

CARDIOVASCULAR AND METABOLIC SCIENCE

Continuation of the Revista Mexicana de Cardiología

2026



PREVENIR ES NUESTRA META



- Science funding and National progress
- Cardiovascular and Metabolic Science, a publication of established solidity
- Ibogaine cardiotoxicity
- Anomalous Aortic Origin of Coronary Arteries: A Latin American Cohort
- Clopidogrel-Associated small vessel vasculitis
- Should you replace the battery of the defibrillator that has not discharged?
- Application for invasive hemodynamics

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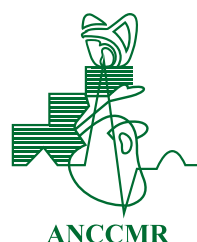
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¿Es compatible un presupuesto insuficiente para la ciencia y la investigación con el progreso de un país?

Eduardo Meaney-Mendiolea*

A nation is a mixture of many elements: a defined territory; sometimes, a single ethnic group or, conversely, an amalgam of different ethnicities and languages; a common historical past; and a combination of cultures and civilizational values. As classically defined, culture is the set of collective systems of values, tenets, customs, and social behavior shared by a human community.¹ The amalgamation of musical, literary, philosophical, pictorial, sculptural, architectural, cinematographic, photographic, handicraft, sports, and culinary traditions on the one hand, and the technical-scientific legacy on the other, forms the core of what could be called «the national soul». To be recognized as a true nation, a society must possess territory, a socio-economic organization, a political system, and a form of government. Equally important, however, is a legacy of cultural, artistic, philosophical, and scientific achievements. Without this heritage, the nation becomes a soulless community of individuals who –as the great Cuban poet Nicolás Guillén put it– are «people already of animal projects» (literal translation for the Spanish line: *gentes ya de proyectos animales*). Furthermore, given the rapid advancement of science and technology—an avalanche that is reshaping contemporary civilization—a country lacking its own scientific capabilities is condemned to remain forever a colony, a protectorate, or the backyard of hegemonic powers. In other words, relegated to being a «banana republic»- a derogatory term used by

hegemonic centers to describe underdeveloped nations that export cheap natural products and import expensive goods resulting from scientific and technical advancement, while also being plagued by political turmoil, weak institutions, widespread corruption, and foreign intrusions.

In a little more than a century, from the years following the end of the armed phase of our 1910 social revolution, between advances and reversals, Mexico transformed from an underdeveloped, semi-feudal society into a capitalist nation with moderate industrialization growth and a flawed liberal democracy. An accelerated urbanization and industrialization shifted populations from rural areas to cities, reducing agricultural production. Meanwhile, manufacturing currently accounts for 20% of the national GDP (Gross Domestic Product) currently,² surpassing the combined revenues of oil, tourism, and migrant remittances. Based on these data, we are far from being a banana republic from an economic standpoint. Instead, amid today's turbulence and international threats, we are building a stable, upper-middle-income economy without the economic crises and currency devaluations of the recent past. Mexico's economy is now the 13th largest in the world –on the same level as Australia, above Spain and South Korea, close to Canada's and Russia's, and ahead of all the Latin American economies except Brazil's. We are no longer a «poor» country, as our nominal GDP is about \$2.12 trillion USD.³ However, 2025 data

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indicate that GDP per capita –national wealth divided by the number of inhabitants– is deplorably low: barely US\$13,889 per person per year, placing it below Uruguay and Chile but above Brazil and Colombia.⁴ This means that, although Mexico is a moderately wealthy country, income inequality across various segments of society condemns vast sectors of our population to relative or absolute poverty. It is estimated that the top 10% of society receive nearly 30% of total income. In contrast, the bottom 10% receive less than 2% of income.⁵ Furthermore, since the economy is not growing beyond 1.3% annually, and tax evasion and corruption, though reduced, continue to weigh on public finances, government revenue is insufficient to meet all the needs of a society that aspires to join the select group of developed nations.

As physicians and scientists, we are directly concerned by this situation, setting aside all political or ideological considerations. For example, contrary to recommendations from the World Health Organization and the Pan American Health Organization (PAHO) for developing nations to invest at least 6% of their GDP in public health, Mexico allocated only about 3.22% through federal public spending.⁶ This falls drastically short of what an overburdened health system requires. This budgetary shortfall in public health funding is not new, as it has persisted for decades. Therefore, a health system constrained by a lack of resources could not fulfill its basic function of providing modern medical care for the population.

On the other hand, the United Nations Educational, Scientific and Cultural Organization (UNESCO), among other bodies, has suggested that nations allocate 1% of their GDP to research and development (R&D) expenditure.⁷ On September 1, 2004, following intense pressure from various political parties and the national scientific community, Article 9 bis of the Law on Science and Technology was amended, establishing an obligation for the State to allocate at least 1 percent of the country's GDP to scientific research.⁸ This constitutional obligation has never been fulfilled. During the previous six-year terms, the proportion of GDP allocated

to research fluctuated around 0.4%, falling far short of the target set by our Constitution. Although conflicting and sometimes malicious figures regarding research spending have circulated over the last two years –during which a renowned researcher has served as the country's highest-ranking executive– the most reliable sources⁹ report a value between 0.25 and 0.5%. Wealthier countries spend the most on research. The United States, Canada, and Europe allocate nearly 2.5% of their GDP to this purpose, while spending in East and Southeast Asia ranges from 2 to 4%. North Africa and the Near East spend about 1%, Latin America and the Caribbean average 0.57%, and sub-Saharan Africa spends 0.38%. It is disappointing that, relative to our economy's size, R&D spending is no higher than –or is even equivalent to– that of some of the world's poorest countries, and lower than the regional average, despite our status as the second-largest economy in Latin America.⁹⁻¹¹

The contribution of the Mexican scientific establishment to global science is very small, as only 0.5 to 1.3% of articles in journals listed in Scopus and Web of Science (WoS) originate from Mexico.^{12,13} Although a combination of circumstances explains the country's poor scientific output, one factor –in our view, the most significant– is the meager funding the Mexican State provides for the development of science. One could politely point out to those responsible for national finances and promoting scientific research that science, as well as the arts and education, hinges on adequate funding. Scientists, artists, and educators need enough funding not only to live with dignity but also to access the necessary facilities, equipment, and supplies. Of course, this is not true for every art form. Writing a sonnet, for instance, requires only a poet's talent, a pencil, and paper. However, other creative works demand heavy funding. Creating a large mural requires a wall, surface preparation, liters of paint, scaffolding, and a team of assistants. The same applies to science. A researcher's talent and training are not enough; access to laboratories, instruments, various sophisticated devices, materials, and reagents is also required. The principle that there is no science without funding applies to both basic and applied science.

At the same time, we are aware of the immense and varied needs of our society. Nothing is more important than the well-being of the most vulnerable segments of the population. The point is not to suggest withdrawing support for the elderly, the disabled, and students, or halting the major infrastructure projects currently underway or planned for the immediate future, to redirect those funds to national science. Nevertheless, the Mexican State must find a way to finance national science, a task in which the private sector should also contribute to this effort. At stake are not only Mexico's sovereignty and techno-scientific independence, but also the further development of vital areas –such as industry, environmental protection, agriculture, energy, and natural resources– that depend directly or indirectly on science and technology.

The bulk of the country's scientific research is conducted at public universities (and a few private ones). Although there is no precise data on the matter, hospital systems under the Mexican Social Security Institute (IMSS) and those belonging to the Health Institutes and High-Specialty Hospitals under the Ministry of Health are the largest contributors –after public universities– to biomedical scientific output, with the Institute for Social Security and Services for State Workers (ISSSTE) trailing in a distant third place. However, only a small proportion of the clinical research studies from these institutions are published in Q1-ranked journals.

In conclusion, scientific research broadly, and biomedicine specifically, have failed to keep pace with national economic development. Historically and today, scientific advancement has not been a primary strategic priority for the Mexican State. We, the members of the medical and scientific community, have failed to demand that successive governments fully comply with our constitutional mandate: investing at least 1% of GDP in science and technology, and, in addition, increasing enrollment in graduate programs and creating jobs for young researchers to prevent «brain

drain» of talent moving abroad. We must explain to our government officials and legislators the truth contained in this quote by Louis Pasteur: «Science is the soul of national prosperity and the lifeblood of all progress».

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Announcement by ANCAM to all its members regarding the recognition of our journal, *Cardiovascular and Metabolic Science*, as a publication of established solidity

Comunicado de la ANCAM a todos sus miembros sobre el reconocimiento de nuestra revista, Cardiovascular and Metabolic Science, como una publicación de sólida trayectoria

Eduardo Meaney-Mendiolea*

Abbreviations:

CONACYT = *CONsejo NAcional de Ciencia Y Tecnología* (National Council of Science and Technology)

SECIHTI = *SEcretaría de Ciencia, Humanidades, Tecnología e Innovación* (Secretariat of Science, Humanities, Technology, and Innovation)

SNPCyH = *Sistema Nacional de Publicaciones Científicas y Humanísticas* (National System of Scientific and Humanistic Publications)

The recent creation of the Federal Government's Secretariat of Science, Humanities, Technology, and Innovation (SECIHTI) –evolving from what was, for many years, the National Council of Science and Technology (CONACYT)– resulted in it a series of significant adjustments, innovations, and reforms that affected all participating institutions and national researchers. In this context, scientific journals were also affected by the new editorial standards. During the CONACYT era, the classification of the country's scientific journals was based on whether they met impact-based metrics; evaluators primarily tallied article citations, and journals with commercial financing –or those requiring payment– were allowed. Nevertheless, inclusion in CONACYT's Index or Catalog of Mexican Science and

Technology Journals, represented a distinction of sorts, as it served as an endorsement from the highest State scientific authority. Our journal received that distinction many years ago. The new regulations established by the National System of Scientific and Humanistic Publications (SNPCyH)–under the auspices of SECIHTI– required journals to align with these parameters and submit the necessary information to the authority within a short timeframe. Alongside academic requirements, the new regulations aim to boost scientific communication through open-access publishing and by recognizing science, above all, as a public good. That is why the term «diamond open-access academic journals» was coined. The term «diamond» refers to the transparency in editorial practices, the peer-review process, and journal financing, as well as a commitment to the public interest and freedom from commercial influence. According to SNPCyH, scientific journals in this concept must be «a non-commercial, sovereign, and inclusive open-access publishing model aimed at conceiving knowledge as a public good, in accordance with the provisions of the Mexican Constitution and the General Law on Humanities, Sciences, Technologies, and Innovation».

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The Editorial Committee –primarily our highly competent executive editor, Pilar Ortíz, MD, PhD– and the ANCAM administration led by the tireless Ms. Angélica Pacheco López promptly and successfully provided the information required by the evaluating body. But the invaluable assistance and solidarity of our Association’s leadership team –its President and Vice President, Dr. José Antonio Magaña Serrano and Dr. Yoloxóchitl García Jiménez– were instrumental to this success. Also, I want to offer special recognition to Medigraphic, our publishing house, which has accompanied us on numerous ventures, and to its directors, Drs. José Rosales Jiménez and María de la Luz Rosales Jiménez, as well as Lic. Irving García Mejía, the diligent Head of the Programming and IT Department, and Mrs. María Loreto Echevarría Torres, one of the company’s managers, who is closely involved in our editorial work. With great professionalism and tireless effort, the publishing team worked closely with us to achieve this milestone.

Two independent reviewers examined the journal, and their final assessment stated that it achieved the *CONSOLIDATED/CONSOLIDATED* rating in the SECIHTI registry. The double

«Consolidated» status indicates that the journal met the requirements for editorial presentation and management, scientific content quality, and online accessibility. Reviewers indicated that we must address issues concerning the use of artificial intelligence and enhance the journal’s international visibility and impact. We are fully aware of these weaknesses and are working to address them. However, to achieve international recognition and attain significant impact factors, our Association’s leadership and the Editorial Committee require the effort of our entire community. The volume and quality of the scientific material we publish directly reflect the diligence, skill, and scientific depth of our academic community.

May this recognition from the federal agency responsible for advancing national science spur us all –our leadership, editors, reviewers, publishers, administrative staff, and every member of our great Association–to redouble our efforts. We have a good journal; let’s make it even better–all together.

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Ibogaine. A new nightmare for cardiologists in tourist cities?

Ibogaina. ¿Un nuevo reto para los cardiólogos en ciudades turísticas?

Rafael Moguel-Ancheita,* Sara Ruggiero-Portocarrero†

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Keywords:

kratom, ibogaine, withdrawal syndrome, long QT, polymorphic ventricular tachycardia, torsade de pointes.

Palabras clave:

kratom, ibogaina, síndrome de abstinencia, QT prolongado, taquicardia ventricular polimórfica, torsade de pointes.

Substance abuse is a growing global health problem, and with it, the need to find medications or other substances that aid in the detoxification process or relieve symptoms associated with withdrawal syndrome. The abuse of kratom is gaining interest in the search for treatments that facilitate detoxification, marketed as a «natural» product for pain management or for reducing opioid use itself; it is a substance derived from a tropical tree native to Southeast Asia that appears to have properties similar to opioids, its main psychoactive constituents, mitragynine and 7-hydroxymitragynine, produce stimulant effects at low doses and sedative and analgesic effects at higher doses.

Prolonged kratom use may lead to tolerance, physical dependence, and withdrawal syndrome.¹ Currently, there are kratom detoxification tourism clinics at vacation points, utilizing ibogaine, a psychoactive alkaloid derived from *Tabernathe iboga*, used for its anti-addiction effects in various substance use disorders. Ibogaine and its primary metabolite, noribogaine, have anti-addiction effects by dual inhibition of the vesicular monoamine transporter-2 and the serotonin transporter, both of which are synaptic reuptake inhibitors.

Additionally, they exert modulatory effects on multiple neurotransmitter systems and exhibit micromolar affinity for the N-methyl-D-aspartate receptor and the κ -, μ -, and sigma-2 opioid receptors. Ibogaine also interacts with the acetylcholine, serotonin, and dopamine

systems. It alters the expression of proteins such as substance P, brain-derived neurotrophic factor, early growth response-1, and the proto-oncogene c-Fos, with a risk of cardiotoxicity, including QT interval prolongation and the onset of potentially fatal arrhythmias such as torsades de pointes.

After oral administration, ibogaine undergoes rapid and extensive metabolism, primarily via cytochrome P450 2D6 (CYP2D6), to its main active metabolite, noribogaine (12-hydroxyibogamine), which persists at clinically relevant concentrations for days after ibogaine plasma clearance.² The cause of the cardiotoxicity lies in the effect on specific types of channels. It acts by blocking the human ether-à-go-go-related gene potassium channels in cardiac myocytes, which are essential for the repolarization phase of cardiac action potentials, delaying ventricular repolarization, prolonging the QT interval on the electrocardiogram resulting in increased dispersion of ventricular repolarization, predisposing to polymorphic ventricular tachycardias and sudden cardiac arrest,³ even at therapeutic doses and in individuals with no history of cardiovascular disease; therefore, the focus should be on finding a safe way to administer this type of medication.

In the last month, we attended two ibogaine-intoxicated patients at Cozumel COSTAMED/The Clinics of the Heart, both men aged 30-40 years, derived from kratom-detoxification clinics; the first one, a 34-year-old, after

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successful resuscitation from cardiac arrest, with evident recurrent torsades de pointes and QT interval > 600 ms, and the second with QT interval > 600 ms without arrhythmia; the first case with requested voluntary discharge still on long QT and the second with confirmed normal QT after 72 hours.

Efforts are underway to enhance ibogaine safety, including optimized dosing strategies, continuous electrocardiographic monitoring during administration to detect arrhythmia risk, and the development of analogs that maintain anti-addiction efficacy without cardiotoxic effects in preclinical models. These initiatives aim to provide safer detoxification options, address clinicians' concerns about adverse cardiac events, and guide future clinical practice.⁴ Meanwhile, it looks like kratom-ibogaine detox tourism may become a new nightmare for cardiologists in tourist destinations.

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Characterization of clinical and anatomical profile of patients with anomalous aortic origin of coronary arteries and their association with major cardiovascular outcomes: the experience of a Latin American third-level center

Caracterización del perfil clínico y anatómico de los pacientes con origen aórtico anómalo de las arterias coronarias y su asociación con eventos cardiovasculares mayores. La experiencia de un centro de tercer nivel en Latinoamérica

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ABSTRACT

Introduction: coronary artery abnormalities are a rare condition but one associated with a potentially serious outcome. **Objectives:** characterization of clinical and anatomical profiles of patients with Anomalous Aortic Origin of Coronary Arteries (AAOCA) and their association with any pre-specified Major Cardiovascular Events (MACE). **Material and methods:** a retrospective study was conducted among patients with AAOCA in a tertiary care center, from January 2000 to June 2022. We analyzed the association between clinical and anatomical characteristics of patients and pre-specified MACE (Acute Coronary Syndrome [ACS], surgical revascularization, or cardiovascular death). **Results:** fifty patients were included. The mean age was 52 ± 15 years, and most patients were male (68%). Systemic hypertension was the most frequent comorbidity (38%). Only five patients (10%) had congenital heart disease. ACS was the most frequent initial clinical presentation (42%). Most AAOCA affected solely the right coronary artery (60%), and nearly half of all individuals (44%) had at least a high-risk characteristic. MACE was recorded in 14 patients (28%) with a median follow-up of 1,636 days [IQR 626-2,345]. Cumulative

RESUMEN

Introducción: las anomalías de las arterias coronarias son una patología rara pero relacionada a un posible desenlace ominoso. **Objetivos:** caracterización de los perfiles clínicos y anatómicos de pacientes con origen aórtico anómalo de las arterias coronarias (AAOCA por sus siglas en inglés) y su asociación con cualquier evento cardiovascular mayor (MACE por sus siglas en inglés) preespecificado. **Material y métodos:** se realizó un estudio retrospectivo en pacientes con AAOCA en un centro de atención terciaria, desde enero de 2000 hasta junio de 2022. Se analizó la asociación entre las características clínicas y anatómicas de los pacientes y los MACE preespecificados (síndrome coronario agudo [SCA], revascularización quirúrgica o muerte cardiovascular). **Resultados:** se incluyeron cincuenta pacientes. La edad media fue de 52 ± 15 años y la mayoría de los pacientes fueron hombres (68%). La hipertensión arterial sistémica fue la comorbilidad más frecuente (38%). Solo cinco pacientes (10%) tenían cardiopatía congénita. El SCA fue la presentación clínica inicial más frecuente (42%). La mayoría de las AAOCA se dieron únicamente en la arteria coronaria derecha (60%) y casi la mitad de todos los individuos (44%)

Keywords:

coronary artery anomalies, anomalous aortic origin of coronary arteries, congenital artery disease, high-risk features in coronary artery anomalies, major cardiovascular events, congenital heart disease.

Palabras clave:

anomalías de las arterias coronarias, origen aórtico anómalo de las arterias coronarias, enfermedad arterial congénita, características de alto riesgo en anomalías de arterias coronarias, evento cardiovascular mayor, cardiopatía congénita.

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probability of MACE was higher in the high-risk group (log-rank $p = 0.04$). **Conclusions:** this study highlights the importance of identifying high-risk profiles in such patients, given their association with adverse outcomes.

*presentaban al menos una característica de alto riesgo. Se registraron MACE en 14 pacientes (28%) durante un tiempo mediano de seguimiento de 1,636 días [RIC 626-2,345]. La probabilidad acumulada de MACE fue mayor en el grupo de alto riesgo (log-rank $p = 0.04$). **Conclusiones:** este estudio destaca la importancia de identificar perfiles de alto riesgo en estos pacientes, dada su asociación con desenlaces adversos.*

Abbreviations:

AAOCA = Anomalous Aortic Origin of a
Coronary Artery

ACS = Acute Coronary Syndromes

CAAs = Coronary Artery Anomalies

CCTA = Coronary Computed

Tomography Angiography

ICA = Invasive Coronary Angiography

MACE = Major Cardiovascular Events

MRI = Magnetic Resonance Imaging

RCA = Right Coronary Artery

SCD = Sudden Cardiac Death

INTRODUCTION

First described by Galen and Vesalius,¹ Coronary Artery Anomalies (CAAs) may involve alterations in origin, structure, and course. Although most CAAs are incidental findings with a benign clinical course, a subset of patients might develop a series of clinical manifestations (e.g., myocardial ischemia, ventricular arrhythmias, acute coronary syndromes, ventricular dysfunction, or even Sudden Cardiac Death [SCD]).²⁻⁴ These adverse outcomes have been attributed to several mechanisms such as morphological and functional alterations that can predispose to ischemia, hypoxemia, and an increased arrhythmogenic substrate.

Among these anomalies, Anomalous Aortic Origin of a Coronary Artery (AAOCA) represents one of the most clinically important entities due to its potential association with major cardiovascular outcomes, particularly in younger patients and during physical exertion. However, their risk stratification might be difficult to assess, since many individuals remain asymptomatic during their lifetime, whereas others might truly experience a major cardiovascular event without a final diagnosis (e.g., SCD). As expected, the true impact

of CAAs in the general population remains unclear, ranging from 0.2 to 5.6%;¹ this variation depends on the diagnostic method employed and the diagnostic criteria used to report them. Most data are derived from registries, and, particularly in Latin America, available information is scarce, with a similar prevalence.^{5,6}

Therefore, this study aimed to obtain the clinical and anatomical profile of patients diagnosed with AAOCA and the association with Major Cardiovascular Events (MACE) in a specialized tertiary center in Latin America.

MATERIAL AND METHODS

A longitudinal, retrospective, and analytic study was conducted. Epidemiological data from a Mexican specialized cardiology center were scrutinized using the terms «coronary artery anomalies» and «coronary artery malformations», coded as Q24.5 in the 10th International Disease Classification (ICD-10). All patients evaluated from January 2000 to July 2022 with a confirmed diagnosis of AAOCA were included; the diagnosis was established by Invasive Coronary Angiography (ICA) or Coronary Computed Tomography Angiography (CCTA). Minor CAAs (e.g., myocardial bridge), coronary fistulae, and CAAs arising from the pulmonary arteries were excluded. Clinical data consisted of general information such as age, sex, and cardiovascular and non-cardiovascular comorbidities. Anatomical and functional data were obtained through a multimodal imaging approach (ICA, CCTA, stress echocardiography, nuclear perfusion imaging, stress Magnetic Resonance Imaging [MRI], or treadmill exercise testing), specifically from the official study report and, if necessary, after re-examination by an independent expert. Every imaging test

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was acquired according to a pre-specified protocol in accordance with the international recommendations available at the time of acquisition. Patients were stratified according to the presence or absence of high-risk features (slit-like ostium, an intramural or interarterial course, acute take-off angle [$< 45^\circ$], high take-off orifice, and proximal significant stenosis [$< 50\%$ normal lumen]) (Figure 1). The above-mentioned features were not mutually exclusive; therefore, their individual frequencies could exceed the total number of patients. Follow-up time was calculated from diagnosis to the last known contact with the patient. MACE was defined as Acute Coronary Syndromes (ACS), surgical revascularization, or cardiovascular death, whichever occurred first. ACS could represent the initial presentation in some patients; therefore, only the occurrence of a new ACS during follow-up was considered a MACE event. These variables were selected

to construct the primary outcome because their occurrence was considered reliable and definitive. Although other hard endpoints were also explored, their occurrence could have been underestimated for multiple reasons; therefore, a robust and reliable composite outcome was constructed using these variables.

Numerical data were presented as mean and standard deviation or median and interquartile range, depending on their distribution. Categorical variables were presented as absolute and relative frequencies. Initial comparisons were performed using an unpaired Student's t test or a Mann-Whitney U test, as appropriate, whereas categorical variables were compared using the χ^2 test or Fisher's exact test. Kaplan-Meier curves were constructed for survival analysis to depict cumulative MACE-free survival according to the presence or absence of high-risk features, and these were compared using the log-rank

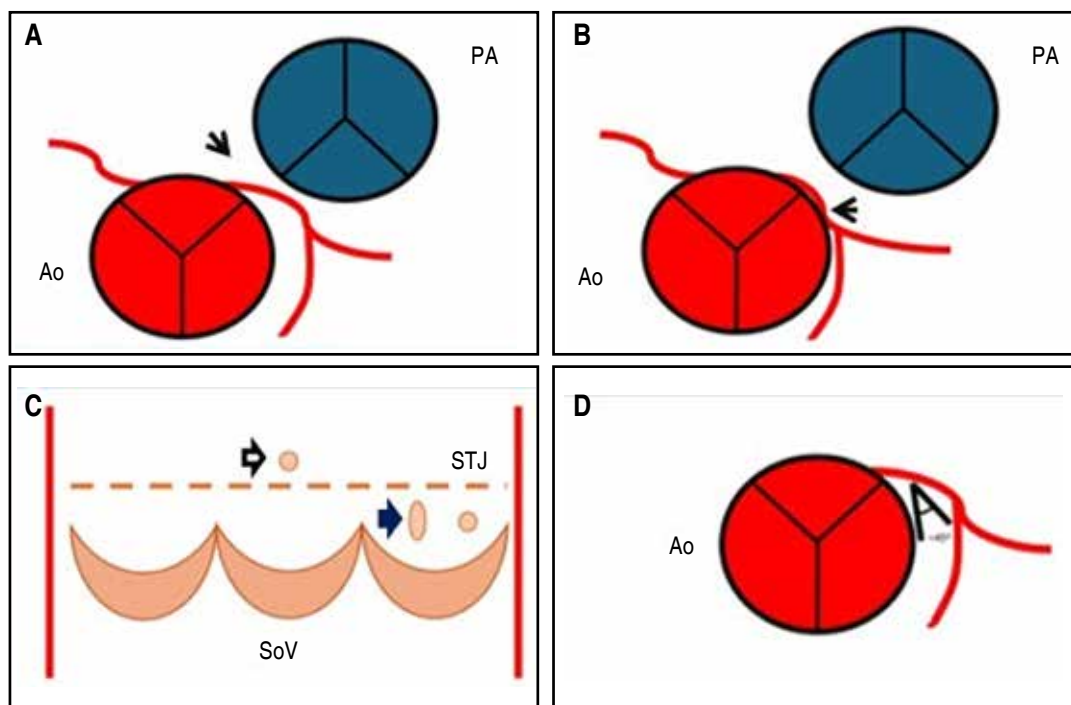


Figure 1: Depiction of high-risk characteristics. Schematic representation of the different anatomical characteristics related to worse outcomes. Anomalous course is seen between the aorta and the pulmonary artery (black arrows), **A)** interarterial and **B)** intramural. **C)** Slit-like ostium (blue solid arrow) and high take-off orifice origin (white filled arrow). **D)** Acute take-off angle ($< 45^\circ$). Finally, proximal lumen narrowing ($< 50\%$), not represented.

Ao = Aorta. PA = Pulmonary Artery. SoV = Sinus of Valsalva. STJ = Sinotubular Junction.

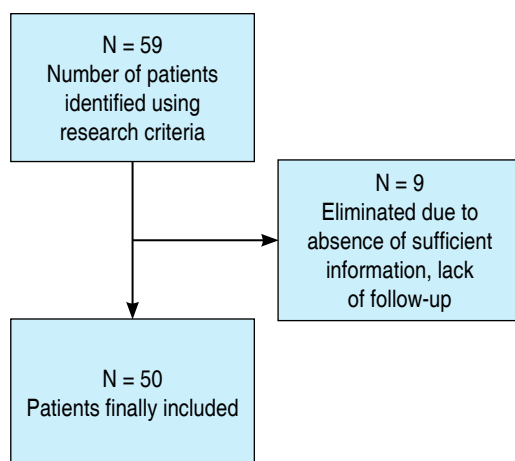


Figure 2: Patient selection flowchart.

test. Additionally, Kaplan-Meier curves were generated based on the number of high-risk characteristics present. For all statistical tests, a p -value < 0.05 was considered statistically significant. The study was conducted in accordance with the ethical standards of the local institutional research committee and the 1964 Declaration of Helsinki and its later amendments. The final protocol was reviewed by the institution's Directorate of Medical Education, and, given its retrospective, non-interventional nature, approval from the local Ethics Committee was obtained. No identifiable personal data were collected or used; therefore, patient confidentiality was strictly maintained. Statistical analyses were performed using RStudio 2024.09.0 + 375 for Windows 11. The study was conducted in accordance with the STROBE guidelines.

RESULTS

Fifty-nine patients were identified with AAOCA after initial exploration. Further review resulted in the exclusion of nine patients, leaving a total of 50 individuals, as shown in [Figure 2](#). Baseline characteristics are summarized in [Table 1](#). Among the 50 included patients, coronary anatomy was evaluated by invasive coronary angiography alone in 29 patients (58%), by coronary CT angiography alone in one patient (2%), and by both imaging modalities in 20 patients (40%).

The mean age was 52 ± 15 years, and the vast majority were male ($n = 34$, 68%). Among the comorbidities, the most frequent was systemic hypertension ($n = 19$, 38%). A small proportion of patients had congenital heart disease.

Nearly half of the patients ($n = 21$, 42%) presented with ACS at diagnosis. Non-ST-segment elevation myocardial infarction was the most frequent subtype, followed by ST-segment elevation myocardial infarction and unstable angina. However, the etiology of these events was not specified. Most hospitalizations and emergency department visits were related to ischemic syndromes or arrhythmic manifestations.

Most anomalies involved coronary artery origin, and the Right Coronary Artery (RCA) was the most frequently affected vessel ($n = 30$, 60%). Only 10% ($n = 5$) of patients had two or more coronary arteries affected. More than half of the anomalous RCAs originated from the opposite coronary sinus. Coronary artery stenosis was described in 30 patients (60%); however, only eight had significant stenosis ($> 50\%$ luminal narrowing). In addition to coronary artery stenosis, several anatomical characteristics associated with a worse prognosis were identified, as shown in [Figure 1](#). Overall, 22 patients (44%) exhibited at least one high-risk anatomical feature.

Patients with positive ischemia testing had a significantly higher incidence of MACE than those without ischemia; however, the anatomical correlation with the anomalous vessel could not be consistently established. Ventricular arrhythmias and syncope were documented in a subset of patients, most of whom were symptomatic at presentation, predominantly with angina or functional limitation.

[Table 1](#) also summarizes the comparison according to MACE status. No significant differences were observed for most baseline characteristics, except for the presence of high-risk anatomical features ($p < 0.01$). The median follow-up was 1,636 days [IQR, 626-2,345]. The primary outcome occurred in 21 patients (42%). Among the components of MACE, six patients (12%) experienced a new ACS during follow-up, five (10%) underwent surgical

Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
Characteristic				
Age (years), mean $\pm$ SD	52 $\pm$ 15	53 $\pm$ 16	50 $\pm$ 14	0.30
Female	16 (32.0)	11 (37.9)	5 (23.8)	0.81
Systolic arterial hypertension	19 (38.0)	13 (44.8)	6 (28.6)	0.28
Diabetes mellitus	6 (12.0)	4 (13.8)	2 (9.5)	0.99
Dyslipidemia	16 (32.0)	10 (34.5)	6 (28.6)	0.76
Atrial fibrillation	5 (10.0)	3 (10.3)	2 (9.5)	0.99
Ventricular tachycardia	4 (8.0)	2 (6.9)	2 (9.5)	0.99
Congenital cardiopathy				0.06
None	45 (90.0)	26 (89.7)	19 (90.5)	
Post-tricuspid valve defect	1 (2.0)	0 (0.0)	1 (4.8)	
Other types	4 (8.0)	3 (10.3)	1 (4.8)	
Concomitant cardiopathy				0.05
None	41 (82.0)	24 (80.0)	18 (85.7)	
Left-sided valve disease	7 (14.0)	5 (20.0)	1 (4.8)	
Others	2 (4.0)	0 (0.0)	2 (9.5)	
Symptoms				0.23
Asymptomatic	5 (10.0)	4 (13.8)	1 (4.8)	
Angina	33 (66.0)	19 (65.5)	14 (66.7)	
Dyspnea	7 (14.0)	5 (17.2)	2 (9.5)	
Syncope	2 (4.0)	1 (3.4)	1 (4.8)	
Palpitations	3 (6.0)	0 (0.0)	3 (14.3)	
Initial clinical presentation				0.69
Acute coronary syndrome	21 (42.0)	13 (44.8)	8 (47.6)	
Unstable angina	4 (8.0)	3 (10.3)	1 (4.8)	
Non-ST elevation AMI	10 (20.0)	4 (13.8)	6 (28.6)	
ST elevation AMI	7 (14.0)	6 (20.7)	1 (4.8)	
Chronic angina	12 (24.0)	7 (24.1)	5 (23.8)	
Others	17 (34.0)	9 (31.0)	8 (38.0)	
ACS related to AAOCA	21 (42.0)	11 (37.9)	10 (50.0)	
Functional and anatomic findings				
LVEF 2D (%), mean $\pm$ SD	52 $\pm$ 14	52 $\pm$ 12	53 $\pm$ 16	0.81
Specific location of the anomaly				
LMCA	4 (8.0)	3 (10.3)	1 (4.8)	
LAD	1 (2.0)	1 (3.4)	0 (0.0)	
LCx	5 (10.0)	4 (13.8)	1 (4.8)	
RCA	30 (60.0)	15 (51.7)	15 (71.4)	
Single coronary artery (single ostium)	5 (10.0)	3 (10.3)	2 (9.5)	
Two or more affected coronary arteries	5 (10.0)	3 (10.3)	2 (9.5)	

Continue Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
RCA origin*				
Left coronary sinus	20 (54.1)	11 (61.1)	9 (47.4)	
High take-off orifice	11 (29.7)	4 (22.2)	7 (36.8)	
From a coronary artery	6 (16.2)	3 (16.7)	3 (15.8)	
LMCA origin*				
Right coronary sinus	1 (14.3)	1 (16.7)	0 (0.0)	
Non-coronary sinus	2 (28.6)	2 (33.3)	0 (0.0)	
High take-off orifice	3 (42.9)	2 (33.3)	1 (100.0)	
From a coronary artery	1 (14.3)	1 (16.7)	0 (0.0)	
LAD origin*				
Right coronary sinus	2 (50.0)	2 (66.7)	0 (0.0)	
Left coronary sinus	1 (25.0)	0 (0.0)	1 (100.0)	
Non-coronary sinus	1 (25.0)	1 (33.3)	0 (0.0)	
Single coronary artery (single ostium)				0.71
Left coronary sinus	3 (80.0)	2 (66.7)	2 (100.0)	
Right coronary sinus	1 (20.0)	1 (33.3)	0 (0.0)	
LCX origin*				0.23
Right coronary sinus	6 (66.7)	5 (83.3)	1 (33.3)	
Left coronary sinus	1 (11.1)	0 (0.0)	1 (33.3)	
From a coronary artery	2 (22.2)	1 (16.7)	1 (33.3)	
Other characteristics				
High take-off orifice	15 (30.0)	5 (33.3)	10 (66.7)	0.05
Acute angle take-off	10 (20.0)	2 (20.0)	8 (80.0)	0.06
Slit like/oval orifice	5 (10.0)	1 (20.0)	4 (80.0)	0.20
Patients with high-risk features	–	8 (27.6)	14 (66.7)	0.01
Coronary artery course				< 0.01
Intramural	3 (6.0)	0 (0.0)	3 (14.3)	
Retroaortic	22 (44.0)	18 (62.1)	4 (19.0)	
Interarterial	21 (42.0)	9 (31.0)	12 (57.1)	
Prepulmonic	4 (8.0)	2 (6.9)	2 (9.6)	
Stenosis of the AAOCA	30 (60.0)	12 (41.4)	18 (85.7)	0.01
Stenosis etiology				
Atherosclerotic	9 (30.0)	7 (58.3)	2 (11.1)	
Both congenital and atherosclerotic	21 (70.0)	5 (41.7)	16 (88.9)	
Degree of stenosis				0.71
> 90%	4 (13.3)	1 (8.3)	3 (16.7)	
70-89%	4 (13.3)	1 (8.3)	3 (16.7)	
50-69%	9 (30.0)	5 (41.7)	4 (22.2)	

Continue Table 1: Distribution of patients according to MACE (N = 50).

Parameter	Total N = 50 n (%)	MACE		p
		No N = 29 n (%)	Yes N = 21 n (%)	
Diagnostic and therapeutic approach				
Functional performed test				
Perfusion myocardial imaging	22 (64.7)	12 (66.7)	10 (62.5)	
Treadmill stress	2 (5.9)	2 (11.1)	0 (0.0)	
Dobutamine-stress MRI	8 (23.5)	3 (16.7)	5 (31.3)	
Stress echocardiography	2 (5.9)	1 (5.6)	1 (6.3)	
Positive for ischemia**	15 (44.7)	20 (69.0)	16 (76.2)	
Follow-up				
Days, median [IQR1-IQR3]	1,636 [626-2,345]	1,379 [451-1,957]	1,904 [1,284-2,647]	0.20
Comparisons were made with: Continuous variables were compared using the unpaired Student's <i>t</i> test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Paired post-hoc analysis showed differences between retroaortic and interarterial (non-adjusted p value 0.008, adjusted 0.12) and interarterial and prepulmonic (non-adjusted p value 0.04, adjusted value 0.63). * Anatomical characteristics were not mutually exclusive; therefore, patients could be included in more than one category, and percentages may not sum to 100%. ** The percentage of positive ischemia tests was calculated among patients who underwent functional testing. ACS = Acute Coronary Syndrome. AMI = Acute Myocardial Infarction. AAOCA = Anomalous Aortic Origin of the Coronary Artery. IQR = InterQuartile Range. LAD = Left Anterior Descending artery. LCx = Left Circumflex Artery. LMCA = Left-Main Coronary Artery. LVEF = Left Ventricle Ejection Fraction. MACE = Major Adverse Cardiovascular Events. MRI = Magnetic Resonance Imaging. PY12i = Inhibitor of Surface Platelet P2Y12 Receptor. RCA = Right Coronary Artery. SD = Standard Deviation.				

revascularization during follow-up, and three (6%) died from cardiovascular causes.

Kaplan-Meier analysis demonstrated a lower MACE-free survival probability among patients with high-risk anatomical features (log-rank $p = 0.04$), as shown in [Figure 3A](#). Likewise, patients with a greater number of high-risk anatomical features exhibited a higher cumulative incidence of MACE (log-rank $p = 0.049$), as shown in [Figure 3B](#).

DISCUSSION

This retrospective study in patients with AAOCA found that most coronary anomalies involved the coronary artery origin and course, predominantly affecting the RCA. Furthermore, a substantial proportion of patients exhibited at least one high-risk anatomical feature,

which was associated with a lower cumulative probability of MACE-free survival over time. Moreover, stratification by the number of high-risk anatomical features showed a progressively higher cumulative incidence of MACE with increasing risk-feature burden.

Our cohort included 50 patients, like previous studies.^{5,6} Although larger cohorts have been reported,⁷⁻⁹ these studies invariably required extended recruitment periods, often spanning several years or even decades, likely reflecting the low prevalence of this condition.¹⁰ This also explains the heterogeneity in age and other baseline characteristics observed across published series.^{7,11} Nearly all our patients were symptomatic, most commonly presenting with angina or other clinically relevant cardiovascular manifestations.

The high-risk anatomical profile has been widely associated with adverse cardiovascular

outcomes.¹²⁻¹⁴ Although an interarterial course is the most frequently reported high-risk anatomical variant in previous series,^{8,15,16} the retroaortic course was the most common anatomical variant in our cohort. Nevertheless, a substantial proportion of patients exhibited an interarterial course, consistent with previous reports.⁸ Similarly, we observed an association between high-risk anatomical features and the occurrence of MACE, in agreement with previous reports. Furthermore, patients with a greater number of high-risk anatomical features exhibited a lower MACE-free survival probability and a higher cumulative incidence of events, suggesting that the accumulation of these anatomical characteristics may identify individuals at progressively higher cardiovascular risk.

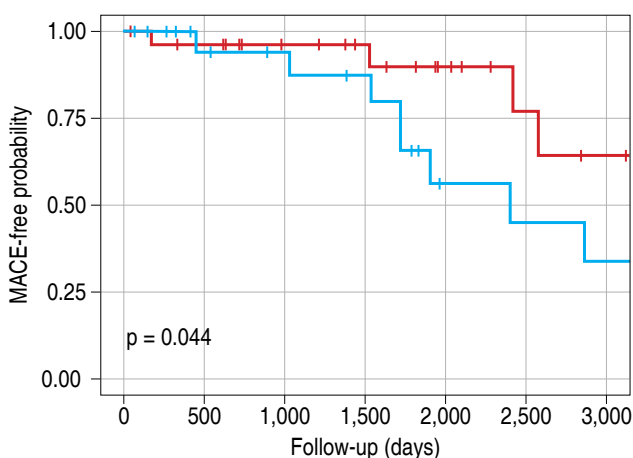
Current recommendations regarding the evaluation and management of patients with coronary artery anomalies are largely based on the identification of high-risk anatomical features. Our findings support the importance of systematically identifying these characteristics during the diagnostic evaluation of patients with AAOCA.

Functional assessment revealed that a significant proportion of patients had evidence of myocardial ischemia. Some of these patients subsequently underwent surgical revascularization and later experienced MACE during follow-up. However, because the available data did not allow us to determine whether these procedures were directly related to AAOCA or whether subsequent events were influenced by prior coronary interventions, no definitive association could be established.

Limitations

A key limitation of this study is its retrospective, single-center design, which may introduce selection bias and limit how broadly the findings can be applied. The relatively small sample size and low number of events, particularly acute coronary syndromes and arrhythmic events, limit the statistical power to establish robust associations between AAOCA and clinical outcomes. In addition, attributing outcomes

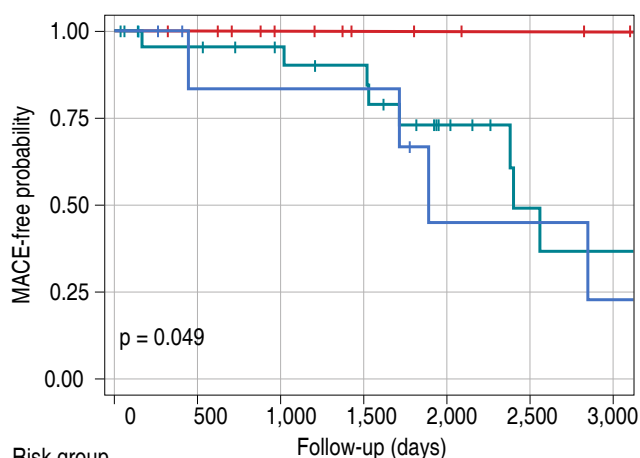
A) By high-risk anatomy



Strata
 + No high risk + High risk

Strata	Number at risk						
No high risk	28	25	19	15	10	6	4
High risk	22	16	14	12	5	4	3
	Follow-up (days)						

B) By grouped number of risk factors



Risk group
 + 0 factor + 1-2 factors + 3-5 factors

Risk group	Number at risk						
0 factors	17	15	10	6	5	4	3
1-2 factors	25	21	18	16	8	4	3
3-5 factors	8	5	5	5	2	2	1
	Follow-up (days)						

Figure 3: Cumulative MACE-free occurrence depicted in Kaplan-Meier curves. Proportion of patients free of MACE throughout observation time distributed according to high-risk factors profile (A) and when patients were stratified according to the number of high-risk factors (B).

such as ACS or cardiovascular death to AAOCA is inherently challenging, as these events may be influenced by comorbid conditions and may not be directly related to the congenital anomaly. Moreover, none of the MACE components could be definitively attributed to AAOCA. The heterogeneity in clinical presentation and management, including the limited number of patients undergoing surgical correction despite high-risk features such as inducible ischemia, further complicates the interpretation of the results and may introduce treatment bias. Additionally, detailed anatomical characterization and functional assessment (e.g., standardized ischemia testing) were not uniformly available for all patients, which may have affected risk stratification. Finally, given the observational nature of the study, causal inferences cannot be established, and the findings should be interpreted as hypothesis-generating, warranting confirmation in larger, prospective, multicenter cohorts.

CONCLUSIONS

In this cohort of patients with AAOCA, high-risk anatomical features were associated with the occurrence of MACE. Moreover, patients with a greater number of high-risk anatomical features exhibited a lower MACE-free survival probability and a higher cumulative incidence of adverse cardiovascular events.

This study also provides a description of the clinical and anatomical characteristics of patients with AAOCA in our setting. Given the rarity of this condition and the heterogeneity of its presentation, larger prospective studies are needed to better define the prognostic significance of high-risk anatomical features and to optimize risk stratification and management.

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Clopidogrel-associated small vessel vasculitis in acute coronary syndrome: a diagnostic and therapeutic challenge

Vasculitis de pequeño vaso asociado al uso de clopidogrel en síndrome coronario agudo: un reto diagnóstico y terapéutico

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Keywords:

clopidogrel, leukocytoclastic vasculitis, small vessel vasculitis, acute coronary syndrome.

Palabras clave:

clopidogrel, vasculitis leucocitoclástica, vasculitis de pequeño vaso, síndrome coronario agudo.

ABSTRACT

The treatment of acute coronary syndrome includes the use of acetylsalicylic acid and a P2Y12 inhibitor, with clopidogrel being the most commonly used agent in clinical practice. Fortunately, hypersensitivity reactions to clopidogrel are uncommon; however, when they occur, they are typically type I reactions mediated by IgE (e.g., urticaria, angioedema, and cutaneous rash). Type III hypersensitivity reactions, such as small vessel vasculitis, are exceedingly rare and pose a therapeutic challenge, particularly in the setting of acute coronary syndrome (ACS). This case report shows an uncommon presentation that should be considered in patients receiving antiplatelet therapy.

RESUMEN

El tratamiento de síndrome coronario agudo incluye el uso de ácido acetil salicílico y un inhibidor de P2Y12, siendo el clopidogrel el más utilizado en la práctica clínica. Afortunadamente, las reacciones adversas por hipersensibilidad con el clopidogrel son inusuales, sin embargo, cuando ocurren, por lo general son tipo I mediadas por IgE (urticaria, angioedema y erupción cutánea). Las reacciones de hipersensibilidad tipo III como la vasculitis de pequeño vaso son extremadamente raras y suponen un reto terapéutico, sobre todo en el contexto de un síndrome coronario agudo (SCA). Este trabajo evidencia la presentación de una reacción infrecuente que debería tenerse presente en pacientes con terapia antiagregante.

Abbreviations:

ACS = Acute Coronary Syndrome
ADP = Adenosine DiPhosphate
AF = Atrial Fibrillation
ANCA = AntiNeutrophil Cytoplasmic Antibodies
DOAC = Direct Oral AntiCoagulant
LCV = LeukoCytoclastic Vasculitis
NSAIDs = Non-Steroidal Anti-Inflammatory Drugs
P2Y12 = P2Y12 receptor
PCI = Percutaneous Coronary Intervention

INTRODUCTION

Acute coronary syndrome (ACS) management relies on dual antiplatelet

therapy, typically consisting of acetylsalicylic acid and a P2Y12 receptor inhibitor, with clopidogrel being one of the most widely used agents in clinical practice.^{1,2} Although clopidogrel has a well-established safety profile, hypersensitivity reactions have been described, most commonly type I reactions mediated by immunoglobulin E, including urticaria, angioedema, and cutaneous rash.²

In contrast, type III hypersensitivity reactions, such as leukocytoclastic vasculitis (LCV),³ are extremely rare and may pose a diagnostic and therapeutic challenge, especially in patients with recent ACS who require antithrombotic

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therapy.² Drug-induced small vessel vasculitis is characterized by immune complex deposition within vessel walls, leading to complement activation and neutrophilic inflammation, manifested typically as palpable purpura with a predilection for the lower extremities.^{3,4}

We describe a case of clopidogrel-associated small vessel vasculitis following an ACS. This case highlights the importance of early recognition and the challenges involved in optimizing antithrombotic therapy in this context.

CASE PRESENTATION

An 87-year-old woman with preserved functional independence (Barthel Index: 100 points), a history of hypothyroidism, and atrial fibrillation (AF) receiving chronic oral anticoagulation with rivaroxaban 20 mg once daily was admitted with acute coronary syndrome consistent with unstable angina. She underwent percutaneous coronary intervention (PCI), during which a significant lesion in the circumflex artery was identified and treated with angioplasty and implantation of a drug-eluting stent. The patient had a favorable clinical course and was discharged on combined antithrombotic therapy with rivaroxaban and clopidogrel because of her concomitant AF.

One month later, she was readmitted because of generalized palpable purpuric lesions, non-

blanching with pressure, predominantly involving the lower extremities, lower abdomen, and periumbilical region (*Figure 1*).

An extensive diagnostic workup was performed to assess for systemic involvement. There was no evidence of renal, gastrointestinal, or neurological involvement based on laboratory tests, clinical assessment, and imaging studies. The morphology and distribution of the lesions raised the initial suspicion of cutaneous small-vessel vasculitis. The differential diagnosis included systemic and immune-mediated conditions such as ANCA-associated vasculitis, hepatitis virus-associated cryoglobulinemia, systemic lupus erythematosus, and rheumatoid arthritis. These conditions were considered unlikely after the corresponding laboratory investigations were negative.

The temporal relationship between clopidogrel initiation and the onset of the skin lesions was then considered. Clopidogrel was the only medication introduced shortly before the onset of the skin lesions. After multidisciplinary assessment by Dermatology, Cardiology and Toxicology, the clinical presentation was considered most consistent with drug-induced cutaneous small-vessel vasculitis, likely representing leukocytoclastic vasculitis. Although skin biopsy would have provided histopathological confirmation, it was deferred because the clinical diagnosis was considered sufficiently clear and the



Figure 1: Initial palpable purpuric lesions, non-blanching on pressure, localized predominantly in the lower extremities, the lower half of the abdomen, and the periumbilical area. Source: authors' own work. Images published with patient consent.



Figure 2:

Evolution of purpuric lesions until resolution (20 days after onset).
Source: authors' own work. Images published with patient consent.

biopsy result was not expected to change the therapeutic approach.

Treatment with prednisolone was started at 0.5 mg/kg for two weeks, followed by a gradual reduction of 5 mg per week until discontinuation. Clopidogrel was withdrawn, as discontinuation of the suspected offending drug represents the main therapeutic measure in drug-induced vasculitis.

The main challenge, however, was how to modify the antithrombotic treatment after discontinuation of clopidogrel. The patient was only one month after PCI with implantation of a drug-eluting stent for an acute coronary syndrome, and antiplatelet therapy remained important to reduce the risk of stent thrombosis. An alternative P2Y12 inhibitor was not considered because of the potential for cross-reactivity among structurally related agents. Therefore, after multidisciplinary discussion, the antithrombotic regimen

was changed to rivaroxaban 15 mg once daily plus acetylsalicylic acid 100 mg once daily, adapting an antithrombotic strategy evaluated in the PIONEER AF-PCI trial. This decision required balancing the need to discontinue the suspected offending drug against the risk of ischemic complications following recent PCI.

The patient was closely followed, with complete resolution of the cutaneous lesions and no apparent ischemic or thrombotic complications during the one-month follow-up (Figure 2).

Figure 3 presents the timeline of the patient's clinical course and the main diagnostic and therapeutic decisions.

DISCUSSION

Clopidogrel is an antiplatelet agent that works through irreversible inhibition of the adenosine diphosphate (ADP) P2Y12 receptor,

thereby reducing platelet aggregation and preventing thrombotic events.^{1,2} It is generally well tolerated, and adverse events are rarely reported; among these, small vessel vasculitis is exceedingly uncommon.² This condition is defined as inflammation of small blood vessels and the skin, clinically characterized by palpable purpura predominantly affecting the lower extremities with a symmetric distribution.³ In the medical literature, only a limited number of cases have been reported, with a highly variable clinical course ranging from 24 hours to up to six weeks after treatment initiation.^{3,4}

Hypersensitivity reactions are immune-mediated responses triggered by exposure to an antigen. Hypersensitivity reactions associated with clopidogrel include urticaria, angioedema, and cutaneous rash.⁴ The pathophysiology of clopidogrel-induced small vessel vasculitis is most commonly associated with a type III hypersensitivity reaction, characterized by immune complex deposition within the walls of blood vessels.⁵ These deposits activate the complement cascade and lead to neutrophil infiltration, resulting in what is known as leukocytoclastic vasculitis

(LCV) with fibrinoid necrosis.^{1,3} Although skin biopsy remains the gold standard for confirming this condition, in cases with a clear temporal relationship to drug exposure, absence of systemic involvement, and clinical improvement following drug withdrawal, the possibility of an alternative etiology is low, making an alternative diagnosis unlikely.⁵⁻⁷

Most cases of small vessel vasculitis are idiopathic or primary (approximately 44% to 55% of cases).^{5,6} Drug-induced vasculitis represents 10% to 24% of cases, with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) being the most commonly implicated agents.^{5,6} Other causes include infections (20%), autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis (15-20%), and, in less than 1% of cases, paraneoplastic processes.^{6,7}

Standard management reported in the literature primarily consists of immediate discontinuation of clopidogrel.² The general treatment of leukocytoclastic vasculitis follows a stepwise approach: conservative measures such as rest, lower limb elevation, and compression stockings are sufficient in mild cases.⁸ In

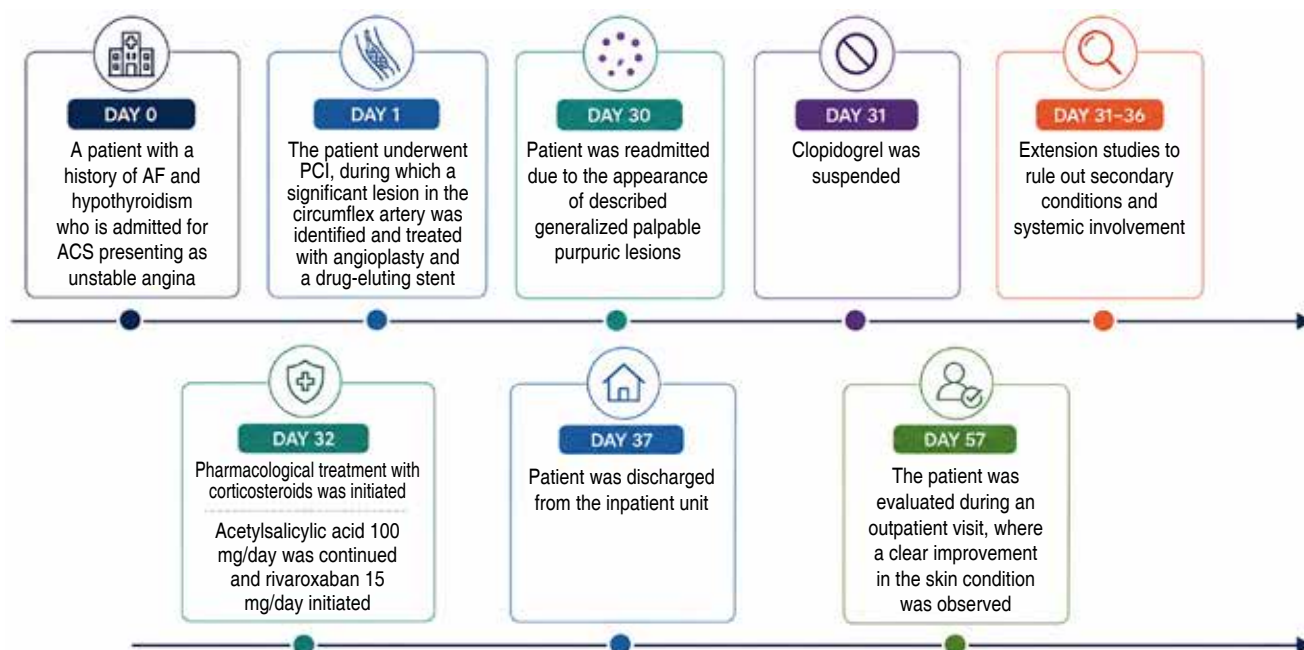


Figure 3: Timeline of the patient's clinical course from admission to resolution of symptoms.

ACS = acute coronary syndrome. AF = atrial fibrillation.

patients with significant or recurrent cutaneous involvement, the use of antihistamines, colchicine, dapsone, and topical or systemic corticosteroids has been described.^{1,3,9}

Cutaneous disease usually resolves within one to two weeks after the discontinuation of the causative drug, in this case, clopidogrel.^{1,2} However, complete remission is achieved only in approximately half of patients within 6-12 months. The remainder may develop a chronic or recurrent course, particularly in the presence of associated arthralgias or cryoglobulinemia.^{8,9} In our patient, skin lesions resolved after clopidogrel withdrawal and corticosteroid therapy, with no recurrence during follow-up.

The occurrence of leukocytoclastic vasculitis in the setting of recent acute coronary syndrome represents a significant therapeutic challenge, as it limits antiplatelet options required to prevent stent thrombosis.¹ Described alternatives include clopidogrel desensitization or switching to another P2Y12 inhibitor such as ticlopidine or ticagrelor; however, the risk of cross-reactivity is well documented and increases the risk of severe adverse events.^{1,5} In our case, the pharmacological management was adjusted to account for the patient's comorbidities. Given her indication for chronic anticoagulation due to AF, antithrombotic therapy could be simplified. After completing one month of dual therapy following drug-eluting stent implantation, clopidogrel was discontinued, and treatment was continued with a combination of a direct oral anticoagulant (DOAC) and acetylsalicylic acid.

This approach is in line with the 2026 ACC Scientific Statement, which recommends limiting the duration of combined antithrombotic therapy in patients with atrial fibrillation undergoing PCI to reduce bleeding risk. In patients requiring long-term oral anticoagulation, a DOAC combined with a single antiplatelet agent is generally preferred after an initial period of triple therapy, with prolonged triple therapy avoided.¹⁰

In our patient, clopidogrel was discontinued after one month because of suspected drug-induced leukocytoclastic vasculitis, and therapy was continued with rivaroxaban and aspirin to provide ongoing antithrombotic protection while avoiding re-exposure to the suspected

culprit drug. The rivaroxaban dose was based on the regimen evaluated in the PIONEER AF-PCI trial in patients with atrial fibrillation undergoing PCI.¹¹ This treatment was chosen considering the need to prevent thrombotic complications while also minimizing the risk of recurrent vasculitis.

CONCLUSIONS

Clopidogrel-associated leukocytoclastic vasculitis should be suspected in any patient presenting with a purpuric rash following acute coronary syndrome treatment onset. Although this is a rare entity, early recognition is crucial to prevent systemic involvement and adjust the pharmacological management. In most cases, patients have a favorable clinical course after discontinuation of the offending agent and conservative management; however, some may require systemic therapy. Overall, these clinical presentations pose a therapeutic challenge and require adjustment of baseline antithrombotic therapy.

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Should the battery of the implantable cardioverter defibrillator be changed or not, due to depletion and the fact that it has never been discharged?

¿Se debe cambiar o no la batería del desfibrilador cardioversor implantable, debido a que se está agotando y a que nunca se ha descargado?

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ABSTRACT

The use of Implantable Cardioverter Defibrillators (ICDs) has proven to be effective and useful to improve survival rates after Sudden Cardiac Death (SCD) in patients with clinical indications for their use. However, replacing a generator that has never administered electrical therapies and now shows battery depletion can generate controversy. In this paper, we analyze different factors that must be considered prior to the generator's replacement in this subset of patients. The main points are improvement or not of the Left Ventricular Ejection Fraction (LVEF), risk re-stratification at the time of replacement, the presence or absence of inappropriate ICD therapies, the severity of the heart disease, the prognosis at the time of the substitution, present comorbidities, life expectancy and advancing age, the possible complications of the new procedure, the possibility of de-escalating the device, financial factors, as well as the patient's own decision and the underlying clinical discussion.

RESUMEN

El uso de desfibriladores cardioversores implantables (DCI) ha demostrado ser eficaz y útil para mejorar las tasas de supervivencia tras una muerte súbita cardíaca (MSC) en pacientes con indicaciones clínicas para su uso. Sin embargo, el reemplazo de un generador que nunca ha administrado terapias eléctricas y que ahora presenta agotamiento de la batería puede generar controversia. En este artículo, analizamos diferentes factores que deben tenerse en cuenta antes del reemplazo del generador en este subgrupo de pacientes. Los puntos principales son la mejora o no de la fracción de eyección del ventrículo izquierdo (FEVI), la reestratificación del riesgo al momento del reemplazo, la presencia o ausencia de terapias inapropiadas del DCI, la gravedad de la enfermedad cardíaca, el pronóstico al momento de la sustitución, las comorbilidades actuales, la esperanza de vida y la edad avanzada, las posibles complicaciones del nuevo procedimiento, la posibilidad de reducir la intensidad del dispositivo, los factores económicos, así como la decisión del propio paciente y la discusión clínica subyacente.

Abbreviations:

CRT = Cardiac Resynchronization Therapy
ERI = Elective Replacement Indicator
HFrEF = Heart Failure and Reduced Ejection Fraction
ICD = Implantable Cardioverter Defibrillators
LVEF = Left Ventricular Ejection Fraction
SCD = Sudden Cardiac Death

INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) have been shown to significantly reduce mortality in patients with ischemic and nonischemic cardiomyopathy who are at high

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risk for ventricular arrhythmias and Sudden Cardiac Death (SCD).^{1,2} The main advantage of these devices has been demonstrated in subjects with reduced Left Ventricular Ejection Fraction (LVEF), although other cardiomyopathies and channelopathies also benefit from ICD-delivered therapies.^{2,3} These devices' battery lifespans can vary depending on several factors, but they will eventually be depleted and require replacement.⁴ Some studies have proposed different criteria to determine when not to do so; however, there are often controversies in this matter. They can be related to the patient's life expectancy, the current state of heart disease at the time of replacement, the number of therapies delivered by the device, and even economic factors.^{5,6}

Replacing an ICD generator, as with any other medical procedure, involves a comprehensive clinical evaluation rather than proceeding in an automatic manner. In some subjects it will be a simple decision, but in others, the medical team and the patient will have to consider all the aspects mentioned plus other clinical problems such as the complication rate and an ethical discussion.

SCD accounts for approximately 50 to 70% of all cardiovascular deaths. In up to 50% of cardiovascular patients, SCD is the first manifestation of heart disease.⁷⁻⁹ ICDs have demonstrated a positive effect on survival in several patient groups. Their placement is a common intervention in subjects who have survived cardiac arrest or have presented with significant ventricular arrhythmias in different pathological settings.² Emergency cardiac care has become more efficient and, although there are significant differences in survival rates between different countries, regions, and populations, there is a tendency toward lower mortality from the acute cardiac arrest event.^{10,11} As a result, the number of ICD implants has increased, as well as generator replacement procedures. The Spanish Society of Cardiology reported in 2023 an ICD implantation rate of 162:1'000,000 inhabitants.¹² They also found a steady increase in the rate of ICD implants, although the COVID-19 pandemic slowed that trend from 2020 to 2022. It is worth mentioning that Spain shows lower implant rates compared to other European countries. Most

ICDs are implanted due to an indication for secondary prevention,¹² but new information has expanded the indications for primary prevention. In both scenarios, patients may not experience ICD therapy, especially high-energy therapies, for extended periods, although the risk of ventricular arrhythmias persists.

The high cost of implantable electronic devices, especially ICDs, is an issue that must be considered, even if several studies have proven their profitability.^{13,14} In Mexico, their use might represent an important bill that can have different implications. From a physician's perspective, to establish the implantation indication, the complications inherent to the procedure and follow-up concerns are likely more significant, but all aspects of their use impact overall medical care costs. This is most evident considering that the number to be treated in primary prevention for SCD is relatively high, even if there is a 28% reduction in mortality with a hazard ratio (HR) 0.72.¹⁴⁻¹⁶ In the context of secondary prevention of SCD, ICD implantation is widely accepted in the absence of reversible causes.^{17,18}

When an ICD generator must be replaced, a careful clinical evaluation must involve the patient in overall decision-making. Aspects such as their life expectancy and expectations, their wishes about quality of life and current comorbidities, as well as how many times the ICD has provided therapies, the implications of repeated high-energy treatments (especially when ablations may or may not be performed or are successful or not), disease progression, costs of devices and procedures (in a private practice setting), should be discussed. Ideally, this should be addressed in a meeting with the patients, their family members, and the medical team to reach the best possible decision. This is particularly important when a patient has a limited life expectancy or an advanced, incurable disease. If prolonging life expectancy is no longer the main goal and the focus shifts to palliative care, the implications of the replacement are different. The same occurs when the patient's clinical situation changes significantly. In these cases, the objective is to prioritize quality of life and avoid unnecessary, distressing, high-energy shocks.¹⁹ An example is the eldest geriatric patients with diabetes and

advanced chronic kidney disease, a group where ICD implantation has shown virtually no benefit. Again, individualization is key.²⁰⁻²² Several trials (e.g. AVID trial) have demonstrated a significant reduction in mortality in patients with an ICD for secondary prevention, compared to medical therapy alone (28% reduction, HR 0.72; 95%CI 0.6-0.87; $p = 0.0006$).^{15,16,18} The same effect is not widely replicated in patients with non-ischemic systolic heart failure.^{23,24}

The lifespan of the ICD battery depends on the implantation parameters (impedance and stimulation thresholds for both pacing and shocks, among others) and the number of low- and high-energy therapies required by the patient. When the battery is depleted, an elective replacement should be envisaged, but there are few studies that address the ideal decision-making route in that context.²⁵

As in other countries and Latin America, a common practice in Mexico is to check any implantable device in a pacemaker clinic, where a team composed of a cardiologist (ideally an electrophysiologist), a nurse, and a technician checks the device and adjusts the parameters according to the patient's clinical condition. During those visits, or through remote monitoring at home, the Elective Replacement Indicator (ERI) will be detected, and the elective replacement should be planned.²⁶⁻²⁸ [Table 1](#) shows several factors to consider when replacing the generator.

RELEVANCE OF THE IMPROVEMENT OF LEFT VENTRICULAR EJECTION FRACTION (LVEF)

The LVEF is an important element in the decision process to implant an ICD.^{29,30} Patients with a LVEF of 35% or less benefit from an ICD, which reduces SCD by 27%.^{19,31} In recent years, optimized therapy for heart failure has shown significant improvement in ventricular function, but the risk of SCD appears to remain, as in some patients there are fluctuations in LVEF during follow-up.³² The DANISH trial (Defibrillator implantation in patients with non-ischemic systolic heart failure) highlighted that these reductions in mortality are less clear in contemporary patients with non-ischemic heart failure.^{24,33} Another study showed a worse prognosis in patients with Heart Failure

and Reduced Ejection Fraction (HFrEF) (LVEF 35%) who received an ICD generator and had a proportional risk of arrhythmic death of 43% compared to controls without ICD. A total of 32 patients with resynchronization therapy were excluded.

Apparently, an improvement in LVEF, because of optimized therapy, can reduce the burden of arrhythmias³⁴⁻³⁶ and, therefore, the need for electrical therapies. There is an apparent time-dependent behavioral change of arrhythmia burden under several conditions.³⁷ A relevant factor is optimized medical therapy. Ablation of ventricular tachycardia has also shown significant benefits.³⁸ Rordorf et al.,³⁹ found that the risk of adequate high-energy therapies after an ICD generator replacement is three times lower in patients with LVEF less than 35% compared to patients with LVEF above 35% and an indication for primary prevention. Several studies suggest that LVEF improvements resulting from optimal medical therapy with angiotensin receptor blockers, neprilysin inhibitors, SGLT2 inhibitors, beta-blockers, aldosterone antagonists, diuretics, etc. are associated with a reduction in arrhythmia burden and thus, a reduced need for ICD therapies. Thirty percent of patients no longer meet the initial implant criteria at the time of generator replacement. It has also been observed that the risk of inappropriate shocks is higher in older subjects or patients with normal or above 35% LVEF.⁴⁰⁻⁴²

These findings have prompted discussion about the possibility of de-escalating the device in patients with a Cardiac Resynchronization Therapy (CRT) pacemaker with defibrillator (CRT-D) to a CRT-alone device. Further studies are needed to better define which patients are suitable candidates for such a change, especially when the device was implanted for primary prevention.^{43,44}

The *Seattle Proportional Risk Model* (SPRM) estimates the risk of SCD in patients with heart failure based on variables such as sex, age, New York Heart Association (NYHA) functional class, digoxin use, diabetes, body mass index, serum creatinine, systolic blood pressure, sodium level, pro-brain natriuretic peptide (Pro-BNP) level, and LVEF.^{45,46} This risk model could be a useful tool for determining whether a patient is a good candidate for a generator or

Table 1: Factors to be considered before replacement of an Automatic Implantable Cardioverter-Defibrillator (AICD) generator battery.

Related with the cardiac condition
Type of cardiac disease
Primary or secondary prevention for the AICD implant
LVEF at the time of the replacement
LVEF when the AICD was inserted
Number, history and type of correct AICD therapies
Number, history and type of incorrect AICD therapies
Cardiac NMR findings (late enhancement)
Not related to a cardiac condition itself
Economic problems (high cost)
Patient decision
Advanced life
Low life expectancy
Multiple comorbidities, life style, not independent, etc.
Others

device replacement.^{47,48} Delayed myocardial enhancement with gadolinium (LGE) on cardiac magnetic resonance imaging (MRI) may play an important role in the decision to replace the battery, as large fibrotic areas act as ventricular arrhythmia substrates even with slight variations in LVEF.^{49,50} On the other hand, an upgrade from ICD to CRT-D should be considered in patients with symptomatic HFrEF, especially among subjects with high ventricular pacing rates. In this subset, the insertion of an additional electrode to stimulate the left ventricle is often performed at the time of a generator replacement. Upgrading to CRT-D in patients with symptomatic HFrEF improves cardiac remodeling.^{51,52} Thomas et al., found that 25% of patients have some degree of LVEF recovery at the time of generator replacement, but 75% of those who do not have high mortality rates in a three-year follow-up.⁵³ These results should be validated in subjects receiving left bundle branch stimulation.^{2,54}

RISK RE-STRATIFICATION AT THE TIME OF ICD REPLACEMENT AND INAPPROPRIATE ICD THERAPIES

International guidelines on ICD indications do not distinguish between early ICD implants and generator replacement, and there are few

clinical trials looking at events following this procedure. There seems to be a gray area in patients who need replacement of an implanted ICD for primary prevention but never received any form of electrical therapy (either low or high energy). Further doubt arises when there is an improvement in ventricular function and the patient no longer meets the original criteria for the implant. In a study of 231 patients with ICD implanted for primary prevention who required generator replacement due to battery depletion, nearly 26% were no longer compliant with the indication for ICD at the time of replacement due to improved LVEF. There was also a significant difference in the incidence of appropriate therapies after generator replacement among patients who still had an indication for ICD at the time of replacement compared to those who did not (2.8 vs 10.7% patients/year).⁵⁵ The MADIT-CRT trial showed that 7.3% had a normal LVEF, and after a two-year follow-up, only one patient had ventricular tachyarrhythmia. The authors concluded that there was a reduction in ventricular arrhythmias when ventricular function improved.⁵⁶ Several studies have shown that up to 65% of patients with an ICD implanted for primary prevention did not receive any therapy during a five-year follow-up.^{33,57} It has been found that 21 to 27% of patients without shocks after the first implant received at least one shock after the device change. On the other hand, when the patient has received shocks and the battery needs to be replaced, the chance of receiving appropriate therapies in the future is three times higher.^{41,58} These findings suggest that lack of therapies is not an appropriate criterion to decide whether to replace a generator or not. On the other hand, generator replacement is usually mandatory if the ICD has administered appropriate electrical therapies.

SEVERE DISEASE WITH POOR PROGNOSIS AND CARDIAC INSTABILITY

Patients with end-stage congestive heart failure (NYHA class IV), who are not candidates for a heart transplant or other advanced therapies, may not benefit from ICD replacement. Similarly, replacement is not recommended in patients with incessant ventricular tachycardia

or fibrillation, as ICD therapy would not be effective in controlling the condition.

COMORBIDITIES, LIFE EXPECTANCY AND ADVANCED AGE

Age is not a factor in determining whether a generator should be replaced. The possibility of death from non-cardiac causes in elderly subjects could reduce the usefulness of an ICD. It is crucial to understand patients' expectations, life expectancy, existing conditions, and the status of their heart disease. Frailty syndrome should also be considered and ideally evaluated by a gerontologist.⁵⁹

If the patient's life expectancy is less than one year, ICD generator's replacement may not be beneficial. High-energy therapy can cause pain and distress without significantly prolonging life.

SEVERE DISEASE WITH POOR PROGNOSIS

Patients with end-stage congestive heart failure (NYHA class IV), who are not candidates for heart transplantation or other advanced therapies, may not benefit from ICD replacement, as previously said. Reoperations on cardiac implantable devices are associated with an increase in complications, including infections, present in 1.4% of patients, while in first-time implants, that rate was 0.8%.^{60,61}

The replacement of the ICD generator is associated with a significant risk of complications; within six months after the procedure, the risk of major complications is 4%, and the risk of minor complications is 7.4%.⁶⁰ Main complications include displacement or damage of the electrode(s), infection of the device requiring removal of the entire ICD system, significant bleeding requiring evacuation of the ICD pouch, and prolonged hospitalization. Minor complications include nerve injury, minor bleeding, skin infection, and pain. The risk of device infection is particularly concerning, as it usually requires the removal of the entire ICD system.

This procedure is associated with substantial cardiac perforation risk with or without tamponade, vascular damage, and even death.^{62,63}

An ICD replacement is not recommended when the risks of surgery outweigh the potential benefits to the patient. This decision is based on a thorough assessment of the patient's health and treatment goals, especially in the context of end-of-life or other serious illnesses.

SERIOUS COMPLICATIONS

A replacement may not be advisable if the patient has experienced severe complications, such as an infection that requires removal of the entire ICD system.

These features, along with a clear explanation of the hazards of a device replacement (infections, for example), should be discussed to arrive at the best possible decision for the patient. Again, individualization is key.⁶⁴

THE PATIENT'S PERSPECTIVE

Most patients are unaware that replacement of the ICD generator is optional, and more than 25%, knowing it, would consider not doing it in our country. Many patients must cover the financial costs of the new generator by themselves because insurance often does not do it. In a significant proportion, this is a factor in the decision to avoid replacement. The perspective of SCD is appealing for some patients with deteriorated functional class and disease progression, so they prefer not to replace the generator. It is also important to clearly state that SCD is a real possibility whenever the patient decides not to replace the generator.

It is of vital importance that the physician guide the patient's decision-making process in collaboration with the cardiology/geriatrics team. The patient must understand that even in low-risk situations, there is a chance of ventricular arrhythmias.^{65,66} The team must ensure that the patient and their family understand that declining an ICD replacement may be contrary to proper medical judgment. This medical opinion, as well, must be based on an objective risk-benefit evaluation in the patient's best interest. If the patient decides to decline the replacement, she/he must also be reassured that the medical team will deliver the best available care to preserve quality of

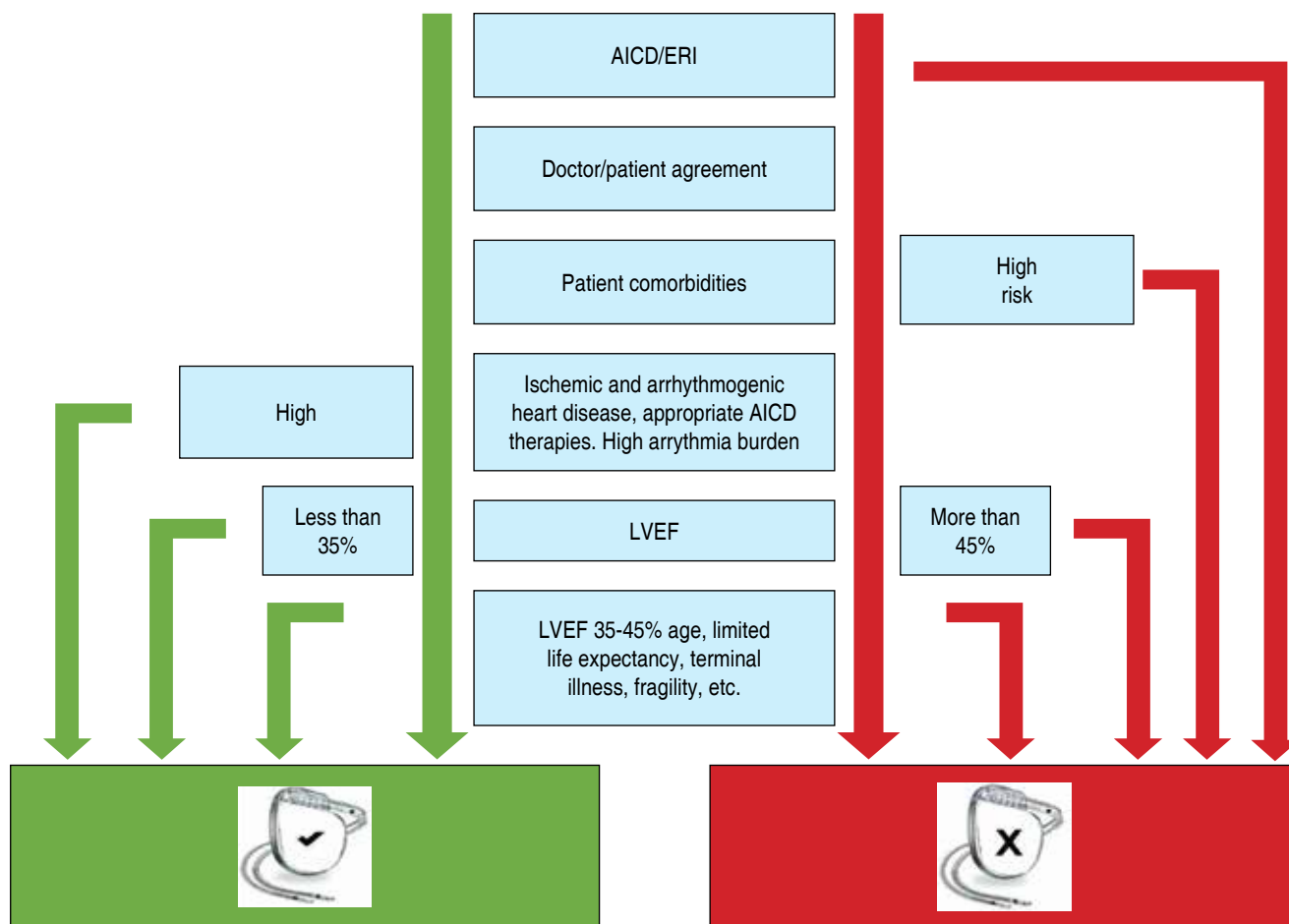


Figure 1: Decision-making diagram for generator replacement.

Modified from: Martínez M et al. Considerations involved in elective generator replacement of implantable cardioverter-defibrillators: balancing risks, benefits and individual factors. *Rev Esp Cardiol.* 2024; 77 (1): 2-5.

AICD = Automatic Implantable Cardioverter-Defibrillator. ERI = Elective Replacement Indicator. LVEF = Left Ventricular Ejection Fraction.

life when possible, and administer palliative care as needed.

DE-ESCALATION TO ANOTHER DEVICE

Many patients will not undergo an ICD replacement although they might require pacing and/or resynchronization therapy. This implies installation of a new ventricular pacing electrode(s) or the selection of a DF-4 compatible generator. In this case, a previous CRT-D device, only the left ventricular electrode could be connected to a conventional pacemaker. If biventricular pacing is to be maintained, the implantation of a new pacing electrode in the right ventricle should also

be considered, with an increased risk of complications.

CLINICAL DECISIONS AND IMPLICATIONS

We need comparative studies in our country to assess the benefit of generator replacements in patients with an ICD. *Figure 1* shows a decision-making diagram for generator replacement. The main problem lies in SCD prediction, something that is harder in certain subgroups such as the elderly.

Among patients with LVEF recovered after resynchronization and optimal medical therapy, without ventricular LGE on MRI, the risk of malignant arrhythmias is reduced. Therefore,

avoidance of ICD replacement could be considered in patients with ICDs placed as primary prevention and who show a recovered LVEF (greater than 45%) in the absence of adequate electrical therapies by the ICD.

Anyway, there is a residual risk, mainly among elderly patients with ischemic heart disease, that must not be neglected, even if the device has not administered any electrical therapy. This specific group of patients is one of the most hesitant in the decision of whether to replace the generator or not, and even more so when it is explained to the patient.⁶⁷

CONCLUSION

The decision to perform an elective generator replacement in a patient with an ICD in ERI is not a simple one. It requires a careful and individualized exhaustive analysis of the risk-benefit ratio in each case and a comprehensive discussion with the patient. Priority considerations are LVEF modifications, etiology of the underlying heart disease, indication for first-time placement, whether it is primary or secondary prevention, whether there have been appropriate therapies or not, life expectancy and quality of life and existing comorbidities. The patient must be involved in the final decision after an explanation about the risks, benefits, and possible complications.

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Mobile application to standardize and facilitate invasive hemodynamic calculations

Aplicación para estandarizar y facilitar cálculos hemodinámicos invasivos

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Keywords:

Swan-Ganz catheter, pulmonary artery monitoring, right heart catheterization, pulmonary catheter, hemodynamics, application.

Palabras clave:

catéter de Swan-Ganz, monitorización de la arteria pulmonar, cateterismo cardíaco derecho, catéter pulmonar, hemodinámica, aplicación.

ABSTRACT

Invasive hemodynamic assessment is crucial in critical cardiac conditions but is frequently subject to calculation and conversion errors due to the use of fragmented methods. In the Android environment, there are general-purpose medical calculators, including some specifically designed for right heart catheterization. Here we present GIPOGO RHC Tools (Android), a clinical tool for right heart catheterization that uses device-managed authentication at the start of the session. These data may be used to generate graphs and reports. Data stored temporarily in memory are used solely to maintain the workflow continuity. The handling of measurement units for variables is based on maintaining canonical units, with centralized conversion decoupled from the user interface, enabling flexible visualization without the risk of double conversion. Invasive hemodynamics is particularly sensitive to errors in calculation, unit conversion, and traceability; relying on multiple independent online calculators can compromise reproducibility and the preservation of clinical context. Standardizing hemodynamic recording at the session level and over time can promote comparability across measurements, support continuous improvement in the quality of care, and potentially generate research data.

RESUMEN

La evaluación hemodinámica invasiva es indispensable en situaciones cardíacas críticas, pero a menudo está sujeta a errores de cálculo y conversión debido al uso de métodos discontinuos. En el entorno Android, existen calculadoras médicas de propósito general diseñadas específicamente para el cateterismo cardíaco derecho. Aquí presentamos GIPOGO RHC Tools (Android), una herramienta clínica para el cateterismo cardíaco derecho que utiliza la autenticación gestionada por el dispositivo al inicio de la sesión. Estos datos pueden emplearse para generar gráficos e informes. El almacenamiento temporal de datos en memoria se limita a mantener la continuidad operativa del flujo de trabajo. El manejo de las unidades de medida de las variables se basa en el uso de unidades canónicas, con una conversión centralizada e independiente de la interfaz de usuario, lo que permite una visualización flexible sin riesgo de doble conversión. La hemodinámica invasiva es especialmente sensible a errores de cálculo, de conversión de unidades y de trazabilidad; depender de múltiples calculadoras en línea independientes puede comprometer la reproducibilidad y la preservación del contexto clínico. Estandarizar el registro hemodinámico a nivel de sesión y a lo largo del tiempo puede favorecer la comparabilidad entre mediciones, apoyar la mejora continua de la calidad asistencial y, potencialmente, generar datos para la investigación.

INTRODUCTION

Invasive hemodynamic assessment is crucial in contexts such as pulmonary hypertension and cardiogenic shock. In daily practice, these calculations are often performed in a fragmented manner, using online calculators without continuity between measurements or traceability, especially when comparing serial

measurements, leading to frequent ambiguities in units. This combination increases the risk of calculation and conversion errors with clinical impact.

In the Android environment, there are general-purpose medical calculators (e.g., MDCalc, Medscape, or Calculate by QxMD) which include multiple formulas. However, in our recent practical review of the app

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store, few offer a tool specifically designed for right heart catheterization that allows recording of a session and preserves the context (inputs, units, and results), rather than relying on isolated calculators. We have also identified applications that provide invasive hemodynamic calculations (e.g., cardiac output by the Fick method, vascular resistances, and pulmonary artery pulsatility index), as well as tools that integrate them with cardiogenic shock monitoring functions.¹⁻³

As an example of this approach, we present GIPOGO RHC Tools (Android), a clinical tool for right heart catheterization, designed to standardize invasive hemodynamic calculations and preserve their traceability. The application is accessible via Google Play (<https://play.google.com/store/apps/details?id=com.gio.gipogo.rhctools>) and organizes information by patient and study session, allowing a specific hemodynamic session to be recorded with preserved inputs, units, and results, as

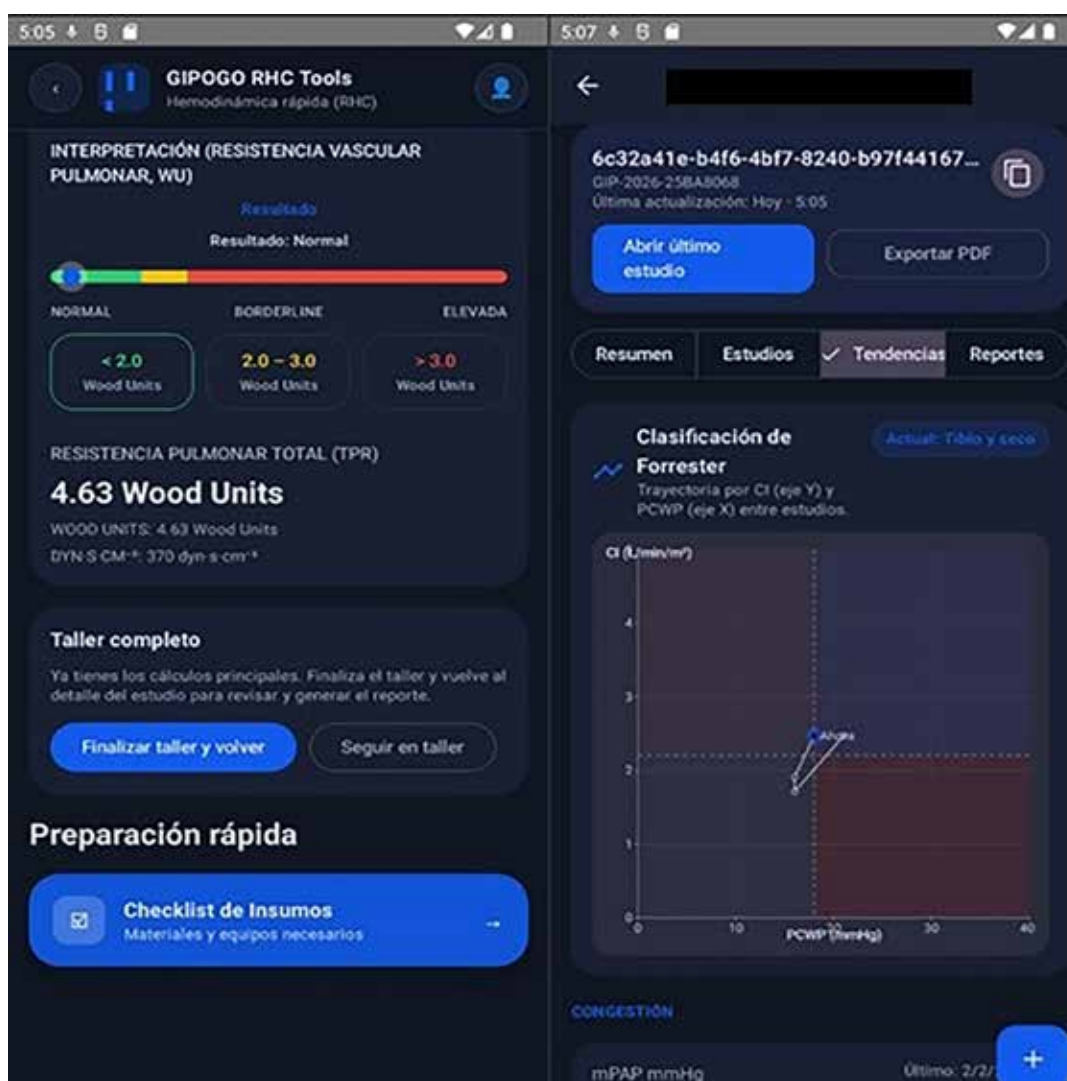


Figure 1: GIPOGO RHC Tools mobile application interface for invasive hemodynamic analysis. Left: module for automatic interpretation of pulmonary vascular resistance expressed in Wood Units, with range-based visual coding and conversion to $\text{dyn}\cdot\text{s}\cdot\text{cm}^5$. Right: longitudinal visualization of the patient with Forrester classification based on cardiac index and pulmonary capillary wedge pressure, allowing structured follow-up between studies.

an alternative to isolated calculators. The design incorporates data protection principles consistent with local clinical use. In accordance with the principles of data minimization and protection, the application uses device-managed authentication (preferably biometric) at the start of the session. Persistent data is stored in an encrypted local database on the user's device and does not require transmission to servers to function. These data are used to generate graphs and reports. Data temporarily stored in memory is used solely to maintain the workflow's operational continuity.

The handling of measurement units for variables is based on maintaining canonical units, with centralized conversion decoupled from the user interface, enabling flexible visualization without the risk of double conversion.⁴

The application groups flow variables (cardiac output and cardiac index), with options for the Fick or thermodilution methods and prior validation; resistance and power measurements; visualizations of the hemodynamic profile (e.g., Forrester classification); longitudinal trends when a series of studies is available; and input safeguards to prevent the storage of invalid or non-finite results as clinical data (*Figure 1*).

This tool operates locally on a mobile device and is intended for a single user. Therefore, it does not replace electronic health records or access controls at healthcare institutions. These limitations are explicitly stated in the application's legal notice/disclaimer, particularly on the «User responsibility» screen, which reminds clinicians to verify the accuracy of the data entered (including units) and to ensure its use complies with institutional policies and applicable regulations. These considerations are presented within the current scope and represent potential areas for expansion.

The discussion of this topic is justified for two main reasons. First, invasive hemodynamics

is particularly sensitive to errors in calculation, unit conversion, and traceability; relying on multiple independent online calculators can compromise reproducibility and preservation of clinical context. Second, standardizing hemodynamic recording at the session level and over time can promote comparability across measurements, support continuous improvement in the quality of care, and potentially generate research data.^{1,3,4} We invite discussion of minimum criteria for these tools (explicit and canonical units, input and output validation, traceability/auditability, and continuity of record).

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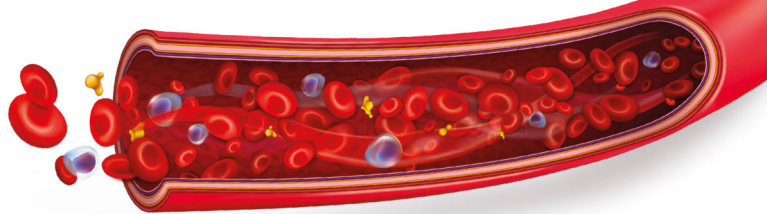


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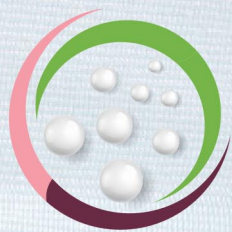
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