Implementation of a clinical screening and response system for the early detection of cardiac complications after noncardiac surgery: feasibility and medicoeconomic impact (Implement-PMI)

Type of Research Project:	Research project in which health-related personal data is collected
Risk Categorisation:	A (clinically recorded routine data, prospective follow up)
Project Identifier:	Implement-PMI
Project Leaders:	Dr. Christian Puelacher, MD-PhD, University Hospital Basel, Petersgraben 4, 4031 Basel, christian.puelacher@usb.ch, +41 76 403 4450 Prof. Christian Müller, University Hospital Basel, Cardiology, Petersgraben 4, 4031 Basel; christian.mueller@usb.ch, +41 61 328 65 49
Health condition / problem	Perioperative myocardial infarction/injury Major adverse cardiac events after major non-cardiac surgery
Project Duration	01.06.2021 – 01.12.2025
Project Plan Version and Date:	Version 1.2, 2022-05-023

Signature Pages

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and the methodologist (Dr. Christian Puelacher MD-PhD, Prof. Christian Müller MD) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Co-Project Leader and project methodologist:
Dr. Christian Puelacher, MD-PhD

Place/Date _____ Signature _____

Co-Project Leader:
Prof. Christian Müller, MD

Place/Date _____ Signature _____

Signature Page 2: Cantonal Hospital Lucerne

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and local principal investigator (PI) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Local PI*:*
Dr. Matthias Bossard, MD

Place/Date	Signature

Signature Page 3: Cantonal Hospital Olten

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and local principal investigator (PI) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Local PI*:*
PD Dr. Nisha Arenja, MD

Place/Date	Signature

Signature Page 4: University Hospital Innsbruck

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and local principal investigator (PI) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Local Co-PI:
PD Dr. Judith Martini

Place/Date	Signature

Local Co-PI:
Dr. Petra Hillinger:

Place/Date	Signature

Signature Page 5: University Hospital Geneva

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and local principal investigator (PI) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Local PI*:*
PD Dr. Bernardo Bollen Pinto, MD, PhD

Place/Date	Signature

Signature Page 5: Cantonal Hospital Solothurn

Project number	Implement-PMI
Project Title	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact

The project leaders and local principal investigator (PI) have approved the research plan Version 1.2, 2022-05-023, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, GCP, the STROBE Guidelines, and the local legally applicable requirements.

Local PI*:*
PD Dr., Nisha Arenja, MD

Place/Date	Signature

Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitor
AHF	Acute heart failure
AHF-PMI	PMI caused by acute heart failure
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor blocker and neprilysin inhibitor
ASA	Acetylsalicylic acid (Aspirin)
BASEL-PMI	Basel Incidence, Patient Characteristics, Outcome and possible Strategies to improve Outcome of Perioperative Myocardial Injury after non-cardiac surgery: 1-Year Follow-up
CAD	Coronary artery disease
CHF	Chronic heart failure
CI	Confidence interval
CTn	Cardiac troponin
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
Hs-cTnT/hs-cTnI	High-sensitivity cardiac troponin T / high-sensitivity cardiac troponin I
IDDM	Insulin-dependent diabetes mellitus
MACE	Major adverse cardiac events
NIDDM	Non-insulin-dependent diabetes mellitus
MS	Milestones
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PI	Principal investigator
PID	Patient identification number
PMI	Perioperative myocardial injury/infarction
SGLT-2	Sodium-glucose cotransporter 2
Implement-PMI	Implementation of a clinical screening and response system for perioperative myocardial infarction/injury after noncardiac surgery: feasibility and medicoeconomic impact
T1MI-PMI	PMI caused by type 1 myocardial infarction
Tachy-PMI	PMI caused by acute tachyarrhythmia
WP	Work package

Administrative structure

Co-Principal investigator, project Leader, methodologist, and coordinating researcher	Institution. University Hospital Basel, Cardiology Name: Christian Puelacher, MD-PhD Address: Petersgraben 4 Email: Christian.puelacher@usb.ch Phone: +41 61 556 58 30 Fax: +41 61 265 85 77
Co-Principal investigator, sponsor, project leader and coordinating researcher	Institution. University Hospital Basel, Cardiology Name: Christian Müller, Professor, MD Address: Petersgraben 4 Email: Christian.mueller@usb.ch Phone: +41 61 328 65 49 Fax: +41 61 265 85 77
Local principal investigator Lucerne:	Name: Matthias Bossard, MD Address: Spitalstrasse 16, 6000 Luzern Email: matthias.bossard@luks.ch Phone: +41 41 205 14 77
Local principal investigator Olten and Solothurn:	Name: Nisha Arenja, MD Address: Baslerstrasse 150, 4600 Olten Email: nisha.arenja@spital.so.ch Phone: +41 62 311 41 30
Key person in Olten	Name: Reto Paganoni, MD Address: Baslerstrasse 150, 4600 Olten Email: reto.paganoni@spital.so.ch Phone: +41 62 311 47 11
Key person in Solothurn	Name: David Garay Address: Schöngrünstrasse 42, 4500 Solothurn Email: david.garay@spital.so.ch Phone: +41 32 627 43 84
Local Co-principal investigator Innsbruck:	Name: Judith Martini, PD, MD Address: Anichstraße 35, 6020 Innsbruck Email: judith.martini@tirol-kliniken.at Phone: +43 512 504 80478 Fax: +43 512 504 22450
Local Co-principal investigator Innsbruck:	Name: Petra Hillinger, MD Address: Anichstraße 35, 6020 Innsbruck Email: petra.hillinger@tirol-kliniken.at Phone: +43 512 504 80449 Fax: +43 512 504 22450
Key person in Innsbruck:	Name: Axel Bauer, MD Address: Anichstraße 35, 6020 Innsbruck Email: axel.bauer@tirol-kliniken.at Phone: +43 50 504 256 21 Fax: +43 50 504 256 22
Local principal investigator Geneva:	Name: Bernardo Bollen Pinto, MD, PhD Address: Geneva University Hospitals Department of Anaesthesia Rue Gabrielle-Perret-Gentil 4 1205 Geneva Email: bernardo.bollenpinto@hcuge.ch Phone: +41 795532125 Fax: +41 22 372 76 90

Key persons involved	Name: Noemi Glarner, MD-PhDc Address: Petersgraben 4, 4031 Basel Email: noemi.glarner@usb.ch Phone: +41 61 328 56 58 Fax: +41 61 265 85 77
Key persons involved	Name: Giovanna Lurati Buse, MD, MSc Address: Moorenstraße 5, 40225 Düsseldorf Email: Giovanna.LuratiBuse@med.uni-duesseldorf.de Phone: +49 211 8118102
Key persons involved	Name: Mirjam Pargger, MD-PhDc Address: Petersgraben 4, 4031 Basel Email: mirjamregula.pargger@usb.ch Phone: +41 61 328 56 58 Fax: +41 61 265 85 77

1. Background

Perioperative setting

The perioperative setting is increasingly recognised as an area of potential improvement. With over 300 million surgical procedures performed annually[1,2], especially in resource-rich countries (~900.000 procedures done per year in Switzerland and Austria, respectively)[1]. Demand for surgery is likely to increase in the coming years with an increasingly elderly and comorbid population[3]. Despite advances in many fields of medicine, there is still a significant risk of death related to major noncardiac surgical procedures: a recent study even estimated postoperative death to be the third leading cause of death worldwide, accounting for 7.7% of global mortality[4]. The observed postoperative 30-day mortality depends on patient as well as procedural factors and ranges between 1% and 10%, much higher than commonly anticipated[5–13].

Perioperative cardiac complications and myocardial infarction/injury

Perioperative myocardial infarction/injury (PMI), has been identified as a major contributor to these perioperative deaths[8,9,13,14]. First studies estimated that PMI, identified using high-sensitivity cardiac troponin (hs-cTn) only, is a major contributor to 34-42% of all deaths following noncardiac surgery within 30 days[5,9]. One of the key differences to spontaneous acute myocardial infarction (AMI) is that the vast majority of patients experiencing PMI do not show any typical ischemic symptoms, e.g. chest pain, or ischaemic changes on the electrocardiogram (ECG)[5,6,8–13,15]. The reasons were hypothesised to include intraoperative analgosedation and intense analgesia following surgery, but different pathophysiological mechanisms underlying PMI likely contribute[14,16–19]. As a consequence of the lack of typical symptoms and signs, most patients with PMI are currently not detected in routine clinical practice[5,6]. An elevated and dynamic value of cardiac troponin (cTn) is the sine-qua-non feature of AMI and due to its independence of symptoms and signs readily identifies patients with PMI if used as a routine screening in the perioperative phase. Importantly, patients with PMI detected via cTn not fulfilling any of these additional criteria of the Universal Definition of myocardial infarction required for the diagnosis of spontaneous AMI, showed a similar mortality to those that did (10.4%, 95% confidence interval [CI] 6.7-15.7 versus 8.7%, 95%CI 4.2-16.7, p=0.68)[13]. The finding that PMI is associated with such high mortality irrespective of whether it fulfils any additional criteria required for spontaneous AMI was also shown by other groups[9,13,15] and highlights the importance of implementing systematic screening using hs-cTnT.

An opportunity to improve outcome?

Detection of a previously often undetected perioperative complication offers an opportunity to improve perioperative noncardiac surgery outcomes. Pilot data generated in previous studies, including the BASEL-PMI study, yielded promising results: in a retrospective study, intensification of medical treatment was associated with a reduced rate of major adverse cardiac events compared to patients without intensification (hazard ratio 2.8, p=0.04)[20]. In a subanalysis of the POISE study, use of aspirin and statins was associated with a reduced risk of death within 30 days[21]. A first randomized controlled trial showed a reduction in a combined cardiovascular endpoint with the use of dabigatran (hazard ratio 0.72, 95% CI 0.55–0.93). Further, in BASEL-PMI we demonstrated a change in mortality trend associated with the threshold that triggered cardiac consultations (Figure 1)[13].

In light of these data, first guidelines have begun advocating for routine troponin screening via perioperative high-sensitivity cTn (hs-cTn) measurements[21–24]. Given that PMI is largely asymptomatic and associated with high mortality rates, developing effective screening and appropriate management strategies to improve perioperative outcomes is paramount.

However, details on implementation of such a PMI-screening as well as management recommendations are currently lacking, creating a situation of uncertainty in which other major guidelines recommend against screening[25]. Such striking differences create a situation of clinical uncertainty, which, if not addressed, will severely hamper the uptake in clinical routine, thus potentially missing an opportunity to improve perioperative care. Conversely, uncritical implementation of perioperative hs-cTn measurements might lead to overtreatment with e.g. coronary angiography. Indeed, previous studies have shown that only a minority of patients have

coronary findings suggestive of type 1 myocardial infarction, the typical presentation of spontaneous AMI[16,26–28]. Further, scarcity of resources calls for a balance in benefit and cost of any health program[29,30], an aspect incompletely understood for this novel hs-cTn-screening.
Currently, a small number of studies concerning PMI are ongoing. However, to the best of our knowledge, no study addresses our research topic. Registered trials currently focus on preventing PMI, with placebo-controlled trials testing colchicine (NCT04139655), ivabradine (NCT04436016), metoprolol (NCT03138603), and tranexamic acid (NCT03505723), as well as management strategies including hypothermia (NCT03111875), or perioperative hypotension avoidance strategies (NCT02533128, NCT03505723).

During the last years, we contributed significantly to the evolving evidence surrounding PMI. We successfully performed BASEL-PMI at three tertiary centres, one of the largest observational studies on this topic and the largest including high-risk patients (NCT02573532)[13,31–35]. Our analyses incorporated a definition of PMI in line with the Universal Definition of Myocardial Infarction, by measuring a preoperative baseline hs-cTn value to reliably distinguish acute events from chronic elevations[13]. Besides corroborating the results from previous studies showing the strong association of PMI with mortality, we undertook efforts to elucidate subtypes of PMI. First, we described in 2546 single centre cases the distinction between “cardiac” PMI (analogous to the previously prospectively derived “myocardial injury after noncardiac surgery (MINS)”[5,9,15]) versus “extracardiac” PMI, caused by primarily extracardiac events such as severe sepsis[13]. We found strikingly different associated outcomes of 6.1% (95%CI 3.6-10.0%) mortality within 30 days after cardiac PMI vs 33% (95%CI 20–48%) after extracardiac PMI.
At our institution we had already implemented routine hs-cTnT screening into clinical practice, with cardiology consultations following detection of PMI. In an exploratory analysis, we found a change in mortality trend associated with the threshold that triggered cardiac consultations (Figure 1)[13], providing further evidence for the potential to improve outcome with PMI screening.

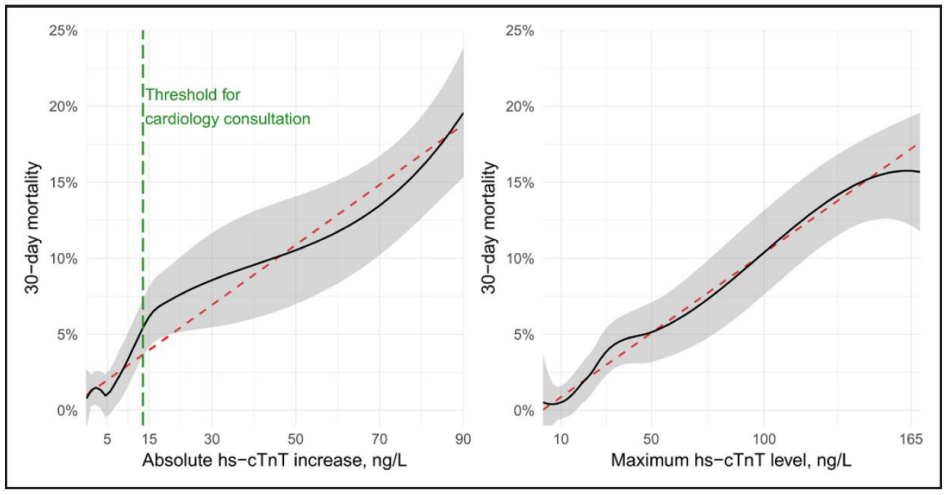

Figure 1 *Association of 30-day mortality in percent with* ***left****) absolute hs-cTnT increase and* ***right****) maximum hs-cTnT level. The green dashed line indicates the threshold for activating the response system of PMI in BASEL-PMI*[13]

We expanded on this first study by engaging two further centres in our prospective observational study and increased the sample size significantly to further explore the aetiology of PMI. After inclusion of 5602 cases with 848 detected PMI, we were able to show that PMI can be further grouped into different aetiologies: only a minority of PMI cases (7%) seems to be caused by type I myocardial infarction due to atherothrombosis, and type II myocardial infarction due to supply-demand mismatch as well as acute injury resulting from tachyarrhythmias, acute heart failure, or extracardiac PMI are as common[33] (Figure 2). These distinct aetiologies show starkly different outcomes (Figure 3), highlighting the unmet clinical need. However, identification of these subtypes also may help clinicians, as guidelines are available, providing management recommendations for clinicians confronted with asymptomatic PMI[36–41].

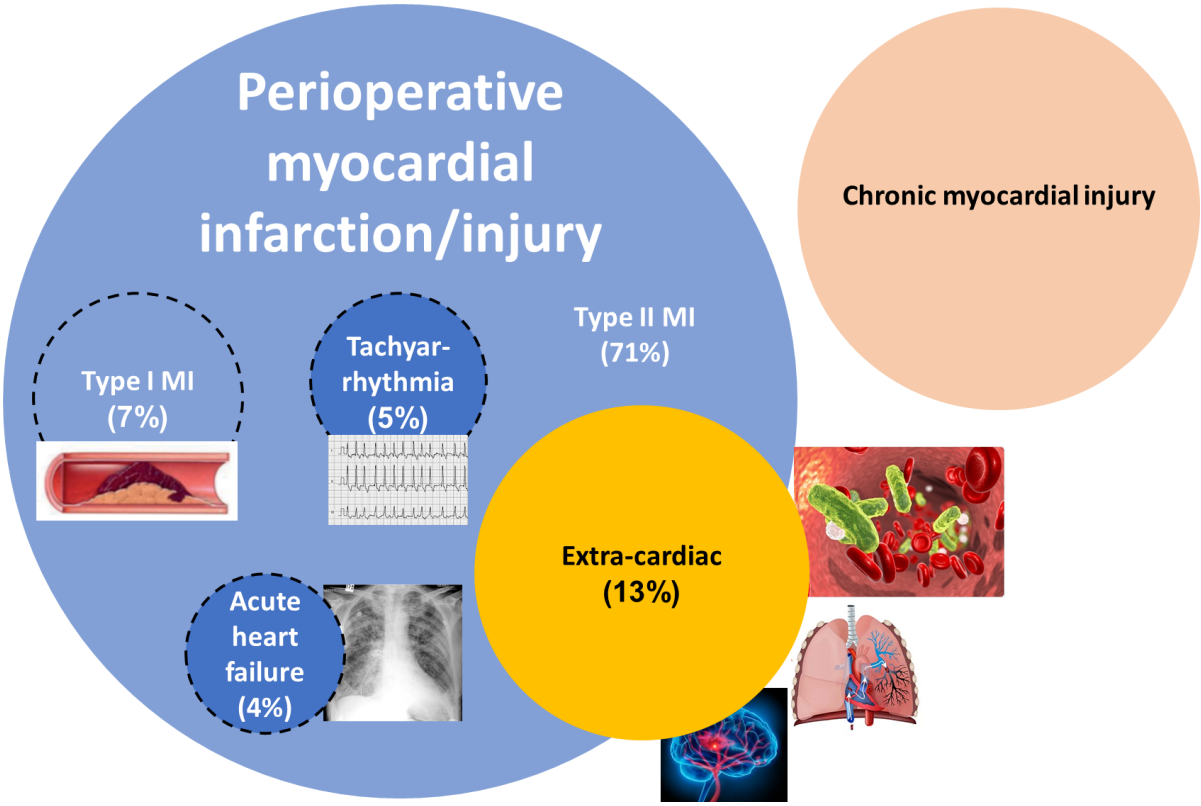

Figure 2 *PMI aetiologies in high-risk patients (adapted from Puelacher et al, JACC 2020[33])*

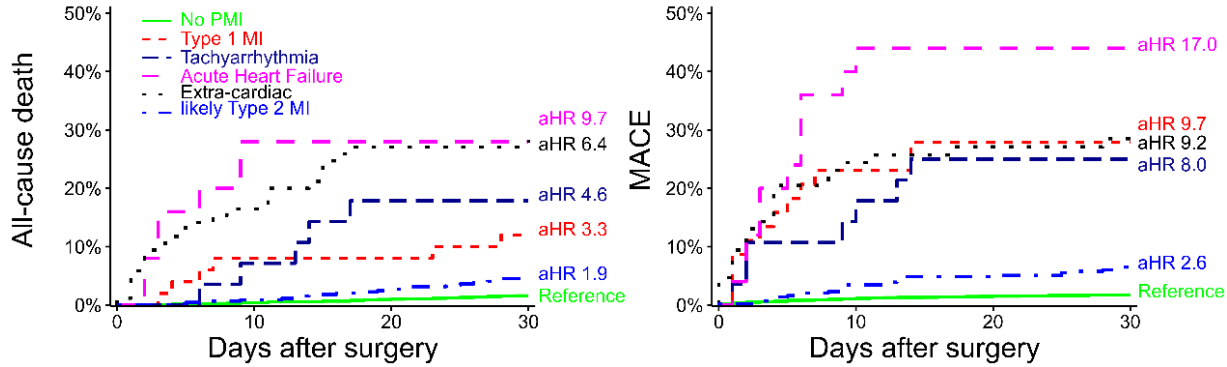

Figure 3 *Kaplan-Meier and adjusted hazard ratios (aHR) for (left) all-cause mortality and (right) major adverse cardiac events (MACE) within 30-days stratified according to PMI-aetiology, showing relevant differences in occurrence and timing (Puelacher et al, JACC 2020 in press[33])*

The way forward: a management trial

Using data generated from our previous work we estimated the required size of an outcome trial evaluating a hs-cTn-based screening for PMI. Assuming an incidence of PMI of ~20%, a MACE rate of 15-45% at 90 days (dependent on PMI aetiology, Figure 2+3) in patients with PMI vs 6% in patients without PMI, a 25% reduction of MACE in screened patients, and screening being performed successfully in 90% of cases, a total of >50.000 patients would be needed in a step-wedge-cluster design to be able to test for superiority of PMI-screening. This high sample size is mainly due to the numerous patients screened without detection of PMI, as their outcome will not be affected by PMI screening. Before initiating such a large scale trial, we think that a feasibility study is paramount. Therefore, the aim of the present study is to generate essential data to quantify assumptions for a large randomised trial, identify and prevent barriers to implementation of the intervention, and generate safety and medicoeconomic data to facilitate buy-in of the required interdisciplinary teams at our potential collaborating partner institutions.

2. Aim

Primary aim

We aim to generate feasibility data for a future randomised step-wedge cluster trial assessing the effect of implementing a clinical routine screening and response system for cardiac complications, including perioperative myocardial infarction/injury (we will use the umbrella term "PMI-screening") in patients at increased cardiovascular risk undergoing inpatient noncardiac surgery. Primary outcomes are the feasibility of implementation and quantifying opportunities to improve care via PMI-screening.

Secondary aims

- Evaluate the medicoeconomic impact of implementing a PMI-screening
- Explore the occurrence and timing of MACE following PMI to find the best follow-up period
- Identify potential barriers to implementation

3. Design and target measurements

This pilot study is a prospective observational multicentre binational before-after-comparison study. Centres which have decided to implement the novel guideline-recommended PMI-screening for routine clinical care are eligible for the present study. We will observe a pre-implementation phase of 3 months prior to implementation of PMI-screening, followed by a two-week blinded transition period, and finally the post-implementation phase of at least 6 months.

Figure 4 *Study flow chart; during the* ***pre-implementation phase*** *patients are managed according to local protocols, during the two-week* ***transition phase (X)*** *the implementation of a PMI-screening according to standard operating procedure is introduced, after which the* ***post-implementation*** *phase begins*

Pre-implementation phase

Patients in the pre-implementation phase are treated according to current local standard of care, which usually includes measurement of cTn and cardiology consultation after noncardiac surgery only at discretion of the treating physician, usually if perioperative myocardial infarction/injury is suspected clinically.
In this phase, patient inclusion begins according to the inclusion criteria set out for the local PMI-screening. The same data as during the post-implementation phase will be collected, even though the screening is not done at this time.

Blinded transition phase

Each centre transitions its standard operating procedure to the guideline-recommended perioperative PMI-screening (see below paragraph "PMI-screening"). The transition will be supported by study staff in form of minimal training requirements, support for generation of local standard operating procedures, presentations for involved disciplines, and information material.
As organisational issues are expected during this transition, no patients are included into the study during these two transition weeks.

Post-implementation phase

During the post-implementation phase, hospitals utilise routine PMI-screening (see below paragraph "PMI-screening"). Hospitals adopt routine PMI-screening for eligible patients. If they satisfy the inclusion criteria for this study, they are included, even if no PMI screening was conducted or PMI screening was incomplete (no or only one troponin measurement).

Special considerations concerning SARS-COV-2
In case of an interruption of planned surgery at one of the participating hospitals, the patient recruitment will be suspended until restrictions are lifted and the local principal investigator (PI) judges the situation to again reflect routine clinical conditions. The total duration of each phase shall be maintained.

Definition of PMI
PMI will be prospectively defined as an absolute increase in hs-cTn of +≥99th percentile above preoperative values (or between two postoperative values if the preoperative value is missing) within three days of surgery.
PMI represents a spectrum of different potential triggers for the acute myocardial injury, including myocardial infarctions as well as acute injuries by cardiac or extracardiac triggers [Puelacher C et al, JACC 2020[33]]. For management of PMI, identification of these aetiologies likely provides an opportunity for individualised care. These include

- **cardiac PMI**: type I myocardial infarction [T1MI-PMI], type II myocardial infarction [T2MI-PMI], acute injury due to acute heart failure or Tako-Tsubo [AHF-PMI], acute injury due to tachyarrhythmia [Tachy-PMI]
- **extra-cardiac PMI:** severe sepsis, systemic inflammatory response syndrome, pulmonary embolism, cardiac trauma, other causes

Based on findings from prior studies showing that asymptomatic elevations in cTn were also associated with increased short-term mortality[5], we do not mandate specific symptoms or specific ECG changes into the definition of PMI. We use delta values instead of maximum postoperative levels to ensure that our definition reflects “acute” myocardial damage and was time-related to surgery, thus avoiding misclassification of chronically elevated levels. Chronic hs-cTn elevations are expected in a relevant amount of (surgical) patients[42], and were previously shown to be independently associated with increased risk of death and major adverse cardiac events[43]. We chose an absolute rather than a relative delta hs-cTn level for the diagnosis of PMI, because absolute changes have shown higher diagnostic accuracy as compared to relative changes in the detection of acute MI in the non-operative setting[44,45]. The absolute increase of ≥99th percentile of each respective assay was chosen as it represents the 99th percentile of healthy individuals and thereby all PMIs invariably would fulfil the change as well as the absolute cTn criteria required for the diagnosis of spontaneous AMI[46]. This definition was evaluated in the prospective observational study BASEL-PMI for three different cTn-assays, using the respective 99th percentiles: Roche Elecsys hs-cTnT (+≥14ng/L)[13,31], Siemens Ultra sensitive cTn assay (+≥45ng/L)[31].

PMI-screening

The PMI-screening is a bundle of care consisting of

- Identification of high-risk patients prior to surgery (for details, see “Origin of the data” and “Inclusion criteria”)
- Measurement of high-sensitivity cardiac troponin within 30 days prior to surgery and on the first and second postoperative day (Figure 5)
- Daily comparison of postoperative hs-cTn values to preoperative values and identification of PMI defined as absolute increase of ≥+99th percentile of hs-cTn without need for symptoms or ischemic electrocardiography changes (for details, see “Definition PMI”)

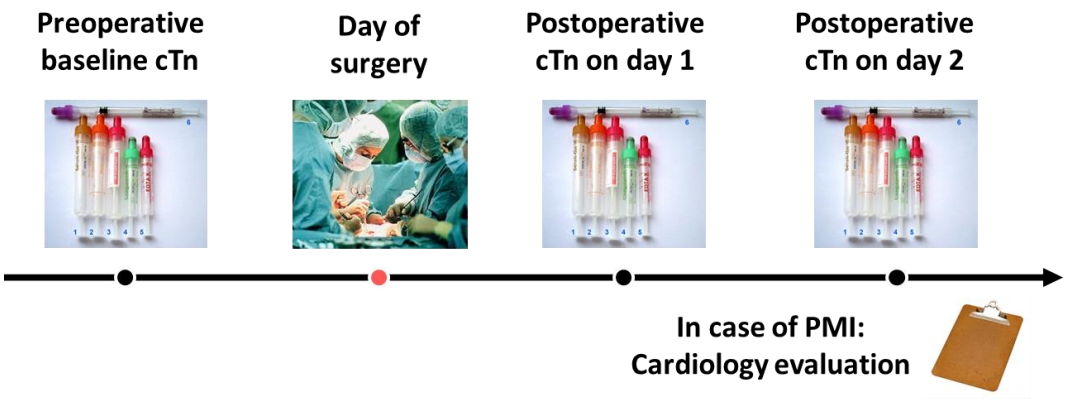

Figure 5 *Schematic flow-chart of PMI-screening*[13]

- Activation of the PMI-screening response system via automated or manual alert
- Clinical evaluation of patients with PMI according to local standardised operating procedure (recommendation see Figure 6)
- Clinical adjudication of PMI aetiology to identify the most likely cause
- Management of PMI according to a recommended management pathway (see below), following ESC guidelines recommendations[36–41]

Screening days

Successful PMI-screening depends on multiple disciplines working together closely. To avoid the chain breaking due to reduced personal resources on weekends and work holidays, participating institutions will prospectively define whether screening will be done on every day or prospectively specify exceptions, e.g. weekends.

PMI management pathway

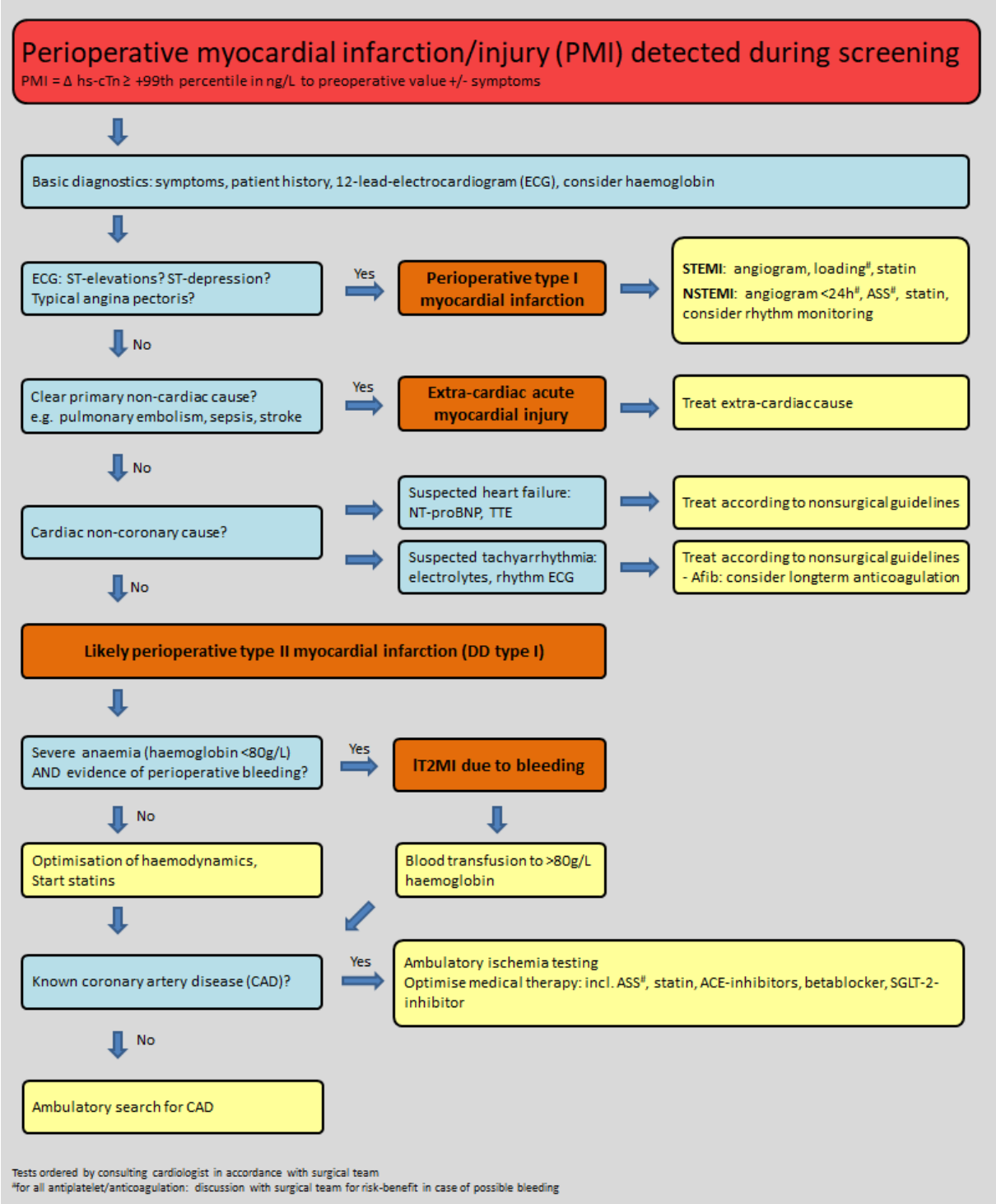

Figure 6 *Recommendation for local standard operating procedure for evaluation and management of patients with PMI detected via PMI-screening*[8,36–41]

Schedule and milestones

Work packages (WP) and milestones (MS)

WP 1 Study initiation

- MS 1: data environment on basis of BASEL-PMI environment created (03/21)
- MS 4 site initiation: Olten (07/21), Lucerne (06/22), Solothurn (06/22) Innsbruck (07/22), Geneva (08/22)

WP 2 Transition phase

- MS 1 preparation for transition complete: Olten (09/21), Lucerne (08/22), Solothurn (08/22), Innsbruck (09/22), Geneva (10/22)
- MS 2 transition phase: Olten (10/21), Lucerne (11/22), Solothurn (11/22) Innsbruck (10/22), Geneva (11/22)

WP 3 Data generation

- MS 1 First patient in: Olten (07/21), Lucerne (06/22), Solothurn (06/22), Innsbruck (07/22), Geneva (08/22)
- MS 2 stop patient enrolment: Olten (05/22), Lucerne (04/23), Solothurn (04/23), Innsbruck (05/23), Geneva (06/23)
- MS 3 follow up complete (Q4/24)
- MS 4 export e-data complete (Q1/25)
- MS 5 monitoring and data cleaning done (Q2/25)

WP 4 Statistical analyses

- MS 1 statistical data file complete (Q3/25)
- MS 2 feasibility data analysed and definite sample size estimation done (Q4/25)
- MS 3 submission of first manuscript (Q2/23)

4. Origin of the data

Consecutive patients at increased cardiovascular risk undergoing inpatient noncardiac surgery with a planned postoperative hospitalisation of ≥2 overnight stays, eligible for routine PMI-screening at the participating institutions.

5. Inclusion criteria

- Patients eligible for routine PMI-screening at participating institutions
- Patients requiring hospitalisation with ≥2 overnight stays after surgery
- Age ≥40 to ≤85 years AND history of coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease/stroke, insulin-dependent diabetes mellitus (IDDM), or chronic heart failure (CHF)
- Elective or non-elective surgery
- Patients undergoing orthopaedic, trauma, vascular, spinal, thoracic, neurological, urology, or visceral surgery

6. Exclusion criteria

- Heart surgery, cardiac valve intervention, or cardiac catheter ablation within 14 days prior to surgery OR involvement of heart surgery at index surgery OR surgery planned on cardiopulmonary bypass
- Patients undergoing plastic/reconstructive, ophthalmologic, dental, hand surgery, or ear-nose-and-throat surgery
- Chronic renal failure in dialysis, patients undergoing renal transplant surgery
- Moderate to severe dementia
- Inclusion into study within the last five days

- Existence of a documented refusal to further use of existing data OR active decline of further use of existing data

6.1 Exclusion from follow-up analysis

- Decline of consent during follow-up (irrespective of mail or telephone)

7. For which health-related personal data should the approval be granted?

We wish to collect data from clinical forms and electronic health records manually and electronically, depending on local availability of electronic health records and complexity of the data extracted. This will be done according to our standard operating procedures, with which we have been successful in implementing such a data collection in a previous study, NCT02573532, at two centres with different clinical management systems. Reporting will adhere to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement[47].

Baseline and preoperative clinical data: We will collect data as assessed by routine pre-operative anaesthesia examination and/or from prior documents, including patient demographics (age, sex, weight, height), medical history (pre-existing CAD, PAD, stroke, CHF, cardiac valve disease, diabetes mellitus, chronic kidney failure, chronic obstructive pulmonary disease, surgery due to malignancy), current cardiovascular medication, basic laboratory data (haemoglobin, creatinine, cardiac troponin), ECG

Intraoperative data: We will collect type of surgery, type of anaesthesia, cardiovascular risk of surgery (classified using the ESC/ESA surgical risk category[21]), and urgency of procedure. If electronic continuous monitoring data and/or ECG-recordings are available, these will be electronically exported.

Postoperative data: Postoperative laboratory data (haemoglobin, creatinine, cardiac troponin). Postoperative complications (sepsis, stroke, pulmonary embolism, pneumonia, need for blood products) will be extracted from the discharge report as diagnosed by the attending physicians.

Resource data: Number of postoperative blood draws on day 1 and 2, length of hospital stay, days on intensive care unit, consultations within day 1-3, ECG within day 1-3, cardiac stress testing within 30 days, and cardiac catheterisation within 30 days.

Barriers to implementation: structured interviews will be conducted with the local PI, local study nurses, and one further person in charge of the local screening (identified by local PI).

8. Request for an exception according to the Swiss Human Research Law (HFG) Art. 34

We request an exemption from the individual prospective consent for our study for data generated during clinical routine according to the Swiss Human Research Law (HFG) Art. 34 during both the pre- and post-implementation phases. Using a consent procedure would be detrimental for this study for the following reasons:

- PMI-screening is increasingly recommended by international guidelines[22–24,48,49]. Hence, implementation in clinical routine is planned with or without parallel scientific evaluation at the participating hospitals and is expected to occur in further hospitals in the coming years. Evaluation of the routine implementation could greatly enhance our understanding of benefits and potential harms of PMI-screening.

- As the institutional standard of practice of perioperative care will be modified, the most relevant data will be generated as part of the clinical routine, not for the study. There will be no study-specific intervention. The only variables collected specifically for this study will be the follow-up and the adjudication of PMI.
- Patients in the pre-implementation and the post-implementation phase need to have identical inclusion criteria during the study to ensure their comparability. Therefore, implementing a new consent process between these phases would introduce a severe selection bias. Both patients and clinicians may be less likely to participate during the post-implementation phase if they must handle an additional consent procedure. Forgoing the analysis of the pre-implementation phase to avoid a different consent procedure would prevent us to observe the effects of PMI-screening implementation.
- Patients undergoing emergency procedures may not be recruited using a standard consent procedure. Retrospective inclusion of recently operated patients would also induce a sampling bias towards patients with a favourable outcome.

During follow-up, patients are informed about the study and asked to return a questionnaire. Returning the questionnaire will be seen as consent for follow-up data. If a patient is contacted by phone, consent is requested after information about the study prior to doing the questionnaire on the phone.
For patients who die before follow-up can be conducted, we request an exemption from individual prospective consent. In this case, follow-up will be done via family physician and/or treating institutions. Our reasoning:

- PMI-screening will occur in patients undergoing elective as well as emergency procedures, and PMI was associated with a mortality at 30 days of 10% in our initial observational study despite early detection and management. Therefore, a consent process would introduce a sampling bias towards elective patients. Retrospectively requesting consent from relatives following the death of a patient shortly after surgery would be intrusive, constitute a breach of piety, and hence yield elevated rates of non-consent.

For this study based on the observation of a novel clinical procedure aimed at improving outcomes, but not tested prospectively, we believe the interest of research seems to outweigh the limited disturbance and risks for the patients. The data generated by this prospective implementation study will help further patient care in the perioperative period by providing data on the benefits and safety of perioperative systematic screening, and on response systems for PMI. Due to the large sample size and representative patient sampling, we expect a good external validity for tertiary centres in Switzerland and worldwide, particularly if we can broadly include patients without selection or sampling bias. Further, the results will provide the much needed pilot data for a future investigator-initiated randomised controlled trial. Finally, the data will be used for internal quality control at the participating hospitals to improve patient care directly.

The risk incurred by patients participating in this study would be minimal. The only threat could be a breach in confidentiality. We will counteract this risk by regularly training our staff, coding patient data at the earliest time point, and using safe data exchange servers.

9. Confirmation that no documented decline of further use of data exists

The PI and the local PIs confirm that no health-related data and no biologic material will be used in patients with a written or documented decline of consent for further use of their routine data or if the patient actively declines further use of data during the follow-up. In case of the patient's death before follow-up, no decline of further use of data is assumed.

10. Informed consent for follow-up questionnaire

During follow-up, patients are informed about the study and asked to return a questionnaire. Returning the questionnaire will be seen as consent for follow-up data. If a patient is contacted by phone, consent is requested after information about the study prior to doing the questionnaire on the phone.
Patients who die prior to contact during follow-up, consent to data collection is assumed.

11. Which person group is responsible for the transmission of biological material and health-related data

Christian Puelacher MD-PhD, Prof. Christian Müller MD
Local PIs:

Geneva:	Bernardo Bollen Pinto MD-PhD
Lucerne:	Matthias Bossard MD
Olten:	Nisha Arenja MD
Innsbruck:	Judith Martini MD, Petra Hillinger MD
Solothurn:	Nisha Arenja MD

No biological material will be collected.

12. Who takes responsibility for receiving this data / material?

Christian Puelacher MD-PhD, Prof. Christian Müller MD
Local PIs:

Geneva:	Bernardo Bollen Pinto MD-PhD
Lucerne:	Matthias Bossard MD
Olten:	Nisha Arenja MD
Innsbruck:	Judith Martini MD, Petra Hillinger MD
Solothurn:	Nisha Arenja MD

No biological material will be collected.

13. Which person group will have access to health-related data during the conduct of this study?

Patient data will be processed by a dedicated research team consisting of future doctoral candidates, study nurses or master students of medicine at the participating institutions as well as the study coordination centre (Cardiovascular Research Institute Basel).
Persons already known are

Coordination centre:	Christian Puelacher MD-PhD, Prof. Christian Müller MD, Danielle Gualandro MD-PhD, Noemi Glarner MD-PhDc, Mirjam Pargger MD-PhDc
Geneva:	Bernardo Bollen Pinto MD-PhD
Lucerne:	Matthias Bossard MD
Olten:	Nisha Arenja MD
Innsbruck:	Judith Martini MD, Petra Hillinger MD
Solothurn:	Nisha Arenja MD

14. Who is responsible for data protection?

The PIs and dedicated data manager will ensure confidentiality, and an audit trail will be done for manual as well as automated data entries. Staff will be trained and regularly retrained in safe data

management and confidentiality according to GCP50. Further, every staff member will at one point sign a document of confidentiality related to patient's medical data from the (digital) hospital archives. Data will not be disclosed to third parties, except during monitoring or audits by the competent authorities.
Data generation, transmission, storage and analysis of health-related personal data within this project will follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.

15. Scientific methodology

Feasibility endpoints

- **Screening:** percentage of patients eligible for PMI-screening according to inclusion criteria, but not screened during the implementation phase (defined as no or only one measurement of hs-cTn done during screening days)
- **Incidence of PMI:** percentage of patients experiencing PMI following noncardiac surgery
- **Cardiology consultation:** percentage of patients with detected PMI by PMI-screening on screening days, seen vs. not seen by a cardiologist
- **Actionable:** percentage of patients with PMI in whom improvements in care are possible, defined as guideline-recommended interventions or changes in medication
    - T1MI-PMI without absolute contraindications to percutaneous coronary intervention (PCI) and/or dual antiplatelet therapy (DAPT)[24,36,37]
    - Tachy-PMI requiring medical treatment or caused by newly diagnosed atrial fibrillation or preexisting atrial fibrillation with CHADS2-VASC-score of ≥2 without preexisting medical anticoagulation[40,41]
    - AHF-PMI with newly detected heart failure, or pre-existing heart failure not already on optimal medical therapy (defined as class I recommendation for angiotensin converting enzyme inhibitors [ACE-I] / angiotensin receptor blockers [ARB] / angiotensin receptor neprilysin inhibitors [ARNI] + aldosterone antagonist + sodium-glucose cotransporter 2 [SGLT-2] inhibitor + beta-blocker in heart failure with reduced ejection fraction) each on >50% target doses, or Tako-Tsubo cardiomyopathy[39]
    - newly diagnosed CAD, or preexisting CAD without optimal medical therapy [defined as class I recommendation for statin, ASS/DAPT, ACE-I/ARB/ARNI, betablocker, and/or SGLT-2-inhibitor][38]
    - extracardiac PMI caused by pulmonary embolism without absolute contraindication to oral/intravenous anticoagulation[50]
    - extracardiac PMI caused by sepsis, pneumonia, or cardiac trauma are judged to not be actionable unless first diagnosis is made during cardiology consultation
- **Management:** percentage of cardiac consultation recommendation for management in line with the proposed algorithm in respect to the suspected initial classification of PMI aetiology
- **Diagnostic challenge:** number of cases with mismatch of initial classification of PMI aetiology (and management pathway) at time of consultation versus final adjudication. In case of two differential diagnoses stated on the cardiology consultation, mismatch is seen when none of the diagnoses correspond to the final adjudication. If three or more differential diagnoses are stated, mismatch is seen in any case even if the final adjudication diagnosis is stated
- **Barriers to outcome:** concepts and themes identified by interviews
- **Safety:** Occurrence of inappropriate interventions or complications of cardiology diagnostics and interventions
    - Overtreatment: Inappropriate coronary angiography, defined as showing no significant coronary stenosis of ≥25% of vessel diameter
    - Diagnostic angiography and interventional or surgical revascularisation: dissection of coronary artery, type 4a myocardial infarction, death attributed to complications of the percutaneous coronary intervention or bypass surgery

- Major bleeding: defined as Bleeding Academic Research Consortium (BARC)[51] type 3 (overt bleeding plus haemoglobin drop of ≥ 3 g/dL or need for transfusion, cardiac tamponade, bleeding requiring surgical intervention for control or vasoactive drugs, and intracranial, intraspinal or intraocular bleeding compromising vision), type 4 (coronary artery bypass associated), and type 5 (fatal bleeding), with onset earliest on postoperative day 1 until twelve months

Medicoeconomic impact

- Clinical resources: number of postoperative blood draws on day 1 and 2, laboratory measurements (troponin, haemoglobin) pre- and postoperatively, length of hospital stay, days on intensive care unit, days on intermediate care unit, number of transfusions
- Intraoperative resources: arterial blood pressure measurement
- Cardiology resources: cardiology consultations or ECG within postoperative day 1-3, cardiac stress testing, cardiac magnetic resonance imaging, or coronary angiography within 30 days, coronary angioplasty or surgical coronary bypass within 90 days
  - Resources which should not be impacted: cardiology consultation preoperatively, ECG preoperatively
- Postoperative cardiovascular medication: new statins, ASS/DAPT, anticoagulation, betablockers, ACE-I/ARB/ARNI, SGLT-2-inhibitors

Clinical endpoints

Occurrence and timing of a composite of major adverse cardiac events (MACE) within twelve months, consisting of:

- all-cause death
- acute myocardial infarction type 1 (according to the fourth universal definition of myocardial infarction[24], AMI)
- survived sudden cardiac death
- acute heart failure (AHF)

Adjudication of PMI

PMI will be prospectively defined as an absolute increase in hs-cTn of ≥+99th percentile above preoperative values (or between two postoperative values if the preoperative value is missing) within three days of surgery.

Adjudication of PMI aetiology

PMI-aetiology will be centrally adjudicated by two independent experts based on all clinical information obtained during index hospitalization, including ECG, serial laboratory measurements including cTn and haemoglobin, monitoring of vital signs in the perioperative and intraoperative period, as well as echocardiography, cardiac stress testing and coronary angiogram if performed, and follow-up. In cases of disagreement between the two reviewers, consensus will be sought and found by discussion with a third reviewer.

PMI will be hierarchically adjudicated into:

1. **extra-cardiac** if caused by a primarily extra-cardiac disease such as: severe sepsis[52], pulmonary embolism, cardiac trauma, other cause
2. **cardiac**, further **subtyped** into type I myocardial infarction (T1MI-PMI), tachyarrhythmia, acute heart failure or Tako-Tsubo cardiomyopathy (AHF-PMI; extra-cardiac: need for acute new haemodialysis)
3. **cardiac:** type II myocardial infarction (T2MI-PMI) if there was absence of abovementioned causes (1, 2) with documented or suspected severe hypotension or anaemia

Follow-up

After one year, patients will be contacted by mail and, if they do not respond, by telephone to complete a questionnaire concerning the predefined MACE. In case of an event occurring, relevant medical files will be requested from the patient's general practitioner and/or treating

hospitals. The follow-up will be assessed after at least 365 days.Data of patients eligible for but not receiving the PMI-screening during the post-implementation phase will be collected similar to that of patients in the pre-screening phase.
In case of decline of consent for the follow-up, we will censor the patient at the time of last known clinical status.

Statistical analyses

95%-confidence intervals (95%CI) of absolute numbers and percentages will be calculated using the formula proposed by Agresti et al[53]. All analysis for the feasibility and resource endpoints will be done overall and repeated for each centre individually.

Feasibility endpoints

Feasibility endpoints will be calculated as absolute numbers and percentages with 95%CI.

- **Screening:** patients eligible for PMI-screening during workdays, but not screened.
- **Incidence of PMI:** the number of patients experiencing a PMI will be calculated. Subanalysis of the incidence for each of the patient characteristics used for inclusion into the screening (CAD, PAD, stroke, IDDM, CHF) will be performed. Further, incidence of each predefined aetiology will be calculated.
- **Cardiology consultation:** patients with detected PMI by PMI-screening on screening days, but not seen by a cardiologist. As supplemental analysis percentage of all detected PMI irrespective of screening days will be calculated.
- **Actionable:** patients with PMI in whom improvements in care were possible. Sensitivity analysis will be performed excluding SGLT-2-inhibitors as actionable medication, due to expected increased uptake in the next years.
- **Management:** cardiac consultation recommendation for management in line with the proposed algorithm. Qualitative and exploratory evaluation of cardiology consultation recommendations deviating from the proposed algorithm will be performed.
- **Diagnostic challenge:** cases with mismatch of initial classification will be calculated as the amount of misclassification when using the final adjudication as reference standard. As further exploration, we will do a comparison of the interobserver agreement Kappa using the initial classification and the final adjudication with the interobserver agreement during the final adjudication process.
- **Barriers to implementation:** semi-structured interviews will be evaluated for common themes as well as identification of all individual problems encountered
- **Safety:** we will calculate the total number of inappropriate interventions, complications and bleedings in the pre-implementation vs post-implementation phase, report them as absolute number at 365 days, and compare them via Fisher's exact test.

Medicoeconomic impact

We will do a cost-consequence analysis with a time horizon of 365 days. We consider the heterogeneous long-term prognosis of patients undergoing noncardiac surgery (i.e. ranging from cancer surgery to orthopaedic surgery) as impedimental for outcome projection and modelling beyond the first postoperative year. We will use the perspective of the statutory/public health care payer. Resource items will be valued using country-specific price weights. Because we will multiply countries specific resource use by country-specific price weights, heterogeneity of unit cost is not expected to bias the pooled results[54]. The main source for price weights will be national tariffs. We will use constant price weights, i.e. those valid at the time of the analysis. Considering the follow-up duration of 1 year, we will not adjust for time preference. Pharmacy cost will be obtained from national formulary lists and relevant professional fees. We will conduct complete case analysis (no imputation of missing data). The main analysis will apply non-parametric bootstrapping (2000 replications) for calculation of the mean effect and mean costs per patient and their 95% CI (nonparametric bootstrap percentile). Disaggregated cost will be reported for the pooled sample and separately for each country.
We will present cost in Swiss Francs as common currency base (exchange rates valid at the time of the analysis will be used), but secondary also in Euro. We will present graphically (cost-

effectiveness plane) the distribution of incremental cost effectiveness ratios (ICER) generated by bootstrapping replications. 95%CI of the ICER point estimate will be calculated using the bootstrap percentile method or bootstrap acceptability method as applicable. Further, we will plot cost-effectiveness acceptability curves (CEAC). Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[55].

Exploration of heterogeneity in medicoeconomic impact

We will present disaggregated cost and health consequences and their incremental ratio (95%CI) and as multiple CEAC for the following predefined subgroups: 1) low, intermediate and elevated procedural risk according to the classification endorsed by the ESC/ESA[21]; 2) elective vs nonelective surgery; 3) major vascular surgery; 4) previous history of coronary artery disease; 5) Revised Cardiac Risk Score56 ≤2 / >2. The same approach will be used to evaluate heterogeneity by jurisdiction.

Finally, we will compare the incidence of preoperative ECG and cardiology consultations (which should not be impacted by the screening), to detect potential changes in management not mandated by the PMI-screening.

Clinical endpoint analysis

For outcome analysis of the pre- and post-implementation phase we will use a censoring phase of 2 days following surgery for AMI and AHF, defining AMI and AHF as occurring between day 3 and 365 after surgery (= after PMI-screening). This will allow to differentiate detection of perioperative AMI and AHF by the PMI-screening vs. events during the follow-up. Death and survived sudden cardiac death occurring on the day of surgery will be blinded as PMI-screening could not affect occurrence of events before postoperative day 1.

- **Estimation of treatment effect:** for comparison of occurrence of death and MACE in the pre- vs post-implementation period, we will first construct univariable Kaplan-Meier plots. As a secondary analysis, this we be repeated for each single component of MACE. Second, we will compare preoperative baseline characteristics of the pre-implementation and post-implementation phase and construct a multivariable binary logistic model including baseline variables statistically significant between the phases as well as each centre and month as independent variables. The number of outcome events will determine the maximum amount of variables in the model (outcome events/10)[56].
- **Timing of MACE following PMI:** to determine the postoperative period during which the MACE rate remains increased following the surgical procedure, we will investigate the time of occurrence of MACE within the follow-up period of 365 days. We will construct a model with days after surgery on the x-axis and pending MACE on the y-axis. We will investigate changes in the slope of the curve, and assume that after postoperative day 300 the MACE rate is no longer affected by the surgical procedure[57]. By comparison of the slope of piece wise linear regression of pending MACE, a change in trend in MACE rate will be estimated.
- **Total number of MACE:** we will calculate the total number of detected MACE in the pre-implementation vs post-implementation phase and report them as absolute number and compare them via Fisher's exact test. No events will be censored for this analysis, all MACE and all cardiac PMI will be counted at 30 days, and 365 days.

Sample size considerations

This observational before-after cohort is designed as a pilot study to assess the feasibility and safety of a step wedge-cluster implementation study. The data generated at different centres with different levels of care will allow us to estimate the feasibility of implementing a screening, quantify the opportunities to improve care following PMI detection, and allow for identification of the optimal follow-up period after surgery to optimise the effect/noise ratio. To observe the full range of the PMI-screening, a sufficient number of patients is required. We expect PMI-screening to be successfully and completely done in >90% of patients, PMI to occur in 20-25% of patients screened, and the PMI aetiologies with lowest incidence (T1MI-PMI, AHF-PMI, Tachy-PMI) to occur in ~5-7% of PMI each. Therefore, each centre would need to include a minimum of 300

patients in the post-implementation phase to provide data on the full range of PMI aetiologies at least twice, assuming worst-case incidences.
We expect that each participating centre will be able to include at least 150 patients in the pre-implementation phase and 300 patients in the post-implementation phase, with Lucerne and Innsbruck being expected to contribute 200 pre-implementation and 400 post-implementation patients each. With a minimum of 900 patients undergoing screening, we will be able to assess feasibility concerning implementation of screening or cardiology consultation. We expect to find a minimum of 160 PMI, allowing for a good approximation of actionability, management, and diagnostic challenge of PMI detected in PMI-screening.

Methods for minimising bias

Selection bias: to avoid positive or negative selection bias, we will include consecutive eligible patients irrespective of whether they received screening or not. Inclusion of hospitals providing different levels of care shall ensure a representative sample.
Misclassification bias: PMI aetiology, management, actionability, and endpoints will be adjudicated by two independent reviewers trained in either cardiology, internal medicine, or anaesthesiology, following a standard operating procedure. In cases of disagreement, a third senior reviewer will aid in finding the correct diagnosis.
Attrition bias: loss to follow-up could have major impact on our study. A three-step procedure using first postal letters, then contacting the patient via telephone, followed by contacting the primary care physician and checking local death records shall ensure completeness of follow-up data. In the BASEL-PMI study, this approach led to a data completeness of 99.7% for death and 99% for MACE at one year[13].
Effect of season: to avoid seasonal effects (e.g. influenza, ice-induced falls), we aim to distribute the site initiations over the year to balance this effect. Further, month of surgery will be implemented in the multivariable model as random effect.

Further potential pitfalls
While judged unlikely, a centre might drop out of the study, e.g. due to potential problems with recruitment or implementation of PMI-screening. In this event we will strive to include one of the centres with whom we are in contact for the potential follow-up step-wedge trial instead. In this case, we would inform the ethics commission immediately.
Conversely, a surge in the number of surgeries (e.g. post-COVID) might provide more eligible patients per week than expected. For this, we would limit the inclusion per centre to 250 patients in the pre-implementation phase and 500 in the post-implementation phase. Recruitment would terminate early instead of reducing patients enrolled per day to avoid a selection bias.
Moreover, the increasing amount of article retractions due to data manipulation or scientific fraud mandate preventive measures. Therefore, all statistical analyses will be double-checked by a second experienced researcher, using a securely held and in double available statistical data file.

16. Obligation of reporting

A change of Principal Investigator and modifications of the contents of the approval must be announced to the ethics commission in advance.
Completion or cancellation of the research project must be announced to the ethics commission within 90 days.
We plan no stopping rule before achieving the necessary patient number. If termination is due to external causes such as lack of funding, or ethical concerns results will be made available by publication of incomplete results, for use in meta-analyses.
Significant changes to the protocol will be sent to the ethics commission for amendment. This includes changes in e.g. eligibility criteria, primary or secondary endpoints, or extent of data acquisition.

17. Data protection: coding and storage

See below at 18.

18. Procedure with non-coded data

Data will be collected by specially trained research staff, and a) entered into a password-protected data environment, or b) automatically extracted from clinical records. Each patient will be attributed a study-specific patient identification number (PID). For statistical analysis, these datasets will be merged using the PID as identifier.
At the end of the data acquisition, including follow-up, patient data will be coded using the PID, and the database will be locked. Coding using the PID will be done at the earliest time point after completion of follow-up data collection.
Data generation, transmission, storage and analysis of health related personal data within this project will follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.
Health related personal data captured during this project are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality.

19. Information about storage

Collected data will be entered into Redcap to allow appropriate storage with tracking of changes made to the data. Database and datasets will be stored on specially protected data folders accessible only for the research teams of the Cardiovascular Research Institute Basel and the respective sites, with regular back-ups in place. Printouts will be kept in a locked room at each site to protect patient confidentiality.
The coding key, containing the PID and all data allowing patient identification (name, birthdate, address), will be stored on two different secured physical hard drives only accessible to the PIs, the study coordinator, or the local PIs.

20. Duration of data storage

Data will be stored for 10 years in the clinical archives and study specific data will be stored for 10 years in a central archive at the Cardiovascular Research Institute in Basel. No biological material is collected.

21. Ethical and regulatory requirements

This project complies to the regulatory requirements of the Swiss human research law (HFG) and human research ordinance (HFV). Acceptance by the cantonal ethics commission is the necessary condition before the conduction of the research project. The research project will be carried out in accordance to the research plan and with principles enunciated in the current version of the Declaration of Helsinki[58], the Essentials of Good Epidemiological Practice issued by Public Health Schweiz, the Swiss Law and Swiss regulatory authority's requirements[59] as applicable.

22. Financing / Publication / Declaration of interest

Funding and support

This project will be supported by the University Hospital Basel and the University Basel. Further funding will be sought from the Swiss National Science Foundation, and the Swiss Heart Foundation. Further support will be sought from industry partners, e.g. diagnostic companies who supported the initial BASEL-PMI study (Roche Diagnostics, Abbott Diagnostics).

Publication strategy
Publication of results is planned as:

- Medical-scientific outreach: a) manuscripts submitted to peer-reviewed medical journals; b) oral and poster presentations at international and national meetings; c) presentation in hospital; d) key results in clinical trial databases
- Public outreach: a) presentation to patient organisations; b) key results on Twitter (@CRIBasel); c) press release for key findings.

Data sharing

Data of the post-implementation phase will be merged with the prospective multicentre observational study BASEL-PMI to answer questions requiring large numbers of PMI, e.g. risk stratification and validation of scores as well as identifying subtypes of PMI.
Data sharing with other research groups will be the responsibility of the PI.
Data for local quality improvement programs will be made available to the local PIs as soon as possible following data base closure.

Planned analysis in combination with BASEL-PMI dataset

Outcome analysis (+BASEL-PMI)
Due to organisational issues, we expect that a certain amount of patients in the post-implementation period will not receive a cardiology consultation despite detection of PMI (seen during implementation at the University Hospital Basel). Therefore, we plan an exploratory analysis of patients with PMI receiving vs not-receiving cardiology consultation.
Population: For this analysis we will exclude patients staying at the intensive care unit for more than the first postoperative night.
Statistical analysis: We will then construct a multivariable model for occurrence of MACE including baseline characteristics (age, coronary artery disease, chronic heart failure, urgency of procedure) and whether patients received cardiology consultation or not. As a sensitivity analysis we will conduct a propensity score model using a 1:1 or 2:1 matching ratio (depending on incidence of not-receiving a cardiology consultation) and a caliper of 0.2 matching using nearest-neighbour matching.

Prediction of perioperative MACE including PMI (+BASEL-PMI)
Aim: Generate a pre- and an immediate postoperative prediction score for occurrence of MACE including PMI.
Statistical analysis: The cohort will be split into a derivation (2/3) and validation (1/3) set using a time dependent split of our cohort. Two different scores will be defined for 1) the preoperative and 2) the immediate postoperative setting, utilizing all data available before and directly after surgery. To generate the scores, first, using the derivation set, potential predictive variables will be pre-specified and included simultaneously into regression analysis. Second, significant variables will be added in descending order of significance until no significant improvement of the Akaike Information Criterion is reached by addition of another variable. Third, risk categories will be derived. Using the validation set, we will then a) calculate likelihood ratios for occurrence of death and MACE for each risk category, and b) calculate the diagnostic accuracy by area under the receiver operating characteristics curve (using bootstrap for estimation of 95%-CI) and compared to established perioperative risk scores by the method proposed by de Long[60].

Exploration of ECG-variables for prediction of perioperative MACE and PMI (+BASEL-PMI)
Aim: Explore association of continuous ECG-markers with occurrence of MACE and PMI
Population: For this analysis only patients with continuous ECG >3 minutes on the day of surgery (e.g. during anaesthesiology preparation) will be included.
Statistical analysis: exploratory.

Risk scores for PMI-subtypes (+Basel-PMI)
Aim: Derive and validate a risk score in patients with different subtypes of PMI for the occurrence of major cardiac adverse events to inform treatment decisions
Population: For this analysis we will only include patients with detected PMI.
Statistical analysis: We will derive the subtype-specific risk score using multivariable Cox proportional hazards analysis to identify predictive variables for the occurrence of death and MACE for the different subtypes of PMI. Candidate variables are selected prior to the analysis using literature analysis and included into the model via forced entry to avoid overfitting of the model. These will be used to generate a comprehensive risk-scoring algorithm using risk categories. Validation will be done by calculating the percentage of correctly classified patients. 95% CI will be calculated using bootstrapping. Sensitivity analysis will be done by generating sets with different prevalence of subtypes and frequency of comorbidities from the validation cohort.

23. Literature

1. Weiser, T. G. *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* **372**, 139–144 (2008).
2. Weiser, T. G. *et al.* Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* **385**, S11 (2015).
3. Etzioni, D. A., Liu, J. H., Maggard, M. A. & Ko, C. Y. The Aging Population and Its Impact on the Surgery Workforce. *Annals of Surgery* vol. 238 170–177 (2003).
4. Nepogodiev, D. *et al.* Global burden of postoperative death. *Lancet* **393**, 401 (2019).
5. Devereaux, P. J. *et al.* Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA - J. Am. Med. Assoc.* **307**, 2295–2304 (2012).
6. Beattie, W. S. *et al.* Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: A single-centre cohort study in 51,701 consecutive patients. *Can. J. Anesth.* **59**, 1013–1022 (2012).
7. Van Waes, J. A. R. *et al.* Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* **127**, 2264–2271 (2013).
8. Devereaux, P. J. *et al.* Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgerya cohort study. *Ann. Intern. Med.* **154**, 523–528 (2011).
9. Botto, F. *et al.* Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. *Anesthesiology* **120**, 564–578 (2014).
10. Ashton, C. M. *et al.* The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann. Intern. Med.* **118**, 504–510 (1993).
11. Badner, N. H., Knill, R. L., Brown, J. E., Novick, T. V. & Gelb, A. W. Myocardial infarction after noncardiac surgery. *Anesthesiology* **88**, 572–578 (1998).
12. Mangano, D. T. *et al.* Association of Perioperative Myocardial Ischemia with Cardiac Morbidity and Mortality in Men Undergoing Noncardiac Surgery. *N. Engl. J. Med.* **323**, 1781–1788 (1990).
13. Puelacher, C. *et al.* Perioperative myocardial injury after noncardiac surgery incidence, mortality, and characterization. *Circulation* **137**, 1221–1232 (2018).
14. Landesberg, G., Beattie, W. S., Mosseri, M., Jaffe, A. S. & Alpert, J. S. Perioperative myocardial infarction. *Circulation* **119**, 2936–2944 (2009).
15. Devereaux, P. J. *et al.* Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA - J. Am. Med. Assoc.* **317**, 1642–1651 (2017).
16. Gualandro, D. M. *et al.* Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: Frequent and dangerous. *Atherosclerosis* **222**, 191–195 (2012).
17. Kamel, H. *et al.* Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation* **126**, 207–212 (2012).
18. Salmasi, V. *et al.* Relationship between Intraoperative Hypotension, Defined by Either

Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology* **126**, 47–65 (2017).
19. Feringa, H. H. H. *et al.* High-dose β-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation* **114**, I344-9 (2006).
20. Foucrier, A. *et al.* The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after Major Vascular Surgery. *Anesth. Analg.* **119**, 1053–1063 (2014).
21. Kristensen, S. D. *et al.* 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. *Eur. Heart J.* **35**, 2383–2431 (2014).
22. Duceppe, E. *et al.* Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can. J. Cardiol.* **33**, 17–32 (2017).
23. Gualandro, D. M. *et al.* 3rd guideline for perioperative cardiovascular evaluation of the Brazilian society of cardiology. *Arq. Bras. Cardiol.* **109**, 1–104 (2017).
24. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).
25. Fleisher, L. A. *et al.* 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American college of cardiology/American heart association task force on practice guidelines. *J. Am. Coll. Cardiol.* **64**, e77–e137 (2014).
26. Sheth, T. *et al.* Incidence of thrombosis in perioperative and non-operative myocardial infarction. *Br. J. Anaesth.* **120**, 725–733 (2018).
27. Hanson, I., Kahn, J., Dixon, S. & Goldstein, J. Angiographic and clinical characteristics of type 1 versus type 2 perioperative myocardial infarction. *Catheter. Cardiovasc. Interv.* **82**, 622–628 (2013).
28. Helwani, M. A. *et al.* Etiology of Acute Coronary Syndrome after Noncardiac Surgery. *Anesthesiology* **128**, 1084–1091 (2018).
29. Wilson, J. & Jungner, G. Principles and practice of screening. *WHO Geneva* **16**, 168 (1968).
30. Eddy, D. M. Comparing Benefits and Harms: The Balance Sheet. *JAMA J. Am. Med. Assoc.* **263**, 2493–2505 (1990).
31. Hidvegi, R. *et al.* Obesity paradox and perioperative myocardial infarction/injury in non-cardiac surgery. *Clin. Res. Cardiol.* **109**, 1140–1147 (2020).
32. Gualandro, D. M. *et al.* Comparison of high-sensitivity cardiac troponin I and T for the prediction of cardiac complications after non-cardiac surgery. *Am. Heart J.* **203**, 67–73 (2018).
33. Puelacher, C. *et al.* Etiology of Peri-Operative Myocardial Infarction/Injury After Noncardiac Surgery and Associated Outcome. *Journal of the American College of Cardiology* vol. 76 1910–1912 (2020).
34. Gualandro, D. M. *et al.* Prediction of major cardiac events after vascular surgery. *J. Vasc. Surg.* **66**, 1826-1835.e1 (2017).
35. Du Fay De Lavallaz, J. *et al.* Daytime variation of perioperative myocardial injury in non-cardiac surgery and effect on outcome. *Heart* **105**, 826–833 (2019).
36. Collet, J.-P. *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* **Online ahe**, (2020).
37. Ibanez, B. *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* **39**, 119–177 (2018).
38. Knuuti, J. *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41**, 407–477 (2020).
39. Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **37**, 2129-2200m (2016).
40. Brugada, J. *et al.* 2019 ESC Guidelines for themanagement of patients with

supraventricular tachycardia. *Eur. Heart J.* **41**, 655–720 (2020).
41. Kirchhof, P. *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* **18**, 1609–1678 (2016).
42. Kavsak, P. A., MacRae, A. R., Yerna, M. J. & Jaffe, A. S. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. *Clin. Chem.* **55**, 573–577 (2009).
43. Weber, M. *et al.* Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. *Eur. Heart J.* **34**, 853–862 (2013).
44. Irfan, A. *et al.* Early diagnosis of myocardial infarction using absolute and relative changes in cardiac troponin concentrations. *Am. J. Med.* **126**, 781-788.e2 (2013).
45. Reichlin, T. *et al.* Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation* **124**, 136–145 (2011).
46. Thygesen, K. *et al.* Third universal definition of myocardial infarction. *J. Am. Coll. Cardiol.* **60**, 1581–1598 (2012).
47. Benchimol, E. I. *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med.* **12**, (2015).
48. Kristensen, S. D. *et al.* 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management. *European Journal of Anaesthesiology* vol. 31 517–573 (2014).
49. De Hert, S. *et al. Pre-operative evaluation of adults undergoing elective noncardiac surgery: Updated guideline from the European Society of Anaesthesiology*. *European Journal of Anaesthesiology* vol. 35 (2018).
50. Konstantinides, S. V. *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS). *European Heart Journal* vol. 41 543–603 (2020).
51. Mehran, R. *et al.* Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. *Circulation* **123**, 2736–2747 (2011).
52. Levy, M. M. *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. in *Critical Care Medicine* vol. 31 1250–1256 (Crit Care Med, 2003).
53. Agresti, A. & Coull, B. A. Approximate is better than “Exact” for interval estimation of binomial proportions. *Am. Stat.* **52**, 119–126 (1998).
54. Glick, H. A., Doshi, J. A., Sonnad, S. S. & Polsky, D. *Economic Evaluation in Clinical Trials*. *Economic Evaluation in Clinical Trials* (Oxford University Press, 2014). doi:10.1093/med/9780199685028.001.0001.
55. Husereau, D. *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* **346**, (2013).
56. Bagley, S. C., White, H. & Golomb, B. A. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J. Clin. Epidemiol.* **54**, 979–985 (2001).
57. Reed, G. W. *et al.* Associations between cardiac troponin, mechanism of myocardial injury, and long-term mortality after noncardiac vascular surgery. *J. Am. Heart Assoc.* **6**, e005672 (2017).
58. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J. Indian Med. Assoc.* **107**, 403–405 (2009).
59. *3. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011*. (2011).
60. DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics* **44**, 837 (1988).