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The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective trial

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Abbreviated title: Obesity and cardiac surgical outcomes

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ABSTRACT:

Introduction: Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass.

Methods and Analysis: Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational trial. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term post-operative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines).

Ethics and Dissemination: This study has been approved by the institutional review board at the Horizon Health Network. Upon completion of the trial, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community.

Summary: The results of this trial will provide an improved understanding and better definition of obesity beyond BMI. We hope to demonstrate how fitness capacity of obese cardiac surgical patients and biomarkers alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery. This study will help clinicians better identify patients

pre-operatively based on fitness levels and associated biomarkers in anticipation of implementing mitigating strategies.

Trial Registration: NCT03248921 at www.clinicaltrials.gov

Protocol Version 7, dated 12 December 2017

Strengths and limitations of this study

- The results of this trial will present an improved understanding and better definition of obesity beyond BMI.
- Determination of the "fitness capacity" of obese cardiac surgical patients will help identify obese patients at risk for adverse outcomes.
- Identification of key biomarkers such as cytokines and adipokines will improve preoperative risk-assessment of obese patients.
- This observational study only assesses elective cardiac surgery patients, and excludes high-risk urgent and frail patients.
- This trial is limited in terms of overall enrolment of participants; and there is unequal representation of higher BMI categories especially females.

Keywords: morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage, clinical chemistry, inflammation, metaflammation, immunometabolism, globesity

BACKGROUND AND RATIONALE

The global epidemic of overweight and obese patients - "globesity" - is steadily rising without abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health complications associated with obesity.(3) Obese populations typically experience comorbid cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These patients are at higher risk for intra-operative and post-operative adverse events, including mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can experience fewer adverse events and lower mortality than patients with normal body mass index (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain to be defined.(18)

In part, this paradox may be attributable to over-reliance on singular anthropometric measures of obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22) Additionally, BMI does not address the physical ability or fitness of obese patients with respect to size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes, while other obese patients and normal BMI patients have poor QoL, low physical ability and negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

able). This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively.

Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26), but are not often measured or easily calculated from routine patient histories. Beyond clinical measures of obesity and functional capacity, levels of circulating hormones, inflammatory cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese individuals that could improve operative risk-assessment is a priority.

Ultimately, the need exists to better differentiate obese patients who experience fewer complications from those with increased rates of adverse events, and to determine if they correspond with the physically distinct populations of "high-fit" vs. "low-fit" obese. This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively. Here, we describe a trial that will address this important knowledge gap, "the impact of Obesity on Postoperative Outcomes following cardiac Surgery (OPOS) trial".

STUDY AIMS AND OUTCOME VARIABLES

The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year adverse events among obese patients undergoing cardiac surgery. We hypothesize that the

mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-inflammation status. We further hypothesize that by using this advanced approach, we may better distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical outcomes.

The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure (defined as post-operative creatinine >176 μmol/L in patients with normal baseline renal function) and wound infection. We have previously validated this composite outcome by demonstrating a linear relationship between severity of obesity and adverse in-hospital patient outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke (transient, permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation, post-operative length of stay and disposition on discharge (home, home with care, transfer to other facility or expired), exercise or functional capacity (by walk-test or questionnaire).

METHODS

1. Research ethics approval

The OPOS trial protocol has been submitted and approved by the institutional committee on human research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre & the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects (2013). The trial has been

registered with the National Clinical Trials Database of the NIH (www.clinicaltrials.gov NCT03248921). We used the SPIRIT checklist when writing our report(30).

2. Study population and subject selection

All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be considered. Patients with a BMI of less than 18.5 kg/m^2 are classified as underweight by the World Health Organization and will be excluded. In addition, patients older than 75 years will be excluded to minimize the effect that frailty may have on exercise and functional capacity.

3. Trial overview

Eligible patients will be screened by the research coordinator for potential enrolment prior to surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the research coordinator and informed consent shall be obtained. Patients who convert from elective to non-elective surgery or patients who choose to no longer participate are automatically withdrawn from the trial. Participants are not offered financial or non-financial incentives to participate in the trial.

4. Trial design

The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of

profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Crude and risk-adjusted analyses will be carried out to determine which of these non-traditional measures of obesity, functional status, and metabolic-inflammatory status may have independent effects on rates of post-operative adverse events among obese patients. Although adverse events related to the trial procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring during the course of the trial will be reported to the REB.

Table-1: Table of Determined Measures:

Category	Variables
Clinical	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
	DASI, SF-12, PSMS (scores)
Calculated	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
Clinical Chemistry	Na, K, Cl, HCO3, Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO2, PaCO2, Lactate, pH, Insulin
Clinical Hematology	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)
Experimental BioMarker Analyses	Cardiac injury & Remodelling (ex. Galectin-3)
	Metabolism (ex. Amino acids, lysophospholipids)
	Inflammation (ex. sSRP, adiponectin, resistin, TNFα, interleukins)

	Functional Capacity (ex. EPO)
Physiology	HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO2, CVP, U/O

Table-2: Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
Socio-demographic	Age, sex
Baseline clinical characteristics	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
Intra-operative details	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
In-hospital post-operative outcomes	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/ readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
30-day and 1 year post-operative outcomes	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

Clinical assessment

Consented patients will participate in various measures of obesity, exercise capacity, functional status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23) waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of

exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate VO_2max). The PSMS assesses a patient's ability to independently perform six personal care tasks. The SF-12 addresses mental and physical function as it relates to QoL.

Blood collection

Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample will be labelled with a unique de-identification code and transferred to clinical chemistry or a research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise, standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**). Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after anaesthetic induction from the arterial central line alongside standard of care parameters that are charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc),

inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex. erythropoietin, irisin, transferrin etc.) regulators.

Tissue collection

During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and inflammatory markers). Tissue protein and gene expression of various biomarkers (ex. adipocytokines) in each of these tissue depots will be analyzed to determine whether current or experimental biomarkers have prognostic relevance in distinguishing "high-fit" from "low-fit" obese patients.

5. Group assignment:

Despite the limitations of BMI as a measure of obesity, it remains an important starting point for patient classification and comparisons given its widespread use and previous work by our group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI ≥25 kg/m^2 as overweight, including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9 kg/m^2) will serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI 35.0–39.9) and III (BMI ≥ 40.0) patients will form the study group.

Table 3: World Health Organization obesity classification

Obesity Classification	BMI (kg/m^2)
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
Pre-obese	25.00–29.99
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

6. Patient and Public involvement

In addition to patient participation by recruitment, participants will be invited to part take in focus groups. Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

Statistical methods

We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m2: 11.1%; BMI 25.0-29.9kg/m2: 11.8%; BMI 30.0-34.9kg/m2: 14.6%; BMI 35.0-39.9kg/m2: 19.4%; BMI ≥ 40.0 kg/m2: 28.5%; p<0.0001)32 to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.01 (following 5-class Bonferroni correction), an estimated sample size of 122 patients per weight classification was derived (overall n=610). Patients' baseline, intra-operative, and post-operative clinical characteristics **(Tables 1 and 2)** will be compared by obesity class, using chi-squared tests for

categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables. Multivariable logistic regression will then be employed to construct a baseline model of the risk-adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics and operative procedure **(Table 2)**, on the composite outcome, based on our previous work.[41] A fully adjusted regression model will initially include all predictor variables having an unadjusted association of at least $p \leq 0.20$ with the composite outcome. Backward selection will then be applied to retain only those covariates having independent predictive power at a significance of $p < 0.05$. Pearson and Spearman correlations for normally and non-normally distributed variables, respectively, among the non-traditional determined measures that are novel in this trial **(Table 1)** will be assessed to avoid including collinear predictor variables in a more enhanced logistic regression model. The ability of these measures to improve risk prediction over and above the baseline model will be evaluated by comparing the c-statistics of the candidate enhanced model with the baseline model. Analyses will be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), and R Statistical Software (http://www.r-project.org/).

Data and safety monitoring

The quality of all data collected will be carefully supervised by the investigators. The research team will be responsible for data collection and will be in close contact with the investigators for timely follow-up of the study procedures, data update and corrections. An interim analysis will be conducted when 50% of the patients have been recruited and have completed all data collection procedures and follow-up.

Intra data sharing

All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on hospital secure drives at the site created for the study, and all data sets will be password protected. Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

DISCUSSION

The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and functional capacity, and correlating these factors with molecular biomarkers of obesity at the systemic and cellular level. Previous studies have been unable to completely elucidate the mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most salient of which is its inability to account for muscle mass or functional capacity. While alternate techniques can directly measure body composition, such as magnetic resonance imaging or dual-energy X-ray absorptiometry(38), these are impractical in the clinical setting. Despite its limitations, BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design. Studies like this one are necessary to help segregate the high-risk obese patient likely to experience adverse outcomes from the lower risk obese patient. Thus we plan to better define “high-fit” versus “low-fit obese” patients in order to assist surgical planning and follow-up practices.

The assessments chosen for this trial are clinically validated, self-reported measures of functional capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of administration, reliability, validity and brevity acting as a reliable surrogate to more complex analyses of life quality.(39) The PSMS is an effective tool determining independence of cardiac

patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS allows us to determine which is more effective as a measure of QoL in this patient population and provides the opportunity to compare or consolidate the two measures in determining "high-fit" vs "low-fit" patient categorization. Similarly, the DASI is a valid measure of the functional capacity measure for cardiac patients, determining the impact of the patient's cardiovascular disease on self-reported physical work capacity to estimate peak metabolic equivalents.(40) The DASI, as a self-reported test, will be correlated with the objective measure of the 6MWT, another effective tool for assessing functional capacity in patients with cardiovascular and pulmonary diseases.(41) These two tests in combination compensate for potential patient ineligibility due to disease burden for the 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly, many patients are accompanied by family and that strengthens the legitimacy of the DASI because of two-person recall.

Biomarkers are sensitive, specific objective measures that can be used alone or in combination and are known to be predictive of outcomes.(42) Here we elected to design a trial amenable to conventional and experimental biomarkers, to identify measures that are potentially highly sensitive, translatable across centres and immutable to humanistic influences at the point of collection **(Table-1).** Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac function and may likely influence the heart following cardiac surgery. Previous studies have shown that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity, and are sensitive and specific markers of cardiovascular risk.(43, 44) Thus, it is important to examine cytokines and chemokines in circulation, specifically adipokine expression in distinct

adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine secretion of biomolecules in close proximity to the heart.(45) With this trial we are building the "OPOS Biobank" as a valuable and unique repository of adipose tissue from different depots and blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we can link clinical history and blood sample analyses with gene, protein and cellular expression profiles of critical regulators of cardiovascular and metabolic disease.(46, 47)

The knowledge gained by consolidating this information for iterative utility would potentially help identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets. Additionally, these patient samples provide opportunity to investigate associated disease processes like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation etc. It has been shown that the power of two well characterized biomarkers can determine differences of 1-year mortality by more than 50% predictively.(42) Assessment of clinical and biomarker panels could thus potentially help identify predictive biomarkers that would help clinicians treat cardiac patients more effectively.

Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future studies might include more comprehensive QoL assessments, including mental health assessments, and socio-economic status, that contribute to health related QoL. Mental fortitude could be a deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial. Underweight patients were excluded due to the significantly higher risks associated with early major adverse clinical outcomes.(48) Patients above the age of 75 were not included in this trial, to exclude the effect of frailty on physical capacity for recovery. Future studies could account for

frailty as a confounding variable and incorporate this into a more complete assessment of surgical fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded. This was a practical and safety decision; however, the results of this trial should allow for more open inclusion once the criterion to define surgical fitness is clear. Additional studies should explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional patient populations could be followed over a longer term to assess outcomes like 5-year mortality or to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial is limited in terms of patients enrolled, future studies could also have higher enrollment targets that would allow for broader multivariate analyses.

PRESENT STATUS

The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due to change in patient's condition becoming more urgent, patients passing the age limit of 75 years, and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion of additional sites.

DIRECTION

Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac surgeons and allied health care professionals on the important relationships that exist between

obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and health care administrators will be better able to identify an obese patient who is more likely to experience adverse outcomes and require additional hospital resources in their recovery.

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AUTHOR CONTRIBUTIONS

JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical sample collection and processing. JM and AY contributed to statistical design. All authors have read and approved the article.

Declarations of interest: none

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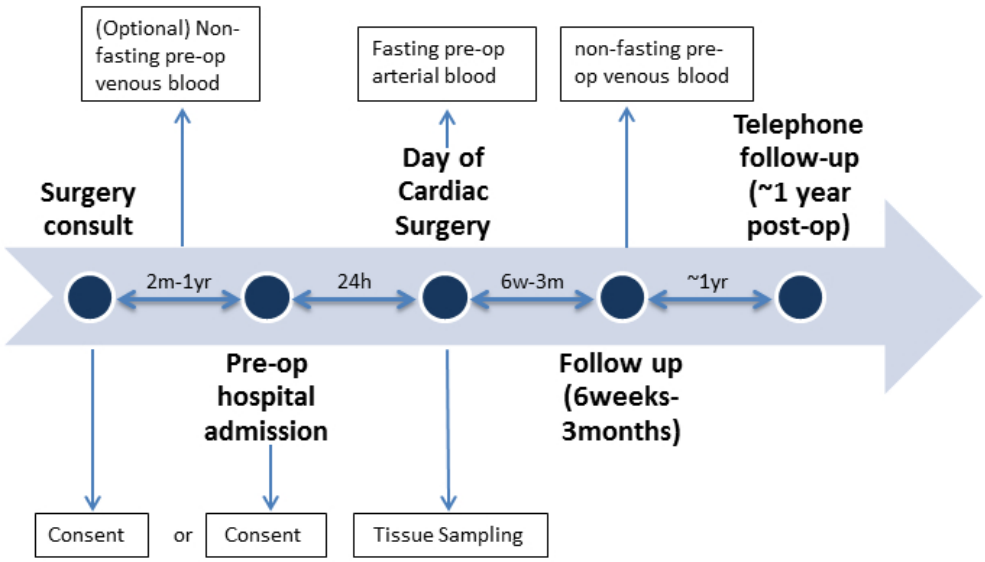
FIGURE LEGENDS:

Fig. 1: Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

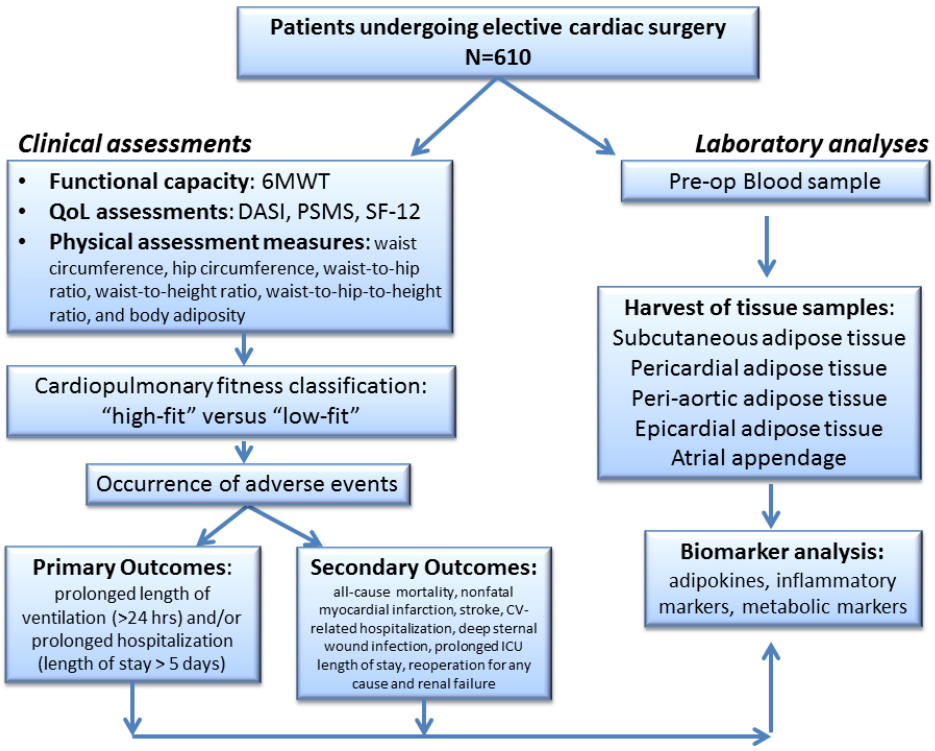
Figure 2: Flowchart showing protocol for the OPOS trial.

Date and Version Identifier:
*Issue Date***:** 28 November, 2014
Protocol Version Number: 7 dated 12 December 2017



Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

58x33mm (300 x 300 DPI)



Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	17

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	4,5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6,7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	NA

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9,10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset,	NA

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9,10

BMJ Open

The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	inflammation, morbidity, Coronary artery bypass grafting, adipose tissue, atrial appendage, globesity

The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

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Abbreviated title: Obesity and cardiac surgical outcomes

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Word Count: 3,464

ABSTRACT:

Introduction: Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass.

Methods and Analysis: Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational trial. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term post-operative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines).

Ethics and Dissemination: This study has been approved by the institutional review board at the Horizon Health Network. Upon completion of the trial, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community.

Summary: The results of this trial will provide an improved understanding and better definition of obesity beyond BMI. We hope to demonstrate how fitness capacity of obese cardiac surgical patients and biomarkers alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery. This study will help clinicians better identify patients

pre-operatively based on fitness levels and associated biomarkers in anticipation of implementing mitigating strategies.

Trial Registration: NCT03248921 at www.clinicaltrials.gov

Protocol Version 7, dated 12 December 2017

Strengths and limitations of this study

- The results of this prospective trial will present an improved understanding and better definition of obesity beyond BMI by identifying key biomarkers such as cytokines and adipokines
- This trial will determine the "fitness capacity" of obese cardiac surgical patients by segregating patients into "high-fit" and "low-fit" categories.This observational study only assesses elective cardiac surgery patients, and excludes high-risk urgent and frail patients.
- This trial is limited in terms of overall enrolment of participants; and there is unequal representation of higher BMI categories especially females.

Keywords: morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage, clinical chemistry, inflammation, metaflammation, immunometabolism, globesity

BACKGROUND AND RATIONALE

The global epidemic of overweight and obese patients - "globesity" - is steadily rising without abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health complications associated with obesity.(3) Obese populations typically experience comorbid cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These patients are at higher risk for intra-operative and post-operative adverse events, including mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can experience fewer adverse events and lower mortality than patients with normal body mass index (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain to be defined.(18)

In part, this paradox may be attributable to over-reliance on singular anthropometric measures of obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22) Additionally, BMI does not address the physical ability or fitness of obese patients with respect to size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes, while other obese patients and normal BMI patients have poor QoL, low physical ability and negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

able). This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively.

Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26)' but are not often measured or easily calculated from routine patient histories. Beyond clinical measures of obesity and functional capacity, levels of circulating hormones, inflammatory cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese individuals that could improve operative risk-assessment is a priority.

Ultimately, the need exists to better differentiate obese patients who experience fewer complications from those with increased rates of adverse events, and to determine if they correspond with the physically distinct populations of "high-fit" vs. "low-fit" obese. This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively. Crude and risk-adjusted analyses will be carried out to determine which non-traditional measures of obesity, functional status, and metabolic-inflammatory status may have independent effects on rates of post-operative adverse events among obese patients. Here, we describe a trial that will address this important knowledge gap, "the impact of Obesity on Postoperative Outcomes following cardiac Surgery (OPOS) trial".

STUDY AIMS AND OUTCOME VARIABLES

The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year adverse events among obese patients undergoing cardiac surgery. We hypothesize that the mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-inflammation status. We further hypothesize that by using this advanced approach, we may better distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical outcomes.

The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure (The Society of Thoracic Surgeons score for renal failure is defined as an increase in serum creatinine levels 4 mg/dL or greater (176.8 mmol/L), a 50% or greater increase in serum creatinine levels over the baseline preoperative value, or a new requirement for dialysis) and wound infection. We have previously validated this composite outcome by demonstrating a linear relationship between severity of obesity and adverse in-hospital patient outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke (transient, permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation, post-operative length of stay and disposition on discharge (home, home with care, transfer to other facility or expired), exercise or functional capacity (by walk-test or questionnaire).

METHODS

1.Research ethics approval

The OPOS trial protocol has been submitted and approved by the institutional committee on human research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre & the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects (2013). The trial has been registered with the National Clinical Trials Database of the NIH (www.clinicaltrials.gov NCT03248921). We used the SPIRIT checklist when writing our report(30).

2.Study population and subject selection

All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be considered. Patients with a BMI of less than 18.5 kg/m^2 are classified as underweight by the World Health Organization and will be excluded. In addition, patients older than 75 years will be excluded to minimize the effect that frailty may have on exercise and functional capacity.

3. Trial overview

Eligible patients will be screened by the research coordinator for potential enrolment prior to surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the research coordinator and informed consent shall be obtained. Patients who convert from elective to non-elective surgery or patients who choose to no longer participate are automatically withdrawn from the trial. Participants are not offered financial or non-financial incentives to participate in the trial.

4. Trial design

The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Although adverse events related to the trial procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring during the course of the trial will be reported to the REB.

Table-1: Table of Determined Measures:

Category	Variables
Clinical	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
	DASI, SF-12, PSMS (scores)
Calculated	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
Clinical Chemistry	Na, K, Cl, HCO3, Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO2, PaCO2, Lactate, pH, Insulin
Clinical Hematology	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)

Experimental BioMarker Analyses	Cardiac injury & Remodelling (ex. Galectin-3)
	Metabolism (ex. Amino acids, lysophospholipids)
	Inflammation (ex. sSRP, adiponectin, resistin, TNFα, interleukins)
	Functional Capacity (ex. EPO)
Physiology	HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO2, CVP, U/O

Table-2: Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
Socio-demographic	Age, sex
Baseline clinical characteristics	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
Intra-operative details	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
In-hospital post-operative outcomes	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/ readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
30-day and 1 year post-operative outcomes	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

Clinical assessment

Consented patients will participate in various measures of obesity, exercise capacity, functional status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23) waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate VO_2max). The PSMS assesses a patient's ability to independently perform six personal care tasks. The SF-12 addresses mental and physical function as it relates to QoL.

Blood collection

Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample will be labelled with a unique de-identification code and transferred to clinical chemistry or a research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise, standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**). Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after anaesthetic induction from the arterial central line alongside standard of care parameters that are charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative

consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc), inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex. erythropoietin, irisin, transferrin etc.) regulators.

Tissue collection

During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and inflammatory markers). Tissue protein and gene expression of various biomarkers (ex. adipocytokines) in each of these tissue depots will be analyzed to determine whether current or experimental biomarkers have prognostic relevance in distinguishing "high-fit" from "low-fit" obese patients.

5. Group assignment:

Despite the limitations of BMI as a measure of obesity, it remains an important starting point for patient classification and comparisons given its widespread use and previous work by our group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI ≥25 kg/m^2 as overweight, including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9 kg/m^2) will

serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI 35.0–39.9) and III (BMI ≥ 40.0) patients will form the study group.

Table 3: World Health Organization obesity classification

Obesity Classification	BMI (kg/m^2)
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
Pre-obese	25.00–29.99
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

6.Patient and Public involvement

Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

Statistical methods

We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m2: 11.1%; BMI 25.0-29.9kg/m2: 11.8%; BMI 30.0-34.9kg/m2: 14.6%; BMI 35.0-39.9kg/m2: 19.4%; BMI ≥ 40.0 kg/m2: 28.5%; p<0.0001)(38) to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.0125 (following 5-class Bonferroni correction), an estimated sample size of 116 patients per weight classification was

derived (overall n=580). Patients' baseline, intra-operative, and post-operative clinical characteristics **(Tables 1 and 2)** will be compared by obesity class, using chi-squared tests for categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables. Multivariable logistic regression will then be employed to construct a baseline model of the risk-adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics and operative procedure **(Table 2)**, on the composite outcome, based on our previous work.(38). Similar to the primary outcome of interest, separate multivariable regression models will be employed to explore the secondary outcomes of interest and adjust for potential confounders. Multiple logistic regression modeling will be used for categorical outcomes and multiple linear regression modeling will be used for continuous variables. In the instance where missing data are present, we will either remove patients with incomplete data from the analysis or employ a sensitivity analysis.

A fully adjusted regression model will initially include all predictor variables having an unadjusted association of at least $p \leq 0.20$ with the composite outcome. Pearson and Spearman correlations for normally and non-normally distributed variables, respectively, among the non-traditional determined measures that are novel in this trial (Table 1) will be assessed to avoid including collinear predictor variables in a more enhanced logistic regression model. The ability of these measures to improve risk prediction over and above the baseline model will be evaluated by comparing the c-statistics of the candidate enhanced model with the baseline model. Analyses will be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), and R Statistical Software (http://www.r-project.org/).

Data and safety monitoring

The quality of all data collected will be carefully supervised by the investigators. The research team will be responsible for data collection and will be in close contact with the investigators for timely follow-up of the study procedures, data update and corrections. An interim analysis will be conducted when 50% of the patients have been recruited and have completed all data collection procedures and follow-up. The purpose of the interim analysis will be to re-evaluate the sample size calculation and to test/refine the statistical models as needed. The statistical evaluations to be performed at this interim point are identical to the ones have been proposed following the completion of patient recruitment.

Intra data sharing

All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on hospital secure drives at the site created for the study, and all data sets will be password protected. Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

DISCUSSION

The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and functional capacity, and correlating these factors with molecular biomarkers of obesity at the systemic and cellular level. Previous studies have been unable to completely elucidate the mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most salient of which is its inability to account for muscle mass or functional capacity. While alternate techniques can directly measure body composition, such as magnetic resonance imaging or dual-

energy X-ray absorptiometry(39), these are impractical in the clinical setting. Despite its limitations, BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design. Studies like this one are necessary to help segregate the high-risk obese patient likely to experience adverse outcomes from the lower risk obese patient. Thus we plan to better define "high-fit" versus "low-fit obese" patients in order to assist surgical planning and follow-up practices.

The assessments chosen for this trial are clinically validated, self-reported measures of functional capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of administration, reliability, validity and brevity acting as a reliable surrogate to more complex analyses of life quality.(40) The PSMS is an effective tool determining independence of cardiac patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS allows us to determine which is more effective as a measure of QoL in this patient population and provides the opportunity to compare or consolidate the two measures in determining "high-fit" vs "low-fit" patient categorization. Similarly, the DASI is a valid measure of the functional capacity measure for cardiac patients, determining the impact of the patient's cardiovascular disease on self-reported physical work capacity to estimate peak metabolic equivalents.(41) The DASI, as a self-reported test, will be correlated with the objective measure of the 6MWT, another effective tool for assessing functional capacity in patients with cardiovascular and pulmonary diseases.(42) These two tests in combination compensate for potential patient ineligibility due to disease burden for the 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly, many patients are accompanied by family and that strengthens the legitimacy of the DASI because of two-person recall.

Biomarkers are sensitive, specific objective measures that can be used alone or in combination and are known to be predictive of outcomes.(43) Here we elected to design a trial amenable to conventional and experimental biomarkers, to identify measures that are potentially highly sensitive, translatable across centres and immutable to humanistic influences at the point of collection **(Table-1).** Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac function and may likely influence the heart following cardiac surgery. Previous studies have shown that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity, and are sensitive and specific markers of cardiovascular risk.(44, 45) Thus, it is important to examine cytokines and chemokines in circulation, specifically adipokine expression in distinct adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine secretion of biomolecules in close proximity to the heart.(46) With this trial we are building the "OPOS Biobank" as a valuable and unique repository of adipose tissue from different depots and blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we can link clinical history and blood sample analyses with gene, protein and cellular expression profiles of critical regulators of cardiovascular and metabolic disease.(47, 48)

The knowledge gained by consolidating this information for iterative utility would potentially help identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets. Additionally, these patient samples provide opportunity to investigate associated disease processes like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation etc. It has been shown that the power of two well characterized biomarkers can determine differences of 1-year mortality by more than 50% predictively.(43) Assessment of clinical and biomarker panels

could thus potentially help identify predictive biomarkers that would help clinicians treat cardiac patients more effectively.

Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future studies might include more comprehensive QoL assessments, including mental health assessments, and socio-economic status, that contribute to health related QoL. Mental fortitude could be a deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial. Underweight patients were excluded due to the significantly higher risks associated with early major adverse clinical outcomes.(49) Patients above the age of 75 were not included in this trial, to exclude the effect of frailty on physical capacity for recovery. Future studies could account for frailty as a confounding variable and incorporate this into a more complete assessment of surgical fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded. This was a practical and safety decision; however, the results of this trial should allow for more open inclusion once the criterion to define surgical fitness is clear. Additional studies should explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional patient populations could be followed over a longer term to assess outcomes like 5-year mortality or to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial is limited in terms of patients enrolled, future studies could also have higher enrollment targets that would allow for broader multivariate analyses.

Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac

surgeons and allied health care professionals on the important relationships that exist between obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and health care administrators will be better able to identify an obese patient who is more likely to experience adverse outcomes and require additional hospital resources in their recovery.

PRESENT STATUS

The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due to change in patient's condition becoming more urgent, patients passing the age limit of 75 years, and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion of additional sites.

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AUTHOR CONTRIBUTIONS

JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical

sample collection and processing. JM and AY contributed to statistical design. All authors have read and approved the article.

Declarations of interest: none

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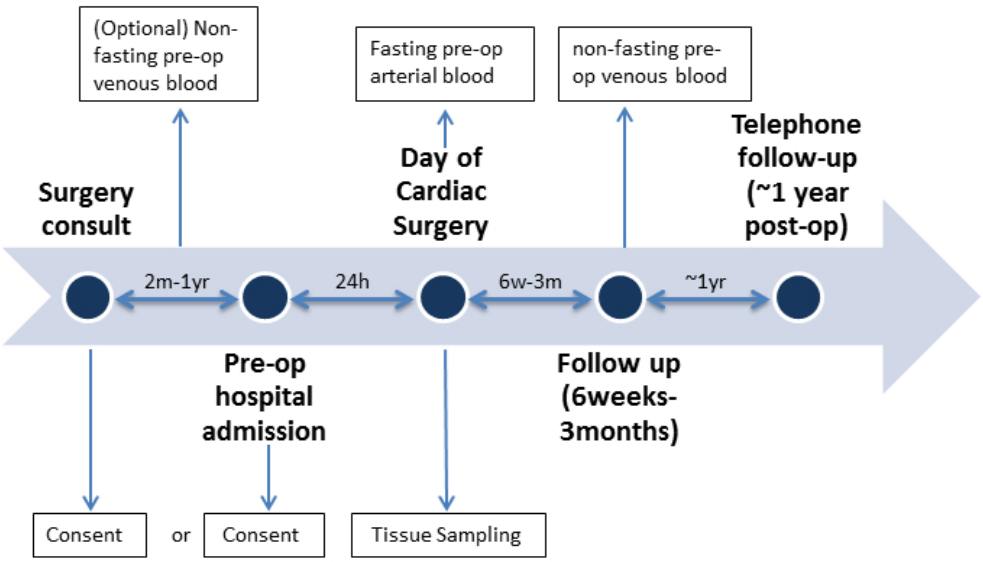
FIGURE LEGENDS:

Fig. 1: Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

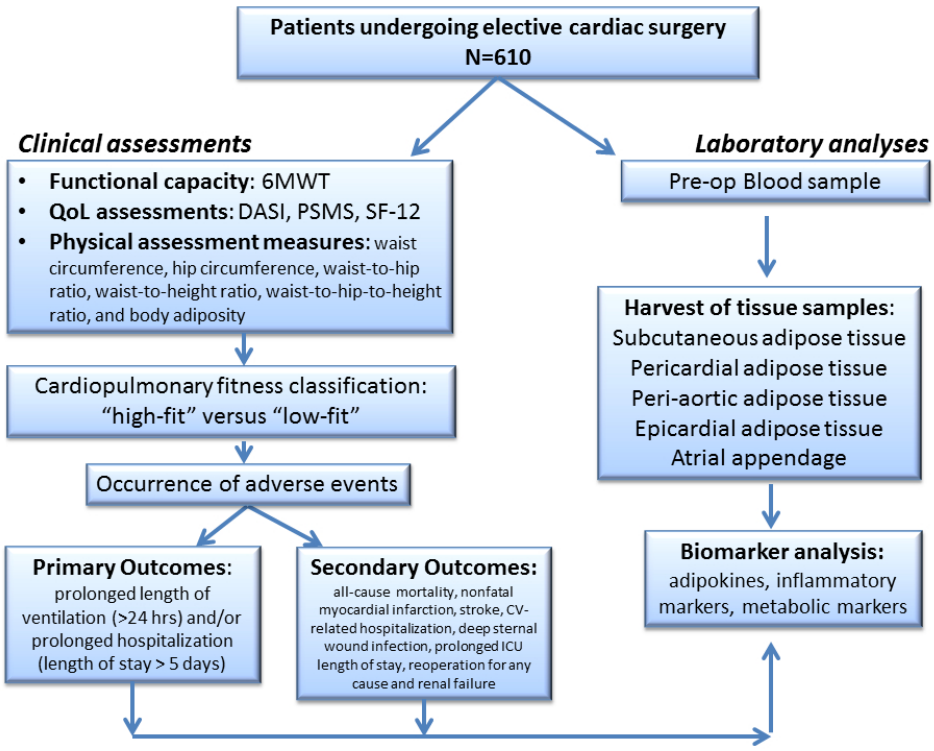
Figure 2: Flowchart showing protocol for the OPOS trial.

Date and Version Identifier:
*Issue Date***:** 28 November, 2014
Protocol Version Number: 7 dated 12 December 2017



Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

58x33mm (300 x 300 DPI)



Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	17

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	4,5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6,7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	NA

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9,10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset,	NA

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9,10

BMJ Open

The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	inflammation, morbidity, Coronary artery bypass grafting, adipose tissue, atrial appendage, globesity

The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

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Abbreviated title: Obesity and cardiac surgical outcomes

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Word Count: 3,464

ABSTRACT:

Introduction: Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass. The objective of this trial is to determine if fitness capacity of obese cardiac surgical patients and biomarkers, alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery.

Methods and Analysis: Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational trial. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term post-operative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines).

Ethics and Dissemination: This study has been approved by the institutional review board at the Horizon Health Network. Upon completion of the trial, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community.

Trial Registration: NCT03248921 at www.clinicaltrials.gov

Protocol Version 7, dated 12 December 2017

Strengths and limitations of this study

- The results of this prospective trial will present an improved understanding and better definition of obesity beyond BMI by identifying key biomarkers such as cytokines and adipokines.
- Patients will undergo a clinical assessment consisting of functional capacity, quality of life, and physical assessment measures. Laboratory analyses include blood sample and cardiac adipose tissue analyses for predictive biomarkers.
- This trial will determine the "fitness capacity" of obese cardiac surgical patients by segregating patients into "high-fit" and "low-fit" categories. This observational study only assesses elective cardiac surgery patients, and excludes high-risk urgent and frail patients.
- This trial is limited in terms of overall enrolment of participants; and there is unequal representation of higher BMI categories especially females.

Keywords: morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage, clinical chemistry, inflammation, metaflammation, immunometabolism, globesity

BACKGROUND AND RATIONALE

The global epidemic of overweight and obese patients - "globesity" - is steadily rising without abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health complications associated with obesity.(3) Obese populations typically experience comorbid cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These patients are at higher risk for intra-operative and post-operative adverse events, including mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can experience fewer adverse events and lower mortality than patients with normal body mass index (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain to be defined.(18)

In part, this paradox may be attributable to over-reliance on singular anthropometric measures of obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22) Additionally, BMI does not address the physical ability or fitness of obese patients with respect to size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes, while other obese patients and normal BMI patients have poor QoL, low physical ability and negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

able). This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively.

Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26), but are not often measured or easily calculated from routine patient histories. Beyond clinical measures of obesity and functional capacity, levels of circulating hormones, inflammatory cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese individuals that could improve operative risk-assessment is a priority.

Ultimately, the need exists to better differentiate obese patients who experience fewer complications from those with increased rates of adverse events, and to determine if they correspond with the physically distinct populations of "high-fit" vs. "low-fit" obese. This distinction could be of critical importance in determining which obese patients are more likely to do well post-operatively. Crude and risk-adjusted analyses will be carried out to determine which non-traditional measures of obesity, functional status, and metabolic-inflammatory status may have independent effects on rates of post-operative adverse events among obese patients. Here, we describe a trial that will address this important knowledge gap, "the impact of Obesity on Postoperative Outcomes following cardiac Surgery (OPOS) trial".

STUDY AIMS AND OUTCOME VARIABLES

The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year adverse events among obese patients undergoing cardiac surgery. We hypothesize that the mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-inflammation status. We further hypothesize that by using this advanced approach, we may better distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical outcomes.

The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure (The Society of Thoracic Surgeons score for renal failure is defined as an increase in serum creatinine levels 4 mg/dL or greater (176.8 mmol/L), a 50% or greater increase in serum creatinine levels over the baseline preoperative value, or a new requirement for dialysis) and wound infection. We have previously validated this composite outcome by demonstrating a linear relationship between severity of obesity and adverse in-hospital patient outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke (transient, permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation, post-operative length of stay and disposition on discharge (home, home with care, transfer to other facility or expired), exercise or functional capacity (by walk-test or questionnaire).

METHODS

1. Research ethics approval

The OPOS trial protocol has been submitted and approved by the institutional committee on human research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre & the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects (2013). The trial has been registered with the National Clinical Trials Database of the NIH (www.clinicaltrials.gov NCT03248921). We used the SPIRIT checklist when writing our report(30).

2. Study population and subject selection

All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be considered. Patients with a BMI of less than 18.5 kg/m^2 are classified as underweight by the World Health Organization and will be excluded. In addition, patients older than 75 years will be excluded to minimize the effect that frailty may have on exercise and functional capacity.

3. Trial overview

Eligible patients will be screened by the research coordinator for potential enrolment prior to surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the research coordinator and informed consent shall be obtained. Patients who convert from elective to non-elective surgery or patients who choose to no longer participate are automatically withdrawn from the trial. Participants are not offered financial or non-financial incentives to participate in the trial.

4. Trial design

The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Although adverse events related to the trial procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring during the course of the trial will be reported to the REB.

Table-1: Table of Determined Measures:

Category	Variables
Clinical	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
	DASI, SF-12, PSMS (scores)
Calculated	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
Clinical Chemistry	Na, K, Cl, HCO3, Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO2, PaCO2, Lactate, pH, Insulin
Clinical Hematology	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)

Experimental BioMarker Analyses	Cardiac injury & Remodelling (ex. Galectin-3)
	Metabolism (ex. Amino acids, lysophospholipids)
	Inflammation (ex. sSRP, adiponectin, resistin, TNFα, interleukins)
	Functional Capacity (ex. EPO)
Physiology	HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO2, CVP, U/O

Table-2: Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
Socio-demographic	Age, sex
Baseline clinical characteristics	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
Intra-operative details	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
In-hospital post-operative outcomes	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/ readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
30-day and 1 year post-operative outcomes	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

Clinical assessment

Consented patients will participate in various measures of obesity, exercise capacity, functional status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23) waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate VO_2max). The PSMS assesses a patient's ability to independently perform six personal care tasks. The SF-12 addresses mental and physical function as it relates to QoL.

Blood collection

Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample will be labelled with a unique de-identification code and transferred to clinical chemistry or a research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise, standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**). Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after anaesthetic induction from the arterial central line alongside standard of care parameters that are charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative

consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc), inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex. erythropoietin, irisin, transferrin etc.) regulators.

Tissue collection

During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and inflammatory markers). Tissue protein and gene expression of various biomarkers (ex. adipocytokines) in each of these tissue depots will be analyzed to determine whether current or experimental biomarkers have prognostic relevance in distinguishing "high-fit" from "low-fit" obese patients.

5. Group assignment:

Despite the limitations of BMI as a measure of obesity, it remains an important starting point for patient classification and comparisons given its widespread use and previous work by our group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI ≥25 kg/m^2 as overweight, including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9

kg/m^2) will serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI 35.0–39.9) and III (BMI ≥ 40.0) patients will form the study group.

Table 3: World Health Organization obesity classification

Obesity Classification	BMI (kg/m^2)
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
Pre-obese	25.00–29.99
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

6. Patient and Public involvement

Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

Statistical methods

We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m2: 11.1%; BMI 25.0-29.9kg/m2: 11.8%; BMI 30.0-34.9kg/m2: 14.6%; BMI 35.0-39.9kg/m2: 19.4%; BMI ≥ 40.0 kg/m2: 28.5%; p<0.0001)(38) to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.0125 (following Bonferroni correction), an estimated sample size of 116 patients per weight classification was

derived (overall n=580). Patients' baseline, intra-operative, and post-operative clinical characteristics **(Tables 1 and 2)** will be compared by obesity class, using chi-squared tests for categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables. Multivariable logistic regression will then be employed to construct a baseline model of the risk-adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics and operative procedure **(Table 2)**, on the composite outcome, based on our previous work.(38). Similar to the primary outcome of interest, separate multivariable regression models will be employed to explore the secondary outcomes of interest and adjust for potential confounders. Multiple logistic regression modeling will be used for categorical outcomes and multiple linear regression modeling will be used for continuous variables. In the instance where missing data are present, we will either remove patients with incomplete data from the analysis or employ a sensitivity analysis.

A fully adjusted regression model will initially include all predictor variables having an unadjusted association of at least $p \leq 0.20$ with the composite outcome. Pearson and Spearman correlations for normally and non-normally distributed variables, respectively, among the non-traditional determined measures that are novel in this trial (Table 1) will be assessed to avoid including collinear predictor variables in a more enhanced logistic regression model. The ability of these measures to improve risk prediction over and above the baseline model will be evaluated by comparing the c-statistics of the candidate enhanced model with the baseline model. Analyses will be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), and R Statistical Software (http://www.r-project.org/).

Data and safety monitoring

The quality of all data collected will be carefully supervised by the investigators. The research team will be responsible for data collection and will be in close contact with the investigators for timely follow-up of the study procedures, data update and corrections. An interim analysis will be conducted when 50% of the patients have been recruited and have completed all data collection procedures and follow-up. The purpose of the interim analysis will be to re-evaluate the sample size calculation and to test/refine the statistical models as needed. The statistical evaluations to be performed at this interim point are identical to the ones have been proposed following the completion of patient recruitment.

Intra data sharing

All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on hospital secure drives at the site created for the study, and all data sets will be password protected. Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

DISCUSSION

The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and functional capacity, and correlating these factors with molecular biomarkers of obesity at the systemic and cellular level. Previous studies have been unable to completely elucidate the mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most salient of which is its inability to account for muscle mass or functional capacity. While alternate techniques can directly measure body composition, such as magnetic resonance imaging or dual-

energy X-ray absorptiometry(39), these are impractical in the clinical setting. Despite its limitations, BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design. Studies like this one are necessary to help segregate the high-risk obese patient likely to experience adverse outcomes from the lower risk obese patient. Thus we plan to better define "high-fit" versus "low-fit obese" patients in order to assist surgical planning and follow-up practices.

The assessments chosen for this trial are clinically validated, self-reported measures of functional capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of administration, reliability, validity and brevity acting as a reliable surrogate to more complex analyses of life quality.(40) The PSMS is an effective tool determining independence of cardiac patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS allows us to determine which is more effective as a measure of QoL in this patient population and provides the opportunity to compare or consolidate the two measures in determining "high-fit" vs "low-fit" patient categorization. Similarly, the DASI is a valid measure of the functional capacity measure for cardiac patients, determining the impact of the patient's cardiovascular disease on self-reported physical work capacity to estimate peak metabolic equivalents.(41) The DASI, as a self-reported test, will be correlated with the objective measure of the 6MWT, another effective tool for assessing functional capacity in patients with cardiovascular and pulmonary diseases.(42) These two tests in combination compensate for potential patient ineligibility due to disease burden for the 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly, many patients are accompanied by family and that strengthens the legitimacy of the DASI because of two-person recall.

Biomarkers are sensitive, specific objective measures that can be used alone or in combination and are known to be predictive of outcomes.(43) Here we elected to design a trial amenable to conventional and experimental biomarkers, to identify measures that are potentially highly sensitive, translatable across centres and immutable to humanistic influences at the point of collection **(Table-1).** Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac function and may likely influence the heart following cardiac surgery. Previous studies have shown that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity, and are sensitive and specific markers of cardiovascular risk.(44, 45) Thus, it is important to examine cytokines and chemokines in circulation, specifically adipokine expression in distinct adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine secretion of biomolecules in close proximity to the heart.(46) With this trial we are building the "OPOS Biobank" as a valuable and unique repository of adipose tissue from different depots and blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we can link clinical history and blood sample analyses with gene, protein and cellular expression profiles of critical regulators of cardiovascular and metabolic disease.(47, 48)

The knowledge gained by consolidating this information for iterative utility would potentially help identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets. Additionally, these patient samples provide opportunity to investigate associated disease processes like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation etc. It has been shown that the power of two well characterized biomarkers can determine differences of 1-year mortality by more than 50% predictively.(43) Assessment of clinical and

biomarker panels could thus potentially help identify predictive biomarkers that would help clinicians treat cardiac patients more effectively.

Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future studies might include more comprehensive QoL assessments, including mental health assessments, and socio-economic status, that contribute to health related QoL. Mental fortitude could be a deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial. Underweight patients were excluded due to the significantly higher risks associated with early major adverse clinical outcomes.(49) Patients above the age of 75 were not included in this trial, to exclude the effect of frailty on physical capacity for recovery. Future studies could account for frailty as a confounding variable and incorporate this into a more complete assessment of surgical fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded. This was a practical and safety decision; however, the results of this trial should allow for more open inclusion once the criterion to define surgical fitness is clear. Additional studies should explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional patient populations could be followed over a longer term to assess outcomes like 5-year mortality or to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial is limited in terms of patients enrolled, future studies could also have higher enrollment targets that would allow for broader multivariate analyses.

Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac

surgeons and allied health care professionals on the important relationships that exist between obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and health care administrators will be better able to identify an obese patient who is more likely to experience adverse outcomes and require additional hospital resources in their recovery.

PRESENT STATUS

The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due to change in patient's condition becoming more urgent, patients passing the age limit of 75 years, and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion of additional sites.

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AUTHOR CONTRIBUTIONS

JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical

sample collection and processing. JM and AY contributed to statistical design. All authors have read and approved the article.

Declarations of interest: none declared

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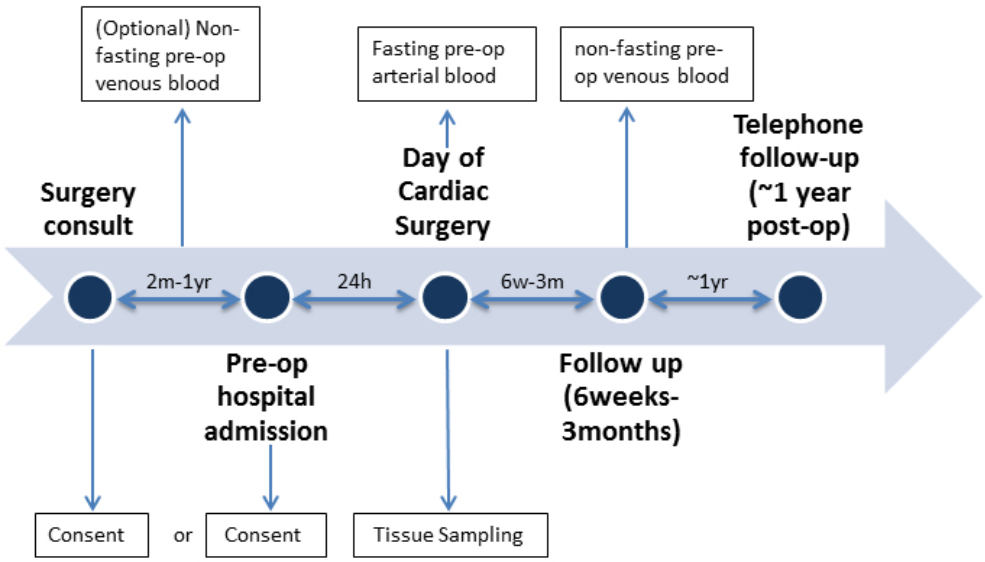
FIGURE LEGENDS:

Fig. 1: Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

Figure 2: Flowchart showing protocol for the OPOS trial.

Date and Version Identifier:
*Issue Date***:** 28 November, 2014
Protocol Version Number: 7 dated 12 December 2017



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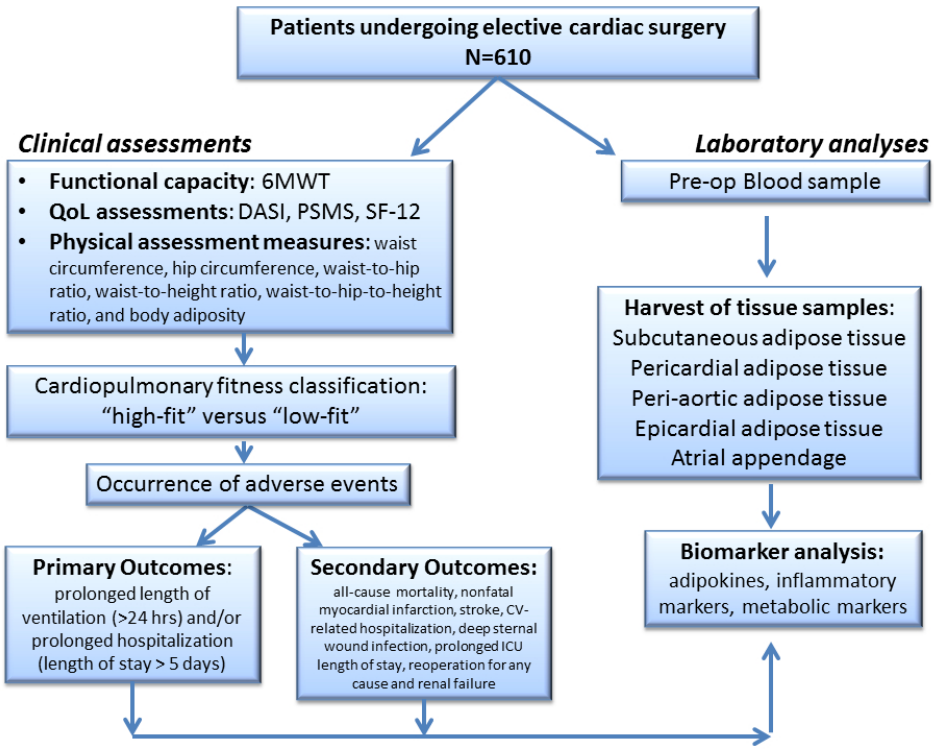

Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)