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PROTOCOL PAPER
Interventional cardiology and cardiac surgery

Gender, diversity, and inclusion in phenotypic and genetic characterization of acute coronary syndromes: rationale and design of the prospective multicentre GEDI-ACS registry

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Aims Despite an overall decline in cardiovascular mortality in recent years and advances in diagnosis and treatment, acute coronary syndromes (ACS) remain a leading cause of morbidity and mortality among women worldwide. Sex-specific risk factors and mechanisms remain under-recognized and complicate early diagnosis and management.

Methods and results The GEDI-ACS registry (PNRR-MCNT2-2023-12377431; NCT06441942) is a prospective, multicentre, non-randomized clinical study aiming to identify the phenotypic and genetic profiles of women with ACS. The study is enrolling 100 consecutive women presenting with ACS (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina) in Northern and Southern Italy. In these patients, comprehensive clinical, imaging, biochemical, and molecular phenotyping (including whole exome sequencing, transcriptomics, proteomics, and metabolomics) will be performed. Data on socioeconomic status, health literacy, and awareness of cardiovascular risk factors will be collected through standardized questionnaires. Follow-up, scheduled at 1 and 12 months, will assess clinical outcomes, quality of life, adherence to therapies, and lifestyle modifications.

Conclusion The GEDI-ACS registry will provide novel insights into the sex-specific profile of ACS by integrating clinical, genetic, molecular, and socioeconomic data from female patients. The results may support the development of personalized interventions that account for gender diversity.

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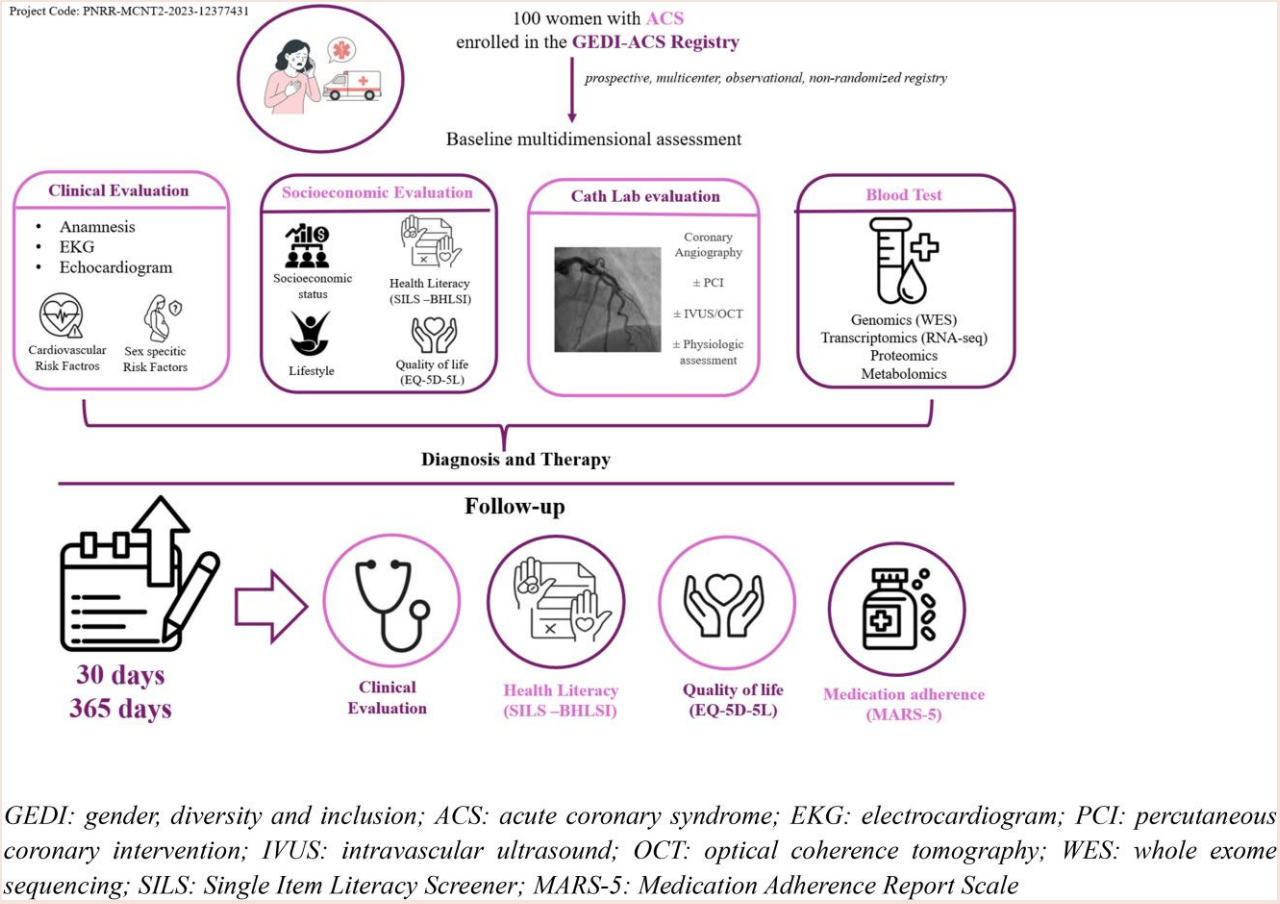
Graphical Abstract



GEDI: gender, diversity and inclusion; ACS: acute coronary syndrome; EKG: electrocardiogram; PCI: percutaneous coronary intervention; IVUS: intravascular ultrasound; OCT: optical coherence tomography; WES: whole exome sequencing; SILS: Single Item Literacy Screener; MARS-5: Medication Adherence Report Scale

Keywords Acute coronary syndrome • Gender disparities • MINOCA • Multi-omics analysis • Health literacy • Quality of life

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality among women.[1] In recent years, an increasing incidence and mortality of acute coronary syndromes (ACS) have been recognized among younger patients.[2–4] Persistent sex-related disparities have also been reported, with women experiencing a higher short-term mortality risk following successful primary percutaneous coronary intervention (PCI) compared with men.[5,6] The Lancet Women and CVD Commission has conducted a thorough analysis of the existing evidence on this issue, highlighting gaps in medical knowledge and providing clear, specific recommendations to reduce the burden of CVD in women by 2030.[2] Contributing factors to this sex-related gap include a lack of awareness among patients and healthcare providers about the burden of CVD and its typical symptoms and therapeutic options. In addition to conventional risk factors common to both sexes, such as hypertension, diabetes, dyslipidaemia, smoking, and obesity, women are also exposed to sex-specific risks (i.e. fluctuations in pro-thrombotic activity, pregnancy-related complications, menopause, and polycystic ovary syndrome) and more frequently to under-investigated conditions (i.e. domestic violence, socioeconomic status, and poor health literacy).[7,8] Other determinants, including low socioeconomic status, poor health literacy, and psychosocial stressors, may further impact the clinical management of women with ACS. Moreover, myocardial infarction with non-obstructive coronary artery disease (MINOCA) is more prevalent in women; however, its prevalence, endotypes, and genetic and pathophysiological mechanisms remain poorly understood. To address these gaps, the GEDI-ACS registry was designed to prospectively enrol women with ACS across Italian centres and to characterize their clinical, imaging, biochemical, and molecular profiles along with detailed socioeconomic and health literacy assessments. This integrated clinical and translational approach aims to expand current knowledge on the sex-specific presentation of ACS.

Methods

Study design and eligibility

The GEDI-ACS registry (PNRR-MCNT2-2023-12377431; ClinicalTrials.gov Identifier: NCT06441942) is a prospective, multicentre, observational, non-randomized, open-label clinical study designed to evaluate

Table 1 Inclusion and exclusion criteria

No.	Criterion	Answer	
01	Women aged 18 years or older	✓ Yes	□ No
02	Diagnosis of acute coronary syndrome, including unstable angina or myocardial infarction	✓ Yes	□ No
03	Written informed consent provided by the participant	✓ Yes	□ No
04	Ability to communicate and understand study procedures and follow-up requirements	✓ Yes	□ No
05	Willingness to comply with the study protocol, to undergo genetic testing and provide blood or tissue samples for molecular phenotyping	✓ Yes	□ No
06	Agreement to adhere to the prescribed treatment plan, to attend scheduled visits and provide necessary information, including medication regimen and lifestyle modifications	✓ Yes	□ No
07	Inability to provide informed consent or comply with study procedures	□ Yes	✗ No
08	Life expectancy of <1 year	□ Yes	✗ No
09	Any condition that, in the opinion of the investigator, may jeopardize the participant's safety or interfere with the study objectives	□ Yes	✗ No

the clinical, imaging, biochemical, and molecular profiles of women with ACS. Consecutive women presenting with ACS (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], and unstable angina [UA]) will be asked to provide written informed consent to participate in the registry. Inclusion and exclusion criteria are summarized in *Table 1*.

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Study procedures

Enrolled patients will undergo comprehensive diagnostic assessment and management according to current European Society of Cardiology (ESC) guidelines and the consensus document on MINOCA.[9–12] All clinical, imaging, procedural baseline, and follow-up data will be recorded in a dedicated electronic case report form (eCRF). Follow-up visits will be scheduled at 1 and 12 months post-discharge, conducted either in person or by telephone if the patient is unable to attend in person. These evaluations will systematically assess clinical status, risk factor control, lifestyle modifications, adherence to medical therapy, level of awareness, and quality of life, in accordance with standard care protocols.

Mediolanum Cardio Research (MCR; Milan, Italy) has been appointed as the contract research organization (CRO) for the study, with overall responsibility for study setup, data management, and monitoring activities. Specifically, MCR oversees the definition of CRF requirements and the setup and validation of the clinical database. Data management activities include query generation and tracking, ongoing data cleaning, centralized data monitoring, and final database reconciliation leading to database lock. Project management activities include regular communication with participating sites and on-site monitoring visits to ensure adherence to the study protocol and data integrity.

The following variables will be specifically assessed:

- Risk factors: this includes *traditional risk factors* (i.e. hypertension, dyslipidaemia, diabetes mellitus, smoking status, family history of coronary artery disease [CAD], obesity), *sex-specific risk factors* (such as history of live birth, miscarriages, pregnancy-related complications, menopause, hormone replacement therapy, polycystic ovary syndrome, inflammatory and autoimmune disorders, effects of physical and psychological violence, anxiety, and depression), and *under-recognized risk factors* that may contribute differently across populations (including psychosocial stressors, health literacy, and socioeconomic determinants of health).
- Characteristics of symptoms: the study will assess whether patients present with *classical* (e.g. chest pain and radiation to the jaw or arm) or *non-classical/atypical symptoms* (e.g. stabbing, burning or pleuritic chest pain, epigastric discomfort, back pain, isolated shortness of breath, nausea, and fatigue).
- Clinical presentation: patients will be classified, based on standard diagnostic criteria, as having unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI) according to the clinical presentation.
- Timing variables: time intervals will be recorded to analyse potential delays in recognition and treatment. These include *time from symptom onset to first medical contact*, *time from first medical contact to diagnostic evaluation or reperfusion therapy*, and *door-to-balloon time* for patients undergoing primary PCI.
- Aetiology: diagnoses will be categorized as obstructive or non-obstructive coronary disease. For non-obstructive myocardial infarction, further classification of MINOCA endotypes will be performed, including coronary causes (coronary embolism, coronary microvascular dysfunction, coronary spasm, coronary thrombosis, myocardial bridging, plaque rupture/erosion, and spontaneous coronary artery dissection), cardiac causes (e.g. myocarditis and Takotsubo syndrome), and non-cardiac causes (e.g. supply–demand mismatch secondary to systemic illness), consistent with the latest ESC guidelines and consensus documents.[9–12] Myocardial infarction with non-obstructive coronary artery disease classification and final diagnosis will be assessed by experienced investigators at each participating centre, using standardized definitions and guideline-based criteria for the interpretation of intravascular imaging (OCT/IVUS), physiological assessments, and intracoronary acetylcholine provocation tests.[13–15] Although no formal central core laboratory will be employed, consistent data collection standards and definitions will be applied across centres to ensure comparability; a clinical event committee will evaluate serious adverse events.
- Procedural data: detailed information will be collected for diagnostic and therapeutic interventions, including coronary angiography findings, lesion characteristics, use of intravascular imaging, functional assessment, revascularization strategies, and procedural complications.
- Medications: all medications used prior to presentation, during hospitalization, at discharge, and at follow-up will be documented.
- Quality of life: patient-reported outcomes will be assessed using validated questionnaires to evaluate physical, psychological, and

functional aspects of quality of life following the acute event and throughout follow-up.

At baseline and at follow-up (30 days and 1 year), all patients will undergo a comprehensive clinical assessment, including medical and family history and physical examination. Visits will be conducted according to standard care and hospital practice.[9]

Eligibility for inclusion in the GEDI-ACS registry is defined by biological sex (female). To capture the multidimensional aspects of gender, psychosocial, and behavioural variables, including obstetric and gynaecological history, education, employment, health literacy, exposure to violence, and other gender-related factors, validated questionnaires will be administered under standardized conditions and supervised by trained personnel to ensure consistent completion and data collection. This approach maintains conceptual clarity in addressing both biological sex and gender identity within the study. Socioeconomic status will be assessed by collecting information on total household income using predefined income categories, highest level of educational attainment, current occupation and employment status, and housing conditions, including ownership status and type of housing. Health literacy will be evaluated using two complementary tools: the Brief Health Literacy Screening Italian (BHLSI),[16] a five-item self-report instrument assessing the ability to read, understand, exchange, and use health information; and the Single Item Literacy Screener (SILS),[17] which asks participants to rate their confidence in completing medical forms on a five-point scale (from 1, never, to 5, always), with scores greater than 2 indicating some difficulty with reading printed health materials. Quality of life will be measured using the EuroQoL (EQ-5D-5L),[18] a widely used self-administered questionnaire in which higher scores represent better quality of life (scored from 0.59 to 1.00). Sex-specific and gender-related risk factors will also be collected, including data on ethnicity, pregnancy-related complications, polycystic ovary syndrome, menopause, hormone replacement therapy, depression, and indirect consequences of physical or psychological abuse.

Adherence to medical therapy will be assessed using the five-item version of the Medication Adherence Report Scale (MARS-5), with higher scores (5–25) indicating greater reported adherence. Finally, lifestyle modifications after ACS will be evaluated by self-report questionnaires asking participants to rate the frequency, duration, or intensity of engagement in various lifestyle behaviours (e.g. physical activity, dietary changes, smoking cessation, LDL target achievement, and glycaemic control) according to the latest ESC guidelines.[9]

Blood sampling and multiomics analysis

In addition to standard-of-care blood tests, the GEDI-ACS registry includes a dedicated multiomics profiling panel designed to capture molecular signatures associated with different ACS subtypes in women (*Figure 1*). All enrolled patients (n = 100) will undergo the complete multiomics pipeline, which includes whole exome sequencing (WES), transcriptomics, proteomics, and metabolomics, to enable integrated analyses across the full cohort. At baseline, 15 mL of peripheral blood will be collected in ethylenediaminetetraacetic acid (EDTA) tubes using standardized protocols and processed within 4 h of collection to ensure optimal preservation of nucleic acids, proteins, and metabolites. Whole blood aliquots will be preserved for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) extraction. The remaining blood will be fractionated to obtain plasma and peripheral blood mononuclear cells (PBMCs) via Ficoll-based density-gradient centrifugation. Peripheral blood mononuclear cell aliquots will be stored in cryopreservation medium in liquid nitrogen for subsequent proteomic analyses. Plasma samples will be immediately centrifuged, aliquoted to avoid freeze–thaw cycles, and stored at −80°C.

To minimize pre-analytical variability across enrolling centres, standardized operating procedures for blood collection, processing, and shipping will be implemented at all sites. All samples will be shipped on dry ice to a single central laboratory (Institute of Molecular and Translational Cardiology, IRCCS Policlinico San Donato, San Donato Milanese) for nucleic acid extraction, library preparation, sequencing, and mass spectrometry-based analyses. Centralized processing eliminates inter-laboratory technical batch effects and ensures uniform analytical conditions across the cohort.

Genomic analysis will include WES performed on DNA extracted from whole blood using automated extraction methods (Maxwell RSC Blood DNA kit, Promega). Sequencing libraries will be prepared with standard enrichment kits (Illumina DNA Prep with Exome 2.0 Plus Enrichment kit) and sequenced to a minimum average coverage of 80–100×. Sequencing will be performed using the Illumina NextSeq 2000 platform.

Bioinformatic pipelines will follow GATK best practices (https://gatk.broadinstitute.org/hc/en-us/sections/360007226651-Best-Practices-Workflows). Variant filtering will be based on quality scores, read depth, and genotype quality. Functional annotation will be conducted using Ensembl Variant Effect Predictor (VEP), integrating ClinVar, OMIM, and CVD-specific databases. Variants will be classified according to American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) guidelines, focusing on genes associated with cardiomyopathies, channelopathies, familial hypercholesterolaemia, and thrombophilia. Rare variants will be prioritized using pathogenicity prediction tools, such as CCADD, SIFT, or PolyPhen. Genetic variants will be compared against reference population databases (e.g. gnomAD and 1000 Genomes Project) and evaluated for association with ACS phenotypes, risk factors, age at onset, and MINOCA subtypes.

Transcriptomic analysis will include bulk RNA sequencing (RNA-seq) on total RNA extracted from whole blood samples using glass fibre filter–based isolation methods (Tempus Spin RNA Isolation kit, Thermo Fisher Scientific). RNA integrity will be assessed by measuring the RNA integrity number (RIN) using the Agilent TapeStation system. Libraries will be prepared using the Illumina Stranded Total RNA Prep with ligation according to the Ribo-Zero Plus protocol. During the first step of library preparation, highly abundant ribosomal RNA will be depleted. Final cDNA library quality checks will be performed using the Agilent TapeStation system and sequenced on an Illumina NextSeq 2000 sequencer, generating paired-end 30 million reads, 75 nt long, for each sample. The sequences will be aligned to the reference human genome GRCh38/hg38 using Illumina DRAGEN RNA 4.2.7 software. Gene-level quantification will generate normalized expression values (TPM) and raw counts for differential expression analysis using established methods, such as DESeq2[19] and cell type estimation through deconvolution with methods, such as xCell[20] and Cybersortx.[21] Batch effects will be assessed and corrected when necessary. Functional enrichment analysis will be performed against Gene Ontology, Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome databases, focusing on inflammation, coagulation, oxidative stress, and lipid metabolism pathways relevant to CVD.

Proteomic profiling will be performed using mass spectrometry–based approaches. Untargeted proteomics will be conducted on plasma and PBMC lysates. Plasma samples will undergo a depletion step before processing to remove the 14 most abundant circulating proteins. Then, 100 μg of protein will be processed using the EasyPep Mini MS Sample Prep Kit according to the manufacturer's instructions. Briefly, samples will undergo reduction and alkylation by adding the respective solutions and incubating at 95°C for 10 min. After cooling, a trypsin/Lys-C protease mixture will be added, and samples will be digested for 3 h at 37°C. The resulting tryptic digests will be purified using dry Peptide Clean-up columns to remove contaminants and salts. Liquid chromatography-high resolution mass spectometry (LC-HRMS) analysis will be performed using an Ultimate 3000 RSLCnano system coupled online to a Q-Exactive Plus mass spectrometer. An appropriate volume of a 100 ng/μL solution will be injected onto a nano-high performance liquid chromatography (HPLC) column coupled to a pre-column, using a suitable chromatographic separation method. All analyses will be performed in duplicate. Data acquisition will be controlled by Xcalibur 2.11 and Tune software 4.4. Raw data will be processed using Proteome Discoverer (PD) software (version 2.5). All spectra will be submitted for protein identification to the Sequest HT search engine using the *Homo sapiens* database and a common contaminant

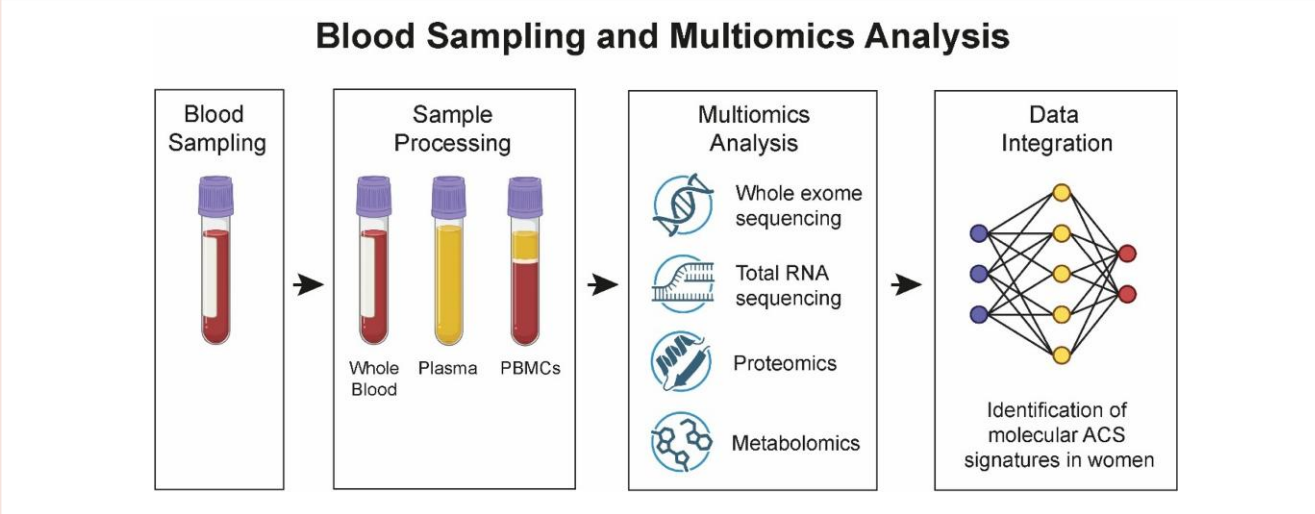


Figure 1 Blood sampling and multiomics analysis. PBMCs: peripheral blood mononuclear cells.

database from Thermo Fisher. The false discovery rate (FDR) will be set at 5%, as calculated with the Percolator algorithm in the PD workflow. The Precursor Ions Quantifier node will be used for quantification. Differential protein expression analysis will use statistical methods with FDR and fold change thresholds. Functional analysis will include pathway enrichment, focusing on the complement cascade, coagulation factors, and acute phase response.

Metabolomic analysis will be performed on plasma samples by untargeted metabolomics using ultra-high performance liquid chromatography (UHPLC)–HRMS workflows. Statistical analysis will include univariate and multivariate approaches [principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA)] with appropriate validation procedures. Discriminant metabolites will be identified based on variable importance scores and FDR-corrected significance thresholds. Pathway enrichment analysis will focus on energy metabolism, fatty acid oxidation, amino acid metabolism, and lipid pathways relevant to CVD.

Across all omics layers, potential batch effects from sample processing date, sequencing run, or mass spectrometry acquisition batch will be assessed using principal component analysis and visualization of known technical covariates. When significant batch effects are detected, correction will be applied using established methods (e.g. ComBat or limma::removeBatchEffect for expression and proteomic data and median-centring or QC-based normalization for metabolomics). Enrolling centre will be included as a covariate in all downstream differential analyses to account for residual site-level variation.

Missing values, which are inherent to mass spectrometry–based platforms, will be addressed using a combination of filtering (removing features with more than 50% missingness) and imputation. For proteomic and metabolomic datasets, missing values will be imputed using k-nearest neighbours (kNN) or minimum value imputation for left-censored patterns, as appropriate. Sensitivity analyses will be conducted to evaluate the impact of the imputation strategy on downstream results. Samples with excessive missingness across multiple omics layers will be flagged and, if necessary, excluded according to predefined quality thresholds.

To explore the molecular consequences of reperfusion, an additional 15 mL blood sample will be collected immediately after PCI in patients with occlusion of the infarct-related artery. This time point enables comparative analysis of biological markers reflecting reperfusion injury, inflammatory activation, and microvascular dysfunction.

Multiomics datasets will initially be analysed independently to identify differentially expressed genes, proteins, and metabolites, as well as potentially pathogenic genetic variants associated with ACS subtypes in women. Prior to integration, each omics dataset will undergo independent quality control, normalization, and feature filtering to ensure data quality and comparability across platforms. Integration will then be performed using a combination of dimensionality reduction, clustering, and network-based approaches, including the following:

- Multiomics factor analysis (MOFA) to identify common patterns and hidden relationships across the different omics layers, with evaluation of variance explained per factor and per dataset.
- Network-based models linking molecular features to clinical variables. Network-based integration will include construction of multiomics correlation networks, protein-protein interaction networks, and identification of key molecular hubs. Co-expression or co-regulation analysis may be applied to identify coordinated modules across different molecular layers.

Machine learning algorithms will be used to explore predictive signatures for disease severity and recovery. Machine learning approaches will include supervised methods, such as random forest, extreme gradient boosting (XGBoost), elastic net regression, and data integration analysis for biomarker discovery using latent components (DIABLO) for classification and prediction tasks using multiomics data. To ensure methodological rigour despite the limited sample size, model development will use nested cross-validation, with an outer loop for performance estimation and an inner loop for hyperparameter tuning, along with regularization techniques (e.g. elastic net regression) and stringent feature selection to mitigate overfitting and ensure unbiased evaluation. Internal split-sample validation will also be performed by reserving a held-out subset of the cohort for independent assessment of final model performance. Evaluation metrics will include area under the curve-receiver operating characteristic (AUC-ROC), sensitivity, specificity, and calibration measures (Brier score). Permutation-based null distributions will be computed to determine whether model performance exceeds chance expectation. Feature importance analysis will identify the most relevant molecular predictors and provide biological interpretability. Given the sample size, regularization techniques and feature selection methods will be applied to ensure model robustness and generalizability. Only features consistently selected

across multiple validation iterations will be retained in the final models. To control for multiple testing, FDR correction (Benjamini–Hochberg) will be applied within each omics layer for univariate analyses. For integrative analyses, methods, such as multi-omics factor analysis (MOFA) and DIABLO, inherently address the high-dimensional, multi-layer structure of the data through latent factor decomposition and regularization, reducing the effective number of independent tests. Permutation testing will be used to assess the statistical significance of integrated models and to guard against overfitting. Given the sample size (n = 100), all multiomics analyses are considered exploratory and hypothesis generating. The study is designed to identify candidate molecular signatures and biological pathways for subsequent confirmation in larger, independent cohorts, rather than to provide definitive inferential conclusions. External validation in independent ACS cohorts will be pursued as data become available and is considered a priority for translating candidate signatures into clinical practice.

Combined genomic, transcriptomic, proteomic, and metabolomic signatures will be correlated with clinical presentation, severity of coronary disease, risk factors, socioeconomic determinants, and both short- and long-term outcomes.

Study objectives

The main objectives of the GEDI-ACS registry are (i) to establish a prospective multicentre registry including women with ACS from diverse regions of Italy, capturing heterogeneity in ethnic, cultural, and geographic backgrounds; (ii) to conduct comprehensive clinical, biochemical, genetic, and molecular characterization of these patients, focusing on differences between obstructive and non-obstructive coronary phenotypes, as well as among younger women from different ethnic and regional origins; and (iii) to evaluate health literacy, awareness of cardiovascular risk factors, and socioeconomic status to identify barriers to access and continuity of optimal care across different geographic areas.

The study will also explore both established modifiable and unmodifiable cardiovascular risk factors, as well as sex-specific and often under-recognized determinants, such as pregnancy complications, menopause, and psychosocial factors, to provide novel insights into sex-related mechanisms of ACS and their impact on patient management, treatment adherence, and long-term outcomes.

Sample size and statistical analysis

Based on historical data from hospitals in Milan and Naples, women account for approximately one-quarter of patients admitted with ACS at participating centres; therefore, enrolling 100 consecutive women with ACS within 12 months is feasible. In 2022, at the Milan Centre, 247 patients were hospitalized for ACS, with 59 (23.8%) being women. Among these women, 35.6% presented with STEMI; 38.9% presented with NSTEMI; 5% were young women; and 6.7% were from other ethnicities. Similarly, at the Naples Centre in 2022, 257 ACS patients were admitted, with 63 (24.5%) being women. Among these, 76.1% presented with STEMI; 23.8% presented with NSTEMI; 5% were young women; and 1% were from other ethnicities.

This study is not hypothesis driven but will be predominantly descriptive, aimed at collecting prevalence data and demographic characteristics of women with ACS, contributing to improve understanding and management of this specific population. We will estimate the frequency of risk factors (traditional and sex-specific), clinical presentation (unstable angina, NSTEMI, and STEMI), age distribution, ethnicity, and other factors under study, calculating 95% confidence intervals (95% CIs). Categorical variables will be expressed as frequencies and percentages, and continuous variables as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Comparisons will be made using χ^2/Fisher's exact tests for categorical variables, Student's t-test or Mann–Whitney U test for continuous variables, and Mantel–Haenszel test for ordinal variables. Time-to-event outcomes (mortality and re-hospitalization) will be analysed with Kaplan–Meier survival curves and log-rank tests. Multivariable regression models will examine associations between molecular, clinical, and socioeconomic variables. Subgroup analyses based on age, ethnicity, or other relevant factors will also be conducted to assess potential differences in phenotypes, socioeconomic status, health literacy, and risk factor awareness. For metabolites, given the quantity and variability of the data, statistical analysis will be conducted at multiple levels to highlight different aspects emerging from the project.

Discussion

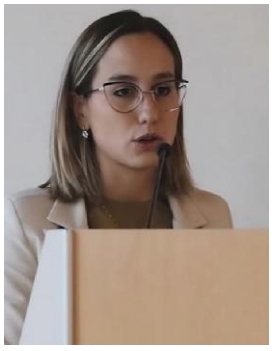
The GEDI-ACS registry represents the first prospective, multicentre registry in Italy specifically designed to investigate gender, diversity, and inclusion in women affected by ACS. Despite growing awareness of sex differences in CVD, women remain underrepresented in most studies. Existing registries and trials have primarily focused on the general population, limiting understanding of the biological, demographic, and social factors that may uniquely affect women. In recent years, international efforts have highlighted the importance of sex-specific research in cardiovascular care.[22–24] This has led to the development of dedicated studies, such as GEDI-ACS, to promote the creation of sex-specific diagnostic and therapeutic strategies. Through an integrated clinical, imaging, molecular, and psychosocial design, the registry will analyse the mechanisms underlying the heterogeneous presentation of ACS in women. Comprehensive genomic, transcriptomic, proteomic, and metabolomic profiling will also enable identification of the biological characteristics associated with different ACS presentations, ranging from obstructive to non-obstructive coronary phenotypes, thus contributing to a better understanding of the pathophysiological mechanisms of ACS in women. This multidimensional characterization will improve understanding of sex-related biological determinants and genetic variants that may predispose women to distinct clinical presentations and outcomes. Importantly, the standardized data collection and large-scale characterization are expected to ensure robust, generalizable findings, enabling interpretation of the results within a real-world context and enhancing their translational and clinical relevance. In parallel, it is equally important to focus on social and behavioural determinants of cardiovascular health, which remain insufficiently studied in female ACS populations. By systematically assessing patients' socioeconomic status, health literacy, awareness of cardiovascular risk factors, quality of life, and adherence to medical therapy, the registry will evaluate the interaction between biological and social determinants of health in women. This will enable the identification and evaluation of possible social disparities and their influence on disease management, recovery, and prognosis. This perspective reflects the growing recognition that cardiovascular outcomes cannot be explained by clinical and biological findings alone and that integrating psychosocial and environmental dimensions is fundamental to achieve optimal care and equity across genders and diverse backgrounds.[25] Integrating clinical variables with consideration of biological vulnerability and social disadvantages may help characterize patients in distinct clusters based on the risk of adverse outcomes. More generally, the study may inform the development of new diagnostic algorithms, targeted prevention strategies, and tailored therapeutic interventions for women. Moreover, the findings could support the implementation of public health initiatives to improve cardiovascular awareness, equity of access to care, and treatment adherence among women of different socioeconomic and cultural backgrounds.

Some limitations of the GEDI-ACS registry should be acknowledged. While the study focuses exclusively on female

patients, addressing their persistent underrepresentation in cardiovascular research, comparative analyses with male patients could offer additional insights. However, the primary objective of the registry is to provide an in-depth characterization of female patients with ACS, with the aim of generating robust sex-specific hypotheses that may inform the design of future comparative studies including both sexes. This targeted approach will enhance understanding of sex-related pathophysiological mechanisms and inform tailored prevention and treatment strategies. In this context, the exploratory design and small sample size may limit definitive conclusions for multiomics and machine learning analyses. In addition, the requirement for informed consent for genetic analyses and extensive biological sampling may result in some selection bias. However, it should be noted that the multi-omics analyses planned within the GEDI-ACS registry are exploratory and hypothesis generating. The study is not powered for definitive causal inference from omics data. Rather, the integration of genomic, transcriptomic, proteomic, and metabolomic data aims to identify candidate molecular signatures and biological pathways potentially associated with sex- and gender-specific ACS phenotypes, which will require validation in larger, independent cohorts.

In conclusion, by highlighting the complex interaction between biological and social factors, the registry aims to redefine women's cardiovascular health management and prevention.

Lead author biography



Dr Francesca Napoli is an early career interventional cardiologist and clinical researcher working at IRCCS San Raffaele Hospital in Milan. Her clinical and research activity focuses on ACS, with particular interest in sex-specific cardiovascular differences. She holds a PNRR-funded research contract and is involved in the GEDI-ACS registry, a prospective multicentre study supported by PNRR (PNRR-MCNT2-2023-12377431), aimed at the clinical, genetic, and molecular characterization of women with ACS. Her research integrates clinical data with advanced imaging and multiomics approaches, including genomics, transcriptomics, proteomics, and metabolomics, to support the development of personalized and inclusive strategies in interventional cardiology.

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Conflict of interest: A.C. reports speaker consultant fees from Abbott Vasc, Abiomed, Boehringer, Cordis, Penumbra, and Menarini. M.M. reports consultant fees from Abbott, Boston, Kardia, and Medtronic. A.F. reports speaker's fees from Edwards Lifesciences and Medtronic. The other authors have nothing to declare.

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