Multi-center prospective cohort study to compare the impact of severe COVID-19 infection on the incidence of Coronary Microvascular Dysfunction.

The incidence of coronary microvascular dysfunction in patients with stable angina and a history of severe COVID-19 infection requiring oxygen supplementation: A prospective cohort study "COMET-19 Study"

STUDY PROTOCOL
June 2023

Main sponsor:	**Lithuanian University of Health Sciences**
Study coordination centre:	**Lithuanian University of Health Sciences**
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Sponsor:
Lithuanian University of Health Sciences is the main research sponsor for this study. For further information regarding the sponsorship conditions.

Funder: NA

This protocol outlines the COMET-19 Study, which stands for "Comparative Study of Microvascular Dysfunction in COVID-19 Survivors with Stable Angina". The purpose of this study is to determine if severe COVID-19 infections is associated with an increased prevalence of persistent coronary microvascular dysfunction (CMD). The study will use a pressure temperature wire to assess for CMD in a prospective, comparative design. The procedures for participant recruitment, data collection, and analysis will be outlined in this protocol, and any necessary corrections or amendments will be circulated to investigators. In case of any study-related problems, the Chief Investigator will be the first point of contact. This study will be conducted in accordance with the principles of the Declaration of Helsinki and will comply with local regulatory requirements as appropriate.

This protocol is strictly confidential and not for public distribution.

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Study overview

1.1. Study summary

Design

The COMET-19 study is a prospective cohort study that aims to compare the prevalence of coronary microvascular dysfunction (CMD) in patients with stable angina who have a history of severe COVID-19 infection and those with stable angina without a history of COVID-19.

Aims

The primary aim of the study is to determine whether a history of severe COVID-19 infection impacts the prevalence of CMD and its endotypes in stable angina patients.

Outcome measures

The primary outcome measure will be the prevalence of CMD in both groups, measured by both coronary flow reserve (CFR) and index of microvascular resistance (IMR) using a pressure-temperature wire.

Population

The study population for the COMET-19 trial consists of adult patients (aged 40 -80 years) with a clinical diagnosis of stable angina. They will be recruited from two university hospitals in Lithuania: Seamen's Branch, Klaipeda University Hospital, Klaipeda, and the Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Kaunas.

Eligibility

Eligible patients will be those who have been diagnosed with stable angina and are scheduled to undergo angiography and possible revascularization. The study population will be divided into two groups:

Group A: Patients with stable angina and a history of severe COVID-19 infection.

Group B: Patients with stable angina without a history of COVID-19 infection. This group serves as a comparison group to assess the potential differences in CMD prevalence.

Duration

Anticipated recruitment is 6 months. Follow-up will occur 3 months after coronary angiography

1.2. Glossary of abbreviations

CAD	Coronary artery disease
CVD	Cardiovascular disease
CMD	Coronary Microvascular Dysfunction
IMR	Index of Microvascular Resistance
PCI	Percutaneous Coronary Intervention
SAQ	Seattle Angina Questionnaire
IVUS	Intravascular ultrasound

2. Introduction

2.1. Background

Cardiac involvement has been well-documented during the acute phase of SARS-CoV-2 infection, with some patients experiencing persistent symptoms even after recovery, referred to as long-COVID-19 syndrome(1). A subset of these patients may develop angina-like chest pain, which remains a poorly understood phenomenon(2).

In recent years, there has been growing attention towards the assessment of microvascular function in patients with coronary artery disease, as it has been shown to be a predictor of adverse clinical outcomes, including persistent angina (3). The invasive measurement of the index of microcirculatory resistance (IMR) along with coronary flow reserve (CFR) has been established as a reliable tool for evaluating microvascular function in this context(3).

However, the mechanisms underlying persistent chest pain and potential microvascular dysfunction in patients with long-COVID-19 syndrome have not been adequately explored. To address this gap in knowledge, the preset study aims to compare the prevalence of CMD in patients with stable angina and a history of severe COVID-19 infection requiring oxygen supplementation, with those without a history of COVID-19. The study will employ a prospective design, utilizing a pressure-temperature wire to assess CMD in both groups of patients.

The findings from this study have the potential to contribute to a better understanding of the underlying mechanisms of persistent chest pain in patients with long-COVID-19 syndrome and may have implications for the management of this patient population.

3. Study objectives

3.1 Primary, Secondary and Tertiary Objectives

1. Primary objectives:
   To determine if there is a significant difference in the prevalence of coronary microvascular dysfunction (CMD) between patients with stable angina who have had a severe COVID-19 infection (Group A) and those stable angina without a history of COVID-19 (Group B). This will be measured using both coronary flow reserve (CFR) and index of microvascular resistance (IMR) through the pressure-temperature wire.

2. Secondary Objectives:

   I. To assess the severity of CMD, as indicated by the CFR and IMR values, in both groups. This will allow for a deeper understanding of the extent of CMD in each group.

   II. To evaluate any potential correlation between the duration of oxygen supplementation (in days) in the COVID-19 group and the incidence and severity of CMD. This could provide insight into whether the length of severe illness contributes to the risk or extent of CMD.

   III. To investigate which CMD endotype (structural or functional) predominates in both groups.

3. Tertiary Objectives:

   I. To investigate the patient-reported outcomes in both groups, especially in relation to symptoms of angina, quality of life, and functional status. This would give insight into how CMD affects patients' day-to-day lives and well-being.

3.2 Rationale for the study

The aftermath of the COVID-19 pandemic has unveiled a plethora of lingering health complications in those who have recovered, notably the 'long-COVID' or 'post-acute sequelae of SARS-CoV-2 infection' (PASC). Among these post-recovery symptoms, cardiovascular complications, especially angina-like chest pain, have surfaced as a significant area of concern. The possible mechanisms range from direct viral injury to the heart, systemic inflammatory responses, microvascular damage, to increased thrombotic events. Given this backdrop, understanding the potential link between severe COVID-19 infection and coronary microvascular dysfunction (CMD) becomes crucial, especially since CMD is known to predict adverse outcomes, such as persistent angina and heart failure, in other contexts.

Established diagnostic methods, such as the IMR and CFR measurements via a pressure-temperature wire, offer a reliable avenue to investigate this microvascular function. Currently, there is a knowledge gap regarding the long-term cardiovascular implications of COVID-19, specifically in relation to CMD. By investigating the incidence of CMD in those with a history of severe COVID-19 against those without, the study aims to ascertain whether the virus plays a direct role in the onset of CMD, providing clarity in an area currently clouded with uncertainties.

In essence, the COMET-19 study seeks to bridge the existing knowledge chasm concerning cardiovascular consequences in post-COVID-19 patients. The findings will not only provide insights into the causative relationship between COVID-19 and CMD but will also guide clinical decisions, and patient management, ultimately improving outcomes for those recovering from severe forms of the virus.

3.3 Study hypotheses

- Primary Hypothesis:

    i. Patients with a history of severe COVID-19 infection (those who required oxygen supplementation) (Group A) will have a higher prevalence of CMD (IMR > 25 or CFR < 2.0) than patients without a history of COVID-19 infection (Group B).

- Secondary Hypotheses:

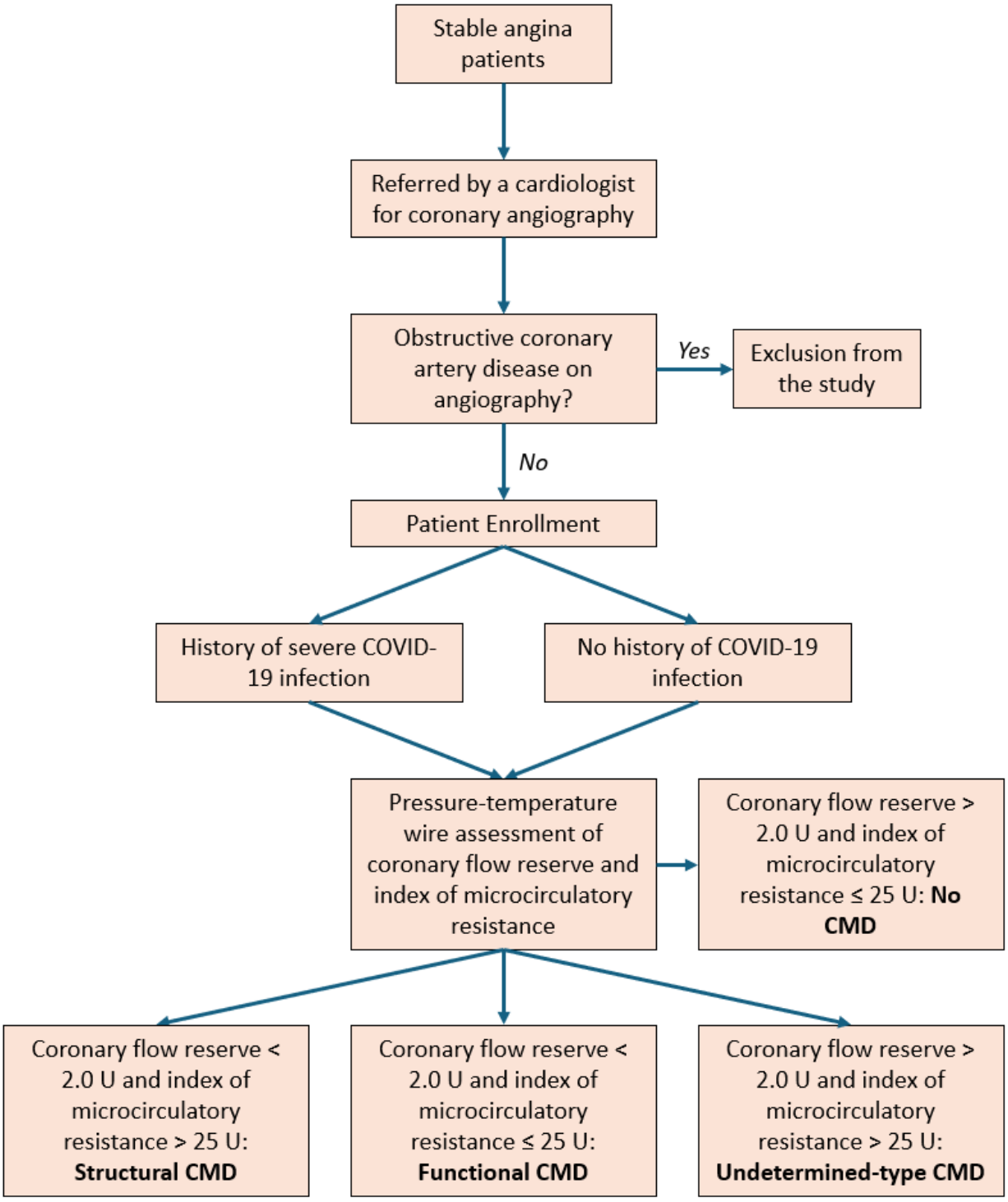
    i. Patients in Group A will have more severe CMD than patients in Group B.
    ii. The severity of CMD will correlate with the duration of oxygen supplementation.

- Tertiary Hypothesis:

    i. Group A will have worse patient-reported health outcomes than patients in Group B.

13.Study design

4.1 Study overview diagram



4.2 Study protocol:

Following enrollment in the study patients should undergo the following:

Baseline assessment:

A. Demographics:
   - Age
   - Gender
   - Center
   - Rural vs Urban

B. Medical History:
   - History of cardiovascular diseases (specifically any known coronary artery disease)
   - History of diabetes, hypertension, or other comorbid conditions
   - Medications currently being taken
   - Past surgeries or medical interventions

C. COVID-19 Specific History (for Group A):
   - - Date of COVID-19 diagnosis
   - - Duration of hospitalization
   - - Length of time on oxygen supplementation
   - - Any other COVID-19 related complications experienced

D. Clinical Assessment:
   - Vital signs (Blood Pressure, Heart Rate, Respiratory Rate, Temperature, Oxygen Saturation)
   - - Body Mass Index (BMI)
   - -Physical examination focusing on the cardiovascular system

E. Symptom Assessment:
   - Onset, frequency, duration, and severity of angina symptoms
   - Presence of any other cardiovascular symptoms (e.g., shortness of breath, palpitations)
   - New York Heart Association classification

F. Diagnostic Tests:
   - Electrocardiogram
   - Echocardiogram or other imaging if available and relevant
   - Blood tests (cardiac markers, lipid profile, Inflammatory markers, blood glucose, blood counts and renal function panel)

G. Patient-Reported Outcomes:
   - Quality of Life assessment, (Seattle angina score)

H. Risk Factors:
   - Smoking history
   - Alcohol consumption
   - Physical activity levels
   - Family history of cardiovascular diseases

I. Review of Previous Treatments (if any):
   - Medications previously prescribed for angina (Trimetazidine, Ranolazine, cardiovascular related drugs)

Functional assessment

Functional assessment will be performed just after undergoing the diagnostic coronary angiography

Invasive functional assessment

- Upon intubation of the guiding catheter, 300 mcg of intra-coronary glyceryl-trinitrate will be administered to control coronary vasomotor tone.
- Coronary flow reserve (CFR), fractional flow reserve (FFR), and index of microvascular resistance (IMR) will be assessed using the CoroFlow system (Coroventis Research AB, Uppsala, Sweden).
- A coronary pressure/temperature sensor-tipped guidewire (Pressure Wire X; Abbott Vascular, Santa Clara, CA, United States) will be equalized to the guide catheter pressure with the pressure sensor positioned at the tip of the catheter at the aortic sinus, then advanced to the distal to the lesion.
- Three milliliters of normal saline will be administered through the guiding catheter in triplicates during rest and during the state of maximal hyperemia.
- The CFR will be determined as the difference between the baseline and hyperemic mean transit times (Tmn).
- IMR will be computed by multiplying the distal coronary pressure during maximal hyperemia by the hyperemic Tmn.
- The ratio of mean distal (d) to mean proximal (p) coronary artery pressure (P) during maximal hyperemia will be used to calculate FFR (FFR = Pd/Pa).

Seattle Angina Score Assessment

The Seattle Angina Score questionnaire will be administered to all patients regarding symptoms prior to coronary angiography. The questionnaire will be conducted by a trained study nurse or research assistant.

4.3. Study outcome measures

Primary Outcome:

- Prevalence of coronary microvascular dysfunction (CMD)

Secondary Outcomes:

- Severity of CMD
- Correlation of the severity of CMD and the duration of oxygen supplementation (days) in group A.
- Prevalence of CMD endotypes in both groups
- Seattle Angina Questionnaire score.

4.4. Relevance and Implications of the Trial Results

1. Clarity in Cardiovascular Consequences: With COVID-19 known to affect multiple organ systems, including the cardiovascular system, understanding the potential long-term implications becomes paramount. Determining whether there's a direct link between severe COVID-19 infection and CMD will shed light on this critical area of uncertainty.
2. Guidance for Clinical Decisions: If a significant association between severe COVID-19 and CMD is established, this could directly impact clinical decisions. It may necessitate a different approach or more frequent monitoring for COVID-19 survivors presenting with angina-like symptoms.
3. Informed Patient Management: For patients who have recovered from severe COVID-19 infections, knowing the potential risks and understanding the importance of regular cardiac check-ups will be pivotal. An informed patient is better equipped to participate actively in their care and adhere to medical advice.
4. Potential for Further Research: The results of this trial could set the stage for additional studies, especially focused on therapeutic interventions, management strategies, and possibly preventive measures for at-risk populations.

4.5. Sample size/Power calculation

Prior literature suggests that the prevalence of CMD in patient with stable angina is approximately 10% (4). There is minimal data on the prevalence of CMD in stable angina patients with a history of COVID-19 infection. Limited preliminary data from the ANGI-Covid study suggests the prevalence to be approximately 50% (5).

After adjusting each estimated prevalence 5% towards each other, the estimated prevalence of CMD in patients with stable angina was set at 15% and in patients with stable angina with a history of COVID-19 infection at 45%. For a study power of 0.9, we will require a total of 94 patients in the study, with 47 patients in each arm of the study. Given the uncertainty regarding the estimated prevalence of CMD in patients with stable angina with a history of COVID-19 infection, this study will adopt an adaptive study design. Once enrollment has been completed based on the abovementioned estimates, the necessary sample size will be re-assessed to statistical power based on the observed prevalence of CMD within in each of the present cohort. At that time, the decision will be made to continue or halt enrollment depending on whether the necessary number of enrollees for statistical significance for the primary endpoint has been reached.

13.Participant entry

5.1. Pre-registration evaluation

Recruitment

Recruitment will be conducted in two main university hospitals in Lithuania. Physicians will be trained to identify potential candidates during their regular visits. Information brochures will be

provided in waiting rooms and clinics to raise awareness about the study. Additionally, potential participants might be contacted via phone or email, if they previously agreed to be informed about research opportunities.

5.2. Inclusion criteria

1. Adult patients aged between 40 and 80 years.
2. Clinical diagnosis of stable angina.
3. For Group A: A history of severe COVID-19 infection, defined as a positive polymerase chain reaction test for COVID-19 and requiring supplemental oxygen therapy for a SpO_2 < 90% on room air.
4. For Group B: No history of COVID-19 infection.

5.3. Exclusion criteria

1. Acute coronary syndromes (unstable angina, non-ST elevation myocardial infarction, or ST-elevation myocardial infarction).
2. History of myocardial infarction.
3. Ejection Fraction ≤ 40%
4. Obstructive coronary artery disease
5. History of coronary artery bypass graft surgery.
6. Severe kidney disease (eGFR <30 mL/min/1.73 m2).
7. Severe liver disease or liver function test abnormalities (aspartate aminotransferase or alanine aminotransferase levels >3 times the upper limit of normal).
8. Patients who are allergic to adenosine (since hyperemia during IMR measurement is achieved by adenosine injection).
9. Significant valvular heart disease or cardiomyopathy.
10. Patients who are pregnant or breastfeeding.
11. Patients on chronic supplemental oxygen therapy prior to their diagnosis of COVID-19 infection
12. Patients who are unable to comply with study requirements.

5.4. Withdrawal criteria

1. Participant’s decision to leave the study at any time.
2. Any serious adverse event or complication related to the study procedure.
3. Development of a condition in a participant that falls under the exclusion criteria after the start of the study.

13.Clinical events

6.1. Definitions

The following definitions will be employed in this study.

Serious adverse event or complication related to the study procedure: myocardial infarction, coronary dissection, coronary perforation, stroke, retroperitoneal hemorrhage, mechanical hardware failure, anaphylactoid contrast reaction, death, or other serious complication arising directly from the study procedure.

Stable angina: Grade II or grade III angina according to the Canadian Cardiovascular Society angina grading system (6,7).

Severe COVID-19 infection: A positive COVID-19 polymerase chain reaction test in the setting of appropriate clinical symptoms, with an oxygen saturation < 90% on room air measured by pulse oximetry, requiring supplemental oxygen (8).

Myocardial infarction: Detection of an elevated cardiac troponin value above the 99th percentile upper reference limit with a rise and/or fall of cardiac troponin values with at least one of the following: symptoms of acute myocardial ischemia, new ischemic electrocardiographic changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or identification of a coronary thrombus by angiography including intracoronary imaging (6).

Severe kidney disease: estimated glomerular filtration rate <30 mL/min/1.73 m^2 by Cockcroft-Gault equation (9).

CMD is defined as either an IMR > 25 or CFR < 2.0 (3). It is further categorized as the following endotypes: 1) structural CMD (IMR > 25 and a CFR < 2.0), 2) functional CMD (IMR ≤ 25 and a CFR < 2.0), and 3) undetermined CMD (IMR > 25 and a CFR > 2.0).

6.2 Reporting procedures

Clinical Events Committee (CEC)
The CEC is made up of cardiologists who are not participants in the trial. The CEC is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the CEC will be blinded to the treatment arm and the primary results of the trial.

The CEC will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. The CEC will also review and rule on all deaths that occur throughout the trial.

Reports of clinical events should be submitted within 15 days of the Chief Investigator becoming aware of the event.

Local investigators should report any clinical events as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting clinical events: Kasparas Briedis
Email : kasparas.briedis@kaunoklinikos.lt

Case report form
An online CRF form will be used throughout the study. This will be secure, and compatible with currently guidelines to ensure security of patient data. It will be managed via the Lithuanian University of Health Sciences Clinical Trials Unit.

7. Assessment and follow-up

Upon completion of the procedure, participants will immediately undergo vital sign monitoring, including assessments of blood pressure, heart rate, and oxygen saturation to ensure stability. A post-procedural ECG will be administered to identify any new irregularities or changes potentially induced by the intervention. Clinicians will also conduct a prompt clinical evaluation to detect any immediate complications stemming from the invasive functional assessment or a worsening of existing symptoms. Furthermore, while still on-site, patients will be requested to provide feedback regarding the procedure, detailing any discomfort or concerns they may have experienced. Lastly, for consistency and comprehensive data capture, all pertinent findings and observations from the post-procedure evaluation will be documented using a standardized data collection form.

8. Statistics and data analysis

For the successful interpretation of results derived from the COMET-19 study, the data will undergo rigorous statistical analysis. Here's a brief overview:

1. Data Management: All data collected will be entered into a secure, electronic database with backup systems in place. Double-entry methods and routine cross-checks will be implemented to minimize data-entry errors.

2. Descriptive Statistics: Basic statistics like mean, median, standard deviation, and interquartile ranges will be utilized to describe continuous variables. For categorical variables, frequencies and percentages will be used.

3. Comparative Analysis: To compare the incidence of CMD between Group A (COVID-19 with oxygen supplementation) and Group B (no history of COVID-19), a Chi-square test or Fisher's exact test will be employed for categorical variables, and the t-test or Mann-Whitney U test will be used for continuous variables, depending on the data distribution.

4. Correlation Analysis: Pearson's or Spearman's rank correlation will be used to assess the relationship between the duration of oxygen supplementation and the severity of CMD.

5. Significance Level : A p-value of less than 0.05 will be considered statistically significant for all tests.

6. Multiple Testing: Adjustments for multiple comparisons, if applicable, will be done using methods like the Bonferroni correction to prevent type I errors.

7. Missing Data: Any missing data will be addressed using suitable imputation methods. The extent and pattern of missing data will be analyzed, and if it's determined to be missing at random, multiple imputation methods may be used.

8. Subgroup Analysis: If sample size permits, further subgroup analyses might be performed to identify any trends or patterns within specific subsets of the population, such as based on age, gender, or other relevant factors.

9. Graphical Representation: Key results will be depicted using appropriate charts and graphs to aid in the visualization and interpretation of findings.

10. Software: All statistical analyses will be performed using a validated statistical software package like SPSS, R, or Stata.

11. Reporting: Results will be reported in accordance with relevant guidelines for observational studies, ensuring clarity, transparency, and reproducibility.

9. Regulatory issues

9.1. Ethics approval

This study will involve human subjects and as such, ethical considerations will be paramount. The study will be conducted in accordance with the principles of the Declaration of Helsinki and will comply with all relevant laws and regulations. All patients will be fully informed of the risks and benefits of participation in the study and will provide written informed consent prior to enrolment. The Chief Investigator will obtain approval from the Kaunas regional biomedical research ethics committee.

9.2. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3. Risks of procedure

The procedure carries certain risks including potential vascular injury during catheter insertion, which might lead to bleeding or hematoma. It can also induce abnormal heart rhythms, some potentially life-threatening, and in rare instances, provoke heart attacks or worsen angina. Patients are exposed to ionizing radiation due to fluoroscopy, and while the risk is minimal, it's still present. Additionally, there's a possibility of allergic reactions to the contrast dye and, as

with any invasive procedure, a risk of infection at the insertion site. Despite these risks, the procedure's benefits usually outweigh potential downsides, but patients should be well-informed and provide consent.

9.4. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5. Indemnity

Lithuanian University of Health Sciences holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.6. Sponsor

Lithuanian University of Health Sciences will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.7. Funding

This study is not funded

9.8. Audits

The study may be subject to inspection and audit by Lithuanian University of Health Sciences under their remit as sponsor and other regulatory bodies to ensure adherence to GCP.

10. Study management

The day-to-day management of the study will be co-ordinated through **Lithuanian University of Health Sciences**.

10.1. Study reporting

Upon the completion of the study and subsequent data analysis, our findings will be compiled and prepared for dissemination in May 2024. The results will be structured following the typical format of an original research article, with sections including Introduction, Methods, Results, Discussion, and Conclusion. Preliminary findings will first be presented to the investigative team.

Feedback will be incorporated, and a finalized report will be prepared for submission to a peer-reviewed medical journal. Besides, we will seek opportunities to present our findings at relevant conferences and symposia, ensuring a wider reach among the medical and research community. All data will be archived as per regulatory guidelines, ensuring transparency and facilitating future reference or studies. Any post-publication queries or feedback will be addressed promptly by the research team.

10.2. Study sites and enrollment

The COMET-19 study will be conducted at two primary sites in Lithuania:

1. Klaipeda University Hospital, Klaipeda: This facility has established itself as a reputable institution for patient care and clinical research. The infrastructure, coupled with the expertise of the clinical team, makes it a suitable site for the study's requirements.

Given its strategic location and catchment area, it is anticipated that a significant portion of the study's participants will be enrolled from this facility.

2. Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Kaunas: As a part of one of Lithuania's premier health sciences universities, this hospital boasts state-of-the-art facilities and a team of experienced clinicians and researchers. Its reputation and accessibility will undoubtedly contribute to a smooth recruitment process.

Both sites will be equipped with the necessary equipment, specifically the CoroFlow system and the Pressure Wire X, to ensure uniformity in the functional assessments. Enrolment targets will be set for each site, considering their patient volume and the prevalence of eligible patients. Regular coordination and communication between the two sites will be maintained to ensure consistency in recruitment, assessment, and documentation. The chief investigator, alongside site coordinators, will continuously monitor the enrolment pace and address any discrepancies or challenges that may arise during the study's course.

10.3. Documentation

All trial documentation will be systematically collected and managed using Google Sheets, which offers robust functionality for multi-center international studies such as ours. The use of Google Sheets facilitates real-time, secure data entry and retrieval across study sites.

10.3.1 Data Handling Procedures

- Google Sheets Setup: A master file with individual tabs for each site will be used to record clinical and physiological data.
- Data Security: Access is restricted to authorized personnel, ensuring confidentiality and integrity in line with GCP guidelines.
- Data Review: Routine checks will be performed to verify data accuracy, with corrections logged for audit purposes.
- Backups: Data will be regularly exported and backed up onto DVDs and a central server to prevent data loss and ensure recovery if needed.

10.3.2 Training and Compliance

Personnel will receive training on protocol-specific data handling in Google Sheets, with ongoing oversight to maintain GCP compliance.

13.Publication policy

Publication and future studies committee
A publication committee, consisting of member of the steering committee and study principal investigators will meet to formulate a publication plan to disseminate the principal findings of the study, and the primary and secondary endpoints.

Future studies, and sub-studies will be actively encouraged, by investigators and other interested parties. These will be assessed via the formal application process, and the committee will decide on the applicability and suitability of the study request. Sub-study proposals which aim to look at subset analyses of the primary and secondary endpoints will be underpowered and in general discouraged.

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13.Appendix

13.1 Seattle Angina Questionnaire

The Seattle Angina Questionnaire-7

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness or angina** **over the past 4 weeks**.

Place an X in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately Limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
a. Walking indoors on level ground	☐	☐	☐	☐	☐	☐
b. Gardening, vacuuming or carrying groceries	☐	☐	☐	☐	☐	☐
c. Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐

2. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness or angina**?

I have had **chest pain, chest tightness or angina…**

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness or angina**?

I have taken nitroglycerin…

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, how much has your **chest pain, chest tightness or angina** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

5. If you had to spend the rest of your life with your **chest pain, chest tightness or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐