



# Argentine Journal of Cardiology

## Revista Argentina de Cardiología

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# Inflammation, Hemodynamics, and Carotid Plaque: A Phenotype in Need of Validation

*Inflamación, hemodinamia y placa carotídea: un fenotipo que pide validación*

PAULA B. PÉREZ TERNS<sup>1,2</sup>, MTSAC

More than two decades ago, we stopped thinking of atherosclerosis as a simple lipid deposit in the arterial wall and began to understand it as a chronic inflammatory disease. (1) For years, this idea was supported by observational data, until the JUPITER and CANTOS studies were published, showing that reducing inflammation without altering LDL cholesterol decreases cardiovascular events. (2,3) However, in clinical practice, high-sensitivity C-reactive protein (hs-CRP) is still ordered inconsistently, and the other half of the story—the hemodynamics to which the endothelium is exposed—is virtually never measured in the routine evaluation of patients at cardiometabolic risk.

The study by Chong et al., published in this issue of the journal, attempts to bring these two dimensions together. (4) The authors analyzed 243 outpatients with hypertension and diabetes or prediabetes, evaluated at a center in the Buenos Aires metropolitan area, and defined a low-flow, high-resistance hemodynamic-inflammatory phenotype (FIBFAR) based on the combination of hs-CRP  $\geq 2.5$  mg/L, cardiac index (CI)  $< 2.5$  L/min/m<sup>2</sup>, and systemic vascular resistance (SVR)  $> 1600$  dynes·s·cm<sup>-5</sup>, with the latter two measures obtained via impedance cardiography. Twenty-three percent of the cohort met the FIBFAR criteria, and of these, three out of four had carotid plaque. The association was maintained in the multivariate analysis (OR 8.60; 95% CI: 4.39–17.70), with a well-calibrated model and moderate discriminatory power (AUC 0.73).

The study has several merits. The objective is highly clinical: to identify, using a blood sample and a test that takes only a few minutes, patients who likely already have plaque, without resorting to expensive methods or highly specialized centers. Methodologically, the cutoff points were established before analyzing the data; the number of covariates adheres to the

ratio of ten events per variable (5); and the authors are careful to speak of association rather than prediction. Furthermore, we find it significant that the data are from Argentina, involving real outpatient patients, in a field where almost all the data we use come from cohorts in the Northern Hemisphere. The pathophysiological hypothesis is also consistent. Low-grade inflammation impairs endothelial function, reduces nitric oxide availability, and increases vasoconstrictor tone; it is reasonable to assume that patients with both inflammation and high-resistance, low-flow circulation are more susceptible to arterial wall damage. I would like to add a few reflections on the path this phenotype might take to extend beyond the center where it originated.

One has to do with thresholds. The authors' exploratory analysis shows that the optimal cutoff for cardiac index (CI) coincided with the chosen value (2.5 L/min/m<sup>2</sup>), that the cutoff for hs-CRP was somewhat higher (3.2 mg/L), and that the cutoff for SVR was significantly higher (2235 dynes·s·cm<sup>-5</sup>). In treated hypertensive patients, SVR tends to be high in almost all cases, and in fact, the median exceeded 2000 dynes·s·cm<sup>-5</sup>, with and without plaque. Testing more stringent thresholds, or using the systemic vascular resistance index so that cardiac output and resistance are expressed in the same way, could refine the hemodynamic component. Regarding hs-CRP, the value of 2.5 mg/L falls between the classic thresholds of the AHA and CDC (6) and the 2 mg/L threshold from JUPITER, making it a reasonable choice.

Another factor is physiological, and I believe it strengthens the authors' hypothesis. In this cohort, low flow coexists with a preserved ejection fraction (median of 63–65%), which points more toward a problem with afterload, ventricular-arterial coupling, or preload than with systolic function. Consistent

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with this, the pulse pressure was somewhat higher in patients with plaque, and the use of diuretics was more frequent in them, although the differences are small. It is possible that part of what FIBFAR captures is arterial stiffness and vascular aging. (7) If so, FIBFAR would serve as a comprehensive marker of arterial wall status, a concept that could be further explored by incorporating pulse wave velocity in future studies. (8)

It remains to be seen to what extent hemodynamics contributes to inflammation. The two phenotypes with elevated hs-CRP had the highest prevalence of plaque (75% in FIBFAR and 56% in the inflammatory-vasoconstrictor phenotype), and hs-CRP alone achieved an AUC of 0.70. Comparing models with and without hemodynamic components, using likelihood ratio tests or reclassification indices (9) would allow us to quantify the incremental value of impedance. In a validation cohort, it would also be useful to use the adaptive phenotype as a reference, expand the adjustment to include LDL cholesterol, lipid-lowering therapy, and renal function, and acknowledge that, with two-thirds of patients on statins, LDL measured in a cross-sectional study provides little insight into the cumulative exposure that led to plaque formation.

The authors honestly acknowledge the remaining limitations: the lack of assessment of intra- and inter-observer variability in impedance cardiography; the exclusion of patients with a body mass index  $>35$  kg/m<sup>2</sup> for technical reasons, which leaves out a significant portion of the highest-risk population; and the cross-sectional design, which does not allow to establish the direction of the relationship. This relationship may well be bidirectional, because inflammation promotes plaque formation, but plaque also causes inflammation.

The value of this study lies in proposing a different way of assessing risk—beyond lipid profiles and traditional scores—using tools that are accessible and applicable to our population. The next step is to validate the phenotype in an independent, multicenter cohort, examine how it varies by sex, age, and degree of obesity, and follow these patients over time. I am left with one question that really intrigues me: whether the phenotype changes with interventions that act on both axes—such as statins, colchicine, or GLP-1 re-

ceptor agonists (2, 10, 11)—and whether that change is accompanied by slower plaque progression. The authors have opened a line of research that deserves to be continued, and hopefully we will soon see the next steps in these very pages.

#### Conflicts of interest

The author declares that she has no conflicts of interest related to the editorial

(See authors conflicts of interest forms on the website).

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# Corrected QT Interval Variability as a Predictor of Malignant Ventricular Arrhythmia Due to Anthracyclines in Breast Cancer

*Variabilidad del intervalo QT corregido como predictor de arritmia ventricular maligna por antraciclinas en cáncer de mama*

JOSÉ LEANDRO PÉREZ-GUERRERO<sup>1</sup>, LUIS ALBERTO ESCALONA-FERNÁNDEZ<sup>2</sup>, YANOT GONZÁLEZ-GONZÁLEZ<sup>3</sup>, ANDRIA TORRES GUERRA<sup>4</sup>

## ABSTRACT

**Background:** One of the most common cardiotoxic effects of anthracyclines is malignant ventricular arrhythmia. Corrected QT interval (QTc) variability has emerged as a potential electrocardiographic predictor.

**Objective:** The aim of this study was to determine the influence of QTc variability on the onset of malignant ventricular arrhythmia in patients with breast cancer treated with anthracyclines.

**Methods:** A prospective, longitudinal, observational study was conducted at Lenin Hospital in Holguín (Cuba) from June 2023 to June 2025. A total of 150 patients with breast cancer treated with anthracyclines were included. QTc was measured at baseline, after each treatment cycle, and at 3 and 12 months. Descriptive and inferential statistics were used, including multivariate logistic regression.

**Results:** Mean age was  $55.3 \pm 9.8$  years, and mean body mass index (BMI) was  $32.4 \pm 2.1$  kg/m<sup>2</sup>. Eighty-one percent of patients had at least one cardiovascular risk factor. QTc showed a progressive increase from baseline ( $418 \pm 19$  ms) to post-cycle 4 ( $463 \pm 26$  ms). The intra-subject QTc variability (coefficient of variation) was  $15.3 \pm 4.2\%$ . There was a significant positive correlation between the number of risk factors and QTc prolongation ( $\rho = 0.55$ ;  $r^2 = 0.30$ ;  $p < 0.001$ ). Obesity ( $\beta = 24.7$  ms) and hypertension ( $\beta = 15.2$  ms) were the strongest independent predictors of QTc prolongation. Twenty-five patients (16.7%) developed malignant ventricular arrhythmia during follow-up. In the multivariate analysis, QT variability was independently associated with malignant ventricular arrhythmia (adjusted OR = 5.90; 95% CI 2.41–14.46;  $p < 0.001$ ).

**Conclusions:** QTc interval variability during anthracycline therapy is an early and independent marker of risk for malignant ventricular arrhythmia. Obesity and hypertension enhance this effect. Serial QTc interval assessment and variability calculation could improve risk stratification in cardiooncology.

**Key words:** Ventricular arrhythmia - Anthracyclines - Cardiotoxicity - Breast cancer - Risk factors - QT interval

## RESUMEN

**Introducción:** Uno de los efectos cardiotóxicos más frecuentes de las antraciclinas es la arritmia ventricular maligna. La variabilidad del intervalo QT corregido (QTc) emerge como un predictor electrocardiográfico potencial.

**Objetivo:** Determinar la influencia de la variabilidad del QTc en la aparición de arritmia ventricular maligna en pacientes con cáncer de mama tratadas con antraciclinas.

**Material y métodos:** Se realizó un estudio observacional longitudinal prospectivo en el Hospital Lenin de Holguín (Cuba) de junio de 2023 a junio de 2025. Se incluyeron 150 pacientes con cáncer de mama tratadas con antraciclinas. Se midió el QTc basal, post-cada ciclo, a los 3 y 12 meses. Se utilizó estadística descriptiva e inferencial, incluyendo regresión logística multivariante.

**Resultados:** La edad media fue  $55,3 \pm 9,8$  años y el índice de masa corporal (IMC) promedio de  $32,4 \pm 2,1$  kg/m<sup>2</sup>. El 81,3% presentó al menos un factor de riesgo cardiovascular. El QTc mostró un incremento progresivo desde el basal ( $418 \pm 19$  ms) hasta el post-ciclo 4 ( $463 \pm 26$  ms). La variabilidad intra-sujeto del QTc (coeficiente de variación) fue del  $15,3 \pm 4,2\%$ . Existió correlación positiva significativa entre el número de factores de riesgo y la prolongación del QTc ( $\rho = 0,55$ ;  $r^2 = 0,30$ ;  $p < 0,001$ ). La obesidad ( $\beta = 24,7$  ms) y la hipertensión arterial (HTA) ( $\beta = 15,2$  ms) constituyeron los predictores independientes más fuertes del incremento del QTc. Veinticinco pacientes (16,7%) desarrollaron arritmia ventricular maligna durante el seguimiento. En el análisis multivariante, la variabilidad del QT se asoció de forma independiente con la arritmia ventricular maligna (OR ajustado = 5,90; IC95% 2,41-14,46;  $p < 0,001$ ).

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**Conclusiones:** La variabilidad del intervalo QTc durante el tratamiento con antraciclinas constituye un marcador precoz e independiente de riesgo de arritmia ventricular maligna. La obesidad y la HTA potencian este efecto. La medición seriada del QTc y el cálculo de su variabilidad podrían mejorar la estratificación del riesgo en cardiooncología.

**Palabras clave:** Arritmia ventricular - Antraciclinas - Cardiotoxicidad - Cáncer de mama - Factores de riesgo - Intervalo QT

## INTRODUCTION

Cancer, characterized by uncontrolled cell proliferation and tissue invasion, is an ancient disease that has accompanied humankind since its origins, with records dating back three or four million years. (1) By 2030, there are projected to be more than 20 million new cases and 9.8 million cancer deaths worldwide, surpassed only by cardiovascular diseases (more than 17 million); in the United States, deaths will exceed 2 million. (2) In Cuba, in 2023, malignant tumors were the second leading cause of death (crude rate of 246.0/100.000 inhabitants, 25 199 deaths), only preceded by cardiovascular diseases and together, they accounted for 48.67% of overall mortality. In Holguín, 2300 deaths from malignant tumors were recorded (rate of 241.7/100 000 inhabitants), the second leading cause of death behind cardiovascular diseases. (3)

New cancer therapies have increased survival rates, but at the cost of increasing the risk of cardiovascular events due to cardiotoxicity, (4) defined as cardiovascular conditions resulting directly or indirectly from anticancer treatment. (5) This cardiotoxicity can be acute or subacute—including ventricular repolarization abnormalities, corrected QT interval (QTc) changes, supraventricular or ventricular arrhythmias, coronary syndromes, pericarditis, and myocarditis, occurring from the onset of treatment to the first year post-treatment—or chronic. (6)

In breast cancer, treatment regimens include anthracyclines, which are highly effective but limited by cardiotoxicity. (7,8) Chemotherapy can induce arrhythmias through multifactorial pathogenesis: primary arrhythmias due to potassium channel inhibition (QTc prolongation and torsade de pointes [TdP]), or secondary arrhythmias due to structural damage that leads to ischemia, inflammation, and arrhythmias. (9)

QTc interval prolongation is an established risk factor for malignant ventricular arrhythmias (MVA): TdP, sustained/non-sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death, raising growing concern about cancer-related cardiotoxicity. (10,11) Currently, there are limited data on the incidence of serious QTc-related events in cancer patients. In the non-cancer population, it ranges from 2.5 events per million years and 12.5% with antiarrhythmic drugs. (12) Drugs such as anthracyclines, despite their specificity, prolong QTc interval, alter repolarization, and increase the risk of MVA and sudden death. (13)

Cancer patients are particularly prone to QTc

prolongation due to multiple risk factors and comorbidities: (12) advanced age, diabetes mellitus, left ventricular hypertrophy, and ischemic heart disease, common conditions in this population and that increase susceptibility to repolarization abnormalities. (14,15)

The European Society of Cardiology Cardio-Oncology Guideline, (16) adopted by the Provincial Cardiology Service at Vladimir Ilich Lenin Hospital in Holguín, establishes a monitoring protocol for anthracycline therapy that includes a baseline electrocardiogram to assess QTc, but does not require its repetition in subsequent cycles, regardless of the patient's cardiovascular risk.

A review of the literature reveals a gap in the systematization of electrical cardiotoxicity prediction and in the analysis of the dynamic relationship between QTc interval variability, cardiovascular risk factors, and the onset of MVA during anthracycline treatment. Current protocols do not include serial electrocardiographic follow-up after each cycle nor do they incorporate the integrated assessment of comorbidities as modulators of arrhythmic risk. Validated tools are needed for clinical decision-making to stratify individual risk of serious arrhythmias. It is essential that cardiologists and electrophysiologists understand the association between each anticancer agent and specific arrhythmias for an early identification of drug-induced arrhythmias, in order to treat them effectively, and improve the survival of these patients.

## OBJECTIVE

The aim of this study was to determine the influence of QTc interval variability on the occurrence of MVA in patients with breast cancer treated with anthracyclines at Vladimir Ilich Lenin Hospital in Holguín from June 2023 to June 2025.

## METHODS

### Study Design and Population

A prospective, longitudinal, observational study was conducted at Vladimir Ilich Lenin University Hospital. The study population consisted of 150 female patients diagnosed with breast cancer and undergoing chemotherapy with anthracyclines, meeting the inclusion and exclusion criteria.

**Inclusion criteria:** Adult patients (age  $\geq 18$  years) with a histopathological diagnosis of breast cancer, scheduled to begin a chemotherapy regimen including doxorubicin (adriamycin), with a left ventricular ejection fraction (LVEF)  $\geq 50\%$  confirmed by baseline echocardiography, and who signed an informed consent form.

**Exclusion criteria:** Patients with known history of structural heart disease, coronary artery disease, congenital channelopathies, sustained atrial or ventricular arrhythmias on the baseline ECG, use of medications that prolong the

QTc interval, uncorrected hypokalemia or hypomagnesemia, or end-stage renal disease.

A total of 150 female patients were included, with a mean age of  $55.3 \pm 9.8$  years (range: 32–75 years). Demographic variables such as age and body mass index (BMI) and cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking) were collected using a standardized questionnaire at the onset the study.

### Follow-up

Of the 150 patients included, 145 completed the 12-month follow-up (retention rate of 96.7%). The 5 losses (3.3%) were due to relocation to another province ( $n = 2$ ), treatment discontinuation ( $n = 2$ ), and death from a non-cardiovascular cause ( $n = 1$ ). Given the low percentage of losses, no data imputation was performed, and the analysis is based on the cases available at each time point.

### Chemotherapy and Intervention Protocol

Drug: doxorubicin (Adriamycin, Pfizer Inc., New York, NY, USA).

Dose: 60 mg/m<sup>2</sup> of body surface area per cycle.

Administration: diluted in 500 mL 5% dextrose, infused intravenously over 60 minutes.

Regimen: Four cycles were administered, with a 21-day interval between each cycle.

Electrocardiographic evaluations and QTc measurements.

Timing of recordings: ECGs were performed at 7 time points: baseline (pre-chemotherapy), at the end of each of the 4 cycles, and 3 months and 12 months post-treatment.

QT correction and analysis: The QT interval was corrected for heart rate (QTc) using the Fridericia formula:

$QTc = QT \text{ (sec)} / \text{cube root of the RR interval (sec)}$ . Prolonged QTc was defined as  $>470$  ms.

**Definition of malignant ventricular arrhythmia (MVA):** MVA was defined as the documented presence of at least one of the following events during follow-up: sustained ventricular tachycardia (duration  $\geq 30$  seconds or requiring intervention), non-sustained ventricular tachycardia ( $\geq 3$  beats, heart rate  $\geq 100$  bpm, duration  $<30$  seconds) in the context of symptoms or electrical instability, TdP, or ventricular fibrillation. Detection was performed using a 12-lead ECG (if the event occurred during consultation), scheduled 24-hour Holter monitoring (performed in all patients one month post-cycle 4), or continuous monitoring during unscheduled hospitalizations due to palpitations or syncope. All events were independently adjudicated by two cardiologists of the team.

**QTc variability metrics:** Three parameters were calculated to quantify the temporal variability of repolarization:

- Maximum  $\Delta QTc$ : Maximum difference (in ms) between any post-treatment QTc and the baseline value.
- QTc coefficient of variation (QTV): Calculated as (standard deviation of each patient's 7 QTc measurements / mean of those 7 measurements)  $\times 100\%$ . It represents the temporal instability of repolarization.
- Absolute maximum QTc: The highest value recorded throughout the follow-up period.

### Definitions

Complex PCI is defined as that involving the treatment of multiple vessels, unprotected left main coronary artery approach, intervention on a venous bypass graft, management of a true bifurcation, or treatment of lesions with severe calcification requiring calcium ablation techniques or thrombotic lesions. Ad hoc PCI is defined as PCI performed immediately after diagnostic coronary angiography, while planned PCI is performed as a scheduled intervention at a later time after coronary angiography. CIN was defined as an increase of  $\geq 0.5$  mg/dL or  $\geq 25\%$  of baseline serum creatinine within 48–72 hours after the procedure.

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### Statistical Analysis

The analysis was performed using SPSS software v.28.0 (IBM Corp., Armonk, NY, USA), with a significance level of  $\alpha = 0.05$  (two-sided).

Descriptive statistics: mean  $\pm$  standard deviation (SD) was used for normally distributed variables or median and interquartile range (IQR) for non-normally distributed variables, and frequencies and percentages were used for categorical variables.

Inferential statistics: The Shapiro-Wilk test was used for normality. Group comparisons: Student's t-test or the Mann-Whitney U test was used to compare 2 groups and one-way ANOVA or the Kruskal-Wallis test for  $\geq 3$  groups. Repeated measures were assessed using ANOVA for repeated-measures or mixed linear models. Categorical associations were evaluated with the chi-square or Fisher's exact tests, and Pearson or Spearman coefficients were used for correlation.

Multivariate models: Multiple linear regression was performed to identify independent predictors of maximum  $\Delta QTc$ . Multivariate binary logistic regression (stepwise method) was implemented to identify factors associated with the occurrence of MVA, including QT variability (dichotomized: QTV  $\geq 15\%$  vs.  $<15\%$ ), age, obesity, hypertension, and diabetes as covariates. Crude and adjusted odds ratios (OR) are reported with their 95% confidence intervals (95% CI). The goodness of fit was assessed using the Hosmer-Lemeshow test and Nagelkerke's R<sup>2</sup>.

### Ethical Considerations

The study was approved by the Ethics Committee of Vladimir Ilich Lenin University Hospital and was conducted in accordance with the Declaration of Helsinki. (17) All participants signed a written informed consent form, guaranteeing confidentiality, the right to withdraw without penalty, and the absence of additional risks arising from the research.

### RESULTS

Table 1 shows the distribution of patients according to their cardiovascular risk profile. The cohort had a mean age of  $55.3 \pm 9.8$  years and mean BMI of  $32.4 \pm 2.1$  kg/m<sup>2</sup>, falling within the range for Class I obesity. Obesity was the most prevalent cardiovascular risk factor (45.3%), followed by hypertension (34.0%). Stratification by cardiovascular risk factor (CVRF) burden revealed that 26.7% of the patients had no risk factors, while the majority (73.3%) had at least one, and more than a quarter (26.7%) had three or more, indicating a high baseline cardiovascular risk profile prior to exposure to anthracyclines.

Table 2 shows the evolution of QTc over the course of the study. A progressive and sustained electrical deterioration was observed, characterized by a significant increase in QTc from baseline to post-cycle 4, with partial recovery at 12 months, although values did not return to baseline levels. The mean maximum

$\Delta$ QTc was  $38.2 \pm 12.1$  ms. The intra-subject QTV was  $15.3 \pm 4.2\%$ , reflecting significant electrical instability during follow-up.

It is important to note that the intra-subject QTV of 15.3% reflects the standard deviation of each patient's 7 QTc measurements expressed as a percentage of their mean QTc (temporal instability), and not a direct 15% increase from baseline value. The mean percentage increase from baseline was approximately 9% (38 ms out of 418 ms).

Table 3 shows the correlation between the CVRF burden and QTc prolongation. A positive and significant correlation was identified between the number of CVRFs and the magnitude of the QTc value attained ( $p = 0.55$ ; 95% CI: 0.43–0.65). The number of CVRFs explained approximately 30% of QTc variability (coefficient of determination  $r_s^2 = 0.30$ ;  $p < 0.001$ ). Patients with  $\geq 3$  CVRFs had a significantly greater maximum  $\Delta$ QTc ( $40 \pm 15.7$  ms) than those with 1–2 CVRFs ( $25 \pm 10.3$  ms) or no CVRFs ( $0 \pm 5.1$  ms) ( $p < 0.001$  for both comparisons)

**Table 1.** Distribution of patients by cardiovascular risk profile

| Characteristic                          | Total (n=150)  |
|-----------------------------------------|----------------|
| Age (years), mean $\pm$ SD              | 55.3 $\pm$ 9.8 |
| BMI (kg/m <sup>2</sup> ), mean $\pm$ SD | 32.4 $\pm$ 2.1 |
| HTN, n (%)                              | 51 (34.0)      |
| Obesity, n (%)                          | 68 (45.3)      |
| Diabetes mellitus, n (%)                | 42 (28.0)      |
| Dyslipidemia, n (%)                     | 49 (32.7)      |
| Smoking, n (%)                          | 29 (19.3)      |
| 0 CVRF, n (%)                           | 40 (26.7)      |
| 1–2 CVRF, n (%)                         | 70 (46.6)      |
| $\geq 3$ CVRF, n (%)                    | 40 (26.7)      |

BMI: body mass index; CVRF: cardiovascular risk factors; HTN: hypertension; SD: standard deviation

A multiple linear regression model was performed to identify the independent effect of each CVRF on the maximum  $\Delta$ QTc (dependent variable). Table 4 shows that obesity was the strongest independent predictor of QTc interval prolongation, with an unstandardized  $\beta$  coefficient of 24.7 ms (standardized  $\beta = 0.42$ ;  $p < 0.001$ ). Hypertension also made a significant contribution ( $\beta = 15.2$  ms;  $p < 0.001$ ). The model as a whole explained 35% of  $\Delta$ QTc maximum variability ( $R^2 = 0.35$ ; adjusted  $R^2 = 0.33$ ;  $p < 0.001$ ).

Among the 150 patients, 25 (16.7%) experienced at least one episode of MVA during follow-up. The incidence was significantly higher in the group with high QT variability (QTV  $\geq 15\%$ ). In the multivariate logistic regression analysis (Table 5), QT variability (QTV  $\geq 15\%$ ) remained an independent predictor of MVA, with an adjusted OR of 5.90 (95% CI 2.41–14.46;  $p < 0.001$ ), after adjusting for age, obesity, hypertension, and diabetes. Obesity also showed a significant independent association (OR = 2.20; 95% CI: 1.02–4.75;  $p = 0.045$ ). The model showed good fit (Hosmer-Lemeshow:  $p = 0.418$ ) and explained 32% of the outcome variability (Nagelkerke  $R^2 = 0.32$ ).

## DISCUSSION

The analyzed cohort consists predominantly of patients in their 50s, consistent with numerous international reports. Osorio (18) notes that age is the most important risk factor for breast cancer: two out of every three cases occur in women aged 50 and older, and more than 75% are diagnosed after menopause. Abdel-Qadir (19) highlights that the highest incidence of chemotherapy-associated cardiovascular events is concentrated in the fifth and sixth decades of life, particularly in breast and hematologic cancers—a stage marked by an increase in comorbidities and subclinical cardiovascular abnormalities, which heightens susceptibility to iatrogenic damage. (16) In Cuba, the rapid aging of the population makes this issue particularly relevant, as reduced myocardial reserve and

**Table 2.** Patient distribution according to QTc interval variability during treatment and follow-up. For definitions, see "QTc Variability Metrics" in Methods

| Time of evaluation       | QTc (ms) Mean $\pm$ SD (range) | $\Delta$ QTc vs. baseline (ms) * Mean $\pm$ SD | QTV among patients (%) † Median (IQR) | p-value ‡ |
|--------------------------|--------------------------------|------------------------------------------------|---------------------------------------|-----------|
| Baseline (pre-treatment) | 418 $\pm$ 19 (380–458)         | —                                              | 4.5 (3.8–5.2)                         | Reference |
| Post-Cycle 1             | 425 $\pm$ 20 (385–468)         | +7 $\pm$ 4.1                                   | 4.7 (4.0–5.4)                         | 0.045     |
| Post-Cycle 2             | 435 $\pm$ 22 (392–479)         | +17 $\pm$ 6.3                                  | 5.1 (4.3–5.9)                         | <0.001    |
| Post-Cycle 3             | 450 $\pm$ 24 (403–498)         | +32 $\pm$ 8.9                                  | 5.3 (4.5–6.1)                         | <0.001    |
| Post-Cycle 4             | 463 $\pm$ 26 (412–512)         | +45 $\pm$ 11.5                                 | 5.6 (4.8–6.4)                         | <0.001    |
| 3 months post-treatment  | 445 $\pm$ 23 (399–491)         | +27 $\pm$ 9.7                                  | 5.2 (4.4–6.0)                         | <0.001    |
| 12 months post-treatment | 438 $\pm$ 21 (394–484)         | +20 $\pm$ 8.2                                  | 4.8 (4.1–5.5)                         | <0.001    |

IQR: interquartile range; QTc: corrected QT;  $\Delta$ QTc: difference in QTc; QTV: QTc coefficient of variation; SD: standard deviation;

\*Absolute difference from baseline.

† Coefficient of variation among patients at each time point.

‡ Comparison vs. baseline using ANOVA for repeated measures.

**Table 3.** Correlation between groups of cardiovascular risk factors (CVRF) and QTc prolongation

| CVRF Group       | n   | QTc (ms)<br>Mean $\pm$ SD | $\Delta$ QTc vs. Baseline<br>(ms) | p-value<br>(vs. 0 CVRF) | Spearman's<br>correlation ( $r_s$ ) | Coefficient of<br>Determination ( $r_s^2$ ) |
|------------------|-----|---------------------------|-----------------------------------|-------------------------|-------------------------------------|---------------------------------------------|
| 0 factors        | 40  | 418 $\pm$ 19              | +0                                | Reference               | —                                   | —                                           |
| 1–2 factors      | 70  | 443 $\pm$ 24              | +25                               | <0.01                   | 0.45                                | 0.20                                        |
| $\geq 3$ factors | 40  | 458 $\pm$ 31              | +40                               | <0.001                  | 0.67                                | 0.45                                        |
| TOTAL            | 150 |                           |                                   |                         | 0.55 (95% CI 0.43–0.65)             | 0.30                                        |

CVRF: cardiovascular risk factors; QTc: corrected QT; SD: standard deviation

**Table 4.** Multiple linear regression model to predict maximum  $\Delta$ QTc (increase from baseline)

| Variable               | $\beta$ Coefficient<br>(unstandardized) | Standard error | Standardized $\beta$ | t-value | p-value | 95% CI for $\beta$ |
|------------------------|-----------------------------------------|----------------|----------------------|---------|---------|--------------------|
| Constant ( $\beta_0$ ) | 418.3                                   | 4.2            | —                    | 99.6    | <0.001  | —                  |
| Obesity                | 24.7                                    | 3.1            | 0.42                 | 7.97    | <0.001  | 18.6 – 30.8        |
| Hypertension           | 15.2                                    | 2.8            | 0.28                 | 5.43    | <0.001  | 9.7 – 20.7         |
| Diabetes               | 8.9                                     | 3.5            | 0.13                 | 2.54    | 0.012   | 2.0 – 15.8         |
| Dyslipidemia           | 6.3                                     | 3.2            | 0.10                 | 1.97    | 0.051   | -0.03 – 12.6       |
| Smoking                | 4.1                                     | 2.9            | 0.07                 | 1.41    | 0.160   | -1.6 – 9.8         |

Model  $R^2 = 0.35$ ; adjusted  $R^2 = 0.33$ ;  $p < 0.001$ .**Table 5.** Factors associated with the occurrence of malignant ventricular arrhythmias (MVAs). Multivariate logistic regression analysis

| Variable                                   | Crude OR (95% CI) | Adjusted OR* (95% CI) | p-value |
|--------------------------------------------|-------------------|-----------------------|---------|
| QT variability (QTV $\geq 15\%$ )          | 7.57 (3.12–18.38) | 5.90 (2.41–14.46)     | <0.001  |
| Age (per 10 years)                         | 1.38 (0.91–2.09)  | 1.21 (0.76–1.93)      | 0.425   |
| Obesity (BMI $\geq 30$ kg/m <sup>2</sup> ) | 2.85 (1.18–6.88)  | 2.20 (1.02–4.75)      | 0.045   |
| Hypertension                               | 2.41 (1.02–5.69)  | 1.78 (0.78–4.06)      | 0.172   |
| Diabetes mellitus                          | 1.67 (0.68–4.10)  | 1.25 (0.51–3.06)      | 0.628   |

\*Model adjusted for all variables in the table. Hosmer-Lemeshow test:  $p = 0.418$ . Nagelkerke  $R^2 = 0.32$ .

BMI: body mass index; QTV: QTc coefficient of variation.

alterations in the electrical conduction system create a proarrhythmic substrate. It is therefore crucial to understand this impact on our population.

López (20) suggests an association between overweight, obesity, and metabolic syndrome and an increased risk of breast cancer in postmenopausal women—a finding consistent with this study. The high prevalence of obesity (45.3%) and hypertension (34.0%) in our series reflects a population with increased cardiovascular risk.

Progressive prolongation of the QTc interval between cycles of chemotherapy is a cardinal sign of anthracycline-induced electrical toxicity. This study reveals a significant increase, with mean values  $>460$  ms by the fourth cycle and an initial increase of +7 ms that becomes more pronounced. Previous reports describe average increases of 35–50 ms after four or more cycles, especially in patients with risk factors,

which indicates oxidative stress, mitochondrial damage, and alterations in ion channels in ventricular myocytes. (21) QTc variability, quantified by the intra-subject coefficient of variation (15.3%), reflects the temporal instability of repolarization and constitutes a more dynamic marker than mere absolute prolongation. In our study, this variability was strongly associated with the occurrence of MVA, even after adjusting for confounding factors (adjusted OR = 5.90), suggesting that electrical instability, beyond the absolute QTc value, is a relevant predictor of arrhythmias.

The incidence of MVA in our series (16.7%) is consistent with reports from pharmacovigilance studies and oncology cohorts. Salem et al. (22), in an analysis of the WHO's VigiBase database, described a progressive increase in reports of ventricular arrhythmias associated with anticancer drugs, although with absolute incidences below 5% in the general population.

Our slightly higher incidence may be explained by intensive monitoring (scheduled Holter monitoring, serial ECGs) and the inclusion of non-sustained ventricular tachycardia in the definition of MVA, as well as by the high-risk profile of our cohort.

The burden of CVRFs in our population was high: only 26.7% of patients had no risk factors. While Zamorano et al. (23) reported only 22% with  $\geq 3$  CVRFs in Europe, our results show 26.7% in that category, reflecting significant exposure to chronic degenerative diseases. Consistent with our findings, Gerodias et al. (24) observed in 341 patients with anthracycline-induced cardiotoxicity, that those with comorbidities (especially HTN and atrial fibrillation) were 12.37 times more likely to experience cardiotoxicity.

Multivariate analysis identified obesity as the main independent predictor of QTc prolongation ( $\beta = 24.7$  ms). Consistent with our results, Dykiert found in 81 adults with overweight or grade I obesity, significantly greater QT dispersion in obese individuals. (25) Hypertension also showed a significant independent effect ( $\beta = 15.2$  ms). Dyslipidemia showed a trend that did not reach statistical significance ( $p = 0.051$ ), suggesting that its contribution might be more modest or mediated by other factors, an aspect requiring confirmation in studies with greater statistical power.

Damage caused by anthracyclines, especially doxorubicin, is dose-dependent and mediated by oxidative stress, mitochondrial dysfunction, and inflammation, which impair myocardial architecture and electrical function, explaining QTc prolongation and the predisposition to lethal arrhythmias. In agreement with our findings, Martínez Riverón, in 2024, demonstrated in patients treated with taxanes that QTc prolongation and QTc dispersion are among the electrocardiographic variables showing significant variation. (10) Mazur (26) found a high incidence of sustained ventricular tachycardia (56.6%) in 23 patients with anthracycline-induced cardiomyopathy, which is also consistent with our findings.

In the logistic regression model, QTc variability remained a significant independent predictor of MVA (adjusted OR = 5.90), while obesity also showed an independent effect (OR = 2.20). Hypertension and diabetes lost statistical significance in the multivariate analysis, suggesting that part of their effect may be mediated by QTc variability or obesity.

The literature supports including QTc assessment in standardized protocols for cardiovascular surveillance in cancer patients, especially in those with multiple comorbidities. Preventive interventions—optimal control of hypertension, diabetes, and obesity, plus cardioprotective pharmacological strategies, such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors—can mitigate QTc progression and reduce adverse events. (27) In practice, this profile requires a comprehensive pre-chemotherapy evaluation (blood pressure, BMI, blood glucose, and harmful habits) and early intervention.

Combining QTc variability with the number of CVRFs and the cumulative dose of anthracyclines allows for effective risk stratification, which should be incorporated into clinical protocols for decisions regarding dose modification, cardioprotective therapies, and post-treatment follow-up.

### Study Limitations

Several limitations should be acknowledged. First, the case series design, though longitudinal, lacks a control group, which limits the ability to establish causality. Second, the definition of MVA included non-sustained ventricular tachycardia, which may have increased the incidence compared with studies that consider only sustained or symptomatic events. Third, although a multivariate analysis was performed, variables such as the exact cumulative dose or the use of other concomitant medications—which could act as residual confounders—were not included. Finally, sample size, while adequate for the primary analyses, precludes subgroup analyses by cancer subtypes or specific chemotherapy regimens.

### CONCLUSIONS

QTc interval variability during treatment with anthracyclines constitutes an early and independent marker of risk for malignant ventricular arrhythmias, even after adjusting for classic cardiovascular risk factors. Obesity and hypertension potentiate this effect. The implementation of serial QTc measurements and the calculation of its variability (intra-subject coefficient of variation) in cardio-oncological monitoring protocols could improve risk stratification and enable earlier preventive interventions, particularly in populations with a high burden of comorbidities.

### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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# FIBFAR: Hemodynamic-Inflammatory Phenotype Associated with Subclinical Carotid Atherosclerosis in Patients with Cardiometabolic Risk

*FIBFAR: Fenotipo hemodinámico-inflamatorio asociado con aterosclerosis carotídea subclínica en pacientes con riesgo cardiometabólico*

PAOLA CHONG VELÁSQUEZ<sup>1</sup>, PEDRO FORCADA<sup>2</sup>, MTSAC, NICOLÁS MOSTEIRO<sup>3</sup>

## ABSTRACT

**Background:** Systemic inflammation and hemodynamic alterations represent complementary pathophysiological mechanisms involved in cardiovascular disease. The identification of integrative phenotypes using noninvasive tools could contribute to better characterization of subclinical atherosclerosis.

**Objective:** To evaluate the association between the low-flow, high-systemic vascular resistance hemodynamic-inflammatory phenotype (FIBFAR) and the presence of carotid plaque in patients with cardiometabolic risk, defined by the presence of hypertension and diabetes or prediabetes.

**Methods:** An observational, analytical, cross-sectional study based on a retrospective analysis of 243 outpatients aged  $\geq 18$  years with hypertension and diabetes mellitus or prediabetes. Clinical, biochemical, and hemodynamic variables were analyzed, including high-sensitivity C-reactive protein (hs-CRP), cardiac index (CI), and systemic vascular resistance (SVR) measured by impedance cardiography. Carotid plaque was assessed using Doppler ultrasound. The association between FIBFAR (hs-CRP  $\geq 2.5$  mg/L, CI  $< 2.5$  L/min/m<sup>2</sup>, and SVR  $> 1600$  dynes·s·cm<sup>-5</sup>) and carotid plaque was assessed using multivariate logistic regression.

**Results:** The median age was 58 years (IQR 49–67), and 64.0% were male. The prevalence of carotid plaque was 37.0%. The FIBFAR phenotype was present in 23.0% of the cohort and was independently associated with carotid plaque (OR 8.60; 95% CI: 4.39–17.70;  $p < 0.001$ ), along with age  $\geq 65$  years (OR 1.94; 95% CI: 1.01–3.72;  $p = 0.047$ ). The model showed appropriate calibration (Hosmer-Lemeshow  $p = 0.374$ ) and moderate discriminatory power (AUC = 0.73; 95% CI: 0.66–0.79;  $p < 0.001$ ).

**Conclusions:** In patients with cardiometabolic risk, the FIBFAR phenotype was independently associated with subclinical carotid atherosclerosis. Given the cross-sectional design, these findings should be interpreted as statistical associations and require prospective validation before their clinical application can be considered.

**Key words:** Hemodynamic phenotype – Inflammation – Impedance cardiography – Carotid atherosclerosis – Carotid plaque

## RESUMEN

**Introducción:** La inflamación sistémica y las alteraciones hemodinámicas representan mecanismos fisiopatológicos complementarios involucrados en la enfermedad cardiovascular. La identificación de fenotipos integradores mediante herramientas no invasivas podría contribuir a una mejor caracterización de la aterosclerosis subclínica.

**Objetivo:** Evaluar la asociación entre el fenotipo hemodinámico-inflamatorio de bajo flujo y alta resistencia vascular sistémica (FIBFAR) y la presencia de placa carotídea en pacientes con riesgo cardiometabólico, definido por la presencia de hipertensión arterial y diabetes o prediabetes.

**Material y métodos:** Estudio observacional, analítico y transversal con análisis retrospectivo de 243 pacientes ambulatorios  $\geq 18$  años con hipertensión arterial y diabetes mellitus o prediabetes. Se analizaron variables clínicas, bioquímicas y hemodinámicas, incluyendo proteína C reactiva ultrasensible (PCR-us), índice cardíaco (IC) y resistencia vascular sistémica (RVS) mediante cardiografía por impedancia. La placa carotídea fue evaluada mediante ecografía Doppler. La asociación entre el FIBFAR (PCR-us  $\geq 2,5$  mg/L, IC  $< 2,5$  L/min/m<sup>2</sup> y RVS  $> 1600$  dinas·s·cm<sup>-5</sup>) y placa carotídea se determinó mediante regresión logística multivariada.

**Resultados:** La mediana de edad fue de 58 años (RIC 49-67) y el 64,0% fueron varones. La prevalencia de placa carotídea fue del 37,0%. El fenotipo FIBFAR estuvo presente en el 23,0% de la cohorte y se asoció independientemente con placa carotídea (OR 8,60; IC95% 4,39-17,70;  $p < 0,001$ ), junto con la edad  $\geq 65$  años (OR 1,94; IC95% 1,01-3,72;  $p = 0,047$ ). El modelo mostró adecuada calibración (Hosmer-Lemeshow  $p = 0,374$ ) y capacidad discriminativa moderada (AUC 0,73; IC 95% 0,66-0,79;  $p < 0.001$ ).

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**Conclusiones:** En pacientes con riesgo cardiometabólico, el fenotipo FIBFAR se asoció independientemente con aterosclerosis carotídea subclínica. Debido al diseño transversal, estos hallazgos deben interpretarse como asociaciones estadísticas y requieren validación prospectiva antes de considerar su aplicación clínica.

**Palabras clave:** Fenotipo hemodinámico – Inflamación - Cardiografía por impedancia - Aterosclerosis carotídea - Placa carotídea

## INTRODUCTION

Atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality worldwide, and its burden is increasing in parallel with the rising prevalence of obesity, diabetes mellitus, dyslipidemia, and metabolic syndrome. (1,2) Although current risk stratification models incorporate traditional risk factors, a significant proportion of cardiovascular events occurs in individuals whose atherosclerotic burden is not fully explained by these determinants, prompting the search for biomarkers and phenotypes that integrate subclinical vascular risk. (3-5)

Low-grade chronic inflammation plays a central role in atherosclerosis, and high-sensitivity C-reactive protein (hs-CRP) has become established as a marker of residual inflammation and cardiovascular risk. (6-13) In parallel, hemodynamic abnormalities such as increased systemic vascular resistance (SVR) and reduced cardiac index are associated with vascular remodeling and progression of atherosclerotic disease and may be assessed noninvasively using impedance cardiography. (14-19)

Carotid ultrasound is a validated method for detecting atherosclerotic plaque, one of the markers of subclinical atherosclerosis with the greatest prognostic value. (20-24) However, inflammatory and hemodynamic mechanisms are typically studied separately.

Based on this, we propose the low-flow, high-systemic vascular resistance hemodynamic-inflammatory phenotype (FIBFAR), defined by hs-CRP  $\geq 2.5$  mg/L, cardiac index (CI)  $< 2.5$  L/min/m<sup>2</sup>, and SVR  $> 1600$  dynes·s·cm<sup>-5</sup>, with these thresholds established *a priori* according to widely accepted physiological and clinical references. (12,13,18,25)

The combination of low-grade chronic inflammation (defined by hs-CRP  $\geq 2.5$  mg/L), reduced cardiac index (CI  $< 2.5$  L/min/m<sup>2</sup>), and increased systemic vascular resistance (SVR  $> 1600$  dynes·s·cm<sup>-5</sup>) represents a prespecified hemodynamic-inflammatory construct associated with a greater burden of subclinical carotid atherosclerosis in patients with cardiometabolic risk. Low-grade chronic inflammation and physical inactivity may promote endothelial dysfunction, increased vasoconstrictor tone and vascular resistance, ventricular-arterial uncoupling, and vascular remodeling.

## OBJECTIVE

The objective of this study was to evaluate the association between the FIBFAR phenotype and the presence of subclinical carotid atherosclerosis in patients with cardiometabolic risk. Given the cross-sectional design of the study, the results were interpreted exclusively

in terms of association and do not allow causal relationships or predictive capacity to be established (Figure 1).

## METHODS

### Design and population

We conducted an observational, analytical, cross-sectional study based on a retrospective analysis of medical records of outpatients referred to the Cardiology Department of Sanatorio Modelo de Caseros (Buenos Aires, Argentina) between August 2024 and August 2025 for cardiometabolic risk assessment.

For the purposes of this study, cardiometabolic risk was operationally defined as the concomitant presence of hypertension and diabetes mellitus (or prediabetes), which were referral criteria for 100% of the cohort. The definition of both conditions is detailed in the section on clinical and biochemical variables. Although dyslipidemia, obesity, and metabolic syndrome were common in the study population (Table 1), they were not mandatory inclusion criteria.

A total of 243 patients aged 18 years or older were consecutively enrolled and underwent complete clinical, biochemical, hemodynamic, and carotid ultrasound evaluations.

### Inclusion criteria

- Age  $\geq 18$  years.
- Concomitant diagnosis of hypertension and diabetes mellitus or prediabetes at the time of referral.
- Availability of high-sensitivity C-reactive protein (hs-CRP) testing.
- Hemodynamic assessment by impedance cardiography with measurement of cardiac index (CI) and systemic vascular resistance (SVR).
- Complete carotid Doppler ultrasound for the assessment of atherosclerotic plaque.

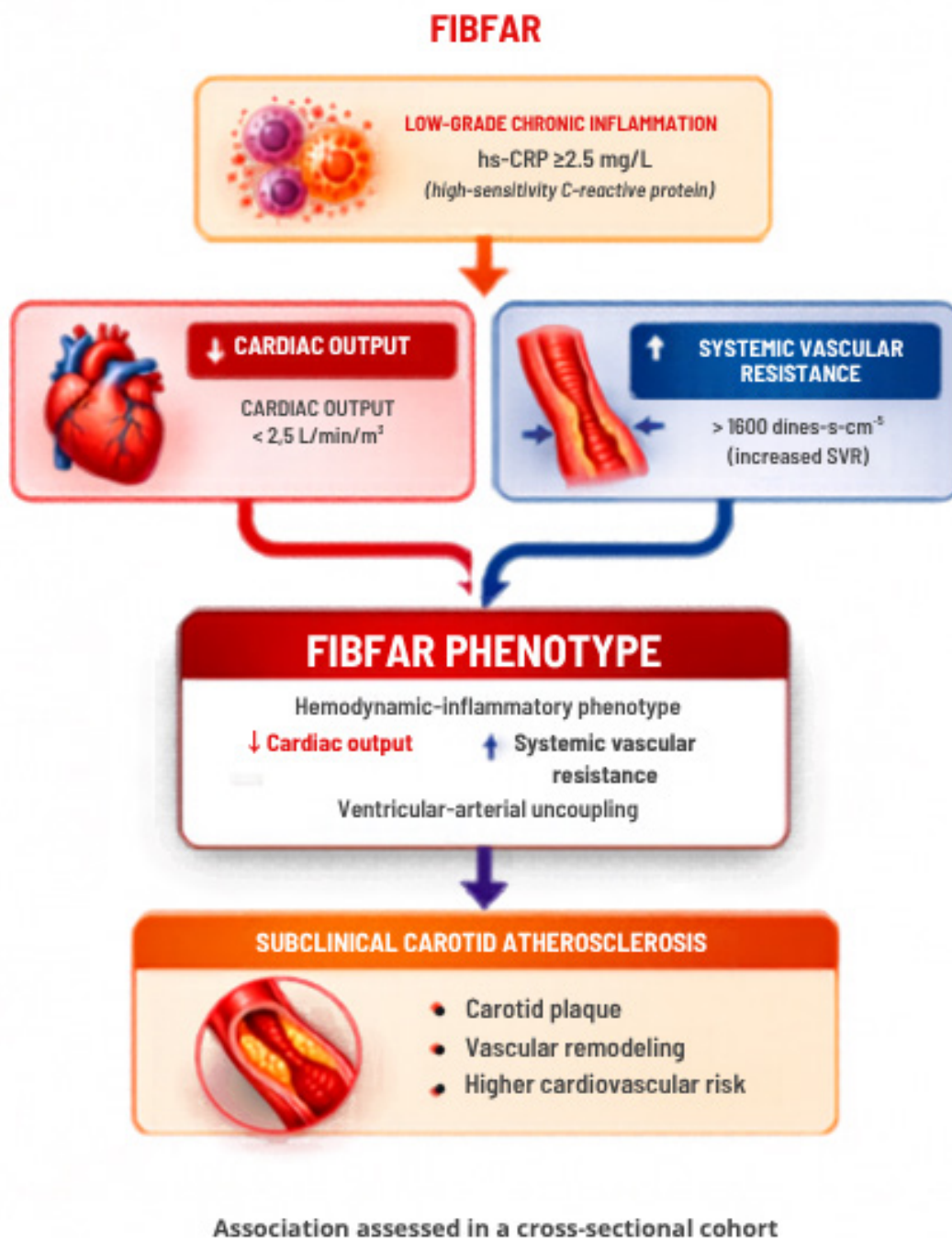
### Exclusion criteria

- Incomplete clinical or biochemical data.
- Body mass index  $> 35$  kg/m<sup>2</sup>, due to technical limitations of impedance cardiography.
- Acute infectious processes, active systemic inflammatory diseases, or neoplasms undergoing active treatment.
- Cardiac arrhythmias, hemodynamic instability, or decompensated heart failure.
- Any other clinical condition that could significantly alter hemodynamic parameters or hs-CRP levels at the time of assessment.

### Clinical and biochemical variables

Age, sex, and the main traditional cardiovascular risk factors were recorded. Hypertension was defined by a prior diagnosis or antihypertensive therapy. Diabetes mellitus was defined by a prior diagnosis, hypoglycemic therapy, or glycated hemoglobin (HbA1c)  $\geq 6.5\%$ . Dyslipidemia was defined by a prior diagnosis, lipid-lowering therapy, or low-density lipoprotein (LDL) cholesterol  $\geq 160$  mg/dL. Smoking was defined as current smoking or having quit within the past year. Obesity was defined by body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>.

**Fig. 1.** Hypothetical pathophysiological framework of the FIBFAR hemodynamic-inflammatory phenotype



The figure was created using artificial intelligence.

Metabolic syndrome was defined according to the joint 2009 IDF/AHA/NHLBI criteria. (2)

In addition, drug therapy with potential anti-inflammatory or vasoactive effects (statins, renin-angiotensin system inhibitors, and antiplatelet agents) was recorded, as was estimated renal function using the CKD-EPI equation. These variables were considered potential confounding factors because of their known associations with systemic inflamma-

tion, hemodynamics, and carotid atherosclerosis, and were evaluated during construction of the multivariate model.

Biochemical measurements were performed after a 12-hour fast and included total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, HbA1c, creatinine, and hs-CRP. Pulse pressure was calculated as the difference between systolic blood pressure and diastolic blood pressure.

### Hemodynamic assessment

Hemodynamic assessment was performed using impedance cardiography (Z-Logic® system, Exxer Ingeniería Electrónica, Buenos Aires, Argentina), a noninvasive technique validated against reference methods such as thermodilution and Doppler echocardiography and previously used for the assessment and management of patients with hypertension and heart failure. (18,19) Several studies have demonstrated good agreement between this method and these reference techniques for estimating cardiac output in various clinical settings.

Measurements were taken in the morning, after 10 minutes of rest in supine position, with caffeine consumption, smoking, and strenuous exercise avoided during the preceding 12 hours. The studies were performed by operators trained and experienced in impedance cardiography, following a standardized acquisition protocol recommended by the manufacturer.

CI (L/min/m<sup>2</sup>) and SVR (dynes·s·cm<sup>-5</sup>) values were recorded. The SVR cutoff point >1600 dynes·s·cm<sup>-5</sup> was selected based on the upper limit of the physiological reference range (700–1600 dynes·s·cm<sup>-5</sup>) established in the literature and has previously been used to define elevated vascular resistance in clinical studies. (18,25,30–31)

No formal assessment of intraobserver or interobserver variability was performed in the present cohort. The reproducibility of the method is supported by previously published validation studies comparing it with thermodilution and Doppler echocardiography. (18,19)

### Definition of hemodynamic-inflammatory phenotypes

The cutoff points used to define the phenotypes were established *a priori*, before the analysis of the database, based on pathophysiological principles and previously published clinical evidence, without deriving them from ROC curves or percentiles from the present cohort. This strategy aimed to preserve the reproducibility of the construct and avoid threshold optimization based on the observed results.

A CI <2.5 L/min/m<sup>2</sup> corresponds to the threshold used to define a low-flow state in impedance cardiography studies and previously published clinical algorithms. (18) A hs-CRP ≥2.5 mg/L falls within the range associated with increased inflammatory risk according to the AHA/CDC classification and is close to the threshold ≥2 mg/L used to define residual inflammatory risk in contemporary studies. (12,13,26,27) An SVR >1600 dynes·s·cm<sup>-5</sup> corresponds to the upper limit of the physiological reference range (700–1600 dynes·s·cm<sup>-5</sup>) and was selected as an indicator of increased arterial afterload and elevated vascular resistance. (25,30–31)

These thresholds were not specifically developed for the assessment of subclinical carotid atherosclerosis. Therefore, the FIBFAR phenotype should be interpreted as a prespecified pathophysiological construct whose association with subclinical atherosclerosis requires confirmation in independent populations and prospective studies.

As an exploratory analysis, the performance of the individual components of the phenotype was subsequently evaluated using univariate ROC curves against the presence of carotid plaque. This analysis was purely exploratory and did not alter the initially defined cutoff points.

Four mutually exclusive hemodynamic-inflammatory phenotypes were defined:

- Adaptive phenotype: hs-CRP <2.5 mg/L, CI ≥2.5 L/min/m<sup>2</sup>, and SVR ≤1600 dynes·s·cm<sup>-5</sup>.
- Vasoconstrictor inflammatory phenotype: hs-CRP ≥2.5 mg/L, CI ≥2.5 L/min/m<sup>2</sup>, and SVR >1600 dynes·s·cm<sup>-5</sup>.

- FIBFAR (low-flow, high-resistance inflammatory phenotype): hs-CRP ≥2.5 mg/L, CI <2.5 L/min/m<sup>2</sup>, and SVR >1600 dynes·s·cm<sup>-5</sup>.
- Indeterminate phenotype: patients who did not simultaneously meet the criteria for the preceding phenotypes.

### Carotid atherosclerosis assessment

Carotid assessment was performed using Doppler ultrasound (Mindray Consona 7®, 7–14 MHz linear transducer), with bilateral examination of the common carotid artery, the carotid bulb, and the internal carotid artery. Operators experienced in vascular imaging performed the examinations in accordance with a standardized protocol for image acquisition and interpretation based on international recommendations for the ultrasound evaluation of carotid disease.

The presence of carotid plaque was defined according to the recommendations of the American Society of Echocardiography and the Mannheim Consensus as a focal thickening protruding into the arterial lumen or an intima-media thickness ≥1.5 mm in any carotid segment. (20,21)

### Statistical Analysis

The analysis was performed using SPSS software v.28.0 (IBM Corp., Armonk, NY, USA), with a significance level of  $\alpha = 0.05$  (two-sided).

Descriptive statistics: mean ± standard deviation (SD) was used for normally distributed variables or median and interquartile range (IQR) for non-normally distributed variables, and frequencies and percentages were used for categorical variables.

Inferential statistics: The Shapiro-Wilk test was used for normality. Group comparisons: Student's t-test or the Mann-Whitney U test was used to compare 2 groups and one-way ANOVA or the Kruskal-Wallis test for ≥3 groups. Repeated measures were assessed using ANOVA for repeated-measures or mixed linear models. Categorical associations were evaluated with the chi-square or Fisher's exact tests, and Pearson or Spearman coefficients were used for correlation.

Multivariate models: Multiple linear regression was performed to identify independent predictors of maximum  $\Delta$ QTc. Multivariate binary logistic regression (stepwise method) was implemented to identify factors associated with the occurrence of MVA, including QT variability (dichotomized: QTV ≥15% vs. <15%), age, obesity, hypertension, and diabetes as covariates. Crude and adjusted odds ratios (OR) are reported with their 95% confidence intervals (95% CI). The goodness of fit was assessed using the Hosmer-Lemeshow test and Nagelkerke's.

### Ethical Considerations

The protocol was approved by the Ethics Committee of the Sanatorio Modelo de Caseros. The requirement for informed consent was waived because anonymized data was used.

### Statistical analysis

Clinical, biochemical, and hemodynamic characteristics were compared according to the presence of carotid plaque. Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), depending on their distribution as assessed by the Shapiro-Wilk test; categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the  $\chi^2$  test or Fisher's exact test for categorical variables, as appropriate.

A univariate analysis was performed to identify varia-

bles associated with the presence of carotid plaque. Variables with predefined clinical relevance and/or univariate association ( $p < 0.10$ ) were considered candidates for inclusion in a binary logistic regression model.

The multivariate model included the FIBFAR phenotype (primary exposure variable), age  $\geq 65$  years, sex, smoking status, body mass index, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use. Covariate selection combined prespecified clinical criteria with the results of the univariate analysis, prioritizing a parsimonious model and avoiding redundant or highly correlated variables. Hypertension and diabetes mellitus were not included as dichotomous variables because they were present in 100% of the cohort by definition of the inclusion criteria; their biological severity was represented by systolic blood pressure and HbA1c. Hs-CRP was not included as an independent covariate because it is a defining component of the FIBFAR phenotype, thereby avoiding collinearity.

With 90 events (presence of carotid plaque) and nine variables in the model, there were approximately 10 events per variable (EPV), which was considered adequate to minimize the risk of overfitting in binary logistic regression models.

Model calibration was assessed using the Hosmer-Lemeshow test, and its discriminatory ability was evaluated using the area under the ROC curve (AUC). Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated, as well as sensitivity, specificity, positive predictive value, and negative predictive value at the optimal cutoff point. As an exploratory analysis, the individual diagnostic performance of hs-CRP, CI, and SVR was evaluated using univariate ROC curves. A  $p$ -value  $< 0.05$  was considered statistically significant. All analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Population characteristics

A total of 243 outpatients with cardiometabolic risk were included; all had hypertension and diabetes mellitus or prediabetes, in accordance with the predefined inclusion criteria. The median age was 58 years (IQR 49–67), and 64.0% were male.

The overall prevalence of carotid plaque was 37.0% (90/243). Table 1 shows the clinical, biochemical, and hemodynamic characteristics and concomitant drug therapy, stratified according to the presence of carotid plaque.

Patients with carotid plaque had a higher prevalence of smoking (62.2% vs. 47.1%;  $p = 0.020$ ) and a larger hip circumference (89 vs. 85 cm;  $p = 0.001$ ), with no significant differences in the prevalence of dyslipidemia (66.6% vs. 64.1%;  $p = 0.900$ ) or in body mass index (32.0 vs. 30.9 kg/m<sup>2</sup>;  $p = 0.080$ ). Note that, despite the high overall prevalence of dyslipidemia (66% in the cohort), it showed no association with the presence of carotid plaque, highlighting the independent contribution of the inflammatory and hemodynamic components of the FIBFAR phenotype.

From a biochemical and hemodynamic perspective, patients with plaque had higher values of HbA1c (7.4% vs. 6.9%;  $p = 0.002$ ), hs-CRP (3.5 vs. 1.6 mg/L;  $p = 0.001$ ), SVR (2250 vs. 2165 dynes·s·cm<sup>-5</sup>;  $p = 0.012$ ), and pulse pressure (63 vs. 60 mmHg;

$p = 0.002$ ), together with lower CI (2.4 vs. 2.6 L/min/m<sup>2</sup>;  $p = 0.009$ ) and HDL cholesterol levels (38 vs. 42 mg/dL;  $p = 0.022$ ). No significant differences were observed in age, sex, LDL cholesterol, triglycerides, or left ventricular ejection fraction (LVEF).

Regarding concomitant drug therapy, the use of diuretics was more frequent among patients with carotid plaque (29% vs. 18%;  $p = 0.043$ ). No significant differences were observed in the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta-blockers, statins, ezetimibe, fenofibrate, or sodium-glucose cotransporter 2 inhibitors.

### Distribution of hemodynamic-inflammatory phenotypes

The distribution of the four hemodynamic-inflammatory phenotypes is shown in Table 2. The most common phenotype was the indeterminate phenotype (131 patients; 53.9%), followed by the FIBFAR phenotype (56; 23.0%), the inflammatory vasoconstrictor phenotype (32; 13.2%), and the adaptive phenotype (24; 9.9%).

The prevalence of carotid plaque differed significantly across the various phenotypes (overall  $\chi^2$ ;  $p < 0.001$ ). The FIBFAR phenotype (low-flow, high-resistance inflammatory phenotype) had the highest proportion of patients with carotid plaque (75.0%), followed by the inflammatory vasoconstrictor phenotype (56.2%), while the lowest prevalences were observed in the adaptive phenotype (25.0%) and the indeterminate (18.5%) phenotype.

### Sensitivity analysis of cutoff points

The CI showed modest discriminatory power (AUC = 0.60), and the optimal cutoff point determined by the Youden index was 2.5 L/min/m<sup>2</sup>, exactly matching the threshold used to define the phenotype.

Hs-CRP showed moderate discriminatory power (AUC = 0.70), with a population median of 2.7 mg/L and an optimal cutoff point of 3.2 mg/L. This value was slightly higher than the 2.5 mg/L predefined threshold, suggesting that the selected cutoff point prioritizes sensitivity over specificity for identifying residual inflammation.

SVR showed the lowest individual discriminatory power (AUC = 0.60). The optimal cutoff point according to the Youden index was 2235 dynes·s·cm<sup>-5</sup>, higher than the 1600 dynes·s·cm<sup>-5</sup> prespecified value, which corresponds to the upper limit of the physiological reference range. These findings suggest that SVR alone has limited ability to discriminate the presence of carotid plaque in this cohort.

However, the simultaneous combination of elevated systemic inflammation, low cardiac index, and increased SVR in the FIBFAR composite phenotype showed a considerably stronger association with the presence of carotid plaque (adjusted OR 8.60; 95% CI: 4.39–17.70) than any of its components evaluated individually, supporting the hypothesis that integrating these domains provides complementary information.

**Table 1.** Clinical, biochemical, and hemodynamic characteristics and concomitant drug therapy according to the presence of carotid plaque

| Variable                                           | With plaque (n = 90) | Without plaque (n = 153) | p     |
|----------------------------------------------------|----------------------|--------------------------|-------|
| Age, years, median (IQR)                           | 60 (52–67)           | 57 (52–65)               | 0.200 |
| Male sex, n (%)                                    | 58 (64.4)            | 85 (55.6)                | 0.200 |
| Smoking, n (%)                                     | 56 (62.2)            | 72 (47.1)                | 0.020 |
| Dyslipidemia, n (%)                                | 59 (66.6)            | 98 (64.1)                | 0.900 |
| BMI, kg/m <sup>2</sup> , median (IQR)              | 32 (28.7–33.9)       | 30.9 (28.1–33.7)         | 0.080 |
| Hip circumference, cm, median (IQR)                | 89 (84–101)          | 85 (77–89)               | 0.001 |
| SBP, mmHg, median (IQR)                            | 140 (134–146)        | 140 (124–145)            | 0.018 |
| LDL-C, mg/dL, median (IQR)                         | 100 (74–123)         | 110 (84–140)             | 0.120 |
| HDL-C, mg/dL, median (IQR)                         | 38 (34–45)           | 42 (36–54)               | 0.022 |
| Triglycerides, mg/dL, median (IQR)                 | 145 (137–187)        | 168 (116–211)            | 0.400 |
| HbA1c, %, median (IQR)                             | 7.4 (6.8–7.5)        | 6.9 (6.4–7.5)            | 0.002 |
| hs-CRP, mg/L, median (IQR)                         | 3.5 (2.6–5.9)        | 1.6 (0.85–3.45)          | 0.001 |
| LVEF, %, median (IQR)                              | 65.5 (58–68)         | 63 (58–68)               | 0.500 |
| Cardiac index, L/min/m <sup>2</sup> , median (IQR) | 2.4 (2.2–2.6)        | 2.6 (2.2–3.4)            | 0.009 |
| SVR, dynes·s·cm <sup>-5</sup> , median (IQR)       | 2,250 (1,182–2,613)  | 2,165 (1,238–2,551)      | 0.012 |
| Pulse pressure, mmHg, median (IQR)                 | 63 (59–64)           | 60 (45–64)               | 0.002 |
| <b>Concomitant drug therapy, n (%)</b>             |                      |                          |       |
| ACE inhibitors                                     | 19 (21.1)            | 38 (24.8)                | 0.500 |
| ARAs                                               | 63 (70.0)            | 105 (68.6)               | 0.900 |
| Calcium channel blockers                           | 36 (40.0)            | 52 (34.0)                | 0.400 |
| Beta-blockers                                      | 40 (44.4)            | 77 (50.5)                | 0.300 |
| Diuretics                                          | 26 (28.9)            | 27 (17.6)                | 0.043 |
| Aldosterone antagonists                            | 0 (0.0)              | 1 (0.7)                  | 0.990 |
| Statins                                            | 59 (65.6)            | 101 (66.0)               | 0.900 |
| Ezetimibe                                          | 3 (3.3)              | 10 (6.6)                 | 0.400 |
| Fenofibrates                                       | 10 (11.1)            | 14 (9.2)                 | 0.600 |
| SGLT2 inhibitors                                   | 35 (39.9)            | 52 (34.0)                | 0.500 |

ACE inhibitors: angiotensin-converting enzyme inhibitors; ARAs: angiotensin II receptor antagonists; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; SGLT2: sodium-glucose cotransporter 2; SVR: systemic vascular resistance. Comparisons were performed using the Mann-Whitney test for continuous variables or the  $\chi^2$  test or Fisher's exact test for categorical variables, as appropriate.

**Table 2.** Distribution of hemodynamic-inflammatory phenotypes and prevalence of carotid plaque

| Phenotype                    | n (%)      | Carotid plaque, n (%) |
|------------------------------|------------|-----------------------|
| Adaptive                     | 24 (9.9)   | 6 (25.0)              |
| Inflammatory vasoconstrictor | 32 (13.2)  | 18 (56.2)             |
| FIBFAR                       | 56 (23.0)  | 42 (75.0)             |
| Indeterminate                | 131 (53.9) | 24 (18.5)             |
| Total                        | 243 (100)  | 90 (37.0)             |

FIBFAR: low-flow, high-resistance inflammatory phenotype.

Overall  $\chi^2$  test for the association between phenotype and plaque:  $p < 0.001$ .

Multivariate analysis

In the multivariate logistic regression analysis (Table 3), adjusted for smoking status, sex, body mass index, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of carotid plaque (OR 8.60; 95% CI: 4.39–17.70;  $p < 0.001$ ). Age  $\geq 65$  years was also independently associated with carotid plaque (OR 1.94; 95% CI: 1.01–3.72;  $p = 0.047$ ), while none of the remaining covariates reached statistical significance. It is worth noting that dyslipidemia, despite its high prevalence in the cohort (66%), was not included in the multivariate model because it did not show a significant association in the univariate analysis ( $p = 0.90$ ), which reinforces the independent contribution of the FIBFAR phenotype beyond traditional lipid risk factors.

The model demonstrated adequate calibration, as evidenced by the Hosmer-Lemeshow test ( $p = 0.374$ ), and moderate discriminatory power (AUC = 0.73; 95% CI: 0.66–0.79;  $p < 0.001$ ; Figure 2). At the optimal cut-

off point, sensitivity was 65% and specificity was 73%. Considering the prevalence of carotid plaque observed in the cohort (37%), the positive predictive value was 58.6% and the negative predictive value was 78.0%.

DISCUSSION

In this observational cross-sectional study, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of sub-clinical carotid atherosclerosis in patients with cardio-metabolic risk, even after adjusting for age and other potential confounding factors. The magnitude of the observed association (adjusted OR 8.60) suggests that the integration of systemic inflammation and hemodynamic abnormalities may reflect a biological profile associated with a higher atherosclerotic burden. Given the cross-sectional design, these findings should be interpreted exclusively as statistical associations and do not allow causal or temporal relationships or predictive capacity to be established.

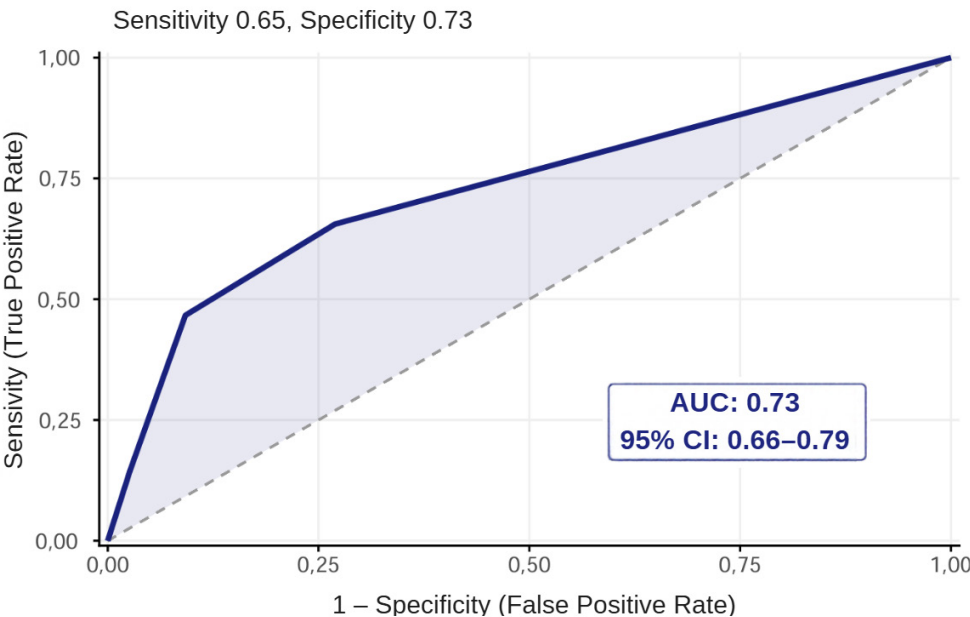
The multivariate model showed moderate discrim-

Table 3. Multivariate logistic regression model for predicting carotid plaque

| Variable            | OR   | 95% CI     | p      |
|---------------------|------|------------|--------|
| FIBFAR              | 8.6  | 4.39–17.70 | <0.001 |
| Age $\geq 65$ years | 1.94 | 1.01–3.72  | 0.047  |

95% CI: 95% confidence interval; OR: odds ratio. The model was adjusted for smoking status, sex, BMI, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use; none of these covariates showed a significant independent association in the final model. The model included nine variables and 90 events, corresponding to 10 events per variable.

Fig. 2. ROC curve of the multivariate model for predicting carotid plaque



inatory power ( $AUC = 0.73$ ) and adequate calibration, supporting the internal consistency of the proposed phenotype. Although no formal comparison was made with traditional cardiovascular risk stratification models, this performance is comparable to that reported in studies integrating inflammatory biomarkers and arterial stiffness parameters. (28,29)

Our findings are consistent with the high prevalence of subclinical atherosclerosis described in patients with cardiometabolic risk in the PESA study, (22) as well as with the prognostic value of carotid plaque demonstrated in the ARIC and MESA cohorts. (23,24) Unlike those studies, which evaluated inflammatory and hemodynamic components independently, the present study proposes a pathophysiological construct that integrates both domains into a single clinical phenotype.

The cutoff points used to define FIBFAR were established *a priori* based on pathophysiological principles and previously published clinical evidence, rather than through statistical optimization within the cohort. (12,13,18,25) Exploratory analysis showed a higher prevalence of carotid plaque when elevated systemic inflammation, low CI, and increased SVR coexisted, compared with the isolated presence of each of these components.

From a pathophysiological perspective, low-grade chronic inflammation and physical inactivity have been associated with endothelial dysfunction, reduced nitric oxide bioavailability, and increased vasoconstrictor tone—phenomena considered early events in the atherogenic cascade. This process may contribute to increased SVR, arterial stiffness, and, subsequently, ventricular-arterial uncoupling and vascular remode-

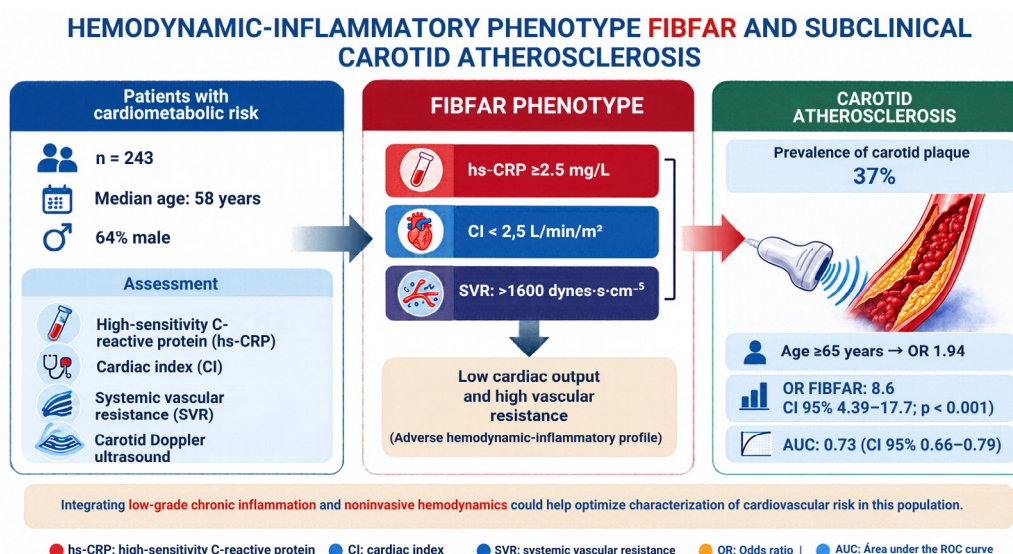
ling. (6–9, 14–17) In this context, FIBFAR represents a clinical manifestation of the coexistence of residual inflammation and hemodynamic abnormalities potentially mediated, at least in part, by endothelial dysfunction. Although the present study design does not allow us to demonstrate that these mechanisms directly explain the presence of carotid plaque, the observed results are consistent with the pathophysiological model described in the literature.

It is relevant to note that dyslipidemia, despite its high prevalence in the cohort (66%), was not significantly associated with the presence of carotid plaque in the univariate analysis ( $p = 0.90$ ), whereas the FIBFAR phenotype remained strongly and independently associated with carotid plaque ( $OR = 8.60$ ,  $p = 0.001$ ). This finding suggests that the integration of inflammatory and hemodynamic parameters could provide complementary information to traditional lipid risk factors.

The weak positive correlation between SVR and hs-CRP ( $p = 0.37$ ;  $p < 0.001$ ) suggests that both components represent partially independent pathophysiological dimensions within the FIBFAR phenotype, supporting their integration into a composite construct.

From a clinical standpoint, the combination of impedance cardiography and hs-CRP represents a completely noninvasive strategy that could potentially be applied in the outpatient setting. If confirmed in prospective studies, identification of the FIBFAR phenotype could help select patients with a higher subclinical atherosclerotic burden who may be candidates for more intensive evaluation or therapeutic strategies targeting both residual inflammatory risk and hemodynamic abnormalities. (30,31)

### Graphical abstract



### Limitations

The main limitations stem from the cross-sectional design, which does not allow causal relationships or predictive capacity to be established. The cohort was single-center and included exclusively patients with hypertension and diabetes mellitus or prediabetes, which may limit the generalizability of the findings. The cutoff points used to define the FIBFAR phenotype were established according to pathophysiological principles and previous clinical evidence; however, they require specific validation in independent populations. Finally, intraobserver and interobserver reproducibility of impedance cardiography was not assessed in this cohort, although this technique has been previously validated against reference methods. (18,19)

### CONCLUSIONS

In this cohort of patients with cardiometabolic risk, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of subclinical carotid atherosclerosis. These findings suggest that the integration of inflammatory and hemodynamic parameters could provide complementary information for characterizing vascular risk. However, given the cross-sectional design, causal relationships and predictive capacity cannot be established. Validation of the FIBFAR phenotype requires prospective, multicenter studies evaluating its reproducibility, association with cardiovascular events, and potential clinical utility.

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### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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# Glycemic Control, Drug Therapy, and Cardiovascular Risk in Older Adults with Type 2 Diabetes: A Cohort Analysis in Rosario

*Relación entre el control glucémico, el tratamiento farmacológico hipoglucemiante y el riesgo cardiovascular en adultos mayores con diabetes tipo 2: análisis de una cohorte en Rosario*

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## ABSTRACT

**Background:** The global acceleration of population aging is reflected in Argentina, with projections anticipating a progressive rise in the burden of chronic diseases. The prevalence of type 2 diabetes mellitus (T2DM) increases with age; older adults constitute the largest and most complex group in terms of clinical management. Planning care strategies requires a regional characterization of this population.

**Objective:** The aim of this study is to describe the association between glycemic control, glucose-lowering drug therapy, and cardiovascular risk in older adults with T2DM.

**Methods:** We conducted a descriptive, non-interventional study of 350 functionally independent patients  $\geq 60$  years with T2DM, using patient laboratory records of Policlínico PAMI I in Rosario between January and December 2023. The clinical characteristics, comorbidities, glucose-lowering treatment, and glycemic control as measured by glycated hemoglobin (HbA1c) were analyzed, as well as the atherogenic indices derived from the lipid profile. Missing data were handled using multiple imputation by fully conditional specification.

**Results:** Two or more comorbidities were identified in 65.1% of patients, and only 7.1% had no associated comorbidities. The most common comorbidities were overweight/obesity (92.3%), hypertension (83.4%), dyslipidemia (36.6%), and cardiovascular disease (16.0%); 54.7% were receiving combination drug therapy, with metformin being the most commonly used drug (72.8%), while glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors accounted for only 5.7% of treatments. Adequate glycemic control was achieved by 63.2% (HbA1c  $<7.5\%$ ), yet 15% had HbA1c  $\leq 6\%$ , consistent with possible overtreatment. More than half of the patients with adequate glycemic control had abnormal atherogenic indices.

**Conclusion:** Most patients in this cohort of older adults with T2DM achieved traditional glycemic control targets; however, utilization of hypoglycemic drugs with proven cardiovascular benefits was low, and a significant proportion of patients presented potential overtreatment and persistent residual cardiovascular risk as evidenced by abnormal atherogenic indices even in the presence of good glycemic control. These findings support a comprehensive assessment combining glycemic control and residual cardiovascular risk reduction.

**Key words:** Older adults - Type 2 diabetes - Cardiovascular risk - Glycemic control

## RESUMEN

**Introducción:** La aceleración del envejecimiento poblacional global se refleja en Argentina; las proyecciones anticipan una progresión creciente en la carga de enfermedades crónicas. La prevalencia de la diabetes mellitus tipo 2 (DM2) aumenta con la edad; los adultos mayores constituyen el grupo mayoritario y más complejo para su manejo clínico. La planificación de estrategias para su cuidado requiere de la caracterización regional de esta población.

**Objetivo:** Describir la relación entre el control glucémico, el tratamiento farmacológico hipoglucemiante y el riesgo cardiovascular en adultos mayores con DM2.

**Material y métodos:** Se realizó un estudio descriptivo, no intervencionista, en 350 pacientes funcionalmente independientes, mayores de 60 años, con diagnóstico de DM2, atendidos entre enero y diciembre de 2023 en el Laboratorio del Policlínico PAMI I de Rosario. Se analizaron características clínicas, comorbilidades, tratamiento hipoglucemiante, control glucémico mediante hemog-

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lobina glicosilada (HbA1c) e índices aterogénicos derivados del perfil lipídico. Los datos faltantes del perfil lipídico fueron tratados mediante imputación múltiple.

**Resultados:** El 65,1% de los pacientes presentó dos o más comorbilidades y solo el 7,1% no registró comorbilidades asociadas. Predominaron el sobrepeso/obesidad (92,3%), la hipertensión arterial (83,4%), la dislipidemia (36,6%) y la enfermedad cardiovascular (16,0%). El 54,7% recibía tratamiento farmacológico combinado. La metformina fue el fármaco más utilizado (72,8%), mientras que los agonistas de los receptores del péptido semejante al glucagón tipo 1 (arGLP-1) y los inhibidores del cotransporte sodio glucosa tipo 2 (iSGLT2) representaron únicamente el 5,7% de los tratamientos. El 63,2% alcanzó un control glucémico adecuado (HbA1c <7,5%), aunque el 15% presentó HbA1c ≤6%, compatible con posible sobretratamiento. Más de la mitad de los pacientes con adecuado control glucémico presentó índices aterogénicos alterados.

**Conclusión:** En esta cohorte, la mayoría de los adultos mayores alcanzó las metas tradicionales de control glucémico; sin embargo, se observó una baja utilización de fármacos con beneficio cardiovascular demostrado, una proporción relevante de pacientes con posible sobretratamiento hipoglucemiante y persistencia de riesgo cardiovascular residual, evidenciada por índices aterogénicos alterados aun en presencia de buen control glucémico. Estos hallazgos respaldan una evaluación integral que combine el control de la glucemia con la reducción del riesgo cardiovascular.

**Palabras clave:** Adulto mayor - Diabetes tipo 2 - Riesgo cardiovascular - Control glucémico

## INTRODUCTION

Population aging is a rapidly growing global phenomenon. The World Health Organization underscores that, for the first time in history, most people can expect to live beyond the age of 60 and predicts that trend will continue over the coming decades, driven by reduced mortality and healthcare advances in all regions of the world. (1) The Baseline Report for the Decade of Healthy Ageing 2021–2030 highlights the accelerating pace of population aging in low-, middle-, and high-income countries and the need to adapt health systems to respond to this demographic shift. (2) In Latin America, the population aging process continues to accelerate. According to recent estimates by the Economic Commission for Latin America and the Caribbean (ECLAC), the proportion of people aged 60 and older will increase steadily over the coming decades, reaching around 18% by 2030 and exceeding 25% by 2050. (3) In Argentina, this phenomenon has been observed since the mid-20th century, positioning the country as one of the most aged populations in the region. The 2010–2040 Population Projections published by the National Institute of Statistics and Censuses (INDEC) predict this trend will continue, with an increase in the number of older adults and a progressive rise in the burden of chronic diseases. (4) At the same time, diabetes mellitus (DM) has become one of the chronic diseases with the greatest global impact. It is a leading cause of blindness, chronic kidney disease, and cardiovascular disease, and was the ninth leading cause of death globally in 2019. (5) Type 2 diabetes mellitus (T2DM), its most common form, is characterized by insulin resistance and varying degrees of pancreatic dysfunction. Its prevalence increases significantly with age, driven by physiologic changes associated with aging, such as increased visceral adiposity, decreased lean body mass, reduced insulin sensitivity, and diminished regenerative capacity of beta cells. (6) Globally, according to the latest International Diabetes Federation (IDF) report, nearly 589 million adults aged 20 to 79 live with DM, a figure projected to reach 853 million by 2050. (7) In Argentina,

the prevalence is 14%, and data from the latest National Risk Factor Survey indicate a steady increase over the past few decades. (8)

Traditionally, excess weight has been considered the primary modifiable risk factor for T2DM. However, recent evidence indicates that age has an independent and strong effect on the incidence of this disease, even in individuals with a normal body mass index (BMI). (9) Consequently, older adults constitute the group with the highest prevalence of T2DM and, at the same time, the most complex one for clinical management due to the high frequency of frailty, multimorbidity, and risk for hypoglycemia. (10) In older adults, hypoglycemia is associated with falls, cognitive decline, hospitalizations, cardiovascular events, and increased mortality. (11) Several studies have documented cases of potential overtreatment, demonstrating a notable incidence of hypoglycemia and its association with adverse events. (12–14) Glycated hemoglobin (HbA1c) is the gold standard for evaluating glycemic control, as it reflects average blood glucose levels over the previous 8–12 weeks. However, evidence about the optimal values in older adults remains limited, partly due to their historical underrepresentation in clinical trials and the growing need to tailor goals based on frailty, comorbidities, and risk for hypoglycemia. (15,16) Consequently, guidelines for the management of T2DM in this population (17) recommend tailored targets based on functional status, comorbidities, and life expectancy, proposing stricter targets (HbA1c < 7.5%) for independent individuals and more flexible values (≈8%) for frail older adults or those with cognitive impairment. (18,19) Beyond glycemic control, managing other key aspects of comprehensive care, particularly cardiovascular comorbidities, is imperative. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with T2DM, with dyslipidemia being one of the most significant risk factors for its development. (20) Atherogenic dyslipidemia is common in these patients, characterized by elevated low-density lipoprotein cholesterol (LDL-C)—with a predominance of small, dense particles—increased

triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDL-C). (21) Although reducing LDL-C remains the initial therapeutic goal, (22) there is growing evidence that measures such as non-HDL cholesterol (non-HDL-C) and apolipoprotein B (ApoB), as well as the TG/HDL-C ratio, may better predict cardiovascular risk than standard lipid parameters. (23) In our country, population aging—which, as previously noted, increases the burden of noncommunicable diseases and places a growing demand on healthcare systems—requires careful planning of strategies for the care of older adults. (24) Therefore, it is essential to understand the characteristics of this population, paying particular attention to prevalent diseases such as T2DM.

## OBJECTIVE

The aim of this study was to describe the association between glycemic control, hypoglycemic drug therapy, and cardiovascular risk in older adults with T2DM managed at a medical center in the city of Rosario, Argentina.

## METHODS

We conducted an observational descriptive study using conveniently anonymized data collected from patient laboratory records at the Policlínico PAMI I in Rosario.

We estimated a sample size of 350 patients for a 95% confidence level and a 5% margin of error. Data from patients presenting between January and December 2023 were included in the study.

The study included functionally independent patients of both sexes,  $\geq 60$  years, diagnosed with T2DM.

## Statistical Analysis

Qualitative variables are presented as frequency and percentage; quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether their distribution is normal or non-normal.

The variables analyzed included age, sex, BMI, associated comorbidities, hypoglycemic drug therapy, glycemic control (YES/NO), and plasma parameters including total cholesterol (TC), HDL-C, LDL-C, TG, fasting glucose (G0), and HbA1c.

The following indices were calculated: non-HDL-C (TC – HDL-C); Castelli I index (TC/HDL-C); Castelli II index (LDL-C/HDL-C); and the TG/HDL ratio.

Glycemic control was achieved when G0 levels were  $< 120$  mg/dL and HbA1c levels were  $< 7.5\%$ . (25)

The lipid profile variables had missing values in 15% of cases. Because these variables were relevant to the objectives of the study, the missing data were handled using multiple imputation by fully conditional specification. Five imputed datasets were generated, using regression models appropriate for the type of variable and incorporating related clinical variables as predictors. Statistical analyses were performed by combining the estimates obtained from the imputed datasets, in accordance with Rubin's rules. (26)

## Ethical considerations

The project was approved by the Ethics Committee of the School of Medical Sciences at the National University of Ro-

sario and endorsed by the authorities of Policlínico PAMI I in Rosario.

## RESULTS

Data from 350 older adults diagnosed with T2DM were analyzed; 167 were women (47.7%), and 183 were men (52.3%).

Table 1 shows the values for plasma parameters and age, analyzed across the complete dataset (including both original and imputed data).

Mean BMI was  $30.6 \text{ kg/m}^2$ ; 323 patients (92.3%) were in the overweight or obesity range ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ).

Mean G0 and HbA1c values were  $142.1 \pm 45.0 \text{ mg/dL}$  and  $7.2 \pm 1.7\%$ , respectively. Based on the established criteria, 63.2% of patients achieved adequate glycemic control; the remaining 36.8% did not meet the proposed targets, and 15% had an  $\text{HbA1c} \leq 6\%$ .

Regarding the lipid profile, mean values were as follows: TC,  $165.0 \pm 42.4 \text{ mg/dL}$ ; HDL-C,  $51.2 \pm 13.3 \text{ mg/dL}$ ; LDL-C,  $91.2 \pm 36.0 \text{ mg/dL}$ ; and TG,  $136.3 \pm 74.0 \text{ mg/dL}$ . The atherogenic indices calculated from these values are shown in Table 2, analyzed according to the level of glycemic control achieved.

The most common comorbidities were hypertension in 292 patients (83.4%), followed by dyslipidemia in 128 (36.6%), and cardiovascular disease, detected in 56 patients (16.0%). Two or more comorbidities were identified in 228 patients (65.1%), and only 25 (7.1%) patients had no associated comorbidities.

Regarding glucose-lowering drugs, Table 3 presents the frequency of use of each one as monotherapy or combination therapy. Metformin was the drug most commonly used ( $n = 255$ , 72.8%), with 51.0% ( $n = 130$ ) receiving it as monotherapy. The most common combinations were metformin with sulfonylureas and/or dipeptidyl peptidase-4 (DPP-4) inhibitors. Cardioprotective antidiabetic drugs, such as GLP-1 receptor agonists and SGLT2 inhibitors, were used in 5.7% of all patients, always in combination therapy.

**Table 1.** Baseline characteristics ( $n = 350$ )

| Variable                | Mean $\pm$ SD    |
|-------------------------|------------------|
| Age (years)             | $72.0 \pm 7.7$   |
| BMI ( $\text{kg/m}^2$ ) | $30.6 \pm 4.9$   |
| G <sub>0</sub> (mg/dL)  | $142.1 \pm 45.0$ |
| HbA1c (%)               | $7.2 \pm 1.7$    |
| *TC (mg/dL)             | $165.0 \pm 42.4$ |
| *HDL-C (mg/dL)          | $51.2 \pm 13.3$  |
| *LDL-C (mg/dL)          | $91.2 \pm 36.0$  |
| *TG (mg/dL)             | $136.3 \pm 74.0$ |

Note: \*Values correspond to data obtained after multiple imputation to handle missing data; number of original values  $n = 297$ .

BMI: body mass index; G0: fasting blood glucose; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides

**Table 2.** Patient's distribution according to glycemic control and atherogenic indices

| Atherogenic indices              | Categories                              | Glycemic control      |         |                   |         |
|----------------------------------|-----------------------------------------|-----------------------|---------|-------------------|---------|
|                                  |                                         | Adequate<br>(n = 221) |         | Poor<br>(n = 129) |         |
| non-HDL-C<br>(p=0,297) *         | Normal ( $\leq 130$ mg/dl)              | 161                   | (72.8%) | 87                | (67.4%) |
|                                  | Abnormal ( $>130$ mg/dl)                | 60                    | (27.2%) | 42                | (32.6%) |
| Castelli index I<br>(p=1,000)*   | Normal (M: $< 3.5$ ; F: $< 3$ )         | 122                   | (55.2%) | 72                | (55.8%) |
|                                  | Abnormal (M: $\geq 3.5$ ; F: $\geq 3$ ) | 99                    | (44.8%) | 57                | (44.2%) |
| Castelli index II<br>p=0,312) *  | Normal (M: $< 2.5$ ; F: $< 2$ )         | 164                   | (74.2%) | 88                | (68.2%) |
|                                  | Abnormal (M: $\geq 2.5$ ; F: $\geq 2$ ) | 57                    | (25.8%) | 41                | (31.8%) |
| Atherogenic index<br>(p=0,276) * | Normal ( $< 3$ )                        | 147                   | (66.5%) | 76                | (58.9%) |
|                                  | Abnormal ( $\geq 3$ )                   | 74                    | (33.5%) | 53                | (41.1%) |

Note: Data are expressed as percentages by column. \* Fisher's exact test was applied for each index.  
F: female; M: male

## DISCUSSION

The well-established trend of population aging in Argentina—which, according to ECLAC and INDEC, will continue to increase the burden of chronic diseases—justifies conducting studies such as this one, focused on the older adult population. (3,4)

Within the context of the demographic and risk factors analyzed, the high prevalence of overweight or obesity detected in the sample is consistent with the global trend reported by the IDF Atlas, which identifies obesity as one of the primary drivers of the T2DM epidemic. (8) Although excess weight has traditionally been the key risk factor, it is worth noting that, as Suastika et al. (6) concluded, in older adults, age is a strong independent factor, primarily due to reduced insulin sensitivity.

Our study found adequate glycemic control in 63.2% of patients, with a mean HbA1c value of 7.2%. These values are in line with the recommendations of the Argentine Society of Diabetes and the ADA, which suggest HbA1c targets below 7.5% for functionally independent older adults. (27,28) However, this apparent therapeutic success should be interpreted with caution, because 15.0% of the entire cohort had HbA1c levels  $\leq 6.0\%$ , which may indicate potential overtreatment. Studies in similar populations, such as those by Lega in Ontario and Mata-Cases in Catalonia, have shown that intensive glycemic control (HbA1c  $< 7\%$ ) in older adults—especially with the use of insulin or sulfonylureas—is associated with an almost 50% increase in the risk of emergency department visits, hospitalizations, and death due to episodes of hypoglycemia. (13,14) Given that 33.1% of our cohort uses combination therapy with sulfonylureas or DPP-4 inhibitors, it would be advisable to emphasize the importance of close monitoring in these cases.

Regarding the lipid profile, mean plasma lipid levels were within acceptable ranges. However, analysis of atherogenic indices revealed a significant residual risk. (29,30) The literature highlights that the TG/HDL-C ratio is a better predictor of cardiovascular risk

**Table 3.** Pharmacological groups used

| Pharmacological group | As monotherapy or combination therapy |      |
|-----------------------|---------------------------------------|------|
|                       | n                                     | %    |
| Metformin             | 72.8                                  | 72.8 |
| Sulfonylureas         | 25.1                                  | 25.1 |
| DPP-4 inhibitors      | 8.0                                   | 8.0  |
| SGLT2i                | 5.1                                   | 5.1  |
| Insulin               | 2.0                                   | 2.0  |
| Thiazolidinediones    | 0.6                                   | 0.6  |
| GLP-1 RAs             | 0.6                                   | 0.6  |

Note: Percentages were calculated based on the total number of patients (n=350). The sum of the percentages exceeds 100% because some patients received more than one drug as part of combination therapy.  
DPP-4: dipeptidyl peptidase-4; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; SGLT2i: sodium-glucose cotransporter-2 inhibitors

and insulin resistance than LDL-C alone, especially for identifying the presence of small, dense LDL-C particles, which are highly atherogenic. (31–34) In our study, the persistence of abnormal lipid indices even in patients with good glycemic control suggests that metabolic management must go beyond blood glucose levels to address atherogenic dyslipidemia with a comprehensive approach.

A notable finding in our study regarding pharmacological treatment is the low use of cardioprotective agents (GLP-1 receptor agonists and SGLT2 inhibitors) prescribed to only 5.7% of patients. This figure is striking given the presence of significant cardiovascular risk factors, such as age, T2DM, and the high prevalence of hypertension in the sample. Current ADA and ESC/EAS guidelines (22,28) emphasize that these agents should be considered essential for managing patients at high cardiovascular risk, regardless of the HbA1c target achieved, due to their proven benefit in reducing major events. In turn, another cardiovascular risk factor—the presence of overweight

or obesity (92.3% in our sample)—should guide the choice toward medications that not only control glucose levels but also promote weight loss, because this is associated with better glycemic control. GLP-1 RAs and SGLT2i also have beneficial effects in this regard. (28)

In line with our results, the Argentine Society of Cardiology underscores the use of cardioprotective drugs. (35) A document from the Argentine Federation of Cardiology (36) notes their low usage rate—less than 10% of cases—a finding consistent with other sources. (37,38) Therapeutic inertia and high costs limit the adoption of these therapies. To avoid therapeutic inertia and ensure optimal control, the Argentine Society of Diabetes (SAD) recommends periodic treatment reassessment every 3–6 months. In terms of costs, the recent introduction of domestically manufactured drugs into the market—compared with imported alternatives—will facilitate access to a therapeutic option previously restricted by financial constraints.

**Strengths and limitations.** This study provides data on a cohort of older adults with T2DM in Argentina, a population that is often underrepresented in large clinical trials. Furthermore, the use of multiple imputation to handle missing data contributes to the robustness of the results. Among the limitations, the descriptive nature of our study prevents establishing cause-and-effect relationships. Furthermore, because the cohort was from a single center in Rosario city, caution is warranted when extrapolating the findings nationwide.

In addition, the patients were enrolled in the PAMI health insurance system, whose policies regarding access to and coverage for certain glucose-lowering drugs with proven cardiovascular benefits—such as GLP-1 receptor agonists and SGLT2 inhibitors—may have influenced the low utilization rates observed for these medications.

In conclusion, while most patients in this cohort of older adults with T2DM achieved traditional glycemic control targets, utilization of glucose-lowering drugs with proven cardiovascular benefits was low, and a significant proportion of patients presented potential overtreatment. More than half of the patients with adequate glycemic control had atherogenic indices consistent with a high residual cardiovascular risk, indicating that glycemic target achievement alone does not ensure cardiovascular risk reduction. These findings highlight the need to integrate atherogenic indices into routine cardiovascular risk assessment and support the need for therapeutic strategies that simultaneously address glycemic control and residual cardiovascular risk reduction.

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#### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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# ST-Segment Elevation Acute Myocardial Infarction in Argentina: 11 Years of the ARGEN-IAM-ST Registry

## *Infarto agudo de miocardio con elevación del ST en Argentina. 11 años del Registro ARGEN-IAM-ST*

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ON BEHALF OF THE ARGEN-IAM-ST RESEARCHERS. CONDUCTED BY THE ARGENTINE SOCIETY OF CARDIOLOGY AND THE ARGENTINE FEDERATION OF CARDIOLOGY

### ABSTRACT

**Background:** ST-segment elevation acute myocardial infarction (STEMI) is the leading cause of morbidity and mortality worldwide and in our country. Having a registry with sufficiently robust data can enable the adoption of public policies and guidelines tailored to national needs.

**Objective:** To identify clinical aspects, delays, treatment regimens, and outcomes, as well as potential barriers that need to be addressed in the care of STEMI.

**Methods:** Since December 2014, a national registry has been in place that includes patients with STEMI with a duration of less than 36 hours.

**Results:** As of December 2025, 8,073 patients had been included, with a mean age of 61 years; 79% were male. The infarct location was anterior in 50% of cases. Fifty percent of patients were admitted after being referred from another institution, but only 27% received fibrinolytics prior to referral. The overall reperfusion rate was 93% (10% with fibrinolytics and 80% with primary angioplasty), with treatment times that remain inadequate. Delays in treatment were reported in >60% of cases, particularly during the patient's initial consultation and transport to the facility; among reperfused patients, the rate was 8%, and 15% among non-reperfused patients. Heart failure at admission was observed in 23% of patients and was one of the most significant predictors of mortality in the multivariate analysis.

**Discussion:** These data provide a snapshot of the current state of acute myocardial infarction (AMI) in Argentina and its evolution over the past 11 years. Despite high reperfusion rates, no significant changes in mortality have been observed. Delays in treatment are significant. There is a need to implement corrective strategies that could help reduce mortality.

**Keywords:** Myocardial infarction - Registries - Epidemiology - Reperfusion - Primary angioplasty

### RESUMEN

**Introducción:** El infarto agudo de miocardio con elevación del segmento ST (IAMCEST) es la principal causa de morbimortalidad en el mundo y en nuestro país. Contar con un registro con información suficientemente sólida puede permitir adoptar políticas públicas y guías ajustadas a las necesidades nacionales.

**Objetivo:** Releva aspectos de la clínica, demoras y esquemas de tratamiento y resultados, así como las eventuales barreras a ser mejoradas en la atención del IAMCEST.

**Material y métodos:** Desde diciembre de 2014 se lleva a cabo un registro nacional que incluye pacientes con IAMCEST de menos de 36 h de evolución.

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**Resultados:** Hasta diciembre de 2025 se incluyeron 8073 pacientes, edad media 61 años, 79% de sexo masculino. La localización del infarto fue anterior en el 50%. El 50% de los pacientes ingresaron derivados de otra institución, pero solo el 27% recibió fibrinolíticos antes de la derivación. La tasa de reperfusión general fue del 93% (10% con fibrinolíticos y 80% con angioplastia primaria) con tiempos al tratamiento que persisten inadecuados. Se reportaron demoras en el tratamiento en >60% de los casos, sobre todo en la consulta del paciente y el traslado para la realización de; en los pacientes reperfundidos fue 8%, y 15% en los no reperfundidos. La insuficiencia cardíaca al ingreso se observó en el 23% y fue uno de los predictores más importantes de mortalidad en el análisis multivariado.

**Discusión:** Estos datos permiten delinear un mapa de la realidad del IAM en la Argentina y su evolución a través de los últimos 11 años. A pesar de altas tasas de reperfusión no se observan cambios significativos en la mortalidad. Las demoras al tratamiento son importantes. Surge la necesidad de implementar estrategias correctivas que podrían colaborar para disminuir la mortalidad.

**Palabras clave:** Infarto de miocardio - Registros - Epidemiología - Reperfusión - Angioplastia primaria

## INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide and in our country, as well as a leading cause of disability and loss of work capacity among adults. Access to diagnostic and therapeutic strategies requires adequate coordination of the healthcare system and goes far beyond the role of specialists. It is essential to have accurate information on its prevalence and treatment, as well as on the various barriers that limit access to appropriate diagnosis and treatment, with a view to addressing them. Both for basic knowledge and for evaluating the relevance and effectiveness of corrective measures, a robust registry of these conditions is required to enable the adoption of public policies and guidelines tailored to national needs.

Acute myocardial infarction with ST-segment elevation (STEMI) is one of the conditions that poses the greatest challenges to the healthcare system. It is the leading cause of morbidity and mortality worldwide (1) and in our country. (2) In Argentina, the annual rate of AMI was estimated at 41.9 per 10 000 inhabitants and, when adjusted for other types of classic heart attacks, at 55.9 per 10 000 among those aged 35 to 64. (3,4)

Early recognition prevents death from arrhythmias in the first few hours and allows for the implementation of strategies to reperfuse the myocardium using thrombolytic drugs or invasive procedures such as primary angioplasty.

Antiplatelet therapy and myocardial reperfusion strategies (both medical and percutaneous) have favorably altered the natural short- and long-term course of the disease, (5,6) and their impact is greater the earlier they are implemented. (7,8)

Multiple barriers hinder adequate treatment: delays in patients seeking care, failure to perform or misinterpretation of electrocardiograms, lack of training among emergency physicians to initiate reperfusion measures early, difficulties in accessing medication, and the absence of coordinated networks to facilitate rapid referral to centers with greater treatment capacity.

All records show, across different areas of the system, a failure to implement reperfusion strategies in a timely and appropriate manner in a large number of

patients, whether due to late arrival, the “unavailability” of fibrinolytics, (9) or the lack of a catheterization lab or referral options. Even in regions where resources are available, a lack of coordination or networking prevents their adequate utilization, and delays persist that result in preventable deaths and disability. (10,11) The Argentine Society of Cardiology (SAC) and the Argentine Federation of Cardiology (FAC) have been conducting cross-sectional registries of the epidemiological, clinical, and therapeutic characteristics of acute coronary syndromes (ACS) for nearly 40 years, (12–14) in which these delays or the failure to implement reperfusion strategies can be observed.

A thorough understanding of the reality of these delays, along with their contributing factors, will help establish strategies to address the barriers that prevent adequate medical care. Similarly, understanding the treatment strategies used and their outcomes will help identify future improvements and ultimately reduce complications and mortality from myocardial infarction.

Establishing a national AMI registry allows for the collection of concrete and representative data from across the country to develop policies aimed at improving survival rates.

## OBJECTIVES

The main objectives of this registry are:

- To evaluate changes in the clinical course of STEMI through a prospective registry with cross-sectional analyses.
- To evaluate the time intervals and causes of delay from symptom onset to reperfusion therapy: pre-hospital and in-hospital delays
- To assess the prevalence of reperfusion therapy in patients admitted with STEMI, reperfusion modalities (thrombolytics/angioplasty), and causes of non-reperfusion.
- To assess in-hospital mortality and complications
- To analyze treatment modalities.

## METHODS

This is a national registry of patients with STEMI admitted to intensive care units throughout the country. Institutions with intensive care units that admit cardiovascular

patients—selected through the Argentine Integrated Health Information System (SISA)—and institutions affiliated with the SAC-FAC scientific societies were invited to participate.

The characteristics of the participating institutions were surveyed to determine the level of complexity of each and their degree of integration into the country's healthcare system.

#### *Inclusion criteria:*

- Patients admitted with STEMI
- Progressed AMI with new Q waves within the past 36 hours.
- Suspected inferoposterior AMI (horizontal ST-segment depression in leads V1 through V3, suggestive of acute occlusion of the circumflex coronary artery).
- New or suspected new left bundle branch block.

#### *Exclusion criteria:*

- Acute Coronary Syndrome without ST-Segment Elevation, or non-Q-wave myocardial infarction.
- Myocardial infarctions with a duration of more than 36 hours.

Demographic and clinical data (age, sex, risk factors, medical history, comorbidities), clinical presentation (location of the myocardial infarction, Killip and Kimball class at admission, duration of symptoms), treatment administered (antiplatelet agents, reperfusion therapy, adjunctive therapy), and in-hospital clinical course (heart failure, post-infarction angina, shock, death) were collected.

Data collection was performed using a specially designed electronic form accessible via the web. In 2020, the system was migrated to a database developed by the SAC on RedCap.

#### *Patient Data Confidentiality*

Patient privacy in the registry is guaranteed, as patients' names or initials are not stored in the database. Patients are identified by a sequential number assigned by each center.

Since this registry does not collect data that would allow patients to be identified, informed consent was not required.

#### *Statistical Analysis*

This is a prospective, cross-sectional, multicenter registry with nationwide coverage.

Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on their distribution, and qualitative variables as proportions with their confidence intervals. Comparative analysis of discrete variables was performed using contingency tables. Comparative analysis of continuous variables was performed using the t-test or the Kruskal-Wallis test for unpaired data, or analysis of variance (ANOVA), as appropriate.

For the multivariate analysis of events with a dichotomous distribution, logistic regression analyses were performed. The relationship between the variables was initially determined through univariate analysis. Subsequently, those variables considered relevant (principle of parsimony) and/or those that had a p-value <0.1 in the previous analysis were manually selected. The variables selected for the final model were expressed with their corresponding odds ratio (OR) and 95% confidence interval (95% CI).

Sample size calculation was based on one of the registry's primary objectives, which was to evaluate predictors of death in patients admitted with STEMI. We used this pa-

rameter because it requires the largest number of patients to ensure stability in the prediction of the regression models.

According to evidence from simulation studies, logistic models require between 12 and 15 events per predictor to generate stable results. (15,16) In our registry, we predefined the possibility of analyzing approximately 25 predictive variables, including clinical, electrocardiographic, and laboratory variables.

Previous registries conducted in our setting have reported a mortality rate of approximately 10%. We set an initial sample size of 3000 patients to ensure stability in the prediction models. Considering the scenario with the lowest mortality rate (8%), we were able to analyze up to 20 predictor variables based on the number of events. A mortality rate of 10% allowed us to analyze up to 25 variables without compromising the validity of the results. Finally, we considered the sample size to be sufficient to carry out the remaining objectives set by the registry related to reperfusion times and strategies.

A p-value <0.05 was considered statistically significant. The analysis was performed using EpiInfo Version 7.2.2.6 and Stata/SE 13.0®.

#### *Ethical Considerations*

The protocol was reviewed and approved by the Bioethics Committee of the Argentine Society of Cardiology (February 15, 2015) and, in accordance with local regulations and institutional policies, was submitted for review by local committees. The protocol was registered on ClinicalTrials.gov under number NCT2458885.

Some of the results have been previously published. (17–21)

## **RESULTS**

### *Demographic and Institutional Characteristics*

During the initial phase of the registry, between December 2014 and December 2015, 247 centers nationwide participated (43% public and 57% private), of which 56.3% were dedicated coronary care units and 57.6% were centers capable of performing primary angioplasty.

During that period, 1759 patients (age  $61 \pm 12$  years) were enrolled, 78% of whom were male. Most were admitted with ST-segment elevation; only 25 patients were admitted with left bundle branch block and 11 with ST-segment depression in leads V1 through V3 due to suspected occlusion of the circumflex coronary artery. The results were previously published. (17) From then until December 2025, although the number of participating institutions decreased, a total of 8073 patients were enrolled. The characteristics of the cohort were similar to those of the cohort included in the initial phase (Table 1). Approximately 13% of patients had a history of coronary artery disease, and about 11% were previously taking aspirin.

The location of the myocardial infarction was anterior in 50.2% of cases and inferior in 45.8%. At admission, 1825 patients (23.1%) showed signs of heart failure, and 588 (7.4%) were in cardiogenic shock.

### *Reperfusion therapy*

The overall reperfusion rate was 93.2%, and the reperfusion strategy consisted of fibrinolytic therapy in

**Table 1.** General Characteristics of the Population

| Variable                             | N           | Data N | %    | 95% CI      |
|--------------------------------------|-------------|--------|------|-------------|
| Age, years (mean $\pm$ SD)           | 61 $\pm$ 12 |        |      |             |
| Male                                 | 6357        | 8062   | 78.9 | 77.9 – 79.7 |
| Coronary risk factors                |             |        |      |             |
| High Blood Pressure                  | 4375        | 8073   | 54.2 | 53.1 – 55.3 |
| Diabetes                             | 2193        | 8073   | 27.2 | 26.2 – 28.2 |
| Dyslipidemia                         | 3047        | 8073   | 37.3 | 36.7 – 38.8 |
| Smoking                              | 1036        | 3130   | 33.1 | 31.1 – 35.0 |
| Family history                       | 1150        | 8073   | 14.3 | 13.5 – 15.0 |
| Cardiovascular history               | 1519        | 8073   | 18.8 | 18.0–19.7   |
| Coronary artery disease              | 1033        | 8073   | 12.8 | 12.1 – 13.5 |
| Heart failure                        | 156         | 8073   | 1.9  | 1.7–2.3     |
| Stroke                               | 129         | 8073   | 1.6  | 1.4 – 1.9   |
| Peripheral vascular disease          | 101         | 8073   | 1.3  | 1.0–1.5     |
| Atrial fibrillation / Atrial flutter | 39          | 8073   | 1.3  | 1.0–1.5     |
| COPD                                 | 249         | 8073   | 3.1  | 2.7 – 3.5   |
| Chronic kidney disease               | 76          | 8073   | 0.9  | 0.8–1.2     |
| Previous use of aspirin              | 876         | 8046   | 10.9 | 10.2–11.6   |
| Location of the Heart Attack         |             | 7918   |      |             |
| Anterior                             | 3,977       |        | 50.2 | 49.1 – 51.3 |
| Inferior                             | 3,624       |        | 45.8 | 44.7 – 46.9 |
| Lateral                              | 267         |        | 3.4  | 3.0 – 3.8   |
| Undetermined                         | 50          |        | 0.6  | 0.5 – 0.8   |
| Killip and Kimball on Admission      |             | 7911   |      |             |
| I                                    | 6086        |        | 76.9 | 76.0 – 77.9 |
| II                                   | 1114        |        | 14.1 | 13.3 – 14.9 |
| III                                  | 123         |        | 1.6  | 1.3 – 1.9   |
| IV                                   | 588         |        | 7.4  | 6.9 – 8.0   |

COPD: chronic obstructive pulmonary disease; SD: standard deviation; 95% CI Confidence interval 95%

10.2% of cases and percutaneous coronary intervention (PCI) in 80.4% (Table 2).

Rescue PCI was performed in 316 (21.2%) of the patients who received thrombolysis, and only 202 (3.2%) underwent a pharmacologically invasive strategy. The thrombolytic agent of choice was streptokinase (92.5%); in the remaining patients, alteplase (7.0%) and tenecteplase (0.5%) were used.

The primary success rate of coronary angioplasty was 96.1%, and 96.3% of patients received stents, most of which were drug-eluting (69.1%). The arteries responsible for the myocardial infarction were: the anterior descending artery (47.8%), the right coronary artery (34.4%), the circumflex artery (12.8%), the diagonal artery (2%), the left main coronary artery (1.3%), and venous bypass grafts (0.5%).

The reason for failure to achieve reperfusion was recorded in 302 patients, with delayed presentation being the main reason (75.5%), followed by lack of availability of thrombolytics (13.3%) and contraindications to thrombolytics (11.3%).

#### Delays

The delay from symptom onset to admission was 120 minutes (IQR 60–270); the door-to-needle time was

59 minutes (IQR 30–120), the total ischemia time was 180 minutes (IQR 105–300) in patients treated with fibrinolytics, the door-to-balloon time was 78 minutes (IQR 45–137), and the total ischemia time was 317 minutes (IQR 190–610) in patients undergoing PCI. Among the main causes of delays, physicians reported patients' delay in seeking medical attention in 38.1% of cases, delay in referral for primary PCI treatment in 24.0%, followed by delays related to the ambulance in 19.0% and emergency department care in 13.2%.

Two-thirds of patients were admitted within 3 hours of symptom onset (Table 3). 68.3% of patients treated with primary PCI were admitted within 3 hours of symptom onset.

#### In-hospital Outcomes

Overall mortality was 8.5%, with the majority due to cardiac causes (72.4%). Mortality among patients with cardiogenic shock was 53.1%, while patients classified as Killip and Kimball Class I had a mortality rate of 3% (Figure 1).

During the hospital stay, heart failure (among those admitted without heart failure) at 13.1% and atrial fibrillation at 4.4% were the most common com-

plications. The incidence of major bleeding was 0.7% (Table 4).

*Patients referred to centers with cardiac catheterization capabilities.*  
The lack of coordinated networks to facilitate rapid referral to centers with the capacity to perform cardiac catheterization leads to delays that can cause

primary angioplasty—currently recognized as the strategy with the best outcomes—to lose its relative advantage. (22)  
In Argentina, more than 90% of patients presenting with STEMI receive reperfusion therapy. (12,14,23) This figure might be considered high, but the actual conditions under which it is administered—and in particular the delays involved—are not ideal.

**Table 2.** Types of reperfusion therapy

| Reperfusion                        | N    | Data N | %    | 95% CI      |
|------------------------------------|------|--------|------|-------------|
| Patients who underwent reperfusion | 7492 | 8039   | 93.2 | 92.6 – 93.7 |
| Fibrinolytics only                 | 772  | 7608   | 10.2 | 9.5 – 10.9  |
| PCI only                           | 6116 | 7608   | 80.4 | 79.5 – 81.3 |
| Both                               | 720  | 7608   | 9.5  | 8.8 – 10.1  |
| Primary angioplasty                | 5611 | 6258   | 89.9 | 89.1 – 90.4 |
| Rescue angioplasty                 | 316  | 6258   | 5.05 | 4.5 – 5.6   |
| Pharmacoinvasive therapy           | 202  | 6258   | 3.2  | 2.8 – 3.7   |
| Angioplasty for another reason     | 129  | 6258   | 2.1  | 1.7 – 2.4   |

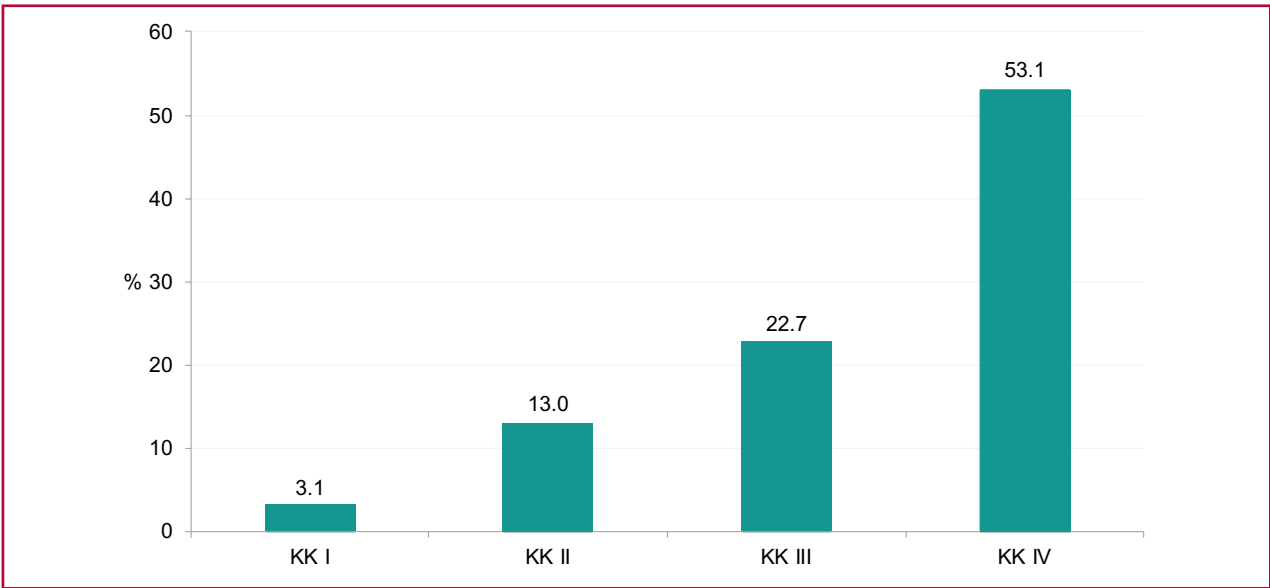
PCI: percutaneous coronary intervention

**Table 3.** Time intervals from symptom onset to admission to the facility.

| Hours to admission | N    | %    | Minutes (Median) | IQR       |
|--------------------|------|------|------------------|-----------|
| 0–3                | 5346 | 66.5 | 60               | 30–120    |
| >3–6               | 1257 | 15.6 | 255              | 215–300   |
| >6–12              | 815  | 10.1 | 492              | 420–600   |
| >12–24             | 402  | 5.0  | 1007             | 840–1200  |
| >24                | 224  | 2.8  | 2160             | 1715–3115 |

IQR: interquartile range

**Fig. 1.** Mortality according to the Killip and Kimball (KK) classification at admission



In this study, we analyzed the prevalence of patients with STEMI who are referred to centers with catheterization laboratories and whether these patients were treated in a timely and appropriate manner in accordance with national and international guidelines, whether referred for primary angioplasty or pharmacologically invasive treatment.

We included 8045 patients in the analysis, of whom 3608 (44.8%) were admitted as referrals from other centers. The characteristics of the population, based on whether or not they were referred, are summarized in Table 5. Patients referred from another center were younger, had a lower prevalence of prior coronary artery disease, and had a higher incidence of anterior AMI and a higher Killip and Kimball class at admission.

#### Reperfusion Therapy

The prevalence of reperfusion therapy among referred patients was lower than among those treated at the first center or on-site, primarily due to a lower use of primary PCI (Figure 2). When comparing referred patients with those treated on-site, the overall use of reperfusion therapies was lower among the referred patients: 91.7% versus 94.5% (OR 0.64; 95% CI 0.54–0.77;  $p=0.001$ ). When the analysis was restricted to patients treated with reperfusion strategies, primary angioplasty was used less frequently in the referred group: 84.6% versus 92.8% (OR 0.42; 95% CI 0.36–0.50), and thrombolytics were used more frequently: 15.4% versus 7.2% (OR 3.10; 95% CI 2.60–3.70;  $p<0.001$ ). Of the 1018 out of 3353 referred patients who received thrombolytics (30.4%), 905 (88.9%) received them prior to referral.

Rescue angioplasty was performed in 316 patients—272 among those referred and 44 among those treated at the initial center; percutaneous coronary intervention was performed in 174 referred patients

and 28 patients at the initial center.

The primary success rate of angioplasty was similar among patients treated at the first center and those referred (96.2% vs. 95.8%).

In 547 patients (6.8%), no reperfusion therapy was performed, with a higher proportion among referred patients (Figure 2).

#### Delays

The delay from symptom onset to admission was 120 minutes (IQR 60–270) in the overall population. Among patients transferred from another institution, the total delay was 360 minutes (IQR: 190–660), whereas among those who presented directly, it was 2 hours shorter: 120 minutes (IQR: 60–270;  $p<0.001$ ). Fewer than one-quarter of patients referred from another institution were admitted within 3 hours of symptom onset (23.5% vs. 66.6%; OR 0.15; 95% CI 0.14–0.17;  $p<0.001$ ) (Table 6).

The door-to-balloon time for patients who underwent primary angioplasty at the first center they visited that was equipped to perform the procedure was 86.5 minutes (IQR: 50–150), whereas for those referred from another center it was 64 minutes (IQR: 36–120) ( $p < 0.001$ ). The total time window from symptom onset to balloon inflation was 450 minutes (IQR: 270–792) for referred patients and 245 minutes (IQR: 155–450) for those treated at the first center ( $p < 0.001$ ). The delay in waiting for treatment at the first center and/or transfer was more than 3 hours.

As summarized in Figure 3, among referred patients, the time to pre-referral thrombolysis was 150 minutes, and the time to primary angioplasty was 315 minutes. The difference in time between the potential administration of thrombolysis prior to transfer versus angioplasty can be analyzed in two ways: a) by comparing the time from symptom onset to on-site thrombolysis (152 minutes) and the time to angioplasty

**Table 4.** Events During Hospitalization

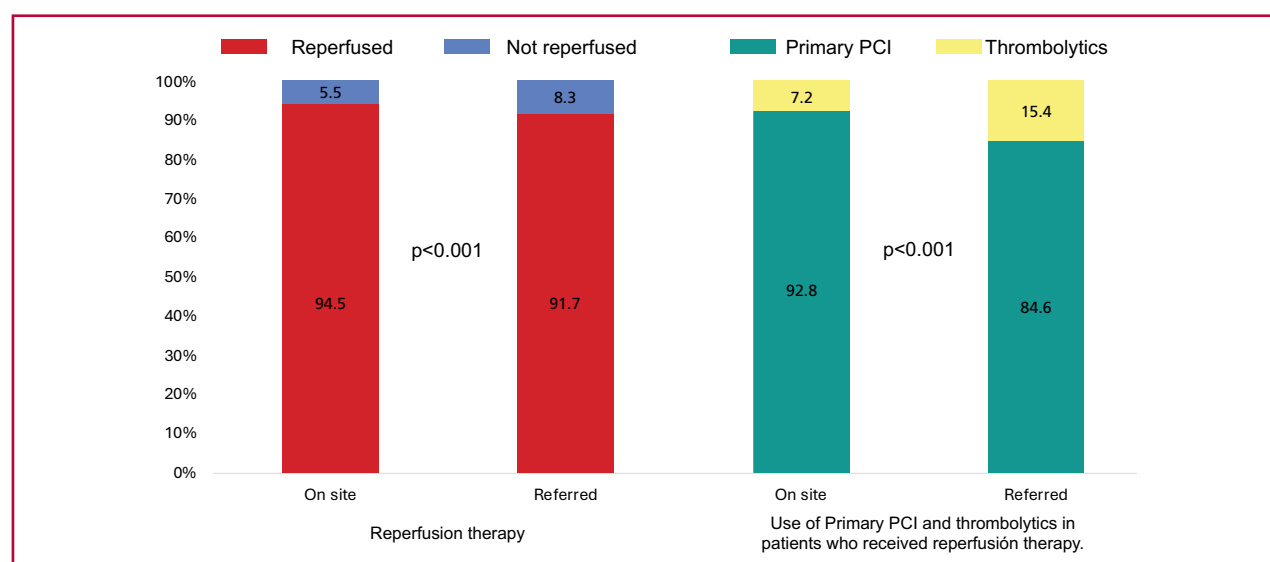
| Reperfusion                     | N    | Data N | %    | 95% CI      |
|---------------------------------|------|--------|------|-------------|
| Overall mortality               | 638  | 7517   | 8.49 | 7.88 – 9.14 |
| Post-infarction angina          | 168  | 8073   | 2.1  | 1.8 – 2.4   |
| Recurrent myocardial infarction | 141  | 8073   | 1.8  | 1.5 – 2.1   |
| Stroke                          | 70   | 8073   | 0.9  | 0.7 – 1.1   |
| Atrial fibrillation             | 356  | 8073   | 4.4  | 3.9–4.9     |
| Heart failure                   | 1055 | 8073   | 13.1 | 12.4 – 13.8 |
| Mechanical complications        | 95   | 8040   | 1.2  | 0.9 – 1.4   |
| Ventricular septal defect       | 43   |        | 0.5  |             |
| Mitral regurgitation            | 31   |        | 0.4  |             |
| External cardiac rupture        | 21   |        | 0.3  |             |
| Hemorrhage                      | 339  | 8039   | 4.2  | 3.8 – 4.7   |
| Minimal                         | 199  |        | 2.5  | 2.2 – 2.8   |
| Moderate                        | 81   |        | 1.0  | 0.8 – 1.3   |
| Major                           | 59   |        | 0.7  | 0.6 – 0.9   |

**Table 5.** Baseline characteristics of the population according to whether or not they were referred.

| Variable                               | Referred (n=3608; 44.8%) |      | Non-referred (n=4439; 55.2%) |      | OR   | 95% CI      | p      |
|----------------------------------------|--------------------------|------|------------------------------|------|------|-------------|--------|
| Age, years (mean $\pm$ SD)             | 59.4 $\pm$ 11.5          |      | 62.4 $\pm$ 12.2              |      | –    | –           | <0.001 |
|                                        | n                        | %    | n                            | %    |      |             |        |
| Male                                   | 2890                     | 80.1 | 3453                         | 77.8 | 11.5 | 1.03 – 1.28 | 0.024  |
| <b>Coronary risk factors</b>           |                          |      |                              |      |      |             |        |
| High blood pressure                    | 1953                     | 54.1 | 2413                         | 54.4 | 0.99 | 0.91 – 1.08 | 0.822  |
| Diabetes                               | 1021                     | 28.3 | 1167                         | 26.3 | 1.11 | 1.00 – 1.22 | 0.045  |
| Dyslipidemia                           | 1281                     | 35.5 | 1763                         | 39.7 | 0.84 | 0.76 – 0.91 | <0.001 |
| Smoking                                | 418                      | 41.8 | 342                          | 26.5 | 2.03 | 1.71 – 2.44 | <0.001 |
| Family history                         | 506                      | 14.0 | 643                          | 14.5 | 0.96 | 0.85 – 1.09 | 0.554  |
| <b>Other medical history</b>           |                          |      |                              |      |      |             |        |
| Coronary heart disease                 | 353                      | 9.8  | 679                          | 15.3 | 0.60 | 0.52 – 0.69 | <0.001 |
| Heart failure                          | 63                       | 1.8  | 93                           | 2.1  | 0.83 | 0.60 – 1.15 | 0.262  |
| COPD                                   | 79                       | 2.2  | 169                          | 3.8  | 0.57 | 0.43 – 0.74 | <0.001 |
| Chronic kidney disease                 | 30                       | 0.83 | 46                           | 1.04 | 0.80 | 0.50 – 1.27 | 0.345  |
| Stroke                                 | 55                       | 1.52 | 74                           | 1.67 | 0.91 | 0.64 – 1.30 | 0.613  |
| Aspirin use                            | 343                      | 9.5  | 533                          | 12.0 | 0.77 | 0.67 – 0.89 | <0.001 |
| Anterior location                      | 1,859                    | 52.5 | 2,107                        | 48.4 | 1.18 | 1.08 – 1.29 | <0.001 |
| <b>Killip and Kimball at admission</b> |                          |      |                              |      |      |             |        |
| I                                      | 2,643                    | 74.6 | 3,430                        | 78.8 |      |             |        |
| II                                     | 529                      | 14.9 | 583                          | 13.4 |      |             |        |
| III                                    | 52                       | 1.5  | 71                           | 1.6  |      |             |        |
| IV                                     | 317                      | 8.9  | 268                          | 6.2  |      |             | <0.001 |
| > I                                    | 898                      | 25.4 | 922                          | 21.2 | 1.26 | 1.13 – 1.40 | <0.001 |

Results expressed as a percentage of the total number of patients with no missing data for each variable

CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation;

**Fig. 2.** Prevalence and type of reperfusion therapy according to whether patients were treated at the first center (on-site) or referred from other centers.

PCI: percutaneous coronary intervention

ty (315 minutes), a difference of 163 minutes, or more than 2.5 hours (Figure 3); b) by comparing the time from arrival at the facility to on-site thrombolysis (60 minutes) with the time from arrival plus the referral time (130 minutes) and the door-to-balloon time (65 minutes), for a total of 195 minutes. The difference was thus 135 minutes, more than 2 hours.

Among patients who received thrombolytics, the door-to-needle time was 45 minutes (IQR: 30–90) for those contacted by the first center and 60 minutes (IQR: 30–125) for those referred; only 32% of the referred patients and 33.9% of those treated at the first center had a door-to-needle time  $\leq 30$  minutes. The total time window from symptom onset to thrombolytic infusion was slightly longer in referred patients (180 minutes; IQR: 100–300) compared with those treated at the center (160 minutes; IQR: 89.5–267) ( $p=0.056$ ).

Referred patients had a lower proportion of positive reperfusion criteria than those treated on-site (41.2% vs. 51.2%; OR 0.67; 95% CI 0.52–0.86;  $p=0.001$ ).

In-hospital mortality was similar between patients referred from other institutions and those treated on-site (Table 7).

#### *Mortality and its relationship to different reperfusion therapies*

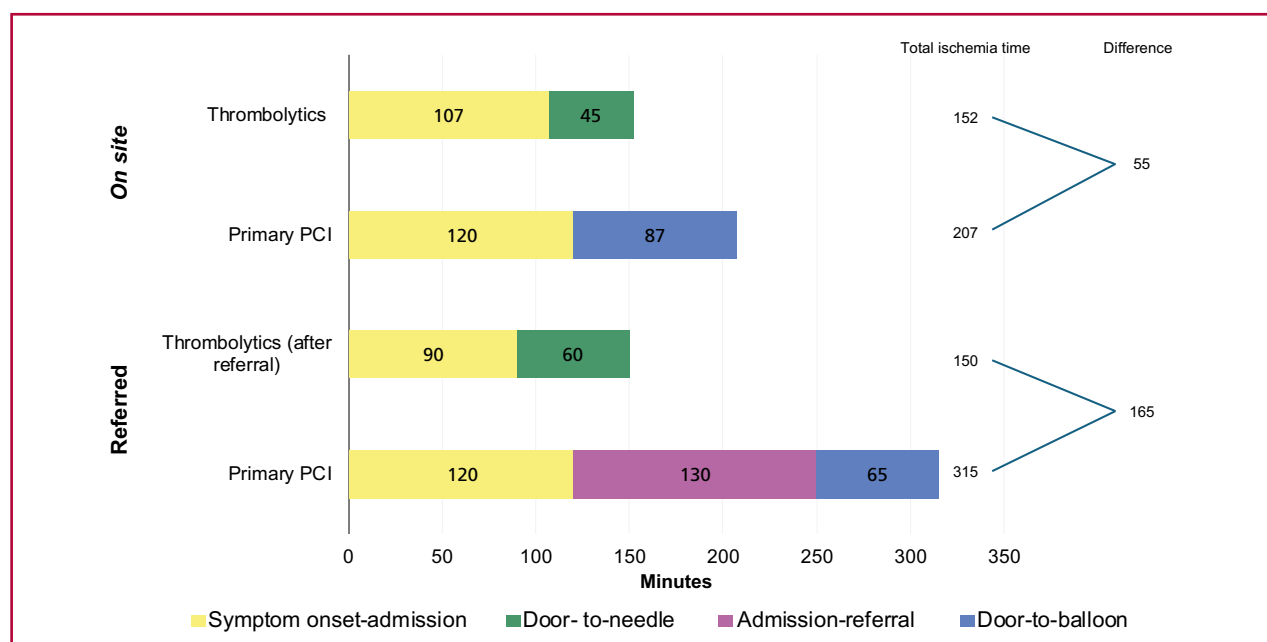
We conducted an analysis to identify the components of overall mortality according to different subgroups of patients who did or did not receive reperfusion therapy and their relationship to delays and total ischemia time.

In-hospital mortality was 8.49%. The population characteristics associated with mortality are summarized in Table 8. Deceased patients were older, one-

**Table 6.** Time intervals from symptom onset to admission

| Hours from symptom onset to admission | Referred (n=3608) |      | Not referred (n=4425) |      |
|---------------------------------------|-------------------|------|-----------------------|------|
|                                       | n                 | %    | n                     | %    |
| 0–3                                   | 847               | 23.5 | 2955                  | 66.6 |
| >3 – 6                                | 1003              | 27.8 | 683                   | 15.4 |
| >6–12                                 | 957               | 26.5 | 470                   | 10.6 |
| >12–24                                | 521               | 14.4 | 208                   | 4.7  |
| >24–36                                | 142               | 3.9  | 60                    | 1.4  |
| >36                                   | 138               | 3.8  | 61                    | 1.4  |

**Fig. 3.** Total ischemia time for patients in different therapeutic scenarios and institutional delays in those treated on-site or referred from other centers without reperfusion capabilities. The time from patient presentation to admission is calculated as the difference between the total (median) myocardial ischemia time minus the door-to-needle or door-to-balloon time (median). In the specific case of patients referred from other centers for primary percutaneous coronary intervention (PPCI); the same presentation time was used as for on-site primary PCI (120 minutes).



TL: thrombolytics

**Table 7.** In-hospital events based on whether patients were referred or treated on-site

| In-hospital events       | Referred (n=3608) |      | Not referred (n=4437) |      | OR   | 95% CI      | p      |
|--------------------------|-------------------|------|-----------------------|------|------|-------------|--------|
|                          | n                 | %    | n                     | %    |      |             |        |
| Overall mortality        | 297               | 8.66 | 340                   | 8.35 | 1.04 | 0.88 – 1.22 | 0.631  |
| Cardiovascular mortality | 239               | 6.62 | 223                   | 5.03 | 1.34 | 1.11 – 1.61 | 0.002  |
| Post-infarction angina   | 90                | 2.49 | 78                    | 1.76 | 1.43 | 1.05 – 1.94 | 0.021  |
| Recurrent heart attack   | 56                | 1.55 | 85                    | 1.92 | 0.81 | 0.57 – 1.13 | 0.222  |
| Stroke                   | 35                | 0.97 | 35                    | 0.77 | 1.23 | 0.77 – 1.97 | 0.384  |
| Atrial fibrillation      | 173               | 4.8  | 183                   | 4.1  | 1.17 | 0.95 – 1.45 | 0.156  |
| Cardiac arrest           | 366               | 10.3 | 424                   | 9.6  | 1.07 | 0.92 – 1.24 | 0.383  |
| Bleeding                 | 191               | 5.3  | 146                   | 3.3  | 1.64 | 1.32 – 2.05 | <0.001 |
| Minimal                  | 120               | 3.3  | 77                    | 1.74 |      |             |        |
| Moderate                 | 41                | 1.14 | 40                    | 0.90 |      |             |        |
| Major                    | 30                | 0.83 | 29                    | 0.66 |      |             |        |
| Heart failure            | 559               | 15.5 | 495                   | 11.2 | 1.46 | 1.28 – 1.66 | <0.001 |
| Cardiogenic shock        | 399               | 11.1 | 359                   | 8.1  | 1.41 | 1.22 – 1.64 | <0.001 |
| Mechanical complications | 53                | 1.47 | 42                    | 0.95 | 1.56 | 1.04 – 2.34 | 0.037  |

third of them were women, and they had a higher prevalence of a history of coronary artery disease and heart failure, as well as a higher prevalence of risk factors, with the exception of smoking and family history. More than 70% of the deceased patients had heart failure according to the Killip classification at admission.

### Mortality

Mortality among patients who did not receive reperfusion therapy was twice that of those who did (15.4% vs. 7.9%; OR 2.12; 95% CI 1.65–2.71;  $p < 0.0001$ ). Most patients received primary angioplasty, with a mortality rate of 7.49%, which was lower than that of patients who received fibrinolytics: 9.93% (OR 0.73; 95% CI 0.60–0.89;  $p=0.002$ ). Rescue angioplasty was performed in 21.2% of patients treated with thrombolytics, with a mortality rate of 11.0%, while pharmacologically invasive treatment was administered to only a small proportion of patients treated with thrombolytics (13.4%) and was associated with a low mortality rate (5.6%) (Figure 4).

We conducted an exploratory and descriptive analysis to examine changes in reperfusion and mortality from 2015 to 2025. While reperfusion rates remained more or less constant, a slight but non-significant downward trend ( $p$  trend = 0.30) in mortality was observed during the last three-year period, despite sustained high reperfusion rates. (Figure 5).

### Mortality and Treatment Duration

Patients admitted to a medical facility within 3 hours of symptom onset (66.5%) had a mortality rate of 7.6%, compared with 10.4% among those admitted

later (OR 0.71; 95% CI 0.59–0.83;  $p < 0.001$ ) (Table 9).

Deceased patients who underwent primary angioplasty had longer time from hospital admission, door-to-balloon time, and total ischemia time than survivors (Figure 6A). No statistically significant differences were detected in patients treated with fibrinolytics, although it was also observed that door-to-needle time and total ischemia time were longer than recommended (Figure 6B).

Patients who died and received rescue angioplasty had a significantly longer total ischemia time compared with survivors (720.5 minutes [IQR 382–795] versus 545.5 minutes [IQR 525–947];  $p=0.005$ ). Patients treated with a pharmacological-invasive strategy had a total ischemia time of 770 minutes (IQR 465–1128); deceased patients had a longer total ischemia time (915 minutes versus 745 minutes;  $p=0.445$ ), though this did not reach statistical significance.

### Mortality. Multivariate analysis

The independent variables associated with higher mortality were the presence of heart failure, defined as a Killip class greater than I at admission (OR: 10.5; 95% CI 8.66–12.62;  $p < 0.001$ ), age  $\geq 65$  years (OR: 1.90; 95% CI 1.59–2.27;  $p < 0.001$ ), and having received reperfusion therapy was protective (OR: 0.62; 95% CI 0.47–0.83;  $p = 0.001$ ).

### DISCUSSION

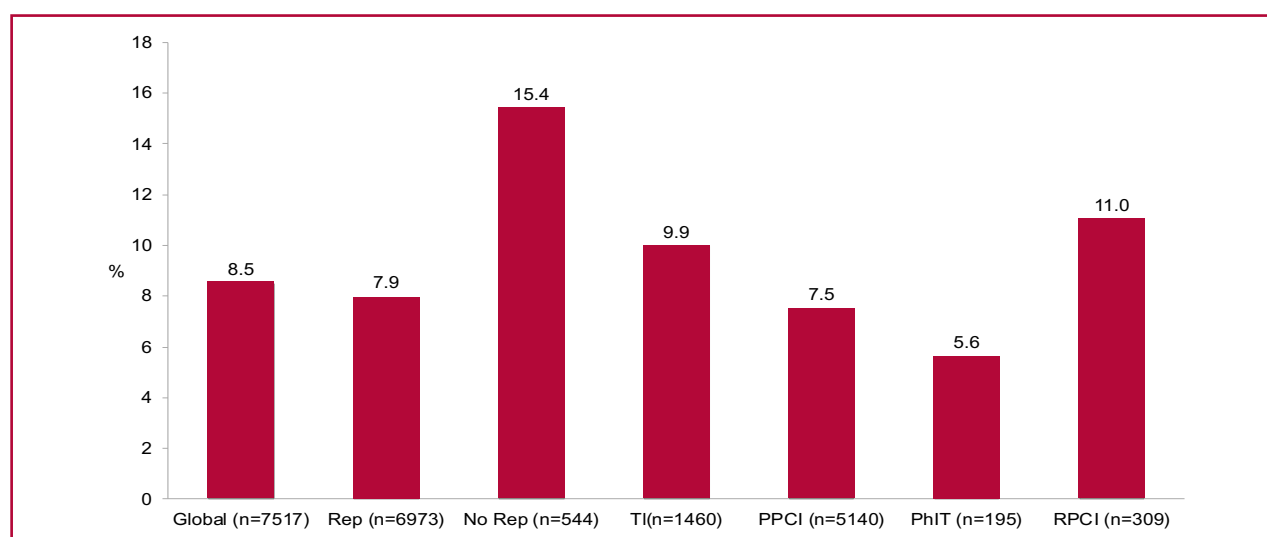
The national STEMI registry (ARGEN-IAM-ST) is, to date, the largest conducted in our country, having enrolled more than 8000 patients over the past 11 years.

The initial phase (2014–2015) had the highest

**Table 8.** Clinical characteristics associated with in-hospital mortality..

| Variable                                       | Survivors<br>(n=6879) |      | Deceased<br>(n=638) |      | Odds Ratio | 95% CI      | p      |
|------------------------------------------------|-----------------------|------|---------------------|------|------------|-------------|--------|
| Age, years, median (IQR)                       | 60 (IQR 53–68)        |      | 67 (IQR 59–76)      |      | -          | -           | <0.001 |
|                                                | n                     | %    | n                   | %    |            |             |        |
| Female                                         | 1389                  | 20.2 | 185                 | 29.0 | 1.61       | 1.35 – 1.94 | <0.001 |
| Age ≥ 65 years                                 | 2334                  | 34.2 | 349                 | 55.5 | 2.39       | 2.03 – 2.83 | <0.001 |
| <b>Coronary risk factors</b>                   |                       |      |                     |      |            |             |        |
| High Blood Pressure                            | 3944                  | 57.3 | 425                 | 66.6 | 1.48       | 1.25 – 1.76 | <0.001 |
| Diabetes                                       | 1959                  | 28.5 | 232                 | 36.4 | 1.44       | 1.21 – 1.70 | <0.001 |
| Dyslipidemia                                   | 2771                  | 40.3 | 274                 | 42.9 | 1.12       | 0.95 – 1.31 | 0.192  |
| Smoking                                        | 686                   | 43.9 | 53                  | 37.3 | 0.76       | 0.53 – 1.08 | 0.134  |
| Family History                                 | 1084                  | 15.8 | 65                  | 10.2 | 0.61       | 0.47 – 0.79 | <0.001 |
| <b>Cardiovascular History</b>                  |                       |      |                     |      |            |             |        |
| Coronary heart disease                         | 908                   | 13.2 | 123                 | 19.3 | 1.57       | 1.27 – 1.94 | <0.001 |
| Heart failure                                  | 120                   | 1.7  | 36                  | 5.6  | 3.37       | 2.30 – 4.93 | <0.001 |
| <b>Other Background Information</b>            |                       |      |                     |      |            |             |        |
| COPD                                           | 205                   | 3.0  | 43                  | 6.7  | 2.35       | 1.68 – 3.30 | <0.001 |
| Previous aspirin use >7 days                   | 697                   | 10.1 | 87                  | 13.6 | 1.40       | 1.10 – 1.78 | 0.006  |
| Anterior Location                              | 3374                  | 50.0 | 339                 | 54.5 | 1.20       | 1.02 – 1.41 | 0.034  |
| <b>Killip and Kimball at admission</b>         |                       |      |                     |      |            |             |        |
| I                                              | 5498                  | 81.5 | 174                 | 27.9 |            |             |        |
| II                                             | 908                   | 13.5 | 136                 | 21.9 |            |             |        |
| III                                            | 85                    | 1.3  | 25                  | 4.0  |            |             |        |
| IV                                             | 254                   | 3.8  | 287                 | 46.1 |            |             | <0.001 |
| > I                                            | 1247                  | 18.5 | 448                 | 72.0 | 11.4       | 9.43 – 13.7 | <0.001 |
| Symptom onset-admission interval ≤ 180 minutes | 4626                  | 67.4 | 379                 | 59.4 | 0.71       | 0.59 – 0.83 | <0.001 |

Results expressed as a proportion of the total number of patients with no missing data for each variable  
 COPD: Chronic obstructive pulmonary disease; IQR: interquartile range

**Fig. 4.** Overall mortality and mortality by type of reperfusion.

No Rep: patients not treated with reperfusion therapy; PhIT pharmacoinvasive therapy; PPCI: primary percutaneous intervention; Rep: patients treated with reperfusion therapy; RPCI: rescue PPCI; TL: thrombolytic therapy

Fig. 5. Annual variation in the reperfusion rate and mortality.

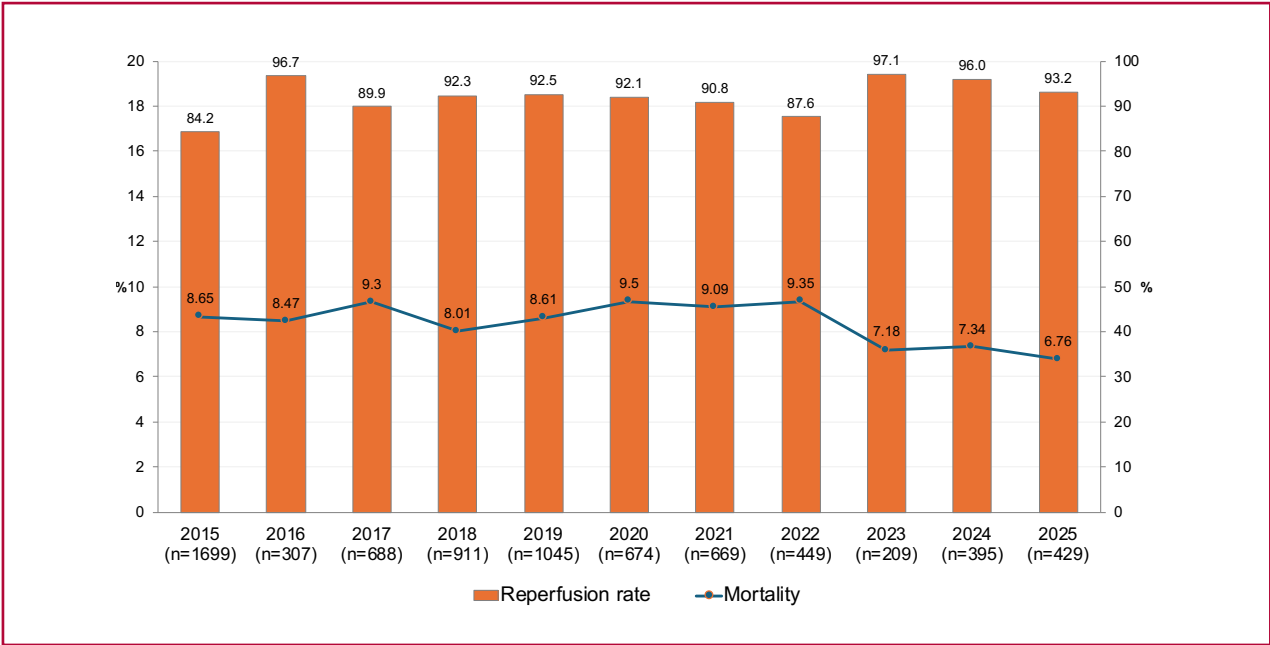


Table 9. Mortality by length of hospital stay

| ≤ 3 hours        | > 3 hours        | Odds Ratio | 95% CI      | P      |
|------------------|------------------|------------|-------------|--------|
| 379/5005 (7.57%) | 259/2493 (10.4%) | 0.71       | 0.59 – 0.83 | <0.001 |
| ≤ 6 hours        | > 6 hours        |            |             |        |
| 479/6157 (7.78%) | 159/1341 (11.9%) | 0.63       | 0.52 – 0.76 | <0.001 |
| ≤ 12 hours       | > 12 hours       |            |             |        |
| 572/6907 (8.28%) | 66/591 (11.2%)   | 0.72       | 0.55 – 0.94 | 0.016  |
| ≤ 24 hours       | > 24 hours       |            |             |        |
| 607/7281 (8.34%) | 31/217 (14.3%)   | 0.55       | 0.28 – 0.80 | 0.002  |

participation, with 247 centers from all Argentine provinces taking part; in some cases, this represented 100% of the centers registered with the National Ministry of Health, with an average participation rate of 22%.(26)

The data obtained during the registry’s initial phase made it possible to map the reality of AMI in Argentina at that time, revealing a reperfusion rate exceeding 80%, high use of primary PCI, and an overall mortality rate of 8.8%.(17)

Barriers to timely and appropriate access to treatment were identified. Although more than 70% of patients sought care within 6 hours of symptom onset, the proportion of patients receiving treatment with door-to-balloon and door-to-needle times in line with recommendations was far from adequate.

Physicians identified treatment delays in more than 60% of cases, primarily attributed to delays in

patient presentation and the need to refer patients to another center for angioplasty. This finding was further corroborated by the fact that the window time for angioplasty and thrombolytic therapy was longer in this group.

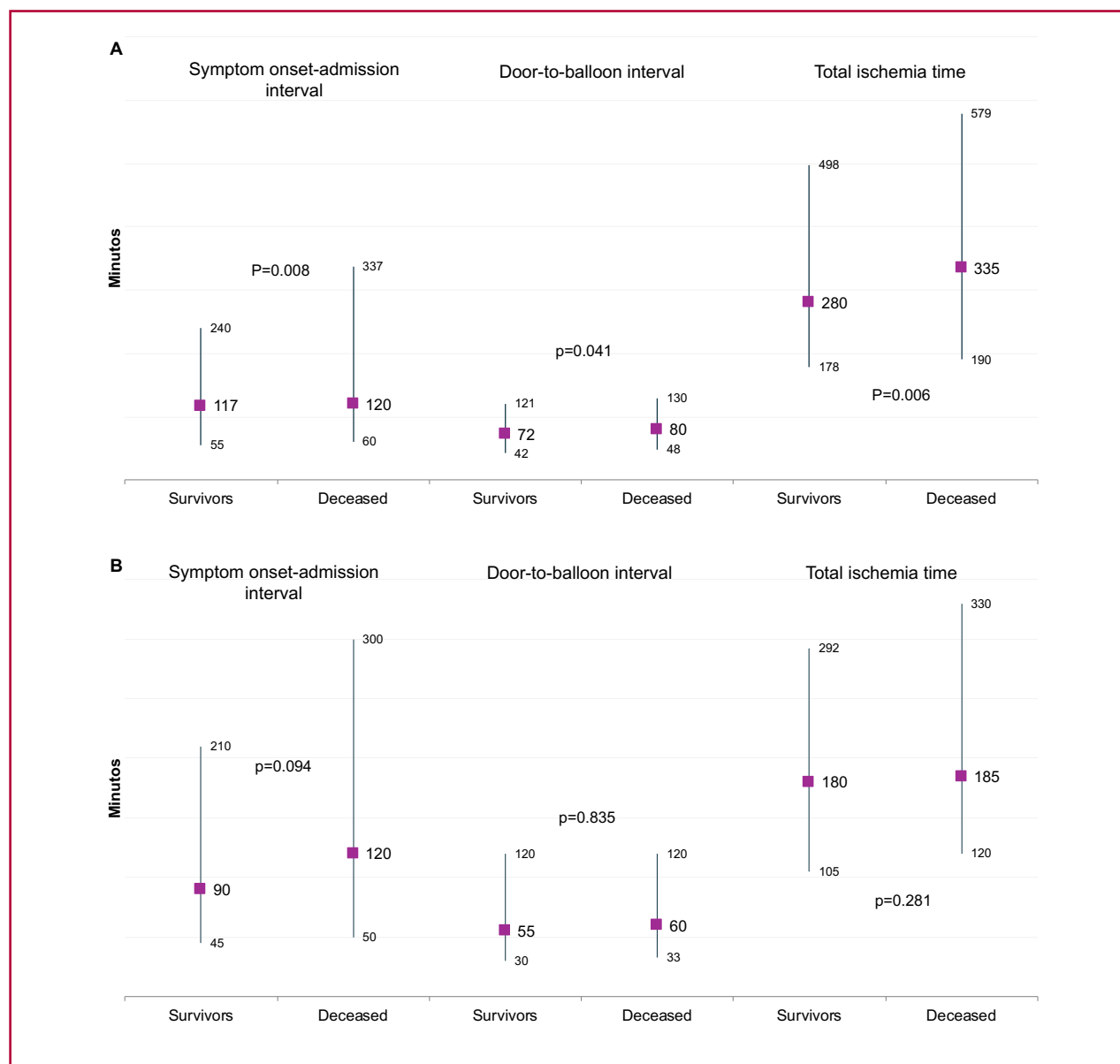
The registry’s ongoing nature has allowed us to monitor the most important parameters related to care and outcomes for patients treated for AMI at centers in different provinces across Argentina. (17,27)

Although the core group of participating centers has decreased, the registry continues to enroll a significant number of patients annually, enabling analysis and a critical examination of real-world practice.

Reperfusion and Mortality

Over the course of these 11 years, we observed no significant changes in times to reperfusion or overall in-hospital mortality compared to what was observed in

**Fig. 6.** Times to admission, to treatment, and total ischemia time, and their relationship to mortality according to the indicated treatment: Primary angioplasty (A) or fibrinolytic therapy (B) (medians and IQR).



the initial phase. These data are similar to previously published registries from more selective centers with cardiology residencies (14,23,28), and while they are somewhat higher than those of some international registries, such as the French one (29), they are similar to those of public registries in that country (30) and somewhat lower than those of American registries (31).

In 2020, a study was published comparing mortality rates between the United Kingdom and Sweden in 842 897 patients with acute coronary syndrome, with or without ST-segment elevation, between 2003

and 2013. (32) These data do not reflect the current situation, particularly in the United Kingdom, but they can help us compare certain aspects with our registry. They reported lower rates of revascularization (primary angioplasty or revascularization surgery)—43.8% in the United Kingdom versus 74.9% in Sweden; however, reperfusion achieved with thrombolytics (tPA and/or fibrinolytics) was higher in the United Kingdom (78.9% versus 75.7%;  $p<0.05$ ). The standardized net probability of death between admission and 1 month was higher in the United Kingdom: 8.0% (95% CI 7.4–8.5) versus 6.7% (95% CI 6.5–6.9)

in Sweden. Mortality in the ARGEN-IAM-ST registry is higher, although our population is much younger than that of Sweden and the United Kingdom ( $61 \pm 12$  years versus  $68.9 \pm 12.6$  and  $65.8 \pm 13.6$  years, respectively) and the reperfusion rate in our registry is higher ( $>90\%$ ). (19) In turn, mortality varies according to the reperfusion procedures performed.

STEMI is a condition in which survival is time-dependent: ideally, the patient should present within 3 hours of symptom onset, and reperfusion therapy should be administered as quickly as possible—either thrombolytic therapy with a door-to-needle time of less than 30 minutes, or primary angioplasty with a door-to-balloon time of less than 90 minutes. In the real world, it is very difficult to meet these time targets. (33)

We have observed that total ischemia time is associated with higher mortality and is significantly longer in transferred patients. (18)

In the registry, 30% of patients present more than 180 minutes after symptom onset, which is associated with higher mortality. Furthermore, the total ischemia time is very prolonged, particularly with regard to reperfusion times, which deviate from the recommendations of clinical practice guidelines. (34–38) An analysis of the temporal variation in two key markers—reperfusion and overall in-hospital mortality—reveals little progress in reversing these outcomes. This mortality rate has remained unchanged over the past 18 years in registries conducted by the SAC and the FAC. (12,17,23,39)

#### *Implications of Referral to Centers with Catheterization Laboratories*

Currently, the way to address this complex problem is to focus on prehospital logistics and regionalization, as demonstrated by the Stent Save Life initiative in our country, (40) which achieved a low mortality rate (3.5%) among patients treated within 3 hours of symptom onset. However, overall mortality remains high (7%), similar to that of patients treated with primary angioplasty in our registry (7.49%).

Referral for reperfusion therapy is required in nearly half of all heart attacks, and there are still inadequate response times in the coordination of the heart attack care system. Forty percent of participating centers do not offer primary angioplasty. (17)

Referred patients were less likely to receive reperfusion therapy, and the quality of their treatment was lower, as 20% fewer primary angioplasties were performed. These findings are consistent with the study by Ting et al. (41) from the U.S. National Acute Myocardial Infarction Registry, which included 440 398 patients, in which the authors observed that the delay between the onset of symptoms and hospital presentation was associated with lower use of reperfusion therapies and higher mortality.

The delay in initiating primary angioplasty in patients is well above the recommendations in the guide-

lines. Patients who received thrombolytic therapy prior to referral also had a door-to-needle time that exceeded the recommended limit (60 minutes).

The observed times show that the difference between access to thrombolysis versus angioplasty in referred patients was 135 or 150 minutes, depending on the measurement criterion—in both cases, a very long delay. It is well established in the literature that after a 2-hour delay from needle to balloon, the benefit of angioplasty is lost. (42–44)

Studies analyzing the strategy of administering thrombolytics at the referral site versus transfer for primary angioplasty showed no benefit for angioplasty when symptom onset was less than 3 hours, but transfer proved beneficial with longer times, particularly regarding the incidence of reinfarction and stroke. (45–47) However, the door-to-balloon times in these studies were very short and very difficult to translate to real-world practice; therefore, based on these data, a large number of patients could benefit from the use of fibrinolytics prior to referral.

In the registry, only 27% of patients received thrombolytic therapy prior to referral. Overall, 5% underwent rescue angioplasty, and only 3.2% received a pharmacologically invasive strategy.

On the other hand, the pharmacologically invasive strategy has proven to be successful and comparable to the outcomes of primary angioplasty, provided that tecteplase is available and rescue angioplasty is performed on patients who do not meet reperfusion criteria. (48,49) The STREAM study demonstrated a mortality rate of approximately 4.5% with a total ischemia time of 100 minutes for a pharmacologically invasive strategy and 179 minutes for primary angioplasty. (50) In the registry, the total ischemia time for thrombolytic therapy was approximately 180 minutes, and for primary angioplasty, it was 280 minutes for survivors and 335 minutes for those who died. It is evident that the doubled mortality rate in the registry correlates with very prolonged total ischemia times. It is striking that in a country with long distances such as Argentina, the rate of use of the pharmacologically invasive treatment is so low and that it has not been a strategic option. (51,52) Even though mortality among patients receiving the pharmacologically invasive strategy was lower in our registry, its application was limited and the patient group was highly selected. The utility of this strategy in a community setting has not been evaluated in the Argentine context.

Twenty-one percent of patients who received fibrinolytics required rescue angioplasty with a total ischemia time of approximately 9 hours, which explains the high mortality rate compared to the aforementioned randomized studies, and a low mortality rate in patients reperfused with thrombolytics who subsequently underwent angioplasty with a longer total ischemia time (12 hours), but pharmacologically invasive treatment cannot be considered in any way without taking into account those patients who do not

achieve reperfusion and require the procedure within less than 2 hours.

### The Role of Heart Failure

Patients with heart failure at admission (HFad) in the context of STEMI account for approximately one in every four or five hospitalized patients. These data are similar to those from other international registries with a comparable population; (53–56) however, the rate is lower than in other South American countries. (57) Furthermore, the presence of HFad is associated with older age, and one in four patients was female. This is consistent with other studies, in which a 5- to 10-year increase in age raises the probability of HF by 30%. (58,59) The incidence is also higher in women, likely due to delays in seeking medical care, diagnosis, and implementation of guideline-recommended treatment, as well as lower use of reperfusion strategies. (60) In addition, there are comorbidities associated with patients admitted with heart failure, such as hypertension, (58,61) atrial fibrillation (62), and diabetes mellitus. (63)

The time from symptom onset to admission was slightly shorter but statistically significant in patients without acute coronary syndrome. The median time to consultation was approximately 120 minutes, which is somewhat shorter than in other registries, where more than 60% of patients waited at least 120 minutes, (54) and even with times exceeding 160 minutes, (64) where variables associated with a delay in consultation include advanced age, absence of acute coronary syndrome (ACS), diabetes, and onset of pain in the early morning hours, among others. (54) However, a non-significant increase in door-to-balloon time was observed in the group of patients with ACS. This could reflect the medical team's preference for the patient to be as stable as possible upon admission to undergo PCI.

As is well known, the reperfusion strategy in STEMI is imperative regardless of the patients' hemodynamic status. (65) However, the presence of HF was significantly associated with lower use of any type of reperfusion strategy. This is consistent with other studies in which reperfusion strategies in patients with heart failure and acute coronary syndrome are used to a lesser extent, (24, 59) even though they are associated with reduced mortality. (66) No differences were observed between the groups regarding the type of reperfusion (fibrinolytics or primary coronary angioplasty), but differences were noted regarding the success of these procedures, which were more frequent in patients without HF. This could be related to the fact that the most commonly used fibrinolytic agent in Argentina is streptokinase (17) and that the longer door-to-balloon time may have reduced the success of primary angioplasty.

Regarding oral pharmacological therapy, we observed significant differences. The dual antiplatelet therapy strategy was less common in patients with

CAD, which could be related to the fact that reperfusion therapy was less common in this group. However, this finding is not supported by previous studies, since dual antiplatelet therapy—regardless of whether patients underwent reperfusion or not—is associated with a significant reduction in mortality. (67) Regarding the use of beta-blockers at admission, although it was more common in the group without CAD, it is noteworthy that one in three patients with CAD still received this type of medication during admission, despite their known increased risk of cardiogenic shock and death, (68) but their use was not associated with increased mortality in the multivariate analysis. On the other hand, the use of renin-angiotensin system inhibitors was less frequent in patients with HF with acute coronary syndrome, which could be related to the lower blood pressure values in this group. Although statin use was high at the time of hospitalization—even higher than in other registries (54)—it was less frequent in patients with acute heart failure. These last two classes of drugs were associated with a significant reduction in mortality in the multivariate analysis.

Finally, mortality in the group with HF was one in every three or four patients, with a nearly 12-fold increased risk compared to those without heart failure in the univariate analysis and more than an 8-fold increased risk in the multivariate analysis. Although HF is one of the strongest predictors of mortality in STEMI, (24,56) the increase observed in this analysis exceeds data from other countries, (24,63) including data from Argentina itself more than 15 years ago, where the mortality rate reported at a specialized cardiovascular care center was 15.6% among patients with STEMI and heart failure. (69) The reperfusion strategy was significantly associated with a reduction in mortality in the multivariate analysis, which continues to highlight the importance of this treatment, which should be attempted in more patients and within the timeframes recommended by the guidelines.

### CONCLUSIONS

These data provide a snapshot of the current state of STEMI in Argentina and its evolution over the past 10 years. The reperfusion rate has increased significantly without any change in in-hospital mortality.

Delays in treatment are significant, and there are areas that need improvement. Delays in treatment were observed in more than 60% of cases, particularly regarding patients consultation and referrals to other centers.

These data suggest the need to implement corrective strategies, such as launching medical education programs, adopting supportive health policies, and considering regional characteristics and the on-the-ground cost-benefit analysis of reperfusion strategies, all of which could help shorten reperfusion times for both thrombolytic therapy and primary angioplasty. Identifying and addressing these barriers could result

in a reduction of up to 2 hours in delays.

Improving the quality of care for cardiovascular patients by optimizing adherence to diagnostic and treatment standards can also be achieved through various approaches. One such approach, already documented internationally, (70-73) involves institutions' self-assessment of their performance levels and the implementation of coordination measures, such as a single phone number for heart attacks, the establishment of protocols, referral and care networks, diagnostic support systems like telemedicine, and other initiatives that can be evaluated at the global or regional level based on identified issues.

There are successful examples of implementing heart attack networks that have been shown to reduce response times and improve mortality rates in Argentina, and this is a viable tool for application in routine clinical practice—especially given that physicians reported delays related to ambulances and emergency department care as significant factors impacting patient care, making it necessary to expand its use as a strategy to improve care for acute myocardial infarction (AMI). (74-77)

Networking will also enable the implementation of initiatives that result in improved quality of care and the development of epidemiological research projects that enhance patient care and outcomes. Ultimately, this involves gaining an in-depth understanding of the problems and adopting measures to improve the quality of care and reduce morbidity and mortality.

Finally, although the registry has methodological weaknesses, it remains the only independent tool open to the scientific community that allows for a discussion of the reality of AMI in Argentina.

#### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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# STS Benchmarking in Congenital Heart Disease Surgery in Argentina: Is Comparison Feasible?

## Uso de Benchmarking STS en cirugía de cardiopatías congénitas en Argentina: ¿es posible compararse?

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### ABSTRACT

**Background:** The Society of Thoracic Surgeons (STS) cardiac surgery database reports the outcomes of benchmark procedures in pediatric cardiac surgery (STS-CHSD). Its primary objective is to support quality improvement in pediatric cardiac surgery programs in North America by evaluating and reporting in-hospital mortality outcomes, expressed as interquartile ranges (IQRs), for the 10 benchmark procedures since 2012, at 5-year intervals.

**Objective:** To evaluate the outcomes of an Argentine pediatric cardiovascular surgery unit for these 10 benchmark procedures by comparing them with those reported by the STS-CHSD.

**Methods:** Using our pediatric cardiovascular surgery unit database, we identified all patients who underwent procedures defined as STS-CHSD benchmarks over the past 15 years and compared the local outcomes with the external, with their international interquartile ranges (IQRs).

**Results:** A total of 412 patients who underwent surgery were identified, including 7 deaths, with the following results: mortality (STS IQR): 1) Surgical repair of aortic coarctation without cardiopulmonary bypass: 0% (0.0–1.71%); 2) ventricular septal defect (VSD) closure: 0% (0–0.78%); 3) tetralogy of Fallot repair: 1.8% (0–1.96%); 4) complete atrioventricular (AV) canal repair: 1.88% (0 to 1.75%); 5) arterial switch operation for simple transposition of the great arteries (TGA): 0% (0 to 3.45%); 6) arterial switch operation for TGA with VSD closure: 10% (0 to 7.14%); 7) Glenn procedure: 1.69% (0 to 2.53%); 8) Fontan-Kreutzer procedure: 1.75% (0 to 1.84%); 9) truncus arteriosus repair: 0% (0 to 18.75%); and 10) Norwood procedure: 6.66% (5.77–15%).

**Conclusion:** Our results are better or similar to STS CHSD. Only in 2 procedures are above the STS IQR, demonstrating the feasibility of using STS benchmarking in our country with excellent results.

**Key words:** benchmarks - pediatric cardiovascular surgery - mortality - Norwood - arterial switch - Fontan-Kreutzer

### RESUMEN

**Introducción:** La base de datos de cirugía cardíaca de la Sociedad de Cirujanos Torácicos de los Estados Unidos (STS) reporta los resultados de procedimientos Benchmark (punto de referencia) en cirugía cardíaca pediátrica (STS-CHSD). El objetivo principal es mejorar la calidad de los programas de cirugía cardíaca pediátrica en América del Norte, al evaluar y reportar desde 2012, en periodos de 5 años, los resultados de mortalidad hospitalaria con rango intercuartilico (RIC) para 10 procedimientos Benchmark.

**Objetivo:** Comparar los resultados de una unidad de cirugía cardiovascular pediátrica argentina en esos 10 procedimientos con los resultados reportados por la STS-CHSD.

**Materiales y métodos:** De nuestra base institucional de los últimos 15 años se identificaron todos los casos correspondientes a los 10 procedimientos benchmark STS-CHSD y se comparó la mortalidad local con la reportada por STS y su RIC.

**Resultados:** Se identificó un total de 412 pacientes sometidos a cirugía, incluidas 7 muertes, con los siguientes resultados: mortalidad (RIC STS): 1) Coartación de aorta sin CEC: 0% (0,0 a 1,71%); 2) Cierre de CIV: 0% (0 a 0,78%); 3) Corrección de Fallot: 1,8% (0 a 1,96%); 4) Corrección de Canal AV completo: 1,88% (0 a 1,75%); 5) Cirugía de switch arterial para TGA simple: 0% (0 a 3,45%); 6) Cirugía de switch para TGA con CIV: 10% (0 a 7,14%); 7) Procedimiento de Glenn: 1,69% (0 a 2,53%); 8) Operación de Fontan-Kreutzer: 1,75% (0 a 1,84%); 9) Corrección de tronco arterioso: 0% (0 a 18,75%); 10) Cirugía de Norwood: 6,66% (5,77 a 15%).

**Conclusión:** Nuestros resultados son en general mejores o similares a los de STS-CHSD; solo en dos procedimientos se encuentran por encima del RIC de referencia, demostrando la posibilidad de utilizar el Benchmarking STS en el país con excelentes resultados.

**Palabras clave:** Benchmarks - Cirugía cardiovascular pediátrica - Mortalidad - Norwood - Switch - Fontan-Kreutzer

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## INTRODUCTION

Surgery for congenital heart diseases in Argentina faces challenges related to variability in clinical outcomes and the lack of standardized indicators for evaluating the quality of care. (1-3) In this context, benchmarking tools, such as the model developed by the Society of Thoracic Surgeons (STS), provide a robust reference framework for comparing outcomes and promoting improvements in surgical practice. (4-5) This national database was established in 1989 as an initiative to improve the quality and safety of cardiothoracic surgery, providing an accurate and valid basis for measuring the performance of units in our specialty. (6) It currently comprises three databases: the STS Adult Cardiac Surgery Database (ACSD), the STS Congenital Heart Surgery Database (CHSD), and the STS General Thoracic Surgery Database (GTSD). (7) It is one of the largest and most comprehensive clinical registries, containing data on nearly 10 million procedures performed by more than 4300 surgeons, including 95% of adult cardiac surgery procedures. (2)

The STS Congenital Heart Surgery Database (STS-CHSD) is the largest of its kind in North America. It reports 30-day postoperative mortality rates for benchmark procedures (3) and publishes results every five years based on four-year datasets. (4-8) To ensure methodological validity in international comparisons, the STS, in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), promoted the universal standardization of diagnoses and surgical procedures through the IPCCC (International Pediatric and Congenital Cardiac Code) nomenclature system. (9) The latest report, from 2022, recorded a total of 623 907 surgeries, with the participation of 92% of the country's pediatric cardiac surgery programs (125 hospitals). (8) The 10 benchmarks were selected by the STS-CHSD working group based on the procedures most commonly performed across all participating centers, to provide more procedure-specific data to the participating institution. (10,11)

Its primary objective is to support quality improvement in pediatric cardiac surgery programs in North America by evaluating and reporting in-hospital mortality outcomes, expressed as interquartile ranges (IQRs), for the 10 benchmark procedures.

## OBJECTIVE

The aim of this study is to evaluate the outcomes of an Argentine pediatric cardiovascular surgery unit for these 10 benchmark procedures by comparing them with those reported by the STS-CHSD.

## METHODS

In 2011, the STS CHSD defined the benchmark procedures for congenital heart surgery. (10,11) The mortality results with their interquartile range (IQR) reported in 2023 are as follows: (4) 1) Surgical repair of aortic coarctation without cardiopulmonary bypass: 0.89% (0 to 1.71%); 2) ventricular septal defect (VSD) closure: 0.35% (0 to 0.78%); 3) tetralogy of Fallot repair: 1.09% (0 to 1.96%); 4) complete atrio-

ventricular (AV) canal repair: 1.38% (0 to 1.75%); 5) arterial switch operation for simple transposition of the great arteries (TGA): 1.83% (0 to 3.45%); 6) arterial switch operation for TGA with VSD: 5.15% (0 to 7.14%); 7) Glenn procedure: 1.99% (0 to 2.53%); 8) Fontan-Kreutzer procedure: 1.08% (0 to 1.84%); 9) truncus arteriosus repair: 8.1% (0 to 18.75%); and 10) Norwood procedure: 11.68% (5.78% to 15%).

Using our pediatric cardiac surgery unit database, we identified 412 patients who underwent procedures defined as STS benchmarks over the past 15 years and assessed 30th postoperative day mortality for each patient.

Operative mortality is defined in all STS databases (5) as: 1) all deaths, regardless of cause, occurring during the episode of care in which the operation was performed, even if after 30 days (including patients transferred to other acute care facilities), and 2) all deaths, regardless of cause, occurring after discharge home from the hospital but before the end of the 30th postoperative day. The interquartile range (IQR), a measure of dispersion, is calculated from the data distribution. In this study, procedure-specific mortality from Hospital Austral is presented as an aggregated value (a single percentage for each type of surgery). Therefore, we cannot calculate an individual IQR for each procedure, as there is no internal variability within each reported value.

Consequently, we calculated only the overall IQR, considering all 10 benchmark procedures.

## Ethical Considerations

The study was approved by the institutional review board.

## RESULTS

The following results were obtained for each benchmark procedure: 1) Surgical repair of aortic coarctation without cardiopulmonary bypass: n=37, mortality 0%; 2) VSD closure: n=80, mortality 0%; 3) tetralogy of Fallot repair: n=55, mortality 1.8%; 4) complete AV<canal repair: n=53, mortality 1.75%; 5) arterial switch operation for TGA: n=21, mortality 0%; 6) arterial switch operation for TGA with VSD: n=10, mortality 10%; 7) Glenn procedure: n=59, mortality 1.69%; 8) Fontan-Kreutzer procedure: n=57, mortality 1.75%; 9) truncus arteriosus repair: n=10, mortality 0%, and, 10) Norwood procedure with Blalock Taussig shunt: n=30, mortality 6.66% (Table 1). The total number of deaths was 7, with an overall mortality rate of 1.7% (7/412). The overall IQR ranged from 0% to 1.86%. This value reflects the central variability of mortality in our institution compared with the interquartile ranges reported by the STS-CHSD.

Causes of death:

- Intracranial bleeding in one patient with Fontan-Kreutzer procedure for LV hypoplasia.
- Rhinovirus pneumonia in one patient with a Glenn procedure and tricuspid valve repair for LV hypoplasia.
- Massive intracranial bleeding in one patient (2.3 kg) with refractory preoperative heart failure and a history of cerebral bleeding with an arterial switch with VSD closure.
- Sepsis in one patient with a complete unbalanced AV canal (26 kg).
- Biventricular failure due to tachyarrhythmia in

one patient with Tetralogy of Fallot and a transannular patch.

- Two deaths associated with Norwood procedure for mitro-aortic atresia: one (2.2 kg) due to supraventricular tachycardia and the other (2.8 kg) due to rotavirus gastroenteritis.

## DISCUSSION

The STS-CHSD is an essential tool for measuring and recording not only mortality in the ten defined benchmark procedures, but also other valuable indicators that help evaluate each surgical program's performance. (4,7) Its use facilitates comparisons between different centers and contributes to the continuous improvement of care. Historically, assessment of surgical quality in congenital heart disease was limited to isolated and non-standardized reporting of in-hospital mortality by each center. However, current trends in quality management and patient safety indicate that objective evaluation requires standardized, reproducible tools adjusted for risk or anatomical complexity, thereby minimizing biases arising from case selection. (4,12) In this context, the ten benchmark procedures selected by the STS-CHSD play a strategic role. Because these procedures encompass the entire spectrum of complexity—from low-mortality operations such as VSD closure or aortic coarctation repair to highly complex palliative or neonatal procedures such as the Norwood procedure or truncus arteriosus repair—they function as a highly sensitive indicator of the overall operational performance of a surgical program, reflecting not only surgical technique but also perfusion, cardiovascular anesthesia, and postoperative intensive care. (10)

In addition to the STS-CHSD, other measurement and statistical systems are widely used in the field of congenital heart diseases, including the RACHS (Risk

Adjustment for Congenital Heart Surgery), (13,14) the Aristotle Score, (15) and the STAT (STS-EACTS Congenital Heart Surgery Mortality Categories) score. (16) RACHS is a stratification system that classifies patients into six risk levels based on the severity of their condition and the type of surgery to be performed, with the aim of predicting associated mortality and morbidity. (13) However, since it encompasses 207 procedures across its categories, the wide heterogeneity within each category requires large sample sizes to achieve significant statistical power, which dilutes or distorts the analysis in small- or medium-volume centers. (13,14) The Aristotle Score, designed by an international group of experts based on the concept of "Aristotle's Doxa," seeks to standardize surgical assessment by assigning a score based on anatomy, ventricular function, and associated anomalies to estimate complexity and predict risk. (15) Although it provides a valuable conceptual framework, the subjectivity inherent in certain factors has limited its systematic adoption as a single indicator. Similarly, the STAT score empirically categorizes surgeries into 5 groups based on mortality observed in tens of thousands of procedures from consolidated registries. (16) Unlike these synthetic risk tools, the fundamental advantage of the STS 10 benchmark procedures lies in their anatomical and technical specificity. (10) By comparing identical procedures "case by case," the model dispenses with numerical abstractions and offers a transparent measurement that is directly interpretable by medical teams, auditors, and institutions. (4,17)

In our department, the outcomes over the last 15 years for the ten benchmark procedures indicate highly favorable performance when compared with North American standards. The recorded mortality rate was lower than that reported by the STS-CHSD for six procedures (aortic coarctation, VSD closure, Glenn

**Table 1.** Benchmark procedure mortality

| Procedure                                                            | n (Hospital Austral) | Mortality STS (IQR) | Hospital Austral mortality |
|----------------------------------------------------------------------|----------------------|---------------------|----------------------------|
| Surgical repair of aortic coarctation without cardiopulmonary bypass | 37                   | 0.89 % (0–1.71)     | 0 %                        |
| VSD closure                                                          | 80                   | 0.35 % (0–0.78)     | 0 %                        |
| Tetralogy of Fallot repair                                           | 55                   | 1.09 % (0–1.96)     | 1.8 %                      |
| Complete AV canal repair                                             | 53                   | 1.38 % (0–1.75)     | 1.88 %                     |
| Arterial switch operation for TGA                                    | 21                   | 1.83 % (0–3.45)     | 0 %                        |
| Arterial switch operation for TGA with VSD                           | 10                   | 5.15 % (0–7.14)     | 10 %                       |
| Glenn procedure                                                      | 59                   | 1.99 % (0–2.53)     | 1.69 %                     |
| Fontan-Kreutzer procedure                                            | 57                   | 1.08 % (0–1.84)     | 1.75 %                     |
| Truncus arteriosus repair                                            | 10                   | 8.1 % (0–18.75)     | 0 %                        |
| Norwood procedure                                                    | 30                   | 11.68 % (5.78–15)   | 6.66 %                     |
| Total                                                                | 412                  | -                   | 1.7% (7/412)               |

AV: atrioventricular; IQR: interquartile range; TGA: transposition of the great arteries; VSD: ventricular septal defect

procedure, truncus arteriosus repair, arterial switch operation in simple TGA, and Norwood procedure). In low-mortality surgeries (surgical repair of aortic coarctation without cardiopulmonary bypass, and VSD closure), in-hospital mortality was 0% vs. 0.89% and 0.35% in the STS, reaffirming the robustness of our care pathways and the effectiveness of early surgical repair. During the cavopulmonary anastomosis, the Glenn procedure had a mortality rate of 1.69% vs. 1.99% in the STS, while the Fontan-Kreutzer procedure had a mortality rate of 1.75% (within the STS IQR range of 0–1.84%); the only death occurred due to massive intracranial bleeding in a patient with single-ventricle physiology and left ventricular hypoplasia, reflecting the high prothrombotic and hemodynamic risk in this population. Among highly complex neonatal procedures, truncus arteriosus repair achieved 100% survival (0% mortality vs. mean STS mortality of 8.10%), and the Norwood procedure showed a mortality rate of 6.66% compared with a mean STS mortality of 11.68%, close to the lower limit of the STS IQR (5.78%–15%). This represents a noteworthy result given the extreme technical and intensive care demands of this condition. (10, 18) In two other cases (Tetralogy of Fallot and Fontan-Kreutzer procedure), the results remained within the IQR.

In only two procedures the values slightly exceeded the upper limit of the IQR published by the STS: complete AV canal repair (1.88% compared with an IQR of 0–1.75% in the STS, which represents a marginal deviation of 0.13%, corresponding to 1 death in 53 cases, caused by sepsis in an infant weighing 2.6 kg) and the arterial switch in TGA with VSD (10% vs. STS IQR 0–7.14%). In this latter subgroup, it is critical to consider the impact of sample size: with a total of 10 patients who underwent surgery, the occurrence of a single death (a newborn with preoperative refractory heart failure and prior intracranial bleeding) results in a drastic percentage jump from 0% to 10%. This statistical instability in small cohorts, known as the “small denominator effect,” is well documented in the clinical literature (17,19), indicating that consolidated analyses over 5- to 10-year periods are needed to identify true trends while minimizing the distortion by isolated events in small subgroups. (4,19)

These results demonstrate the feasibility of applying the STS benchmarking model in our country and in Latin America, where the literature agrees that implementing registration and quality programs reduces morbidity and mortality rates in emerging economies. (17,20) Unlike the historical argument that structural barriers to access prenatal diagnosis, timely referral, equipment, and funding make international standards and interquartile ranges unattainable, (1-3) this empirical evidence confirms that an Argentine university-affiliated center can achieve a consolidated overall mortality rate of 1.7% (7/412), which is equivalent to and even lower than the averages in North America. Moreover, a culture of transparency and systematic

clinical data auditing promotes the development of highly cohesive multidisciplinary teams and provides families and healthcare professionals with access to objective, clearly reported information through the institution’s official website. (4,20)

In summary, adopting the STS benchmarking model for congenital heart disease surgery in Argentina represents a strategic opportunity to raise quality standards, promote equity in care, and improve health outcomes. Although implementing these benchmarks poses considerable challenges, the international experience demonstrates that objective and transparent evaluation systems can generate substantial and sustainable benefits over time.

#### Conflicts of interest

None declared.

(See authors’ conflict of interests forms on the web).

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# In Vivo Gene Editing of PCSK9 in the Prevention of Atherosclerotic Cardiovascular Disease: From Genetic Validation to Clinical Application

*Edición génica in vivo de PCSK9 en la prevención cardiovascular aterosclerótica: de la validación genética a la clínica*

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## ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide, and low-density lipoprotein cholesterol (LDL-C) is the primary causal and modifiable risk factor. Available lipid-lowering therapies—statins, ezetimibe, anti-PCSK9 monoclonal antibodies, and RNA interference—have been shown to reduce cardiovascular events, but they require long-term administration and are limited by efficacy, adherence, cost, and access. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is, to date, the most genetically validated target for the development of in vivo gene-editing strategies aimed at achieving a permanent reduction in LDL-C through a single therapeutic administration. This review describes the biology of PCSK9, the available gene-editing platforms—CRISPR-Cas9, base editing, and primer editing—and their delivery to hepatocytes via lipid nanoparticles. It summarizes preclinical data and ongoing clinical trials (VERVE-101, VERVE-102, and YOLT-101) showing sustained, dose-dependent reductions in LDL-C following a single infusion, with acceptable short-term safety profiles. Finally, the long-term safety, regulatory, economic, and ethical challenges that will determine the eventual translation of this technology into routine clinical practice are discussed.

**Key words:** PCSK9 - Gene editing - CRISPR-Cas9 - Base editing - LDL cholesterol - Atherosclerotic cardiovascular disease

## RESUMEN

La enfermedad cardiovascular aterosclerótica (ECVA) continúa siendo la principal causa de morbimortalidad a nivel mundial, y el colesterol asociado a lipoproteínas de baja densidad (c-LDL) constituye el principal factor de riesgo causal y modificable. Las terapias hipolipemiantes disponibles –estatinas, ezetimibe, anticuerpos monoclonales anti-PCSK9 e interferencia por ARN– han demostrado reducir eventos cardiovasculares, pero requieren administración crónica y están limitadas por la potencia, la adherencia, el costo y el acceso. La proproteína convertasa subtilisina/kexina tipo 9 (PCSK9) es, hasta el momento, el blanco mejor validado genéticamente para el desarrollo de estrategias de edición génica in vivo dirigidas a lograr una reducción permanente del c-LDL mediante una única administración terapéutica. En esta revisión se describe la biología de PCSK9, las plataformas de edición génica disponibles –CRISPR-Cas9, edición de bases y edición prima– y su vehiculización hacia el hepatocito mediante nanopartículas lipídicas. Se resumen los datos preclínicos y los ensayos clínicos en curso (VERVE-101, VERVE-102 y YOLT-101) que muestran reducciones sostenidas y dosis-dependientes del c-LDL tras una infusión única, con perfiles de seguridad aceptables a corto plazo. Finalmente, se discuten los desafíos de seguridad a largo plazo, regulatorios, económicos y éticos que condicionan la eventual traducción de esta tecnología a la práctica clínica habitual.

**Palabras clave:** PCSK9 - Edición génica - CRISPR-Cas9 - Edición de bases - Colesterol LDL - Enfermedad cardiovascular aterosclerótica

## INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death and disability worldwide. (1) Genetic, epidemiological, and randomized clinical trial evidence all point to the same conclusion:

cholesterol bound to low-density lipoproteins (LDL-C) is a causal factor of atherosclerosis, and reducing it proportionally and cumulatively lowers the risk of major cardiovascular events. (2) On this basis, successive generations of lipid-lowering drugs have been devel-

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oped: statins—which inhibit HMG-CoA reductase—; ezetimibe—which blocks intestinal cholesterol absorption—; monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9), and, more recently, small interfering RNA (inclisiran) targeting PCSK9 messenger RNA. (3,4) These tools have demonstrated robust reductions in cardiovascular risk in large patient populations and have benefited millions of people worldwide.

However, a significant therapeutic gap persists. A considerable percentage of high-risk patients do not achieve the LDL-C targets recommended by the guidelines, whether due to lack of efficacy, intolerance, cost, barriers to access, or lack of adherence to treatments that require daily administration or periodic injections for life. (5) Against this backdrop, a distinct therapeutic paradigm is emerging: *in vivo* somatic gene editing, capable of introducing a permanent and targeted modification in hepatocyte DNA with the goal of achieving a lasting or even permanent reduction in LDL-C following a single intravenous infusion.

PCSK9 is the ideal target for this strategy for several reasons, which are discussed in the following section: it is predominantly expressed in the liver, has been validated genetically and pharmacologically for decades, and its complete inactivation—observed naturally in carriers of loss-of-function variants—is not associated with any known adverse clinical consequences. (6) The objective of this review is to summarize, for physicians specializing in cardiovascular prevention and researchers in this field, the current state of knowledge regarding PCSK9 gene editing: its biological basis, the technological platforms used, the results of ongoing clinical trials, and the challenges that still need to be resolved before this technology can be incorporated into clinical practice.

### PCSK9: BASIC BIOLOGY AND GENETIC VALIDATION AS A THERAPEUTIC TARGET

PCSK9 is a secreted serine protease, synthesized mainly in the liver, whose physiological function is to regulate the density of the LDL receptor (LDLR) on the hepatocyte surface. (7) Following secretion, circulating PCSK9 binds to the Epidermal Growth Factor-like repeat A (EGF-A) LDLR domain; this binding prevents the normal recycling of the receptor to the plasma membrane following endocytosis of the LDL-LDLR complex, and instead directs it toward lysosomal degradation. (8) The net result is a lower density of hepatic LDLR, reduced clearance of circulating LDL particles, and, consequently, higher plasma concentrations of LDL-C.

The validation of PCSK9 as a therapeutic target arose from human genetics rather than targeted drug development. In 2003, gain-of-function variants in the PCSK9 gene were identified as the cause of autosomal dominant familial hypercholesterolemia. (9) Shortly thereafter, population-based studies identified the inverse phenomenon: individuals carrying loss-

of-function variants in PCSK9—including nonsense variants that are more common in populations of African descent—exhibited reductions in LDL-C ranging between 28% to 40%, along with a lifetime reduction in the risk of coronary heart disease of up to 88%. (10,11) Crucially, these carriers showed no apparent adverse phenotype associated with the partial or near-total absence of circulating PCSK9, which laid the conceptual safety foundation for the development of pharmacological inhibitors and, subsequently, strategies for permanent gene inactivation.

This genetic validation quickly translated into effective drugs. Anti-PCSK9 monoclonal antibodies (evolocumab, alirocumab) neutralize the circulating protein, reduce LDL-C by 50–60% compared with statin therapy, and have been shown to reduce major cardiovascular events in secondary prevention in the FOURIER and ODDYSEY Outcome trials. (12) Meanwhile, inclisiran—a small interfering RNA conjugated with N-acetylgalactosamine (GalNAc) that silences hepatic PCSK9 translation—achieves similar reductions with a dosing regimen of just two subcutaneous injections per year following the initial dose. (4) These developments demonstrate that the pharmacological inhibition—transient and reversible—of PCSK9 safely replicates the cardiovascular benefit observed in natural carriers of loss-of-function variants, and constitutes the direct rational basis for attempting to replicate that same effect permanently through somatic gene editing of the PCSK9 gene itself in hepatocytes.

### GENE-EDITING TECHNOLOGIES

Clustered Regularly Interspaced Short Palindromic Repeats–CRISPR-associated protein 9 (the CRISPR-Cas9 system)—derived from a bacterial adaptive immune mechanism against bacteriophages—was the first to enable targeted editing of the human genome with clinically relevant efficiency. (13) Its central component is the Cas9 nuclease, which is directed to a specific genomic sequence by a complementary guide RNA (gRNA) that also recognizes a short adjacent sequence called Protospacer Adjacent Motif (PAM). Once positioned, Cas9 generates a double-strand break (DSB) in the DNA, which the cell repairs via non-homologous end joining (NHEJ)—an error-prone mechanism that introduces random insertions or deletions (indels). When these alterations affect a coding region, they can shift the reading frame and generate a premature stop codon, functionally inactivating the gene. This was the principle used in the first preclinical approaches to PCSK9 inactivation using classical CRISPR-Cas9.

Base editing represents a subsequent refinement that prevents the generation of double-strand breaks. In this system, a Cas9 modified to act solely as a nickase (nCas9, which cuts only one of the two strands) is fused to a deaminase enzyme. Cytosine base editors (CBE) temporarily convert a cytosine into uracil, which the cellular machinery interprets as thymine;

adenine base editors (ABE), on the other hand, convert an adenine into inosine, which is interpreted as guanine. Following DNA repair or replication, these modifications are consolidated as permanent C·G·C·A and A·T·G·C conversions, respectively, without the need to generate a double-strand break. (14,15) By eliminating the DSB, base editing substantially reduces the formation of indels and chromosomal rearrangements, and is particularly effective at inactivating genes by introducing premature stop codons or altering splicing sites (the mechanism used by PCSK9 editors currently in clinical development), which introduce a point mutation at the splice donor site at the junction between exon 1 and intron 1, generating a nonfunctional transcript due to intron retention and degradation mediated by the messenger RNA surveillance system.

Prime editing constitutes a third, even more versatile platform capable of introducing all twelve possible types of base substitutions, as well as small insertions and deletions, by fusing a Cas9 nickase with a reverse transcriptase and an extended guide RNA (prime editing guide, pegRNA) that directs the system to the target sequence and contains the template specifying the desired modification. (16) Although it offers a wider range of possible edits, its development for in vivo applications remains less advanced than that of base editing; therefore, the most advanced clinical programs in lipidology continue to rely on base editors.

Delivering this molecular machinery to hepatocytes is, in itself, a central technological challenge. Lipid nanoparticles (LNPs)—spheres ranging from 80 to 200 nm in size composed of ionizable lipids, cholesterol, phospholipids, and pegylated lipids—encapsulate the messenger RNA encoding the base editor along with the gRNA, and following intravenous administration, they naturally accumulate in the liver, where they are taken up by receptor-mediated endocytosis. (17) Transient expression of the editor from the mRNA—which degrades within a few days—limits the time window of nuclease activity and, thereby, the risk of off-target editing. An additional refinement involves conjugating N-acetylgalactosamine (GalNAc) to the surface of the LNP, which promotes its uptake by the liver via the asialoglycoprotein receptor, independent of LDLR; this modification is particularly relevant in patients with familial hypercholesterolemia, in whom the reduced availability of LDLR could limit the uptake of unconjugated LNPs. (18)

## ONGOING STUDIES

Preclinical validation of PCSK9 editing was conducted in a stepwise manner in primary human, rodent, and nonhuman primate hepatocytes. Musunuru et al. demonstrated that an adenine editor targeting the splice donor site between PCSK9 exons 1 and 2 produced a sustained reduction in cholesterol in primates following a single infusion. (19) Subsequent studies in macaques, using the formulation and sequence

that would later be translated to the clinical setting, showed an average hepatic editing rate of 67–83% with sustained reductions in serum PCSK9 and LDL-C of up to 69%, which persisted for more than one year after a single dose, with no evidence of editing in sperm or in the offspring of treated animals. (20)

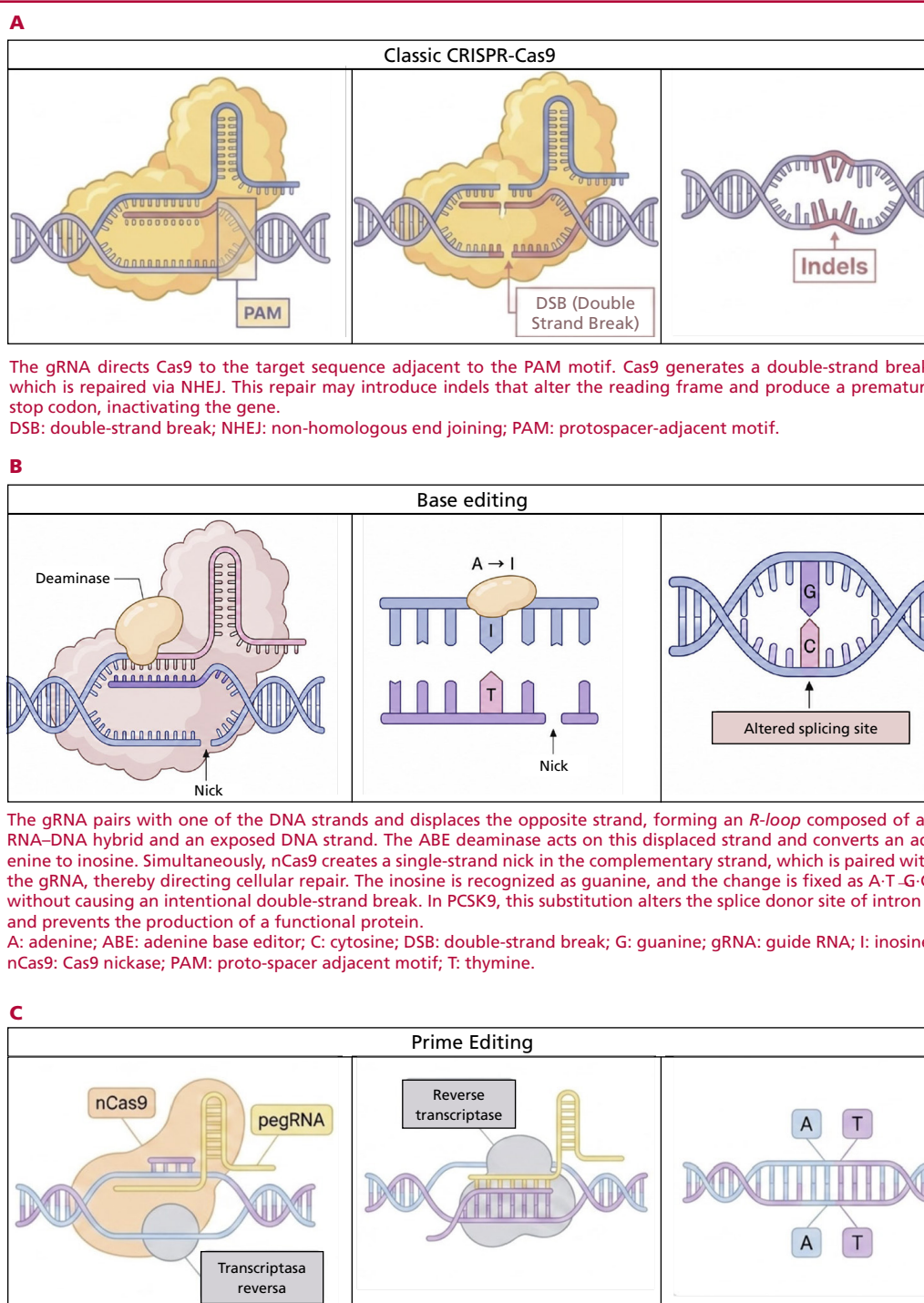
On this basis, the first in-vivo PCSK9 gene-editing clinical trial in humans, VERVE-101 (Heart-1 study, NCT05398029, Verve Therapeutics), was initiated in adult patients with heterozygous familial hypercholesterolemia and established coronary artery disease. (21) Interim results, presented in 2023, showed dose-dependent reductions in LDL-C of up to 55% in the higher-dose cohorts, sustained for at least six months of follow-up. Most adverse events were transient (infusion reactions, mild elevations in transaminases), although three serious cardiovascular events were reported in patients with advanced atherosclerotic disease, including one death from cardiac arrest deemed unrelated to treatment by the independent safety committee. These findings, along with laboratory abnormalities later attributed to the formulation's lipid component, led to the suspension of recruitment for VERVE-101 and the transition of the program to a second-generation nanoparticle. (22)

VERVE-102 (Heart-2 study, NCT06164730) uses the same adenine editor and guide sequence as VERVE-101 but incorporates a new-generation GalNAc-conjugated LNP, designed for LDLR-independent hepatic uptake and a more favorable inflammatory profile. (22) The interim analysis of the study, which included patients with heterozygous familial hypercholesterolemia or premature coronary artery disease, showed mean reductions in PCSK9 and LDLR of 88% and 62%, respectively, in the highest-dose cohort, with an absolute reduction in LDL-C of 78 mg/dL, with no dose-limiting toxicity or deaths, and mild-to-moderate infusion reactions in approximately one-fifth of participants. (23,24) Notably, the magnitude of the LDL-C reduction was comparable to that achieved with anti-PCSK9 monoclonal antibodies in chronic treatment. (23)

In parallel, YOLT-101 (YolTech Therapeutics) is currently in development; this is an adenine editor based on a novel deaminase derived from *Hafnia paralvei*, also delivered via a GalNAc-conjugated LNP, in a trial specifically targeting patients with heterozygous familial hypercholesterolemia. Interim data from six patients, with follow-up of up to 36 weeks, showed nearly 50% mean LDL-C reduction in the 0.6 mg/kg cohort, with a maximum reduction of over 74% sustained for more than six months in one participant, and an adverse event profile consisting of transient infusion reactions and mild, asymptomatic elevations of liver enzymes. (25)

It is useful to compare these three PCSK9 gene-editing programs with the anti-PCSK9 pharmacological strategies already established in clinical practice—monoclonal antibodies, inclisiran, and, more recently,

**Fig. 1.** Comparison of the main gene-editing platforms. A) Classic CRISPR-Cas9: the guide RNA (gRNA) directs Cas9 to the target sequence adjacent to the PAM motif, where it generates a DSB. Repair via non-homologous end joining (NHEJ) introduces insertions or deletions (indels) that can inactivate the gene. B) Base editing: a Cas9 nickase (nCas9) fused to a deaminase modifies a specific base without generating a DSB. In the case of adenine editors (ABE), the A → I conversion—subsequently interpreted as G—allows for the introduction of point mutations, such as the alteration of the PCSK9 splice donor site. C) Prime editing: a nCas9 fused to a reverse transcriptase uses an extended guide RNA (pegRNA) to precisely incorporate defined substitutions, insertions, or deletions, without the need for a double-strand break in the DNA



lerodalcibep, a monthly-administered adnectin-albumin fusion protein that has demonstrated between 59% and 65% LDL-C reductions in heterozygous familial hypercholesterolemia and at least 60% reduction in populations at high cardiovascular risk. (4,12,26,27) The comparison (Table 1) shows that, in terms of the magnitude of LDL-C reduction, gene editing in its most advanced formulation (VERVE-102) matches or exceeds chronic pharmacological therapies, but with a key qualitative difference: while monoclonal antibodies, inclisiran, and lerodalcibep require indefinite periodic administration, gene editing introduces a permanent modification of hepatic DNA following a single infusion, whose safety profile and long-term durability have not yet been established with the same level of evidence.

The principle of targeted hepatic editing has expanded beyond PCSK9. VERVE-201 (Pulse-1 study). CTX310—inactivates ANGPTL3—a regulator of lipoprotein lipase whose genetic deficiency is associated with combined familial hypolipidemia and reduced cardiovascular risk—in patients with homozygous familial hypercholesterolemia or refractory hypercholesterolemia. In its highest-dose cohort, CTX310 demonstrated reductions of up to 75% in ANGPTL3, 82% in triglycerides, and 81% in LDL-C, with no serious treatment-related adverse events. (28) CTX320 applies the same principle to the LPA gene to perma-

nently reduce the synthesis of apolipoprotein(a) and, thereby, lipoprotein(a) concentrations—a causal and independent risk factor for atherosclerotic disease and aortic stenosis that remains virtually refractory to conventional lipid-lowering therapies—with Lp(a) reductions of up to 94% sustained for seven months in nonhuman primates. (29,30) Beyond the field of lipid metabolism, the validation of this hepatic delivery platform has been extended to transthyretin cardiac amyloidosis, where nexiguran ziclumeran (NTLA-2001)—a CRISPR-Cas9 editor targeting the TTR gene—reduced serum transthyretin levels by 90% at twelve months in a Phase 1 trial, which is currently in Phase 3. (31)

### OPPORTUNITIES AND CHALLENGES

The primary safety concern with any permanent gene-editing strategy is off-target activity, which can lead to extensive deletions, chromosomal rearrangements, or oncogene activation. (32) Although base editors substantially reduce this risk by preventing double-strand breaks, they do not eliminate it entirely, and their evaluation requires the combined use of computational tools and highly sensitive experimental methods, such as GUIDE-seq, along with high-fidelity Cas9 variants. (33,34) Added to this is uncertainty regarding the durability of the effect, given that the dose-escalation design of the early trials means that

**Table 1.** Comparison between established anti-PCSK9 pharmacological strategies and PCSK9 gene-editing programs in clinical development

| Strategy                                       | Mechanism / Target                                  | Route and Dosage                                  | Reduction in LDL-C                                | Nature of the effect                                    | Stage of development                                                           |
|------------------------------------------------|-----------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------|
| Monoclonal antibodies (evolocumab, alirocumab) | Neutralization of circulating PCSK9                 | SC, every 2 weeks (or monthly, alirocumab 300 mg) | 50–70%                                            | Reversible; requires ongoing dosing                     | Approved; demonstrated reduction of CV events (FOURIER, ODDYSEY Outcomes) (12) |
| Inclisiran                                     | Hepatic RNA; silences PCSK9 mRNA                    | SC; Day 0, Month 3, then every 6 months           | ~40–50%                                           | Reversible (transient silencing); dose-dependent effect | Approved; ongoing CV outcome trials. (4)                                       |
| Lerodalcibep                                   | Anti-PCSK9 adnectin + albumin fusion protein        | SC, monthly (300 mg)                              | 58.6–65% (HeFH); ≥60% (high CV risk)              | Reversible; requires ongoing dosing                     | Approved (FDA, 2025) (26,27)                                                   |
| VERVE-101 (Heart-1)                            | PCSK9 base editing (ABE); unconjugated LNP          | IV, single infusion                               | Up to 55%                                         | Permanent (irreversible genomic editing)                | Phase 1b; recruitment stopped (21,22)                                          |
| VERVE-102 (Heart-2)                            | Same editor; 2nd-generation LNP-GalNAc              | IV, single infusion                               | PCSK9 –88%; c-LDL –62% (absolute change 78 mg/dL) | Permanent                                               | Ongoing Phase 1b (23,24)                                                       |
| YOLT-101                                       | Base editor (Hafnia paralvei deaminase); LNP-GalNAc | IV, SINGLE INFUSION                               | ~50% (max. >74%)                                  | Permanent                                               | Ongoing Phase 1 (25)                                                           |

CV: cardiovascular; GalNAc: N-acetylgalactosamine; HeFH: heterozygous familial hypercholesterolemia; IV: intravenous; LDL-C: LDL cholesterol; LNP: lipid nanoparticle; RNA: ribonucleic acid; SC: subcutaneous.

the higher-dose cohorts—which exhibit the most pronounced lipid-lowering effect—still have the shortest follow-up periods.

A second area of discussion is the appropriate selection of patients. Unlike severe monogenic diseases with no therapeutic alternatives, hypercholesterolemia has multiple effective and safe treatments backed by decades of clinical experience; therefore, the incremental benefit of a permanent and irreversible intervention must be carefully weighed against the risk, especially in young, reproductive-age populations, in whom the theoretical possibility of germline transmission of the edit becomes relevant—even though it has not yet been detected. Regulatory agencies, including the FDA, currently require a minimum of fifteen years of follow-up for recipients of gene therapies, which poses logistical and sustainability challenges for sponsors and long-term registry systems. (35)

Finally, the clinical implementation of gene editing raises economic, regulatory, and ethical questions that extend beyond the strictly biomedical realm. Funding for a one-time, very high-cost intervention is difficult to integrate into fragmented health care systems or those based on insurers and employers with limited coverage periods. Added to this is the need to ensure equitable access both to these therapies and to the genetic testing necessary to identify potential candidates—testing that is currently underutilized even in cases of familial hypercholesterolemia. Furthermore, the permanent nature of somatic genomic modifications requires specific frameworks for regulation, monitoring, and informed consent, commensurate with technologies whose long-term risks are not yet fully understood. (36,37) On the other hand, the possibility of achieving lifelong cardiovascular protection through a single intervention in individuals at high genetic risk, even before the clinical manifestation of the disease, redefines the horizon of primary prevention and has already led to the first application of personalized N-of-1 base editing in a newborn with a severe monogenic metabolic disorder, serving as a proof of concept for how quickly these platforms can be adapted to an individual genotype. (38)

## CONCLUSIONS

PCSK9 is currently the best-validated gene target—genetically, pharmacologically, and clinically—for the development of in vivo gene-editing therapies aimed at preventing atherosclerotic cardiovascular disease. Ongoing clinical trials, including VERVE-102 and YOLT-101, have demonstrated sustained, dose-dependent reductions of LDL-C comparable to those attained with anti-PCSK9 monoclonal antibodies, achieved through a single intravenous infusion, with generally acceptable short-term safety profiles following the incorporation of second-generation lipid nanoparticles. However, these are still Phase 1 data from small populations with limited follow-up: the durability of the long-term effect, the cumulative risk

of off-target events, and the appropriate selection of candidates are open questions that only larger, randomized studies with prolonged follow-up will be able to answer. For the clinical lipidologist, the immediate challenge is not yet to prescribe this technology, but rather to understand its biological basis, closely monitor its development, and actively participate in the discussion regarding the clinical and ethical criteria that should guide its eventual incorporation into clinical practice.

## Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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# What Do We Assess When Certifying Disability in Cardiology? Clinical Vulnerability and Therapeutic Dependency in the Era of Chronic Cardiovascular Diseases

*¿Qué evaluamos cuando certificamos discapacidad en cardiología? Vulnerabilidad clínica y dependencia terapéutica en la era de las enfermedades cardiovasculares crónicas*

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Disability certification in Argentina, implemented through a unique Disability Certificate (DC), is a key tool for accessing health rights and benefits. (1,2) Its implementation has helped highlight needs, organize coverage, and facilitate access to services for a wide range of clinical conditions. However, in the field of chronic cardiovascular diseases (CVD), tensions are beginning to emerge that call for a reevaluation of what we currently understand by “disability” and which dimensions should really be assessed. In this context, requests for certification are often not directly linked to a disability but rather to the need to document a health status that allows access to coverage or treatments that would otherwise be difficult or impossible to obtain. This raises questions about whether current instruments are being used to assess disability or, in some cases, to overcome barriers to accessing the health care system.

Over the past few decades, therapeutic advances have substantially transformed the natural course of numerous cardiovascular diseases (CVD). The development of highly effective pharmacological treatments, implantable devices, cardiovascular rehabilitation programs, and integrated care models has improved functional capacity, reduced hospitalizations, and prolonged survival. (3,4) As a result, a growing number of patients remain clinically stable for long periods. However, this stability often depends on complex, ongoing, and costly interventions whose

availability, accessibility, and sustainability are not always guaranteed.

Epidemiological transition, population aging, and the sustained increase in chronic diseases challenge models of disability originally conceived for conditions considered more stable or permanent. Today, disability is understood as a dynamic condition resulting from the interaction between a person's health characteristics and the barriers or facilitators in their environment, so it should not be defined exclusively based on a diagnosis. From this perspective, assessment should focus on functional limitations and the supports each person requires to participate fully in social, educational, occupational, and community life.

From a human rights perspective, disability cannot be understood solely as an individual characteristic or as a direct consequence of a medical condition, but rather as the result of the interaction between people and the barriers present in their environment. In this regard, the Convention on the Rights of Persons with Disability recognizes the obligation of States to promote equal opportunities, full participation, and access to the supports necessary for the effective exercise of rights. Within this framework, an analysis of complex chronic CVD conditions invite reflection not only on existing functional limitations but also on the conditions that enable the maintenance of autonomy, social participation, and the continuity of life plans.

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The availability of treatments, medical devices, specialized rehabilitation, and adequate follow-up can thus be understood not only as a clinical necessity but also as an essential component for ensuring the effective exercise of rights and preventing situations of exclusion or inequity. (5)

Increased life expectancy associated with health-care advances has led to a rise in the number of years lived with illness and disability—a phenomenon particularly relevant in an increasingly aging population in the region of the Americas<sup>7</sup>, where the burden of chronic disease is placing a growing strain on health systems. (6–8) Currently, CVD continue to be one of the leading causes of mortality and disease burden worldwide. In the Americas, they account for approximately 47 million disability-adjusted life years (DALYs), while the number of years lived with cardiovascular disability has nearly doubled over the past two decades, reflecting the increased survival of patients with complex conditions. (9–12)

In this regard, a central question arises: What are we really assessing when we certify disability in cardiology? Are we measuring an observable functional limitation, or are we attempting to recognize a state of vulnerability whose stability depends on sustained access to specific healthcare support?

In this conceptual reflection, clinical vulnerability is defined as an increased likelihood of clinical deterioration, loss of functionality, or restrictions on social participation in the event of interruption in the therapeutic support necessary to maintain the stability that has been achieved. Unlike disability—which, according to the International Classification of Functioning, Disability, and Health (ICF) is expressed through limitations in activity and participation resulting from the interaction between a health condition and the environment—clinical vulnerability describes situations in which observed functioning depends heavily on ongoing health care resources. It does not constitute an alternative category to disability nor does it intend to replace existing conceptual frameworks, but rather to provide a complementary dimension for understanding certain complex chronic CVD. (13–18)

The classification used in national registries recognizes visceral disability as a category that includes cardiovascular, respiratory, digestive, endocrine, hematological, and immunological disorders. However, the information currently available continues to group highly heterogeneous conditions together, preventing an adequate epidemiological characterization of specific cardiovascular disability. (6) This limitation makes it difficult to accurately assess the magnitude of the problem and to design appropriate health policies for this population.

Current disability assessment models were developed in a historical context in which numerous diseases caused more stable and visible functional limitations. Contemporary cardiology has transformed many previously fatal diseases into chronic, long-term

conditions. Advanced heart failure, complex congenital heart diseases, pulmonary hypertension, and heart transplantation are prime examples of this transition. As a result, patients with complex diseases can maintain adequate levels of functioning thanks to ongoing therapeutic interventions, which poses new challenges for assessment and certification systems. Recent studies show that factors related to access to healthcare resources, community integration, and social participation continue to significantly influence the outcomes of these patients even when functional capacity is preserved. (19–21)

## ILLUSTRATIVE CLINICAL SCENARIOS

### Case 1. Stabilized advanced heart failure

This is the case of a 58-year-old patient with heart failure and reduced left ventricular ejection fraction (LVEF), who has an implantable cardioverter-defibrillator and is receiving optimized medical treatment. The patient has NYHA Class II functional capacity and has had no recent hospitalizations. From a strictly functional perspective, he might appear to be only minimally limited. However, his stability depends critically on lifelong medication, regular follow-up, and access to specialized healthcare technology.

This situation is particularly evident in heart failure, where therapeutic advances have significantly improved survival and quality of life, although often at the expense of a permanent dependence on pharmacological treatments, devices, and specialized follow-up. (21–24).

### Case 2. Complex Congenital Heart Disease in an Adult

This is the case of a 28-year-old patient who has a history of surgical correction of complex congenital heart disease. He works, studies, and maintains independence in daily-life activities. However, he requires lifelong specialized follow-up, periodic tests, and eventual access to new interventions. His adequate daily functioning coexists with sustained dependence on the healthcare system.

The population of adults with congenital heart disease represents one of the clearest examples of the gap between observable functioning and persistent healthcare needs. Although many patients lead active and productive lives, they continue to require lifelong specialized monitoring, with potential impact on their social participation, use of healthcare resources, and quality of life (20,21,25).

Both cases illustrate a common situation in contemporary cardiology: patients with an adequate level of daily functioning whose stability depends critically on sustained access to treatments, devices, specialized follow-up, and referral centers. This discrepancy between observable functioning and potential vulnerability poses a challenge for current assessment models, since clinical improvement can reduce the visibility of needs whose continuity depends precisely on the supports that made that improvement possible. This let-

ter does not propose equating therapeutic dependence with disability, but rather point out that this vulnerability could constitute a complementary dimension for understanding certain complex clinical situations.

In daily practice, requests for the DC typically arise in a context where clinical, social, and administrative needs converge. Frequently, patients often perceive it less as an identity category associated with disability and more as a necessary tool to ensure therapeutic continuity, access to medications, diagnostic tests, transfers, and specialized follow-up. This suggests that the DC currently fulfills functions that partially transcend the traditional certification of disability.

Regional inequities take on particular significance in this context. In countries with marked regional differences in the distribution of healthcare resources, access to high-complexity centers can become a clinically significant determinant. Geographic distance, the availability of specialists, and difficulties in maintaining continuous treatment are factors that can increase vulnerability even when functional capacity remains intact. (12)

Without intending to define a new certification tool, future reviews could explore complementary indicators that better capture the dynamic nature of certain chronic CVD. These might include dependence on permanent medical devices, the need for highly complex medication, the frequency of hospitalizations or decompensations, the requirement for follow-up at referral centers, and the foreseeable risk of deterioration in the event of treatment interruptions.

These elements should not be interpreted as diagnostic criteria for disability, but rather as potential dimensions for future research aimed at better understanding the relationship between chronicity, functioning, and social and health protection.

Epidemiological changes, an aging population, the expansion of cardiovascular therapies, and increased survival rates have substantially altered the natural history of numerous CVD. In this context, disability in people with chronic CVD could be analyzed less as a condition determined exclusively by functional loss and more as the result of a dynamic interaction between the disease, functionality, social participation, and the availability of healthcare supports capable of sustaining the clinical stability achieved. From this perspective, the assessment of this population should consider not only the limitations observable at a given moment but also the therapeutic and healthcare context on which their functioning depends.

Rather than offering definitive answers, this reflection aims to raise questions. Is traditional functional assessment sufficient to characterize the needs of people with complex chronic CVD? How should therapeutic dependence, clinical vulnerability, and inequities in access to the health care system be incorporated into assessment processes? Is it possible that certain situations are inadequately represented by categories de-

signed in an epidemiological and therapeutic context different from the current one? Are we using disability certification to recognize situations of disability or to guarantee access to rights, benefits, and essential support for certain individuals with complex chronic CVD?

In this context, the DC is much more than an administrative tool: it represents one of the mechanisms through which society seeks to address needs related to health, participation, and protection. The discussion about what we assess when certifying disability in cardiology therefore goes beyond the instrument itself and raises a broader question about how to support the clinical courses of these patients in the contemporary context. Addressing this issue will necessarily require an interdisciplinary debate involving healthcare professionals, disability specialists, healthcare policymakers, patients, and civil society organizations, with the goal of developing responses that are in line with real needs and the current historical moment.

## FINAL CONSIDERATIONS

Addressing chronic CVD from a disability perspective highlights that the vulnerability of this population does not depend exclusively on the medical condition, but also on contextual and structural factors that influence access to care and the necessary support. Throughout this manuscript, it has become evident that timely and equitable access to health care remains a right conditioned by socioeconomic and geographic factors, which deepens the exclusion of those living with these conditions. The lack of continuity in treatment, difficulties in obtaining disability certification, and the scarcity of specialized resources in the public sector create a scenario of social and health vulnerability. Current regulations are often fragmented, bureaucratic, and disconnected from the daily needs of people with chronic CVD. Furthermore, challenges persist regarding the coordination between regulatory frameworks, care systems, and the needs of people with these conditions.

Finally, recognizing the complex relationship between chronic heart disease, functioning, and disability is essential to enrich the debate on protection and support strategies aimed at this population.

Strengthening healthcare systems and consolidating appropriate social and health protection mechanisms are central components of supporting the care pathways of people with complex chronic CVD. Developing sustainable, person-centered institutional responses could help reduce situations of vulnerability and promote greater equity in access to care, regardless of place of residence or socioeconomic status

## Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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# Pericardial Carcinomatosis: Not Always Irreversible

## *Carcinomatosis pericárdica: no siempre irreversible*

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IRENE HERNÁNDEZ-PÉREZ<sup>1</sup>

We present the case of a patient with stage IV lung adenocarcinoma whose clinical presentation was cardiac tamponade secondary to pericardial effusion. Although pericardial effusion is a relatively common complication in patients with cancer, only about 30% of cases are attributable to malignant pericardial infiltration, (1) making its accurate characterization essential due to its diagnostic, prognostic, and therapeutic implications. (2) The case is also notable for the complete resolution of the echocardiographic findings following the initiation of targeted systemic treatment, a phenomenon rarely described in the literature and which highlights the benefit of current oncological therapies.

The patient is a 46-year-old man, an active smoker (30 pack-years), with no other relevant personal medical history, who presented to the emergency department with progressive dyspnea, orthopnea, and pleuritic chest pain that had been present for one month, with clinical worsening and the onset of edema in the left lower extremity within the past 24 hours. Upon arrival, he presented with hypotension (94/65 mmHg), sinus tachycardia (120 bpm), tachypnea (30 bpm), and an oxygen saturation of 92% while breathing room air.

On suspicion of deep vein thrombosis with secondary pulmonary thromboembolism, an urgent thoracic computed tomography (CT) angiography was performed (Figure 1A), which confirmed bilateral pulmonary thromboembolism with associated pulmonary infarction, as well as an unidentified mass in the right upper lobe measuring 25 mm, and another in the anterior mediastinum (60 mm), which was infiltrating the pericardium. The latter showed diffuse nodular thickening suggestive of pericardial carcinomatosis with severe pericardial effusion. A Cardiology evaluation was requested, and a transthoracic echocardiogram confirmed severe pericardial effusion and find-

ings consistent with cardiac tamponade, including respiratory variation in transvalvular flows, a dilated and non-collapsible inferior vena cava, and evident diastolic collapse of the right ventricular chambers.

Given these findings, the patient was admitted to the Coronary Care Unit, where an emergency pericardiocentesis was performed. A total of 500 mL of serosanguineous fluid was obtained. Subsequently, anticoagulation with low-molecular-weight heparin was initiated to treat pulmonary thromboembolism. Although he initially showed clear clinical and hemodynamic improvement, he continued to present with high-volume pericardial drainage, persistent severe pericardial effusion, and very marked nodular pericardial thickening (Figure 2A). Although the cytological examination of the pericardial fluid was negative for malignant cells, the findings on CT angiography were highly suggestive of malignant infiltration: (3) loss of the fatty plane separating the pericardium from the adjacent mediastinal mass, and nodular pericardial thickening. It was ultimately decided to perform a percutaneous balloon pericardiotomy, which stabilized the patient's condition and allowed for hospital discharge a few days later.

The pathological examination confirmed the diagnosis of stage IV A pulmonary adenocarcinoma. After ruling out abnormalities in molecular biomarkers (EGFR, ALK, ROS1, BRAF) and confirming the expression of programmed cell death ligand 1 (PD-L1)—which was not amenable to targeted therapy—first-line palliative treatment with pembrolizumab, pemetrexed, and carboplatin was initiated.

At the three-month follow-up, the patient showed a favorable clinical course, with a partial response characterized by a reduction in the mediastinal mass to 32 mm, the lobar mass to 18 mm, and a significant reduction in pericardial infiltration, with minimal

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pericardial effusion on the follow-up CT scan (Figure 1B) and complete resolution of the findings suggestive of pericardial infiltration visible on echocardiography (Figure 2B).

The clinical presentation of this patient, who presented with a pericardial effusion and cardiac tamponade, leading to a diagnosis of advanced-stage lung adenocarcinoma, is not an exceptional situation in clinical practice. An underlying neoplasm has been reported in 12–23% of patients who present with a pericardial effusion as their initial manifestation. (4) Among malignant etiologies, lung cancer is one of the most common causes, along with breast cancer, melanomas, leukemias, and lymphomas. (1,4)

Although a definitive diagnosis of malignant pericardial effusion requires confirmation of tumor cells, the diagnostic sensitivity of cytology is estimated at 72%, (5) and pericardial biopsy is rarely performed. In cases such as this one, where false negatives in cytol-

ogy are suspected, it is vital to integrate the findings from clinical and various imaging tests to arrive at the most likely diagnosis and adapt the therapeutic management accordingly.

Pericardial effusion of neoplastic origin is associated with a high recurrence rate and an increased risk of cardiac tamponade. (4) For this reason, in addition to pericardiocentesis, complementary strategies may be necessary, such as percutaneous balloon pericardiotomy, creation of a pericardial window, or intrapericardial administration of cytostatic agents, especially in patients with early recurrence. (1) However, treatment of the primary tumor remains the cornerstone for controlling the disease and its cardiovascular manifestations. (1)

The incorporation of immunotherapy and current systemic treatments has transformed the prognosis for many patients with advanced lung cancer, improving both survival and quality of life. In our patient, the

**Fig. 1.** Thoracic CT angiography. A) Pericardium showing irregular thickening and associated severe pericardial effusion. B) Complete resolution of the pericardial effusion and marked reduction in pericardial infiltration at 3 months.

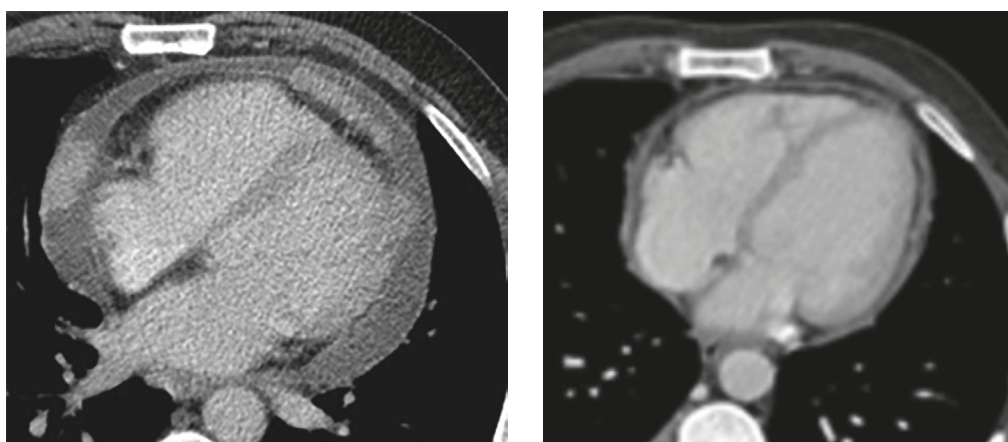
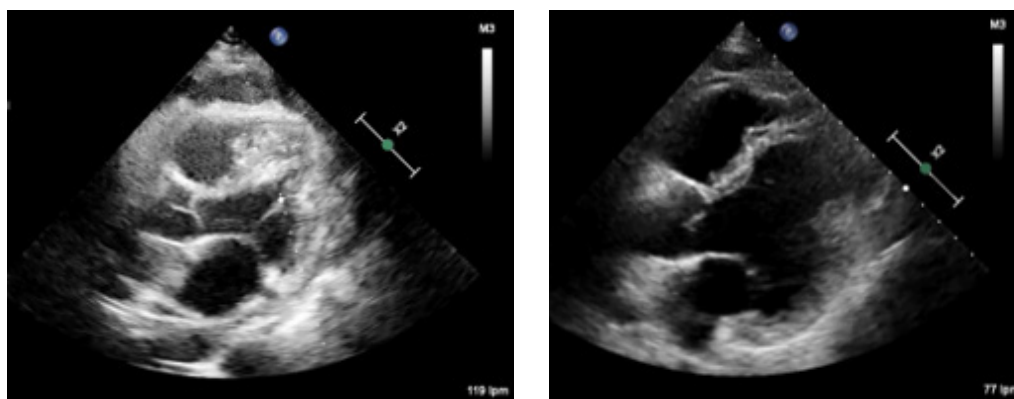


**Fig. 2.** Transthoracic echocardiogram in the parasternal long-axis view. A) Irregular pericardial thickening with associated severe pericardial effusion (with persistence of variationtransvalvular respiratory, but without diastolic involvement of the right chambers following pericardiocentesis). B) Resolution of pericardial thickening and effusion at 3 months.



partial radiological response was accompanied by the complete resolution of the pericardial effusion and of the echocardiographic findings suggestive of pericardial infiltration—a finding not previously described in the literature to the best of our knowledge—which illustrates the efficacy of systemic treatment and the value of echocardiography as a noninvasive tool for monitoring pericardial involvement.

#### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

#### Ethical considerations

Not applicable

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# Unexpected Vascular Anatomy in Pulmonary Sequestration: the Value of Imaging in a Complex Case

## *Anatomía vascular inesperada en secuestro pulmonar: el valor de las imágenes en un caso complejo*

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Pulmonary sequestration is a rare congenital malformation, characterized by nonfunctional lung parenchyma, without communication with the tracheobronchial tree and with aberrant systemic arterial perfusion. Although the identification of an anomalous feeding artery usually guides the diagnosis, complex vascular variants can pose a diagnostic and therapeutic challenge. In this context, imaging techniques play a fundamental role in defining the vascular anatomy and planning treatment.

We present the case of a full-term newborn with a prenatal diagnosis of suspected left pulmonary sequestration, referred to a tertiary care center for evaluation and potential surgical resolution.

Postnatal thoracic ultrasound revealed an image consistent with pulmonary consolidation containing vascular structures. Subsequently, a chest computed tomography scan showed localized opacity in the left lower lobe.

Thoracic angiotomography identified an aberrant arterial vessel originating from the descending aorta that supplied the lesion (Figure 1). In addition, it revealed an anomalous large-caliber venous drainage into the systemic venous system via a left paravertebral collector vein that drained into the innominate vein (Figure 2), a finding that is uncommon for this type of malformation.

To accurately characterize the vascular anatomy, an angiographic study was performed, which confirmed the presence of two systemic arteries originating from the descending thoracic aorta and supplying the left lower lobe (Figure 3). Furthermore, dual venous drainage was observed: one to the left atrium via the left inferior pulmonary vein (Figure 4) and the other to the innominate vein through the paravertebral collector (Figure 5), constituting a mixed venous return.

A left lower lobectomy was performed, including dissection and control of the aberrant vessels, with a favorable postoperative course.

Pulmonary sequestration accounts for between 1% and 6% of congenital pulmonary malformations, with the left lower lobe being the most common site. (1) It is traditionally classified as intralobar or extralobar sequestration. The former shares the visceral pleura with the adjacent lung and usually drains into the pulmonary veins, whereas the extralobar type has its own pleural covering and typically drains into the systemic venous circulation. In addition, the latter may be associated with other congenital anomalies, such as diaphragmatic hernia, cardiovascular malformations, and gastrointestinal abnormalities. (2,3)

Systemic arterial supply is the defining feature of this condition. In most cases, the vascular supply originates from a single branch arising from the descending thoracic aorta; however, less common variants with multiple afferent vessels or originating from the abdominal aorta have been described. In our patient, angiography revealed the presence of two systemic arteries arising from the descending thoracic aorta, associated with a mixed venous drainage pattern. This combination constitutes a rare anatomical variant, which complicates the traditional classification of the lesion and underscores the need for a thorough anatomical evaluation before determining the therapeutic approach.

Currently, the diagnosis is often suspected through prenatal ultrasound, which achieves detection rates exceeding 80% for congenital pulmonary malformations. (3) In the postnatal period, chest X-rays and ultrasound may suggest the diagnosis, although definitive characterization of the vascularization requires advanced studies such as computed tomography angiography or magnetic resonance imaging. When di-

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**Fig. 1.** Thoracic computed tomography angiography. Aberrant vessel arising from the descending aorta.

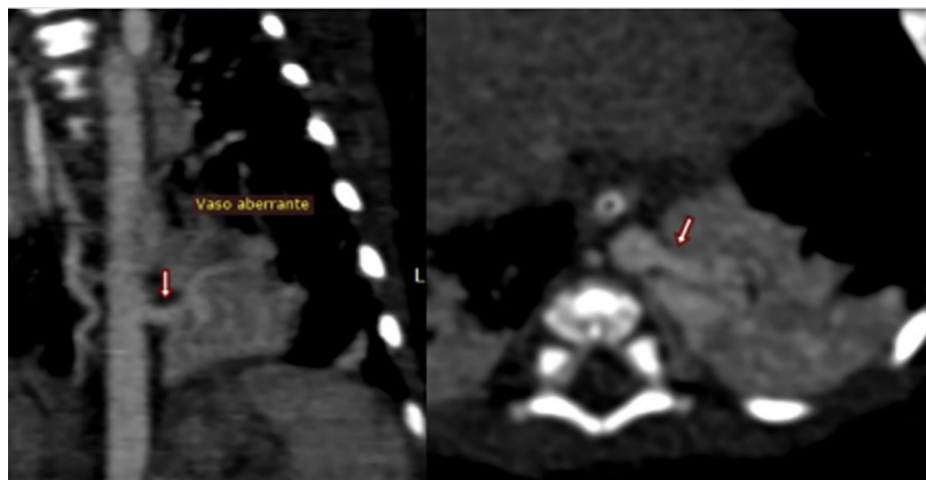
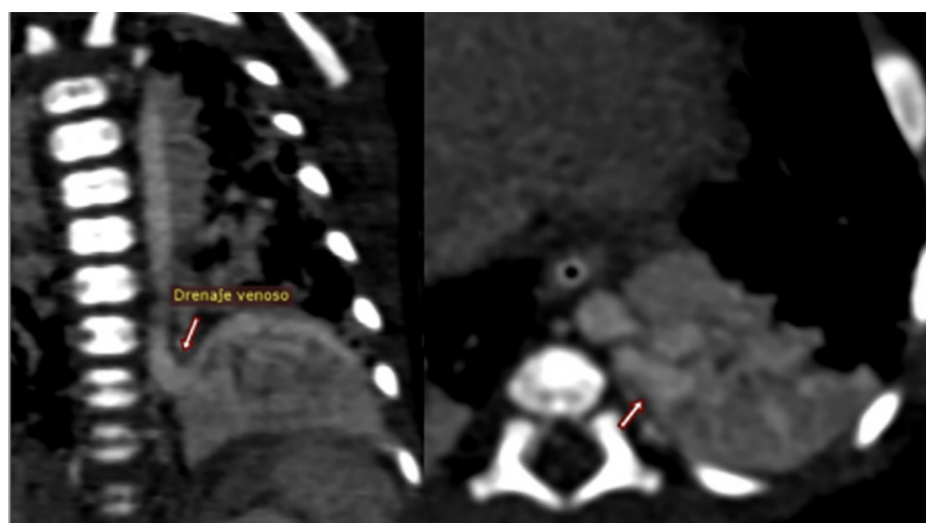


**Fig. 2.** Thoracic computed tomography angiography. Arrow: venous drainage into the innominate vein.



agnostic uncertainty persists or a precise anatomical definition is required for treatment planning, angiography remains an invaluable tool.

In this case, angiotomography made it possible to identify the aberrant arterial supply and detect unexpected systemic venous drainage, while angiography provided a detailed characterization of the afferent and efferent vessels. This information proved essential for surgical planning, as it allowed for the identification of complex vascular anatomy and minimized the risk of intraoperative complications. The importance of this preoperative assessment lies in historical reports of morbidity and mortality associated with

inadvertent injury to aberrant vessels during surgical resection. Although the surgery has a low overall complication rate, close to 5%, intraoperative bleeding remains one of the most significant adverse events, followed by hemothorax and bronchopleural fistula. (3)

Surgical resection remains the strategy of choice in symptomatic patients and in most intralobar sequestrations, due to the risk of recurrent infections. Alternatively, embolization of aberrant systemic vessels has emerged as a valid therapeutic option in selected cases, especially when significant shunts or heart failure are present. (1,4) In our patient, the complexity of the vascular anatomy and the presence of mixed venous

**Fig. 3.** Angiography. Arterial phase.

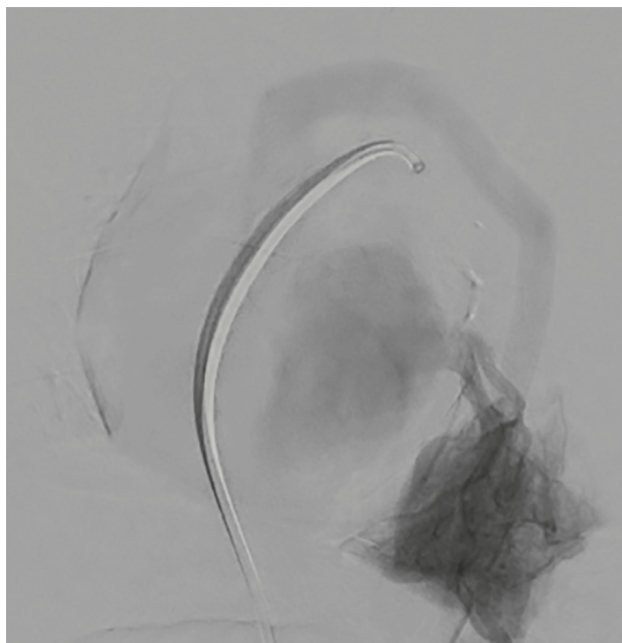
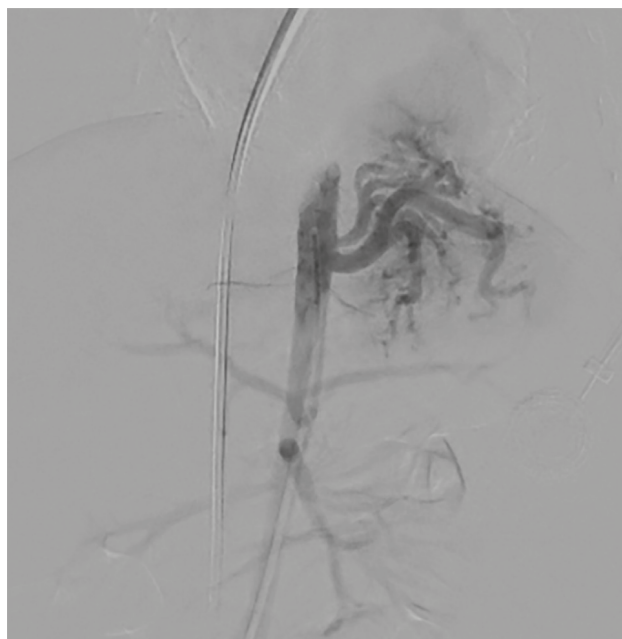


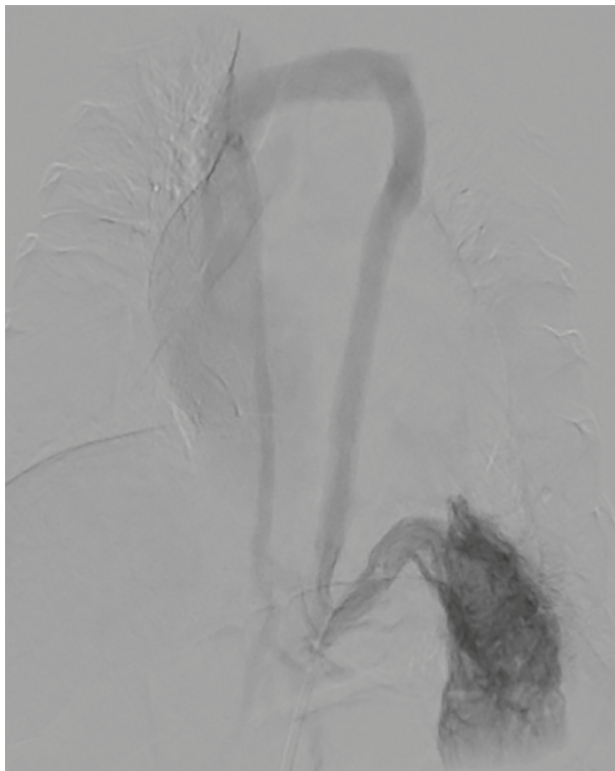
**Fig. 4.** Angiography. Venous phase. Venous drainage to the left atrium via the left inferior pulmonary vein



drainage made surgical resection the most appropriate option, with a favorable postoperative course.

This case highlights the value of imaging techniques in the evaluation of pulmonary sequestration, especially when unusual anatomical variants are pre-

**Fig. 5.** Angiography. Venous phase. Venous drainage to the innominate vein through the paravertebral collector



sent. The thorough characterization of arterial perfusion and venous drainage allowed us to identify unexpected vascular anatomy and appropriately guide the surgical strategy, contributing to a favorable outcome.

#### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

#### Ethical considerations

Not applicable

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# When the Valve Doesn't Explain Everything: Secondary Heart Failure in a Young Woman

*Cuando la válvula no explica todo: insuficiencia cardíaca secundaria en una mujer joven*

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Hyperthyroidism profoundly alters cardiovascular physiology by increasing heart rate, contractility, and stroke volume, expanding circulating volume, and decreasing systemic vascular resistance. Consequently, some patients develop a hyperdynamic state that can progress to heart failure (HF), atrial fibrillation (AF), pulmonary hypertension, and functional valvular regurgitation. (1–5)

High-output heart failure is a rare phenotype in which congestion, elevated filling pressures, and elevated natriuretic peptides may coexist despite a preserved left ventricular ejection fraction (LVEF). (6)

We present the case of a young woman with thyrotoxicosis due to Graves' disease, AF, right-sided HF, and functional valvular heart disease, in whom the integration of cardiac magnetic resonance imaging (CMRI), echocardiography, and computed tomography (CT) angiography allowed us to redefine the etiological interpretation of a heart condition initially considered predominantly structural.

This is a 33-year-old female patient with no conventional cardiovascular risk factors, a history of hyperthyroidism, iron-deficiency anemia, and previous hospitalizations for HF. She was being evaluated for mitral and tricuspid regurgitation, pulmonary hypertension estimated by echocardiography, and an atrial septal defect (ASD).

Gadolinium-enhanced CMR performed on January 29, 2026, showed moderate dilatation of both atria and a severe increase in right ventricular volumes (indexed end-diastolic volume 116 mL/m<sup>2</sup>), with preserved systolic function, as indicated by a right ventricular ejection fraction (RVEF) of 56% and tricuspid annular plane systolic excursion (TAPSE) of 17 mm. There was moderate to severe tricuspid and mitral re-

gurgitation, moderate left ventricular dilation, LVEF 61%, with no late enhancement. An ASD of approximately 4 mm was identified in the fossa ovalis, with bidirectional flow predominantly left-to-right and a Qp/Qs ratio of 1.18 (Figure 1). The cardiac index was 4.73 L/min/m<sup>2</sup>, consistent with hyperdynamic physiology.

An echocardiogram on June 24 showed LVEF of 59%, a markedly dilated left atrium (70 mL/m<sup>2</sup>), a right atrium of 39 cm<sup>2</sup>, a pulmonary artery with left-to-right shunt, a dilated right ventricle, an inferior vena cava measuring 22 mm with no inspiratory collapse, an estimated pulmonary systolic pressure of 48 mmHg, moderate mitral regurgitation, and moderate-to-severe tricuspid regurgitation. (Figures 2 and 3)

On July 26, she was admitted due to a new episode of HF decompensation with systemic congestion. During her hospitalization, AF and markedly elevated natriuretic peptides were documented. Endocrinological testing revealed thyroid-stimulating hormone (TSH) <0.01 mIU/L, free T4 5.47 ng/dL, and thyroid-stimulating hormone receptor antibodies (TRAb) >40 IU/L. Thyroid ultrasound showed diffuse enlargement of the gland and a predominantly hypoechoic structure, findings consistent with Graves' disease. A chest CT angiogram performed on July 29 ruled out pulmonary thromboembolism and revealed a moderate right pleural effusion.

Treatment was initiated with methimazole, iodine, glucocorticoids, and monitoring of ventricular response, combined with diuretic therapy for congestion.

The follow-up echocardiogram on July 31, performed in AF at 90 beats per minute, showed preserved LVEF, significant biauricular dilation, a dilated

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right ventricle with mild impairment of function, and a 42-mm tricuspid annulus with moderate-to-severe functional regurgitation. Mitral regurgitation, which had previously been moderate, was now mild. AAS could not be visualized. On that date, the patient was hemodynamically stable, without dyspnea or need for oxygen, and with mild residual signs of congestion. Free thyroxine decreased from 5.47 to 2.9 mIU/L and subsequently to 1.26 mIU/L.

The main diagnostic challenge was to determine whether the marked right ventricular remodeling and valvular regurgitations corresponded to primary structural heart disease or were, at least partially, consequences of a systemic hemodynamic disturbance.

Thyrotoxicosis increases cardiac output due to its positive chronotropic and inotropic effects, a decrease in systemic vascular resistance, and plasma volume expansion. AF and associated anemia can amplify this mechanism. (4,5) The resulting HF does not require impaired LVEF: patients with high-output HF may present with congestion and elevated filling pressures while maintaining preserved left ventricular systolic function. (6)

In this patient, the cardiac index of approximately 4.73 L/min/m<sup>2</sup>, documented six months prior to decompensation, constitutes objective evidence supporting preexisting hyperdynamic physiology. The persistently preserved LVEF, therefore, should not be interpreted as evidence against the diagnosis of HF.

ASD was a relevant etiological differential diagnosis. However, its approximate diameter of 4 mm and Qp/Qs ratio of 1.18 make it unlikely that it alone accounts for the extent of right ventricular remodeling. Likewise, the absence of late enhancement reduced the likelihood of overt cicatricial or infiltrative cardiomyopathy, while CT angiography ruled out pulmonary embolism as the cause of decompensation.

The course of mitral regurgitation is of pathophysiological significance. Its reduction from moderate to mild during hospitalization, in parallel with hormonal control and decongestion, supports a predominantly functional mechanism. The persistence of right ventricular dilation, a 42-mm tricuspid annulus, and moderate-to-severe tricuspid regurgitation, however, suggests a more established right-sided remodeling.

Current recommendations for HF emphasize identifying and correcting etiological and precipitating factors. (1,2) In AF associated with hyperthyroidism, treatment of the thyroid disorder is essential; rate control should be individualized based on hemodynamic status, and the indication for anticoagulation should be determined according to conventional thromboembolic risk. (3)

The combination of markedly positive TRAb, suppressed TSH, very elevated free thyroxine, and diffuse thyroid enlargement points to Graves' disease as the most likely endocrinological mechanism. In this context, it is more appropriate to interpret the presentation as complex HF with hyperdynamic physi-

ology induced by thyrotoxicosis, associated with AF and right ventricular remodeling, rather than as HF with primarily preserved ejection fraction or isolated valvular disease.

The main limitation of this report is the absence of invasive hemodynamic evaluation and follow-up after the sustained restoration of euthyroidism. A delayed echocardiographic reevaluation will allow us to determine what proportion of the right ventricular remodeling and tricuspid regurgitation is reversible and whether the ASD retains hemodynamic significance.

**Fig. 1.** Cardiac magnetic resonance imaging. Four-chamber view showing biauricular dilation with an atrial septal defect.

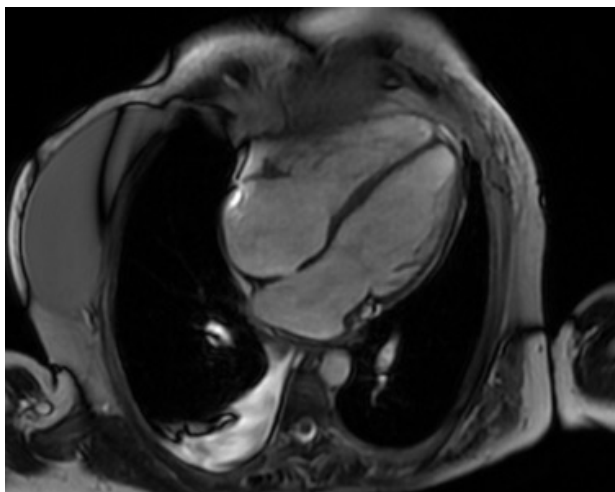
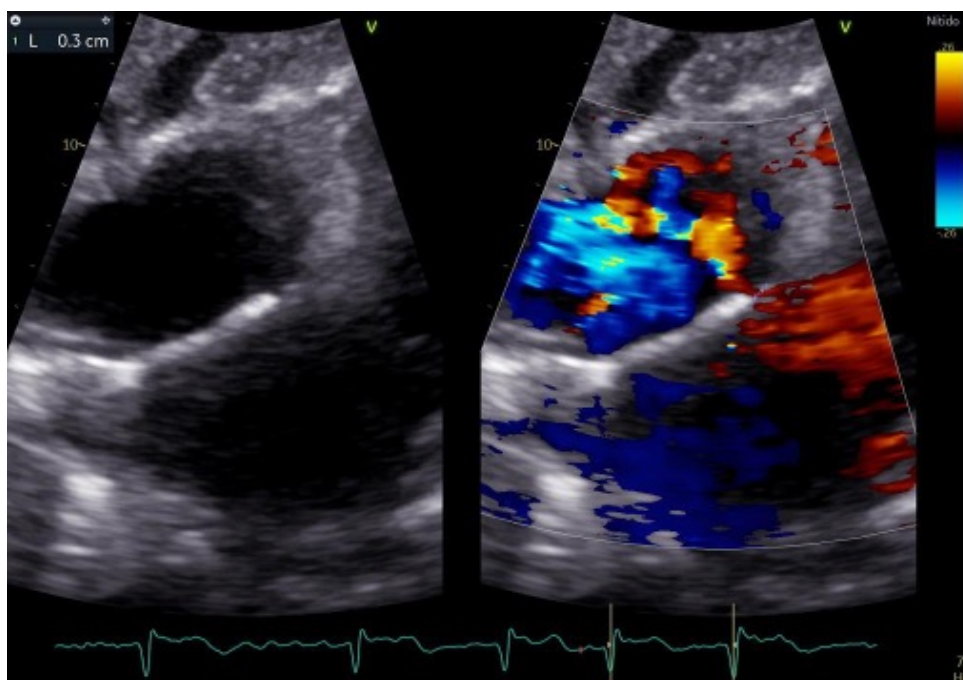


**Fig. 2.** Two-dimensional transthoracic echocardiogram, left parasternal short-axis view. Septal flattening due to right ventricular overload, with right ventricular dilation.



**Fig. 2.** Two-dimensional echocardiogram (left) with color Doppler (right). Subxiphoid view showing flow from the left to the right atrium through the atrial septal defect.



In conclusion, thyrotoxicosis can cause severe HF even with preserved LVEF. The demonstration of an elevated cardiac index, along with AF, right ventricular remodeling, functional valvular heart disease, and Graves' thyrotoxicosis, allowed us to reconsider a heart condition initially attributed primarily to valvular disease.

The main clinical message is that, in the face of unexplained heart failure in a young patient, the systematic search for reversible causes and the integration of serial cardiovascular imaging can substantially alter the diagnosis and prevent premature structural interventions.

#### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

#### Ethical considerations

Not applicable

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# Acute Arterial Ischemia of the Upper Limb Due to Thoracic Operculum Syndrome

*Isquemia arterial aguda de miembro superior por síndrome de opérculo torácico*

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MARIANO NORESE<sup>2</sup>

Thoracic operculum syndrome (TOS) is defined by extrinsic compression of the brachial plexus and/or subclavian vessels due to the presence of bony abnormalities or hypertrophy of the scalene and/or subclavian muscles. Involvement of the subclavian artery is rare but serious, due to the risk of thromboembolic complications such as acute arterial ischemia of the upper limb or posterior stroke caused by retrograde embolism. (1)

We present the case of a 66-year-old woman with a history of poliomyelitis and residual paresis of the left lower limb who used an orthosis and a forearm crutch to walk. She presented to the emergency department with pain in her left shoulder radiating to her forearm, accompanied by paresthesias that had been present for 24 hours. On physical examination, she presented with coldness and cyanosis, absence of radial and ulnar pulses in the left upper limb, with preserved sensation and motor function. The ECG showed a sinus rhythm; the chest X-ray revealed bilateral cervical ribs (Figure 1A); and the echocardiogram showed mild dilatation of the left atrium. Vascular Doppler ultrasound revealed a partially thrombosed aneurysm of the left subclavian artery and thrombosis of the humeral artery, with monophasic flow in the radial and ulnar arteries. Anticoagulation was initiated with intravenous unfractionated sodium heparin via an infusion pump. Computed tomography angiography (CTA) demonstrated thrombosis of the left humeral artery; bilateral supernumerary ribs at the C7 vertebral segment, with a fibrocartilaginous junction to the first left sternal rib, which exerted extrinsic compression on the subclavian artery aneurysm, resulting in right-sided vascular compromise. (Figure 1B and Figure 2)

An emergency thromboembolectomy was performed using a Fogarty catheter on the subclavian, axillary, and humeral arteries via an approach in the middle third of the arm. Postoperatively, the radial pulse was restored, and anticoagulation with heparin was resumed.

During hospitalization, decompressive surgery was performed on the TO via a supraclavicular and infraclavicular approach, including resection of the cervical rib and first sternal rib, anterior and middle scalene resection, and resection of the subclavian aneurysm with arterial reconstruction using a prosthetic subclavian-axillary bypass (6-mm ringed polytetrafluoroethylene graft). Anticoagulation with acenocoumarol was prescribed for 3 months. At the one-year follow-up, the patient remained asymptomatic with a radial pulse, and CT angiography showed a patent bypass.

Acute arterial ischemia in the upper extremities is less common than in the lower extremities due to the extensive collateral circulation around the shoulder and elbow.

Jo et al., in a review of 366 cases, reported a thrombotic cause in 61.7% and an embolic cause in the remainder. The most common causes included thrombosis of a vascular access site and cardiac embolism due to atrial fibrillation. The humeral artery is the most frequently affected, either alone or in combination with other arteries, in 89% of cases. (2)

Arterial TOS is characterized by compression of the subclavian artery, most commonly by a cervical rib or other bony anomalies such as a hypoplastic first rib, clavicle fracture, or hypertrophic calluses from fractures. Lesions in the subclavian artery result from chronic compression that leads to changes in the arterial wall, including intimal injury, ulcers with or with-

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**Fig. 1. A) Chest X-ray: bilateral cervical ribs. B) CT angiography of the thoracic aorta and upper extremities: extrinsic compression of the subclavian artery by a cervical rib (arterial TOS)**

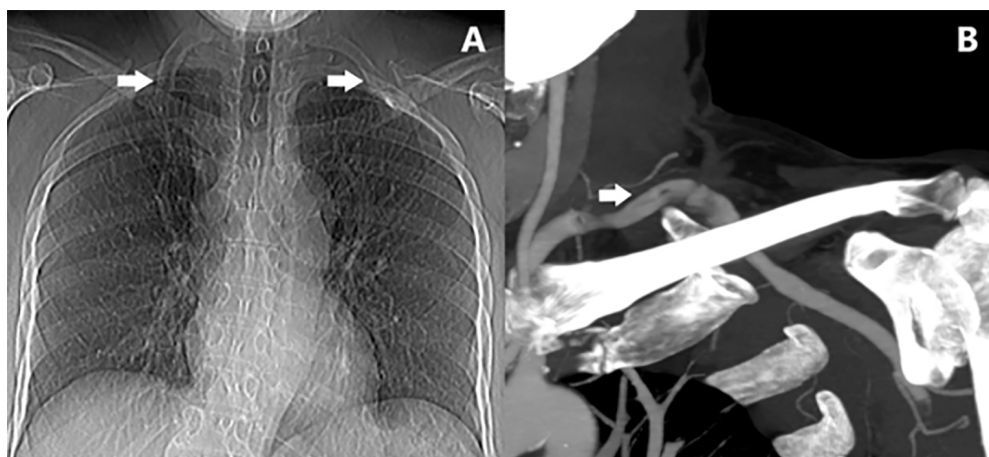
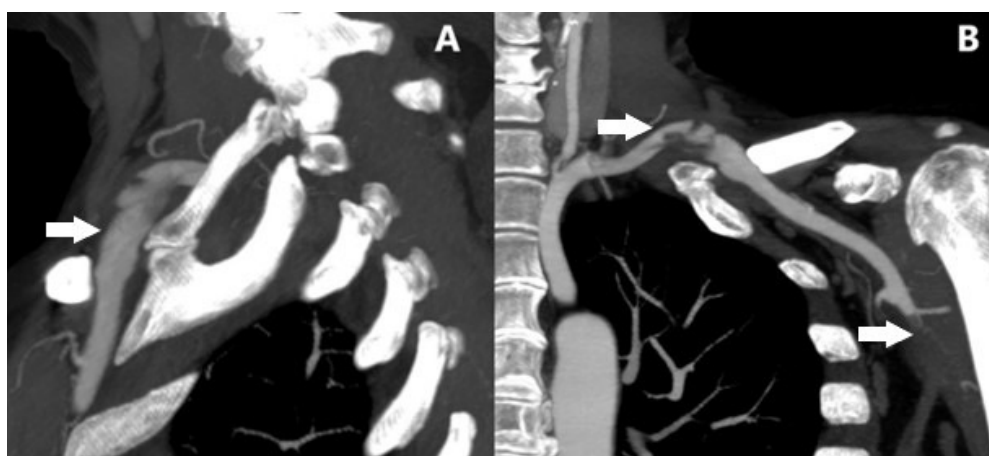


**Fig. 2. A) CT angiography of the thoracic aorta and upper extremities: compression of the subclavian artery due to pseudoarthrosis of the left cervical rib with the first sternal rib. B) CT angiography of the thoracic aorta and upper extremities: partially thrombosed subclavian artery due to TOS, associated to humeral artery thrombosis due to distal embolism.**



out post-stenotic dilation, aneurysms, and occlusive thrombosis. It is the least common form of thoracic operculum, accounting for only 3–4.4% of cases, and is most commonly described in young adult women. (1,3, 4)

The clinical presentation of arterial TOS is diverse, secondary to the broad spectrum of associated bone and arterial pathology. Cases have been described of intermittent claudication, digital ischemic necrosis, acute upper extremity arterial ischemia, posterior stroke, as well as overlap with symptoms of neurogenic TOS and asymptomatic cases identified on imaging studies. (1,3, 5,6)

Acute upper extremity arterial ischemia has been reported in 15–30% of cases of arterial TOS, commonly due to embolization from an aneurysmal and

thrombosed subclavian artery. (1,3,5)

Diagnostic methods include chest X-ray, which identifies bony abnormalities, and Doppler ultrasound to visualize arterial aneurysms or stenoses, as well as thrombosis and distal embolism. CT angiography provides anatomical details of the bony abnormality, subclavian artery involvement, and distal vascular beds for revascularization. Angiography is recommended when the diagnosis is unclear or to confirm subclavian artery compression in the early stages. (3,6)

The initial management of acute limb-threatening ischemia includes surgical thromboembolectomy with a Fogarty catheter or percutaneous thrombolysis-thrombectomy, followed by systemic anticoagulation with heparin. (1,3, 4)

Pitcher et al., in a 30-year retrospective analysis,

reported that 62% of patients with acute arterial ischemia due to arterial TOS experienced a recurrent thromboembolic event, suggesting that decompressive surgery of the operculum during hospitalization may help prevent it. (5)

Decompressive treatment for arterial TOS includes anterior and mid-scalenectomy with resection of the cervical rib and/or first rib or other bony abnormality in all cases, while vascular reconstruction is performed selectively based on the severity of subclavian artery disease. (1,3, 5) The reported reconstruction rate ranges from 38% to 70%, with procedures including saphenous vein bypass, prosthetic bypass, or cryopreserved vessel bypass; resection with end-to-end anastomosis; or surgical angioplasty with a venous patch. (1, 5) In subclavian arteries with mild post-stenotic dilations without intimal disruption, vascular reconstruction is not indicated, and follow-up with Doppler ultrasound is recommended. (1, 5)

The supraclavicular approach is the most commonly used for decompression, and when arterial reconstruction is required, a combined supraclavicular and infraclavicular (paraclavicular) approach is preferred for better vascular exposure. (1,3, 5)

In cases of acute arterial ischemia due to TOS, life-long antiplatelet therapy and anticoagulation for 3 to 6 months are recommended. (5)

Stent angioplasty is not recommended as a primary treatment for arterial SOT, as it does not address the cause of the arterial pathology, and bone compression can lead to stent fracture or thrombosis. (3)

The vascular manifestations of arterial TOS carry the greatest potential for disability, as 30% of patients present with persistent symptoms such as chronic pain and related to the degree of thromboembolism in the distal arteries prior to decompressive treatment. (1–3,5)

In summary, TOS is a rare cause of arterial compromise in the upper extremity. In cases of acute arterial ischemia, thromboembolism and systemic anticoagulation are initially recommended, followed in all cases—and during the same hospital stay—by early decompressive surgery of the operculum to prevent recurrence of a thromboembolic event. Vascular reconstruction is performed selectively based on the extent of subclavian artery involvement.

#### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

#### Ethical considerations

Not applicable

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## Oral PCSK9 Inhibitors: Between Promise and Pending Evidence

*Inhibidores orales de PCSK9: entre la promesa y la evidencia pendiente*

FERNANDO VICHI<sup>1</sup> 

Lowering low-density lipoprotein cholesterol (LDL-C) remains a cornerstone of both the prevention and treatment of atherosclerotic cardiovascular disease (ASCVD), supported by decades of genetic and clinical evidence confirming its causal role. (1) However, a considerable proportion of high-risk patients fail to achieve the recommended targets despite treatment with maximally tolerated statin doses.

Subcutaneous PCSK9 inhibitors (monoclonal antibodies) have represented a substantial advance in this setting, with sustained reductions in LDL-C and demonstrated clinical benefit in terms of cardiovascular events. (2) Nevertheless, their parenteral route of administration and high cost continue to limit their wider adoption.

The systematic review and meta-analysis by Masson et al. (3) updates the available evidence on five oral PCSK9 inhibitors. The authors report LDL-C reductions of nearly 58% compared with placebo, comparable in magnitude to those achieved with injectable drugs, and with no significant difference in adverse events. This meta-analysis incorporates phase 3 data on enlicotide, representing a significant advance over the largely descriptive evidence available until recently. Notably, one of the included studies demonstrated the superiority of an oral inhibitor over ezetimibe and bempedoic acid, two widely used oral alternatives. (4)

That said, several considerations temper this enthusiasm. The number of studies remains small, follow-up does not exceed 12 weeks in most studies, and the results for lipoprotein(a) showed marked statistical heterogeneity ( $I^2 = 99.2\%$ ), which calls for a more cautious interpretation of that point estimate. Furthermore, development of one of the five drugs has already been discontinued for strategic reasons, a reminder that this therapeutic class is still at an early stage. Nor should it be assumed that oral administration alone will resolve the problem of access. Indeed, while this editorial was prepared, the FDA approved enlicotide (Lipfendra) as the first commercially avail-

able oral PCSK9 inhibitor, based on the LDL-C reduction demonstrated in the CORALreef program, at a monthly list price of USD 315 —approximately half that of injectable drugs, but far from a trivial expense. The drug has not yet been approved in Argentina or elsewhere in Latin America, although it is worth noting that several centers in Argentina actively participated in the CORALreef program.

Importantly, no oral PCSK9 inhibitor has yet generated data on hard cardiovascular outcomes. The ongoing CORALreef Outcomes study will be decisive in determining whether these lipid reductions translate into concrete clinical benefits (5).

In conclusion, the study by Masson et al. provides a timely and methodologically sound synthesis of a rapidly evolving therapeutic class. Oral PCSK9 inhibitors represent one of the most promising strategies for optimizing intensive lipid-lowering therapy, but their definitive inclusion in treatment algorithms will have to await larger studies, longer follow-up, and, most importantly, results on hard cardiovascular events.

### Ethical considerations

Not applicable.

### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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#### AUTHORS' REPLY

We thank the author of the letter for his comments and for his assessment of our work. We agree that, at present, the achievement of lipid targets remains sub-optimal due to various patient-related (adherence), physician-related (therapeutic inertia), and health-care system-related (access to treatments) factors. In this context, we believe that oral PCSK9 inhibitors could represent a very promising therapeutic strategy, particularly given the magnitude of LDL-C reduction achieved and the possibility of having an oral alternative to monoclonal antibodies and inclisiran.

Likewise, we agree that these results should be interpreted with caution. As we noted in our study, the available evidence remains relatively recent, with

limited follow-up in a substantial proportion of studies and no data on clinical cardiovascular outcomes for this new therapeutic class. However, it should be noted that, currently, the absence of cardiovascular outcomes data also applies to inclisiran, which nevertheless represents an additional therapeutic tool in clinical practice. The results of ongoing cardiovascular outcomes studies will be essential to establish the clinical benefit of both strategies.

Furthermore, when we prepared our manuscript, we had no information on the prices of these drugs, much less on what they might cost in our country if they were marketed. In this regard, the possibility that an oral formulation could help reduce costs and, more importantly, promote greater market competition must, for the time being, be considered a hypothesis, as we presented in our study. Even if the prices of these drugs in their country of origin were known, any extrapolation to other markets would remain imprecise, given that prices and conditions of access may vary substantially among countries.

We thank the author once again for enriching the discussion on the potential and current limitations of this therapeutic strategy.

Walter Masson 

Hospital Italiano, Buenos Aires

## The Impact of Ischemic Burden on Current Medical Practice

### *El impacto del monto isquémico en la práctica médica actual*

PAULA ELIZABETH BARBOZA<sup>1</sup>, CLAUDIA MARIANA CORTÉS<sup>2</sup>

Historically, the assessment of myocardial ischemia has been a useful tool in clinical cardiology for risk stratification and decision-making. For this assessment, in the field of nuclear cardiology, Hachamovitch and colleagues, in their large-scale observational study, determined that an ischemic burden (IB) exceeding 10% of ventricular mass, in the absence of extensive myocardial necrosis, identified patients who benefited from an invasive strategy and early revascu-

larization compared with medical therapy in terms of survival. (1)

Over the years, both medical treatment and revascularization techniques have improved significantly. This led to the conduct of randomized trials to identify which subgroups benefited from an initial invasive strategy (2–4). Among these was the ISCHEMIA trial, which demonstrated that, in patients with moderate-to-severe ischemia, both initial medical therapy

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and invasive therapy reduce major cardiovascular events and mortality without significant differences. (5) However, it is important to note that this study used the performance of a coronary angiography (via CT angiography) as an initial evaluation criterion to rule out severe left main coronary artery disease or non-obstructive coronary artery disease, thereby excluding these patients from the study.

In light of the bibliographic references presented thus far, it is evident that the study titled “*Evaluation of the Clinical Management and Follow-up of Patients with Severe Myocardial Ischemia Detected by Triggered SPECT*” (6) provides an interesting update on these topics within the context of a public hospital in our country. Of primary relevance is the selection of patients with IB greater than or equal to 10% on a myocardial perfusion scan. The study evaluates the therapeutic approach (invasive versus conservative) adopted by treating physicians in this group upon finding these results of severe myocardial ischemia.

This observational, retrospective, single-center study by Herrero et al. provides valuable insights, as it demonstrates that treating physicians were significantly more likely to order an initial invasive study in the cohort of patients with a IB of 16% or higher. Furthermore, this subgroup of patients had the highest percentage of revascularization. This could be the starting point for reconsidering the value of IB in guiding therapeutic management.

This study had limitations, such as the considerable number of follow-up losses and the short median duration of longitudinal evaluation (18 months). However, it demonstrated a higher number of major cardiovascular events in revascularized patients, with a significant number occurring within the first month after the procedure. Given this finding, longer-term follow-up could be valuable to assess the performance of the medical treatment arm, considering that adherence may decline over time.

In conclusion, this is a valuable observational study that provides evidence to inform decision-making in real-world medical practice.

#### Ethical considerations

Not applicable.

#### Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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#### AUTHORS' REPLY

First, we would like to thank Dr. Barboza and Dr. Cortes for taking the time to read and thoroughly analyze our article; this will encourage those who read this letter to the editor to read the original article.

We agree with the limitations that the authors mention in their letter.

We believe this can serve as a starting point for initiating a multicenter study with longer follow-up to obtain external validation of our results; we consider our publication to be useful as a hypothesis for advancing our understanding of the pathophysiology and decision-making in chronic ischemic heart disease.

Best regards,

The authors

## A Gap That Directly Challenges Cardiology

### *Una brecha que interpela directamente a la cardiología*

ANALÍA L. GUAZZONE<sup>1</sup> 

The study by Forte et al. on the treatment gap in patients with type 2 diabetes and cardiorenal disease deserves careful consideration, not only because of its findings but also because of what it implies for our daily practice. (1)

The key finding is a treatment gap exceeding 90%, in class IIa combinations such as gliflozins (SGLT2i) + GLP-1 receptor agonists (GLP-1 RA), or finerenone + SGLT2i, compared with gaps of less than 10% for renin-angiotensin-aldosterone system inhibitors (RAASi)—a finding that should not surprise us, but should certainly concern us. This aligns with the findings reported by Nelson et al. in the United States, where only 2.7% of eligible patients received the full recommended regimen, (2) and confirms that the problem lies not in the available evidence, but in its translation into daily practice.

What makes this study interesting is that it does not report usage rates therapy by therapy, but rather constructs a weighted index that ranks interventions according to their clinical importance. This reveals that the gap is not uniform: it is concentrated in the most recently introduced cardiorenal therapies, such as SGLT2 inhibitors, GLP-1 RA, and finerenone. Meanwhile, “classic” tools (statins, antiplatelet agents, RAASi) maintain acceptable penetration rates. This distinction is clinically relevant because it suggests that the obstacle is not a general reluctance to prescribe, but something more specific: inertia toward new treatments, uncertainty about who should initiate the medication, or a lack of awareness of updated guidelines.

This is where the article particularly challenges cardiologists. Dixon et al. had already documented that the prescribing of SGLT2i and GLP-1 RA varies significantly depending on the prescribing specialty, with lower utilization specifically in cardiology practices (3). If the cardiologist is, in many healthcare systems, the first or only specialized point of contact for patients with cardiorenal disease, delegating the initiation of these therapies to other specialties per-

petuates the gap rather than reducing it.

Two secondary findings from the study deserve special attention in clinical practice: the wider gap observed in women and in older patients. Both patterns have been described previously—the first by Regensteiner et al. in their scientific statement for the *American Heart Association*, (4) and the second in McCoy et al.’s analysis of *Medicare Advantage* beneficiaries (5)—and their replication in an Argentine cohort suggests that these are not local artifacts but rather systematic biases in the prescribing process, possibly linked to misperceptions of risk or tolerability rather than actual contraindications.

As a limitation, I agree with the authors themselves that the observational design precludes establishing causality, and that unmeasured variables—such as coverage, costs, and adherence—likely account for part of the gap. However, this does not detract from the practical message: having a reproducible index to audit one’s own practice and systematically incorporating an eligibility review for GLP-1 RA and finerenone into every consultation with a cardiorenal patient appears to be a concrete, low-cost step toward narrowing this gap between the guidelines and actual prescribing practices.

#### Ethical considerations

Not applicable.

#### Conflicts of interest

None declared.

(See authors’ conflict of interests forms on the web).

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## AUTHORS' REPLY

Dear Editor:

We thank Dr. Analía L. Guazzone for reviewing our work and for her comments on the implications for cardiology practice. We agree on the need to take an active role in implementing therapies with cardiorenal benefits and to prevent fragmentation across specialties from delaying relevant therapeutic decisions.

The proportional treatment gap index aims to integrate treatment opportunities based on each patient's eligibility. (1) Its potential to guide clinical audits warrants further analysis; its use as a healthcare quality indicator requires an evaluation of its external validity and sensitivity to change. Furthermore, the weighting of its components should not be interpreted as a direct estimate of lost clinical benefit.

We agree with the author that barriers to access deserve special attention. The lack of detailed information on contraindications, tolerability, adherence, coverage, and costs prevents us from attributing the absence of treatment exclusively to therapeutic inertia. (1) Therefore, the identified gap should be understood as a potential opportunity for improvement, which requires reviewing each patient's clinical circumstances and access possibilities.

Regarding differences by age and sex, it should be

noted that the associations with older age and female sex observed in the linear model lost statistical significance in the beta regression. (1) These results are exploratory and warrant further research, but they do not allow us to conclude that systematic prescribing biases exist in our cohort.

As Dr. Guazzone proposes, a structured review of eligibility during the consultation is a reasonable strategy. We suggest complementing this with the documentation of reasons for non-prescription and with agreements among cardiology, diabetes care, and nephrology that define responsibilities for initiating and monitoring treatment. This proposal is consistent with the recommendations of the Argentine Society of Cardiology for implementing cardiorenal units, published in this journal, which promote multidisciplinary teams involving diabetes care, shared protocols, and structured follow-up with quality indicators. (2) In particular, therapeutic combinations should be evaluated based on individual indications and the corresponding recommendation class. Subsequently assessing actual prescribing practices and treatment continuity would help determine whether these actions reduce the observed gap. The purpose of this letter is precisely to encourage the transformation of these findings into concrete interventions whose effectiveness can be measured.

**Ezequiel H. Forte**

On behalf of the authors

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# A Letter to Young Cardiologists

## The Highs and Lows of Practicing Medicine. In Search for Meaning.

*Carta a los cardiólogos jóvenes*

*Luces y sombras de practicar la medicina. En búsqueda del sentido*

*"Where artificial intelligence seeks precision and control, human beings find meaning in ambiguity, in error, in slips of the tongue, in that which does not quite add up. It is not about eliminating doubt, but about living with it."*

**Santiago Kovadloff**

The Argentine Society of Cardiology (SAC) is a pioneering institution that brings together prestigious cardiology centers dedicated to patient care, research, and specialist training. As President of the SAC, I am pleased and proud to write a letter to the young cardiologists who graduate each year from the program offered by our institution. I consider the opportunity to address these cardiologists in this letter a comfort to the spirit, not a boost to the ego—an insatiable creature all physicians must take care not to inflate.

The graduation ceremony of a medical specialty marks a rite of passage into a new chapter of professional life—one that well deserves celebration. They are receiving not only a certificate qualifying them to practice within a cardiology subspecialty, but a human and scientific responsibility toward the needs, vulnerability, and lives of others.

Throughout this journey, the graduates have logged hours on call or during long shifts, taken histories and listened to patients, meticulously reviewed electrocardiographic tracings, interpreted hemodynamic data or imaging, or mastered specific techniques. Yet at the heart of all this technical complexity, the fundamental anthropological question remains unchanged: what does it mean to heal another human being?

In a recent letter, I pointed out that humanism in medicine is the school of thought that holds that medical practice cannot be reduced to a mere application of science and technology but must instead be deeply rooted in empathy, respect for human dignity, and a holistic understanding of the patient. (1)

The rational practice of medicine requires understanding that our object of study is not a malfunctioning machine, but rather a suffering person. Ancient Greek philosophers laid the foundations of our prac-

tice by understanding that technical skill (*techne*) is blind if it lacks practical wisdom (*phronesis*) and moral character (*ethos*). The body cannot be cured without attending to the soul. (2) It is vital to resist the temptation to treat the part while disregarding the whole.

In medicine, as in life, knowing how to win with humility is as crucial as knowing how to lose with dignity. The famous maxim "to cure sometimes, to relieve often, to comfort always" summarizes the essence of human care. Although science cannot always defeat disease, human presence and support are indispensable at all times.

In our contemporary world, the master clinician Francisco Maglio bequeathed a fundamental premise for humanistic medicine: "One cannot be a better physician than one is a person." Maglio taught us to distinguish between *disease* (the biological entity described in textbooks) and *illness* (the biography and the subjective, social, and existential experience of the person suffering it). (3) A physician who is hypertrophied in technical skills yet atrophied in human warmth becomes a mere requester of diagnostic tests or prescriber of drugs. To cure is a biological act; to heal, a relational one. The physician-patient relationship is not a service transaction, but rather an encounter of two wills and two vulnerabilities: one seeking help, and the other offering knowledge and empathy.

To honor this profession, the technique must be guided by a robust ethical framework. Values are not theoretical abstractions; they are validated solely through concrete actions that honor them: (4)

- Honesty: honored by communicating complex diagnoses truthfully and with sensitivity, without false promises or concealment.



- **Responsibility:** honored through the rigorous study of each case, continuous learning, and accepting the consequences of our clinical decisions.
- **Respect:** honored by recognizing patients' autonomy, beliefs, and dignity, regardless of their social status.
- **Gratitude:** honored by acknowledging the efforts of the patients who trust us and the lessons we have learned from our peers and masters.
- **Humility:** honored by acknowledging the limits of our own knowledge and seeking a second opinion when doubt arises.
- **Solidarity:** honored by ensuring that the best medical care also reaches the most vulnerable.
- **Excellence:** honored in the unending pursuit of the perfect detail, shunning mediocrity and routine.
- **Practical wisdom (*Phronesis*):** the clinician's supreme value. It is honored by weighing the benefits against harm and by knowing not only when to act, but also when to abstain.

Continuing with the cultivation of virtues, it is essential to maintain fortitude when it seems impossible or unattainable, to practice justice by being fair and constructive in both error and success, and to promote reflection and empathy over vertical authority when resolving complex issues.

Immanuel Kant bequeathed to us his categorical imperative, reminding us that we must act in such a way that the maxim of our will can always hold as the principle of a universal law. In cardiology, this means: never treat the patient merely as a means to professional advancement, statistical record-keeping, or financial gain, but always as an end in themselves.

Yet, real-world medical practice confronts us with dilemmas in which principles come into conflict. This is where the principle of the lesser evil and Max Scheler's hierarchy of values come into play. Scheler teaches us that values are organized hierarchically: agreeable values are subordinate to vital ones, which in turn are subordinate to spiritual ones (the just, the true, the beautiful), and all of these are subordinate to holy and ethical values. When clinical reality corners us, the prudent physician must know how to sacrifice a lesser value to save a higher one, always prioritizing life, dignity, and the relief of pain over comfort or institutional inertia. These aspects are very well developed in the book *Sabiduría Artificial*, in light of the emergence of artificial intelligence. (4)

The mathematician and physicist Roger Penrose revisits Plato's classical triad as intertwined pillars of reality and knowledge. These concepts correspond directly to the transcendentals of being: unity (*unum*), truth (*verum*), goodness (*bonum*), and beauty (*pulchrum*). (4)

- **The true:** the rigorous adherence to scientific evidence, method, the logic of pathophysiology, and statistics.
- **The good:** ethical intent and pure benevolence oriented toward the patient's well-being.

- **The beauty:** harmony in a medical encounter. There is beauty in an elegantly reasoned diagnosis, in a masterfully performed surgery, and in a word of comfort offered at precisely the right moment.

When a physician succeeds in integrating the truth of science, the goodness of intention, and the beauty of execution, medicine ceases to be a mere craft and rises to the status of a sublime art.

None of this is possible without the imperative of the Oracle of Delphi: *Nosce te ipsum* (know thyself). A physician who is unaware of their own biases, fears, limitations, fatigue, and projections runs the risk of causing unintentional harm. Self-knowledge is the armor against hubris (arrogance) and the only path to managing frustration in professional practice. Far from being a weakness, acknowledging our own intellectual and human frailty is the only path to rigorous discernment. By setting aside the mask of infallibility and the need for constant approval, we rediscover the profound truth of our work, allowing us to learn, connect genuinely with others, and practice with true ethical authority.

Furthermore, we must recall the famous maxim attributed to José de Letamendi and widely popularized in medicine: "He who knows only medicine, does not even know medicine." Cardiology reduced to myocytes and ion channels is blind. To understand a human being suffering from a heart condition, one must sometimes understand history, sociology, philosophy, and language.

However, this does not mean falling into soft subjectivism. Modern medicine requires mastery of the formal language of science: mathematics and statistics. Probabilistic reasoning, the rigorous interpretation of the p-value, confidence intervals, relative risk, and absolute risk reduction are indispensable tools for rational practice. Statistics is the filter that protects us from self-deception, from elevating personal anecdotes to universal rule, and from quackery. But we must be clear: statistics describe populations; clinical practice deals with individuals. The specialist's mastery lies in knowing how to apply population-based evidence to the unique and unrepeatable situation of the patient before them.

Cultivating sensitivity through the arts is no mere pastime; it is a constitutive necessity of the medical mind. Art trains us in observing nuance; poetry teaches us the precision and weight of words; music attunes us to rhythm, pause, and harmony.

If we analyze Maslow's hierarchy of needs in the context of medical life, we observe a troubling paradox. As physicians, we often strive to reach the top of the pyramid—self-actualization, academic prestige, and mastery of our specialty—by sacrificing the foundational layers: adequate rest, proper nutrition, physical activity, emotional safety, and time with our loved ones. (5)

To achieve true personal and professional fulfillment, we must address the holistic needs of both

sides of the health equation:

- What do patients need? They need impeccable technical competence, but also attentive listening, time, direct eye contact, clear explanations, and a serene professional they can trust.
- What do we physicians need? We need dignified working conditions, time for study and reflection, spaces for emotional support, respect for our personal lives, and institutional environments that safeguard our mental health.

Dear young colleagues, cardiology is a highly demanding discipline. Roberto De Vincenzo, the greatest Argentine golfer of all time, used to say: "I'm lucky, but the more I practice, the luckier I get." You will face situations where your efforts will not immediately translate into a favorable result. Resilience—the capacity to maintain one's integrity in the face of adversity—will be your most valuable asset. Do not jeopardize a successful trajectory by putting the cart before the horse. With clear objectives, a sound methodology, and core values—guided by a rational and patient perspective—you will build the personal culture that makes things happen and delivers results. Do not let the pursuit of immediate gratification cloud your medium- and long-term perspectives. In life, there are things that take time: peace, war, love, and a professional career. The meaning of Hippocrates of Cos's famous maxim has changed very little: "Art is long, life is short, experience is deceptive, judgment is difficult, and opportunity is fleeting." (3)

Be leaders in your roles. Deepen team-based learning, propose improvements and innovation, motivate and inspire, celebrate the team's success, and manage your personal ego—letting it be the group that uplifts you, without ever letting it go to your head. In the face of today's culture, which sometimes confuses algorithmic validation with merit, hype and excessive self-promotion generate fleeting expectations that erode credibility. Professional humility acts as an ethical brake against this temptation, reminding us that true prestige is not proclaimed through artifice, but validated through consistency and sustained dedication.

When leaders fail today, it is often due to an inability to adapt to change, weak interpersonal bonds, a failure to build and lead teams, or excessive misdirected ambition. Know that the unit of measure is the team—transforming "I" into "we," or flipping the "M" in "me" to become the "W" in "we." Know that there is no motivation without connection, no connection without conversation, no conversation without time, and no time without conscious purpose. (6)

Likewise, I urge you to tenaciously seek a balance between your professional life and your family. The medical profession is all-consuming and fascinating, but it must not become a sacrificial altar where our primary affections are burned. Family is the safety net that sustains us when clinical practice exhausts us; home is the harbor where the physician, if only for

a time, becomes a person again. Do not postpone the hugs, the celebrations, or your presence in the lives of those you love for the sake of fleeting professional success.

Masters and mentors are the beacon. Caring for and respecting masters is a non-negotiable ethical imperative. A true master in medicine is not the one who knows everything, but the one who teaches how to think, shows how to treat the humble, and demonstrates how to stand firm in the face of complexity.

"If I have seen further, it is by standing on the shoulders of giants." This quote from Bernard of Chartres was popularized by Isaac Newton. He wrote this in a letter acknowledging that he had reached his conclusions on the properties of light only through the pioneering work of Descartes and Hooke. It is important to remember that, beyond effort alone, we have all received gifts that allowed us to cultivate ourselves, and that no one is truly self-made. Cultivate humility and gratitude. Professional development does not occur solely through personal attitude, but also through the fundamental role of mentors, educators, and the institutions that shelter them. In this sense, if the student surpasses the master, the educator will have more than fulfilled their purpose. At times, as parents or educators, we ask ourselves what kind of country or healthcare system we will leave to the next generation. For some time now, I have changed that view to one that depends more on personal action, asking myself what quality of children and physicians we will offer to the country.

Institutions are not mere concrete structures; they are human ecosystems dedicated to the preservation of life and the passing of knowledge across generations. Forming a specialist requires infrastructure, investment, a culture of safety, and a sustained educational vocation.

Throughout the history of medicine, great figures have reflected on the transmission of knowledge and the cycle of professional life:

Hippocrates, in his Invocation and Oath, placed the master on the same level of respect as one's own parents, requiring students to share their resources and honor the old age of those who taught them the art. (7)

Sir William Osler insisted on the need for young physicians to recognize the foundations laid by preceding generations, reminding them that cumulative experience is an indelible treasure. (8)

Alberto Agrest, a master of Argentine medicine, taught us the importance of critical thinking, intellectual honesty, and respect for elders, warning us of the dangers of ingratitude and institutional amnesia. (9)

I would like to make a special and heartfelt mention of those physicians who work to foster institutional educational processes and who are now at a mature stage of their professional careers. Do not forget them; take care of them. This aspect shapes the

culture and values that sustain institutions, serving as a sign of trust for those who choose to commit to the institution.

You owe part of your present to those pioneers. Their footprints are etched in every hallway, in every case conference, in every service standard that you now apply as a matter of course. Institutions that fail to honor their mentors lose their soul and their historical memory.

Dear graduates, today you step out into the world with a formidable toolkit. You have statistics to analyze evidence, mathematics to understand hemodynamics, technical skill to intervene upon the body, and science to support every decision. But never forget that behind every electrocardiographic tracing there is a life story, eyes seeking hope, and a heart that not only pumps blood but loves, suffers, and dreams.

Be rigorous in science, impeccable in ethics, sensitive to humanity, and grateful to your masters. Seek professional fulfillment without sacrificing family harmony. Honor the memory of those who preceded you and become the safe shelter your future patients will need.

*May prudence guide your hands, truth direct your mind, and empathy move your heart.*

**Sergio Baratta** <sup>MTSAC, </sup>

President of the Argentine Society of Cardiology

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