BMJ Open

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078307
Article Type:	Cohort profile
Date Submitted by the Author:	29-Jul-2023
Complete List of Authors:	Noordzij, P.; Sint Antonius Hospital; UMC Utrecht, Intensive Care Ruven, Henk; Sint Antonius Hospital Reniers, Ted; Sint Antonius Hospital Idema, Rene; Amphia Hospital Thio, M.S.Y.; Amphia Hospital Cremer, Olaf; UMC Utrecht, Intensive Care Hollema, Nynke; Sint Antonius Hospital Smit, Kyra; Sint Antonius Hospital Vernooij, Lisette; Utrecht University, Department of Anesthesiology, Intensive Care and Emergency Medicine; Sint Antonius Hospital Dijkstra, Ineke M.; St Antonius Hospital, Department of Clinical Chemistry Rettig, T; Amphia Hospital site Molengracht, Anesthesiology, Intensive Care and Pain Medicine
Keywords:	Cardiothoracic surgery < SURGERY, Colorectal surgery < SURGERY, Pancreatic surgery < SURGERY, Vascular surgery < SURGERY, Risk Factors, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

P.G. Noordzij[1,3], H.J.T. Ruven[1], T. Reniers[1], R.N. Idema[2], M.S.Y. Thio[2], O.L. Cremer[3], N. Hollema[1], K.N. Smit[1], L.M. Vernooij[1,3], I.M. Dijkstra[1], T.C.D. Rettig[2]

1. St. Antonius Hospital, Nieuwegein; 2. Amphia Hospital, Breda; 3. University Medical Centre Utrecht, the Netherlands.

Peter Noordzij, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands

p.noordzij@antoniusziekenhuis.nl

Henk Ruven, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

h.ruven@antoniusziekenhuis.nl

René Idema, M.D., PhD. Department of Clinical Chemistry, Amphia Hospital, Molengracht 21, 4818 CK, Breda rene.idema@gmail.com

Ineke Dijkstra, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

i.dijkstra@antoniusziekenhuis.nl

Ted Reniers, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands

t.reniers@antoniusziekenhuis.nl

Olaf Cremer, M.D., PhD. Department of Intensive Care Medicine, University Medical Centre Utrecht, Utrecht, Netherlands

O.L.Cremer@umcutrecht.nl

Nynke Hollema. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands

n.hollema@antoniusziekenhuis.nl

Maaike Thio, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.

msythio@amphia.nl

Kyra Smit, Ph.D. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

kn.smit@antoniusziekenhuis.nl

Lisette Vernooij, PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands.

l.vernooij@antoniusziekenhuis.nl

Thijs Rettig, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.

trettig@amphia.nl

Corresponding author

Peter Noordzij, M.D., PhD. Dept. of Anaesthesiology, Intensive Care and Pain Medicine, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

Tel: +31 88 320 6948, E-mail: p.noordzij@antoniusziekenhuis.nl

Funding

This study is supported by a research grant from Roche Diagnostics International.

Conflicts of interest

PN has participated in advisory boards for perioperative use of biomarkers, for which he has received a honorarium by Roche Diagnostics (Rotkreuz, Switzerland). PN and TR have held lectures on perioperative biomarkers for which they have received a honorarium by Roche Diagnostics. OC has received research grants from ImmuneXpress Inc. (Seattle, WA) and Abionic SA (Epalinges, Switzerland) for related work. HR, TR, RI, MT, NH, KS, LV and ID have no conflicts of interest.

Word count: 3322

Abstract: 269

Abstract

Purpose: Postoperative complications increase mortality, disability, and costs. Advanced understanding of the risk factors for postoperative complications is needed to improve surgical outcomes. This paper discusses the rationale and profile of the BIGPROMISE (biomarkers to guide perioperative management and improve outcome in high-risk surgery) cohort, that aims to investigate risk factors, pathophysiology, and outcomes related to postoperative complications.

Participants: Adult patients undergoing major surgery in two tertiary teaching hospitals. Clinical data and blood samples are collected before surgery, at the end of surgery, and on the first, second and third postoperative day. At each time point a panel of cardiovascular, inflammatory, renal, haematological, and metabolic biomarkers is assessed. Aliquots of plasma, serum, and whole blood of each time point are frozen and stored. Data on severe complications are prospectively collected during 30 days after surgery. Functional status is assessed before surgery and after 120 days using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0. Mortality is followed up until two years after surgery.

Findings to date: The first patient was enrolled on October 12th 2021. Currently (May 2nd 2023) 1,672 patients were screened for eligibility, of whom 1,174 (70%) provided informed consent for study participation. Most common types of major surgery were cardiac (60%) and gastro-intestinal procedures (20%). The overall incidence of severe postoperative complications was 11%.

Future plans: By the end of the recruitment phase, expected in 2025, approximately 3,000 patients with major surgery will have been enrolled. This cohort allows us to investigate the role of pathophysiological perioperative processes in the cause of postoperative complications, and to discover and develop new biomarkers to improve risk stratification for adverse postoperative outcomes.

Trial registration number NCT05199025

Keywords: major surgery, biomarkers, outcomes, postoperative complications, disability

Strengths and limitations

- A large prospective collection of perioperative blood samples and clinical data in a high-risk surgical population.
- Postoperative complications and functional outcomes are defined according to international standards to facilitate research collaborations.
- A perioperative biomarker panel is prospectively assessed on fresh blood samples to elucidate the role of pathophysiological processes in the cause of postoperative complications.
- Multiple sample aliquots of plasma, serum and whole blood are frozen and stored in a central archive, allowing future perioperative biomarker discovery and development.
- This study is limited to blood samples that are routinely collected and stored until 72 hours after surgery.

Introduction

Worldwide, more than 330 million patients have surgery each year.[1] Depending on type of surgery and co-existing diseases, 10-30% of patients suffer severe postoperative complications.[2-5] Common adverse events are infections (e.g. pneumonia, surgical site infection), myocardial infarction, respiratory failure, and acute kidney injury. Postoperative complications are important determinants of long-term mortality and poor health after surgery[6-8], impair quality of life and may increase hospital costs up to four times.[9, 10]

Surgical trauma triggers a systemic stress response, that involves a complex neuroendocrine and immunological reaction to local tissue injury. Local tissue trauma activates the innate immune system, with pro- and anti-inflammatory cytokines triggering systemic inflammation and the hypothalamic-pituitary-adrenal (HPA) axis. This results in stimulation of the sympathetic nervous system, alongside several other hormonal pathways, to maintain physiological homeostasis.[11] The effects of these pathways change perioperative organ perfusion, water balance and cellular metabolism. A postoperative dysregulated stress response can be detrimental as excessive systemic inflammation, immunosuppression, hypermetabolism, and hypercoagulation can lead to organ failure and death.[11, 12] The most important determinant of a postoperative dysregulated stress response is the nature and extent of surgery. In addition, non-surgical factors such as ageing, co-existing diseases and deconditioning, are contributing factors (Figure 1).[13]

Serum biomarkers provide an objective representation of organ function and tissue injury. Biomarker tests are an integral part of perioperative medicine, but the results are not always decisive for medical treatment.[14] Furthermore, the translation of potentially useful biomarkers into clinical practice has not been successful.[15] In an era where surgical risk is continuously changing, due to population ageing and health care innovations, perioperative

biomarkers are currently underutilized.[16-17] The 'biomarkers to guide perioperative management and improve outcome in high-risk surgery' (BIGPROMISE) cohort will prospectively assess perioperative biomarker panels on fresh blood samples, and systematically collect and store plasma, serum and whole blood samples to allow for future perioperative biomarker discovery and development. This manuscript describes the rationale and design of the BIGPROMISE cohort, which primarily aims to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to postoperative complications in patients undergoing major elective surgery.

Cohort description

The BIGPROMISE cohort prospectively studies patients undergoing elective major cardiac or non-cardiac surgery, and is an initiative of the departments of Anaesthesiology, Intensive Care and Pain Medicine of St. Antonius hospital and Amphia hospital in the Netherlands. The study protocol was filed at Clinicaltrials.gov under registration number NCT05199025, and received approval from the Medical research Ethics Committees United (NL74076.100.20). The current protocol version is 5.0 (21-12-2022) and available upon request. The biobank samples are stored by a third party biobank provider (Azenta, Griesheim, Germany) and managed by Roche Diagnostics (Penzberg, Germany).

Setting

Patients are recruited in two tertiary teaching hospitals (St. Antonius hospital and Amphia hospital, the Netherlands). Based on the historical surgical volumes of both facilities, approximately 2,500 - 3,000 patients are eligible for inclusion each year. BIGPROMISE biobank aims to collect clinical data and blood samples of at least 1,000 patients per year. BIGPROMISE will be recruiting at least until 2025, and possibly longer depending on capacity and funding.

BIGPROMISE biobank is an investigator-initiated research collaboration between anaesthesiologists, intensivists and clinical chemists, in collaboration with surgeons and a dedicated biotech company. Expenses for personnel, materials, biomarker assays and storage of blood samples are financed with an external research grant from Roche Diagnostics International. Roche Diagnostics International is a large biotech company, and worldwide provider of in-vitro diagnostics. External funding enables us to execute this research project, focus on finding new diagnostics (i.e. biomarker discovery), and establishing data-driven insights, that aim to evolve perioperative medicine, and improve patient outcomes.

Inclusion criteria and patient recruitment

Adult patients (>18 years) undergoing elective major surgery under general anaesthesia are eligible for participation. Surgical risk is based on an estimate of procedure-specific risk of 30-day mortality, without taking age, gender, frailty, or coexisting diseases into account.[18,19] The following types of surgery are considered: cardiac, vascular, gastrointestinal, hepatobiliary, urologic, and pulmonary surgery. A full list of surgical procedures is provided in Appendix 1. Patients not providing written informed consent, patients not able to complete questionnaires in the Dutch language, patients who are pregnant, patients undergoing emergency surgery, and patients with a life expectancy less than six months are excluded from participation in this study.

Eligible patients scheduled for surgery are contacted by telephone by trained study personnel. Patients are informed about the purposes of the biobank and will receive an information letter by (e-)mail, if they consider to participate. Written informed consent is obtained at time of hospital admission by a member of the study team. This includes the collection of demographic and clinical data, blood samples for biomarker analysis in fresh blood samples during hospital stay and a functional status questionnaire. Additionally, a written permission is separately obtained for: collection, handling and storage of blood samples in a dedicated biobank for future biomarker discovery, permission to be contacted for further research.

Data collection

Prior to surgery, baseline data are collected regarding patient demographics, medical history, chronic pain, preoperative laboratory results, frailty, and functional status. Preoperative study

data are collected from electronic patient records, from dedicated questionnaires (12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 for functional status, and from a numeric rating scale (NRS) for pain.[20,21] Study data during hospital admission consist of variables related to surgery and anaesthesia, clinical course, laboratory results, complications, and pain, which will be extracted from electronic patient records. After hospital discharge, postoperative complications will be registered until 30 days after surgery. Further outcome data consist of days alive and out of hospital after 120 days, patient-reported information on functional status and pain after 120 days, and mortality up to two years.

Study data are collected and managed using REDCap which is an electronic data capture tool. REDCap is a secure, web-based software platform and compliant with Good Clinical Practice guidelines.[22] Postoperative pain scores, vital parameters (modified early warning scores), and the results of perioperative biomarker panels are extracted semi-automatically from electronic medical files (Epic Systems Corporation, United States; Metavision, iMD Soft, Israel), and the local laboratory information management systems (GLIMS, Clinisys GLIMS, Belgium, and MOLIS, CompuGroup, Belgium). Postoperative complications are noted and classified by a dedicated researcher (TR, MT), and validated by an experienced perioperative physician (PGN, TCDR), prior to manual registration in the database. Follow-up data for functional outcomes are registered using electronic and paper questionnaires (WHODAS 2.0). Long-term mortality is assessed using the Dutch municipality register of deceased persons to obtain date of death. Quality assurance of study data is annually performed by an independent monitor. Data records are coded, the key to the code is kept securely in each participating centre.

Blood sample collection and processing

Blood samples are collected at five perioperative time points: after induction of general anaesthesia (baseline), at the end of surgery, and on the morning of the first, second and third postoperative day. Blood is collected from an arterial line (if applicable) or venepuncture into vacuum blood collecting tubes, according to the schedule presented in Supplementary Table 1.

In all study patients, blood samples are centrifuged at 1800 x g for 5 minutes and used to analyse a panel of 50 biomarkers at each perioperative time point (Table 1, Figure 2). Biomarker analyses are performed at the local hospital laboratory on Roche Cobas 8000 and Sysmex XN platforms. Results of perioperative biomarker analysis are captured in local laboratory information management systems and uploaded to a central web application for research data (REDCap).

In patients with written consent for biobanking, an additional 21 ml blood is processed for storage at -80 degrees Celsius as whole blood (3ml), and serum and plasma after centrifugation at 2000 g for 10 minutes or 4000 g for 5 minutes (Figure 2). Aliquots of plasma, serum, and whole blood are frozen and stored within 6 hours after collection. Aliquots are stored in a dedicated biobank facility (Azenta, Griesheim, Germany).

Biomarker panel

The selection of biomarkers is based on the hypothesis that a postoperative dysregulated stress response, which we briefly explained in the introduction section, is associated with postoperative complications, through systemic inflammation, immunosuppression, hypermetabolism, hypercoagulation, and organ injury, and that serum biomarkers reflect (part of) these pathways or any downstream effect.[11-13] Furthermore, we considered previous literature reports on the pathophysiology of postoperative complications, availability and reproducibility of biomarker assays, current practice, and costs. For pragmatic reasons,

biomarkers are categorized according to pathways involved in the pathogenesis of postoperative complications, as follows (Figure 1):

Cardiovascular

Chronic cardiac disease, such as coronary artery disease (CAD) and heart failure (HF), are key risk factors for postoperative complications. Common risk factors (e.g. diabetes mellitus, renal insufficiency, peripheral artery disease) are strongly associated with undiagnosed cardiac disease. In these patients, biomarkers may improve preoperative cardiac risk assessment. Surgery leads to activation of the sympathetic nervous system, inflammation, hypercoagulable and catabolic states, which put patients at risk for postoperative myocardial infarction/injury (PMI). PMI is the most common CV complication and asymptomatic in the vast majority of surgical patients, but has been associated with myocardial dysfunction, respiratory and renal failure, mortality, and disability.[23-26]

Inflammation

Low grade inflammation causes endothelial- and organ dysfunction in chronic disease (e.g. CAD, HF, renal insufficiency, diabetes mellitus) and puts patients at increased risk for PMI and renal dysfunction.[27-29] Biomarkers reflecting these processes may identity patients with (subclinical) organ dysfunction. Surgery activates the innate immune system, and the production of pro- and anti-inflammatory processes in the body. Although this is essential for healing, a postoperative dysregulated inflammatory response increases the risk of infectious complications by immune suppression, and organ dysfunction through endothelial injury.[30] Biomarkers may aid physicians in discriminating between postoperative dysregulated inflammation and infection.

Metabolic

Preoperative deficiencies of nutrients or vitamins are risk factors for endothelial dysfunction, immune dysfunction, and cardiovascular disease.[28,31] Activation of the HPA axis and several other hormonal pathways change the production of cortisol, growth hormone, thyroid hormone, and insulin. The negative effects are hypermetabolism and hypercatabolism, leading to hyperglycaemia, release of fatty acids, and muscle wasting, which can be detrimental for postoperative recovery.[11]

Haematological

Anaemia is a risk factor for postoperative complications and disability, most likely trough tissue hypoxemia, organ injury and poor functional capacity.[32,33] In surgical patients, anaemia is often caused by (functional) iron deficiency, blood loss, and inflammation. Besides erythropoiesis, iron deficiency also impairs oxidative metabolism and cellular immunity. The negative effects of poor iron metabolism are aggravated by increased hepcidin concentrations in response to a postoperative dysregulated inflammatory response, for instance due to blood loss after major surgery. Besides, systemic inflammation initiates bone marrow reprogramming and a decreased erythrocyte lifespan. This may explain why an abnormal iron status has been associated with postoperative complications, even without anaemia.[34] A high red cell distribution width (RDW) is a common marker of oxidative stress, chronic inflammation, cardiovascular disease, and is associated with adverse events after surgery.[35]

Renal

Chronic kidney disease associated azotaemia, hypervolemia and anaemia increase after surgery, and are considered to be major risks for postoperative complications. As a result of sympathetic nervous activation, vasoconstriction may decrease renal blood flow and

glomerular filtration rate. The renin-angiotensin-aldosterone-system is activated resulting in water and salt retention and further systemic vasoconstriction. Up to 20% of major surgery patients sustain acute kidney injury (AKI). Even when renal function returns to baseline at the time of hospital discharge, the risk for long-term mortality and disability remains increased.

Outcome measures

Postoperative outcomes are registered after review of medical charts and diagnostic test results. Causes of outcome measures are classified according to international criteria (Appendix 2) as follows:

1. Respiratory failure, defined according to European Perioperative Clinical Outcome (EPCO) definitions, including: ARDS, pleural effusion, pneumothorax, atelectasis, respiratory infection, aspiration pneumonitis, bronchospasm, cardiopulmonary oedema, and pulmonary embolism. Postoperative hypoxemia (i.e. saturation <90% on room air, or oxygen therapy >5L O_2/min) will be registered as respiratory failure.
2. Major adverse cardiac events, defined in agreement with the Standardised Endpoints in Perioperative medicine (StEP) criteria for cardiovascular outcomes and the 4th universal definition of myocardial infarction, including: cardiac death, non-fatal cardiac arrest, coronary revascularization, myocardial infarction/injury, heart failure, pulmonary embolism, atrial fibrillation, and stroke.
3. Infections, defined according to StEP criteria for infection and sepsis, including: sepsis, pneumonia, empyema, surgical site infection, urinary system infection, blood stream infection. For all events, the probability of infection will be categorised using a four-point scale (none, possible, probable and definite infection).

4. Acute kidney injury, defined by the StEP criteria and classified as stage 1-3 based on postoperative serum creatinine concentrations or initiation of renal replacement therapy.
5. Bleeding, according to the standardized definitions from the bleeding academic research consortium (BARC) for cardiac surgery. Postoperative bleeding after non-cardiac surgery is graded according to the modified Clavien-Dindo classification.
6. Postoperative pain, registered daily using the NRS. Scores range from 0 (no pain) to 10 (maximum pain). Chronic pain is defined as surgery related pain >3 months after surgery. The impact of chronic pain is assessed with the 12-item WHODAS 2.0 questionnaire, supplemented with several dedicated questions regarding surgery related pain (i.e. duration of pain, severity of pain and relation with the surgical procedure).
7. Disability, measured according to the self-assessment 12-item WHODAS 2.0 before and after surgery, and reported as a percentage score of functional limitations. Scores range from zero (no disability) to one-hundred percent (fully disabled). New clinically important disability is defined as a change >5% or more after surgery.
8. Mortality, registered as failure to rescue (i.e. hospital mortality following a major postoperative complication), 30-day mortality, days alive and out of the hospital at 120 days, 1-year mortality and 2-year mortality.

The severity of a complication is graded according to the modified Clavien-Dindo classification.[36]

Findings to date

Recruitment for BIGPROMISE started in October 2021. The first patient was enrolled on October 12th 2021. Currently (May 2nd 2023), 1,672 patients were screened for eligibility, of

whom 1,174 (70%) provided informed consent for study participation. Most common types of major surgery were cardiac (60%) and gastro-intestinal procedures (20%). The overall incidence of a severe postoperative complications was 11%. We anticipate to enrol >1,000 patients annually.

Collaboration

To enable research collaborations in the field of perioperative medicine, the outcome parameters of BIGPROMISE are defined according to international standards as described in PLUTO, a perioperative longitudinal study of complications and long-term outcomes.[37] The design of the BIGPROMISE biobank is based on the results of scientific research and the social interest in reducing the harmful consequences of postoperative complications. Data and biomaterials from BIGPROMISE can be used for future research within the scope of the scientific aim of the study and the informed consent provided by participants: to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to postoperative complications. Investigators who are interested in scientific collaboration may contact the study team through www.bigpromise.nl/contact. Applications will be reviewed by a scientific board according to methodological, statistical, ethical, and legal criteria, in agreement with BIGPROMISE biobank regulations.

Discussion

The BIGPROMISE biobank is designed to study the postoperative dysregulated stress response in its cause of postoperative complications, by analysing a large collection of perioperative biomarkers in a high-risk surgical population. In recent years, perioperative research on the pathophysiology of postoperative complications has mainly focussed on myocardial injury and inflammation.[23-26,27,29] However, randomized trials that studied

interventions targeting one of these pathways did not result in new recommendations for perioperative treatments.[18] For example, while systemic inflammation is associated with poor outcome, treatment with corticosteroids did not improve outcome in two large international randomized controlled trials in cardiac surgery patients.[38,39] This may be explained by two reasons: First, different contributors to the dysregulated stress response may currently be under-recognized. Interventions targeting only a single known pathophysiological pathway may be insufficient to prevent postoperative organ injury and adverse outcomes. Second, perioperative interventions that use a 'one size fits all approach' overlook the fact that not all patients are identical. That is, some patients may develop an overwhelming stress response to surgery, while others exhibit a more balanced or even an underwhelming response. Treating these patients in the same way may have a beneficial effect in some and a detrimental effect in others, with no net result at all. Biomarkers can inform clinicians on which phenotype of dysregulated stress they are dealing with, and guide targeted interventions. Thus, a refined understanding of the postoperative dysregulated stress response is required to find new strategies to improve surgical outcomes. The BIGPROMISE study will use clinical and molecular data to construct (and validate) perioperative prediction models to improve risk stratification and early diagnosis and treatment of severe complications following major surgery.

In perioperative medicine, a biomarker is considered an indicator of a (patho)physiological process (e.g. ageing, chronic disease), or response to surgery (e.g. organ injury, inflammation). Currently, perioperative biomarkers are mainly used for risk management, but their use for the early diagnosis of complications or targeted interventions has potential added value. Despite that a lot is being invested in perioperative biomarker discovery, few biomarkers have made it from bench to bedside. Partly because few large, well-designed studies have been performed on the association between perioperative

biomarker levels and adverse outcomes in surgical patients. BIGPROMISE will prospectively assess existing biomarker panels on fresh blood samples to validate their prognostic value for outcomes related to postoperative complications, and systematically collect and store plasma, serum and whole blood samples to allow for future perioperative biomarker discovery and development.

Authors' contributions

PGN, HJTR, IMD, TCDR initiated the study, PGN, TR, TCDR wrote the draft manuscript. All authors critically reviewed the draft manuscript and read and approved the final manuscript.

Consent for publication

Not applicable

Acknowledgements

The authors would like to thank all colleagues in the participating centres (St. Antonius Hospital Nieuwegein, Amphia Hospital, Breda) for their support in conducting the BIGPROMISE study.

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. 2015 Apr 27;385 Suppl 2:S11

2. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Sciortino CM, Mandal K, Zehr KJ, Conte JV, Higgins RS, Cameron DE, Whitman GJ. Complications After Cardiac Operations: All Are Not Created Equal. Ann Thorac Surg. 2017 Jan;103(1):32-40

3. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg. 2010 May;251(5):807-18.

4. Paul S, Sedrakyan A, Chiu YL, Nasar A, Port JL, Lee PC, Stiles BM, Altorki NK. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. Eur J Cardiothorac Surg. 2013 Apr;43(4):813-7.

5. International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016; 117:601-9.

6. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005 Sep;242(3):326-41

7. Archer S, Pinto A, Vuik S, Bicknell C, Faiz O, Byrne B, Johnston M, Skapinakis P, Athanasiou T, Vincent C, Darzi A. Surgery, Complications, and Quality of Life: A Longitudinal Cohort Study Exploring the Role of Psychosocial Factors. Ann Surg. 2018 Apr 19.

8. Verwijmeren L, Noordzij PG, Daeter EJ, Emmelot-Vonk MH, Vernooij LM, van Klei

WA, van Dongen EPA. Preoperative frailty and one-year functional recovery in elderly cardiac surgery patients. J Thorac Cardiovasc Surg 2022. Online ahead of print.

9. Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, Clavien PA. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Ann Surg. 2011 Dec;254(6):907-13

10. Healy MA, Mullard AJ, Campbell DA Jr, Dimick JB. Hospital and Payer Costs Associated With Surgical Complications. JAMA Surg. 2016 Sep 1;151(9):823-30.

11. Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ 2020:20(9):321-328.

12. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol. 2009 Jun;69(6):479-91.

13. Manou-Stathopoulou V, Korbonits M, Ackland DL. Redefining the perioperative stress response: a narrative review. Br J Anaesth 2019;123(5):570-583.

14. Siontis KC, Siontis GC, Contopoulos-Ioannidis DG, Ioannidis JP. Diagnostic tests often fail to lead to changes in patient outcomes.J Clin Epidemiol. 2014 Jun;67(6):612-21

15. Ioannidis JPA, Bossuyt PMM. Waste, Leaks, and Failures in the Biomarker Pipeline. Clin Chem. 2017 May;63(5):963-972.

16. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. 2008 May 15;358(20):2107-16

17. Blankenberg S, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, Kuulasmaa K, Yarnell J, Schnabel RB, Wild PS, Münzel TF, Lackner KJ, Tiret L, Evans A, Salomaa V; MORGAM Project. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph

(MORGAM) biomarker project. Circulation. 2010 Jun 8;121(22):2388-97

18. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, Ibanez B, Lenarczyk R, Mansmann UR, McGreavy P, Mueller C, Muneretto C, Niessner A, Potpara TS, Ristić A, Sade LE, Schirmer H, Schüpke S, Sillesen H, Skulstad H, Torracca L, Tutarel O, Van Der Meer P, Wojakowski W, Zacharowski K; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022 Oct 14;43(39):3826-3924.

19. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology. 2010 May;112(5):1105-15.

20. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug;14(7):798-804.

21. International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. Available at: https://www.who.int/classifications/icf/en/

22. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208.

23. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295-304

24. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S;

POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011 Apr 19;154(8):523-8.

25. Beattie WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie K, Paech MJ, Devereaux PJ, Sessler DI, Wallace S, Myles PS; ANZCA Clinical Trials Network and the ENIGMA-II Investigators. Survival After Isolated Post-Operative Troponin Elevation. J Am Coll Cardiol. 2017;70(7):907-908.

26. Beattie, WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie KMBBS, Michael JMBBS, Sessler, DI, Wallace SMPH, Myles PS on behalf of the ANZCA Clinical Trials Network for the ENIGMA-II Investigators. Implication of Major Adverse Postoperative Events and Myocardial Injury on Disability and Survival: A Planned Subanalysis of the ENIGMA-II Trial. Anesthesia & Analgesia 2018;127(5): 1118-1126.

27. Ackland GL, Abbott TEF, Cain D, Edwards MR, Sultan P, Karmali SN, Fowler AJ, Whittle JR, MacDonald NJ, Reyes A, Paredes LG, Stephens RCM, Del Arroyo AG, Woldman S, Archbold RA, Wragg A, Kam E, Ahmad T, Khan AW, Niebrzegowska E, Pearse RM. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. Br J Anaesth. 2019;122(2):180-187.

28. Verwijmeren L, Bosma M, Vernooij LM, Linde EM, Dijkstra IM, Daeter EJ, Van Dongen EPA, Van Klei WA, Noordzij PG. Associations Between Preoperative Biomarkers and Cardiac Surgery-Associated Acute Kidney Injury in Elderly Patients: A Cohort Study. Anesth Analg. 2021;133(3):570-577.

29. Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EMW, Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. Annals of Surgery 2016; 263(6):1207-1212.

30. Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023 Mar;78(3):356-370. doi: 10.1111/anae.15896. Epub 2022 Oct 29. PMID: 36308338.

31. Turan A, Artis AS, Hanline C, Saha P, Maheshwari K, Kurz A, Devereaux PJ, Duceppe E, Patel A, Tiboni M, Ruetzler K, Pearse R, Chan MTV, Wu WKK, Srinathan S, Garg AX, Sapsford R, Sessler DI. Preoperative Vitamin D Concentration and Cardiac, Renal, and Infectious Morbidity after Noncardiac Surgery. Anesthesiology. 2020 Jan;132(1):121-130.

32. Hazen YJJM, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S, Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten JMAA, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD. Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis. Br J Anaesth. 2022;128(4):636-643.

33. Smoor RM, Rettig TCD, Vernooij LM, Huijsmans RLN, Verwijmeren L, Emmelot-Vonk MH, van Dongen EPA, Cremer OL, Noordzij PG. Postoperative anaemia and disability-free survival in older cardiac surgery patients. Br J Anaesth. 2022;129(2):e27-e29.

34. Rössler J, Schoenrath F, Seifert B, Kaserer A, Spahn GH, Falk V, Spahn DR. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth. 2020;124(1):25-34.

35. Yoshida N, Horinouchi T, Toihata T, Harada K, Eto K, Sawayama H, Iwatsuki M, Nagai Y, Ishimoto T, Baba Y, Miyamoto Y, Baba H. Clinical Significance of Pretreatment Red Blood Cell Distribution Width as a Predictive Marker for Postoperative Morbidity After Esophagectomy for Esophageal Cancer: A Retrospective Study. Ann Surg Oncol. 2022;29(1):606-613.

36. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13.

37. de Mul N, Verlaan D, Ruurda JP, van Grevenstein WMU, Hagendoorn J, de Borst GJ, Vriens MR, de Bree R, Zweemer RP, Vogely C, Haitsma Mulier JLG, Vernooij LM, Reitsma JB, de Zoete MR, Top J, Kluijtmans JAJ, Hoefer IE, Noordzij P, Rettig T, Marsman M, de Smet AMGA, Derde L, van Waes J, Rijsdijk M, Schellekens WJM, Bonten MJM, Slooter AJC, Cremer OL. Cohort profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications. BMJ Open. 2023 Apr 19;13(4): e068970.

38. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D; Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012 Nov 7;308(17):1761-7.

39. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum Á, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Sep 26;386(10000):1243-1253.

Table 1. Perioperative biomarkers and analyser systems.

Analyzer system	Biomarkers
Sysmex XN	haemoglobin, haematocrit, erytrocytes, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, mean platelet volume, mean corpuscular haemoglobin concentration, leukocytes, trombocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, reticulocyte haemoglobin equivalent, neutrophil-to-lymphocyte ratio.
Cobas 8000	albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, calcium, cholesterol, C-reactive protein, chloride, creatinin kinase, cystatin C, ferritin, growth differentiation factor-15, gamma-glutamyl transferase, glucose, high-density lipoprotein, high-sensitive troponin T, insulin-like growth factor-1, creatinin, interleukin-6, iron, lactate dehydrogenase, low-density lipoprotein, magnesium, neutrophil gelatinase associated lipocalin, N-terminal pro B-type natriuretic peptide, pro-calcitonin, phosphate, potassium, sex hormone binding globulin, soluble fms-like tyrosine kinase-1, sodium, triglycerides, thyroid stimulating hormone, free thyroxine, 25 hydroxyvitamin D.

Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

Figure 2. Perioperative collection, analysis and storage of blood samples

Supplementary Table 1. Perioperative blood sampling and clinical data collection

Appendix 1. Surgical procedures

Appendix 2. Definitions of outcome measures

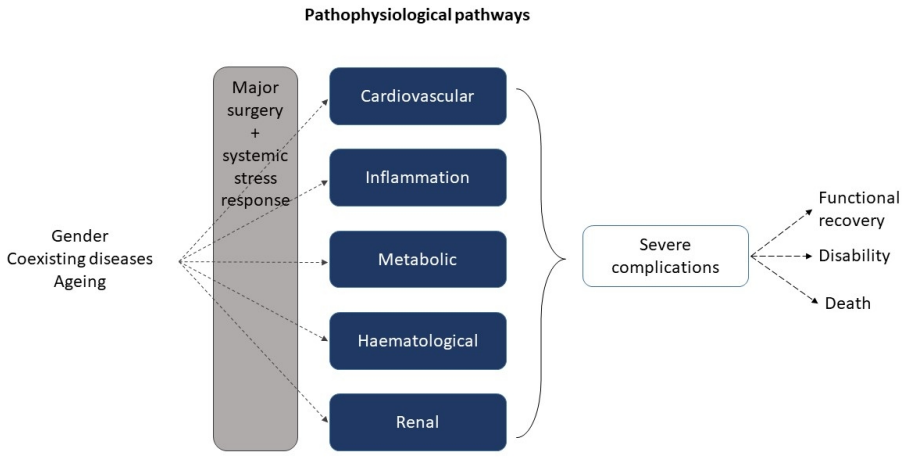


Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

338x190mm (96 x 96 DPI)

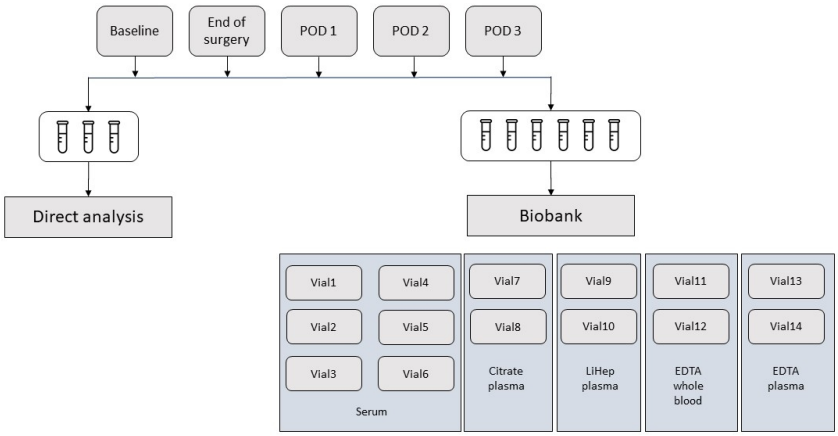


Figure 2. Perioperative collection, analysis and storage of blood samples

338x190mm (96 x 96 DPI)

Supplementary Table 1. Perioperative blood sampling and clinical data collection

	OC	Before surgery	After surgery	POD 1	POD 2	POD 3	30 days	120 days	1 year	2 years
Counselling	X									
Informed consent		X								
Data collection		X					X	X	X	X
Blood sample		X	X	X	X	X				
Questionnaire		X						X		

OC: outpatient clinic, POD: postoperative day

Appendix 1. Surgical procedures

Cardiac surgery

- Coronary artery bypass grafting
- Aortic valve replacement or repair
- Aortic valve replacement with aortic rooth and ascending aorta replacement (Bentall procedure)
- Mitral valve replacement or repair
- Tricuspid valve replacement or repair
- Combination of procedures above

Pulmonary surgery

- Pneumonectomy
- Lobectomy
- Bilobectomy
- Sleeve lobectomy
- Segmentectomy

Gastrointestinal surgery

- Small bowel resection
- Ileocecal resection
- Sigmoid resection
- Hemicolectomy right or left
- Transverse colon resection
- Low Anterior resection
- Abdominoperineal resection
- HIPEC

Hepatobiliary surgery

- Pancreaticoduodenectomy (Whipple)
- Pylorus preserving pancreaticoduodenectomy (PPPD)

- Distal pancreatectomy
- Total pancreatectomy

Vascular surgery

- Open aortic surgery
    - Abdominal aortic aneurysm repair
- Endovascular aortic surgery
    - Endovascular aneurysm repair
    - Fenestrated endovascular aneurysm repair
    - Covered endovascular repair of the aortic bifurcation
- Suprainguinal and/or infrainguinal peripheral vascular surgery
    - Percutaneous transluminal angioplasty
    - Bypass surgery
    - Endarterectomy
    - Thrombectomy
- Combination of procedures above

Urologic surgery

- Ureteroileostomy (Bricker's procedure)

Endpoint definitions:

Table 1: All-cause mortality

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
All-cause mortality	Death within 30 days of surgery		1-year mortality 2-year mortality		[1]STeP mortality

Table 2: Postoperative pulmonary complications

Endpoint	Definition	Excluded		Limitation and comments	Ref.
Respiratory failure	Postoperative PaO2 < 8 kPa (60 mmHg) on room air, a PaO2:FI02 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy or 5L O2/min oxygen therapy when arterial saturation or peripheral saturation on room air is not available OR Need for mechanical ventilation >24h postoperative* Postoperative oxygen supplementation via a nasal cannula on the day of surgery is seen as common practice and therefore not registered as postoperative respiratory failure. Persistent oxygen supplementation on postoperative day 1 will be registered as respiratory failure if fulfilling the above stated criteria.			EPCO definition of respiratory failure (as defined under postoperative pulmonary complications) complemented with *	EPCO definition [2]

Table 3: Causes of severe respiratory failure

Causes of severe respiratory failure		ref
ARDS	Berlin definition for ARDS	Berlin definition for ARDS [3]
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows	EPCO [2]
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura	EPCO [2]

Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung	EPCO [2]
Respiratory infection	See table 7	StEP Infection and sepsis [4]
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents	EPCO [2]
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators	EPCO [2]
Cardiopulmonary edema	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml	Designation trial [5]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan	STeP cardiovascular [6]
Unknown		

Table 4: Postoperative cardiovascular complications

Endpoint	Definition	Excluded	Limitation	Ref.
MACE	Composite outcome including: - Cardiac death - Non-fatal cardiac arrest - Coronary revascularization - Myocardial infarction	- Pulmonary embolism - Hemorrhage - Deep venous thrombosis - All-cause mortality		STeP cardiovascular [6]
Cardiac death	Death with a vascular cause and included those deaths after a myocardial infarction, cardiac arrest, and cardiac revascularization procedure.	- Death after pulmonary embolism - Death after hemorrhage - Multi-organ failure - Cause of death unknown		STeP cardiovascular [6]
Non-fatal cardiac arrest	Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation			STeP cardiovascular [6]
Coronary revascularization	Percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery.			STeP cardiovascular [6]
Myocardial infarction in noncardiac surgery	Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cTn values with at least one value above the 99th percentile URL and at least one of the following:		No routine ECG after noncardiac surgery	STeP cardiovascular and 4th universal definition of myocardial infarction [6,7]

	1. Symptoms of myocardial ischaemia 2. New ischaemic ECG changes 3. Development of pathological Q waves 4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology 5. Identification of a coronary thrombus by angiography or autopsy Post-mortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available.			
Acute myocardial infarction in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In			4th universal definition of myocardial infarction [7]

	addition, one of the following elements is required: 1. Development of new pathological Q waves;* 2. Angiographic documented new graft occlusion or new native coronary artery occlusion; 3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. *Isolated development of new pathological Q waves meets cardiac myocardial infarction criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.			
Acute myocardial injury in noncardiac surgery	Detection of an elevated and increased or decreased cTn value above the 99th percentile URL is defined as myocardial injury. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			StEP cardiovascular, 4th universal definition of myocardial infarction [6,7]
Acute myocardial injury in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the		In rhythm surgery and valve surgery substantial amount of troponin release will be related to the direct procedure related tissue trauma and not ischemia.	4th universal definition of myocardial infarction [7] + own interpretation

	99th percentile URL. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			
Acute heart failure	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml		Definition of heart failure did not reach consensus in the StEP initiative.	StEP cardiovascular, heart failure guideline ESC [6,8]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan		Diagnosis will be missed in a large portion of patients	StEP cardiovascular [6]
Atrial fibrillation/ flutter	New onset of irregularly irregular heart rate in the absence of P waves lasting at least 30 s or for the duration of the ECG recording (if <30 s)		No routine ECG or holter registration postoperatively, except for patients admitted to the ICU or PACU.	StEP [6]
Stroke	An embolic, thrombotic or haemorrhagic cerebral event with motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory). **Mild:** Results in only temporary harm and would not require specific clinical treatment. **Moderate:** More serious complication but one which does not usually result in permanent harm or functional			EPCO definition [2]

	limitation. Requires clinical treatment. **Severe:** Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Requires clinical treatment.			

Table 5: Definitions exclusion criteria

Deep venous thrombosis	Diagnosis confirmed by 2-Point Compression Ultrasonography of the Lower Extremity		StEP [6] + adaptation to Dutch clinical practice standards
Multi-organ failure	Altered function in two or more organ systems during an acute illness such that homeostasis cannot be maintained without intervention		Definitions for sepsis and organ failure [9]
Hemorrhage	Acute blood loss		
All-cause mortality	Any cause of death that doesn't fulfill the criteria for cardiac death		

Table 6: Sepsis

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Sepsis	Increase in SOFA score of 2 or more, with evidence of infection, within 30 days.		Suspected site of infection; SOFA score.		StEP Infection and sepsis [4]

Table 7: Postoperative respiratory infectious complication

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Postoperative respiratory infectious complication **Possible**	**Signs/Symptoms/Laboratory**: one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **OR** • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange **AND** **Imaging:** One chest imaging test result with at least one of the following: Pulmonary infiltrate, consolidation or cavitation		Cause: CAP, HAP, VAP,		
Probable	**Signs/Symptoms/Laboratory**: at least one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **AND:** **Imaging**: two or more serial chest imaging results with either new and persistent OR progressive and persistent changes of		Cause: CAP, HAP, VAP,		StEP infection and sepsis [4]

	- infiltrate - consolidation - cavitation (In patients **without** underlying cardiac or pulmonary disease **one** definitive imaging test result is acceptable **AND** at least two of the following: • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (with PF <200, O2 supplementation >5L/min, or start of (non)-invasive ventilation)				
Definite	Criteria for probable postoperative respiratory infection **AND** One of the following criteria: - Positive culture of causative lung pathogen in respiratory secretions - Positive blood culture with causative pathogen for pneumonia - Isolation of a virus or proof of a viral pathogen in airway secretion by PCR - Histopathologic evidence for pneumonia		Cause: CAP, HAP, VAP,	Definition of StEP + additional criteria	

Table 8: Causes postoperative respiratory infectious complication

Community acquired pneumonia (CAP)	Pneumonia occurring on day 0 or 1 after hospital admission, considering day of admission as day 0				
Hospital acquired pneumonia (HAP)	Pneumonia occurring ≥ day 2 of hospital admission, considering day of admission as day 0				
Ventilator-Associated pneumonia (VAP)	Pneumonia occurring ≥ day 2 after the start of mechanical ventilation (MV) and ≤ day 2 after the end of MV.	Non-invasive ventilation like CPAP, BiPAP, optiflow are not considered mechanical ventilation.			

Table 9: Abscess/Empyema

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Abscess/empyema				
Possible	**1.** Low clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** debatable Imaging test evidence of abscess or other infection			
Probable	**1.** High clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** Imaging test evidence of abscess or other infection			Step[4] with adaptation

Definite	**1.** Organism seen on Gram stain of lung tissue or pleural fluid, or identification of pathogenic organism from fluid or tissue from affected site **2.** Abscess or other evidence of infection on gross anatomical or histopathologic examination			

Table 10: Surgical site infections

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Surgical site infection (SSI)				
Superficial incisional SSI	Involves only skin and subcutaneous tissue of the incision			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Superficial incisional SSI **Definite**	Patient has at least one of the following: - Purulent drainage from the superficial incision. - Organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.			StEP infection and sepsis [4,10]

	- Superficial incision that is deliberately opened and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed **AND** Patient has at least one of the following signs or symptoms: localized pain or tenderness, localized swelling, erythema or heat. - Abscess at physical examination, re-operation, histopathologic or radiologic examination.			
Deep incisional SSI	Involves deep soft tissues of the incision (for example, fascial and muscle layers)			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Definite	Patient has at least **one** of the following: - Purulent drainage from the deep incision. - a deep incision that spontaneously dehisces, or is deliberately opened **AND** organism(s) identified from the deep soft tissues of the incision by microbiologic testing which is performed for purposes of clinical diagnosis or treatment, or microbiologic testing is not performed. **AND**			StEP infection and sepsis [4,10]

	patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness. - an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.			
Organ/Space SSI	Event involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure			
Possible	Patient has at least one of the following signs or symptoms: - Fever > 38 C - Pain in the area of surgical procedure (not superficial)			
Probable	Possible criteria **AND** Imaging test evidence suggestive of infection.			
Definite	Patient has at least one of the following: a. purulent drainage from a drain that is placed into the organ/space b. organism(s) identified from fluid or tissue in the organ/space performed for purposes of clinical diagnosis or treatment. c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam			StEP infection and sepsis [4,10]

Table 11: Urinary system infection, blood stream infection, other infection

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
Urinary tract infection **(Catheter and not catheter related)**	**One** of the following signs or symptoms: - Fever (>38C) - Suprapubic tenderness* - Costovertebral angle pain or tenderness* - Urinary urgency^ - Urinary frequency^ - Dysuria^ Microbiologic cultures: Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥10^5 CFU/ml * Without other recognized cause ^ These symptoms cannot be used when a catheter is in place		Catheter related: If indwelling urinary catheter had been in place for more than 2 consecutive days on the date of event AND was present on the day of the event or removed the day before.		CDC [11]
High Urinary system infection	- Identification of pathogenic organism from fluid or tissue from affected site - Abscess or other evidence of infection on gross anatomical examination, during invasive procedure, or during histopathologic examination OR one of - Fever >38C - localised pain or tenderness with no other recognised cause AND ONE OF				StEP [4]

	- purulent drainage from affected site - organism identified in blood by culture or non-culture based biological testing - imaging suggestive of infection which if equivocal is supported by clinical correlation, specifically physician documented treatment for urinary system infection				
Primary Blood stream infection (BSI)/ Central line blood stream infection (CLBSI)	A Laboratory Confirmed Bloodstream Infection (LCBI) that is not included in the common commensal list and is not secondary to an infection at another body site OR Patient has at least one of the following signs or symptoms: fever >38C, chills or hypotension, and at least one of the following: (a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions (b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy (c) Positive blood antigen test.	Common commensal list: see: Common Commensal organisms include, but are not limited to, diphtheroids (Corynebacterium spp. not C. diphtheria), Bacillus spp. (not B. anthracis), Propionibacterium spp., coagulase-negative staphylococci (including			CDC [12]

		S. epidermidis), viridans group streptococci, Aerococcus spp. Micrococcus spp. and Rhodococcus spp Organisms that are parasites and viruses. Campylobacter, Salmonella, Shigella, Listeria, Vibrio and Yersinia as well as C. difficile, Enterohemorrhagic E. coli, and Enteropathogenic E. coli. Blastomyces, Histoplasma, Coccidioides, Paracocci			

		dioides, Cryptococcus, and Pneumocystis.			
Infection eci/ 'other infection'	Strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, OR infection is not a respiratory infection, surgical site infection, primary bloodstream infection or urinary tract infection: meeting two or more of the following criteria: Core temperature < 36C or >38C; white cell count >12x10^9 l-1 or < 4x10^9 l-1, respiratory rate >20 breaths per minute or PaCO2 < 4.7 kPa (35mmHg); Pulse rate >90 beats per minute			CDC and EPCO definitions are used for 'Infection eci' criteria. We added 'Other infection'	CDC[13] AND EPCO [2]

Table 12: Postoperative renal complications

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Acute Kidney Injury (AKI)	Stage 1: Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours OR increase in serum creatinine to 1.5-1.9 times baseline. Stage 2: increase in serum creatinine to 2.0-2.9 times baseline Stage 3: increase in serum creatinine to ≥ 3 times baseline OR increase in serum creatinine to ≥353.6 µmol/L OR initiation of renal replacement therapy			StEP Renal Endpoints [14]

Table 13: Postoperative blood loss

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Postoperative bleeding in cardiac surgery	Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional. Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation. Type 3a: overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is			[15] BARC

	related to bleed); any transfusion with overt bleeding. Type 3b: overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents. Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. Type 4: coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period. Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.			
Postoperative bleeding noncardiac surgery	Postoperative bleeding Clavien Dindo classification ≥3			

In addition, all adverse events in the postoperative period will be graded according to the Clavien-Dindo system[16]:

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia
Grade IV	Life-threatening complication (e.g. brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks) requiring Intensive Care management
Grade V	Death of a patient

References:

1. Jackson, A. I. R. *et al.* Systematic reviews and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: mortality, morbidity, and organ failure. *Br. J. Anaesth.* **130**, 404–411 (2023).
2. Jammer, I. *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. *Eur. J. Anaesthesiol.* **32**, 88–105 (2015).
3. Ranieri, V. M. *et al.* Acute respiratory distress syndrome: The Berlin definition. *JAMA - J. Am. Med. Assoc.* **307**, 2526–2533 (2012).
4. Barnes, J. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis. *Br. J. Anaesth.* **122**, 500–508 (2019).
5. Hol, L. *et al.* Driving Pressure during General Anesthesia for Open Abdominal Surgery (DESIGNATION): Study protocol of a randomized clinical trial. *Trials* **21**, 1–15 (2020).
6. Beattie, W. S. *et al.* Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes. *Br. J. Anaesth.* **126**, 56–66 (2021).
7. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).
8. McDonagh, T. A. *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, 3599–3726 (2021).
9. Bone, R. C. *et al.* Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *Chest* **101**, 1644–1655 (1992).
10. Cdc, T., Report, H. A. I. P., Care, S. & Project, I. Surgical Site Infection Event (SSI) Introduction : Settings : Requirements : 1–39 (2022).
11. NHSN. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events Definitions : *Centers Dis. Control Prev.* 1–18 (2022).
12. Centers, F. D. C. A. P. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) Table of Contents. . *https//www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf (accessed 27 Jan 2021).* 1–50 (2021).
13. Horan, T. C., Andrus, M. & Dudeck, M. A. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am. J. Infect. Control* **36**, 309–332 (2008).
14. McIlroy, D. R. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: renal endpoints. *Br. J. Anaesth.* **121**, 1013–1024 (2018).
15. 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).
16. Dindo, D., Demartines, N. & Clavien, P. A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* **240**, 205–213 (2004).

BMJ Open

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078307.R1
Article Type:	Cohort profile
Date Submitted by the Author:	07-Feb-2024
Complete List of Authors:	Noordzij, P.; Sint Antonius Hospital; UMC Utrecht, Intensive Care Ruven, Henk; Sint Antonius Hospital Reniers, Ted; Sint Antonius Hospital Idema, Rene; Amphia Hospital Thio, M.S.Y.; Amphia Hospital Cremer, Olaf; UMC Utrecht, Intensive Care Hollema, Nynke; Sint Antonius Hospital Smit, Kyra; Sint Antonius Hospital Vernooij, Lisette; Utrecht University, Department of Anesthesiology, Intensive Care and Emergency Medicine; Sint Antonius Hospital Dijkstra, Ineke M.; St Antonius Hospital, Department of Clinical Chemistry Rettig, T; Amphia Hospital site Molengracht, Anesthesiology, Intensive Care and Pain Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia
Keywords:	Cardiothoracic surgery < SURGERY, Colorectal surgery < SURGERY, Pancreatic surgery < SURGERY, Vascular surgery < SURGERY, Risk Factors, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

P.G. Noordzij[1,3], H.J.T. Ruven[1], T. Reniers[1], R.N. Idema[2], M.S.Y. Thio[2], O.L. Cremer[3], N. Hollema[1], K.N. Smit[1], L.M. Vernooij[1,3], I.M. Dijkstra[1], T.C.D. Rettig[2]

1. St. Antonius Hospital, Nieuwegein; 2. Amphia Hospital, Breda; 3. University Medical Centre Utrecht, the Netherlands.

Peter Noordzij, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands

p.noordzij@antoniusziekenhuis.nl

Henk Ruven, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

h.ruven@antoniusziekenhuis.nl

René Idema, M.D., PhD. Department of Clinical Chemistry, Amphia Hospital, Molengracht 21, 4818 CK, Breda rene.idema@gmail.com

Ineke Dijkstra, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

i.dijkstra@antoniusziekenhuis.nl

Ted Reniers, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
t.reniers@antoniusziekenhuis.nl

Olaf Cremer, M.D., PhD. Department of Intensive Care Medicine, University Medical Centre Utrecht, Utrecht, Netherlands
O.L.Cremer@umcutrecht.nl

Nynke Hollema. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
n.hollema@antoniusziekenhuis.nl

Maaike Thio, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.
msythio@amphia.nl

Kyra Smit, Ph.D. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands
kn.smit@antoniusziekenhuis.nl

Lisette Vernooij, PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands.
l.vernooij@antoniusziekenhuis.nl

Thijs Rettig, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.

trettig@amphia.nl

Corresponding author

Peter Noordzij, M.D., PhD. Dept. of Anaesthesiology, Intensive Care and Pain Medicine, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

Tel: +31 88 320 6948, E-mail: p.noordzij@antoniusziekenhuis.nl

Funding

This study is supported by a research grant from Roche Diagnostics International.

Conflicts of interest

PN has participated in advisory boards for perioperative use of biomarkers, for which he has received a honorarium by Roche Diagnostics (Rotkreuz, Switzerland). PN and TR have held lectures on perioperative biomarkers for which they have received a honorarium by Roche Diagnostics. OC has received research grants from ImmuneXpress Inc. (Seattle, WA) and Abionic SA (Epalinges, Switzerland) for related work. HR, TR, RI, MT, NH, KS, LV and ID have no conflicts of interest.

Word count: 3,802

Abstract: 299

Abstract

Purpose: Postoperative complications increase mortality, disability, and costs. Advanced understanding of the risk factors for postoperative complications is needed to improve surgical outcomes. This paper discusses the rationale and profile of the BIGPROMISE (biomarkers to guide perioperative management and improve outcome in high-risk surgery) cohort, that aims to investigate risk factors, pathophysiology, and outcomes related to postoperative complications.

Participants: Adult patients undergoing major surgery in two tertiary teaching hospitals. Clinical data and blood samples are collected before surgery, at the end of surgery, and on the first, second and third postoperative day. At each time point a panel of cardiovascular, inflammatory, renal, haematological, and metabolic biomarkers is assessed. Aliquots of plasma, serum, and whole blood of each time point are frozen and stored. Data on severe complications are prospectively collected during 30 days after surgery. Functional status is assessed before surgery and after 120 days using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0. Mortality is followed up until two years after surgery.

Findings to date: The first patient was enrolled on October 8th 2021. Currently (Jan 1st 2024) 3,086 patients were screened for eligibility, of whom 1,750 (57%) provided informed consent for study participation. Median age was 66 years (60; 73), 28% were female, and 68% of all patients were American Society of Anaesthesiologists (ASA) physical status class 3. Most common types of major surgery were cardiac (49%) and gastro-intestinal procedures (26%). The overall incidence of 30-day severe postoperative complications was 16%.

Future plans: By the end of the recruitment phase, expected in 2026, approximately 3,000 patients with major surgery will have been enrolled. This cohort allows us to investigate the role of pathophysiological perioperative processes in the cause of postoperative complications,

and to discover and develop new biomarkers to improve risk stratification for adverse postoperative outcomes.

Trial registration number NCT05199025

Data availability statement

Data sharing not applicable as a preliminary dataset was generated for this report.

Keywords: major surgery, biomarkers, outcomes, postoperative complications, disability

Strengths and limitations

- A large prospective collection of perioperative blood samples and clinical data in a high-risk surgical population.
- Postoperative complications and functional outcomes are defined according to international standards to facilitate research collaborations.
- A perioperative biomarker panel is prospectively assessed on fresh blood samples to elucidate the role of pathophysiological processes in the cause of postoperative complications.
- Multiple sample aliquots of plasma, serum and whole blood are frozen and stored in a central archive, allowing future perioperative biomarker discovery and development.
- This study is limited to blood samples that are routinely collected and stored until 72 hours after surgery.

Introduction

Worldwide, more than 330 million patients have surgery each year.[1] Depending on type of surgery and co-existing diseases, 10-30% of patients suffer severe postoperative complications.[2-5] Common adverse events are infections (e.g. pneumonia, surgical site infection), myocardial infarction, respiratory failure, and acute kidney injury. Postoperative complications are important determinants of long-term mortality and poor health after surgery,[6-8] impair quality of life and may increase hospital costs up to four times.[9,10]

Surgical trauma triggers a systemic stress response, that involves a complex neuroendocrine and immunological reaction to local tissue injury. Local tissue trauma activates the innate immune system, with pro- and anti-inflammatory cytokines triggering systemic inflammation and the hypothalamic-pituitary-adrenal (HPA) axis. This results in stimulation of the sympathetic nervous system, alongside several other hormonal pathways, to maintain physiological homeostasis.[11] The effects of these pathways change perioperative organ perfusion, water balance and cellular metabolism. A postoperative dysregulated stress response can be detrimental as excessive systemic inflammation, immunosuppression, hypermetabolism, and hypercoagulation can lead to organ failure and death.[11,12] The most important determinant of a postoperative dysregulated stress response is the nature and extent of surgery. In addition, non-surgical factors such as ageing, co-existing diseases and deconditioning, are contributing factors (Figure 1).[13]

In perioperative medicine, a biomarker is considered an indicator of a preoperative (patho)physiological process (e.g. ageing, chronic disease), or response to surgery (e.g. organ injury, inflammation). Numerous publications have raised awareness of the added value of biomarkers in perioperative medicine. However, heterogeneity in study design and methodological limitations have hindered implementation. First, many studies focussed on the

cardiovascular pathophysiology of postoperative complications, but used a wide range of clinical (non-standardized) outcomes. This complicates the interpretation of results, and makes the usefulness of perioperative biomarkers unclear.[14,15] Second, researchers often use a single-marker approach (e.g. cardiac troponin, interleukin-6) to study perioperative risk and pathophysiology of complications.[16,17] However, the complex aetiology of postoperative complications involves multiple pathophysiological processes, which are likely better reflected by a panel of multiple biomarkers.[11] A concept that has not been well studied in perioperative medicine, yet.[18,19] Third, in addition to risk stratification, and prognosis, the application of perioperative biomarkers covers early diagnosis of complications, and targeted interventions to improve postoperative outcomes, both of which have been incompletely studied. As a result, few biomarkers make it from bench to bedside, despite significant investment in perioperative biomarker research.[20,21] The 'biomarkers to guide perioperative management and improve outcome in high-risk surgery' (BIGPROMISE) cohort will prospectively assess a wide range of perioperative biomarkers in fresh blood samples, and systematically collect and store plasma, serum and whole blood samples to allow for future biomarker discovery. This manuscript describes the rationale and design of the BIGPROMISE cohort, which primarily aims to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to standardized postoperative complications in patients undergoing major elective surgery.

Cohort description

The BIGPROMISE cohort prospectively studies patients undergoing elective major cardiac or non-cardiac surgery, and is an initiative of the departments of Anaesthesiology, Intensive Care and Pain Medicine of St. Antonius hospital and Amphia hospital in the Netherlands. The study protocol was filed at Clinicaltrials.gov under registration number NCT05199025, and received approval from the Medical research Ethics Committees United (NL74076.100.20). The current protocol version is 6.1 (21-06-2023) and available upon request. The biobank samples are stored by a third party biobank provider (Azenta, Griesheim, Germany).

Setting

Patients are recruited in two tertiary teaching hospitals (St. Antonius hospital and Amphia hospital, the Netherlands). Based on the historical surgical volumes of both facilities, approximately 2,500 - 3,000 patients are eligible for inclusion each year. BIGPROMISE biobank aims to collect clinical data and blood samples of at least 1,000 patients per year. BIGPROMISE will be recruiting at least until 2025, and possibly longer depending on capacity and funding.

BIGPROMISE biobank is an investigator-initiated research collaboration between anaesthesiologists, intensivists and clinical chemists, in collaboration with surgeons, and Roche Diagnostics International (Penzberg, Germany), a large biotech company, and worldwide provider of in-vitro diagnostics.

Inclusion criteria and patient recruitment

Adult patients (>18 years) undergoing elective major surgery under general anaesthesia are eligible for participation. Surgical risk is based on an estimate of procedure-specific risk of 30-day mortality, without taking age, gender, frailty, or coexisting diseases into

account.[22,23] The following types of surgery are considered: cardiac, vascular, gastrointestinal, hepatobiliary, urologic, and pulmonary surgery. A full list of surgical procedures is provided in Appendix 1. Patients not providing written informed consent, patients not able to complete questionnaires in Dutch, patients who are pregnant, patients undergoing emergency surgery, and patients with a life expectancy less than six months are excluded from participation in this study.

Eligible patients scheduled for surgery are contacted by telephone by trained study personnel. Patients are informed about the purposes of the biobank and will receive an information letter by (e-)mail, if they consider to participate. Written informed consent is obtained at time of hospital admission by a member of the study team. This includes the collection of demographic and clinical data, blood samples for biomarker analysis in fresh blood samples during hospital stay and a functional status questionnaire. Additionally, a written permission is separately obtained for: collection, handling and storage of blood samples in a dedicated biobank for future biomarker discovery, permission to be contacted for further research.

Data collection

Prior to surgery, baseline data are collected regarding patient demographics, medical history, chronic pain, previous laboratory results, frailty, and functional status (Supplementary Table 1). Preoperative study data are collected from electronic patient records, from dedicated questionnaires (12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 for functional status, and from a numeric rating scale (NRS) for pain.[24,25] Study data during hospital admission are variables related to surgery and anaesthesia, clinical course, laboratory results, complications, and pain, which will be extracted from electronic

patient records. After hospital discharge, postoperative complications will be registered until 30 days after surgery. Further outcome data consist of days alive and out of hospital after 120 days, patient-reported information on functional status and pain after 120 days, and mortality up to two years.

Study data are collected and managed using REDCap which is an electronic data capture tool. REDCap is a secure, web-based software platform and compliant with Good Clinical Practice guidelines.[26] Postoperative pain scores, vital parameters (modified early warning scores), and the results of perioperative biomarker panels are extracted semi-automatically from electronic medical files (Epic Systems Corporation, United States; Metavision, iMD Soft, Israel), and the local laboratory information management systems (GLIMS, Clinisys GLIMS, Belgium, and MOLIS, CompuGroup, Belgium). Postoperative complications are noted and classified by a dedicated researcher (TR, MT), and validated by an experienced perioperative physician (PGN, TCDR), prior to manual registration in the database. Follow-up data for functional outcomes are registered using electronic and paper questionnaires (WHODAS 2.0). Long-term mortality is assessed using the Dutch municipality register of deceased persons to obtain date of death. Quality assurance of study data is annually performed by an independent monitor. Data records are coded, the key to the code is kept securely in each participating centre.

Blood sample collection and processing

Blood samples are collected at five perioperative time points: after induction of general anaesthesia (baseline), at the end of surgery, and on the morning of the first, second and third postoperative day. Blood is collected from an arterial line (if applicable) or venepuncture into vacuum blood collecting tubes, according to the schedule presented in Supplementary Table 2.

In all study patients, blood samples are centrifuged at 1800 x g for 5 minutes and used to analyse a panel of 50 biomarkers at each perioperative time point (Table 1, Figure 2). Biomarker analyses are performed at the local hospital laboratory on Roche Cobas 8000 and Sysmex XN platforms. Results of perioperative biomarker analysis are captured in local laboratory information management systems and uploaded to a central web application for research data (REDCap).

In patients with written consent for biobanking, an additional 21 ml blood is processed for storage at -80 degrees Celsius as whole blood (3ml), and serum and plasma after centrifugation at 2000 g for 10 minutes or 4000 g for 5 minutes (Figure 2). Aliquots of plasma, serum, and whole blood are frozen and stored within 6 hours after collection. Aliquots are stored in a dedicated biobank facility (Azenta, Griesheim, Germany).

Biomarker panel

The selection of biomarkers is based on the hypothesis that a postoperative dysregulated stress response, which we briefly explained in the introduction section, is associated with postoperative complications, through systemic inflammation, immunosuppression, hypermetabolism, hypercoagulation, and organ injury, and that serum biomarkers reflect (part of) these pathways or any downstream effect.[11-13] Furthermore, we considered previous literature reports on the pathophysiology of postoperative complications, availability and reproducibility of biomarker assays, current practice, and costs. For pragmatic reasons, biomarkers are categorized according to pathways involved in the pathogenesis of postoperative complications, as follows (Figure 1):

Cardiovascular

Chronic cardiac disease, such as coronary artery disease (CAD) and heart failure (HF), are key risk factors for postoperative complications. Common risk factors (e.g. diabetes mellitus, renal insufficiency, peripheral artery disease) are strongly associated with undiagnosed cardiac disease. In these patients, biomarkers may improve preoperative cardiac risk assessment. Surgery leads to activation of the sympathetic nervous system, inflammation, hypercoagulable and catabolic states, which put patients at risk for postoperative myocardial infarction/injury (PMI). PMI is the most common CV complication and asymptomatic in the vast majority of surgical patients, but has been associated with myocardial dysfunction, respiratory and renal failure, mortality, and disability.[27-30]

Inflammation

Low grade inflammation causes endothelial- and organ dysfunction in chronic disease (e.g. CAD, HF, renal insufficiency, diabetes mellitus) and puts patients at increased risk for PMI and renal dysfunction.[17,31,32] Biomarkers reflecting these processes may identify patients with (subclinical) organ dysfunction. Surgery activates the innate immune system, and the production of pro- and anti-inflammatory processes in the body. Although this is essential for healing, a postoperative dysregulated inflammatory response increases the risk of infectious complications by immune suppression, and organ dysfunction through endothelial injury.[32] Biomarkers may aid physicians in discriminating between postoperative dysregulated inflammation and infection.

Metabolic

Preoperative deficiencies of nutrients or vitamins are risk factors for endothelial dysfunction, immune dysfunction, and cardiovascular disease.[33,34] Activation of the HPA axis and several other hormonal pathways change the production of cortisol, growth hormone, thyroid

hormone, and insulin. The negative effects are hypermetabolism and hypercatabolism, leading to hyperglycaemia, release of fatty acids, and muscle wasting, which can be detrimental for postoperative recovery.[11]

Haematological

Anaemia is a risk factor for postoperative complications and disability, most likely trough tissue hypoxemia, organ injury and poor functional capacity.[35,36] In surgical patients, anaemia is often caused by (functional) iron deficiency, blood loss, and inflammation. Besides erythropoiesis, iron deficiency also impairs oxidative metabolism and cellular immunity. The negative effects of poor iron metabolism are aggravated by increased hepcidin concentrations in response to a postoperative dysregulated inflammatory response, for instance due to blood loss after major surgery. Besides, systemic inflammation initiates bone marrow reprogramming and a decreased erythrocyte lifespan. This may explain why an abnormal iron status has been associated with postoperative complications, even without anaemia.[37] A high red cell distribution width (RDW) is a common marker of oxidative stress, chronic inflammation, cardiovascular disease, and is associated with adverse events after surgery.[38]

Renal

Chronic kidney disease associated azotaemia, hypervolemia and anaemia increase after surgery, and are considered to be major risks for postoperative complications. As a result of sympathetic nervous activation, vasoconstriction may decrease renal blood flow and glomerular filtration rate. The renin-angiotensin-aldosterone-system is activated resulting in water and salt retention and further systemic vasoconstriction.[11] Up to 20% of major surgery patients sustain acute kidney injury (AKI). Even when renal function returns to

baseline at the time of hospital discharge, the risk for long-term mortality and disability remains increased.[33]

Outcome measures

Postoperative outcomes are registered after review of medical charts and diagnostic test results. Causes of outcome measures are classified according to international criteria (Appendix 2) as follows:

1. Respiratory failure, defined according to European Perioperative Clinical Outcome (EPCO) definitions, including: ARDS, pleural effusion, pneumothorax, atelectasis, respiratory infection, aspiration pneumonitis, bronchospasm, cardiopulmonary oedema, and pulmonary embolism. Postoperative hypoxemia (i.e. saturation <90% on room air, or oxygen therapy >5L O_2/min) will be registered as respiratory failure.
2. Major adverse cardiac events, defined in agreement with the Standardised Endpoints in Perioperative medicine (StEP) criteria for cardiovascular outcomes and the 4th universal definition of myocardial infarction, including: cardiac death, non-fatal cardiac arrest, coronary revascularization, myocardial infarction/injury, heart failure, pulmonary embolism, atrial fibrillation, and stroke.
3. Infections, defined according to StEP criteria for infection and sepsis, including: sepsis, pneumonia, empyema, surgical site infection, urinary system infection, blood stream infection. For all events, the probability of infection will be categorised using a four-point scale (none, possible, probable and definite infection).
4. Acute kidney injury, defined by the StEP criteria and classified as stage 1-3 based on postoperative serum creatinine concentrations or initiation of renal replacement therapy.

5. Bleeding, according to the standardized definitions from the bleeding academic research consortium (BARC) for cardiac surgery. Postoperative bleeding after non-cardiac surgery is graded according to the modified Clavien-Dindo classification.
6. Postoperative pain, registered daily using the NRS. Scores range from 0 (no pain) to 10 (maximum pain). Chronic pain is defined as surgery related pain >3 months after surgery. The impact of chronic pain is assessed with the 12-item WHODAS 2.0 questionnaire, supplemented with several dedicated questions regarding surgery related pain (i.e. duration of pain, severity of pain and relation with the surgical procedure).
7. Disability, measured according to the self-assessment 12-item WHODAS 2.0 before and after surgery, and reported as a percentage score of functional limitations. Scores range from zero (no disability) to one-hundred percent (fully disabled). New clinically important disability is defined as a change >5% or more after surgery.
8. Mortality, registered as failure to rescue (i.e. hospital mortality following a major postoperative complication), 30-day mortality, days alive and out of the hospital at 120 days, 1-year mortality and 2-year mortality.

The severity of a complication is graded according to the modified Clavien-Dindo classification.[39]

Study size

By the end of the recruitment phase approximately 3,000 patients with major surgery will have been enrolled. Our study cohort allows us to validate, update and/or develop prediction models including 55 candidate predictors, based on an incidence of 15% for severe complications, a global shrinkage factor ≥0.9 and a c-statistics of 0.80.[40] To investigate pathophysiological differences between patients with and without a severe postoperative

complications, a minimal effect size of 0.25 can be demonstrated using an α of 0.05 and a β of 0.95.

Future study design

The extensive collection of blood samples in our biorepository, combined with clinical data and prospectively collected patient-reported outcomes, provides the opportunity to answer a broad range of research questions. For aetiological research on the pathophysiology of postoperative complications, perioperative biomarker dynamics will be studied. The use of DAGs will be encouraged to assess the risk of potential residual confounding.[41] Furthermore, BIGPROMISE enables us to do prediction and diagnostic studies, using biomarkers to improve risk stratification. This includes new model development, but also updating and validating existing risk models. To assess the potential for clinical use, reclassification measures and decision curve analysis will be performed. In addition, we will compare the predictive accuracy of new or non-standard biomarkers (e.g. GDF-15, IL-6) for postoperative complications, with biomarkers that are currently often used in clinical practice (e.g. CRP, leucocytes). Sensitivity, specificity, and positive and negative predictive values will be calculated for biomarker cut-off values, and compared with prior literature reports.

Public and patient involvement

During the design of this study, we did not involve patient organisations.

Findings to date

Recruitment for BIGPROMISE started in October 2021. The first patient was enrolled on October 12th 2021. Currently (January 1st 2024), 3,086 patients were screened for eligibility, of whom 1,785 (58%) provided informed consent for study participation (Supplementary

Figure 1). Most common types of major surgery are cardiac (49%) and gastro-intestinal procedures (26%). Median age is 66 years (60; 73), 28% are female, and 68% of all patients are classified as ASA physical status class 3 (Supplementary Table 3). The overall incidence of a severe postoperative complications is 16%. We anticipate to enrol approximately 1,000 patients annually.

Collaboration

To enable research collaborations in the field of perioperative medicine, the outcome parameters of BIGPROMISE are defined according to international standards as described in PLUTO, a perioperative longitudinal study of complications and long-term outcomes.[42] The design of the BIGPROMISE biobank is based on the results of scientific research and the social interest in reducing the harmful consequences of postoperative complications. Data and biomaterials from BIGPROMISE can be used for future research within the scope of the scientific aim of the study and the informed consent provided by participants: to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to postoperative complications. Investigators who are interested in scientific collaboration may contact the study team through www.bigpromise.nl/contact. Applications will be reviewed by a scientific board according to methodological, statistical, ethical, and legal criteria, in agreement with BIGPROMISE biobank regulations.

Funding

Expenses for personnel, materials, biomarker assays and storage of blood samples are financed with an external research grant from Roche Diagnostics International. Roche had no role in the design of our study, collection of data, preparation and publication of this manuscript.

Discussion

The BIGPROMISE biobank is designed to study the postoperative dysregulated stress response in its cause of postoperative complications, by analysing a large collection of perioperative biomarkers in a high-risk surgical population. In recent years, perioperative research on the pathophysiology of postoperative complications has mainly focussed on myocardial injury and inflammation.[17,27-30,31] However, randomized trials that studied interventions targeting one of these pathways did not result in new recommendations for perioperative treatments.[22] For example, while systemic inflammation is associated with poor outcome, treatment with corticosteroids did not improve outcome in two large international randomized controlled trials in cardiac surgery patients.[43,44] This may be explained by two reasons: First, different contributors to the dysregulated stress response may currently be under-recognized. Interventions targeting only a single known pathophysiological pathway may be insufficient to prevent postoperative organ injury and adverse outcomes. Second, perioperative interventions that use a 'one size fits all approach' overlook the fact that not all patients are identical. That is, some patients may develop an overwhelming stress response to surgery, while others exhibit a more balanced or even an underwhelming response. Treating these patients in the same way may have a beneficial effect in some and a detrimental effect in others, with no net result at all. Biomarkers can inform clinicians on which phenotype of dysregulated stress they are dealing with, and guide targeted interventions. Thus, a refined understanding of the postoperative dysregulated stress response is required to find new strategies to improve surgical outcomes. The BIGPROMISE study will use clinical and molecular data to construct (and validate) perioperative prediction models to improve risk stratification and early diagnosis and treatment of severe complications following major surgery. Our study has several limitations: First, blood

samples are routinely collected and stored until 72 hours after surgery. As a result, pathophysiological mechanism related to complications that occur after that period may remain incompletely studied. Second, postoperative complications were defined in agreement with StEP criteria, as a result postoperative cognitive disorders are not recorded.

Currently, perioperative biomarkers are mainly used for risk management, but their use for the early diagnosis of complications or targeted interventions has potential added value. Despite that a lot is being invested in perioperative biomarker discovery, few biomarkers have made it from bench to bedside. Partly because few large, well-designed studies have been performed on the association between perioperative biomarker levels and adverse outcomes in surgical patients. BIGPROMISE will prospectively assess existing biomarker panels on fresh blood samples to validate their prognostic value for outcomes related to postoperative complications, and systematically collect and store plasma, serum and whole blood samples to allow for future perioperative biomarker discovery and development.

Authors' contributions

PGN, HJTR, IMD, TCDR initiated the study, PGN, TR, TCDR wrote the draft manuscript. RNI, MSYT, OLC, NH, KS, LMV and IMD critically reviewed the draft manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable

Acknowledgements

The authors would like to thank all colleagues in the participating centres (St. Antonius Hospital Nieuwegein, Amphia Hospital, Breda) for their support in conducting the BIGPROMISE study.

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. 2015 Apr 27;385 Suppl 2:S11

2. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Sciortino CM, Mandal K, Zehr KJ, Conte JV, Higgins RS, Cameron DE, Whitman GJ. Complications After Cardiac Operations: All Are Not Created Equal. Ann Thorac Surg. 2017 Jan;103(1):32-40

3. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg. 2010 May;251(5):807-18.

4. Paul S, Sedrakyan A, Chiu YL, Nasar A, Port JL, Lee PC, Stiles BM, Altorki NK. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. Eur J Cardiothorac Surg. 2013 Apr;43(4):813-7.

5. International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016; 117:601-9.

6. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005 Sep;242(3):326-41

7. Archer S, Pinto A, Vuik S, Bicknell C, Faiz O, Byrne B, Johnston M, Skapinakis P, Athanasiou T, Vincent C, Darzi A. Surgery, Complications, and Quality of Life: A Longitudinal Cohort Study Exploring the Role of Psychosocial Factors. Ann Surg. 2018 Apr 19.

8. Verwijmeren L, Noordzij PG, Daeter EJ, Emmelot-Vonk MH, Vernooij LM, van Klei

WA, van Dongen EPA. Preoperative frailty and one-year functional recovery in elderly cardiac surgery patients. J Thorac Cardiovasc Surg 2022. Online ahead of print.

9. Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, Clavien PA. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Ann Surg. 2011 Dec;254(6):907-13

10. Healy MA, Mullard AJ, Campbell DA Jr, Dimick JB. Hospital and Payer Costs Associated With Surgical Complications. JAMA Surg. 2016 Sep 1;151(9):823-30.

11. Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ 2020:20(9):321-328.

12. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol. 2009 Jun;69(6):479-91.

13. Manou-Stathopoulou V, Korbonits M, Ackland DL. Redefining the perioperative stress response: a narrative review. Br J Anaesth 2019;123(5):570-583.

14. Lurati Buse, Giovanna; Bollen Pinto, Bernardo; Abelha, Fernando; Abbott, Tom E.F.; Ackland, Gareth; Afshari, Arash; De Hert, Stefan; Fellahi, Jean-Luc; Giossi, Laure; Kavsak, Peter; Longrois, Dan; M'Pembele, Rene; Nucaro, Anthony; Popova, Ekaterine; Puelacher, Christian; Richards, Toby; Roth, Sebastian; Sheka, Mootii; Szczeklik, Wojciech; van Waes, Judith; Walder, Bernhard; Chew, Michelle S. ESAIC focused guideline for the use of cardiac biomarkers in perioperative risk evaluation. European Journal of Anaesthesiology 2023;40(12):888-927

15. Vernooij LM, van Klei WA, Moons KG, Takada T, van Waes J, Damen JAAG. The comparative and added prognostic value of biomarkers to the Revised Cardiac Risk Index for preoperative prediction of major adverse cardiac events and all-cause mortality in patients who undergo noncardiac surgery. Cochrane Database of Systematic Reviews 2021, Issue 12.

16. Writing Committee for the VISION Study Investigators. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA. 2017;317(16):1642–1651. 17. Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EMW, Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. Annals of Surgery 2016; 263(6):1207-1212.

18. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. 2008 May 15;358(20):2107-16

19. Blankenberg S, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, Kuulasmaa K, Yarnell J, Schnabel RB, Wild PS, Münzel TF, Lackner KJ, Tiret L, Evans A, Salomaa V; MORGAM Project. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. Circulation. 2010 Jun 8;121(22):2388-97

20. Siontis KC, Siontis GC, Contopoulos-Ioannidis DG, Ioannidis JP. Diagnostic tests often fail to lead to changes in patient outcomes.J Clin Epidemiol. 2014 Jun;67(6):612-21

21. Ioannidis JPA, Bossuyt PMM. Waste, Leaks, and Failures in the Biomarker Pipeline. Clin Chem. 2017 May;63(5):963-972.

22. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, Ibanez B, Lenarczyk R, Mansmann UR, McGreavy P, Mueller C, Muneretto C, Niessner A, Potpara TS, Ristić A, Sade LE, Schirmer H, Schüpke S, Sillesen H, Skulstad H, Torracca L, Tutarel O, Van Der Meer P, Wojakowski W, Zacharowski K; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022 Oct 14;43(39):3826-3924.

23. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology. 2010 May;112(5):1105-15.

24. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug;14(7):798-804.

25. International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. Available at: https://www.who.int/classifications/icf/en/

26. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208.

27. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295-304

28. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011 Apr 19;154(8):523-8.

29. Beattie WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie K, Paech MJ, Devereaux PJ, Sessler DI, Wallace S, Myles PS; ANZCA Clinical Trials Network and the ENIGMA-II Investigators. Survival After Isolated Post-Operative Troponin Elevation. J Am Coll Cardiol. 2017;70(7):907-908.

30. Beattie, WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie KMBBS, Michael

JMBBS, Sessler, DI, Wallace SMPH, Myles PS on behalf of the ANZCA Clinical Trials Network for the ENIGMA-II Investigators. Implication of Major Adverse Postoperative Events and Myocardial Injury on Disability and Survival: A Planned Subanalysis of the ENIGMA-II Trial. Anesthesia & Analgesia 2018;127(5): 1118-1126.

31. Ackland GL, Abbott TEF, Cain D, Edwards MR, Sultan P, Karmali SN, Fowler AJ, Whittle JR, MacDonald NJ, Reyes A, Paredes LG, Stephens RCM, Del Arroyo AG, Woldman S, Archbold RA, Wragg A, Kam E, Ahmad T, Khan AW, Niebrzegowska E, Pearse RM. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. Br J Anaesth. 2019;122(2):180-187.

32. Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023 Mar;78(3):356-370. doi: 10.1111/anae.15896. Epub 2022 Oct 29. PMID: 36308338.

33. Verwijmeren L, Bosma M, Vernooij LM, Linde EM, Dijkstra IM, Daeter EJ, Van Dongen EPA, Van Klei WA, Noordzij PG. Associations Between Preoperative Biomarkers and Cardiac Surgery-Associated Acute Kidney Injury in Elderly Patients: A Cohort Study. Anesth Analg. 2021;133(3):570-577.Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023 Mar;78(3):356-370. doi: 10.1111/anae.15896. Epub 2022 Oct 29. PMID: 36308338.

34. Turan A, Artis AS, Hanline C, Saha P, Maheshwari K, Kurz A, Devereaux PJ, Duceppe E, Patel A, Tiboni M, Ruetzler K, Pearse R, Chan MTV, Wu WKK, Srinathan S, Garg AX, Sapsford R, Sessler DI. Preoperative Vitamin D Concentration and Cardiac, Renal, and Infectious Morbidity after Noncardiac Surgery. Anesthesiology. 2020 Jan;132(1):121-130.

35. Hazen YJJM, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S,

Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten JMAA, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD. Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis. Br J Anaesth. 2022;128(4):636-643.

36. Smoor RM, Rettig TCD, Vernooij LM, Huijsmans RLN, Verwijmeren L, Emmelot-Vonk MH, van Dongen EPA, Cremer OL, Noordzij PG. Postoperative anaemia and disability-free survival in older cardiac surgery patients. Br J Anaesth. 2022;129(2):e27-e29.

37. Rössler J, Schoenrath F, Seifert B, Kaserer A, Spahn GH, Falk V, Spahn DR. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth. 2020;124(1):25-34.

38. Yoshida N, Horinouchi T, Toihata T, Harada K, Eto K, Sawayama H, Iwatsuki M, Nagai Y, Ishimoto T, Baba Y, Miyamoto Y, Baba H. Clinical Significance of Pretreatment Red Blood Cell Distribution Width as a Predictive Marker for Postoperative Morbidity After Esophagectomy for Esophageal Cancer: A Retrospective Study. Ann Surg Oncol. 2022;29(1):606-613.

39. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13.

40. Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE Jr, Moons KG, Collins GS. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019;38(7):1276-1296.

41. VanderWeele, Tyler J.a; Hernán, Miguel A.b; Robins, James M.b,c. Causal Directed Acyclic Graphs and the Direction of Unmeasured Confounding Bias. Epidemiology

2008:19(5):720-728

42. de Mul N, Verlaan D, Ruurda JP, van Grevenstein WMU, Hagendoorn J, de Borst GJ, Vriens MR, de Bree R, Zweemer RP, Vogely C, Haitsma Mulier JLG, Vernooij LM, Reitsma JB, de Zoete MR, Top J, Kluijtmans JAJ, Hoefer IE, Noordzij P, Rettig T, Marsman M, de Smet AMGA, Derde L, van Waes J, Rijsdijk M, Schellekens WJM, Bonten MJM, Slooter AJC, Cremer OL. Cohort profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications. BMJ Open. 2023 Apr 19;13(4): e068970.

43. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D; Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012 Nov 7;308(17):1761-7.

44. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum Á, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Sep 26;386(10000):1243-1253.

Table 1. Perioperative biomarkers and analyser systems.

Analyzer system	**Biomarkers**
Sysmex XN	haemoglobin, haematocrit, erytrocytes, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, mean platelet volume, mean corpuscular haemoglobin concentration, leukocytes, trombocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, reticulocyte haemoglobin equivalent, neutrophil-to-lymphocyte ratio.
Cobas 8000	albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, calcium, cholesterol, C-reactive protein, chloride, creatinin kinase, cystatin C, ferritin, growth differentiation factor-15, gamma-glutamyl transferase, glucose, high-density lipoprotein, high-sensitive troponin T, insulin-like growth factor-1, creatinin, interleukin-6, iron, lactate dehydrogenase, low-density lipoprotein, magnesium, neutrophil gelatinase associated lipocalin, N-terminal pro B-type natriuretic peptide, pro-calcitonin, phosphate, potassium, sex hormone binding globulin, soluble fms-like tyrosine kinase-1, sodium, triglycerides, thyroid stimulating hormone, free thyroxine, 25 hydroxyvitamin D.

Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

Figure 2. Perioperative collection, analysis and storage of blood samples

Supplementary Table 1. Study variables

Supplementary Table 2. Perioperative blood sampling and clinical data collection

Supplementary Table 3. Baseline characteristics

Supplementary Figure 1. Flow chart

Appendix 1. Surgical procedures

Appendix 2. Definitions of outcome measures

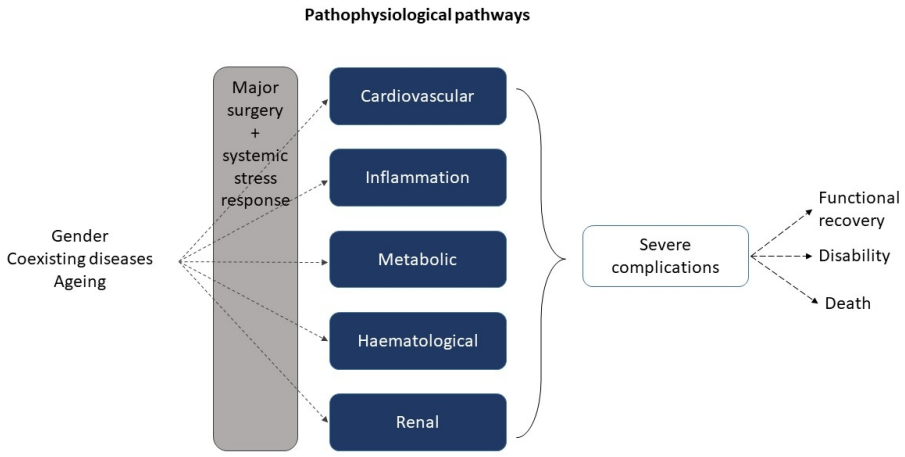


Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

338x190mm (96 x 96 DPI)

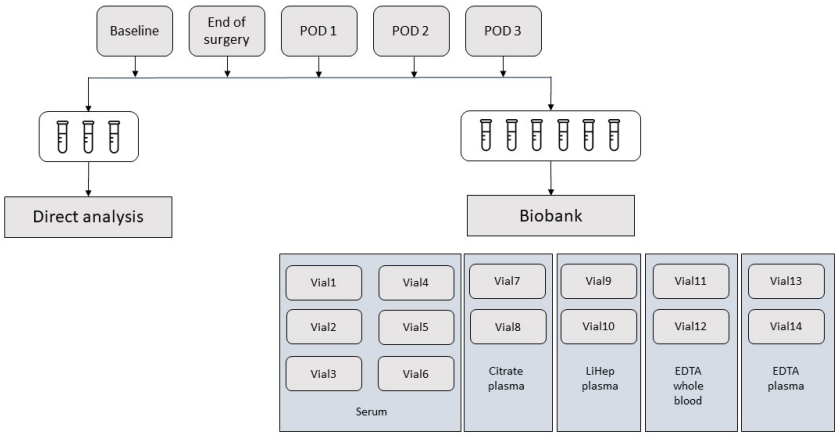


Figure 2. Perioperative collection, analysis and storage of blood samples

338x190mm (96 x 96 DPI)

Appendix 1. Surgical procedures

Cardiac surgery

- Coronary artery bypass grafting
- Aortic valve replacement or repair
- Aortic valve replacement with aortic rooth and ascending aorta replacement (Bentall procedure)
- Mitral valve replacement or repair
- Tricuspid valve replacement or repair
- Combination of procedures above

Pulmonary surgery

- Pneumonectomy
- Lobectomy
- Bilobectomy
- Sleeve lobectomy
- Segmentectomy

Gastrointestinal surgery

- Small bowel resection
- Ileocecal resection
- Sigmoid resection
- Hemicolectomy right or left
- Transverse colon resection
- Low Anterior resection
- Abdominoperineal resection
- HIPEC

Hepatobiliary surgery

- Pancreaticoduodenectomy (Whipple)
- Pylorus preserving pancreaticoduodenectomy (PPPD)

- Distal pancreatectomy
- Total pancreatectomy

Vascular surgery

- Open aortic surgery
    - Abdominal aortic aneurysm repair
- Endovascular aortic surgery
    - Endovascular aneurysm repair
    - Fenestrated endovascular aneurysm repair
    - Covered endovascular repair of the aortic bifurcation
- Suprainguinal and/or infrainguinal peripheral vascular surgery
    - Percutaneous transluminal angioplasty
    - Bypass surgery
    - Endarterectomy
    - Thrombectomy
- Combination of procedures above

Urologic surgery

- Ureteroileostomy (Bricker's procedure)

Endpoint definitions:

Table 1: All-cause mortality

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
All-cause mortality	Death within 30 days of surgery		1-year mortality 2-year mortality		[1]STeP mortality

Table 2: Postoperative pulmonary complications

Endpoint	Definition	Excluded		Limitation and comments	Ref.
Respiratory failure	Postoperative PaO2 < 8 kPa (60 mmHg) on room air, a PaO2:FI02 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy or 5L O2/min oxygen therapy when arterial saturation or peripheral saturation on room air is not available OR Need for mechanical ventilation >24h postoperative* Postoperative oxygen supplementation via a nasal cannula on the day of surgery is seen as common practice and therefore not registered as postoperative respiratory failure. Persistent oxygen supplementation on postoperative day 1 will be registered as respiratory failure if fulfilling the above stated criteria.			EPCO definition of respiratory failure (as defined under postoperative pulmonary complications) complemented with *	EPCO definition [2]

Table 3: Causes of severe respiratory failure

Causes of severe respiratory failure		ref
ARDS	Berlin definition for ARDS	Berlin definition for ARDS [3]
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows	EPCO [2]
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura	EPCO [2]

Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung	EPCO [2]
Respiratory infection	See table 7	StEP Infection and sepsis [4]
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents	EPCO [2]
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators	EPCO [2]
Cardiopulmonary edema	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml	Designation trial [5]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan	STeP cardiovascular [6]
Unknown		

Table 4: Postoperative cardiovascular complications

Endpoint	Definition	Excluded	Limitation	Ref.
MACE	Composite outcome including: - Cardiac death - Non-fatal cardiac arrest - Coronary revascularization - Myocardial infarction	- Pulmonary embolism - Hemorrhage - Deep venous thrombosis - All-cause mortality		STeP cardiovascular [6]
Cardiac death	Death with a vascular cause and included those deaths after a myocardial infarction, cardiac arrest, and cardiac revascularization procedure.	- Death after pulmonary embolism - Death after hemorrhage - Multi-organ failure - Cause of death unknown		STeP cardiovascular [6]
Non-fatal cardiac arrest	Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation			STeP cardiovascular [6]
Coronary revascularization	Percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery.			STeP cardiovascular [6]
Myocardial infarction in noncardiac surgery	Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cTn values with at least one value above the 99th percentile URL and at least one of the following:		No routine ECG after noncardiac surgery	STeP cardiovascular and 4th universal definition of myocardial infarction [6,7]

	1. Symptoms of myocardial ischaemia 2. New ischaemic ECG changes 3. Development of pathological Q waves 4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology 5. Identification of a coronary thrombus by angiography or autopsy Post-mortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available.			
Acute myocardial infarction in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In			4th universal definition of myocardial infarction [7]

	addition, one of the following elements is required: 1. Development of new pathological Q waves;* 2. Angiographic documented new graft occlusion or new native coronary artery occlusion; 3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. *Isolated development of new pathological Q waves meets cardiac myocardial infarction criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.			
Acute myocardial injury in noncardiac surgery	Detection of an elevated and increased or decreased cTn value above the 99th percentile URL is defined as myocardial injury. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			StEP cardiovascular, 4th universal definition of myocardial infarction [6,7]
Acute myocardial injury in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the		In rhythm surgery and valve surgery substantial amount of troponin release will be related to the direct procedure related tissue trauma and not ischemia.	4th universal definition of myocardial infarction [7] + own interpretation

	99th percentile URL. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			
Acute heart failure	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml		Definition of heart failure did not reach consensus in the StEP initiative.	StEP cardiovascular, heart failure guideline ESC [6,8]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan		Diagnosis will be missed in a large portion of patients	StEP cardiovascular [6]
Atrial fibrillation/ flutter	New onset of irregularly irregular heart rate in the absence of P waves lasting at least 30 s or for the duration of the ECG recording (if <30 s)		No routine ECG or holter registration postoperatively, except for patients admitted to the ICU or PACU.	StEP [6]
Stroke	An embolic, thrombotic or haemorrhagic cerebral event with motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory). **Mild:** Results in only temporary harm and would not require specific clinical treatment. **Moderate:** More serious complication but one which does not usually result in permanent harm or functional			EPCO definition [2]

	limitation. Requires clinical treatment. **Severe:** Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Requires clinical treatment.			

Table 5: Definitions exclusion criteria

Deep venous thrombosis	Diagnosis confirmed by 2-Point Compression Ultrasonography of the Lower Extremity		StEP [6] + adaptation to Dutch clinical practice standards
Multi-organ failure	Altered function in two or more organ systems during an acute illness such that homeostasis cannot be maintained without intervention		Definitions for sepsis and organ failure [9]
Hemorrhage	Acute blood loss		
All-cause mortality	Any cause of death that doesn't fulfill the criteria for cardiac death		

Table 6: Sepsis

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Sepsis	Increase in SOFA score of 2 or more, with evidence of infection, within 30 days.		Suspected site of infection; SOFA score.		StEP Infection and sepsis [4]

Table 7: Postoperative respiratory infectious complication

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Postoperative respiratory infectious complication **Possible**	**Signs/Symptoms/Laboratory**: one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **OR** • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange **AND** **Imaging:** One chest imaging test result with at least one of the following: Pulmonary infiltrate, consolidation or cavitation		Cause: CAP, HAP, VAP,		
Probable	**Signs/Symptoms/Laboratory**: at least one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **AND:** **Imaging**: two or more serial chest imaging results with either new and persistent OR progressive and persistent changes of		Cause: CAP, HAP, VAP,		StEP infection and sepsis [4]

	- infiltrate - consolidation - cavitation (In patients **without** underlying cardiac or pulmonary disease **one** definitive imaging test result is acceptable **AND** at least two of the following: • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (with PF <200, O2 supplementation >5L/min, or start of (non)-invasive ventilation)				
Definite	Criteria for probable postoperative respiratory infection **AND** One of the following criteria: - Positive culture of causative lung pathogen in respiratory secretions - Positive blood culture with causative pathogen for pneumonia - Isolation of a virus or proof of a viral pathogen in airway secretion by PCR - Histopathologic evidence for pneumonia		Cause: CAP, HAP, VAP,	Definition of StEP + additional criteria	

Table 8: Causes postoperative respiratory infectious complication

Community acquired pneumonia (CAP)	Pneumonia occurring on day 0 or 1 after hospital admission, considering day of admission as day 0				
Hospital acquired pneumonia (HAP)	Pneumonia occurring ≥ day 2 of hospital admission, considering day of admission as day 0				
Ventilator-Associated pneumonia (VAP)	Pneumonia occurring ≥ day 2 after the start of mechanical ventilation (MV) and ≤ day 2 after the end of MV.	Non-invasive ventilation like CPAP, BiPAP, optiflow are not considered mechanical ventilation.			

Table 9: Abscess/Empyema

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Abscess/empyema				
Possible	**1.** Low clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** debatable Imaging test evidence of abscess or other infection			
Probable	**1.** High clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** Imaging test evidence of abscess or other infection			Step[4] with adaptation

Definite	**1.** Organism seen on Gram stain of lung tissue or pleural fluid, or identification of pathogenic organism from fluid or tissue from affected site **2.** Abscess or other evidence of infection on gross anatomical or histopathologic examination			

Table 10: Surgical site infections

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Surgical site infection (SSI)				
Superficial incisional SSI	Involves only skin and subcutaneous tissue of the incision			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Superficial incisional SSI **Definite**	Patient has at least one of the following: - Purulent drainage from the superficial incision. - Organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.			StEP infection and sepsis [4,10]

	- Superficial incision that is deliberately opened and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed **AND** Patient has at least one of the following signs or symptoms: localized pain or tenderness, localized swelling, erythema or heat. - Abscess at physical examination, re-operation, histopathologic or radiologic examination.			
Deep incisional SSI	Involves deep soft tissues of the incision (for example, fascial and muscle layers)			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Definite	Patient has at least **one** of the following: - Purulent drainage from the deep incision. - a deep incision that spontaneously dehisces, or is deliberately opened **AND** organism(s) identified from the deep soft tissues of the incision by microbiologic testing which is performed for purposes of clinical diagnosis or treatment, or microbiologic testing is not performed. **AND**			StEP infection and sepsis [4,10]

	patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness. - an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.			
Organ/Space SSI	Event involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure			
Possible	Patient has at least one of the following signs or symptoms: - Fever > 38 C - Pain in the area of surgical procedure (not superficial)			
Probable	Possible criteria **AND** Imaging test evidence suggestive of infection.			
Definite	Patient has at least one of the following: a. purulent drainage from a drain that is placed into the organ/space b. organism(s) identified from fluid or tissue in the organ/space performed for purposes of clinical diagnosis or treatment. c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam			StEP infection and sepsis [4,10]

Table 11: Urinary system infection, blood stream infection, other infection

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
Urinary tract infection **(Catheter and not catheter related)**	**One** of the following signs or symptoms: - Fever (>38C) - Suprapubic tenderness* - Costovertebral angle pain or tenderness* - Urinary urgency^ - Urinary frequency^ - Dysuria^ Microbiologic cultures: Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥10^5 CFU/ml * Without other recognized cause ^ These symptoms cannot be used when a catheter is in place		Catheter related: If indwelling urinary catheter had been in place for more than 2 consecutive days on the date of event AND was present on the day of the event or removed the day before.		CDC [11]
High Urinary system infection	- Identification of pathogenic organism from fluid or tissue from affected site - Abscess or other evidence of infection on gross anatomical examination, during invasive procedure, or during histopathologic examination OR one of - Fever >38C - localised pain or tenderness with no other recognised cause AND ONE OF				StEP [4]

	- purulent drainage from affected site - organism identified in blood by culture or non-culture based biological testing - imaging suggestive of infection which if equivocal is supported by clinical correlation, specifically physician documented treatment for urinary system infection				
Primary Blood stream infection (BSI)/ Central line blood stream infection (CLBSI)	A Laboratory Confirmed Bloodstream Infection (LCBI) that is not included in the common commensal list and is not secondary to an infection at another body site OR Patient has at least one of the following signs or symptoms: fever >38C, chills or hypotension, and at least one of the following: (a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions (b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy (c) Positive blood antigen test.	Common commensal list: see: Common Commensal organisms include, but are not limited to, diphtheroids (Corynebacterium spp. not C. diphtheria), Bacillus spp. (not B. anthracis), Propionibacterium spp., coagulase-negative staphylococci (including			CDC [12]

		S. epidermidis), viridans group streptococci, Aerococcus spp. Micrococcus spp. and Rhodococcus spp Organisms that are parasites and viruses. Campylobacter, Salmonella, Shigella, Listeria, Vibrio and Yersinia as well as C. difficile, Enterohemorrhagic E. coli, and Enteropathogenic E. coli. Blastomyces, Histoplasma, Coccidioides, Paracocci			

		dioides, Cryptococcus, and Pneumocystis.			
Infection eci/ 'other infection'	Strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, OR infection is not a respiratory infection, surgical site infection, primary bloodstream infection or urinary tract infection: meeting two or more of the following criteria: Core temperature < 36C or >38C; white cell count >12x10^9 l-1 or < 4x10^9 l-1, respiratory rate >20 breaths per minute or PaCO2 < 4.7 kPa (35mmHg); Pulse rate >90 beats per minute			CDC and EPCO definitions are used for 'Infection eci' criteria. We added 'Other infection'	CDC[13] AND EPCO [2]

Table 12: Postoperative renal complications

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Acute Kidney Injury (AKI)	Stage 1: Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours OR increase in serum creatinine to 1.5-1.9 times baseline. Stage 2: increase in serum creatinine to 2.0-2.9 times baseline Stage 3: increase in serum creatinine to ≥ 3 times baseline OR increase in serum creatinine to ≥353.6 µmol/L OR initiation of renal replacement therapy			StEP Renal Endpoints [14]

Table 13: Postoperative blood loss

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Postoperative bleeding in cardiac surgery	Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional. Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation. Type 3a: overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is			[15] BARC

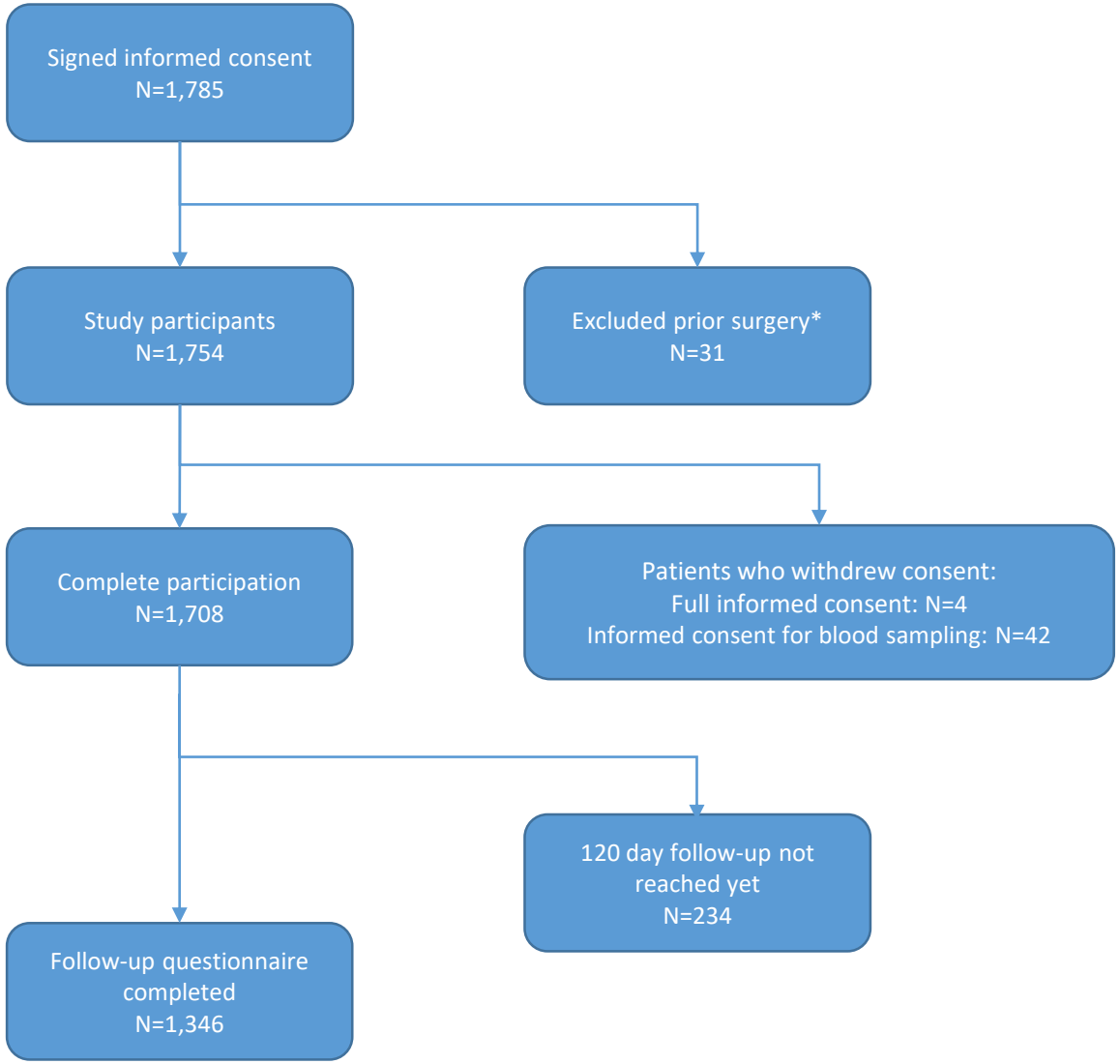
	related to bleed); any transfusion with overt bleeding. Type 3b: overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents. Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. Type 4: coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period. Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.			
Postoperative bleeding noncardiac surgery	Postoperative bleeding Clavien Dindo classification ≥3			

In addition, all adverse events in the postoperative period will be graded according to the Clavien-Dindo system[16]:

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia
Grade IV	Life-threatening complication (e.g. brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks) requiring Intensive Care management
Grade V	Death of a patient

References:

1. Jackson, A. I. R. *et al.* Systematic reviews and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: mortality, morbidity, and organ failure. *Br. J. Anaesth.* **130**, 404–411 (2023).
2. Jammer, I. *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. *Eur. J. Anaesthesiol.* **32**, 88–105 (2015).
3. Ranieri, V. M. *et al.* Acute respiratory distress syndrome: The Berlin definition. *JAMA - J. Am. Med. Assoc.* **307**, 2526–2533 (2012).
4. Barnes, J. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis. *Br. J. Anaesth.* **122**, 500–508 (2019).
5. Hol, L. *et al.* Driving Pressure during General Anesthesia for Open Abdominal Surgery (DESIGNATION): Study protocol of a randomized clinical trial. *Trials* **21**, 1–15 (2020).
6. Beattie, W. S. *et al.* Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes. *Br. J. Anaesth.* **126**, 56–66 (2021).
7. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).
8. McDonagh, T. A. *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, 3599–3726 (2021).
9. Bone, R. C. *et al.* Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *Chest* **101**, 1644–1655 (1992).
10. Cdc, T., Report, H. A. I. P., Care, S. & Project, I. Surgical Site Infection Event (SSI) Introduction : Settings : Requirements : 1–39 (2022).
11. NHSN. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events Definitions : *Centers Dis. Control Prev.* 1–18 (2022).
12. Centers, F. D. C. A. P. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) Table of Contents. . *https//www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf (accessed 27 Jan 2021).* 1–50 (2021).
13. Horan, T. C., Andrus, M. & Dudeck, M. A. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am. J. Infect. Control* **36**, 309–332 (2008).
14. McIlroy, D. R. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: renal endpoints. *Br. J. Anaesth.* **121**, 1013–1024 (2018).
15. 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).
16. Dindo, D., Demartines, N. & Clavien, P. A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* **240**, 205–213 (2004).



* Reasons for exclusion: Logistics, surgical indication, blood draw not possible or competing study

BIGPROMISE study parameters

Biomarkers

PCT, CRPhs, IL-6, GDF-15, sFLT, NT-proBNP, cTNThs, CysC and NGAL, Hb, Ht, MCV, RDW, reticulocytes, RET-He thrombocytes, leucocytes, MPV, urea, creatinine, sodium, potassium, chloride, calcium, phosphate, magnesium, ASAT, ALAT, LDH, ALP, gamma GT, bilirubin, CK, albumin, glucose, Cholesterol, Triglycerides, HDL-cholesterol, LDL-cholesterol, serum iron, ferritin, transferrin saturation, vitamin D, TSH, FT4, igf-1, SHBG, NLR.

Medical History

Age in years, Sex, BMI (kg/m2), Unintentional weight loss (>3kg) over the past 3 months, Smoking status, Alcohol consumption, Diabetes Mellitus, COPD
Hypertension, Congestive heart failure, Atrial fibrillation, Stroke, Myocardial infarction, Prior cardiac surgery, Peripheral artery disease, Chronic renal failure, history of cancer, Left ventricular ejection fraction, NYHA class, EuroSCORE, ASA classification, Charlson comorbidity index, Disability, Clinical Frailty Scale

Medication Use

Beta blockers, ACE inhibitor, Angiotensin receptor blockers, Diuretics, Plateletinhibitors, Steroids, Calciumchannel inhibitors, Non-steroidal anti-inflammatory drugs, Statins, other immunosuppressive drugs, levothyroxin use, Paracetamol, Opioids, Anitdepressants, Anticonvulsiva

Operative details

Surgery type, surgical approach, urgency, Epidural Analgesia, Sevoflurane use, Oxygen saturation before induction of anaesthesia (first measured on the OR), Intraoperative hypotension (MAP <55 mmHg, non-cardiac surgery only), Fluid balance end of surgery (in ml), Estimated operative blood loss (in ml), Cell saver use, Lowest mean arterial pressure, Lowest operative heart rate (bpm), Surgical APGAR score (number), Allogenic blood product transfusion, Coagulation products and medication,
Intraoperative steroids, Cardiopulmonary bypass time, Aortic cross clamping, (minutes), surgery duration (min)

Postoperative details

Modified early warning score (postoperative day 1-7), postoperative pain score (NRS, max and mean, postoperative day 1-7), Packed Red Blood cells transfusion (postoperative day 1-7), other allogenic blood products (postoperative day 1), Coagulation products and medication (postoperative day 1), reoperation.

Admission and Discharge

Hospital length of stay (LOS), ICU LOS, ICU re-admission, hospital re-admission, days alive and out of hospital 120 days.

Supplementary Table 1. Perioperative blood sampling and clinical data collection

	OC	Before surgery	After surgery	POD 1	POD 2	POD 3	30 days	120 days	1 year	2 years
Counselling	X									
Informed consent		X								
Data collection		X					X	X	X	X
Blood sample		X	X	X	X	X				
Questionnaire		X						X		

Supplementary Table 1

Characteristics	**N (%)**	**Missing values N (%)**
Number of participants	1,750	
Age	66 [60, 73]	7 (0.4%)
Female	481 (27.6%)	5 (0.3%)
ASA class		28 (1.6%)
ASA I	30 (1.7%)	
ASA II	422 (24.5%)	
ASA III	1,169 (67.9%)	
ASA IV	101 (5.9%)	
ASA V	0 (0.0%)	
Clinical Frailty Score, age >65 years	1,029	13 (1.2%)
Fit (1-3)	642 (62.4%)	
Risk of frailty (4)	231 (22.4%)	
Mild frailty (5)	84 (8.2%)	
Frail (6-8)	59 (5.7%)	
Cardiac Surgery	852 (48.7%)	0 (0%)
CABG	444 (25.4%)	
AVR	157 (9.0%)	
MVP/R	107 (6.1%)	
CABG + AVR	106 (6.1%)	

Bentall procedure	46 (2.6%)	
CABG + MVP/R	16 (0.9%)	
AVR + MVP/R	13 (0.7%)	
TVP	3 (0.2%)	
AVR + TVP	2 (0.1%)	
Other	4 (0.2%)	
Pulmonary Surgery	76 (4.3%)	0 (0%)
Segmentectomy	61 (3.5%)	
Lobectomy	3 (0.2%)	
Pneumonectomy	12 (0.7%)	
Gastro-Intestinal- and Hepatobiliary surgery	452 (25.8%)	0 (0%)
Colorectal surgery	280 (16.0%)	
Pancreatic surgery	118 (6.7%)	
Other Gastro-intestinal surgery	54 (3.1%)	
Vascular Surgery	194 (10.1%)	0 (0%)
Aortic surgery	100 (5.7%)	
Peripheral vascular surgery	94 (5.4%)	
Cystectomy	41 (2.4%)	0 (0%)
Reoperation	39 (2.2%)	0 (0%)
Open approach	1,106 (63.2%)	0 (0%)
Biobank participant	1,593 (91.0%)	0 (0%)

Baseline characteristics of the BIGPROMISE cohort at January 1st 2024. Data are displayed in numbers (%) or median (Interquartile range). ASA: American Society of Anaesthesiologists. CABG: Coronary artery bypass grafting. AVR: Aortic valve replacement. MVP/R: Mitral valve plasty / Replacement. TVP: Tricuspid valve plasty.

BMJ Open

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078307.R2
Article Type:	Cohort profile
Date Submitted by the Author:	18-Apr-2024
Complete List of Authors:	Noordzij, P.; Sint Antonius Hospital; UMC Utrecht, Intensive Care Ruven, Henk; Sint Antonius Hospital Reniers, Ted; Sint Antonius Hospital Idema, Rene; Amphia Hospital Thio, M.S.Y.; Amphia Hospital Cremer, Olaf; UMC Utrecht, Intensive Care Hollema, Nynke; Sint Antonius Hospital Smit, Kyra; Sint Antonius Hospital Vernooij, Lisette; Utrecht University, Department of Anesthesiology, Intensive Care and Emergency Medicine; Sint Antonius Hospital Dijkstra, Ineke M.; St Antonius Hospital, Department of Clinical Chemistry Rettig, T; Amphia Hospital site Molengracht, Anesthesiology, Intensive Care and Pain Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia
Keywords:	Cardiothoracic surgery < SURGERY, Colorectal surgery < SURGERY, Pancreatic surgery < SURGERY, Vascular surgery < SURGERY, Risk Factors, Adult surgery < SURGERY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population

P.G. Noordzij[1,3], H.J.T. Ruven[1], T. Reniers[1], R.N. Idema[2], M.S.Y. Thio[2], O.L. Cremer[3], N. Hollema[1], K.N. Smit[1], L.M. Vernooij[1,3], I.M. Dijkstra[1], T.C.D. Rettig[2]

1. St. Antonius Hospital, Nieuwegein; 2. Amphia Hospital, Breda; 3. University Medical Centre Utrecht, the Netherlands.

Peter Noordzij, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands

p.noordzij@antoniusziekenhuis.nl

Henk Ruven, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

h.ruven@antoniusziekenhuis.nl

René Idema, M.D., PhD. Department of Clinical Chemistry, Amphia Hospital, Molengracht 21, 4818 CK, Breda rene.idema@gmail.com

Ineke Dijkstra, PhD, EuSpLM. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

i.dijkstra@antoniusziekenhuis.nl

Ted Reniers, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
t.reniers@antoniusziekenhuis.nl

Olaf Cremer, M.D., PhD. Department of Intensive Care Medicine, University Medical Centre Utrecht, Utrecht, Netherlands
O.L.Cremer@umcutrecht.nl

Nynke Hollema. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
n.hollema@antoniusziekenhuis.nl

Maaike Thio, M.D. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.
msythio@amphia.nl

Kyra Smit, Ph.D. Department of Clinical Chemistry, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands
kn.smit@antoniusziekenhuis.nl

Lisette Vernooij, PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands and Department of Anaesthesiology and Intensive Care, University Medical Centre Utrecht, Utrecht, Netherlands.
l.vernooij@antoniusziekenhuis.nl

Thijs Rettig, M.D., PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, Amphia Hospital, Molengracht 21, 4818 CK, Breda.

trettig@amphia.nl

Corresponding author

Peter Noordzij, M.D., PhD. Dept. of Anaesthesiology, Intensive Care and Pain Medicine, Koekoekslaan 1, 3435 CM Nieuwegein, Netherlands

Tel: +31 88 320 6948, E-mail: p.noordzij@antoniusziekenhuis.nl

Funding

This study is supported by a research grant from Roche Diagnostics International.

Conflicts of interest

PN has participated in advisory boards for perioperative use of biomarkers, for which he has received a honorarium by Roche Diagnostics (Rotkreuz, Switzerland). PN and TR have held lectures on perioperative biomarkers for which they have received a honorarium by Roche Diagnostics. OC has received research grants from ImmuneXpress Inc. (Seattle, WA) and Abionic SA (Epalinges, Switzerland) for related work. HR, TR, RI, MT, NH, KS, LV and ID have no conflicts of interest.

Word count: 3,818

Abstract: 299

Abstract

Purpose: Postoperative complications increase mortality, disability, and costs. Advanced understanding of the risk factors for postoperative complications is needed to improve surgical outcomes. This paper discusses the rationale and profile of the BIGPROMISE (biomarkers to guide perioperative management and improve outcome in high-risk surgery) cohort, that aims to investigate risk factors, pathophysiology, and outcomes related to postoperative complications.

Participants: Adult patients undergoing major surgery in two tertiary teaching hospitals. Clinical data and blood samples are collected before surgery, at the end of surgery, and on the first, second and third postoperative day. At each time point a panel of cardiovascular, inflammatory, renal, haematological, and metabolic biomarkers is assessed. Aliquots of plasma, serum, and whole blood of each time point are frozen and stored. Data on severe complications are prospectively collected during 30 days after surgery. Functional status is assessed before surgery and after 120 days using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0. Mortality is followed up until two years after surgery.

Findings to date: The first patient was enrolled on October 8th 2021. Currently (Jan 1st 2024) 3,086 patients were screened for eligibility, of whom 1,750 (57%) provided informed consent for study participation. Median age was 66 years (60; 73), 28% were female, and 68% of all patients were American Society of Anaesthesiologists (ASA) physical status class 3. Most common types of major surgery were cardiac (49%) and gastro-intestinal procedures (26%). The overall incidence of 30-day severe postoperative complications was 16%.

Future plans: By the end of the recruitment phase, expected in 2026, approximately 3,000 patients with major surgery will have been enrolled. This cohort allows us to investigate the role of pathophysiological perioperative processes in the cause of postoperative complications,

and to discover and develop new biomarkers to improve risk stratification for adverse postoperative outcomes.

Trial registration number NCT05199025

Data availability statement

Data sharing not applicable as a preliminary dataset was generated for this report.

Keywords: major surgery, biomarkers, outcomes, postoperative complications, disability

Strengths and limitations

- A large prospective collection of perioperative blood samples and clinical data in a high-risk surgical population.
- Postoperative complications and functional outcomes are defined according to international standards to facilitate research collaborations.
- A perioperative biomarker panel is prospectively assessed on fresh blood samples to elucidate the role of pathophysiological processes in the cause of postoperative complications.
- Multiple sample aliquots of plasma, serum and whole blood are frozen and stored in a central archive, allowing future perioperative biomarker discovery and development.
- This study is limited to blood samples that are collected and stored until 72 hours after surgery.

Introduction

Worldwide, more than 330 million patients have surgery each year.[1] Depending on type of surgery and co-existing diseases, 10-30% of patients suffer severe postoperative complications.[2-5] Common adverse events are infections (e.g. pneumonia, surgical site infection), myocardial infarction, respiratory failure, and acute kidney injury. Postoperative complications are important determinants of long-term mortality and poor health after surgery,[6-8] impair quality of life and may increase hospital costs up to four times.[9,10]

Surgical trauma triggers a systemic stress response, that involves a complex neuroendocrine and immunological reaction to local tissue injury. Local tissue trauma activates the innate immune system, with pro- and anti-inflammatory cytokines triggering systemic inflammation and the hypothalamic-pituitary-adrenal (HPA) axis. This results in stimulation of the sympathetic nervous system, alongside several other hormonal pathways, to maintain physiological homeostasis.[11] The effects of these pathways change perioperative organ perfusion, water balance and cellular metabolism. A postoperative dysregulated stress response can be detrimental as excessive systemic inflammation, immunosuppression, hypermetabolism, and hypercoagulation can lead to organ failure and death.[11,12] The most important determinant of a postoperative dysregulated stress response is the nature and extent of surgery. In addition, non-surgical factors such as ageing, co-existing diseases and deconditioning, are contributing factors (Figure 1).[13]

In perioperative medicine, a biomarker is considered an indicator of a preoperative (patho)physiological process (e.g. ageing, chronic disease), or response to surgery (e.g. organ injury, inflammation). Numerous publications have raised awareness of the added value of biomarkers in perioperative medicine. However, heterogeneity in study design and methodological limitations have hindered implementation. First, many studies focussed on the

cardiovascular pathophysiology of postoperative complications, but used a wide range of clinical (non-standardized) outcomes. This complicates the interpretation of results, and makes the usefulness of perioperative biomarkers unclear.[14,15] Second, researchers often use a single-marker approach (e.g. cardiac troponin, interleukin-6) to study perioperative risk and pathophysiology of complications.[16,17] However, the complex aetiology of postoperative complications involves multiple pathophysiological processes, which are likely better reflected by a panel of multiple biomarkers.[11] A concept that has not been well studied in perioperative medicine, yet.[18,19] Third, in addition to risk stratification, and prognosis, the application of perioperative biomarkers covers early diagnosis of complications, and targeted interventions to improve postoperative outcomes, both of which have been incompletely studied. As a result, few biomarkers make it from bench to bedside, despite significant investment in perioperative biomarker research.[20,21] The 'biomarkers to guide perioperative management and improve outcome in high-risk surgery' (BIGPROMISE) cohort will prospectively assess a wide range of perioperative biomarkers in fresh blood samples, and systematically collect and store plasma, serum and whole blood samples to allow for future biomarker discovery. This manuscript describes the rationale and design of the BIGPROMISE cohort, which primarily aims to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to standardized postoperative complications in patients undergoing major elective surgery.

Cohort description

The BIGPROMISE cohort prospectively studies patients undergoing elective major cardiac or non-cardiac surgery, and is an initiative of the departments of Anaesthesiology, Intensive Care and Pain Medicine of St. Antonius hospital and Amphia hospital in the Netherlands. The study protocol was filed at Clinicaltrials.gov under registration number NCT05199025, and received approval from the Medical research Ethics Committees United (NL74076.100.20). The current protocol version is 6.1 (21-06-2023) and available upon request. The biobank samples are stored by a third party biobank provider (Azenta, Griesheim, Germany).

Setting

Patients are recruited in two tertiary teaching hospitals (St. Antonius hospital and Amphia hospital, the Netherlands). Based on the historical surgical volumes of both facilities, approximately 2,500 - 3,000 patients are eligible for inclusion each year. BIGPROMISE biobank aims to collect clinical data and blood samples of at least 1,000 patients per year. BIGPROMISE will be recruiting at least until 2025, and possibly longer depending on capacity and funding.

BIGPROMISE biobank is an investigator-initiated research collaboration between anaesthesiologists, intensivists and clinical chemists, in collaboration with surgeons, and Roche Diagnostics International (Penzberg, Germany), a large biotech company, and worldwide provider of in-vitro diagnostics.

Inclusion criteria and patient recruitment

Adult patients (>18 years) undergoing elective major surgery under general anaesthesia are eligible for participation. Surgical risk is an estimate of procedure-specific risk of 30-day mortality, without taking age, gender, frailty, or coexisting diseases into account.[22,23] The

following types of major surgery are considered in our study: cardiac, vascular, gastrointestinal, hepatobiliary, urologic, and pulmonary surgery. A full list of surgical procedures is provided in Appendix 1. Patients not providing written informed consent, patients not able to complete questionnaires in Dutch, patients who are pregnant, patients undergoing emergency surgery, and patients with a life expectancy less than six months are excluded from participation in this study.

Eligible patients scheduled for surgery are contacted by telephone by trained study personnel. Patients are informed about the purposes of the biobank and will receive an information letter by (e-)mail, if they consider to participate. Written informed consent is obtained at time of hospital admission by a member of the study team. This includes the collection of patient characteristics and clinical data, blood samples for biomarker analysis in fresh blood samples during hospital stay and a functional status questionnaire. Additionally, a written permission is separately obtained for: collection, handling and storage of blood samples in a dedicated biobank for future biomarker discovery, permission to be contacted for further research.

Data collection

Prior to surgery, baseline data are collected regarding patient characteristics, medical history, chronic pain, previous laboratory results, frailty, and functional status (Supplementary Table 1). Preoperative study data are collected from electronic patient records, from dedicated questionnaires (12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 for functional status, and from a numeric rating scale (NRS) for pain.[24,25] Study data during hospital admission are variables related to surgery and anaesthesia, clinical course, laboratory results, complications, and pain, which will be extracted from electronic

patient records. After hospital discharge, postoperative complications will be registered until 30 days after surgery. Further outcome data consist of days alive and out of hospital after 120 days, patient-reported information on functional status and pain after 120 days, and mortality up to two years.

Study data are collected and managed using REDCap which is an electronic data capture tool. REDCap is a secure, web-based software platform and compliant with Good Clinical Practice guidelines.[26] Postoperative pain scores, vital parameters (modified early warning scores), and the results of perioperative biomarker panels are extracted semi-automatically from electronic medical files (Epic Systems Corporation, United States; Metavision, iMD Soft, Israel), and the local laboratory information management systems (GLIMS, Clinisys GLIMS, Belgium, and MOLIS, CompuGroup, Belgium). Postoperative complications are noted and classified by a dedicated researcher (TR, MT), and validated by an experienced perioperative physician (PGN, TCDR), prior to manual registration in the database. Follow-up data for functional outcomes are registered using electronic and paper questionnaires (WHODAS 2.0). Long-term mortality is assessed using the Dutch municipality register of deceased persons to obtain date of death. Quality assurance of study data is annually performed by an independent monitor. Data records are coded, the key to the code is kept securely in each participating centre.

Blood sample collection and processing

Blood samples are collected at five perioperative time points: after induction of general anaesthesia (baseline), at the end of surgery, and on the morning of the first, second and third postoperative day. Blood is collected from an arterial line (if applicable) or venepuncture into vacuum blood collecting tubes, according to the schedule presented in Supplementary Table 2.

In all study patients, blood samples are centrifuged at 1800 x g for 5 minutes and used to analyse a panel of 50 biomarkers at each perioperative time point (Table 1, Figure 2). Biomarker analyses are performed at the local hospital laboratory on Roche Cobas 8000 and Sysmex XN platforms. Results of perioperative biomarker analysis are captured in local laboratory information management systems and uploaded to a central web application for research data (REDCap).

In patients with written consent for biobanking, an additional 21 ml blood is processed for storage at -80 degrees Celsius as whole blood (3ml), and serum and plasma after centrifugation at 2000 g for 10 minutes or 4000 g for 5 minutes (Figure 2). Aliquots of plasma, serum, and whole blood are frozen and stored within 6 hours after collection. Aliquots are stored in a dedicated biobank facility (Azenta, Griesheim, Germany).

Biomarker panel

The selection of biomarkers is based on the hypothesis that a postoperative dysregulated stress response, which we briefly explained in the introduction section, is associated with postoperative complications, through systemic inflammation, immunosuppression, hypermetabolism, hypercoagulation, and organ injury, and that serum biomarkers reflect (part of) these pathways or any downstream effect.[11-13] Furthermore, we considered previous literature reports on the pathophysiology of postoperative complications, availability and reproducibility of biomarker assays, current practice, and costs. For pragmatic reasons, biomarkers are categorized according to pathways involved in the pathogenesis of postoperative complications, as follows (Figure 1):

Cardiovascular

Chronic cardiac disease, such as coronary artery disease (CAD) and heart failure (HF), are key risk factors for postoperative complications. Common risk factors (e.g. diabetes mellitus, renal insufficiency, peripheral artery disease) are strongly associated with undiagnosed cardiac disease. In these patients, biomarkers may improve preoperative cardiac risk assessment. Surgery leads to activation of the sympathetic nervous system, inflammation, hypercoagulable and catabolic states, which put patients at risk for postoperative myocardial infarction/injury (PMI). PMI is the most common CV complication and asymptomatic in the vast majority of surgical patients, but has been associated with myocardial dysfunction, respiratory and renal failure, mortality, and disability.[27-30]

Inflammation

Low grade inflammation causes endothelial- and organ dysfunction in chronic disease (e.g. CAD, HF, renal insufficiency, diabetes mellitus) and puts patients at increased risk for PMI and renal dysfunction.[17,31,32] Biomarkers reflecting these processes may identify patients with (subclinical) organ dysfunction. Surgery activates the innate immune system, and the production of pro- and anti-inflammatory processes in the body. Although this is essential for healing, a postoperative dysregulated inflammatory response increases the risk of infectious complications by immune suppression, and organ dysfunction through endothelial injury.[32] Biomarkers may aid physicians in discriminating between postoperative dysregulated inflammation and infection.

Metabolic

Preoperative deficiencies of nutrients or vitamins are risk factors for endothelial dysfunction, immune dysfunction, and cardiovascular disease.[33,34] Activation of the HPA axis and several other hormonal pathways change the production of cortisol, growth hormone, thyroid

hormone, and insulin. The negative effects are hypermetabolism and hypercatabolism, leading to hyperglycaemia, release of fatty acids, and muscle wasting, which can be detrimental for postoperative recovery.[11]

Haematological

Anaemia is a risk factor for postoperative complications and disability, most likely trough tissue hypoxemia, organ injury and poor functional capacity.[35,36] In surgical patients, anaemia is often caused by (functional) iron deficiency, blood loss, and inflammation. Besides erythropoiesis, iron deficiency also impairs oxidative metabolism and cellular immunity. The negative effects of poor iron metabolism are aggravated by increased hepcidin concentrations in response to a postoperative dysregulated inflammatory response, for instance due to blood loss after major surgery. Besides, systemic inflammation initiates bone marrow reprogramming and a decreased erythrocyte lifespan. This may explain why an abnormal iron status has been associated with postoperative complications, even without anaemia.[37] A high red cell distribution width (RDW) is a common marker of oxidative stress, chronic inflammation, cardiovascular disease, and is associated with adverse events after surgery.[38]

Renal

Chronic kidney disease associated azotaemia, hypervolemia and anaemia increase after surgery, and are considered to be major risks for postoperative complications. As a result of sympathetic nervous activation, vasoconstriction may decrease renal blood flow and glomerular filtration rate. The renin-angiotensin-aldosterone-system is activated resulting in water and salt retention and further systemic vasoconstriction.[11] Up to 20% of major surgery patients sustain acute kidney injury (AKI). Even when renal function returns to

baseline at the time of hospital discharge, the risk for long-term mortality and disability remains increased.[33]

Outcome measures

Postoperative outcomes are registered after review of medical charts and diagnostic test results. Causes of outcome measures are classified according to international criteria (Appendix 2) as follows:

1. Respiratory failure, defined according to European Perioperative Clinical Outcome (EPCO) definitions, including: ARDS, pleural effusion, pneumothorax, atelectasis, respiratory infection, aspiration pneumonitis, bronchospasm, cardiopulmonary oedema, and pulmonary embolism. Postoperative hypoxemia (i.e. saturation <90% on room air, or oxygen therapy >5L O_2/min) will be registered as respiratory failure.
2. Major adverse cardiac events, defined in agreement with the Standardised Endpoints in Perioperative medicine (StEP) criteria for cardiovascular outcomes and the 4th universal definition of myocardial infarction, including: cardiac death, non-fatal cardiac arrest, coronary revascularization, myocardial infarction/injury, heart failure, pulmonary embolism, atrial fibrillation, and stroke.
3. Infections, defined according to StEP criteria for infection and sepsis, including: sepsis, pneumonia, empyema, surgical site infection, urinary system infection, blood stream infection. For all events, the probability of infection will be categorised using a four-point scale (none, possible, probable and definite infection).
4. Acute kidney injury, defined by the StEP criteria and classified as stage 1-3 based on postoperative serum creatinine concentrations or initiation of renal replacement therapy.

5. Bleeding, according to the standardized definitions from the bleeding academic research consortium (BARC) for cardiac surgery. Postoperative bleeding after non-cardiac surgery is graded according to the modified Clavien-Dindo classification.
6. Postoperative pain, registered daily using the NRS. Scores range from 0 (no pain) to 10 (maximum pain). Chronic pain is defined as surgery related pain >3 months after surgery. The impact of chronic pain is assessed with the 12-item WHODAS 2.0 questionnaire, supplemented with several dedicated questions regarding surgery related pain (i.e. duration of pain, severity of pain and relation with the surgical procedure).
7. Disability, measured according to the self-assessment 12-item WHODAS 2.0 before and after surgery, and reported as a percentage score of functional limitations. Scores range from zero (no disability) to one-hundred percent (fully disabled). New clinically important disability is defined as a change >5% or more after surgery.
8. Mortality, registered as failure to rescue (i.e. hospital mortality following a major postoperative complication), 30-day mortality, days alive and out of the hospital at 120 days, 1-year mortality and 2-year mortality.

The severity of a complication is graded according to the modified Clavien-Dindo classification.[39]

Study size

By the end of the recruitment phase approximately 3,000 patients with major surgery will have been enrolled. Our study cohort allows us to validate, update and/or develop prediction models including 55 candidate predictors, based on an incidence of 15% for severe complications, a global shrinkage factor ≥0.9 and a c-statistics of 0.80.[40] To investigate pathophysiological differences between patients with and without a severe postoperative

complications, a minimal effect size of 0.25 can be demonstrated using an α of 0.05 and a β of 0.95.

Future study design

The extensive collection of blood samples in our biorepository, combined with clinical data and prospectively collected patient-reported outcomes, provides the opportunity to answer a broad range of research questions. For aetiological research on the pathophysiology of postoperative complications, perioperative biomarker dynamics will be studied. The use of DAGs will be encouraged to assess the risk of potential residual confounding.[41] Furthermore, BIGPROMISE enables us to do prediction studies, using biomarkers to improve risk stratification. This includes new model development, but also updating and validating existing risk models. To assess the potential for clinical use, reclassification measures and decision curve analysis will be performed. In addition, we will compare the predictive accuracy of new or non-standard biomarkers (e.g. GDF-15, IL-6) for postoperative complications, with biomarkers that are currently often used in clinical practice (e.g. CRP, leucocytes). Sensitivity, specificity, and positive and negative predictive values will be calculated for biomarker cut-off values, and compared with prior literature reports.

Public and patient involvement

During the design of this study, we did not involve patient organisations.

Findings to date

Recruitment for BIGPROMISE started in October 2021. The first patient was enrolled on October 12th 2021. Currently (January 1st 2024), 3,086 patients were screened for eligibility, of whom 1,785 (58%) provided informed consent for study participation (Supplementary

Figure 1). Most common types of major surgery are cardiac (49%) and gastro-intestinal procedures (26%). Median age is 66 years (60; 73), 28% are female, and 68% of all patients are classified as ASA physical status class 3 (Supplementary Table 3). The overall incidence of a severe postoperative complications is 16%. We anticipate to enrol approximately 1,000 patients annually.

Collaboration

To enable research collaborations in the field of perioperative medicine, the outcome parameters of BIGPROMISE are defined according to international standards as described in PLUTO, a perioperative longitudinal study of complications and long-term outcomes.[42] The design of the BIGPROMISE biobank is based on the results of scientific research and the social interest in reducing the harmful consequences of postoperative complications. Data and biomaterials from BIGPROMISE can be used for future research within the scope of the scientific aim of the study and the informed consent provided by participants: to facilitate biomarker research on risk factors, pathophysiology, and outcomes related to postoperative complications. Investigators who are interested in scientific collaboration may contact the study team through www.bigpromise.nl/contact. Applications will be reviewed by a scientific board according to methodological, statistical, ethical, and legal criteria, in agreement with BIGPROMISE biobank regulations.

Funding

Expenses for personnel, materials, biomarker assays and storage of blood samples are financed with an external research grant from Roche Diagnostics International. Roche had no role in the design of our study, collection of data, preparation and publication of this manuscript.

Discussion

The BIGPROMISE biobank is designed to study the postoperative dysregulated stress response in its cause of postoperative complications, by analysing a large collection of perioperative biomarkers in a high-risk surgical population. In recent years, perioperative research on the pathophysiology of postoperative complications has mainly focussed on myocardial injury and inflammation.[17,27-30,31] However, randomized trials that studied interventions targeting one of these pathways did not result in new recommendations for perioperative treatments.[22] For example, while systemic inflammation is associated with poor outcome, treatment with corticosteroids did not improve outcome in two large international randomized controlled trials in cardiac surgery patients.[43,44] This may be explained by two reasons: First, different contributors to the dysregulated stress response may currently be under-recognized. Interventions targeting only a single known pathophysiological pathway may be insufficient to prevent postoperative organ injury and adverse outcomes. Second, perioperative interventions that use a 'one size fits all approach' overlook the fact that not all patients are identical. That is, some patients may develop an overwhelming stress response to surgery, while others exhibit a more balanced or even an underwhelming response. Treating these patients in the same way may have a beneficial effect in some and a detrimental effect in others, with no net result at all. Biomarkers can inform clinicians on which phenotype of dysregulated stress they are dealing with, and guide targeted interventions. Thus, a refined understanding of the postoperative dysregulated stress response is required to find new strategies to improve surgical outcomes. The BIGPROMISE study will use clinical and molecular data to construct (and validate) perioperative prediction models to improve risk stratification and early diagnosis and treatment of severe complications following major surgery. Our study has several limitations: First, blood

samples are collected and stored for study purposes until 72 hours after surgery. As a result, pathophysiological mechanism related to complications that occur after that period may remain incompletely studied. Second, postoperative complications were defined in agreement with StEP criteria, as a result perioperative neurocognitive disorders are not recorded.

Currently, perioperative biomarkers are mainly used for risk management, but their use for the early diagnosis of complications or targeted interventions has potential added value. Despite that a lot is being invested in perioperative biomarker discovery, few biomarkers have made it from bench to bedside (e.g. cardiac troponin, N-terminal pro B-type natriuretic peptide).[22] Partly because few large, well-designed studies have been performed on the association between perioperative biomarker levels and adverse outcomes in surgical patients. BIGPROMISE will prospectively assess existing biomarker panels on fresh blood samples to validate their prognostic value for outcomes related to postoperative complications, and systematically collect and store plasma, serum and whole blood samples to allow for future perioperative biomarker discovery and development.

Authors' contributions

PGN, HJTR, IMD, TCDR initiated the study, PGN, TR, TCDR wrote the draft manuscript. RNI, MSYT, OLC, NH, KS, LMV and IMD critically reviewed the draft manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable

Acknowledgements

The authors would like to thank all colleagues in the participating centres (St. Antonius Hospital Nieuwegein, Amphia Hospital, Breda) for their support in conducting the BIGPROMISE study.

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. 2015 Apr 27;385 Suppl 2:S11

2. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Sciortino CM, Mandal K, Zehr KJ, Conte JV, Higgins RS, Cameron DE, Whitman GJ. Complications After Cardiac Operations: All Are Not Created Equal. Ann Thorac Surg. 2017 Jan;103(1):32-40

3. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg. 2010 May;251(5):807-18.

4. Paul S, Sedrakyan A, Chiu YL, Nasar A, Port JL, Lee PC, Stiles BM, Altorki NK. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. Eur J Cardiothorac Surg. 2013 Apr;43(4):813-7.

5. International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016; 117:601-9.

6. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005 Sep;242(3):326-41

7. Archer S, Pinto A, Vuik S, Bicknell C, Faiz O, Byrne B, Johnston M, Skapinakis P, Athanasiou T, Vincent C, Darzi A. Surgery, Complications, and Quality of Life: A Longitudinal Cohort Study Exploring the Role of Psychosocial Factors. Ann Surg. 2018 Apr 19.

8. Verwijmeren L, Noordzij PG, Daeter EJ, Emmelot-Vonk MH, Vernooij LM, van Klei

WA, van Dongen EPA. Preoperative frailty and one-year functional recovery in elderly cardiac surgery patients. J Thorac Cardiovasc Surg 2022. Online ahead of print.

9. Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, Clavien PA. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Ann Surg. 2011 Dec;254(6):907-13

10. Healy MA, Mullard AJ, Campbell DA Jr, Dimick JB. Hospital and Payer Costs Associated With Surgical Complications. JAMA Surg. 2016 Sep 1;151(9):823-30.

11. Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ 2020:20(9):321-328.

12. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol. 2009 Jun;69(6):479-91.

13. Manou-Stathopoulou V, Korbonits M, Ackland DL. Redefining the perioperative stress response: a narrative review. Br J Anaesth 2019;123(5):570-583.

14. Lurati Buse, Giovanna; Bollen Pinto, Bernardo; Abelha, Fernando; Abbott, Tom E.F.; Ackland, Gareth; Afshari, Arash; De Hert, Stefan; Fellahi, Jean-Luc; Giossi, Laure; Kavsak, Peter; Longrois, Dan; M'Pembele, Rene; Nucaro, Anthony; Popova, Ekaterine; Puelacher, Christian; Richards, Toby; Roth, Sebastian; Sheka, Mootii; Szczeklik, Wojciech; van Waes, Judith; Walder, Bernhard; Chew, Michelle S. ESAIC focused guideline for the use of cardiac biomarkers in perioperative risk evaluation. European Journal of Anaesthesiology 2023;40(12):888-927

15. Vernooij LM, van Klei WA, Moons KG, Takada T, van Waes J, Damen JAAG. The comparative and added prognostic value of biomarkers to the Revised Cardiac Risk Index for preoperative prediction of major adverse cardiac events and all-cause mortality in patients who undergo noncardiac surgery. Cochrane Database of Systematic Reviews 2021, Issue 12.

16. Writing Committee for the VISION Study Investigators. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA. 2017;317(16):1642–1651. 17. Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EMW, Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. Annals of Surgery 2016; 263(6):1207-1212.

18. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. 2008 May 15;358(20):2107-16

19. Blankenberg S, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, Kuulasmaa K, Yarnell J, Schnabel RB, Wild PS, Münzel TF, Lackner KJ, Tiret L, Evans A, Salomaa V; MORGAM Project. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. Circulation. 2010 Jun 8;121(22):2388-97

20. Siontis KC, Siontis GC, Contopoulos-Ioannidis DG, Ioannidis JP. Diagnostic tests often fail to lead to changes in patient outcomes.J Clin Epidemiol. 2014 Jun;67(6):612-21

21. Ioannidis JPA, Bossuyt PMM. Waste, Leaks, and Failures in the Biomarker Pipeline. Clin Chem. 2017 May;63(5):963-972.

22. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, Ibanez B, Lenarczyk R, Mansmann UR, McGreavy P, Mueller C, Muneretto C, Niessner A, Potpara TS, Ristić A, Sade LE, Schirmer H, Schüpke S, Sillesen H, Skulstad H, Torracca L, Tutarel O, Van Der Meer P, Wojakowski W, Zacharowski K; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022 Oct 14;43(39):3826-3924.

23. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology. 2010 May;112(5):1105-15.

24. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug;14(7):798-804.

25. International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. Available at: https://www.who.int/classifications/icf/en/

26. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208.

27. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295-304

28. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011 Apr 19;154(8):523-8.

29. Beattie WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie K, Paech MJ, Devereaux PJ, Sessler DI, Wallace S, Myles PS; ANZCA Clinical Trials Network and the ENIGMA-II Investigators. Survival After Isolated Post-Operative Troponin Elevation. J Am Coll Cardiol. 2017;70(7):907-908.

30. Beattie, WS, Wijeysundera DN, Chan MTV, Peyton PJ, Leslie KMBBS, Michael

JMBBS, Sessler, DI, Wallace SMPH, Myles PS on behalf of the ANZCA Clinical Trials Network for the ENIGMA-II Investigators. Implication of Major Adverse Postoperative Events and Myocardial Injury on Disability and Survival: A Planned Subanalysis of the ENIGMA-II Trial. Anesthesia & Analgesia 2018;127(5): 1118-1126.

31. Ackland GL, Abbott TEF, Cain D, Edwards MR, Sultan P, Karmali SN, Fowler AJ, Whittle JR, MacDonald NJ, Reyes A, Paredes LG, Stephens RCM, Del Arroyo AG, Woldman S, Archbold RA, Wragg A, Kam E, Ahmad T, Khan AW, Niebrzegowska E, Pearse RM. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. Br J Anaesth. 2019;122(2):180-187.

32. Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023 Mar;78(3):356-370. doi: 10.1111/anae.15896. Epub 2022 Oct 29. PMID: 36308338.

33. Verwijmeren L, Bosma M, Vernooij LM, Linde EM, Dijkstra IM, Daeter EJ, Van Dongen EPA, Van Klei WA, Noordzij PG. Associations Between Preoperative Biomarkers and Cardiac Surgery-Associated Acute Kidney Injury in Elderly Patients: A Cohort Study. Anesth Analg. 2021;133(3):570-577.Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023 Mar;78(3):356-370. doi: 10.1111/anae.15896. Epub 2022 Oct 29. PMID: 36308338.

34. Turan A, Artis AS, Hanline C, Saha P, Maheshwari K, Kurz A, Devereaux PJ, Duceppe E, Patel A, Tiboni M, Ruetzler K, Pearse R, Chan MTV, Wu WKK, Srinathan S, Garg AX, Sapsford R, Sessler DI. Preoperative Vitamin D Concentration and Cardiac, Renal, and Infectious Morbidity after Noncardiac Surgery. Anesthesiology. 2020 Jan;132(1):121-130.

35. Hazen YJJM, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S,

Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten JMAA, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD. Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis. Br J Anaesth. 2022;128(4):636-643.

36. Smoor RM, Rettig TCD, Vernooij LM, Huijsmans RLN, Verwijmeren L, Emmelot-Vonk MH, van Dongen EPA, Cremer OL, Noordzij PG. Postoperative anaemia and disability-free survival in older cardiac surgery patients. Br J Anaesth. 2022;129(2):e27-e29.

37. Rössler J, Schoenrath F, Seifert B, Kaserer A, Spahn GH, Falk V, Spahn DR. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth. 2020;124(1):25-34.

38. Yoshida N, Horinouchi T, Toihata T, Harada K, Eto K, Sawayama H, Iwatsuki M, Nagai Y, Ishimoto T, Baba Y, Miyamoto Y, Baba H. Clinical Significance of Pretreatment Red Blood Cell Distribution Width as a Predictive Marker for Postoperative Morbidity After Esophagectomy for Esophageal Cancer: A Retrospective Study. Ann Surg Oncol. 2022;29(1):606-613.

39. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13.

40. Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE Jr, Moons KG, Collins GS. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019;38(7):1276-1296.

41. VanderWeele, Tyler J.a; Hernán, Miguel A.b; Robins, James M.b,c. Causal Directed Acyclic Graphs and the Direction of Unmeasured Confounding Bias. Epidemiology

2008:19(5):720-728

42. de Mul N, Verlaan D, Ruurda JP, van Grevenstein WMU, Hagendoorn J, de Borst GJ, Vriens MR, de Bree R, Zweemer RP, Vogely C, Haitsma Mulier JLG, Vernooij LM, Reitsma JB, de Zoete MR, Top J, Kluijtmans JAJ, Hoefer IE, Noordzij P, Rettig T, Marsman M, de Smet AMGA, Derde L, van Waes J, Rijsdijk M, Schellekens WJM, Bonten MJM, Slooter AJC, Cremer OL. Cohort profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications. BMJ Open. 2023 Apr 19;13(4): e068970.

43. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D; Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012 Nov 7;308(17):1761-7.

44. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum Á, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Sep 26;386(10000):1243-1253.

Table 1. Perioperative biomarkers and analyser systems.

Analyzer system	**Biomarkers**
Sysmex XN	haemoglobin, haematocrit, erytrocytes, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, mean platelet volume, mean corpuscular haemoglobin concentration, leukocytes, trombocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, reticulocyte haemoglobin equivalent, neutrophil-to-lymphocyte ratio.
Cobas 8000	albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, calcium, cholesterol, C-reactive protein, chloride, creatinin kinase, cystatin C, ferritin, growth differentiation factor-15, gamma-glutamyl transferase, glucose, high-density lipoprotein, high-sensitive troponin T, insulin-like growth factor-1, creatinin, interleukin-6, iron, lactate dehydrogenase, low-density lipoprotein, magnesium, neutrophil gelatinase associated lipocalin, N-terminal pro B-type natriuretic peptide, pro-calcitonin, phosphate, potassium, sex hormone binding globulin, soluble fms-like tyrosine kinase-1, sodium, triglycerides, thyroid stimulating hormone, free thyroxine, 25 hydroxyvitamin D.

Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

Figure 2. Perioperative collection, analysis and storage of blood samples

Supplementary Table 1. Study variables

Supplementary Table 2. Perioperative blood sampling and clinical data collection

Supplementary Table 3. Baseline characteristics

Supplementary Figure 1. Flow chart

Appendix 1. Surgical procedures

Appendix 2. Definitions of outcome measures

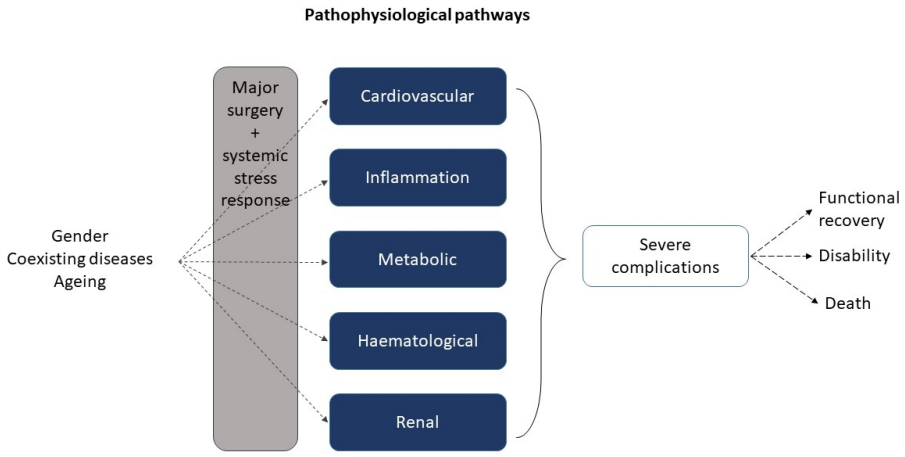


Figure 1. Potential perioperative pathways in the pathogenesis of postoperative complications.

338x190mm (96 x 96 DPI)

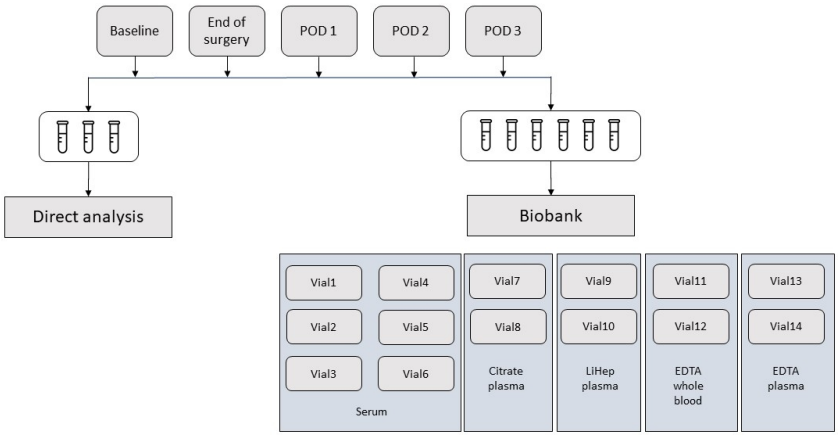


Figure 2. Perioperative collection, analysis and storage of blood samples

338x190mm (96 x 96 DPI)

Appendix 1. Surgical procedures

Cardiac surgery

- Coronary artery bypass grafting
- Aortic valve replacement or repair
- Aortic valve replacement with aortic rooth and ascending aorta replacement (Bentall procedure)
- Mitral valve replacement or repair
- Tricuspid valve replacement or repair
- Combination of procedures above

Pulmonary surgery

- Pneumonectomy
- Lobectomy
- Bilobectomy
- Sleeve lobectomy
- Segmentectomy

Gastrointestinal surgery

- Small bowel resection
- Ileocecal resection
- Sigmoid resection
- Hemicolectomy right or left
- Transverse colon resection
- Low Anterior resection
- Abdominoperineal resection
- HIPEC

Hepatobiliary surgery

- Pancreaticoduodenectomy (Whipple)
- Pylorus preserving pancreaticoduodenectomy (PPPD)

- Distal pancreatectomy
- Total pancreatectomy

Vascular surgery

- Open aortic surgery
    - Abdominal aortic aneurysm repair
- Endovascular aortic surgery
    - Endovascular aneurysm repair
    - Fenestrated endovascular aneurysm repair
    - Covered endovascular repair of the aortic bifurcation
- Suprainguinal and/or infrainguinal peripheral vascular surgery
    - Percutaneous transluminal angioplasty
    - Bypass surgery
    - Endarterectomy
    - Thrombectomy
- Combination of procedures above

Urologic surgery

- Ureteroileostomy (Bricker's procedure)

Endpoint definitions:

Table 1: All-cause mortality

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
All-cause mortality	Death within 30 days of surgery		1-year mortality 2-year mortality		[1]STeP mortality

Table 2: Postoperative pulmonary complications

Endpoint	Definition	Excluded		Limitation and comments	Ref.
Respiratory failure	Postoperative PaO2 < 8 kPa (60 mmHg) on room air, a PaO2:FI02 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy or 5L O2/min oxygen therapy when arterial saturation or peripheral saturation on room air is not available OR Need for mechanical ventilation >24h postoperative* Postoperative oxygen supplementation via a nasal cannula on the day of surgery is seen as common practice and therefore not registered as postoperative respiratory failure. Persistent oxygen supplementation on postoperative day 1 will be registered as respiratory failure if fulfilling the above stated criteria.			EPCO definition of respiratory failure (as defined under postoperative pulmonary complications) complemented with *	EPCO definition [2]

Table 3: Causes of severe respiratory failure

Causes of severe respiratory failure		ref
ARDS	Berlin definition for ARDS	Berlin definition for ARDS [3]
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows	EPCO [2]
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura	EPCO [2]

Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung	EPCO [2]
Respiratory infection	See table 7	StEP Infection and sepsis [4]
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents	EPCO [2]
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators	EPCO [2]
Cardiopulmonary edema	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml	Designation trial [5]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan	STeP cardiovascular [6]
Unknown		

Table 4: Postoperative cardiovascular complications

Endpoint	Definition	Excluded	Limitation	Ref.
MACE	Composite outcome including: - Cardiac death - Non-fatal cardiac arrest - Coronary revascularization - Myocardial infarction	- Pulmonary embolism - Hemorrhage - Deep venous thrombosis - All-cause mortality		STeP cardiovascular [6]
Cardiac death	Death with a vascular cause and included those deaths after a myocardial infarction, cardiac arrest, and cardiac revascularization procedure.	- Death after pulmonary embolism - Death after hemorrhage - Multi-organ failure - Cause of death unknown		STeP cardiovascular [6]
Non-fatal cardiac arrest	Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation			STeP cardiovascular [6]
Coronary revascularization	Percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery.			STeP cardiovascular [6]
Myocardial infarction in noncardiac surgery	Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cTn values with at least one value above the 99th percentile URL and at least one of the following:		No routine ECG after noncardiac surgery	STeP cardiovascular and 4th universal definition of myocardial infarction [6,7]

	1. Symptoms of myocardial ischaemia 2. New ischaemic ECG changes 3. Development of pathological Q waves 4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology 5. Identification of a coronary thrombus by angiography or autopsy Post-mortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available.			
Acute myocardial infarction in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In			4th universal definition of myocardial infarction [7]

	addition, one of the following elements is required: 1. Development of new pathological Q waves;* 2. Angiographic documented new graft occlusion or new native coronary artery occlusion; 3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. *Isolated development of new pathological Q waves meets cardiac myocardial infarction criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.			
Acute myocardial injury in noncardiac surgery	Detection of an elevated and increased or decreased cTn value above the 99th percentile URL is defined as myocardial injury. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			StEP cardiovascular, 4th universal definition of myocardial infarction [6,7]
Acute myocardial injury in cardiac surgery	Elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the		In rhythm surgery and valve surgery substantial amount of troponin release will be related to the direct procedure related tissue trauma and not ischemia.	4th universal definition of myocardial infarction [7] + own interpretation

	99th percentile URL. **The diagnosis will be acute myocardial injury if there is no confirmed diagnosis of myocardial infarction**			
Acute heart failure	An elevated jugular venous pressure, respiratory rales/crackles and crepitations, presence of S3 and at least one of the following radiographic findings: (a) Vascular redistribution (b) Interstitial pulmonary oedema (c) Frank alveolar pulmonary oedema AND NT-proBNP >300 pg/ml		Definition of heart failure did not reach consensus in the StEP initiative.	StEP cardiovascular, heart failure guideline ESC [6,8]
Pulmonary embolism	A clinical diagnosis of PE confirmed by helical CT-scan		Diagnosis will be missed in a large portion of patients	StEP cardiovascular [6]
Atrial fibrillation/ flutter	New onset of irregularly irregular heart rate in the absence of P waves lasting at least 30 s or for the duration of the ECG recording (if <30 s)		No routine ECG or holter registration postoperatively, except for patients admitted to the ICU or PACU.	StEP [6]
Stroke	An embolic, thrombotic or haemorrhagic cerebral event with motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory). **Mild:** Results in only temporary harm and would not require specific clinical treatment. **Moderate:** More serious complication but one which does not usually result in permanent harm or functional			EPCO definition [2]

	limitation. Requires clinical treatment. **Severe:** Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Requires clinical treatment.			

Table 5: Definitions exclusion criteria

Deep venous thrombosis	Diagnosis confirmed by 2-Point Compression Ultrasonography of the Lower Extremity		StEP [6] + adaptation to Dutch clinical practice standards
Multi-organ failure	Altered function in two or more organ systems during an acute illness such that homeostasis cannot be maintained without intervention		Definitions for sepsis and organ failure [9]
Hemorrhage	Acute blood loss		
All-cause mortality	Any cause of death that doesn't fulfill the criteria for cardiac death		

Table 6: Sepsis

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Sepsis	Increase in SOFA score of 2 or more, with evidence of infection, within 30 days.		Suspected site of infection; SOFA score.		StEP Infection and sepsis [4]

Table 7: Postoperative respiratory infectious complication

Endpoint	Definition	Excluded	Additionally reported	Limitation	Ref.
Postoperative respiratory infectious complication **Possible**	**Signs/Symptoms/Laboratory**: one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **OR** • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange **AND** **Imaging:** One chest imaging test result with at least one of the following: Pulmonary infiltrate, consolidation or cavitation		Cause: CAP, HAP, VAP,		
Probable	**Signs/Symptoms/Laboratory**: at least one of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm3) or leukocytosis (≥ 12,000 WBC/mm3) • For adults ≥ 70 years old, altered mental status with no other recognized cause **AND:** **Imaging**: two or more serial chest imaging results with either new and persistent OR progressive and persistent changes of		Cause: CAP, HAP, VAP,		StEP infection and sepsis [4]

	- infiltrate - consolidation - cavitation (In patients **without** underlying cardiac or pulmonary disease **one** definitive imaging test result is acceptable **AND** at least two of the following: • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (with PF <200, O2 supplementation >5L/min, or start of (non)-invasive ventilation)				
Definite	Criteria for probable postoperative respiratory infection **AND** One of the following criteria: - Positive culture of causative lung pathogen in respiratory secretions - Positive blood culture with causative pathogen for pneumonia - Isolation of a virus or proof of a viral pathogen in airway secretion by PCR - Histopathologic evidence for pneumonia		Cause: CAP, HAP, VAP,	Definition of StEP + additional criteria	

Table 8: Causes postoperative respiratory infectious complication

Community acquired pneumonia (CAP)	Pneumonia occurring on day 0 or 1 after hospital admission, considering day of admission as day 0				
Hospital acquired pneumonia (HAP)	Pneumonia occurring ≥ day 2 of hospital admission, considering day of admission as day 0				
Ventilator-Associated pneumonia (VAP)	Pneumonia occurring ≥ day 2 after the start of mechanical ventilation (MV) and ≤ day 2 after the end of MV.	Non-invasive ventilation like CPAP, BiPAP, optiflow are not considered mechanical ventilation.			

Table 9: Abscess/Empyema

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Abscess/empyema				
Possible	**1.** Low clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** debatable Imaging test evidence of abscess or other infection			
Probable	**1.** High clinical suspicion with one of: - Fever - Cough, increased respiratory secretions **AND** **2.** Imaging test evidence of abscess or other infection			Step[4] with adaptation

Definite	**1.** Organism seen on Gram stain of lung tissue or pleural fluid, or identification of pathogenic organism from fluid or tissue from affected site **2.** Abscess or other evidence of infection on gross anatomical or histopathologic examination			

Table 10: Surgical site infections

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Surgical site infection (SSI)				
Superficial incisional SSI	Involves only skin and subcutaneous tissue of the incision			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Superficial incisional SSI **Definite**	Patient has at least one of the following: - Purulent drainage from the superficial incision. - Organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.			StEP infection and sepsis [4,10]

	- Superficial incision that is deliberately opened and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed **AND** Patient has at least one of the following signs or symptoms: localized pain or tenderness, localized swelling, erythema or heat. - Abscess at physical examination, re-operation, histopathologic or radiologic examination.			
Deep incisional SSI	Involves deep soft tissues of the incision (for example, fascial and muscle layers)			
Possible	Patient has at least two of the following signs or symptoms: - localized pain or tenderness - localized swelling - erythema - heat.			
Definite	Patient has at least **one** of the following: - Purulent drainage from the deep incision. - a deep incision that spontaneously dehisces, or is deliberately opened **AND** organism(s) identified from the deep soft tissues of the incision by microbiologic testing which is performed for purposes of clinical diagnosis or treatment, or microbiologic testing is not performed. **AND**			StEP infection and sepsis [4,10]

	patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness. - an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.			
Organ/Space SSI	Event involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure			
Possible	Patient has at least one of the following signs or symptoms: - Fever > 38 C - Pain in the area of surgical procedure (not superficial)			
Probable	Possible criteria **AND** Imaging test evidence suggestive of infection.			
Definite	Patient has at least one of the following: a. purulent drainage from a drain that is placed into the organ/space b. organism(s) identified from fluid or tissue in the organ/space performed for purposes of clinical diagnosis or treatment. c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam			StEP infection and sepsis [4,10]

Table 11: Urinary system infection, blood stream infection, other infection

Endpoint	Definition	Excluded	Additionally reported	Limitation and comments	Ref.
Urinary tract infection **(Catheter and not catheter related)**	**One** of the following signs or symptoms: - Fever (>38C) - Suprapubic tenderness* - Costovertebral angle pain or tenderness* - Urinary urgency^ - Urinary frequency^ - Dysuria^ Microbiologic cultures: Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥10^5 CFU/ml * Without other recognized cause ^ These symptoms cannot be used when a catheter is in place		Catheter related: If indwelling urinary catheter had been in place for more than 2 consecutive days on the date of event AND was present on the day of the event or removed the day before.		CDC [11]
High Urinary system infection	- Identification of pathogenic organism from fluid or tissue from affected site - Abscess or other evidence of infection on gross anatomical examination, during invasive procedure, or during histopathologic examination OR one of - Fever >38C - localised pain or tenderness with no other recognised cause AND ONE OF				StEP [4]

	- purulent drainage from affected site - organism identified in blood by culture or non-culture based biological testing - imaging suggestive of infection which if equivocal is supported by clinical correlation, specifically physician documented treatment for urinary system infection				
Primary Blood stream infection (BSI)/ Central line blood stream infection (CLBSI)	A Laboratory Confirmed Bloodstream Infection (LCBI) that is not included in the common commensal list and is not secondary to an infection at another body site OR Patient has at least one of the following signs or symptoms: fever >38C, chills or hypotension, and at least one of the following: (a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions (b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy (c) Positive blood antigen test.	Common commensal list: see: Common Commensal organisms include, but are not limited to, diphtheroids (Corynebacterium spp. not C. diphtheria), Bacillus spp. (not B. anthracis), Propionibacterium spp., coagulase-negative staphylococci (including			CDC [12]

		S. epidermidis), viridans group streptococci, Aerococcus spp. Micrococcus spp. and Rhodococcus spp Organisms that are parasites and viruses. Campylobacter, Salmonella, Shigella, Listeria, Vibrio and Yersinia as well as C. difficile, Enterohemorrhagic E. coli, and Enteropathogenic E. coli. Blastomyces, Histoplasma, Coccidioides, Paracocci			

		dioides, Cryptococcus, and Pneumocystis.			
Infection eci/ 'other infection'	Strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, OR infection is not a respiratory infection, surgical site infection, primary bloodstream infection or urinary tract infection: meeting two or more of the following criteria: Core temperature < 36C or >38C; white cell count >12x10^9 l-1 or < 4x10^9 l-1, respiratory rate >20 breaths per minute or PaCO2 < 4.7 kPa (35mmHg); Pulse rate >90 beats per minute			CDC and EPCO definitions are used for 'Infection eci' criteria. We added 'Other infection'	CDC[13] AND EPCO [2]

Table 12: Postoperative renal complications

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Acute Kidney Injury (AKI)	Stage 1: Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours OR increase in serum creatinine to 1.5-1.9 times baseline. Stage 2: increase in serum creatinine to 2.0-2.9 times baseline Stage 3: increase in serum creatinine to ≥ 3 times baseline OR increase in serum creatinine to ≥353.6 µmol/L OR initiation of renal replacement therapy			StEP Renal Endpoints [14]

Table 13: Postoperative blood loss

Endpoint	Definition	Excluded	Limitation and comments	Ref.
Postoperative bleeding in cardiac surgery	Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional. Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation. Type 3a: overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is			[15] BARC

	related to bleed); any transfusion with overt bleeding. Type 3b: overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents. Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. Type 4: coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period. Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.			
Postoperative bleeding noncardiac surgery	Postoperative bleeding Clavien Dindo classification ≥3			

In addition, all adverse events in the postoperative period will be graded according to the Clavien-Dindo system[16]:

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia
Grade IV	Life-threatening complication (e.g. brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks) requiring Intensive Care management
Grade V	Death of a patient

References:

1. Jackson, A. I. R. *et al.* Systematic reviews and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: mortality, morbidity, and organ failure. *Br. J. Anaesth.* **130**, 404–411 (2023).
2. Jammer, I. *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. *Eur. J. Anaesthesiol.* **32**, 88–105 (2015).
3. Ranieri, V. M. *et al.* Acute respiratory distress syndrome: The Berlin definition. *JAMA - J. Am. Med. Assoc.* **307**, 2526–2533 (2012).
4. Barnes, J. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis. *Br. J. Anaesth.* **122**, 500–508 (2019).
5. Hol, L. *et al.* Driving Pressure during General Anesthesia for Open Abdominal Surgery (DESIGNATION): Study protocol of a randomized clinical trial. *Trials* **21**, 1–15 (2020).
6. Beattie, W. S. *et al.* Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes. *Br. J. Anaesth.* **126**, 56–66 (2021).
7. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).
8. McDonagh, T. A. *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, 3599–3726 (2021).
9. Bone, R. C. *et al.* Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *Chest* **101**, 1644–1655 (1992).
10. Cdc, T., Report, H. A. I. P., Care, S. & Project, I. Surgical Site Infection Event (SSI) Introduction : Settings : Requirements : 1–39 (2022).
11. NHSN. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events Definitions : *Centers Dis. Control Prev.* 1–18 (2022).
12. Centers, F. D. C. A. P. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) Table of Contents. . *https//www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf (accessed 27 Jan 2021).* 1–50 (2021).
13. Horan, T. C., Andrus, M. & Dudeck, M. A. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am. J. Infect. Control* **36**, 309–332 (2008).
14. McIlroy, D. R. *et al.* Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: renal endpoints. *Br. J. Anaesth.* **121**, 1013–1024 (2018).
15. 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).
16. Dindo, D., Demartines, N. & Clavien, P. A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* **240**, 205–213 (2004).

Supplementary Table 1. Study parameters

Biomarkers

PCT, CRPhs, IL-6, GDF-15, sFLT, NT-proBNP, cTNThs, CysC and NGAL, Hb, Ht, MCV, RDW, reticulocytes, RET-He thrombocytes, leucocytes, MPV, urea, creatinine, sodium, potassium, chloride, calcium, phosphate, magnesium, ASAT, ALAT, LDH, ALP, gamma GT, bilirubin, CK, albumin, glucose, Cholesterol, Triglycerides, HDL-cholesterol, LDL-cholesterol, serum iron, ferritin, transferrin saturation, vitamin D, TSH, FT4, igf-1, SHBG, NLR.

Medical History

Age in years, Sex, BMI (kg/m2), Unintentional weight loss (>3kg) over the past 3 months, Smoking status, Alcohol consumption, Diabetes Mellitus, COPD
Hypertension, Congestive heart failure, Atrial fibrillation, Stroke, Myocardial infarction, Prior cardiac surgery, Peripheral artery disease, Chronic renal failure, history of cancer, Left ventricular ejection fraction, NYHA class, EuroSCORE, ASA classification, Charlson comorbidity index, Disability, Clinical Frailty Scale

Medication Use

Beta blockers, ACE inhibitor, Angiotensin receptor blockers, Diuretics, Plateletinhibitors, Steroids, Calciumchannel inhibitors, Non-steroidal anti-inflammatory drugs, Statins, other immunosuppressive drugs, levothyroxin use, Paracetamol, Opioids, Anitdepressants, Anticonvulsiva

Operative details

Surgery type, surgical approach, urgency, Epidural Analgesia, Sevoflurane use, Oxygen saturation before induction of anaesthesia (first measured on the OR), Intraoperative hypotension (MAP <55 mmHg, non-cardiac surgery only), Fluid balance end of surgery (in ml), Estimated operative blood loss (in ml), Cell saver use, Lowest mean arterial pressure, Lowest operative heart rate (bpm), Surgical APGAR score (number), Allogenic blood product transfusion, Coagulation products and medication,
Intraoperative steroids, Cardiopulmonary bypass time, Aortic cross clamping, (minutes), surgery duration (min)

Postoperative details

Modified early warning score (postoperative day 1-7), postoperative pain score (NRS, max and mean, postoperative day 1-7), Packed Red Blood cells transfusion (postoperative day 1-7), other allogenic blood products (postoperative day 1), Coagulation products and medication (postoperative day 1), reoperation.

Admission and Discharge

Hospital length of stay (LOS), ICU LOS, ICU re-admission, hospital re-admission, days alive and out of hospital 120 days.

Supplementary Table 2. Perioperative blood sampling and clinical data collection

	OC	**Before surgery**	**After surgery**	**POD 1**	**POD 2**	**POD 3**	**30 days**	**120 days**	**1 year**	**2 years**
Counselling	X									
Informed consent		X								
Data collection		X					X	X	X	X
Blood sample		X	X	X	X	X				
Questionnaire		X						X		

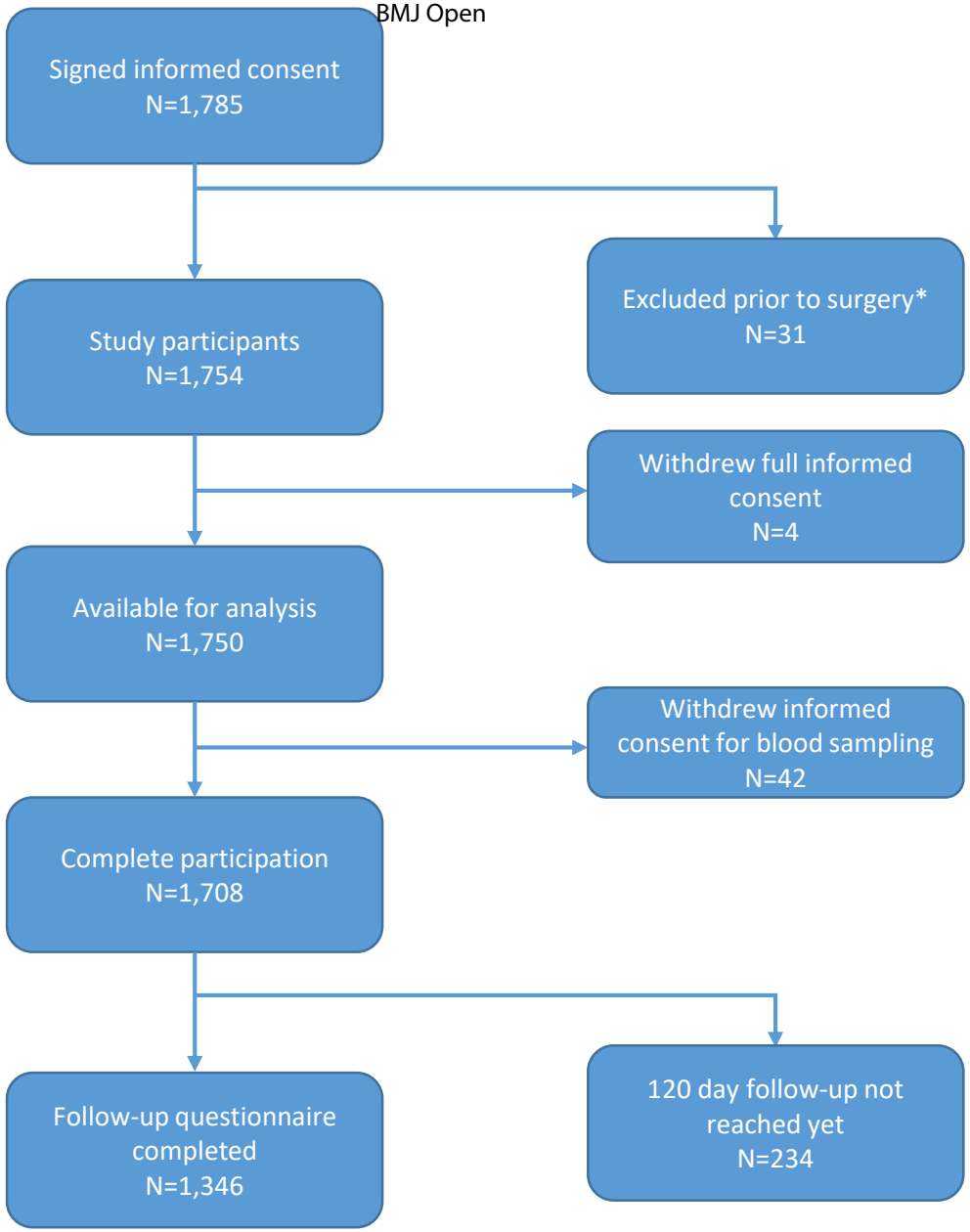
OC: outpatient clinic, POD: postoperative day

Supplementary Table 3

Characteristics	**N (%)**	**Missing values N (%)**
Number of participants	1,750	
Age	66 [60, 73]	7 (0.4%)
Female	481 (27.6%)	5 (0.3%)
ASA class		28 (1.6%)
ASA I	30 (1.7%)	
ASA II	422 (24.5%)	
ASA III	1,169 (67.9%)	
ASA IV	101 (5.9%)	
ASA V	0 (0.0%)	
Clinical Frailty Score, age >65 years	1,029	13 (1.2%)
Fit (1-3)	642 (62.4%)	
Risk of frailty (4)	231 (22.4%)	
Mild frailty (5)	84 (8.2%)	
Frail (6-8)	59 (5.7%)	
Cardiac Surgery	852 (48.7%)	0 (0%)
CABG	444 (25.4%)	
AVR	157 (9.0%)	
MVP/R	107 (6.1%)	
CABG + AVR	106 (6.1%)	

Bentall procedure	46 (2.6%)	
CABG + MVP/R	16 (0.9%)	
AVR + MVP/R	13 (0.7%)	
TVP	3 (0.2%)	
AVR + TVP	2 (0.1%)	
Other	4 (0.2%)	
Pulmonary Surgery	76 (4.3%)	0 (0%)
Segmentectomy	61 (3.5%)	
Lobectomy	3 (0.2%)	
Pneumonectomy	12 (0.7%)	
Gastro-Intestinal- and Hepatobiliary surgery	452 (25.8%)	0 (0%)
Colorectal surgery	280 (16.0%)	
Pancreatic surgery	118 (6.7%)	
Other Gastro-intestinal surgery	54 (3.1%)	
Vascular Surgery	194 (10.1%)	0 (0%)
Aortic surgery	100 (5.7%)	
Peripheral vascular surgery	94 (5.4%)	
Cystectomy	41 (2.4%)	0 (0%)
Reoperation	39 (2.2%)	0 (0%)
Open approach	1,106 (63.2%)	0 (0%)
Biobank participant	1,593 (91.0%)	0 (0%)

Baseline characteristics of the BIGPROMISE cohort at January 1st 2024. Data are displayed in numbers (%) or median (Interquartile range). ASA: American Society of Anaesthesiologists. CABG: Coronary artery bypass grafting. AVR: Aortic valve replacement. MVP/R: Mitral valve plasty / Replacement. TVP: Tricuspid valve plasty.



* Reasons for exclusion: Logistics, surgical indication, blood draw not possible or competing study