




# BMJ Open 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

Ada del Mar Carmona-Segovia <sup>1,2</sup>, María Victoria Doncel-Abad,<sup>1,2</sup>  
 Víctor M Becerra-Muñoz <sup>1,2,3</sup>, Jorge Rodríguez-Capitán,<sup>1,2,3</sup>  
 Fernando Sabatel-Pérez,<sup>2</sup> María Flores-López,<sup>1,4</sup> María José Sánchez-Quintero,<sup>1,2,3</sup>  
 Dina Medina-Vera <sup>1,2,4</sup>, Ana Isabel Molina-Ramos,<sup>1,2,4</sup> Rajaa El Bekay,<sup>1,5,6</sup>  
 José Miguel Morales-Asencio,<sup>1,7</sup> María Angullo-Gómez,<sup>2</sup> Luis García-Rodríguez,<sup>2</sup>  
 Lucía Palma-Martí,<sup>2</sup> Francisco Javier Pavón-Morón,<sup>1,2,3,4</sup>  
 Manuel F. Jiménez-Navarro<sup>1,2,3</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Francisco Javier Pavón-Morón;  
 javier.pavon@ibima.eu and  
 Dr Manuel F. Jiménez-Navarro;  
 mjimeneznavarro@uma.es

## 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 revascularisation (CR) or incomplete revascularisation (ICR) 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 revascularisation 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 revascularisation 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 revascularisation 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 (PIO131/2020)). The results will be disseminated in international peer-

## 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 revascularisation (CR) and incomplete revascularisation (ICR) strategies.
- Because this prospective study will allow follow-up patients over time, relevant explanatory data will be analysed to develop predictive models for both revascularisation 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 centre, which affects the sample size and restricts the extrapolation of results to other populations, but the decision-making of the clinicians for CR or ICR will be more uniform than in a multicentre 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 populations are more likely to develop severe illness by SARS-CoV-2.

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

## INTRODUCTION

Ischaemic 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.<sup>1</sup> 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% of the population is  $\geq 70$  years old, and it is estimated that 27.4% of patients with ischaemic heart diseases are between 70 and 80 years of age.<sup>2</sup>

Despite their demographic importance, older adults are usually excluded or under-represented in most clinical trials and large studies of cardiovascular diseases because of the high prevalence of comorbidities (eg, psychiatric disorders, metabolic diseases such as diabetes mellitus, cancer and chronic inflammatory diseases) and the presence of geriatric syndromes (eg, 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 hospitalisation, disability and mortality.<sup>3–5</sup> Furthermore, several lines of evidence demonstrate that dysregulation of the regulation of energy metabolism occur during ageing and contribute to low-grade inflammation and oxidative stress.<sup>6,7</sup> This systemic dysregulation in major molecular processes has adverse effects on the structure and function of the cardiovascular system, among others.<sup>7,8</sup> 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 ischaemic heart diseases.

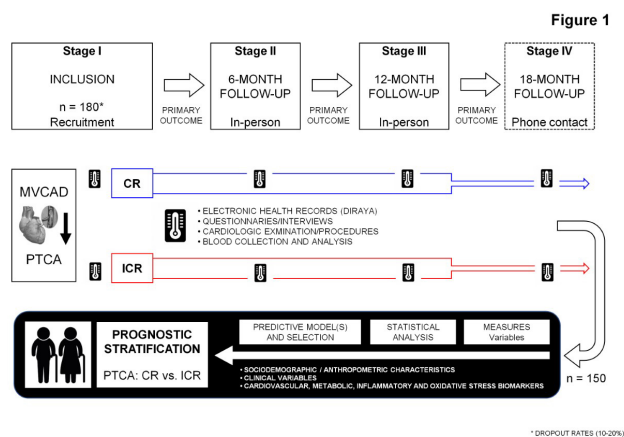
There are considerable differences between older patients hospitalised for acute coronary syndrome (ST and non-ST segment elevation acute coronary syndromes (STE-ACS and NSTEMI-ACS)) and the general population. Thus, older patients with ischaemic heart diseases present particular clinical and electrocardiographic characteristics that affect their prognosis relative to younger patients. Specifically, there is a higher rate of all cause-mortality, stroke, myocardial infarction, bleeding and unscheduled revascularisation, atypical symptoms (eg, lower percentage of chest pain and more dyspnoea), syncope, vegetative alterations (eg, arterial hypotension and sweating), nausea and/or confusion.<sup>9,10</sup> Regarding electrocardiographic manifestations, older patients show high prevalence of repolarisation disorders, left ventricular hypertrophy, left bundle branch block and atrial fibrillation.<sup>9,11,12</sup>

An important point is that older adults with ischaemic 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.<sup>13,14</sup> In fact, patients with MVCAD show major adverse cardiac events (MACE) such

as heart failure, reinfarction, stroke, hospitalisation for cardiovascular-related illness, unscheduled revascularisation and all-cause death and mortality. A critical step is to decide the most appropriate strategy for revascularisation through percutaneous transluminal coronary angioplasty (PTCA). While a complete revascularisation (CR) treats all haemodynamically significant coronary artery lesions, an incomplete revascularisation (ICR) treats the culprit-lesion-only when MVCAD exists, leaving any untreated lesion.<sup>13,15,16</sup> However, the main limitation is the lack of uniformity in the definition of both revascularisation strategies because there is no consensus on relevant angiographic criteria related to the functional and anatomical relevance of the coronary lesions (eg, coronary segment diameter ( $\geq 1.5$  mm– $\geq 2.5$  mm), diameter stenosis ( $\geq 50\%$ – $\geq 70\%$ )).<sup>17</sup> 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.<sup>18</sup> In contrast, these observations with CR are much more limited in older patients because comorbidities progressively reduce the revascularisation benefit.<sup>19,20</sup> Because of the lack of consensus on angiographic criteria and clinical guidelines for the coronary revascularisation strategy in older patients, the decision-making is complex, variable and open to considerable influence from human factors.<sup>13,21</sup>

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 ageing, which causes declining adaptive homeostasis, low-grade inflammation and oxidative stress.<sup>7,22</sup> Because we hypothesise that these measures are susceptible to change over time, clinical data linked to geriatric syndromes, comorbidities and MVCAD (eg, patient health records and angiographic parameters) will be analysed in combination with cardiovascular (eg, cardiac T/I troponins, NT-proBNP, soluble ST2 and CKMB) metabolic (eg, glucose, transaminases, lipoproteins and urea), inflammatory (ie, cytokines (eg, tumour necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$  and IL-6), chemokines (eg, IL-8/CXCL8, fractalkine/CX<sub>3</sub>CL1) and others (eg, C reactive protein)) and stress oxidative (eg, reduced glutathione (GSH), oxidised glutathione (GSSG), malondialdehyde (MDA), oxidised low-density lipoprotein (LDL) and myeloperoxidase (MPO)) biomarkers.<sup>23–25</sup> Finally, sexual dimorphism is common in the expression of these biomarkers, mainly in proinflammatory 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 revascularisation 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.



**Figure 1** Schematic representation of the study design. CR, complete revascularisation; ICR, incomplete revascularisation; MVCAD, multivessel coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty.

There is no consensus on which revascularisation strategy is more recommendable for older patients with MVCAD because of the lack of clinical trials addressing this question. Given that a randomised 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-centre study will allow that the decision-making procedures of clinicians are uniform.

## METHODS AND ANALYSIS

### Study design

This prospective, observational, longitudinal study consists of three main in-person stages: (1) patient recruitment during the first year; (2) 6-month follow-up; and (3) 12-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.

### Participants and eligibility criteria

#### Participants

Eligible volunteers with MVCAD who will undergo a coronary revascularisation 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.

#### Eligibility criteria

1. Inclusion criteria: men and women, 70 years and older (older adults) on admission to the hospital, hospitalisation for acute coronary syndrome (NSTEMI-ACS and

STEMI-ACS), diagnosis of MVACD (criteria:  $\geq 2$  coronary arteries with  $\geq 2.0$  mm segment diameter and  $\geq 70\%$  diameter stenosis), treatment with revascularisation using PTCA, and signed informed consent.

2. Exclusion criteria: life expectancy less than 1 year, refused informed consent, decisional impairment with no legally authorised representative, inability to complete questionnaires or interviews, inability to contact for follow-up or non-English/non-Spanish speaking.

### 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 (ie,  $HR_{ICR/CR}=3.3$ ).<sup>26 27</sup> In addition, dropout rates of 10%–20% have been reported in prospective studies evaluating ischaemic heart disease.<sup>28</sup>

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 ( $\alpha$ )=0.05, power ( $1-\beta$ )=0.8 and  $HR=3.3$ . 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.

### 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 (eg, frailty), comorbidity, disability, MVCAD and revascularisation (eg, angiographic and electrocardiographic measures) will be obtained using questionnaires, interviews and cardiological procedures. In addition, biochemical variables (eg, inflammatory biomarkers) will be obtained through different laboratory techniques such as selective ELISA and multiplex immunoassays.

### 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 Fatigue, Resistance, Ambulation, Illness and Loss of weight scale 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 Alcohol Use Disorders Identification test for alcohol-related problems; the Pfeiffer Short Portable



Mental Status Questionnaire for cognitive decline; the 36-item Short Form survey for quality of life related to health; the Global Registry of Acute Coronary Events risk score estimates admission—6-month mortality for patients with acute coronary syndrome; and the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines bleeding score estimates major bleeding risk in patients with acute coronary syndrome.

#### 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<sub>2</sub> EDTA tubes (BD, Franklin Lakes, New Jersey, USA) and centrifuged at 1200×g for 10 min (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.

#### Variables

- ▶ *Sociodemographic and anthropometric variables* (eg, age, ethnicity, sex, body mass, index, educational status, marital status, family size and socioeconomic status).
- ▶ *Clinical variables* (eg, cardiovascular risks (eg, arterial hypertension, dyslipidaemia, smoking and chronic inflammatory diseases such as diabetes) and variables related to quality of life and geriatric syndromes (eg, frailty, comorbidity, functional and cognitive disability, polypharmacy and use of psychoactive substances)
- ▶ *Cardiovascular variables related to MVCAD and revascularisation* (eg, acute coronary syndrome (STE-ACS and NSTEMI-ACS), revascularisation (CR and ICR), electrocardiographic evolution (T-waves, R-waves and ST-segment), ventricular ejection fraction, angiographic variables (eg, diameters, stenosis), SYNTAX score for evaluating the complexity of coronary artery lesions (eg, 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*: (1) cardiovascular (eg, cardiac troponins (cTnT and cTnI), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), soluble suppression of tumorigenicity (ST2) and creatine kinase MB isoenzyme (CKMB)); (2) metabolic (eg, glucose, transaminases, lipoproteins and urea); (3) inflammatory (ie, cytokines (eg, TNF- $\alpha$ , IL-1 $\beta$  and IL-6), chemokines (eg, IL-8/CXCL8, fractalkine/CX<sub>3</sub>CL1) and others (eg, C reactive protein)); and stress oxidative (eg, GSH and GSSG, MDA, oxidised LDL and MPO) biomarkers.

#### Primary outcome

The primary outcome measures will be a combination of MACE: heart failure, reinfarction, stroke, hospitalisation for cardiovascular-related illness, unscheduled revascularisation 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.

#### Statistical analysis

Descriptive variables will be expressed as the number and percentage of subjects (n (%)), mean and SD (mean $\pm$ SD), or median and IQR. The significance of differences in categorical and continuous variables between the revascularisation groups (CR and ICR) will be determined using the  $\chi^2$  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 will be performed to evaluate the main effects and interaction of dependent categorical variables (eg, revascularisation strategy and occurrence of MACE) on explanatory variables (eg, clinical and biochemical variables) while controlling covariates. Levene's test will be used to test the homoscedasticity of the independent explanatory variables and log<sub>10</sub>-transformation will be used for positively skewed distributions.

Cox proportional-hazards models and binary logistic regression models will be constructed with independent explanatory variables as predictors of primary and secondary outcomes and/or revascularisation strategy. Receiver operating characteristics analyses will be performed to evaluate the discriminative power of these regression models through the area under the curve. 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 V.24 (IBM). 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 ischaemic heart disease who require angioplasty or percutaneous coronary revascularisation. However, these studies are inconclusive because of different factors (eg, 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, characterise 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 to contribute improving the welfare and quality of life of older adults in modern society.

## ETHICS AND DISSEMINATION

### 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.

### 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>).

### Author affiliations

<sup>1</sup>Hospitales y Universidad de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain

<sup>2</sup>Unidad de Gestión Clínica Área del Corazón, Hospital Universitario Virgen de la Victoria, Málaga, Spain

<sup>3</sup>Centro de Investigación en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain

<sup>4</sup>Unidad de Gestión Clínica de Salud Mental, Hospital Regional Universitario de Málaga, Málaga, Spain

<sup>5</sup>Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Regional Universitario de Málaga, Málaga, Spain

<sup>6</sup>Centro de Investigación en Red de la Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

<sup>7</sup>Departamento de Enfermería, Facultad de Ciencias de la Salud, Universidad de Málaga, Málaga, Spain

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**Contributors** The study concept and design was conceived by FJP-M and MJ-N. Patient recruitment process and collection of clinical data are performed by ADMC-S, MVD-A, VMB-M, JR-C and AIM-R. Angiographic data are collected by FS-P, MA-G, LG-R and LP-M. Questionnaires and interviews are designed and applied by ADMC-S and MF-L. Biochemical determinations in blood samples are performed by FJP-M, MJS-Q, DM-V and REB. Statistical analyses are conducted by VMB-M, JMM-A, FJP-M and MJ-N. ADMC-S 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** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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### ORCID iDs

Ada del Mar Carmona-Segovia <http://orcid.org/0000-0002-2031-2760>

Víctor M Becerra-Muñoz <http://orcid.org/0000-0001-6454-7644>

Dina Medina-Vera <http://orcid.org/0000-0002-0342-1287>

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