Clinical features and long-term outcomes in patients under 35 years with coronary artery disease: nested case-control study

Pablo Juan-Salvadores Dahyr Olivas-Medina Luis Mariano de la Torre Fonseca Cesar Veiga Silvia Campanioni Francisco Caamaño Isorna Andrés Iñiguez Romo Víctor Alfonso Jiménez Díaz

PII: S0870-2551(24)00267-1

DOI: https://doi.org/doi:10.1016/j.repc.2024.06.004

Reference: REPC 2372

To appear in: *Revista Portuguesa de Cardiologia*

Received Date: 26 December 2023

Accepted Date: 12 June 2024

Please cite this article as: Juan-Salvadores P, Olivas-Medina D, de la Torre Fonseca LM, Veiga C, Campanioni S, Caamaño Isorna F, Iñiguez Romo A, Jiménez Díaz VA, Clinical features and long-term outcomes in patients under 35 years with coronary artery disease: nested case-control study, *Revista Portuguesa de Cardiologia* (2024), doi: https://doi.org/10.1016/j.repc.2024.06.004

Clinical features and long-term outcomes in patients under 35 years with coronary artery disease: nested case-control study

Características clínicas e resultados a longo prazo em pacientes com menos de 35 anos com doença arterial coronária: estudo caso-controle aninhado

Pablo Juan-Salvadores[1,2], Dahyr Olivas-Medina[1,2,*], Luis Mariano de la Torre Fonseca[4,5], Cesar Veiga[1,2], Silvia Campanioni[1,2], Francisco Caamaño Isorna[6,7], Andrés Iñiguez Romo[2,8,9], Víctor Alfonso Jiménez Díaz[1,2,3]

[1]Unidade de Investigação Cardiovascular, Departamento de Cardiologia, Hospital Álvaro Cunqueiro, Área Sanitária de Vigo

[2]Grupo de Pesquisa Cardiovascular, Instituto de Investigación Sanitaria Galicia Sur (IIS Galicia Sur). SERGAS-UVIGO

[3]Unidade de Cardiologia Intervencionista, Departamento de Cardiologia, Hospital Álvaro Cunqueiro, Área Sanitária de Vigo

[4]Unidade de Cuidados Intensivos, Hospital Universitário Clínico-Quirúrgico comandante Manuel Fajardo, La Habana, Cuba

[5]Facultade de Ciências Médicas Manuel Fajardo, Universidad de Ciencias Médicas de la Habana, La Habana, Cuba.

[6]Departamento de Medicina Preventiva, Universidade de Santiago de Compostela, Santiago de Compostela, Espanha.

[7]Consórcio de Investigação Biomédica em Epidemiologia e Saúde Pública (CIBERESP), Santiago de Compostela, Espanha.

[8]Departamento de Cardiologia, Hospital Álvaro Cunqueiro, Área Sanitária de Vigo.

[9]Consórcio de Investigação Biomédica em Cardiologia (CIBERCV), Vigo, Espanha.

Corresponding author:

Dahyr Olivas-Medina

Hospital Álvaro Cunqueiro. Cardiovascular Research Unit. 4th floor, section B.

Estrada Clara Campoamor Nº341. Vigo. Pontevedra. Spain. CP: 36213

Phone: +34986825564 / Fax: +34986825573 Email: dr.dahyrolivas@gmail.com

Resumo

Introdução e objetivos: A doença arterial coronária (DAC) é uma condição cardiovascular globalmente significativa, classificada entre as principais causas de morbidade e mortalidade. A DAC tem sido predominantemente associada à idade avançada e aos fatores de risco cardiovasculares clássicos. No entanto, nas últimas décadas, tem havido um aumento preocupante na sua ocorrência entre adultos jovens, incluindo pacientes com menos de 35 anos. O presente estudo analisa as características clínicas e os desfechos de pacientes com idade ≤35 anos com DAC, em comparação com dois grupos controle pareados por idade.

Método: estudo caso-controle aninhado de pacientes com idade ≤35 anos encaminhados para cineangiocoronariografia por suspeita clínica de DAC. Os pacientes foram divididos em três grupos: pacientes ≤35 anos com DAC, indivíduos ≤35 anos sem DAC e pacientes jovens ≥36-40 anos com DAC.

Resultados: das 19 321 coronariografias realizadas no nosso centro num período de 10 anos, 408 (2,1%) pacientes tinham idade ≤40 anos, sendo 109 pacientes com idade ≤35 anos. Os fatores de risco que apresentaram relação com a presença de DAC foram tabagismo (OR 2,49; IC95% 1,03-6,03; p=0,042) e história familiar de doença coronariana (OR 6,70; IC95% 1,46-30,65; p=0,014). O grupo com idade ≤35 anos com DAC apresentou risco de MACE (HR 13,3, IC95% 1,75-100; p<0,001) do que indivíduos ≤35 anos sem DAC. A probabilidade de MACE foi associada a idade ≤35 anos, diabetes, dislipidemia e depressão.

Conclusão: Pacientes com idade ≤35 anos apresentaram mau prognóstico a longo prazo, com alto risco de nova revascularização e enfarte agudo do miocárdio durante o período de seguimento. O foco em medidas preventivas pode impactar significativamente o prognóstico geral.

PALAVRAS-CHAVE

Doença arterial coronária; Factores de risco; Adultos jovens; Intervenção coronária percutánea; Epidemiologia clínica

ABSTRACT

Introduction and objectives: Coronary artery disease (CAD) is a globally significant cardiovascular condition, ranking among the leading causes of morbidity and mortality. CAD has been predominantly associated with advanced age and classic cardiovascular risk factors. However, over the past decades, there has been a concerning rise in its occurrence among young adults, including patients under 35 years old. The present study analyzes the clinical features and outcomes of patients aged ≤35 years with CAD, compared to two age-matched control groups.

Method: A nested case-control study of ≤35-year-old patients referred for coronary angiography due to clinical suspicion of CAD. Patients were divided into three groups: patients ≤35 years with CAD, subjects ≤35 years without CAD, and young patients ≥36-40 years with CAD.

Results: Of the 19 321 coronary angiographies performed at our center over 10 years, 408 (2.1%) patients were ≤40 years old, 109 patients aged ≤35 years. Risk factors that showed a relationship with the presence of CAD were smoking (OR 2.49; 95%CI 1.03-6.03; p=0.042)

and family history of coronary disease (OR 6.70, 95%CI 1.46-30.65; p=0.014). The group aged ≤35 years with CAD exhibited a risk of major cardiovascular adverse events (MACE) (HR 13.3, 95%CI 1.75-100; p<0,001) than subjects ≤35 years without CAD. The probability of major adverse cardiovascular events was associated with being ≤35 years old, diabetes, dyslipidemia, and depression.

Conclusion: Patients aged ≤35 exhibited a poor long-term prognosis, with a high risk of new revascularization and acute myocardial infarction during the follow-up period. Focusing on preventive measures can have a significant impact on overall prognosis.

Clinical features and long-term outcomes in patients under 35 years with coronary artery disease: A nested case-control study

Pablo Juan-Salvadores[1,2], Dahyr Olivas-Medina[1,2], Luis Mariano de la Torre Fonseca[4,5], Cesar Veiga[1,2], Silvia Campanioni[1,2], Francisco Caamaño Isorna[6,7], Andrés Iñiguez Romo[2,8,9], Víctor Alfonso Jiménez Díaz[1,2,3]

[1]Cardiovascular Research Unit, Department of Cardiology, Hospital Álvaro Cunqueiro, Área Sanitaria de Vigo; [2]Cardiovascular Research Group, Instituto de Investigación Sanitaria Galicia Sur (IIS Galicia Sur). SERGAS-UVIGO. [3]Interventional Cardiology Unit, Department of

Cardiology, Hospital Álvaro Cunqueiro, Área Sanitaria de Vigo; [4]Unidad de Cuidados Intensivos, Hospital Universitario Clínico-Quirúrgico comandante Manuel Fajardo, La Habana, Cuba. [5]Facultad de Ciencias Médicas Manuel Fajardo, Universidad de Ciencias Médicas de la Habana, La Habana, Cuba. [6]Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain. [7]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Santiago de Compostela, Spain. [8]Department of Cardiology, Hospital Álvaro Cunqueiro, Área Sanitaria de Vigo. [9]Consortium for Biomedical Research in Cardiology (CIBERCV), Vigo, Spain

INTRODUCTION

Coronary artery disease (CAD) is a globally significant cardiovascular condition, ranking among the leading causes of morbidity and mortality in the adult population [1,2]. CAD has been predominantly associated with advanced age and classic cardiovascular risk factors, such as hypertension, dyslipidemia, smoking, obesity and diabetes [3–5]. However, over the past decades, there has been a concerning rise in its occurrence among young adults, including patients under 35 years old [5–7].

This worrisome trend of CAD in younger patients has raised the alarm among the medical and scientific community, as its impact may have significant implications for affected individuals and healthcare systems. CAD in younger populations poses unique challenges

due to lack of consensus on its pathophysiology, risk factors, and long-term prognosis[9]. Therefore, this has a direct impact on patients' healthcare; they become premature chronic CAD patients, which results in increasing economic and healthcare needs and burden for the community[8]. Hence, focusing efforts on a proper understanding and management of CAD should be a priority.

OBJECTIVES

The aim of this study is to compare three groups of patients undergoing coronary angiography: very young patients (≤35 years) with CAD, subjects aged ≤35 years without CAD, and young patients (≥36-40 years) with CAD. Additionally, we investigated these differences in terms of the number of years lived without major adverse cardiovascular events (MACE) and explored the risk-adjusted association of various risk factors.

METHODS

Design and study population

It was a single-center, retrospective, nested case-control study in a cohort of ≤40-year-old patients, referred for the first time for coronary angiography due to clinical suspicion (electrocardiographic changes, biomarkers of myocardial injury, or positive ischemia stress test) of CAD, including acute coronary syndrome (ACS) or stable angina. The sample was divided in three groups: 1) Patients ≤35 years with CAD (cases), 2) subjects ≤35 years without CAD (control A), and 3) young patients ≥36-40 years with CAD (control B)

Definition of variables

The variables have been defined according to the diagnosis in the patient's clinical history, categorizing the variables whether or not they have significant CAD, based on coronary angiography, or whether or not they have cardiovascular risk factors, a previous publication provides more information[9]. CAD was defined by stenosis ≥75% on angiography or a positive invasive ischemia test or diagnostic of myocardial infarction with nonobstructive coronary arteries (MINORCA).

Ethical and legal aspects

The investigators participating in this study followed the applicable ethical and legal standards. This study was approved by the Regional Research Ethics Committee with registration code 2015/506.

Statistical analysis

Descriptive statistics are reported as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. A univariate analysis was performed to detect significant differences between the three groups for the primary variables using the Fisher exact test, $\chi 2$ test, Student t test, or Mann-Whitney U test, as appropriate. To determine the risk combination contribution, a multivariate model was used using binary logistic regression analysis. The cardiovascular risk factors analyzed are given as odds ratios (OR) together with their 95% confidence intervals. Kaplan-Meier curves and the log rank test were used to compare the

time to the occurrence of a combination of events between the three groups of patients. To identify the factors associated with the combination of events tested, a multivariate Cox regression analysis was performed, calculating the hazard ratio (HR) and 95% confidence intervals. The SPSS program for Windows, version 19, was used for data analysis.

RESULTS

From 1 January 2006 to 31 December 2015, a total of 19 321 coronary angiographies were conducted at our center. After applying the exclusion criteria, 299 patients with coronary disease were included in the study, comprising 107 patients aged ≤35 years and 190 patients aged 36-40 years. The control group A consisted of 54 patients aged ≤35 years without CAD in the coronary angiography. At admission, chest pain emerged as the predominant symptom, accounting for ≥94% of the cases in both groups with CAD (cases and control B group). Conversely, the percentage was lower in patients aged ≤35 years without CAD (control A group), at 83.3% (p=0.008). Dyspnea was reported in 11.2% of the ≤35 years group with CAD, 4.7% in the 36-40 years group with CAD, and 13% in the control A group (p=0.048). Regarding the indication for coronary angiography, suspicious acute coronary syndrome was the primary reason in 94 (87.9%) of the patients in the ≤35 years group, 177 (93.2%) in the control B group, and 34 (63%) in the control A group without CAD (p=0.001). The prevalence of MINOCA was 13 (12.1%) and 20 (10.6%) in patients ≤35 years with CAD and 36-40 years group respectively.

In all study groups, there is a notable predominance of males. Among the identified risk factors, a higher percentage of smokers, individuals with a BMI >30, a positive family history

of CAD, and dyslipidemia were prominent in the CAD groups. Statistically significant differences were observed between the groups, not only for dyslipidemia but also for the consumption of toxic substances, as shown in Table 1, other variables presented comparable values across the study groups. No differences were observed between the two groups with CAD with regards laboratory parameters (Table 2). However, significant differences were found between young individuals without CAD and patients aged 35 with ischemic disease. Angiographic characteristics of groups with CAD are displayed in Table 3. Single-vessel CAD was the predominant feature, while 20% of individuals manifest multivessel disease. The left anterior descending coronary artery stands out as the most affected, with a mean stenosis exceeding 80%, showing minimal calcification. Additionally, more than half of the patients presented with thrombus. The pharmacological treatment at hospital discharge is shown in Table 4.

To compare the groups ≤35 years, cases vs. controls, the risk factors that showed a statistically significant relationship with the presence of CAD were smoking (OR 2.49; 95%CI 1.03-6.03; p=0.042) and family history of CAD (OR 6.70; 95%CI 1.46-30.65, p=0.014). Other risk factors such as dyslipidemia, cannabis use lost statistical significance in the multivariate analysis.

The mean follow-up time in the ≤35 years with CAD (cases) was 4.8 ± 2.4 years, in control A group ≤35 years was 4.87 ± 2.1, and 5.2 ± 2.2 years in the control B group 36-40 years with CAD. During this time, 56 events were detected, all of them listed in Table 5. The group aged ≤35 years with CAD exhibited a 4.5-fold increase in the risk of acute myocardial infarction

during follow-up compared to the 36-40 years with CAD group, and more than 1.6-fold increase in the risk of experiencing new coronary revascularization compared to the control group A. Furthermore, both the ≤35 years with CAD group and the 36-40 years with CAD group showed a higher risk of MACE when compared to the control group A (HR 13.3 95%CI 1.75-100; p<0,001 and HR 7.42, 95%CI 0.86 – 64.05, p=0.068; respectively). The probability of MACE was associated with being ≤35 years old, having diabetes, dyslipidemia, and depression (Figure 1). Kaplan-Meier curves for MACE-free survival among the three study groups are displayed in Figure 2.

DISCUSSION

To the best of our knowledge, this is the first report investigating the risk factors and long-term outcomes in patients aged ≤35 years, compared to two age-matched control groups. The main findings of our study can be summarized as follows: first, only smoking and having a family history of CAD revealed a risk of presentation of premature CAD. Second, patients ≤35 years showed unfavorable long-term prognosis. Third, subjects ≤35 years with a history of diabetes, dyslipidemia and depression have a higher risk of MACE at long-term follow-up.

Patients sought healthcare primarily for chest pain, but younger individuals and those without CAD presented more dyspnea as index symptom. The CAD groups showed single vessel disease in most of cases, characterized by atherosclerotic plaques with low calcium content and presence of abundant thrombotic material[10]. This correlates with the predominant presentation as ACS. Thrombus formation due to plaque erosion is a frequent

occurrence in the young population with ACS, predominantly observed on sites of pathological intimal thickening or fibroatheromas [11–13]. Furthermore, it is worth noting that over 10% of young patients with CAD received a diagnosis of MINOCA. This finding highlights the importance of considering MINOCA as a potential cause of acute myocardial infarction in a subset of CAD patients and underscores the need for precise diagnostic evaluation and tailored management strategies for this specific population[14,15].

The baseline characteristics of the sample reveal a low representation of females, potentially attributed to estrogen protection[16]. Additionally, Lorca et al. found that premature ST elevation myocardial infarction was significantly more likely to have chromosome Y [2]. Classic risk factors, such as hypertension and diabetes, are present at a relatively low percentage in all three groups, consistent with findings reported by previous authors[17-21]. The prevalence of obesity is highest in the 36-40 years group, while the other two groups exhibit similar rates, suggesting a direct correlation of obesity with advancing age. It is noteworthy that the prevalence of dyslipidemia is 33% in the group of patients aged ≤35 years with CAD, while, in the 36-40 years group, it is observed in over half of the population. We found significant variability among the reviewed studies about dyslipidemia prevalence. Kofflard et al. 28 (49%) and Hosseini et al. 51 (47%) present higher percentages compared to the studies by Ruiz et al. 20 (32%) and Lv et al. 74 (21%), which show ratios consistent with our results. This divergence could potentially be attributed to differences in sample sizes, methodologies employed or variations in the populations under study [10,18,19,22], but not exhibiting a direct correlation in this age group. These findings emphasize the potential value of early primary prevention for reducing the occurrence of CAD.

Moreover, the consumption of toxic substances, particularly cannabis and cocaine, are markedly higher in our entire study population compared to what is published in the general population[23]. Notably, in our group of patients aged ≤35 years with CAD, the prevalence of substance use exceeds 20%[19]. A relationship was found between these patients and a family history of CAD and smoking habits, resulting thus in very premature CAD. These results are similar to the findings of other studies[10,14,19,22]. They highlight the importance of adequate primary prevention in these patients who are at very high ischemic risk.

Our study results are in line with previous studies [10,19]. Kelly et al. found that young patients without standard modifiable risk factors exhibited unfavorable prognoses, accentuating the importance of addressing alternative risk factors[24], particularly those associated with oxidative stress and inflammation[25,26]. For other classic risk factors such as dyslipidemia, hypertension, or diabetes, there was no significant relationship in our population. However, the proportion of diabetic and hypertensive patients among very young individuals is very low. Furthermore, the short duration of the influence of these diseases appears to have a limited impact on the manifestation of CAD in young patients. While there is limited evidence comparing such young populations with and without ischemic heart disease, studies have indeed found similar results [19,27,28]. The potential role of a family history of CAD in the development of CAD in the young can be attributed to genetic variants and an inherited lifestyle that predisposes people to CAD [29–32]. Additionally, tobacco consumption is one of the main triggers of plaque erosion, a mechanism that promotes acute thrombosis [33,34]. So, the duration of smoking should not influence the associated risk.

During the follow-up period, there was a significantly higher incidence of reinfarction and MACE in the ≤35 years group, compared to the 36-40 years group and the group of young individuals without CAD [19,22,28]. This unexpected finding may be attributed to subclinical familial/genetic factors leading to earlier and more aggressive CAD. Alternatively, poor adherence to lifestyle changes and medical treatment may also contribute to the observed differences. In our study, a significant association was observed between MACE and diabetes, suggesting that metabolic dysfunction may play a role in the acute presentation and progression of premature cardiovascular disease [19,25,35]. Also, the results revealed a positive correlation with dyslipidemia, emphasizing the importance of the lipid profile in the progression of cardiovascular diseases [19,25]. Our findings highlight a significant relationship between MACE and depression. The study by Ankit Vyas et al. compares two cohorts of young patients with depression and their relationship with MACE, revealing a positive association[36], similar to others reviews[36,38]. This underscores the need for comprehensive mental health evaluation in patients with premature CAD to improve clinical management and long-term outcomes [39,40]. It is important to note that there is a scarcity of published data on the long-term outcomes of these very young patients. Moreover, previous studies investigating the prognosis of ≤35 years old patients are limited and present discordant finding[19,22,24,28]. Therefore, our study adds valuable insights to this underexplored area of research. Perhaps leveraging novel advanced computational techniques, such as machine/deep learning, could aid physicians in the decision-making process for the chronic management of this young population [41,42].

This study has several limitations. Firstly, it did not encompass an analysis of non-traditional cardiovascular risk factors, such as lipoprotein A, hyperhomocysteinemia, and familial hypercholesterolemia. Additionally, the relationship between prothrombotic diseases and the early onset of ischemic heart disease could not be thoroughly assessed due to insufficient data available for most patients. Other limitations, such as the compliance to medication, blood pressure control and recovery of left ventricular fraction and bias, were not measured or collected for the current model.

Although efforts were made to minimize selection biases, the nature of our study inherently prevents complete elimination of such biases. However, it is important to highlight that our investigation features a consecutive cohort of patients, yielding the largest sample size reported in the literature for this specific context.

CONCLUSION

In our study, patients aged ≤35 with CAD exhibited poor long-term prognosis, with a high risk of new revascularization and acute myocardial infarction during follow-up. The presence of diabetes, dyslipidemia, depression, and age <35 years old were identified as factors that increased the risk of MACE at follow-up. To improve outcomes for this group of patients, it is crucial to concentrate efforts on both primary and secondary prevention strategies aimed at preventing recurrences. Focusing on preventive measures can significantly impact the overall prognosis and enhance the quality of life for these individuals.

Author contribution statement

Conceptualization: Pablo Juan-Salvadores. Data curation: Pablo Juan-Salvadores, Dahyr Olivas-Medina. Formal analysis: Cesar Veiga, Silvia Campanioni. Funding acquisition: Andrés Íñiguez Romo. Methodology: Pablo Juan-Salvadores, Víctor Alfonso Jiménez Díaz. Project administration: Pablo Juan-Salvadores. Writing–original draft: Pablo Juan-Salvadores, Dahyr Olivas-Medina, Victor Alfonso Jiménez Díaz. Writing–review & editing: Andrés Iñiguez Romo, Francisco Caamaño Isorna, Cesar Veiga, Silvia Campanioni.

ACKNOWLEDGMENTS

The authors want to thank the Cardiovascular Department staff for their support and help.

Ethics in publishing

1. Does your research involve experimentation on animals?:
No
2. Does your study include human subjects?:
Yes
If yes; please provide name of the ethical committee approving these experiments and the registration number. :
Territorial Research Ethics Committee of Pontevedra-Vigo-Ourense, with registration code 2015/506
If yes; please confirm authors compliance with all relevant ethical regulations. :
Yes
If yes; please confirm that written consent has been obtained from all patients. :
Yes
3. Does your study include a clinical trial?:
No
4. Are all data shown in the figures and tables also shown in the text of the Results section and
discussed in the Conclusions?:
Yes

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. *Heart Disease and Stroke Statistics-2022*

Update: A Report from the American Heart Association. Vol 145.; 2022. doi:10.1161/CIR.0000000000001052

2. Lorca R, Aparicio A, Salgado M, et al. Chromosome Y Haplogroup R Was Associated with the Risk of Premature Myocardial Infarction with ST-Elevation: Data from the CholeSTEMI Registry. *J Clin Med*. 2023;12(14). doi:10.3390/jcm12144812

3. Syed S. Mahmood, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*. 2014;383(9921):1933-1945. doi:10.1016/S0140-6736(13)61752-3.The

4. Mornar Jelavic M, Babic Z, Pintaric H. OBESITY PARADOX IN THE INTRAHOSPITAL AND FOLLOW-UP PHASES OF THE ACUTE CORONARY SYNDROME: A META-ANALYSIS AND SYSTEMATIC REVIEW. *Cardiology*. Published online August 2023. doi:10.1159/000531985

5. Aggarwal R, Yeh RW, Joynt Maddox KE, et al. Cardiovascular Risk Factor Prevalence, Treatment, and Control in US Adults Aged 20 to 44 Years, 2009 to March 2020. *JAMA*. 2023;329(11):899-909. doi:10.1001/jama.2023.2307

6. Hannan EL, Wu Y, Tamis-Holland J, et al. Sex differences in the treatment and outcomes of patients hospitalized with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2020;95(2):196-204. doi:10.1002/ccd.28286

7. Meirhaeghe A, Montaye M, Biasch K, et al. Coronary heart disease incidence still decreased between 2006 and 2014 in France, except in young age groups: Results

from the French MONICA registries. *Eur J Prev Cardiol*. 2020;27(11):1178-1186. doi:10.1177/2047487319899193

8. Page RL 2nd, Ghushchyan V, Gifford B, et al. The economic burden of acute coronary syndromes for employees and their dependents: medical and productivity costs. *J Occup Environ Med*. 2013;55(7):761-767. doi:10.1097/JOM.0b013e318297323a

9. Juan-Salvadores P, Díaz VAJ, Carreño CI, et al. Coronary Artery Disease in Very Young Patients: Analysis of Risk Factors and Long-Term Follow-Up. *J Cardiovasc Dev Dis*. 2022;9(3):1-13. doi:10.3390/jcdd9030082

10. Hosseini SK, Soleimani A, Salarifar M, et al. Demographics and angiographic findings in patients under 35 years of age with acute ST elevation myocardial infarction. *J Tehran Univ Hear Cent*. 2011;6(2):62-67.

11. Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114(12):1852-1866. doi:10.1161/CIRCRESAHA.114.302721

12. Nakajima A, Sugiyama T, Araki M, et al. Plaque Rupture, Compared With Plaque Erosion, Is Associated With a Higher Level of Pancoronary Inflammation. *JACC Cardiovasc Imaging*. 2022;15(5):828-839. doi:10.1016/j.jcmg.2021.10.014

13. Gulati R, Behfar A, Narula J, et al. Acute Myocardial Infarction in Young Individuals. *Mayo Clin Proc*. 2020;95(1):136-156. doi:10.1016/j.mayocp.2019.05.001

14. Juan-Salvadores P, Jiménez Díaz VA, Rodríguez González de Araujo A, et al. Clinical

Features and Long-Term Outcomes in Very Young Patients with Myocardial Infarction with Non-Obstructive Coronary Arteries. Bil J, ed. *J Interv Cardiol*. 2022;2022:9584527. doi:10.1155/2022/9584527

15. Bergamaschi L, Foà A, Paolisso P, et al. Prognostic Role of Early Cardiac Magnetic Resonance in Myocardial Infarction With Nonobstructive Coronary Arteries. *JACC Cardiovasc Imaging*. Published online 2023. doi:https://doi.org/10.1016/j.jcmg.2023.05.016

16. Kwapong YA, Sharma G, Valero-Elizondo J, et al. The association of sex-specific hormones with coronary artery plaque characteristics from Miami Heart (MiHeart) study. *Am J Prev Cardiol*. 2023;14:100479. doi:10.1016/j.ajpc.2023.100479

17. Sagris M, Antonopoulos AS, Theofilis P, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res*. 2022;118(10):2281-2292. doi:10.1093/cvr/cvab264

18. Lv S, Liu W, Zhou Y, et al. Hyperuricemia and severity of coronary artery disease: An observational study in adults 35 years of age and younger with acute coronary syndrome. *Cardiol J*. 2019;26(3):275-282. doi:10.5603/CJ.a2018.0022

19. Ruiz Pizarro V, Palacios-Rubio J, Cruz-Utrilla A, et al. ST-Elevation Myocardial Infarction in Patients ≤35 Years of Age. *Am J Cardiol*. 2019;123(6):889-893. doi:10.1016/j.amjcard.2018.12.017

20. Osadnik T, Pawlas N, Lonnie M, et al. Family history of premature coronary artery disease (P-CAD)—A non-modifiable risk factor? dietary patterns of young healthy

offspring of P-CAD patients: A case-control study (magnetic project). *Nutrients*. 2018;10(10). doi:10.3390/nu10101488

21. Eduardo Flores-Umanzor, Pedro Cepas-Guillén, Xavier Freixa, et al. Clinical profile and prognosis of young patients with ST-elevation myocardial infarction managed by the emergency-intervention Codi IAM network. Rev Esp Cardiol. 2023 (April). doi: 10.1016/j.rec.2023.03.008

22. Kofflard MJ, de Jaegere PP, van Domburg R, et al. Immediate and long-term clinical outcome of coronary angioplasty in patients aged 35 years or less. *Heart*. 2007;73(1):82-86. doi:10.1136/hrt.73.1.82

23. Observatorio Español de las Drogas y las Adicciones. Monografía alcohol 2022. Consumo y consecuencias. *Obs español las Drog y las adicciones*. Published online 2022:1-293. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/informesEstadisticas/pdf/2022OEDA-INFORME.pdf

24. Kelly C, Lan NSR, Phan J, et al. Characteristics and Outcomes of Young Patients With ST-Elevation Myocardial Infarction Without Standard Modifiable Risk Factors. *Am J Cardiol*. 2023;202:81-89. doi:https://doi.org/10.1016/j.amjcard.2023.06.045

25. Balogh DB, Wagner LJ, Fekete A. An Overview of the Cardioprotective Effects of Novel Antidiabetic Classes: Focus on Inflammation, Oxidative Stress, and Fibrosis. *Int J Mol Sci*. 2023;24(9). doi:10.3390/ijms24097789

26. Pashkow FJ. Oxidative Stress and Inflammation in Heart Disease: Do Antioxidants

Have a Role in Treatment and/or Prevention? *Int J Inflam*. 2011;2011:514623. doi:10.4061/2011/514623

27. Lv S, Liu W, Zhou Y, et al. Hyperuricemia and smoking in young adults suspected of coronary artery disease ≤ 35 years of age: A hospital-based observational study. *BMC Cardiovasc Disord*. 2018;18(1):1-7. doi:10.1186/s12872-018-0910-5

28. Rallidis LS, Gialeraki A, Triantafyllis AS, et al. Characteristics and Long-Term Prognosis of Patients ≤35 Years of Age with ST Segment Elevation Myocardial Infarction and "Normal or Near Normal" Coronary Arteries. *Am J Cardiol*. 2017;120(5):740-746. doi:10.1016/j.amjcard.2017.06.002

29. Motovska Z, Kvasnicka J, Widimsky P, et al. Platelet glycoprotein GP VI 13254C allele is an independent risk factor of premature myocardial infarction. *Thromb Res*. 2010;125(2):e61-4. doi:10.1016/j.thromres.2009.09.002

30. Isordia-Salas I, Leaños-Miranda A, Sainz IM, et al. Association of the Plasminogen Activator Inhibitor-1 Gene 4G/5G Polymorphism With ST Elevation Acute Myocardial Infarction in Young Patients. *Rev Española Cardiol (English Ed*. 2009;62(4):365-372. doi:10.1016/S1885-5857(09)71663-9

31. Rallidis LS, Gialeraki A, Fountoulaki K, et al. G-455A polymorphism of beta-fibrinogen gene and the risk of premature myocardial infarction in Greece. *Thromb Res*. 2010;125(1):34-37. doi:10.1016/j.thromres.2009.02.017

32. Isordia-Salas I, Trejo-Aguilar A, Valadés-Mejía MG, et al. C677T polymorphism of the 5,10 MTHFR gene in young Mexican subjects with ST-elevation myocardial

infarction. *Arch Med Res*. 2010;41(4):246-250. doi:10.1016/j.arcmed.2010.04.008

33. Aminuddin A, Cheong SS, Roos NAC, Ugusman A. Smoking and Unstable Plaque in Acute Coronary Syndrome: A Systematic Review of The Role of Matrix Metalloproteinases. *Int J Med Sci*. 2023;20(4):482-492. doi:10.7150/ijms.79889

34. Siasos G, Tsigkou V, Kokkou E, et al. Smoking and Atherosclerosis: Mechanisms of Disease and New Therapeutic Approaches. *Curr Med Chem*. 2014;21(34):3936-3948. doi:http://dx.doi.org/10.2174/092986732134141015161539

35. Hazin FM, Jamil D, Sharma C, et. Re-catheterization in a young patient with acute myocardial infarction: is it preventable? *Am J Transl Res*. 2023;15(1):281-287.

36. Vyas A, Desai R, Patel V, et al. Rising Burden of Cardiovascular Disease Risk Factors and Acute Cardiac Events in Young Adults With Comorbid Depression: A Comparison Nationwide US Cohorts Hospitalized 10-years Apart. *Curr Probl Cardiol*. 2023;48(8):101755. doi:10.1016/j.cpcardiol.2023.101755

37. Garrels E, Kainth T, Silva B, et al. Pathophysiological mechanisms of post-myocardial infarction depression: a narrative review. *Front Psychiatry*. 2023;14(August):1-9. doi:10.3389/fpsyt.2023.1225794

38. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: A clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi:10.1093/eurheartj/eht462

39. Hare DL, Toukhsati SR, Johansson P, et al. Depression and cardiovascular disease: a clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi:10.1093/eurheartj/eht462

40. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi:10.1093/eurheartj/eht462

41. Juan-Salvadores P, Veiga C, Jiménez Díaz VA, et al. Using Machine Learning Techniques to Predict MACE in Very Young Acute Coronary Syndrome Patients. *Diagnostics (Basel, Switzerland)*. 2022;12(2). doi:10.3390/diagnostics12020422

42. Tesche C, Bauer MJ, Baquet M, et al. Improved long-term prognostic value of coronary CT angiography-derived plaque measures and clinical parameters on adverse cardiac outcome using machine learning. *Eur Radiol*. 2021;31(1):486-493. doi:10.1007/s00330-020-07083-2

TABLES

Table 1. Clinical characteristics of patients ≤35 years old undergoing coronary angiography. Data are given as number (percentage) or mean ± SD.

CAD: coronary artery disease.

Table 2. Laboratory parameters and quantitative variables. Data are given as mean ± SD. CAD: coronary artery disease. HDL: high-density lipoproteins. LDL: low-density lipoproteins. LVEF: left ventricle ejection fraction.

Table 3: Angiographic characteristics of patients with CAD. AHA: American Heart Association. CAD: coronary artery disease. PCI: Percutaneous coronary intervention.

Table 4: Pharmacological treatment at hospital discharge. Data are given as number (percentage). ACE inhibitors; angiotensin converting enzyme inhibitors. ARBs: angiotensin II receptor blocker. ASA: acetylsalicylic acid. CAD: Coronary artery disease.

Table 5. Adverse events in the study period. AMI: acute myocardial infarction. CAD: coronary artery disease. CI: confidence interval. MACE: mayor adverse cardiac event.

FIGURES

Figure 1. Odds ratio.

CAD: Coronary artery disease, BMI: Body mass index.

Figure 2. Kaplan-Meier graphic.

CAD: Coronary artery disease, MACE: Major adverse cardiovascular event.

TABLES

Table 1. Clinical characteristics of patients ≤35 years old undergoing coronary angiography.

	CAD ≤35 (n =107)	**No CAD ≤35 (n =54)**	**CAD 36-40 (n=190)**	**p-value CAD ≤35 vs No CAD ≤35**	**p-value CAD ≤35 vs CAD 36-40**

Age	31.59 ± 3.4	29.52 ± 4.77	38.14 ± 1.44	0.006	<0.001
Women	18(16.8%)	7(13%)	19 (10%)	0.523	0.101
Body max index >30	27 (25.2%)	11 (20.4%)	69 (36.3%)	0.493	0.054
Hypertension	21 (19.6%)	8 (14.8%)	41 (21.6%)	0.453	0.767
Diabetes	5(4.7%)	1(1.9%)	15 (7.6%)	0.372	0.342
Smoking	92(86%)	30(55.6%)	158 (83.2%)	<0.001	0.620
Dyslipidemia	39(36.4%)	6(11,1%)	101 (53.2%)	0.0001	0.008
Family history of CAD	31(29%)	4(7.4%)	53 (27.9%)	0.002	0.893
Illicit drugs and alcohol	36(33.6%)	11(20.4%)	36 (18,9%)	0.080	0.007
Cannabis	26(24.3%)	6(11.1%)	15 (7.9%)	0.048	<0.001
Opioids	0	1(1,9%)	5 (2.6%)	0.158	0.163
Alcohol	17(15.9%)	2(3.7%)	18 (9.5%)	0.024	0.133
Cocaine	24(22.4%)	7(13%)	14 (7.4%)	0.150	<0.001
Depression	6(5.6%)	6(11.1%)	17 (8.9%)	0.209	0.370

Data are given as number (percentage) or mean ± SD.

CAD: coronary artery disease.

Table 2. Laboratory parameters and quantitative variables.

	CAD ≤35 (n =107)	**No CAD ≤35 (n =54)**	**CAD 36-40 (n=190)**	**p-value CAD ≤35 vs No CAD ≤35**	**p-value CAD ≤35 vs CAD 36-40**
Total cholesterol (mg/dl)	192.95±47.77	163.23±36.36	204±56.05	<0.001	0.069
LDL cholesterol (mg/dl)	122.19±41.31	95.89±27.91	134.40±53.26	<0.001	0.061
HDL cholesterol (mg/dl)	39.82±11.58	42.54±15.17	37.54±9.72	0.319	0.105
Triglycerides (mg/dl)	158.07±106.7	113±55.29	165.8±107.65	0.001	0.569
Creatinine (mg/dl)	1.06±1.36	1.39±2.34	1.02±0.79	0.360	0.778
Glucose (mg/dl)	106.41±51.06	93.74±26.21	108.41±38.32	0.115	0.717
LVEF (%)	54.54±10.53	54.95±10.40	55.74±7.95	0.849	0.366
Hospitalization days	6.33±4.92	6.64±11.22	7.51±8.14	0.848	0.181

Data are given as mean ± SD. CAD: coronary artery disease. HDL: high-density lipoproteins. LDL: low-density lipoproteins. LVEF: left ventricle ejection fraction.

Table 3: Angiographic characteristics of patients with CAD.

	CAD ≤35 (n =107)	**CAD 36-40 (n=190)**	**p-value**
Multivessel disease	20 (21.1%)	49 (28,8%)	0.167
Affected coronary artery			
Left anterior descending and branches	44 (66.4%)	93 (48.9%)	0.270
Circumflex and branches	19 (17.7%)	23 (12.2%)	
Right Coronary and branches	34 (31.7%)	54 (28.3%)	
Left Main	2 (1.8%)	5 (2.7%)	
TIMI Flow pre-PCI			
TIMI 0	43 (43.4%)	71 (40.6%)	0.582

TIMI 1	5 (5.1%)	17 (9.7%)	
TIMI 2	9 (9.1%)	17 (9.7%)	
TIMI 3	42 (42.4%)	70 (40.0%)	
AHA Classification			
Type A	12 (14.8%)	11 (8.5%)	
Type B1	11 (13.6%)	29 (22.3%)	0.118
Type B2	28 (34.6%)	33 (25.4%)	
Type C	30 (37.0%)	57 (43,8%)	
Calcified Lesion	4 (5.8%)	10 (7.9%)	0.590
Lesion with thrombus	51 (58%)	81 (52.6%)	0.421
Bifurcation Lesion	13 (14.0%)	27 (17.8%)	0.437
Number of diseased vessels	1.17±0.76	1,31±0,95	0.174
Number of treated lesions	1.06±0.76	1.01±0,82	0.639
Number of treated vessels	0.95±0.59	0.88±0,57	0.323
Baseline percentage of stenosis	83.88±26.19	84.75±26.24	0.783
Number of implanted stents	0.93±0.81	1.06±0.87	0.233
Thrombectomy	41 (43.2%)	54 (33.3%)	0.115

Stent diameter (mm)	3.31±0.62	3.22±0.49	0.260
Stent length (mm)	20.46±10.63	20.29±6.32	0.983
Bare-metall Stent	44 (56.4%)	66 (46.8%)	0.287
Drug-eluting Stent	34 (41.6%)	75 (53.2%)	0.287
TIMI Flow post-PCI			
TIMI 0	7 (7.2%)	18 (10.7%)	0.356
TIMI 1	0 (0%)	0 (0%)	
TIMI 2	0 (0%)	2 (1.2%)	
TIMI 3	90 (92.8%)	149 (88.2%)	
Final percentage of stenosis	10.42±27.27	12.78±31.92	0.521
Procedure success	87 (91.6%)	146 (86.9%)	0.252
Referred for coronary revascularization surgery	2 (1.9%)	9 (4.8%)	0.198

AHA: American Heart Association. CAD: coronary artery disease. PCI: Percutaneous coronary intervention. TIMI: thrombolysis in myocardial infarction.

Table 4: Pharmacological treatment at hospital discharge.

	CAD ≤35 (n =107)	**No CAD ≤35 (n =54)**	**CAD 36-40 (n=190)**	**p-value CAD ≤35 vs No CAD ≤35**	**p-value CAD ≤35 vs CAD 36-40**
P2Y12 Inhibitors	92 (90.2%)	8 (15.1%)	164 (88.6%)	<0.001	0.686
ASA	102(99%)	14(26.4%)	180 (97.3%)	<0.001	0.324
Anticoagulants	6(5.9%)	2 (3.8%)	3 (1.7%)	1.000	0.077
Beta-blockers	79(77.5%)	10(18.9%)	143 (79.9%)	<0.001	0.630
ACE inhibitors	43(42.2%)	6 (11.3%)	86 (48%)	<0.001	0.341
ARBs	5 (4.9%)	0	6 (3.4%)	0.171	0.535
Calcium channel blockers	13 (12.7%)	4 (7.5%)	15 (8.4%)	0.429	0.240
Statins	90(87.4%)	4(7.7%)	161 (89.4%)	<0.001	0.598
Diuretics	7 (6.9%)	3(5.7%)	12(6.7%)	1.000	0.969
Antidiabetics	3 (2.9%)	0	2 (1.1%)	0.551	0.358
Antiarrhythmics	1(1%)	1 (1.9%)	4 (2.2%)	1.000	0.656

Table 4. Data are given as number (percentage). ASA: acetylsalicylic acid. ACE inhibitors; angiotensin converting enzyme inhibitors. ARBs: angiotensin II receptor blocker. CAD: Coronary artery disease.

Table 5. Adverse events in the study period.

	CAD ≤35 (n = 106)	**No CAD ≤35 (n = 52)**	**CAD 36-40 (n =206)**	**HR CI95% p-value CAD ≤35 vs No CAD ≤35**	**HR CI95% p-value CAD ≤35 vs CAD 36-40**
New coronary revascularizations	14 (13.2%)	0	26 (14.2%)	0.005 (1.56 CI 1.38-1.77)	0.812 (1.09 CI 0.54-2.19)
Death	6 (5.7%)	1 (1.9%)	4 (2.2%)	0.426 (3.08 CI 0.36-26.31)	0.178 0.37 CI 0.10-1.34
AMI	8 (7.5%)	0	3 (1.6%)	0.053 (1.53 CI 1.36-1.72)	0.021 (HR 4.9 CI 1.27-18.87)
Stroke	1 (0.9%)	0	4 (2.2%)	1.000 (1.49 CI 1.34-1.66)	0.655 (2.35 CI 0.26-21.27)

MACE	22 (20.89%)	1 (1.9%)	33 (18%)	<0.001 (HR 13.3 CI 1.75-100)	0.570 (0.84 CI 0.46-1.53)

CAD: coronary artery disease. AMI: acute myocardial infarction. MACE: mayor adverse cardiac event. CI: confidence interval

FIGURES

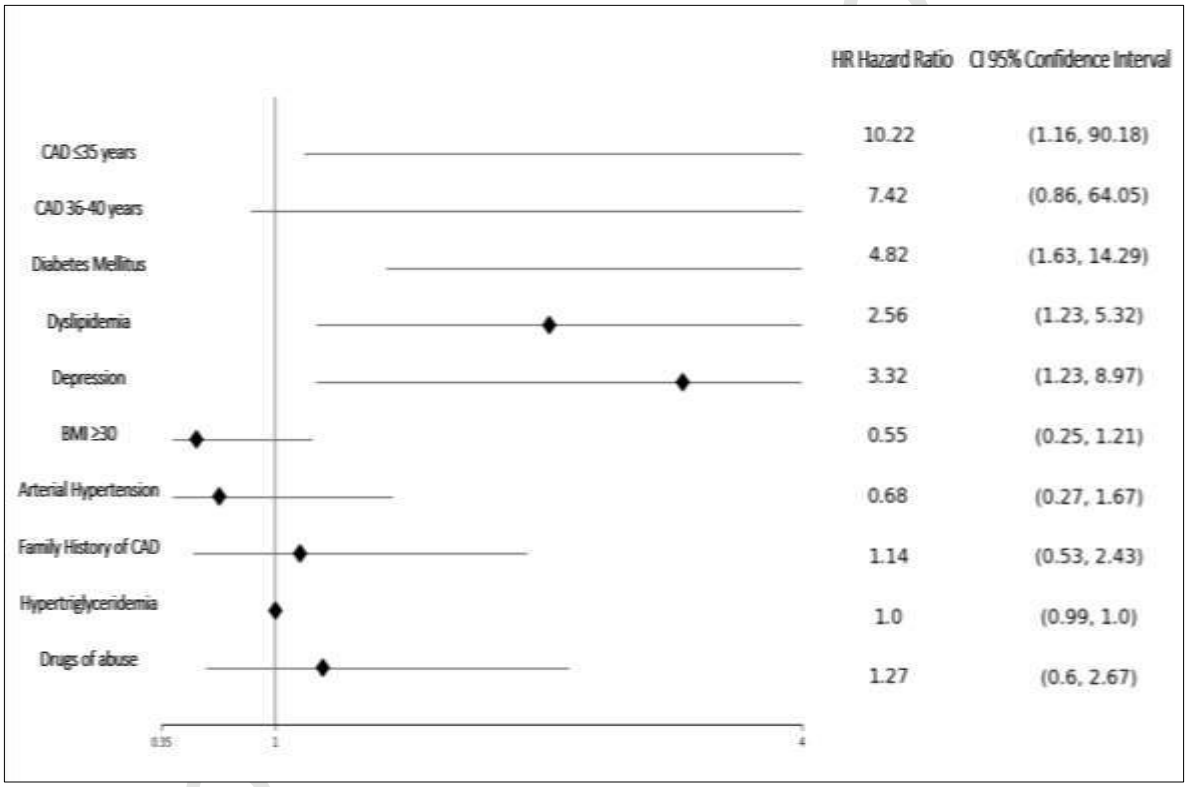

Figure 1. Odds ratio.

BMI: Body mass index. CAD: Coronary artery disease.

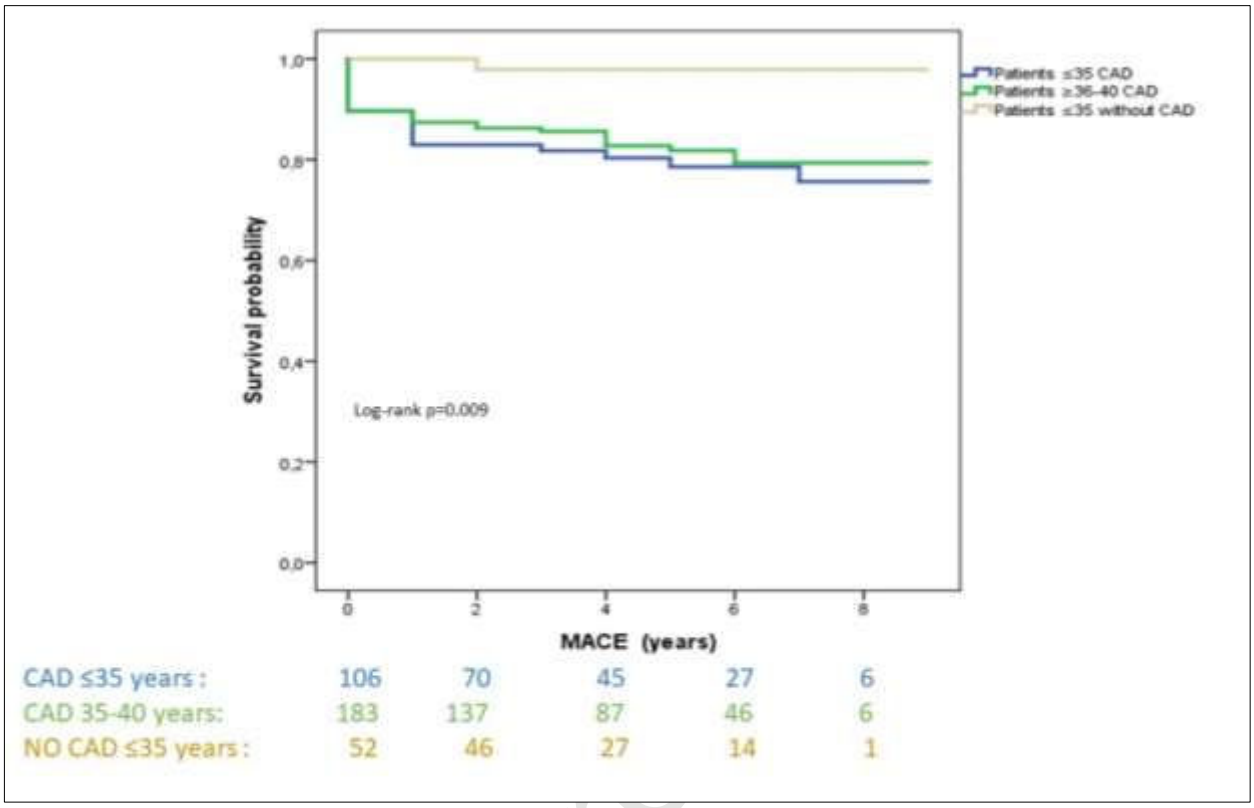

Figure 2. Kaplan-Meier graphic. CAD: Coronary artery disease, MACE: Mayor adverse cardiovascular event.