws. At postoperative day 2, an electrocardiogram (ECG) and transthoracic echo (TTE) will be performed. Six months after surgery, patients will be asked to fill out the WHODAS 2.0 for the second time and their GPs will be approached to assess whether clinically relevant events have occurred. The study is associated with a negligible risk as only noninvasive imaging procedures will be performed

and blood will be drawn. The treating physician will be notified in case any unexpected findings from the ECG and TTE are observed meaning that participation to this study could lead to early recognition of heart disease.

1. INTRODUCTION AND RATIONALE

Worldwide, over 300 million patients undergo major noncardiac surgery every year[1] and this number has been increasing continuously[2]. Despite the beneficial aspects of surgery, approximately 19% of these patients will suffer an in-hospital major adverse postoperative event (MAPE)[3]. The most common MAPE had an infectious (33%) or cardiovascular origin (19%) with highest mortality rates observed in patients with a major adverse cardiac event (7.0%)[3]. Major adverse cardiac events (MACE) are a leading cause of postoperative morbidity and mortality[4–7] and is associated with prolonged hospitalization and increased medical costs[8].

Several new guidelines regarding perioperative cardiac risk assessment in patients undergoing noncardiac surgery recommend routine postoperative surveillance of troponin to improve early recognition of postoperative myocardial injury (PMI)[4]. Cardiac troponin is a highly sensitive, specific biomarker for myocardial injury and has been found to be independently associated with mortality[4,9]. PMI is defined as an elevation in cardiac troponin I above the 99th percentile with a 10% variation[10]. Reported incidences of PMI in patients undergoing major noncardiac surgery are between 11 and 19%[4,6], depending on the study population and emergency status of the surgery. However, the etiology and long term effects of PMI are largely unknown. The most common phenotype of PMI is a myocardial infarction, which occurs in approximately one third of the patients with PMI. Diagnosis of myocardial infarction in patients with PMI is hard as only 10-15% of the patients experience typical ischemic symptoms due to the analgesic and sedative effects of anesthetics[7,9]. However, PMI is also seen in other cardiac pathologies including heart failure, arrhythmias and pulmonary embolism, but is also associated with noncardiac adverse events, such sepsis, respiratory and renal failure[11]. Therefore, we consider PMI as either myocardial infarction (by the third universal definition[10]) or as noninfarct troponin elevation (NITE). Higher mortality rates are observed in patients with myocardial infarction compared to patients suffering NITE (adjusted hazard ratio (HR) 3.4, 95% CI 2.6-4.5 and adjusted HR 1.9 95% CI 1.4-2.5, respectively)[12]. However, the risk of death in patients with NITE is still significantly higher compared to patients without PMI meaning that identification of these patients in appropriate disease entities is essential.

The effect of the phenotypic diversity of PMI on MAPE, including cardiac and noncardiac events, has not been fully investigated. A pilot study found that measuring additional biomarkers (i.e. high sensitive troponin, brain natriuretic peptide, C-reactive protein, hemoglobin, creatinine, electrocardiography and transthoracic echocardiography) could easily discern the varied etiologies of PMI. Perioperative measuring of these biomarkers could potentially uncover the underlying disease entities, including ischemia (myocardial infarction), cardiac function (heart failure) and renal

function, in patients with PMI and thereby, patients will be treated more appropriately and major complications could (hopefully) be prevented.

Nowadays, the Revised Cardiac Risk index (RCRI) is commonly used as a predictive tool to estimate the probability of MACE or mortality[13]. The RCRI includes six predictors, which are high risk surgery, history of myocardial infarction (MI), history of cerebrovascular disease, chronic heart failure, elevated creatinine and insulin dependent diabetes. Ford et al. performed a review on the performance of the RCRI in several validation studies and found that this cardiac index only moderately predicts, does not predict events in vascular surgery, and has not been prospectively validated using troponin or other biomarkers to predict MI or other cardiac events[14]. Since this publication, several studies reported the added predictive value to the RCRI of one (or more) biomarker(s), including (high sensitive) troponin [15–17], (NT-pro)BNP [15,16,18–20], eGFR[21,22], CRP[18,20], ECG [23,24]and transthoracic echocardiography[19,25]. Addition of (high sensitive) troponin, (NT-pro)BNP and/or CRP to the RCRI seems promising for the prediction of MACE as the predictive performance significantly improves compared to the RCRI by itself. To our knowledge, different combinations of several biomarkers together in addition to the RCRI have not been reported yet.

Our primary objective is to investigate and compare the independent prognostic effect of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability. We will be diagnosing the differing PMI phenotypes using clinical evaluation and biomarkers. The primary endpoint is disability. Disability is assessed using the World Health Organization Disability Assessment Score 2.0 (WHODAS 2.0) [26]. Our primary hypothesis is that any postoperative troponin elevation regardless of its association with MACE or noncardiac MAPE is independently associated with an increased risk of death and disability.

2. OBJECTIVES

2.1 Primary objective

To investigate and compare the independent prognostic effect of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability in patients undergoing elective noncardiac surgery.

2.2 Secondary objectives

1. To investigate and compare the independent prognostic effect of the different PMI phenotypes (myocardial infarction and NITE) and noncardiac MAPE on disability free survival in patients undergoing elective noncardiac surgery.
2. To examine whether (combinations of) perioperatively measured cardiac biomarkers are associated with in-hospital major adverse postoperative events (MAPE) in patients undergoing elective noncardiac surgery. MAPE are divided in different subtypes, including:
    a. Major adverse cardiovascular events (MACE), which is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal ventricular fibrillation, ventricular hemodynamic compromise, atrial fibrillation requiring cardioversion, pulmonary embolism and stroke.
    b. Noncardiac major adverse postoperative events (MAPE) including sepsis, renal failure, unexpected ICU admission and respiratory failure.
    c. All-cause mortality
3. To examine whether (combinations of) perioperatively measured cardiac biomarkers are associated with 6-month MACE and all-cause mortality in patients undergoing elective noncardiac surgery.
4. To assess the added value of the perioperatively measured biomarkers on top of the currently used Revised Cardiac Risk Index (RCRI) to predict major adverse cardiac events (MACE) after noncardiac surgery.

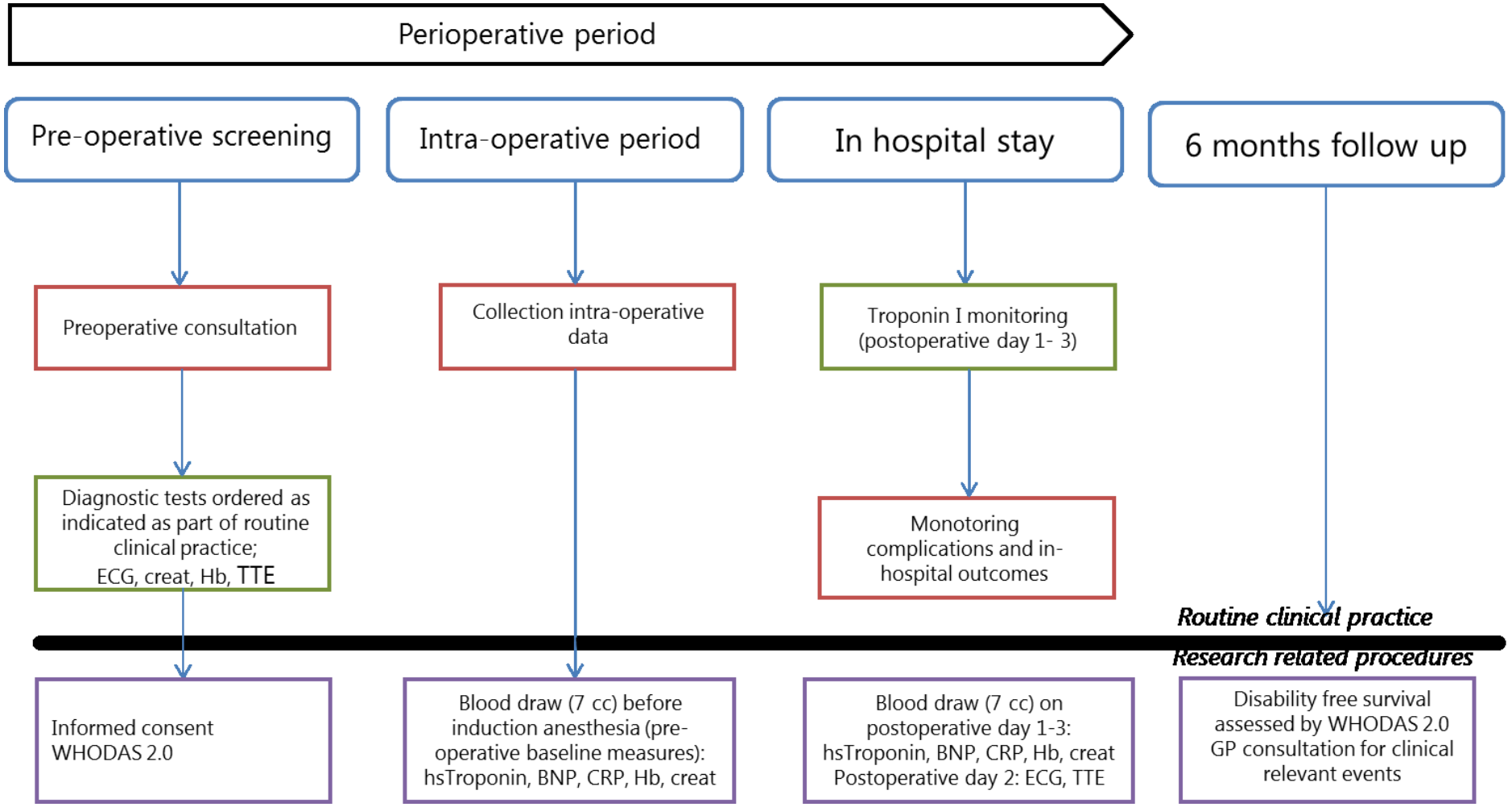
3. STUDY DESIGN

This prospective observational cohort study includes patients undergoing major elective noncardiac surgery. Major elective noncardiac surgery is defined as all surgical procedures under spinal or general anesthesia with a postoperative hospital admittance of at least 24 hours that have been preceded by a preoperative consultation at the preanesthesia outpatient clinic. Patients are treated at the University Medical Center Utrecht (UMCU).

Each year, approximately 1,200 patients undergo major noncardiac surgery at the UMCU. We intend to include 500 patients in this study. Taking non-participation into account and lower inclusion rate at the initial study phase, the expected duration of inclusion will be one year with a 6 month follow up leading to a total study period of 18 months.

In figure 1, an overview of the proposed study procedures is shown. In short, patients visit the preanesthesia outpatient clinic for preoperative consultation and will be asked to participate in our study. Standard diagnostic tests, such as ECG, will be performed based on local protocol or additional diagnostic tests or markers are requested at the discretion of the screening anesthesiologist. One week before surgery, patients will be approached by telephone and asked if they are interested in participation in our study. In case patients are willing to participate, the WHODAS 2.0 questionnaire is taken off by the researcher. Informed consent will be signed at the day of hospital admission before surgery . Extra blood will be drawn before induction of anesthesia and stored for biobanking. Postoperatively, blood samples will be drawn at postoperative days 1-3. At postoperative day 2, additional imaging (i.e. ECG and TTE) will be performed. In addition, in-hospital clinical relevant outcomes, including MACE and major noncardiac events, will be monitored. Patients are followed up until 6 months after surgery by sending them the WHODAS 2.0 and a questionnaire regarding the clinical relevant events (i.e. MACE and mortality) since the date of the surgery. Patients will be contacted by the researcher to take off the questionnaires by telephone. In addition, their general practitioners will be approached to ask similar questions regarding the patients' clinically relevant events during these 6 months follow up to verify details of the events.

Figure 1. Flowchart of proposed study procedures



ECG: electrocardiography; creat: creatinine; Hb: hemoglobin, TTE: transthoracic echocardiography, WHODAS 2.0: 12-item World Health Organization Disability Assessment Score 2.0; hsTroponin: high sensitive troponin; BNP: brain natriuretic peptide; CRP: C-reactive protein; GP: general practitioner.

4. STUDY POPULATION

4.1 Population (base)

Patients aged 60 years or older, undergoing major elective non-cardiac surgery under general or spinal anesthesia are eligible for study participation. Major elective noncardiac surgery is defined as all noncardiac surgical procedures requiring an expected hospital admittance of ≥ 24 hours that have been preceded by a preoperative consultation at the anesthesia preoperative screening outpatient clinic. For patients who undergo surgery more than once, the first surgery will be included in the analysis. Reoperations will not be included.

4.2 Inclusion criteria

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

- ≥ 60 years old;
- Major noncardiac surgery defined as all noncardiac surgical procedures requiring an expected hospital stay of at least 24 hours;
- Elective surgery, defined as surgery that that has been preceded by a preoperative consultation at the anesthesia preoperative screening outpatient clinic.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients unable to fully comply to study needs (e.g. legally incapablepatients or patients unable to communicate in Dutch or English).
- Patients with an American Society of Anesthesiologists (ASA) Physical status 5

4.4 Sample size calculation

For this study, we aim to include 500 patients at the UMCU in this study. A similar study will be conducted at the University Health Network Toronto (UHNT), Toronto, Canada and they will include 500 patients with the same in- and exclusion criteria. After including all patients in both centers, we will combine the data resulting in a total study population of 1,000 patients. In a previous conducted pilot study by the UHNT (registered at ClinicalTrial.gov: NCT02146560), 300 patients undergoing major elective noncardiac surgery were included and disability was assessed by the WHODAS 2.0 after 6 months. The incidence of troponin elevation in this pilot was 14.1%. We do however expect an incidence of 11.0% as patients included in the pilot were mainly vascular patients, who are more

prone to have postoperative troponin elevations[4]. The mean WHODAS 2.0 in patients with an elevation in troponin was 29% compared to 15% in patients without troponin elevation. Based on these results, and using a level of significance of 0.05 and a power of 0.8 we expect 104 patients with troponin elevation. As the ratio between troponin elevation and no troponin elevation is 0.89/0.11 = 8, we need to include 832 patients. We expect a dropout of 20% (based on the number of patients who did not fill out the WHODAS 2.0 after 6 months in the pilot study), leading to a final sample size of approximately 1,000 patients.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

Disability is expressed by the WHODAS 2.0, which is based on difficulties experienced by the respondent in different functional domains including, cognition, mobility, self-care, getting along, life activities and participation during the previous 30 days. Disability is defined as a decrement in each functioning domain corresponding to score between 0% and 100%, in which no disability stands for a score of 0% and full disability represents a score of 100%, including death. The WHODAS 2.0 is easy to use and patient centered (see F1 for the questionnaire). In a validation study including noncardiac surgical patients, the WHODAS 2.0 has been found to be a clinically acceptable, valid, reliable and responsive instrument for measuring postoperative disability[27].

5.1.2 Secondary study parameters/endpoints

- *Disability free survival* is defined as being alive with a WHODAS score ≤ 25% and no increase of the pre-operative score ≥ 25% at 6 months after surgery.
- *An in-hospital major adverse postoperative events (MAPE)*, which could be distinguished in:
    - *Major adverse cardiovascular event (MACE),* which is defined as the composite endpoint of:
        - Cardiovascular death, defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and any acute death unconfirmed yet probably due to a cardiovascular cause.
        - Non-fatal myocardial infarction, defined in accordance to the third universal definition of myocardial infarction[10].
        - Non-fatal cardiac arrest.
        - Non-fatal ventricular fibrillation.
        - Ventricular arrhythmia with hemodynamic compromise.
        - Atrial fibrillation requiring cardioversion.
        - Pulmonary embolism, defined as a new thrombus within the pulmonary arterial system confirmed on CTA
        - Stroke confirmed on CT.
    - Noncardiac MAPE, which is a composite outcome consisting of:
        - Respiratory failure including pneumonia and hypoxia or hypercapnia leading to ICU admission for respiratory support

  - Sepsis and/or systemic inflammatory response syndrome (SIRS), defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[28].
  - Renal failure, defined as AKIN criteria or renal replacement therapy.
  - Unplanned ICU admission
  - Unplanned medium care admission
  - Reoperation
- *Length of hospital stay, defined as the number of days from the end of surgery until day of discharge*
- *In-hospital all-cause mortality*
- *6-month all-cause mortality*
- *6-month MACE*

5.1.3 Other study parameters

- Baseline characteristics including:
  - Demographics, i.e. age, gender, BMI, smoking status, American Society of Anesthesiologists class (ASA).
  - Comorbidities, including history of the following diseases: myocardial infarction, cerebrovascular disease, congestive heart failure and cancer. Currently diagnosed with: diabetes, coronary artery disease, chronic renal failure, cancer, chronic obstructive pulmonary disease, peripheral vascular disease, and hypertension.
  - Medication use, including beta blockers, angiotensin converting enzyme inhibitors, calcium blockers, diuretics, statins, insulin, oral antidiabetics.
  - Surgical history, including coronary revascularization, pacemaker or implantable cardioverter defibrillator (ICD).
  - Laboratory results of preoperatively measured blood biomarkers, i.e. hsTroponin, C-reactive protein (CRP), brain natriuretic peptide (BNP), hemoglobin (Hb) and creatinine in blood. Imaging biomarkers are electrocardiogram (ECG) and transthoracic echocardiogram (TTE).
  - Referral of the screening anesthesiologist at the preanesthesia consultation clinic to a cardiologist or other specialist before surgery
  - Preoperative WHODAS 2.0
- Intraoperative:
  - Anesthesia related including type of anesthesia (general or spinal), vital signs (i.e. blood pressure, heart rate, eCO2).

- Surgical related factors: surgical risk, surgical specialty, blood loss, number of blood transfusions and fluid balance.

- Postoperative:
  - Troponin I monitoring at postoperative day 1-3 as being part of routine care.
  - Laboratory results of postoperative measured blood biomarkers, i.e. hsTroponin, CRP, BNP, Hb and creatinine in blood on postoperative day 1-3. Imaging biomarkers (ECG and TTE) on postoperative day 2.
  - Rehospitalization within 6 months after surgery.

5.2 Randomization, blinding and treatment allocation

Not applicable

5.3 Study procedures

Patient recruitment and preoperative clinical practice

Study eligibility will be checked by study personnel working at the preanesthesia outpatient clinic. Patients will be approached during the preoperative consultation and will be informed about the proposed study. Patients will receive extra study information together with the WHODAS 2.0 questionnaire, in case they are interested in participation in this study. Patients will be approached by telephone one week before surgery and asked if they would like to participate on this study. Hence, patients have the time between the preanesthesia visit and one week before surgery, which is more than 24 hours, to decide if they are willing to participate. If the patient is interested in participation, the WHODAS 2.0 survey will be taken by the researcher during this telephone call and patients will be assigned a study number. This number is used as a reference for storage of study data in the Case Report File (CRF). Access to study numbers correlating to patient names will only be available to the principal study investigator, research personnel involved in including patients and study monitors/auditors. Informed consent will be signed at hospital admission before surgery. If patients decline study participation, they will receive perioperative care as usual. Study material collected before signing informed consent (e.g. WHODAS 2.0 survey) will be deleted for patients who were interested during the telephone call but rejected participation at the moment of signing informed consent.

All patients are required to visit the preanesthesia outpatient clinic for preoperative consultation as part of usual care (i.e. non-study related). The following procedures will be performed:

- Patient characteristics regarding demographics, comorbidities, medication use, surgical and anesthetic factors will be collected by the anesthesiologist.

- If requested by the screening anesthesiologist, venous blood will be sampled for additional diagnostic testing as part of routine care. Data regarding information about preoperative biomarker determination will be collected. This means that not all patients require preoperative venous sampling, only if indicated.
- An ECG will be performed and assessed by the screening anesthesiologist.

All data collected at the preoperative consultation clinic, including biomarker determination (i.e. ECG and blood biomarkers) will be interpreted as baseline measurements.

Hospital admittance and intraoperative data collection

For patients who agreed on study participation during the telephone call one week before surgery, informed consent will be signed by the patient and study investigator. If a patient decides to decline study participation at this point, this patient will receive routine care as usual. The treating anesthesiologist will be informed about participation and 7 cc blood will be drawn at the operation theatre immediately before induction of anesthesia. Blood will be collected, processed and stored at the Centrale Biobank (CBB) with corresponding study number. Blood biomarkers will be considered preoperative baseline values. During surgery, the following data will be collected:

- Vital signs, i.e. blood pressure, heart rate and ET-CO2.
- Blood loss and number of blood transfusions
- Duration of surgery

Collection of intraoperative data is part of routine clinical care; no study related procedures will be conducted.

Postoperative in hospital stay

At postoperative day 1-3, the following procedures will be performed:

- Extra blood (7 cc each time) will be drawn during the standard blood sampling rounds in the morning. Blood will be processed and stored at the CBB.
- At postoperative day 2, an ECG and TTE will be performed by certified study personnel and uploaded at the local electronic health record (EHR) and a digital databank.
- In-hospital MAPE, such as MACE, unplanned ICU admission, respiratory disorders, renal failure, sepsis and/or SIRS and mortality will be monitored.

At the UMCU, troponin-I is routinely monitored in all patients, aged ≥ 60 years, undergoing major noncardiac surgery. In case troponin-I is elevated, routine (i.e. non-study related) hospital protocol procedures involve an ECG and consultation by an anesthesiologist. The anesthesiologist could consult a cardiologist for further examination. Additional diagnostic tests or initiation of therapy is

based on the cardiologist's discretion which is done in deliberation with the treating physician. Patients without troponin elevation only undergo cardiac assessment if deemed necessary by the ward physician. The treating physician will be blinded from the extra study related biomarker values except they request determination of (one or more) biomarkers as being part of usual care.
The imaging biomarkers (i.e. ECG and TTE) will be uploaded in the EHR and on a digital databank. Due to logistical reasons, blinding of the imaging results is hardly feasible as all these results are uploaded to our local EHR automatically. By nature of the procedure, it might happen that an unexpected finding which could compromise the patient's health will be observed by the study personnel performing the ECG or TTE. In that occasion, the treating physician will be notified and the treatment strategy will be adapted if deemed necessary.

Hospital discharge of last patient

All blood samples stored at the CBB will be analyzed for the previous mentioned biomarkers in one batch after hospital discharge of the last patient, meaning that this information will not be available to the treating physician. High sensitive troponin will be determined in addition to the routinely measured troponin I as recent studies concluded that the detection rate of myocardial infarction is increased by factor 2 when using the high sensitive troponin compared to the contemporary assay[29]. Only if the physician requested determination of (one or more) biomarkers as part of clinical care, the biomarker value is known as being part of routine clinical practice. Availability of these biomarkers to the treating physician will also be registered as these biomarkers could influence clinical care of these patients, and hence patient outcomes. Imaging biomarkers, i.e. ECG and TTE, will be assessed by an independent cardiologist who was unaware of any patient related clinical factors. All preoperative patient data will be merged to the biomarker results using the corresponding study number and hospital identifier.

6 month follow up

Patients will be followed up for 6 months after the day of surgery. Follow-up involves:

- Answering the WHODAS 2.0 questionnaire and a questionnaire regarding patient's health since the surgery (see F1. Vragenlijst 6 maanden follow up and F1. Vragenlijst WHODAS). Both questionnaires will be sent to the patient's home address and in the accompanying letter, a date with time will be mentioned during which patients could expect a telephone call by the researcher. The questionnaires will be taken off by telephone. In case of nonresponse, the researcher will approach the patient at another time to keep the response rate as high as possible.

- Approaching the patient's general practitioner to obtain information regarding postoperative events in the previous 6 months after surgery. This information will include clinically relevant events, such as MACE, hospital admission/consultation and change in medication prescription. In case patients are admitted or consulted at a hospital, the corresponding treating physician will be approached as well for clinically relevant information.

Before sending the questionnaires to the patient's home address, the GBA (Gemeentelijke Basisadministratie) will be used to find out whether the patient is still alive, to avoid sending questionnaires and calling patients who have deceased. Follow up will end after completion of both questionnaires. All results will be merged to the preoperative patient characteristics and biomarker data using the corresponding study number and hospital identifier.

5.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. After withdrawal, subjects will be treated according standard of care. Subjects can withdraw informed consent for participation in 'deelbiobank' at any time for any reason. Samples and data already used for research, will not be destroyed, but stored in coded form after withdrawal from the 'deelbiobank'.

5.5 Replacement of individual subjects after withdrawal

Subjects who withdraw informed consent will not be replaced by new study participants. The time between signing informed consent and preoperative blood sampling is quite short (on average 30 minutes), hence we assume that it is very unlikely that patients withdraw informed consent before surgery. The collected data up to withdrawal of informed consent is still valid and will therefore be included in the analysis.

5.6 Follow-up of subjects withdrawn from treatment

Not applicable

5.7 Premature termination of the study

Since this is an observational cohort study measuring the difference in pre- and postoperative disability status, premature termination due to futility is not applicable.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, related to study procedures including venous blood sampling and noninvasive cardiac imaging. All blood draws for the current study are conducted during venous sampling for routine clinical care, hence potential undesirable experiences related to venous sampling (e.g., pain, bruising), are not to be attributed to the current study.

Adverse events related to noninvasive cardiac imaging, i.e. ECG and TTE include:

- Allergic reaction to the lubricating gel used during the TTE
- Mild skin rash where the electrodes for the ECG were attached

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. As these adverse events for both venous blood sampling and noninvasive cardiac imaging are very rare, the risk of participation in this study based on these procedures is low.

6.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

6.3 Annual safety report

Not applicable

6.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7. STATISTICAL ANALYSIS

7.1 Data description

Baseline characteristics will be presented using percentages for categorical covariates, means with standard deviations and/or medians with interquartile ranges for continuous variables. Comparison between baseline characteristics will be done using the chi-square test for categorical variables and Student's t-test or Mann Whitney-U test for continuous variables as appropriate. Based on a pilot study conducted at UHNT, we assume a patient dropout of 20% at 6 months follow up (see Sample size calculation). Baseline characteristics of patients who did and did not respond at 6 months follow up will be compared to examine whether selective dropout occurred. Multiple imputation will be performed in case of any missing data. Throughout the analyses, a *p-value* of 0.05 is considered statistically significant.

7.2 Primary study parameter(s)

The primary outcome, postoperative WHODAS 2.0 after 6 months, will be compared among patients with and without PMI, using Student's t-test or a nonparametric Mann Whitney U test. In case of normality, the mean 6-months WHODAS 2.0 will be calculated together with the accompanying 95% confidence intervals. Otherwise, the median WHODAS 2.0 with interquartile range will be reported.

With respect to the association between the different phenotypes of PMI (i.e. myocardial infarction, NITE and MAPE) and disability, the preoperative, postoperative and the change (meaning difference between pre- and postoperative measurements) in biomarkers are of particular interest. The biomarkers will be analyzed both as continuous variables and using predefined clinical thresholds to define when the each of the biomarkers are elevated. Combination(s) of different biomarkers and the biomarker by itself in association with postoperative WHODAS 2.0 will be performed. These combination(s) of biomarkers will be related to one of the different phenotypes of PMI. Multivariable linear regression analyses will be performed to adjust for potential confounders including age, gender, comorbidities (cardiovascular risk factors), preoperative WHODAS 2.0 score, RCRI and surgical specialty.

7.3 Secondary study parameter(s)

- Disability free survival will be described as percentages with their accompanying 95% confidence interval (CI) among patients with or without PMI. Different combinations of elevation in biomarkers will be tested. Comparison between different PMI phenotypes will be performed using chi-square test or Fisher's exact and multivariable logistic regression

analyses will be done to take several covariates into account, which are similar to confounders described for the primary analyses.

- Similar to disability free survival, MACE (including PMI and NITE), noncardiac MAPE and all-cause mortality will be presented as proportions with their accompanying 95% CI. Multivariable logistic regression analyses will be performed using MACE, noncardiac MAPE or all-cause mortality as outcomes, both in-hospital events and at 6 months (except for noncardiac MAPE as these will not be measured at 6 months). Different combinations of elevations in biomarkers (preoperative, postoperative and change between pre- and postoperative) will be tested against these outcomes to uncover correlations between particular combinations of elevated biomarkers to assess what disease entities are related to the outcome.
- A Kaplan-Meier method will be used to assess whether the cumulative incidence of 6-month mortality differs between patients with and without PMI. The probabilities of 6-month mortality between patients with and without elevation in (one or more) biomarker(s) will be compared using log-rank tests provided assumptions for this test are met. Cox-proportional hazard analyses will be performed to examine whether (one or a combination of several) biomarker(s) are associated with 6-month mortality adjusted for potential confounders.
- The added prognostic value of each of the biomarkers (or combinations of biomarkers) will be tested to predict MACE, both in-hospital and at 6-months. The biomarkers will be analyzed as continuous variables and using predefined clinical thresholds to define whether that particular biomarker is elevated. Multivariable logistic regression analyses will be performed using the predictors of the RCRI (i.e. high risk surgery, history of cerebrovascular disease, history of myocardial infarction, congestive heart failure, elevated creatinine and insulin dependent diabetes) as predictors together with the addition of elevation in biomarkers. Discrimination and calibration of the prediction models will be assessed using the c-statistic, Hosmer-Lemeshow test. The net reclassification index (NRI) and the Integrated Discrimination Index (IDI) will be calculated to quantify how well the updated RCRI reclassifies patients as compared to the traditional RCRI.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA general Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

Study eligibility will be checked by study personal working at the anesthesia preoperative consultation clinic. If study in- and exclusion criteria are met, patients will be informed about the proposed study by the anesthesiologist at the preanesthesia outpatient clinic. If interested, the patient will receive a written study information letter. One week before surgery, patients will be approached for the second time by telephone by the study investigator or a trained research nurse. In case patients are willing to participate, informed consent will be signed by the participant and the study investigator at the day of hospital admission before surgery. If patients decline study participation, they will receive perioperative care as usual.

8.3 Benefits and risks assessment, group relatedness

This is a non-therapeutic study without involvement of minors and/or incapacitated adults studying the independent prognostic effect of different PMI phenotypes and noncardiac MAPE on postoperative disability status. The burden to patients is low as in addition to routine care, only noninvasive imaging techniques (i.e. TTE and ECG) will be performed, extra venous blood will be drawn during standard blood sampling rounds, and a short questionnaire needs to be filled out twice. The study is associated with a negligible risk as appearance of any adverse events due to the study is very low. The patient might benefit from participation in this study as unexpected findings from the TTE and/or ECG might change the treatment strategy and individual prognosis of that patient.

8.4 Compensation for injury

The sponsor, University Medical Center Utrecht, wishes to obtain dispensation from the statutory obligation to provide insurance, because participating in the study is without risks. The Medical Ethical Committee of the UMCU agreed to provide dispensation for this study.

8.5 Incentives

No travel or other expenses will be reimbursed as all hospital visits are being part of usual care.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Study data will be collected in encrypted electronic Case Report Forms (CRF's) using unique identification numbers to ensure confidentiality. A separate document will contain the key to link the subject identification numbers to the study participants. This key will be safeguarded by the data manager. Data will be accessible to the research team, study monitors/auditors and the inspection. Results of the blood and imaging biomarkers will not be available for treating physicians meaning that this data will not be used in clinical practice, except if the treating physician requests determination of one (or more) biomarker(s). Patients will be followed up after 6 months by sending two questionnaires using name and address details. Data will be stored for 15 years.

Blood samples will be stored at the Centrale Biobank of the UMC Utrecht for undetermined period of time. Usage of these blood samples by other investigators (from the UMC Utrecht) for future research purposes will be possible if they submit a specific research question to the 'Toetingscommissie Biobanken'.

9.2 Monitoring and Quality Assurance

Monitoring will be performed by a qualified monitor according to the monitoring plan (see K6. Monitoring plan for a more detailed description).

9.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as collection of the last patient's 6-months WHODAS

2.0. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.6 Public disclosure and publication policy

The results of the proposed study are publically disclosed on the basis of the participation of patients in it, following the principles of the CCMO's statement on disclosure of publication of results. The sponsor is entitled to examine the manuscript prior to publication and to make comments on it.

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