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SoutheAsTern eUrope microciRculATION (SATURATION) registry - Design and rationale

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ABSTRACT

Background: A considerable number of symptomatic patients leave the cardiac catheterization lab without a definitive diagnosis for their symptoms because no epicardial stenoses are found. The significance of disorders of coronary microvasculature and vasomotion as the cause of symptoms and signs of ischemia has only recently been appreciated. Today we have a wide spectrum of invasive coronary physiology tools but little is known about when and how these tools are used in clinical practice.

Study design and methodology: SoutheAsTern eUrope microciRculATION (SATURATION) registry will study the regional practice of patient selection for coronary function testing, indications, non-invasive ischemia testing, medications, procedural aspects of invasive physiology evaluation, and treatment changes after testing. The registry is expected to include 1600 patients in participating centers in Southeastern Europe from 2024 to 2029, using the thermodilution technique for evaluation of microcirculation. Major adverse cardiovascular events as well as patient-centered outcomes such as burden of angina and quality of life using Seattle Angina Questionnaire (SAQ) and EQ-5D-5L will be recorded. The study will include patients with different stages of coronary artery disease (presence of disease or degree of stenosis) to elucidate the effect of coronary microcirculation on the outcomes in this broad group.

Conclusion: The registry will provide information regarding the current practice of invasive coronary physiology assessment in populations at high cardiovascular risk in Southeastern Europe. This could lead to a better understanding of

Abbreviations: ANOCA, angina with no obstructive coronary artery disease; CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; INOCA, ischemia and no obstructive coronary artery disease; MVA, microvascular angina; RFR, resting full-cycle ratio; RRR, resistive reserve ratio; SAQ, Seattle Angina Questionnaire; VSA, vasospastic angina.

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coronary microvascular dysfunction and its relationship to various degrees of coronary atherosclerosis together with potential interventions that can be beneficial.

1. Introduction

Less than 40 % of patients referred for coronary angiograms for symptoms of angina are found to have obstructive coronary artery disease, while in almost 40 % of patients no coronary artery disease at all is detected [1]. This implies that an alarming number of symptomatic patients leave the cardiac catheterization lab without a definitive diagnosis or explanation for their symptoms. Consequently, these patients often do not receive appropriate treatment, experience recurrent hospitalizations, and undergo numerous unnecessary repeat procedures without a definitive diagnosis or symptom relief. It was not until recently that the significance of disorders of coronary microvasculature and vasomotion as the cause of symptoms and signs of ischemia, or in complicating existing cardiac conditions, has been appreciated.

Disturbances in coronary microvasculature and vasomotion include the functional disturbance of the epicardial blood vessels resulting in endothelial dysfunction and epicardial vasospasm, responsible for the clinical syndrome of vasospastic angina (VSA), as well as dysfunction of the microvascular bed, responsible for the clinical syndrome of microvascular angina (MVA). Over the years, interventional cardiologists worldwide have developed methods to study the functional disturbances of the coronary tree in patients presenting with ischemia and no obstructive coronary artery disease (INOCA) or angina with no obstructive coronary artery disease (ANOCA). Existing guidelines provide recommendations on VSA and MVA testing, which include their invasive diagnosis in the cardiac catheterization lab [2,3]. These tests have entered clinical practice and have become the standard of care for the investigation of the disturbances of coronary physiology [4,5].

We designed the SoutheAsTern eUrope microciRculATION (SATURATION) registry in order to study the regional practice of patient selection for coronary function testing, including indications, ischemia tests performed, medications prescribed, procedural aspects of invasive physiology evaluation, and treatment changes after testing. Moreover, we aim to study major adverse cardiovascular events in these patients after invasive coronary function testing as well as patient-centered outcomes such as quality of life and freedom from angina.

2. Study design

2.1. Design, aims, inclusion and exclusion criteria

SATURATION is a prospective multicenter registry of consecutive patients who undergo coronary function testing using the Coroventis CoroFlow Cardiovascular System and Pressure Wire X (Abbott Vascular, Abbott Park, IL, USA) from March 1, 2024 until March 1, 2029, and provide informed consent to being included in the registry. All physiology tests will be performed according to local institutional protocols. We plan to enroll around 1600 patients in study centers in Croatia, Czech Republic, Greece, Hungary, Israel, Serbia and Slovenia. The list of sites and respective responsible investigators is provided in Supplement 1.

The following is a list of study aims:

- Aim 1: To assess the regional practice of patient selection for assessment of invasive coronary physiology including vasospasm testing and invasive estimation of microcirculation by measuring guidewire-based CFR and IMR.
- Aim 2: To assess regional procedural aspects of invasive coronary function testing – how aforementioned parameters (CFR, IMR, vasospasm) are measured in the catheterization laboratory
- Aim 3: To assess patients' treatment and treatment changes after invasive coronary physiology measurements at each follow up visit.
- Aim 4: To investigate cardiovascular outcomes and additional procedures (stress testing, angiography, etc.) done after comprehensive invasive coronary physiology evaluation.

The study will include consecutive patients undergoing invasive coronary function testing using the Coroventis CoroFlow Cardiovascular System software regardless of the presence of coronary artery disease and initial clinical presentation. Inclusion and exclusion criteria for the study are listed in Table 1. Study enrollment has started, and 106 patients have been enrolled so far.

2.2. Data collection

Data collection will be managed by the investigators using CASTOR® Electronic Data Capture (EDC) platform.

The following data will be collected at enrollment:

- De-identified demographic data
- Cardiovascular risk factors and significant co-morbidities
- Laboratory investigations of interest
- Prior cardiovascular events
- Pre-procedure medications
- Echocardiogram within 3 months of invasive coronary procedure
- Non-invasive ischemia testing within 3 months of invasive coronary procedure (exercise treadmill test, nuclear perfusion tests- single photon emission computed tomography (SPECT) and positron emission tomography (PET), stress echocardiograms or stress cardiac magnetic resonance imaging (MRI))
- Seattle Angina Questionnaire (SAQ)
- EQ-5D-5L
- Details of the coronary angiography and invasive physiology procedure including procedural complications
  - Resting Pd/Pa
  - Fractional flow reserve (FFR)
  - Resting full-cycle ratio (RFR)
  - Coronary flow reserve (CFR)
  - Index of microcirculatory resistance (IMR)
  - Microcirculatory Resistance Reserve (MRR)
  - Resistive reserve ratio (RRR)
  - Resting and hyperemic transit time (RestT and HypT)
  - Details of VSA testing (presence of epicardial or microvascular spasm)
- Post-procedure medications

The following data will be collected at follow up, every 6 months for up to 5 years:

- Major adverse cardiovascular events (death from any cause, myocardial infarction, cerebrovascular accident, coronary revascularization)
- Hospitalization for angina or cardiovascular causes
- Repeated invasive coronary angiography since last visit

Table 1
SATURATION registry inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Adults of both sexes older than 18 years	Persons under the age of 18
Angina symptoms or angina equivalent	Pregnant of nursing
Referred to Cath lab for evaluation of coronary artery disease	No coronary physiology measurements performed
Invasive coronary function testing performed (microcirculation testing ± vasospasm testing) using Coroventis CoroFlow Cardiovascular System (Abbott Vascular, Abbott Park, IL, USA)	

- Current medications
- SAQ
- EQ-5D-5L
- Non-invasive ischemia testing since last visit

Complete case report form (CRF) is provided in Supplement 2.

2.3. Outcomes

Outcomes (Table 2) will be evaluated every 6 months for 5 years via direct patient contact by research staff at each participating site or at follow-up visits. Outcomes will be collected based on existing medical documentation.

2.4. Statistical analysis

Results will be presented as count (%) for nominal or ordinal data and mean (SD), median (IQR) and minimum and maximum for numeric data. Ordinal data with sufficient number of categories will be analyzed as numeric, while variables with only a few categories will be analyzed as nominal.

2.5. Missing data

In order to minimize missing data in follow up, all patients will be scheduled for in-person visits at each follow up interval. In case the patient does not come to the follow up visit, they or their family members will be contacted by phone by research staff and follow up information will be obtained over the phone. Imputation techniques will be considered based on completeness and quality of collected data. Only last observation carried forward (LOCF) would be considered, and only if one visit between two is unavailable. In case imputation is used, sensitivity analysis will be performed in order to evaluate possible bias introduced by imputation.

2.6. Limitations

The limitations of SATURATION Registry are that like every real-world registry we expect substantial heterogeneity among different protocols for coronary physiology testing between different institutions resulting in different prevalences of coronary vasomotor disorders. There is a possibility of selection bias as the registry only includes patients who underwent invasive physiology testing and does not include patients who had a non-invasive diagnosis of coronary vasomotor disorders.

Table 2
Study outcomes.

Primary outcomes	Secondary outcomes	Patient-centered outcomes
All-cause death and non-fatal myocardial infarction	All-cause death	Freedom from angina (SAQ questionnaire)
Composite MACE: all-cause death, non-fatal myocardial infarction, coronary revascularization, hospitalization for cardiovascular causes (acute coronary syndrome, heart failure, angina, repeated coronary angiography)	Cardiovascular death	Quality of life (EQ-5D-5L questionnaire)
	Non-fatal myocardial infarction	Follow up non-invasive ischemia testing (if performed)
	Coronary revascularization	
	Stroke	
	Hospitalization for heart failure	
	Hospitalization for acute coronary syndrome	
	Repeated coronary angiography	

3. Discussion

There is increasing awareness that patients undergoing invasive coronary function testing should be studied and followed in a systematic way. Several registries are currently enrolling patients who underwent coronary function testing: DISCOVER INOCA, NL-CFT, CMDR and others [6–8]. DISCOVER-INOCA is a comprehensive registry of INOCA patients that includes not only coronary function testing but also protocol-mandated intracoronary imaging for quantification of the degree of non-obstructive atherosclerosis and is likely the only ongoing study that can quantify to what degree non-obstructive atherosclerosis is a confounding factor in INOCA outcomes. NL-CFT is a multi-center registry in Netherlands recruiting all patients with INOCA who underwent coronary function testing, with the potential to be used for registry-based randomized clinical trials. It has already been used to recruit patients for EDIT-CMD, a randomized controlled trial of diltiazem versus placebo for coronary microvascular dysfunction [9]. Finally, CMDR is the largest coronary function testing registry in North America that will recruit both patients with stable angina (INOCA or ANOCA) who underwent coronary function testing but also patients who had ST-elevation myocardial infarction after successful completion of primary percutaneous coronary intervention. Other retrospective registries like ILIAS have already provided important insights on different aspects of coronary vasomotor disorders [10,11].

The SATURATION registry has many similarities and some differences compared to existing registries. It is a multi-center registry in Southeastern Europe that includes 18 centers in 7 countries with a total population of 49 million people. This places us in a position to prospectively recruit a large number of patients which will help inform on important yet rare clinical outcomes. The registry will also focus on patient-centered outcomes such as angina burden and quality of life. Comprehensive procedural data will be collected allowing for careful examination of how procedural differences in patient preparation and medication administration affect diagnosis and outcomes [12]. In contrast to existing registries where coronary functional testing is standardized per registry requirements, SATURATION is a real-world registry that will inform on the landscape of procedural specifics used in different countries and by different centers. The follow up effort which is investigator-led at scheduled follow up visits every 6 months or by telephone is likely to ensure good follow up.

While we expect the majority of included patients to have INOCA, patients with existing coronary artery disease will also be included. A subgroup of studied patients will include those who have undergone percutaneous revascularization but remained symptomatic despite an optimal angiographic result [13] as well as patients with acute coronary syndrome including myocardial infarction with no obstructive coronary arteries (MINOCA).

Finally, the registry could be useful for identifying and recruiting patients for future studies regarding medical therapy of patients suffering from microvascular disturbances as has been demonstrated in other registries of this type.

4. Conclusion

The SATURATION registry will provide important information regarding the current practice of invasive coronary function testing in a population of patients in Southeastern Europe. The large amount of data to be collected could contribute to a better understanding of microvascular dysfunction and its relationship to various degrees of coronary atherosclerosis together with potential interventions that can improve this condition.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2024.11.012.

CRediT authorship contribution statement

Natalija Odanovic: Writing – original draft, Methodology, Investigation, Conceptualization. **Konstantinos Tsioufis:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Kyriakos Dimitriadis:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Athanasios Sakalidis:** Writing – review & editing, Methodology, Investigation. **Michail I. Papafaklis:** Writing – review & editing, Supervision, Methodology, Investigation. **Periklis Davlouros:** Writing – review & editing, Supervision, Methodology. **Igor Ivanov:** Writing – review & editing, Investigation, Conceptualization. **Milenko Cankovic:** Writing – review & editing, Investigation, Conceptualization. **Andreas S. Kalogeropoulos:** Writing – review & editing, Methodology, Investigation. **Michalis Hamilos:** Writing – review & editing, Investigation. **Emmanuel Sideras:** Investigation. **Maayan Konigstein:** Supervision, Investigation. **Lior Zornitzki:** Supervision, Investigation. **Tomas Kovarnik:** Supervision, Investigation. **Zoltan Ruzsa:** Supervision, Investigation. **Zsolt Piroth:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Marija Zdravkovic:** Investigation. **Zlatko Mehmedbegovic:** Writing – review & editing, Investigation. **Zoran Miovski:** Investigation. **Hrvoje Jurin:** Investigation. **Jan Kanovsky:** Investigation. **Ehud Regev:** Investigation. **Samit Shah:** Writing – review & editing, Methodology. **Ivan Ilic:** Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethical approval

The study was approved by the Ethical Committee of the Institute for Cardiovascular Diseases “Dedinje” (Decision No. 4026) and ethical approval was obtained by individual participating sites from their respective Ethical Committees prior to participant inclusion. The study is registered at clinicaltrials.gov (NCT06393478).

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Declaration of competing interest

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