PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Carmona-Segovia, Ada; Doncel-Abad, Maria; Becerra-Muñoz, Víctor; Rodríguez-Capitán, Jorge; Sabatel-Pérez, Fernando; Flores-López, María; Sánchez-Quintero, María; Medina-Vera, Dina; Molina-Ramos, Ana; El Bekay, Rajaa; Miguel Morales-Asencio, Jose; Angullo-Gómez, María; García-Rodríguez, Luis; Palma-Martí, Lucía; Pavón-Morón, Francisco; Jiménez-Navarro, Manuel

VERSION 1 – REVIEW

REVIEWER	Nuccia Morici Università degli Studi di Milano
REVIEW RETURNED	12-Nov-2021

GENERAL COMMENTS	The Authors should be commended for their project and the nice research question they would like to address. However, the data analysis, study endpoints and, mostly important, sample size to achieve reasonable results, should be described in detail. How they justify the sample size of 150 patients? On which estimation have they based their confidence? Please, describe. Thanks

REVIEWER	Melvin George SRM Medical College Hospital and Research Centre, Clinical Pharmacology
REVIEW RETURNED	13-Dec-2021

GENERAL COMMENTS	1. The study tries to address an important objective of prognosticating older patients who underwent revascularization procedures and is worth exploring. 2. The abstract does not have objective, only the conclusion of the abstract tells the readers what the purpose of the study is about. 3. To create a predictive model for determining the best revascularization strategy, will a sample size of 150 be sufficient?Assuming we have 10 or 20 events during the follow-up, will that be enough to draw conclusions that are meaningful 4. The authors suse words such as long term prognosis but the duration of follow up is only 6 months. Please explain 5. In line 22, the follow up duration is stated as 24 months and then 2 lines later, it says 6 months. this is confusing. please clarify 6. To create a predictive model, the statistical analysis plan seems inadequate. A logistic regression or cox regression may be required

	for this study. Please check the stats again. 7. The article requires major language editing.

VERSION 1 – AUTHOR RESPONSE

--Reviewer 1
Dr. Nuccia Morici, Università degli Studi di Milano
Comments to the Author:
The Authors should be commended for their project and the nice research question they would like to address. However, the data analysis, study endpoints and, mostly important, sample size to achieve reasonable results, should be described in detail. How they justify the sample size of 150 patients? On which estimation have they based their confidence? Please, describe. Thanks
R. We thank the reviewer for positive comments on our study. The original manuscript has been changed to address these statistical issues, and a schematic representation of the study design has been included as Figure 1 to improve the clarity of the "Methods and analysis" section.
As an example, a description of the sample size calculation has been added as follows:
"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..."

References:
26. Harada M, Miura T, Kobayashi T, et al. Clinical impact of complete revascularization in elderly patients with multi-vessel coronary artery disease undergoing percutaneous coronary intervention: A sub-analysis of the SHINANO registry. Int J Cardiol 2017;230:413-19.
27. Berezhnoi K, Kokov L, Vanyukov A. Effects of complete revascularization on long-term treatment outcomes in patients with multivessel coronary artery disease over 80 years of age admitted for acute coronary syndrome. Cardiovasc Diagn Ther 2019;9(4):301-09
28. Stocks NP, Broadbent JL, Lorimer MF, et al. The Heart Health Study - increasing cardiovascular risk assessment in family practice for first degree relatives of patients with premature ischaemic heart disease: a randomised controlled trial. BMC Fam Pract 2015;16:116.

--Reviewer 2
Dr. Melvin George, SRM Medical College Hospital and Research Centre
Comments to the Author
1. The study tries to address an important objective of prognosticating older patients who underwent revascularization procedures and is worth exploring.
2. The abstract does not have objective, only the conclusion of the abstract tells the readers what the purpose of the study is about.
R. We apologize for this mistake. The "Abstract" section has been changed according to the BMJ Open Instructions for Authors and the aim of the study is now included in the "Methods and analysis" subsection as follows:

“...The aim of this study is to evaluate changes of clinical and biochemical parameters in older patients with multivessel coronary artery disease undergoing revascularization and to establish a prognostic stratification model for complete and incomplete revascularization...”

3. To create a predictive model for determining the best revascularization strategy, will a sample size of 150 be sufficient? Assuming we have 10 or 20 events during the follow-up, will that be enough to draw conclusions that are meaningful.
R. Because the original version was not sufficiently described, we have addressed the rationale of our study and detailed information about the “Methods and analysis” section has been also added. For clarity, we have included a schematic representation of the study design (Figure 1).
As an example, a description of the sample size calculation has been added as follows:
“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...”

References:
26. Harada M, Miura T, Kobayashi T, et al. Clinical impact of complete revascularization in elderly patients with multi-vessel coronary artery disease undergoing percutaneous coronary intervention: A sub-analysis of the SHINANO registry. Int J Cardiol 2017;230:413-19.
27. Berezhnoi K, Kokov L, Vanyukov A. Effects of complete revascularization on long-term treatment outcomes in patients with multivessel coronary artery disease over 80 years of age admitted for acute coronary syndrome. Cardiovasc Diagn Ther 2019;9(4):301-09
28. Stocks NP, Broadbent JL, Lorimer MF, et al. The Heart Health Study - increasing cardiovascular risk assessment in family practice for first degree relatives of patients with premature ischaemic heart disease: a randomised controlled trial. BMC Fam Pract 2015;16:116.

4. The authors suse words such as long term prognosis but the duration of follow up is only 6 months. Please explain
R. The original manuscript was confusing regarding the study design and fundamental information was omitted. Accordingly, we have revised the “Methods and analysis” section with a better description of the study design and its stages.
“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 major adverse cardiac event or the completion of follow-ups (primary endpoints). A schematic summary is shown in Figure 1...”

5. In line 22, the follow up duration is stated as 24 months and then 2 lines later, it says 6 months. this is confusing. please clarify

R. We apologize for this mistake. The manuscript has been completely revised to avoid these confusing statements regarding the study design.

6. To create a predictive model, the statistical analysis plan seems inadequate. A logistic regression or cox regression may be required for this study. Please check the stats again.
R. We thank the reviewer for his constructive recommendations. The “Statistical analysis” subsection has been now revised as follows:
“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 major adverse cardiac events) 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 log10-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 complete and incomplete revascularization. The identification of these predictive variables will help with the prognostic stratification of patients with multivessel coronary artery disease who need a percutaneous transluminal coronary angioplasty.
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...”

7. The article requires major language editing.
R. The manuscript has been edited for American English grammar and spelling and a careful proofreading was completed.

VERSION 2 – REVIEW

REVIEWER	Melvin George SRM Medical College Hospital and Research Centre, Clinical Pharmacology
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	The authors have made the necessary changes in the manuscript. It may be accepted by the Journal.