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PROGNOSIS STRATIFICATION AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN OLD PATIENTS HOSPITALIZED FOR ACUTE CORONARY SYNDROME. EVALUATION OF INFLAMMATORY MARKERS AND OXIDATIVE STRESS BIOMARKERS. Design of a prospective cohort study.

Ongoing research*Ongoing research*

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Keywords: Older patients, Myocardial infarction, Acute Coronary Syndrome, Percutaneous Transluminal Coronary Angioplasty, Revascularization, Gender, Frailty.

ABSTRACT

Introduction: Ischaemic heart disease is the main cause of death globally. It is responsible for 16% of the world's total deaths, and caused 8,9 million in 2019. Incidence in Acute Coronary Syndrome is increasing over time such as the life expectancy. An increased age in patients with coronary artery disease has been related with in-hospital mortality and it is increasing in a short period of time. In older patients who suffer an acute coronary syndrome there is no consensus in the revascularization strategy, depending on the prognosis. As differences in prognosis have not been accurately described yet. Although the population is turning older in last decades however older patients are usually excluded from the majority of clinical trials. **Methods and analysis:** Observational, longitudinal, prospective study that will include a total of 150 patients attended at the Cardiology and Cardiovascular Surgery Department. Patients will be recruited during the first year of the study. The primary exposure variable will be the revascularization strategy (complete or incomplete). The primary outcome will be a combination of: cardiovascular death, re-infarction, re-hospitalization due to cardiac insufficiency and stroke. **Ethics and dissemination:** This study was approved by the Málaga Provincial Research Ethics Committee and the Hospital's Committee. With the reference number PI 0131/2020. Previous information will be given to the patients prior signing the written informed consent for collecting any data. **Conclusions**: This observational study pretends to create predictive models to determine the appropriate revascularization type for ischaemic heart disease in aged patients who require therapeutic intervention.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

Providing evidence in a lack of knowledge in the management of the Acute Coronary Syndrome in older patients.

This prospective study will allow patients to be followed over time, and developing a predictive model of long-term prognosis layering depending on a complete *vs* incomplete revascularization in older patients with acute coronary syndrome.

It is an observational research, we cannot establish causality relations, only association between known and computed factors/ outcomes.

Participants will be recruited from a single centre.

Data and participants may be missed on recruitment or follow-up assessment.

LIST ABBREVIATIONS

ACS: Acute Coronary Syndrome

CAD: Coronary Artery Disease

CR: Complete Revascularization

CRP: C-reactive protein

CRUSADE: Can Rapid risk stratification of Unstable Angina patients Suppress Adverse outcomes with early implementation of the ACC/AHA guidelines

EKG: Electrocardiogram

GRACE: Global Registry of Acute Coronary Events

ICR: Incomplete Revascularization

LBBB: Left Bundle Branch Block

MACE: Major Adverse Cardiac Event

MVD: Multivessel Disease

NSTE-ACS: Non ST- Segment elevation acute coronary syndrome

PCI: Percutaneous Coronary Intervention

PTCA: Percutaneous Transluminal Coronary Angioplasty

STE-ACS: ST- Segment elevation acute coronary syndrome

STEMI: ST- Segment elevation acute myocardial infarction

INTRODUCTION

Ischaemic heart disease is the main cause of death globally. It is responsible for 16% of the world's total deaths, and caused 8,9 million of deaths in 2019. (1) An increased age in patients with coronary artery disease has been related with hospital mortality in a short period of time. (2) The 14,52 % of population in Spain is >70 years old, and it is estimated that 27,4% of patients with ischaemic heart diseases are between 70 and 80 years old. (3)

Patients with ischaemic heart disease usually present a multi-vessel CAD (Coronary Artery Disease), and they will be classified by the revascularization strategy into two groups: complete or incomplete percutaneous transluminal coronary angioplasty (PTCA). Complete revascularization (CR) can be defined as the revascularization of all the coronary artery lesions with ≥1.5 mm diameter and ≥70 % stenosis. As previously described, incomplete revascularization (ICR) will be defined as the revascularization of at least one coronary artery lesion, with ≥1,5 mm and ≥ 70% stenosis when there exists a multivessel disease, leaving any untreated lesion. (4)

In patients with MVD (Multivessel Disease), some studies have shown mild rates of death, MACE (Major Adverse Cardiac Event) and repeated revascularization in patients with CR in comparison with ICR. Patients with MVD (Multivessel Disease) and ST elevation who underwent primary PCI (Percutaneous Coronary Intervention) had more MACE and death than patients with single-vessel disease and STEMI (ST- Segment elevation acute myocardial infarction). (4) Moreover, the anatomical location of the coronary lesion is also prognostic of clinical outcome. (5)

It has been shown that coronary artery disease's severity, ischaemia grade and acute hemodynamic deterioration are treatable risks. While prior myocardial damage, ageing, chronic kidney dysfunction and other comorbidities are not treatable risks. There exist considerable differences between patients older than 70 years old hospitalized with (NSTE-ACS, STE-ACS) and general population. (6) Older patients with coronary artery disease usually show differences compared to younger patients; with a higher rate of all cause-mortality, stroke, myocardial infarction, bleeding and unplanned revascularization, less chest pain, more dyspnoea, nausea and syncope. Thereby, the treatment should not be the same in different age groups, and the practitioner must value the risk-benefit for using any procedure. (7)

Geriatric syndrome includes frailty, comorbidity and disability. (8) The accumulation of molecular and cellular damages due to regulation mechanisms, causes ageing. Frailty is characterized by vulnerability to the adaptation of homoeostasis after a stress event. It is as well associated with adverse health outcomes, which relates with prognosis and vulnerability in older patients. Frailty is the most common cause of death in aged patients (27,9%), and it is related with hospitalization, falls, care home admission, and mortality. It has although an influence in the clinical evolution in older patients, and it is an important factor for evaluating and analysing treatment strategies. (8, 9) Furthermore, older patients are usually excluded from the majority of randomized clinical trials, which make the basis of clinical guidelines.

Inflammatory and oxidative systemic states are common in metabolic, cardiovascular and neurodegenerative diseases, increasing in older patients. (10) Some pro-inflammatory markers as cytokines TNF-α or IL-1β, which are responsible of the expression of the CRP (C-reactive protein) and the production of cortisol, show sex differences. Pro-inflammatory markers in cardiovascular diseases, can predict some outcomes in women. Especially when menopause occurs, associated with hormonal changes. (11, 12)

Previous studies have established a prognosis stratification in ischaemic heart disease for percutaneous transluminal coronary angioplasty (PTCA). A systematic review about it in multivessel coronary artery disease, showed that the CR was associated with less mortality risk and MACE. (13) Other study showed that in old patients with NSTE-ACS who underwent a revascularization during the hospitalization, it has been shown a relation with less mortality in one year. Although, if the patient has comorbidities, the benefit is not that big. (14)

These studies usually have specific samples, and do not include patients older than 70 years because of added health complications. So there exists a lack in the evidence knowledge in older patients. (15) The present project is focused in the elderly, who require a higher assistance because of a higher life expectancy, also having high cardiovascular diseases prevalence.

The aim of this study is to establish a cardiovascular prognosis stratification in old patients with acute coronary syndrome and multivessel disease. This prognosis stratification would integrate inflammatory and oxidative stress markers with clinical, angiographic and metabolic variables in elderly patients taking account of gender differences, and a precision medicine. It will have a direct impact on quality of life in these patients.

Given that it is difficult to establish a generalization, there exist many limitations in a randomized controlled trial when comparing the outcomes of CR and ICR, specially concerning ethical issues. However, there is no consensus in deciding a method, due to a lack of clinical trials addressing this topic. Ethical considerations in randomizing patients into one or another treatment strategy has been a concerning issue. For this reason, an observational focus may be of interest to determine whether the prognosis can be different in older patients.

METHODS AND ANALYSIS

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Participants

In this longitudinal cohort study, will be recruited older participants who assist Virgen de la Victoria's Hospital because of an ischemic heart disease and who will undergo a coronary revascularization. Inclusion criteria will be: men and women ≥70 years old. Hospitalized because of an acute coronary syndrome (NSTE-ACS, STE-ACS) with multivessel disease (severe stenosis >70% in ≥ 2 coronary arteries over 2.5 mm diameter) who underwent PCI. (14) Patients must accept and sign the informed consent.

Exclusion criteria: Life expectancy under 1 year, not signing the informed consent, not having a legal representative if needed, not being able to complete any questionnaire, not having a fixed place of living, or not being able to go to the 6 month's monitoring.

Study Outcomes

The primary aim of the study is to establish a prognosis layering in older patients (≥70 years old) with ischaemic heart disease. Evaluating differences in prognosis according to clinical characteristics as sex, previous comorbidities and frailty as well as treatment strategies

(complete or incomplete coronary revascularization). As a secondary outcome, we will evaluate the patient's inflammatory status and the clinical, angiographic and metabolic variables that seem sensitive and specific for the evolution after the initial therapeutic approach and the monitoring. A key factor to be analysed will be the decision of a complete versus an incomplete revascularization, which is the primary exposure variable.

STUDY DESIGN AND EVOLUTION

This observational, longitudinal, and prospective study is taking the entry phase in the first year of the study. The first patient was included in June 2021. It is expected to end the inclusion period by March 2022. The 6 month follow-up is expected to end in September 2022.

Primary outcome

Patients attending the Cardiology and Cardiovascular Surgery Service in the Virgen de la Victoria University Hospital and who meet the criteria will be invited to participate. Patients will be followed for 18 months.

The follow-up information will be obtained at the visit 6 months after the selection. A blood sample will be collected, also will have some life habits, dependence, and life related questionnaires to answer and an EKG. Also, any problem related to health during the 6 months, will be recorded.

Study Variables

Demographic, clinical and angiographic variables will be recorded.

Baseline demographic and anthropometric variables. We take into account: gender, weight and height, BMI, educational level, cohabitation, smoking situation.

Clinical and angiographic variables include comorbidities such as arterial hypertension, dyslipidaemia or diabetes.

Also include others like presentation (NSTE-ACS, STE-ACS),ventricular ejection fraction, coronagraph result with classic classification, Syntax Score for evaluating the complexity of coronary artery lesions, medical treatment at hospital and at home and revascularization type, number of lesions, tortuosity, bifurcation, long, diffuse

Inflammatory biochemistry and Oxidative stress variables

We will study some parameters such as ELISAs: Cytokine proinflammatory (IL-6, IL-1β y TNF-α), chemokines CX3CL1/fractalkine, C - reactive protein (CRP); and oxidative stress markers as glutathione concentration (GSH), oxidized glutathione (GSSG), total glutathione (GT) and Malondialdehyde (MDA).

Also we will record parameters such as creatinine clearance, troponins or ACE.

Statistical Analysis

Continuous variables will be studied with mean +/- SD, categorical ones as proportions.

Descriptive and exploratory analysis will study measures of central tendency and dispersion or percentages. For evaluating the normal distribution, it will be used kurtosis, asymmetry and Kolmogorov-Smirnov test. In normally-distributed variables, Chi square test will be used for bivariate analysis, and for bivariate analysis in continuous variables for independent samples, it will be performed using Student`s t test. In case, the distribution is not normal, it will be used Mann- Whitney U test and Wilcoxon test as non- parametric tests. For multivariate analysis,

ANOVA will be used for determining relations between quantitative and qualitative variables, with central robustness analysis if there is no homoscedasticity (proved by Levene test). For all parameters, the precisions will be estimated with confidence intervals at 95%. Statistical analysis will be performed using SPSS 24.

Sample Size Calculation

We estimated a total of 150 patients for the study. The calculation assumes 5 alpha and 20 beta errors respectively.

Database recording

Data will be recorded and analyzed using SPSS 25. Personal data will be anonymized

Data from the health digitized history, interview and questionnaires will be recorded by a nurse and physicians. Data from the PTCA, as the syntax score or the injury characteristics will be filled in by two hemodynamicist, and if needed, there will be a third one.

Clinical questionnaires

Patients will fill several questionnaires in the basal and the monitoring follow-up as Frail (frailty), Charlson Index (comorbidity), dependence (Barthel Index), Instrumental disability (Lawton-Brody scale), alcohol consumption (Audit test), cognitive decline (Pfeiffer Scale) and Quality of Life related to health (SF-36). GRACE (Global Registry of Acute Coronary Events) and CRUSADE bleeding score (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines).

Blood samples

Blood samples will be collected by venepuncture using 2 tubes of 10 ml of blood, BD Vacutainer with K2 EDTA by a nurse. Each blood drawn will be centrifuged in 2200 x G 4 ºC during 15 minutes to obtain plasma. Samples will be stored at -80ºC for further analysis.

ETHICS AND DISSEMINATION

The present study was authorized by the Málaga Provincial Research Ethics Committee and the Hospital's Committee. Patients must have received previous information and written, informed consent to participate will be obtained from all participants. All data will be stored segregated and will be anonymized. The study will be conducted in accordance with the Declaration of Helsinki and its ethical principles for research. All data will be treated respecting the Organic Law 3/2018: Personal Data Protection, and the Law 41/2002 of 14 November: Patient Autonomy and Rights and Obligations of Information and Clinical Documentation.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

Clinical implications

The aim of the present study is to make a prognosis layering in elderly patients presenting with ischaemic heart disease. Our goal is to create a useful tool to guide and support clinicians in surgical acting, avoiding important risks and complications that could be secondary to complete vs incomplete revascularization.

AUTHOR STATEMENT

M.J.-N, F.J.P.-M and J.R.-C. conceived the original idea. A.D.M.C-S and M.J.-N wrote the paper with input from all authors. M.J.-N, A.D.M.C-S, M.V.D.-A, V.M.B.-M, F.J.P.-M, J.R.-C, F.S.-P, M.J.S.-Q, M.F.-L, D.M.-V, A.I.M.-R, A.G.-M, L.G.-R and L.P.-M are contributing to the development of the research. All authors have read and agreed to the published version of the manuscript.

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Prognostic stratification of older patients with multivessel coronary artery disease treated with percutaneous transluminal coronary angioplasty based on clinical and biochemical measures: Protocol for a prospective cohort study

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Protocol

Prognostic stratification of older patients with multivessel coronary artery disease treated with percutaneous transluminal coronary angioplasty based on clinical and biochemical measures: Protocol for a prospective cohort study

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ABSTRACT

Introduction: The incidence of acute coronary syndrome is rising in step with the growth of life expectancy. An increase in the age of patients with coronary artery disease has been related to in-hospital mortality, which has seen an upsurge over a short period of time. However, there is no consensus about the percutaneous coronary angioplasty strategy to follow for older patients with multivessel coronary artery disease (MVCAD). Complete (CR) or incomplete (ICR) revascularization strategy depends on prognosis but this has not yet been accurately described because of geriatric conditions and comorbidities. The aim of this study is to evaluate changes of clinical and biochemical parameters in older patients with MVCAD undergoing revascularization and to establish a prognostic stratification model for CR and ICR.

Methods and analysis: This observational, longitudinal, prospective study will include 150 patients with MVCAD and subsequent revascularization who attend the Hospital Universitario Virgen de la Victoria (Málaga, Spain). Because of the dropout rates, 180 patients will be recruited at the beginning. Sociodemographic characteristics, clinical and angiographic parameters, and biochemical variables, such as cardiovascular, metabolic, inflammatory, stress oxidative biomarkers, will be collected in the admission for coronary revascularization and three follow-ups at 6, 12 and 18 months. Statistical analyses will be conducted with these data using CR and ICR as the primary exposure variable. Relevant explanatory variables will be selected from a predictive model for their inclusion in a prognostic stratification model. The primary outcome measures will be major adverse cardiovascular events.

Ethics and dissemination: Protocols and patient information have been approved by the regional research ethics committee (CEIm Provincial de Málaga-PEIBA (PI0131/2020). The results will be disseminated in international peer-reviewed journals,

presented at conferences in Cardiology and Gerontology, and sent to participants, medical and health service managers, clinicians and other researchers.

KEYWORDS: Aging, Acute Coronary Syndrome, Ischemia, Multivessel Coronary Artery Disease, Revascularization, Geriatric Syndromes, Inflammation, Oxidative Stress.

Word count: 2,556

STRENGTHS AND LIMITATIONS OF THIS STUDY

• This study will collect a comprehensive range of clinical and biochemical data from older patients with multivessel coronary artery disease treated with percutaneous coronary angioplasty to compare complete and incomplete revascularization strategies.

• Because this prospective study will allow follow-up patients over time, relevant explanatory data will be analyzed to develop predictive models for both revascularization strategies with the objective of establishing a prognostic stratification.

• Causality cannot be established between outcomes because this is an observational research and we will be unable to control for all confounding factors, only associations between outcomes will be explored.

• All participants will be recruited from a single center, which affects the sample size and restricts the extrapolation of results to other populations, but the decision making of the clinicians for complete or incomplete revascularizations will be more uniform than in a multicenter-study.

• The COVID-19 pandemic and the health system saturation risk may produce high rates of delay and loss of follow-up in the study because older population are more likely to develop severe illness by SARS-CoV-2.

INTRODUCTION

Ischemic heart disease is the main cause of death globally. It is responsible for 16% of the world's total mortality and caused 8.9 million deaths in 2019.[1] The progressive increase of age of patients with coronary artery disease, such as angina, myocardial infarction and cardiac arrest, has been related to in-hospital mortality over a short period of time. In Spain, 14.2 percent of the population is ≥70 years old, and it is estimated that 27.4 percent of patients with ischemic heart diseases are between 70 and 80 years of age.[2]

Despite their demographic importance, older adults are usually excluded or underrepresented in most clinical trials and large studies of cardiovascular diseases because of the high prevalence of comorbidities (e.g., psychiatric disorders, metabolic diseases such as diabetes mellitus, cancer and chronic inflammatory diseases) and the presence of geriatric syndromes (e.g., frailty, falls, pressure ulcers, cognitive impairment, delirium, mood disorders, polypharmacy, and urinary incontinence), which are related to a worse quality of life with high rates of hospitalization, disability and mortality.[3-5] Furthermore, several lines of evidence demonstrate that dysregulation of the regulation of energy metabolism occur during aging and contribute to low-grade inflammation and oxidative stress.[6-7] This systemic dysregulation in major molecular processes has adverse effects on the structure and function of the cardiovascular system, among others.[7-8] Therefore, the scientific evidence for this group of the population is quite limited and the current management in clinical practice is usually carried out on the basis of studies in younger patients and the experience of the doctors, which causes a great variability in the prognosis and therapeutic approaches of ischemic heart diseases.

There are considerable differences between older patients hospitalized for acute coronary syndrome [ST and non-ST segment elevation acute coronary syndromes

(STE-ACS and NSTE-ACS)] and the general population. Thus, older patients with ischemic heart diseases present particular clinical and electrocardiographic characteristics that affect their prognosis relative to younger patients. Specifically, there is higher rate of all cause-mortality, stroke, myocardial infarction, bleeding and unscheduled revascularization, atypical symptoms (e.g., lower percentage of chest pain and more dyspnea), syncope, vegetative alterations (e.g., arterial hypotension and sweating), nausea and/or confusion.[9-10] Regarding electrocardiographic manifestations, older patients show high prevalence of repolarization disorders, left ventricular hypertrophy, left bundle branch block (LBBB) and atrial fibrillation.[9 11-12]

An important point is that older adults with ischemic heart disease usually present multivessel coronary artery disease (MVCAD), which makes treatment difficult because of the complex coronary anatomy and differences in the severity and extension of the coronary artery disease in these vessels.[13-14] In fact, patients with MVCAD show major adverse cardiac events (MACE) such as heart failure, reinfarction, stroke, hospitalization for cardiovascular-related illness, unscheduled revascularization and all-cause death and mortality. A critical step is to decide the most appropriate strategy for revascularization through percutaneous transluminal coronary angioplasty (PTCA). While a complete revascularization (CR) treats all hemodynamically significant coronary artery lesions, an incomplete revascularization (ICR) treats the culprit-lesion-only when MVCAD exists, leaving any untreated lesion.[13 15-16] However, the main limitation is the lack of uniformity in the definition of both revascularization strategies because there is no consensus on relevant angiographic criteria related to the functional and anatomical relevance of the coronary lesions [e.g., coronary segment diameter (≥1.5 mm to ≥2.5 mm), diameter stenosis (≥50% to ≥70%)].[17] There is greater evidence that CR is associated with reduced risk of mortality and MACE, and this magnitude of risk relates to degree of CR.[18] In contrast, these observations with CR are much more limited in older patients because comorbidities progressively reduce the

revascularization benefit.[19-20] Because of the lack of consensus on angiographic criteria and clinical guidelines for the coronary revascularization strategy in older patients, the decision-making is complex, variable and open to considerable influence from human factors.[13 21]

Several determining factors may participate in the prognosis of older patients with MVCAD undergoing PTCA. The present study will be focused on clinical and biochemical measures associated with the dysregulation of physiological processes that is observed during aging, which causes declining adaptive homeostasis, low-grade inflammation and oxidative stress.[7 22] Because we hypothesize that these measures are susceptible to change over time, clinical data linked to geriatric syndromes, comorbidities and MVCAD (e.g., patient health records and angiographic parameters) will be analyzed in combination with cardiovascular (e.g., cardiac T/I troponins, NT-proBNP, soluble ST2 and CKMB) metabolic (e.g., glucose, transaminases, lipoproteins and urea), inflammatory [i.e., cytokines (e.g., TNF-α, IL-1β and IL-6), chemokines (e.g., IL-8/CXCL8, fractalkine/CX_3CL1) and others (e.g., C-reactive protein)] and stress oxidative (e.g., GSH, GSSG, MDA, oxidized LDL and MPO) biomarkers.[23-25] Lastly, sexual dimorphism is common in the expression of these biomarkers, mainly in pro-inflammatory and oxidative stress biomarkers.

This study aims to evaluate changes over time of a comprehensive range of sociodemographic/anthropometric, clinical and biochemical data from older patients with MVCAD treated with coronary revascularization through PTCA. Subsequently, relevant explanatory variables will be selected to develop a first predictive model based on MACE as primary outcome with the objective of establishing a reliable prognostic stratification for CR and ICR strategies.

There is no consensus on which revascularization strategy is more recommendable for older patients with MVCAD because of the lack of clinical trials addressing this

question. Given that a randomized controlled trial to compare outcomes of CR and ICR presents important ethical issues related to the random distribution of patients into one or another treatment group, an observational study will be of great utility to collect parameters and evaluate their validity in the prognosis of PTCA strategies in patients with MVCAD. Furthermore, a single-center study will allow that the decision-making procedures of clinicians are uniform.

METHODS AND ANALYSIS

1 Study design

This prospective, observational, longitudinal study consists of three main in-person stages: 1) Patient recruitment during the first year; 2) six-month follow-up; and 3) twelve-month follow-up. Finally, an 18-month follow-up will conclude with a phone contact to assess health status using clinical questionnaires. Participants will finish the study after a MACE or the completion of follow-ups (primary endpoints). A schematic summary is shown in **Figure 1**.

2 Participants and eligibility criteria

2.1 Participants

Eligible volunteers with MVCAD who will undergo a coronary revascularization will be recruited from the Department of Cardiovascular Surgery and Cardiology in the Hospital Universitario Virgen de la Victoria (Málaga, Spain). The first patient was included in June 2021.

2.2 Eligibility criteria

1) Inclusion criteria: Men and women, 70 years and older (older adults) upon admission to the hospital, hospitalization for acute coronary syndrome (NSTE-ACS and STE-ACS), diagnosis of MVACD (criteria: ≥2 coronary arteries with ≥2.0 mm segment diameter and ≥70% diameter stenosis), treatment with revascularization using PTCA, and signed informed consent.

2) Exclusion criteria: Life expectancy less than 1 year, refused informed consent, decisional impairment with no legally authorized representative, inability to complete

questionnaires or interviews, inability to contact for follow-up or non-English/non-Spanish speaking.

3 Sample size and power calculation

The sample size was calculated using MACE as the primary outcome measures. Previous studies in older patients with MVCAD have revealed significant differences between CR and ICR groups in the primary outcome measures after a 12-month follow-up. Specifically, 20-30% of MACE in the ICR group and 5-10% of MACE in the CR group [i.e., Hazard ratio (HR) $_{ICR/CR}$ = 3.3].[26-27] In addition, dropout rates of 10-20% have been reported in prospective studies evaluating ischemic heart disease.[28]

Considering these preceding observations, the statistical parameters that were used to calculate the sample size for two independent groups (CR and ICR) were as follows: Type I error (α) = 0.05, power (1-β) = 0.8 and hazard ratio (HR) = 3.3. The calculation revealed that the minimum number of participants for adequate study power was 138 patients, which is concordant with the historical records of older adults admitted to our hospital with coronary artery disease. Therefore, we aim to ensure a sample size of 150 older patients through the recruitment of 180 participants at the beginning of the study.

4 Data collection and variables

Relevant sociodemographic, anthropometric and clinical measures of the participants will be obtained through the electronic health records (DIRAYA, Servicio Andaluz de Salud - Junta de Andalucía). Clinical data related to geriatric syndromes (e.g., frailty), comorbidity, disability, MVCAD and revascularization (e.g., angiographic and electrocardiographic measures) will be obtained using questionnaires, interviews and cardiologic procedures. In addition, biochemical variables (e.g., inflammatory

biomarkers) will be obtained through different laboratory techniques such as selective enzyme-linked immunosorbent assay (ELISA) and multiplex immunoassays.

4.1 Clinical questionnaires

Patients will complete various questionnaires and interviews at the baseline and follow-ups under supervision by trained and experienced staff:

The 5-item FRAIL scale (Fatigue, Resistance, Ambulation, Illness and Loss of weight) for frailty; Charlson Comorbidity Index predicts 10-year survival in patients with multiple comorbidities; the 10-item Barthel Index measures performance in activities of daily living; the Lawton-Brody scale measures instrumental activities of daily living; the 10-item AUDIT (Alcohol Use Disorders Identification test) for alcohol-related problems; the Pfeiffer SPMSQ (Short Portable Mental Status Questionnaire) for cognitive decline; the SF-36 (36-item Short Form survey) for quality of life related to health; the GRACE risk score (Global Registry of Acute Coronary Events) estimates admission-6 month mortality for patients with acute coronary syndrome; and the CRUSADE bleeding score (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) estimates major bleeding risk in patients with acute coronary syndrome.

4.2 Collection of blood samples

Blood extractions will be collected by experienced nurses at the baseline and follow-up stages. Venous blood will be extracted into two 10-mL K_2 EDTA tubes (BD, Franklin Lakes, NJ, USA) and centrifuged at 1,200xg for 10 minutes (4°C) to obtain plasma. Plasma samples will be aliquoted into 0.5 mL tubes and immediately encoded and stored at -80°C until biochemical determinations.

4.3 Variables

- *Sociodemographic and anthropometric variables* (e.g., age, ethnicity, sex, body mass, index, educational status, marital status, family size and socioeconomic status).

- *Clinical variables* [e.g., cardiovascular risks (e.g., arterial hypertension, dyslipidemia, smoking and chronic inflammatory diseases such as diabetes) and variables related to quality of life and geriatric syndromes (e.g., frailty, comorbidity, functional and cognitive disability, polypharmacy and use of psychoactive substances)

- *Cardiovascular variables related to MVCAD and revascularization* [e.g., acute coronary syndrome (STE-ACS and NSTE-ACS), revascularization (CR and ICR), electrocardiographic evolution (T waves, R-waves and ST-segment), ventricular ejection fraction, angiographic variables (e.g., diameters, stenosis), SYNTAX score for evaluating the complexity of coronary artery lesions (e.g., dominance, total occlusion, trifurcation, bifurcation, aorto-ostial lesion, severe tortuosity, length >20 mm, heavy calcification, thrombus and diffuse disease) and in-hospital and domiciliary care and pharmacological treatments.

- *Biochemical markers*: a) Cardiovascular [e.g., cardiac troponins (cTnT and cTnI), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), soluble suppression of tumorigenicity (ST2) and creatine kinase MB isoenzym (CKMB)]; b) Metabolic (e.g., glucose, transaminases, lipoproteins and urea); c) Inflammatory [i.e., cytokines (e.g., TNF-α, IL-1β and IL-6), chemokines (e.g., IL-8/CXCL8, fractalkine/CX_3CL1) and others (e.g., C-reactive protein)]; and stress oxidative [e.g., reduced and oxidized glutathione (GSH and GSSG), malondialdehyde (MDA), oxidized LDL and myeloperoxidase (MPO)] biomarkers.

4.4 Primary outcome

The primary outcome measures will be a combination of MACE: heart failure, reinfarction, stroke, hospitalization for cardiovascular-related illness, unscheduled revascularization, and all-cause mortality. Otherwise, older patients will complete the study to the 18-month follow-up. Severe changes in the quality of life, geriatric syndromes and disability will be examined as secondary outcome measures.

5 Statistical Analysis

Descriptive variables will be expressed as the number and percentage of subjects [n (%)], mean and standard deviation (mean ± SD), or median and interquartile range [median (IQR)]. The significance of differences in categorical and continuous variables between the revascularization groups (CR and ICR) will be determined using the chi-square test and Student's t-test (normal distribution) or Mann-Whitney U test (non-normal distribution), respectively.

Correlation analyses between quantitative variables will be performed using the correlation coefficients of Pearson (*r*) and Spearman (rho) with continuous and categorical variables, respectively to determine the association and dependency between explanatory variables.

Multivariate analyses such as analyses of covariance (ANCOVA) will be performed to evaluate the main effects and interaction of dependent categorical variables (e.g., revascularization strategy and occurrence of MACE) on explanatory variables (e.g., clinical and biochemical variables) while controlling covariates. Levene's test will be used to test the homoscedasticity of the independent explanatory variables and $\log_{10}$-transformation will be used for positively skewed distributions.

Cox proportional-hazards models and binary logistic regression models will be constructed with independent exploratory variables as predictors of primary and secondary outcomes and/or revascularization strategy. Receiver operating characteristics (ROC) analyses will be performed to evaluate the discriminative power of these regression models through the area under the curve (AUC). A final model will include the most predictive clinical and biochemical variables to distinguish older patients with CR and ICR. The identification of these predictive variables will help with the prognostic stratification of patients with MVCAD who need a PTCA.

All statistical analyses of the database will be performed using IBM SPSS Statistics version 24 (IBM, Armonk, NY, USA). A *p*-value <0.05 will be considered statistically significant.

CONCLUSION

In summary, there have been numerous studies focused on the establishment of a prognostic stratification of patients with ischemic heart disease who require angioplasty or percutaneous coronary revascularization. However, these studies are inconclusive because of different factors (e.g., very specific study samples, limited inclusion of parameters, and exclusion of older patients with health complications). This study focuses on the elderly population, whose demand for care is increasing rapidly in parallel to the life expectancy and the high prevalence of cardiovascular diseases. This research intends to identify, characterize and integrate metabolic, inflammatory and oxidative biomarkers with clinical and cardiovascular factors in older patients taking into account sex differences. This information will contribute to improving the prognostic stratification of patients diagnosed with MVCAD who need treatment with percutaneous

CR or ICR. The ultimate goal of this study is contribute to improve the welfare and quality of life of older adults in modern society.

ETHICS AND DISSEMINATION

1 Ethics

The study has been approved by the regional research ethics committee (the CEIm-Provincial de Málaga and the Portal de Ética de la Investigación Biomédica de Andalucía-PEIBA) (Id. PI0131/2020) in accordance with the Ethical Principles for Medical Research Involving Human Subjects adopted in the Declaration of Helsinki by the World Medical Association (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Regulation (EU) 2016/679 of the European Parliament and of the Council 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). In Spain, the Law 41/2002 on regulating patient autonomy and rights and obligations regarding clinical information and documentation; and the Organic Law 3/2018 on the protection of personal data and guarantee of digital rights. Written informed consents were obtained from each participant after a complete description of the study. All the participants will have the opportunity to discuss any questions or issues. All collected data and samples will be registered and stored with alphanumeric codes in order to maintain privacy and confidentiality.

2 Dissemination

The proposed study is based on two issues that are of special interest to society, but also to the scientific community: Aging and Heart Disease. The results will be disseminated in international peer-reviewed journals, presented at conferences in Cardiology and Gerontology, and sent to participants, medical and health service managers, clinicians and other researchers. Additional activities will contribute to the

divulgation of relevant results in social networks and education/research institution websites [Universidad de Málaga (https://www.uma.es); CIBERCV (https://www.cibercv.es); IBIMA (http://www.ibima.eu); and Hospital Universitario Virgen de la Victoria (http://www.huvv.es).

CONTRIBUTORS

The study concept and design was conceived by FJPM and MJN. Patient recruitment process and collection of clinical data are performed by ADMCS, MVDA, VMBM, JRC and AIMR. Angiographic data are collected by FSP, MAG, LGR and LPM. Questionnaires and interviews are designed and applied by ADMC and MFL. Biochemical determinations in blood samples are performed by FJPM, MJSQ, DMV and REB. Statistical analyses are conducted by VMBM, JMMA, FJPM and MJN. ADMCS prepared the first draft of the manuscript. All authors critically read, edited and approved the final manuscript and approved the submitted version.

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COMPETING INTERESTS

The authors declare no conflict of interest.

PATIENT AND PUBLIC INVOLVEMENT

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

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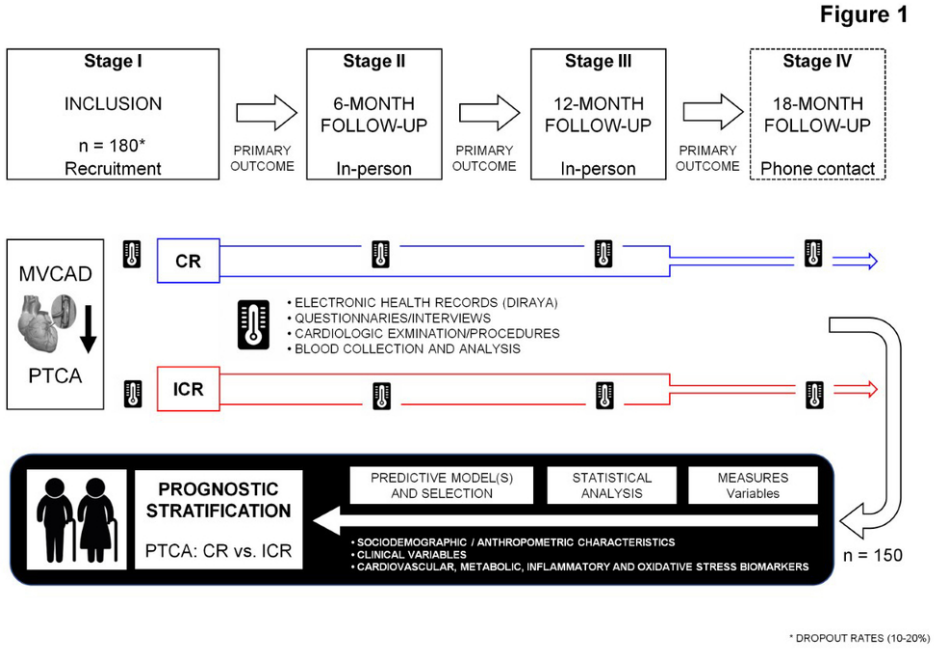
FIGURE LEGEND

Figure 1. Schematic representation of the study design. Abbreviations: MVCAD = multivessel coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty; CR = complete revascularization; ICR = incomplete revascularization.



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