Argentine Journal of Cardiology
Revista Argentina de Cardiología

AUGUST 20265 - Vol 94 Nº 4

www.sac.org.ar

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ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 94 N° 4 AUGUST 2026
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: + 54 (11) 5031-5884 / e-mail: revista@sac.org.ar
web site: https://rac.sac.org.ar/
Editorial and graphic production
Graphic design - digital edition
CF Brand Design & Communication - e-mail: estanislao@cfdisenografico.com.ar / www.cfdisenografico.com.ar

VOL 94 N° 4
AUGUST 2026

Summary

EDITORIAL

Beyond the Guidelines: When Biological Reserve Outweighs Chronological Age

Más allá de las guías: cuando la reserva biológica desbanca a la edad cronológica

ALBERTO BARÓN CASTAÑEDA[1, 2, 3, 4]

Individual longevity and population aging have become increasingly evident during the second half of the 20th century and so far in the current century. This demographic transition is the result of a better understanding of cellular and systemic pathophysiology, improvements in the management of chronic diseases, the impact of health promotion and disease prevention programs, and more effective control of infections due to the availability of state-of-the-art vaccines and antimicrobials.

One of the direct consequences of this phenomenon is the progressive increase in the incidence and prevalence of degenerative cardiovascular diseases. Among these, heart failure, calcific aortic stenosis, coronary artery disease, hypertension, and clinically significant arrhythmias such as atrial fibrillation are particularly salient. (1,2)

This scenario presents new and complex challenges. Multimorbidity is common among older patients, with chronic kidney disease, chronic obstructive pulmonary disease, and anemia being particularly prevalent, as well as the onset of geriatric syndromes, including frailty, sarcopenia, and cognitive decline. These conditions worsen the prognosis and oblige us to rethink traditional therapeutic approaches. Factors such as polypharmacy and the pharmacokinetic changes associated with aging require much more rigorous and personalized prescribing practices.

People > 80 years remain significantly underrepresented in clinical trials that form the basis of clinical practice guidelines, despite this population constituting the predominant users of health care services and drug therapy. (3) This exclusion is even more pronounced at the extremes of age, beginning with patients > 75 years with type 2 diabetes and lung cancer, and becomes critical by the ninth decade (≥80 years) in conditions such as atrial fibrillation, heart failure, and osteoporosis. (4) There are various causes for this methodological gap, ranging from restrictive exclusion criteria based on chronological age or multimorbidity, to logistical barriers such as mobility issues, lack of social support, and patients' fear or distrust of the research setting.

In light of this persistent lack of evidence, the expert consensus led by Dr. Patricia Blanco et al. (5) addresses these gaps by applying a structured methodology. The panel highlights the importance of assessing the degree of frailty in older patients with cardiovascular disease as a fundamental guideline for management and recommends that therapeutic decision-making be guided primarily by the functional phenotype (robust, mild frailty, or moderate frailty).

The prevalence and incidence of atrial fibrillation increase exponentially with age, becoming an authentic epidemic in the 21st century. Active screening for atrial fibrillation should be encouraged, as its clinical presentation is often atypical or even asymptomatic. In this context, the presence of comorbidities and cognitive impairment is associated with greater disability and mortality. (6) Perhaps the greatest challenge is the need for antithrombotic therapy in a population with an inherently high risk of bleeding. The consensus reached in Argentina confirms a lower tendency toward rhythm control and lower acceptance of anticoagulation in frail patients. Furthermore, the panel expressed low confidence in the applicability of the traditional HAS-BLED score and CHA_2DS_2-VASc score in this group of patients.

Acute coronary syndromes are a major cause of hospitalization, with mortality rates particularly high among octogenarians. Despite the high baseline risk, there is a clear tendency to recommend an early invasive strategy in robust patients; however, this approach has not demonstrated a net benefit in frail patients

Rev Argent Cardiol 2026;94:249-250. https://doi.org/10.7775/rac.v94.i4.21023

SEE RELATED ARTICLE: Rev Argent Cardiol 2026;94:253-262. https://doi.org/10.7775/rac.v94.i4.21014

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with non-ST-segment elevation myocardial infarction (NSTE-ACS). Reperfusion therapy with fibrinolytics for the management of ST-segment elevation myocardial infarction (STE-ACS) carries significant risks of major bleeding complications in this population. (7) The panel cautiously acknowledges that the myocardial benefit of thrombolysis does not always outweigh the high risk of intracranial bleeding.

Based on the considerations made above, it is clear that managing older patients with cardiovascular disease is a complex process that cannot be reduced to the implementation of algorithms recommended by clinical practice guidelines. Older patients are underrepresented in the evidence and present a substantially different clinical reality. Before defining any therapeutic strategy, it is essential to assess frailty, cognitive function, nutritional conditions, muscle mass, and balance, among other factors. The ideal scenario requires a comprehensive geriatric assessment , in which cardiologists and geriatricians work together to establish the optimal strategy, centered on the patient's functional status and dignity.

Conflicts of interest
None declared
(See authors conflicts of interest forms on the website).

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EDITORIAL

The Face as a Window into Blood Flow: Facial Thermography, Artificial Intelligence, and the Quest for Noninvasive Hemodynamic Monitoring

El rostro como ventana a la circulación: termografía facial, inteligencia artificial y la búsqueda del monitoreo hemodinámico no invasivo

DIEGO DELGADO[1]

Measuring cardiac output remains central to managing critically ill patients. For decades, this role was filled by the pulmonary artery catheter (PAC), which served as both the gold standard and a source of arrhythmias, infections, and mechanical complications, with an impact on mortality that was never fully demonstrated. Hence, the long and still ongoing search for less invasive alternatives. At the same time, critical care cardiology turned its attention back to the periphery. Skin mottling and capillary refill time regained prominence as perfusion markers. The ANDROMEDA-SHOCK trial showed that these parameters can even guide resuscitation—with much of this work conducted by Latin American groups. (1–4) Once again, the skin serves as a mirror of circulation.

The study by Atamañuk et al. fits into this line of research, posing a question so simple that it surprises it had not been asked before: Can the use of an infrared camera and artificial intelligence (AI) on the face predict low cardiac output? This is supported by physiology. When cardiac output decreases, the sympathetic response diverts blood flow to vital organs and sacrifices the skin; thus, skin temperature falls early. The idea is not new. In 1969, Joly and Weil showed that the hallux temperature indicated shock severity for the first time. (5) What changes here is the chosen area: the face, which is always visible in hospitalized, well-perfused, and easy-to-photograph patients.

The study design has strengths worth acknowledging. The thermal images were taken simultaneously with PAC measurements—that is, against a reference standard and in real time—using a standardized protocol, regional facial readings by blinded evaluators, and machine learning processing. I am not aware of any previous report that combines these three elements at the same time: facial thermography, concurrent invasive monitoring, and AI. The figures are consistent with the hypothesis. Various regions and gradients correlated significantly with cardiac index, with the thermal gradient showing the best performance ($r = -0.45$), and a neural network achieved an area under the curve (AUC) of 0.75 for detecting low cardiac output. There is a signal.

That said, an editorial that only compliments is not very helpful. It is worth taking a moment to consider the limitations, many of which the authors acknowledge. The sample size is small: 35 monitoring sessions across 18 patients, nine of whom contributed repeated measurements. Unless properly accounted for using mixed-effects models, this non-independence of observations inflates statistical significance. Even more fundamental is the underlying pharmacological issue. Nearly all patients were receiving vasoactive drugs, and more than half were receiving two or more agents. Norepinephrine causes cutaneous vasoconstriction, whereas dobutamine leads to vasodilation; added to this are the effects of fever, sedation, mechanical ventilation, and room temperature. Ultimately, facial appearance reflects this interplay of variables—not cardiac output alone. Separating the hemodynamic signal from the noise will be the truly difficult part. (6)

In addition, discriminative ability is still modest. An AUC of 0.75 is encouraging, but a negative predictive value of 50% means that, at present, the method does not confidently rule out low cardiac output—which is precisely what one would expect from noninvasive monitoring. Training a neural network with just a few dozen cases invites overfitting: the result is

Rev Argent Cardiol 2026;94:251-252. https://doi.org/10.7775/rac.v94.i4.21040

SEE RELATED ARTICLE: Rev Argent Cardiol 2026;94:283-288.. https://doi.org/10.7775/rac.v94.i4.21036

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Table 1. Methodological considerations and what remains to be done

Dimension	Status in the current study	What Is Needed
Data size and structure	18 patients, 35 monitoring sessions; repeated measurements in 9 patients.	Larger multicenter cohorts; mixed-effects models that account for non-independence.
Physiological and pharmacological confounders	≥90% with vasoactive drugs; fever, sedation, ventilation, and uncontrolled room temperature.	Adjustment or stratification by vasoactive agents and temperature; controlled capture protocols.
AI model performance	AUC 0.75; NPV 50%; trained on a small number of observations (risk of overfitting).	Cross-validation and independent external validation; reporting according to TRIPOD+AI.
Acquisition technology	Consumer-grade camera, 160 × 120 px resolution.	Clinical-grade cameras and standardization of data acquisition.
Clinical implementation	Cross-sectional proof of concept, point-in-time diagnosis.	Prospective and dynamic designs; evaluating thermography as a trend monitor.

AI: artificial intelligence; AUC: area under the curve; NPV: negative predictive value.

only as good as its validation—first internal and then, above all, external. The TRIPOD+AI guidelines are a good reference for reporting these models transparently. (7) The low-resolution, consumer-grade camera is sufficient for a proof of concept but not for a clinical product.

None of this invalidates the proposal; rather, it highlights what is missing (Table 1). The study is part of an exciting trend—of digital biomarkers and contactless monitoring—where AI promises to extract useful information from noisy data, with applications ranging from telemedicine to remote heart failure monitoring. Thermography, when combined with AI, has already shown promise in distinguishing acute decompensated heart failure from other conditions. (8) And there is one detail that has been on my mind: in some patients, thermal improvement paralleled that of the cardiac index over time. If confirmed, thermography would evolve from a single snapshot into a continuous stream, serving as a dynamic trend monitor.

That said, we must not confuse promise with proof. Medical AI has produced brilliant models in a single center that later fail to withstand external validation. Before this approach can reach the bedside, the field will need the usual requirements—and the most expensive ones: larger more homogeneous multicenter cohorts, prospective studies that track thermal patterns during interventions, statistical analyses that account for the structure of the data, and standardized reporting. Thermography will not replace echocardiography or catheterization. Its place, if it has one, will be as a physiological, inexpensive, and noninvasive adjunct.

The authors dared to propose a high-risk hypothesis and tested it honestly, without hiding its limitations. They showed that a patient's face with shock holds clinical information waiting to be read. It remains to be seen whether that something can translate into a clinical decision—and that is a collective effort, the kind of work regional cardiology excels at when properly organized. For now, the patient's face offers only a hint of how their heart is beating. That is no small thing, and it deserves our continued attention.

Conflicts of interest
None declared
(See authors conflicts of interest forms on the website).

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ORIGINAL ARTICLE

Cardiovascular Evidence Gaps in Adults Over 80 Years of Age. Part 2. Roundtable Results: Atrial Fibrillation and Acute Coronary Syndromes*

Brechas en la evidencia cardiovascular en adultos mayores de 80 años. Parte 2. Resultados de la roundtable: fibrilación auricular y síndromes coronarios agudos

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ABSTRACT

Background: Clinical practice guidelines have limitations when applied to patients > 80 years with atrial fibrillation (AF) or acute coronary syndrome (ACS), due to their underrepresentation in clinical trials and the interplay between frailty, multimorbidity, polypharmacy, functional status, and cognitive decline—factors that influence the appropriateness of interventions.
Objectives: The aim of this paper is to discuss gaps in management and to describe consensus-based therapeutic strategies for patients > 80 years with AF or ACS using a structured consensus methodology.
Methods: An in-person roundtable was held with 34 cardiologists and 6 geriatricians. Clinical scenarios for AF and ACS were analyzed and stratified into three functional categories: robust, mild frailty, and moderate frailty, with structured discussion and anonymous voting.
Results: Therapeutic decisions varied consistently with frailty category. In AF, the acceptance rate of rhythm control in newly diagnosed cases decreased with frailty (66.5% in the robust group versus 15.4% in the moderate frail group), even in the presence of cognitive decline. Beta-blockers were the most widely accepted pharmacologic option, with low support for digoxin and chronic amiodarone. Confidence in the CHA_2DS_2-VASc and HAS-BLED scores was low and decreased with frailty. Direct oral anticoagulants were the preferred option, although they were less widely accepted in cases of moderate frailty; acetylsalicylic acid was not supported as an alternative. In non-ST-segment elevation acute coronary syndrome (NSTE-ACS), acceptance of an early invasive strategy and the use of ticagrelor decreased with frailty. In ST-segment elevation ACS (STE-ACS) without access to cardiac catheterization laboratory, fibrinolytic therapy was considered an alternative, with greater support for more extensive infarcts and lower acceptance in cases of moderate frailty.
Conclusions: Frailty consistently influenced the treatment decisions reached by consensus in patients > 80 years with AF or ACS, with less acceptance of intensive strategies with higher levels of frailty. These findings underscore the need to incorporate a comprehensive assessment into cardiovascular decision-making.

Key words: Frailty - Comprehensive assessment in cardiology - Evidence-based medicine - Atrial fibrillation - Acute coronary syndromes - Older adults

RESUMEN

Introducción: Las guías de práctica clínica muestran limitaciones cuando se aplican a pacientes mayores de 80 años con fibrilación auricular (FA) o síndrome coronario agudo (SCA), por su baja representación en ensayos clínicos y por la interacción entre fragilidad, multimorbilidad, polifarmacia, funcionalidad y deterioro cognitivo, factores que condicionan la proporcionalidad de las intervenciones.
Objetivos: Discutir brechas en el manejo y describir estrategias terapéuticas consensuadas para pacientes mayores de 80 años con FA o SCA mediante una metodología estructurada de consenso.
Material y métodos: Se realizó una roundtable presencial con 34 cardiólogos y 6 geriatras. Se analizaron escenarios clínicos de FA y SCA estratificados en tres categorías funcionales: robusto, fragilidad leve y fragilidad moderada, con discusión estructurada y votación anónima.

Rev Argent Cardiol 2026;94:251-262. https://doi.org/10.7775/rac.v94.i4.21014

SEE RELATED ARTICLE: Rev Argent Cardiol 2026:94:249-250. https://doi.org/10.7775/rac.v94.i4.21023

Received: 04/16/2026 – *Accepted:* 05/28/2026

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*This publication constitutes the second part of the results of the national roundtable. For the full context regarding methodology and results of rounds 1–4, see Part 1: Rev Argent Cardiol 2025;93(3):192–201. https://doi.org/10.7775/rac.es.v93.i3.20897

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Resultados: Las decisiones terapéuticas variaron de manera consistente según el grado de fragilidad. En FA, la aceptación del control del ritmo en escenarios de reciente diagnóstico disminuyó con la fragilidad (66,5 % en robustos frente a 15,4 % en fragilidad moderada), incluso en presencia de deterioro cognitivo. Los betabloqueantes fueron la opción farmacológica más respaldada, con bajo apoyo para digoxina y amiodarona crónica. La confianza en los scores CHA_2DS_2-VASc y HAS-BLED fue baja y decreciente con la fragilidad. Los anticoagulantes orales directos fueron la opción preferida, aunque con menor aceptación en fragilidad moderada; el ácido acetilsalicílico no fue respaldado como alternativa. En síndrome coronario agudo sin elevación del segmento ST (SCASEST), la aceptación de una estrategia invasiva precoz disminuyó con la fragilidad, al igual que el uso de ticagrelor. En síndrome coronario agudo con elevación del segmento ST (SCACEST) sin disponibilidad de hemodinamia, la fibrinólisis fue considerada una alternativa, con mayor respaldo en infartos más extensos, y menor aceptación en fragilidad moderada.
Conclusiones: La fragilidad condicionó de manera consistente las decisiones terapéuticas consensuadas en pacientes mayores de 80 años con FA o SCA, con menor aceptación de estrategias intensivas a medida que aumentó su grado. Estos hallazgos refuerzan la necesidad de incorporar la valoración integral en la toma de decisiones cardiovasculares.

Palabras clave: Fragilidad - Valoración integral en cardiología - Medicina basada en la evidencia - Fibrilación auricular - Síndromes coronarios agudos - Adultos mayores

INTRODUCTION

In people > 80 years, chronological age alone does not describe the biological reserve or predict tolerance to interventions. In practice, highly heterogeneous patient profiles coexist along a clinical-functional continuum ranging from robustness to frailty, disability, and advanced disease, which directly impacts prognosis and therapeutic appropriateness. (1-4)

In this context, atrial fibrillation (AF) and acute coronary syndromes (ACS) represent common and highly complex clinical scenarios. The extrapolation of guidelines to this age group is limited by the underrepresentation of frail patients in clinical trials and by the frequent coexistence of multimorbidity, polypharmacy, cognitive decline, falls, and dependency. These factors influence the balance between ischemic benefit, hemorrhagic safety, and functional preservation. (3-5)

Following the initial publication of this consensus method, the present study reports the results for the AF and ACS scenarios obtained through a structured roundtable methodology. (6)

OBJECTIVES

The aim of this study was to identify and reach consensus on therapeutic strategies for patients > 80 years with AF or ACS, stratified by robustness, mild frailty, and moderate frailty.

METHODS

The roundtable was held in person in June 2024 in Buenos Aires, Argentina, and was attended by 40 referring physicians, 34 cardiologists and 6 geriatricians, with recognized clinical and academic careers.

The methodological process was structured in three stages to address the knowledge gaps systematically (Figure 1).

-*Gap identification:* In this initial phase, the organizing team of the Board of Directors of the Council on Cardiogeriatrics conducted an exhaustive review of recent literature and clinical practice guidelines. This analysis identified areas with insufficient evidence in the management of cardiovascular diseases in older adults and drew a preliminary list of knowledge gaps.

-*Scenario design:* In this stage, the usefulness of various frailty tools and diagnostic and therapeutic strategies in patients > 80 years was discussed and analyzed. In scenarios with comorbidities, the condition was considered stable, without end-stage disease. This population was divided into robust, mild frailty, and moderate frailty categories, which differ in terms of prognosis and treatment. Based on the proposed clinical scenarios, the different rounds were designed. Selected literature was sent to the participating physicians and and voting forms were designed to record votes that would be used during the discussion.

-*Discussion and consensus session:* Finally, the meeting was conducted using a structured methodology that combined open discussion followed by anonymous voting.

Votes were recorded on an electronic form (Google Forms®) with three options (Yes / Uncertain / No) and analyzed with a spreadsheet, without using statistical software packages. All the results are presented in Appendix 1. In each case, the strength of recommendation was classified into five categories based on the resulting percentage distribution. (Table 1)

All these stages were designed to ensure a comprehensive and systematic approach for generating practical recommendations to optimize cardiovascular care in older adults.

In each case, the strength of the recommendation is presented on a scale ranging from recommended to not recommended (Figure 2).

RESULTS (Central illustration)

Discussion scenarios

Round 1: Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its prevalence increases markedly with age. In patients > 80 years, the decision between rate control, rhythm control, and anticoagulation strategy must take into account not only thromboembolic and bleeding risks but also functional status, cognition, comorbidities, therapeutic burden, and care goals. (5)

a. Rate control vs. rhythm control (Figure 3)

In patients without cardiovascular disease (CVD) with preserved ejection fraction and a normal or mildly dilated left atrium, rhythm control was accepted by 66.5% in robust patients, 33.3% in those with mild frailty (with 28.2% being uncertain), and 15.4% in those with moderate frailty (with 20.5% being uncertain).

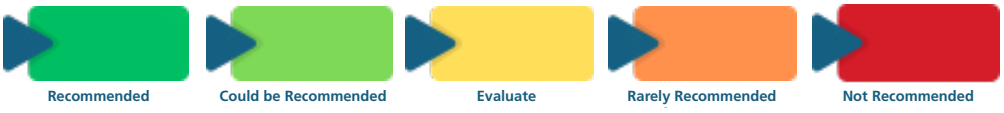
In the same scenario, but with cognitive decline, acceptance of rhythm control showed a stepwise pattern: 64% for robust patients (with 30.8% being un-

Table 2. Categories of strength of recommendation based on the distribution of the panel votes

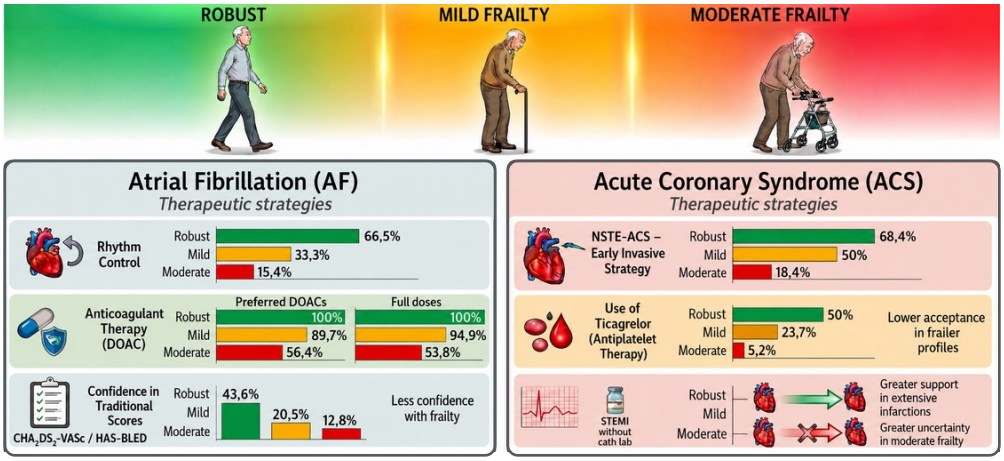
Category	Classification rule
Recommended	≥75% "Yes" votes
Could be recommended	50–74% "Yes" votes and <25% "No" votes
Evaluate	No option exceeds 50%, or "Uncertain" response predominates
Barely recommended	50–74% "No" votes and <25% "Yes" votes
Not recommended	≥75% "No" votes

Fig. 1. Roundtable methodology

Fig. 2. Level of recommendation



Central illustration. In subjects ≥ 80 years, frailty modulates the acceptance of therapeutic strategies for atrial fibrillation and acute coronary syndromes



DOACs: direct oral anticoagulants; F: frailty; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STE-ACS: ST-segment elevation acute coronary syndrome;

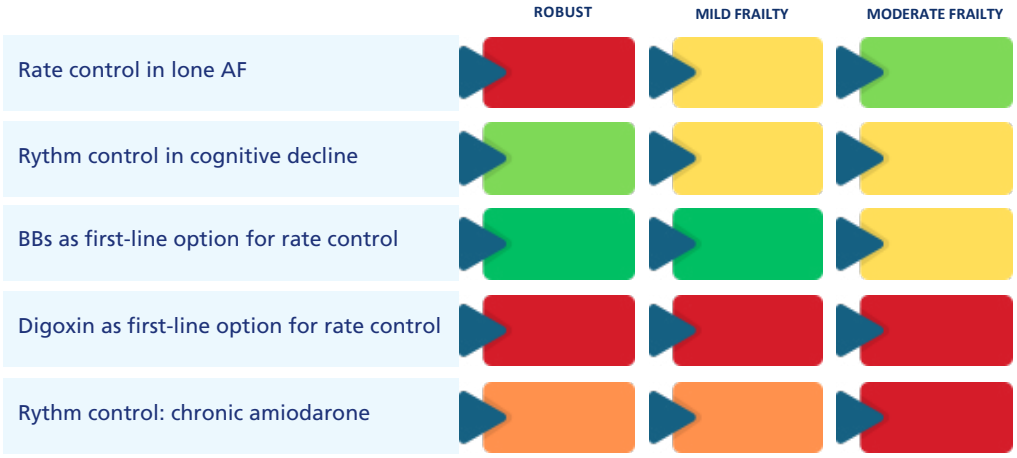
certain), 41% for mild frailty patients (with 36.9% being uncertain), and 30.8% for patients with moderate frailty (with 17.9% being uncertain).

For beta-blockers as first-line treatment, the acceptance rate was 94.9% for robust patients, 92.3% for patients with mild frailty, and 59% for patients with moderate frailty, (with 28.2% being uncertain).

Digoxin as first-line treatment had low acceptance across all profiles: 7.7% for robust patients, 2.5% for patients with mild frailty, and 5.1% for patients with moderate frailty.

The use of amiodarone for an indefinite period in a rhythm control strategy was accepted by 30.8% of participants for robust patients, 12.8% for mild frailty,

Fig. 3. AF: Rate control vs. rhythm control



AF: atrial fibrillation; BBs: beta blockers; HR: heart rate

and 7.7% for moderate frailty, with declining acceptance as frailty increased. (Appendix 1)

Opinion: The higher acceptance rate of rhythm control in robust patients and its marked decline in frail patients are consistent with the available evidence and its limitations on applicability. The EAST-AFNET 4 study demonstrated a clinical benefit of early rhythm control in patients with newly diagnosed AF; however, that study included a younger population with limited representation of frail patients; therefore, extrapolation to octogenarians should be done cautiously. (5,7,8) The lower acceptance in the presence of cognitive decline and the observed level of uncertainty suggest that participants considered broader objectives than mere symptom control, in a context where AF has been associated with an increased risk of cognitive decline and dementia even after adjusting for overt cerebrovascular events. (9) Regarding rate control, the high acceptance of beta-blockers among robust and mildly frail patients is consistent with guidelines. Conversely, the lower support among those with moderate frailty likely reflects concerns about hypotension, bradycardia, and falls. In this subgroup, a strategy of lenient heart rate control may be a particularly relevant option. (5,10) The limited support for digoxin and the growing reluctance toward chronic amiodarone can also be interpreted as a prudent stance, given their narrow therapeutic range, variability in renal function, and the risk of cumulative toxicity in very old adults. (5)

b. Anticoagulation (Figure 4)

Confidence in the CHA_2DS_2-VASc and HAS-BLED scores was 43.6% for robust patients, 20.5% for those with mild frailty, and 12.8% for those with moderate frailty, with a predominance of negative responses in all groups.

Regarding the choice of anticoagulants, direct oral anticoagulants (DOACs) had an acceptance rate of 100% for robust patients, 89.7% for those with mild frailty, and 56.4% for those with moderate frailty. Apixaban was the preferred option, followed by rivaroxaban.

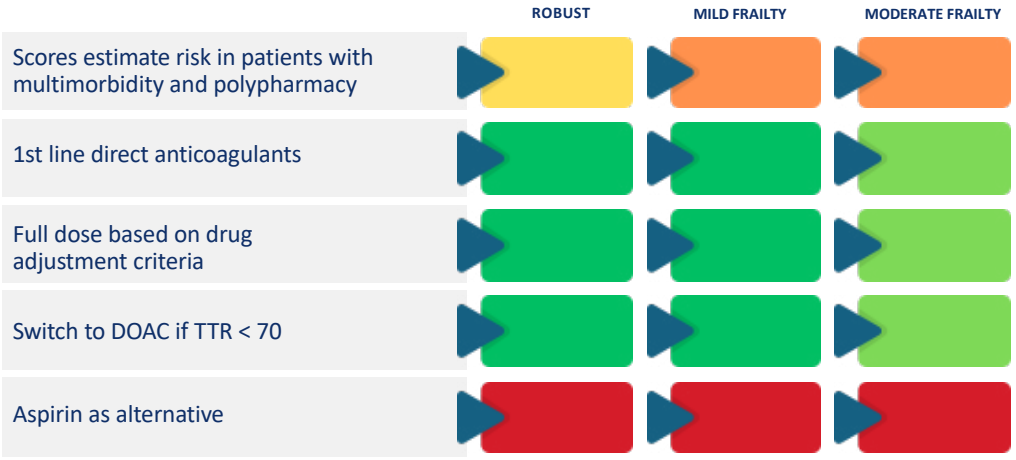
The use of full-dose therapy showed 100% acceptance for robust patients, 94.9% for those with mild frailty, and 53.8% for those with moderate frailty; in the latter group, 30.8% expressed uncertainty and 15.4% reported disapproval.

Regarding transition strategies, switching from vitamin K antagonists (VKAs) to DOACs in the event of suboptimal time in the therapeutic range (TTR) (<70%) showed an acceptance rate of 94.9% for robust patients, 79.5% for those with mild frailty, and 66.7% for those with moderate frailty.

The use of acetylsalicylic acid (ASA) as an alternative in patients at risk of falls or bleeding had very low acceptance rates across all groups: 15.4% for robust patients, 12.8% for mildly frail patients, and 12.8% for moderately frail patients.

Opinion: The decline in confidence in the CHA_2DS_2-VASc and HAS-BLED scores as frailty increases is to be expected in this context, since both tools estimate thromboembolic risk and bleeding risk but do not explicitly incorporate variables common in octogenarians, such as functional status, cognitive decline, medication burden, dependence, or social vulnerability. However, their usefulness does not disappear in this group: they remain a starting point for risk stratification and, in the case of the HAS-BLED score, for identifying modifiable factors rather than to contraindicate anticoagulation. (5,8) The preference for DOACs, with apixaban as the most commonly chosen option, is consistent with the available evidence and with the analyses of older patients from pivotal trials, which demonstrated at least comparable efficacy and a favorable safety profile compared with

Fig. 4. Anticoagulation



DOAC: direct oral anticoagulant; TTR: time in the therapeutic range

VKAs. (5,11) The lower acceptance rate for patients with moderate frailty may reflect reasonable caution rather than a disapproval of anticoagulation per se. In patients ≥80 years ineligible for standard anticoagulation, the ELDERCARE-AF study showed that edoxaban 15 mg reduced thromboembolic events compared with placebo. However, this was a highly selected population; therefore, these results should not be interpreted as supporting an empirical reduction in DOAC dosage outside the adjustment criteria established for each drug. Along these lines, the available evidence yields two practical messages: in non-anticoagulated patients or those initiating therapy, DOACs are generally the preferred strategy. Conversely, in frail patients who are stable on VKAs with good control, a routine switch to DOACs should not be assumed to be necessarily safer, as demonstrated by the FRAIL-AF trial. The limited support for ASA as an alternative was consistent with the available evidence: it is not an effective substitute for anticoagulation in preventing embolism in AF while increasing bleeding risk without a comparable benefit. (5,15)

Round 2: Acute coronary syndrome

Ischemic heart disease remains one of the leading causes of cardiovascular morbidity and mortality in older adults. In this group, ST-segment elevation ACS (STE-ACS) or non-ST-segment elevation ACS (NSTE-ACS), typically present with a higher burden of comorbidities, less typical symptoms, and frequent coexistence with frailty, cognitive decline, and polypharmacy—factors that complicate both prognostic stratification and the choice between invasive and conservative strategies. (16,17)

a. Management strategy for NSTE-ACS (Figure 5)

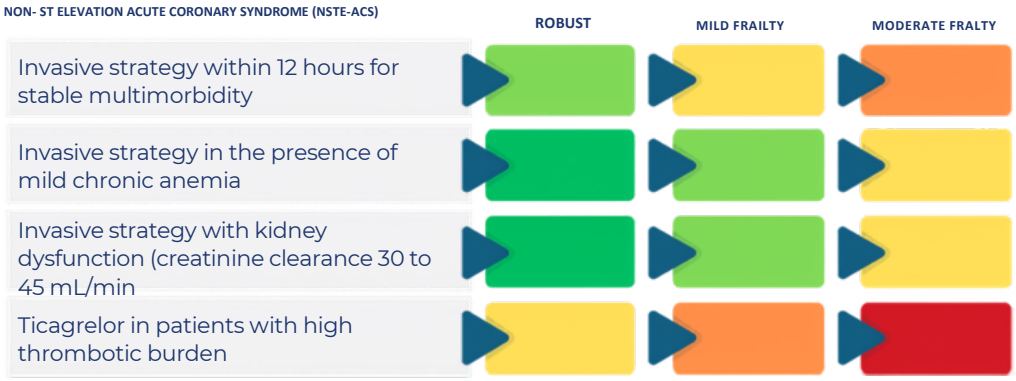
The acceptance of acceptance for an early invasive strategy was 68.4% for robust patients, 50% for those with mild frailty, and 18.4% for those with moderate frailty (with 39.5% being uncertain).

In the same scenario but with the presence of mild chronic anemia, 73.7% agreed with an early invasive strategy for robust patients, 57.9% for those with mild frailty, and 23.7% for those with moderate frailty, with 44.7% of uncertainty in the latter group. In the presence of chronic kidney disease (creatinine clearance of 30–45 mL/min), acceptance rates were 71.1%, 55.3%, and 21.1%, respectively.

Regarding the use of ticagrelor, the acceptance rate was 50% for robust patients, 23.7% for those with mild frailty, and 5.2% for those with moderate frailty.

Opinion: The decline in the acceptance rate for an early invasive strategy as frailty increases is consistent with current evidence and recommendations for individualized care. In the SENIOR-RITA trial, conducted in patients >75 years with NSTE-ACS, a routine invasive strategy did not reduce the composite primary outcome of cardiovascular death or nonfatal myocardial infarction at 4.1 years; yet the rate of nonfatal myocardial infarction was lower. Therefore, the overall benefit was inconclusive and must be weighed against comorbidities, functional prognosis, and care goals. The individual meta-analysis by Kotanidis et al. also showed no reduction in mortality with an invasive strategy in elderly patients, even though the reinfarction and urgent revascularization rates were lower. (19) In specifically frail patients, data from the MOSCA-FRAIL study and its subsequent analyses reinforce that the Clinical Frailty Scale can modify the risk-benefit balance and that the utility of an invasive strategy decreases as frailty increases. (20) Therefore, the lower acceptance rate in cases of moderate frailty could be interpreted not as an unjustified omission, but as a prudent assessment of a more uncertain benefit. The persistence of the same pattern in the presence of mild anemia or renal impairment suggests

Fig. 5. Strategy in NSTE-ACS



that, in the panel's decision-making process, frailty carried at least as much weight as these comorbidities. The low preference for ticagrelor in cases of mild and moderate frailty is consistent with the POPular AGE study, in which clopidogrel reduced bleeding and was non-inferior for the net clinical outcome in patients ≥ 70 years or older with NSTE-ACS. (21)

b. Management strategy for STE-ACS (Figures 6 and 7)

In the absence of catheterization laboratory capability, the use of fibrinolytic therapy for inferior myocardial infarction was supported by 81.6% for robust patients, 65.8% for those with mild frailty, and 23.7% for those with moderate frailty, with 39.5% of uncertainty for the latter group.

The acceptance rate of fibronolytic therapy for inferoposterolateral infarctions was 97.4% for robust patients, 84.2% for those with mild frailty, and 57.9% for those with moderate frailty. For anterior infarctions, 97.4% supported the use of fibrinolytic therapy for robust patients, 94.7% for those with mild frailty, and 65.8% for those with moderate frailty.

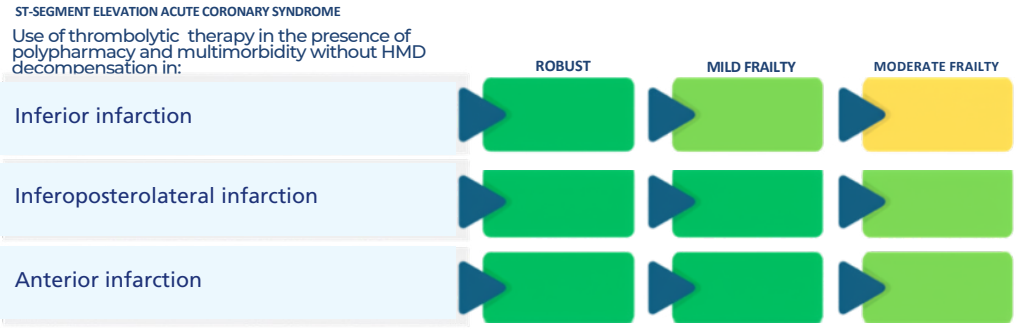
Opinion: The higher acceptance rate of fibrinolytic therapy in infarctions involving a larger area at risk is clinically consistent with a greater willingness to indicate a pharmaco-invasive strategy when timely primary percutaneous coronary intervention is not feasible. Nevertheless, primary percutaneous intervention remains the preferred strategy whenever it is feasible within the recommended time windows. (16) In older adults, fibrinolytic therapy requires rigorous screening for contraindications and a particularly careful assessment of the bleeding risk. The STREAM-2 study showed that a pharmaco-invasive strategy using half-dose tenecteplase in patients > 60 years or older without timely access to the catheterization laboratory achieved clinical efficacy comparable to that of primary percutaneous coronary intervention, but at the cost of a higher rate of intracranial hemorrhage. (22) Consequently, the support observed for robust patients and for those with mild frailty can be interpreted as reasonable in the absence of catheterization laboratory capability, while the higher uncertainty for patients with moderate frailty adequately reflects the potential hemorrhagic risk.

Regarding antithrombotic strategies and shortening the duration of dual antiplatelet therapy, the acceptance rate was 10.5% for the robust group, 18.4% for the mildly frail group, and 44.7% for the moderately frail group.

The use of a P2Y12 receptor inhibitor without ASA showed an acceptance rate of 26.3% for robust patients, 18.4% for mild frailty, and 23.7% for the moderate frailty. In the presence of AF in this scenario, the use of P2Y12 inhibitors in combination with anticoagulants and without ASA had an acceptance rate of 78.9% for the robust group, 65.8% for the mild frailty group, and 31.6% for the moderate frailty group, with 42.1% expressing uncertainty in the latter situation.

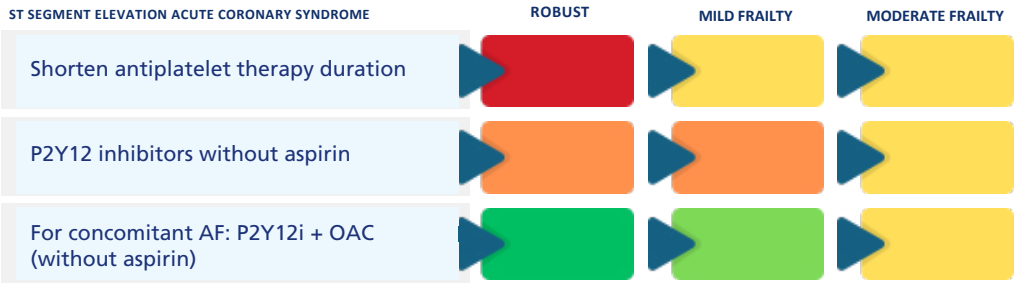
Opinion: The higher level of consensus on shortening dual antiplatelet therapy (DAPT) in moderate frailty is consistent with the increasing prominence of bleeding risk in this subgroup but requires prudent formulation. The MASTER DAPT trial demonstrated that, in patients at high risk of bleeding, an abbreviated therapy one month after a PCI was non-inferior in terms of net clinical events and reduced bleeding, supporting shorter strategies in selected patients. (23) However, this finding should not be automatically extrapolated to all frail octogenarians with ACS. in the STOPDAPT-2 ACS trial, clopidogrel monotherapy after 1 to 2 months of DAPT failed to attest noninferiority for the net clinical benefit with a numerical increase in cardiovascular events despite reduction in bleeding events. (24) Therefore, the results of the panel can be interpreted as consistent with a selective strategy in patients at high bleeding risk and not as a general rule. The low acceptance rate of a P2Y12 inhibitor monotherapy without ASA as a stand-alone strategy is also consistent with the fact that evidence on ACS in very old adults remains limited. In the presence of concomitant AF, the preference for oral anticoagulation combined with a single P2Y12 inhibitor

Fig. 6. Thrombolytic therapy in STE-ACS



HMD: hemodynamic

Fig. 7. Antithrombotic strategies in STE-ACS



AF: atrial fibrillation; OAC: oral anticoagulants; P2Y12i: P2Y12 inhibitor

and without ASA is consistent with the AUGUSTUS, ENTRUST-AF PCI, and PIONEER AF-PCI studies, which showed less bleeding rate with dual regimens than with triple therapy, without a consistent signal of reduction in ischemic efficacy. (25-27)

STUDY LIMITATIONS

The main limitations stem from the methodology used, which is based on expert consensus; this implies that the recommendations reflect the experience and clinical judgment of the participants. Although the group consisted of leading experts in cardiology and geriatrics, most are not exclusively dedicated to cardiogeriatrics. Therefore, these recommendations should be validated in future studies to confirm and refine these findings in clinical practice. Addressing multiple scenarios also limited the time available for discussion

CONCLUSION

In subjects > 80 years, AF and ACS present therapeutic decisions in which age alone is insufficient to guide management. Across the scenarios analyzed, frailty emerged as a consistent moderator of the acceptance of invasive strategies, the use of antiarrhythmic drugs, and the intensity of antithrombotic therapy.

In AF, the consensus consistently supported beta-blockers and DOACs, with less support for rhythm control and more intensive strategies when frailty or cognitive decline increased. In ACS, acceptance of early invasive strategies and more potent antiplatelet agents declined with frailty. Fibrinolysis was considered an alternative when timely access to a catheterization laboratory was not available, with greater support for larger infarcts.

These findings underscore the need to incorporate comprehensive assessment—along with ischemic and bleeding risk—into cardiovascular decision-making for the very elderly. Rather than replacing guidelines, this roundtable proposes a practical framework for tailoring approaches in common scenarios where evidence remains insufficient.

Conflicts of interest

None declared.

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

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Acknowledgments: To Laboratorio Baliarda for the logistical support; the company did not participate in the design, analysis, or writing of the manuscript.

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APPENDIX 1.

The results are expressed as percentages (%)

ATRIAL FIBRILLATION	Robust			Mild frail			Moderate frail		
	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO
Controlled multimorbidity, no CVD, PEF with normal or mild dilated LA. New onset AF. Do you use a rate-control strategy?	25.6	7.7	66.7	38.5	28.2	33.3	64.1	20.5	15.4
In the event of cognitive decline, do you use a rhythm-control strategy?	61.5	30.8	7.7	41	35.9	23.1	30.8	17.9	51.3
Rate control: BB as first-line treatment	94.9	0	5.1	92.3	5.1	2.6	59	28.2	12.8
Rate control: Digoxin as first-line treatment	7.7	25.6	66.7	2.6	15.4	82.1	5.1	20.5	74.4
If we choose for RHYTHM control: do you use chronic amiodarone?	30.8	25.6	43.6	12.8	41	46.2	7.7	28.2	64.1
Multimorbidity and polypharmacy: Do the scores estimate the risk for these groups?	43.6	20.5	35.9	20.5	28.2	51.3	12.8	30.8	56.4
Do you indicate direct anticoagulants as first-line treatment?	100	0	0	89.7	10.3	0	56.4	30.8	12.8
Do you indicate full dose according to dosage adjustment criteria for each drug?	100	0	0	94.9	5.1	0	53.8	30.8	15.4
Do you switch VKAs to DOACs with a TTR < 70?	94.9	0	5.1	79.5	12.8	7.7	66.7	12.8	20.5
In cases of multiple falls, do you consider ASA 100 mg as an alternative?	12.8	5.1	82.1	12.8	7.7	79.5	15.4	2.6	82.1
ACUTE CORONARY SYNDROME WITHOUT ST-SEGMENT ELEVATION	**Robust**			**Mild frail**			**Moderate frail**		
	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO
Multimorbidity presenting to the emergency department with a diagnosis of NSTE-ACS, clinically stable. Do you indicate an invasive procedure within 12 hours of admission?	68.4	15.8	15.8	50	28.9	21.1	18.4	39.5	42.1
In cases of mild chronic anemia, do you indicate an invasive strategy?	73	13.2	13.2	57.9	23.7	18.4	23.7	44.7	31.6
With a creatinine clearance of 30 to 45, would you indicate an invasive strategy?	71.1	23.7	5.3	55.3	31.6	13.2	21.1	36.8	42.1
For a patient with high thrombotic burden, would you prescribe ticagrelor?	50	15.8	3.2	23.7	28.9	47.4	5.3	23.7	71.1
ACUTE CORONARY SYNDROME WITH ST-SEGMENT ELEVATION	**Robust**			**Mild frail**			**Moderate frail**		
	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO	YES	UNCERTAIN	NO
Multimorbidity and polypharmacy, without hemodynamic impairment—does this indicate thrombolytic therapy for an inferior myocardial infarction?	81.6	13.2	5.3	65.8	23.7	10.5	23.7	39.5	36.8
And for an IPL infarction?	97.4	2.6	0	84.2	15.8	0	57.9	28.9	13.2
In cases of anterior infarction?	97.4	0	2.6	94.7	5.3	0	65.8	28.9	5.3
Do you shorten the antiplatelet therapy time?	10.5	10.5	78.9	18.4	36.8	44.7	44.7	47.4	7.9
Would you use P2Y12 inhibitors without ASA in either case?	26.3	7.9	65.8	18.4	26.3	55.3	23.7	36.8	39.5
And in the presence of AF: P2Y12 inhibitors alone + AC?	78.9	2.6	18.4	65.8	21.1	13.2	31.6	42.1	26. 3

AC: anticoagulation; AF: atrial fibrillation; ASA: acetylsalicylic acid; BB: beta-blockers; CVD: cardiovascular disease; DOAC: direct oral anticoagulants; HR: heart rate; IPL: inferoposterolateral; LA: left atrium; NSTE-ACS: Non-ST-segment elevation acute coronary syndrome; PEF: preserved left ventricular ejection fraction; TTR: therapeutic range time; VKAs: vitamin K antagonists.

ORIGINAL ARTICLE

Evaluation of Clinical Management and Follow-up of Patients with Severe Myocardial Ischemia Detected by Gated-SPECT

Evaluación del manejo clínico y seguimiento de pacientes con isquemia miocárdica grave detectada mediante SPECT gatillado

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ABSTRACT

Background: Ischemic heart disease (IHD) is one of the leading causes of death and disability. Many studies have shown that patients with angina and severe myocardial ischemia, as evidenced by functional studies, have an unfavorable clinical course, with a higher risk of cardiovascular events and mortality.
Objectives: The primary aim of this study was to analyze the management adopted by treating physicians (invasive vs. conservative) in patients with a left ventricular mass ischemic burden (IB) ≥10% on a gated-SPECT (single-photon emission computed tomography) myocardial perfusion study, and to explore whether higher ischemia values (15% cutoff point) significantly influence this decision. The secondary goal was to identify clinical and/or functional variables associated with the decision to implement an initial invasive strategy and to compare the incidence of cardiovascular events (acute myocardial infarction, unstable angina, rehospitalization due to cardiovascular causes, heart failure, arrhythmias, and cardiovascular death) between patients treated medically and those undergoing revascularization during long-term follow-up.
Methods: A retrospective, observational, single-center study was conducted including consecutive patients referred for a gated-SPECT myocardial perfusion study (n=142) between January 2021 and December 2024. Patients with an IB ≥10% were selected and divided into two cohorts: 1) IB ≥ 16% (n=50, 32.2%) and 2) IB between 10 to 15% (n=92, 64.8%)
Results: The proportion of patients managed with an initial invasive strategy was higher in the group with IB ≥16% (84% vs. 68.4%, p=0.044). Major cardiovascular events occurred in 16 patients (11.4%); 9 (9.8%) had an IB between 10–15% and 7 (14%) in the group with IB ≥16%. Among all patients who experienced events, 11 (68.5%) had previously undergone revascularization: 9 via PCI (81%) and 2 via CABG (18%). The mean time between revascularization and the event was 8.3 months (range: 1 day–21 months), with 5 events occurring within the first month after the procedure.
Conclusion: The presence of severe myocardial ischemia with a left ventricular mass IB ≥ 16% was associated with a higher indication for coronary angiography and revascularization. The incidence of major events during follow-up was low, limiting the ability to draw prognostic conclusions and highlighting the need for additional studies with a larger number of patients and longer follow-up.

Key words: Myocardial perfusion - Gated-SPECT - Ischemic burden - Coronary artery disease

RESUMEN

Introducción: La cardiopatía isquémica (CI) es una de las principales causas de muerte y discapacidad. Diversos estudios han demostrado que los pacientes con angina e isquemia miocárdica grave evidenciada mediante estudios funcionales presentan una evolución clínica desfavorable, con mayor riesgo de eventos cardiovasculares y mortalidad.
Objetivos: Analizar la conducta adoptada por los médicos tratantes (invasiva vs conservadora) en pacientes con un monto isquémico (MI) igual o superior al 10% de la masa del ventrículo izquierdo en un estudio de perfusión miocárdica (PM) con SPECT (tomografía computarizada por emisión de fotón único) gatillado, así como explorar si valores de isquemia mayores (punto de corte en 15%) influyen significativamente en esta decisión.
Identificar variables clínicas y/o funcionales que se asocian con la decisión de adoptar una estrategia invasiva inicial.
Comparar la incidencia de eventos cardiovasculares (infarto agudo de miocardio, angina inestable, reinternación por causa cardiovascular, insuficiencia cardíaca, arritmias y muerte de causa cardiovascular) en el seguimiento a largo plazo en los pacientes tratados médicamente y aquellos sometidos a revascularización.
Material y métodos: Estudio retrospectivo, observacional y unicéntrico. Se seleccionaron pacientes consecutivos entre enero de 2021 y diciembre de 2024 derivados para la realización de estudio de PM con SPECT gatillado, con MI mayor o igual a 10% (n=142),

Rev Argent Cardiol 2026;94:263-269. https://doi.org/10.7775/rac.v94.i4.21025

Received: 11/06/2025 – *Accepted:* 03/11/2026

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dividiéndolos en dos cohortes: 1) MI ≥ 16 % (n=50, el 35,2%) y 2) MI 10-15% (n=92, el 64,8%).
Resultados: La proporción de pacientes estudiados con estrategia invasiva inicial fue mayor en el grupo con MI ≥ 16 % (84 % vs 68,4 %, p=0,044). Se registraron eventos cardiovasculares mayores en 16 pacientes (11,4 %), 9 (7%) en el grupo con MI entre 10–15 % y 7 (5%) en el grupo con MI ≥ 16 %; p= 0,476. Del total de pacientes con eventos, 11 (68,5%) habían sido revascularizados previamente: 9 mediante angioplastia y 2 mediante cirugía. El tiempo medio entre la revascularización y el evento fue de 8,3 meses (rango: 1 día–21 meses), con 5 eventos dentro del primer mes posterior a la intervención.
Conclusión: La presencia de isquemia miocárdica grave con un monto isquémico ≥ 16 % de la masa del VI se asoció a mayor indicación de cinecoronariografía y revascularización. La incidencia de eventos mayores durante el seguimiento fue baja, lo que limita la posibilidad de establecer conclusiones pronósticas y resalta la necesidad de estudios adicionales con mayor número de pacientes y seguimiento prolongado.

Palabras clave: Perfusión miocárdica - SPECT gatillado - Monto isquémico - Enfermedad coronaria

INTRODUCTION

Ischemic heart disease (IHD) is one of the leading causes of death and disability. (1) According to data from the Pan American Health Organization (PAHO), approximately 73.6 deaths per 100 000 inhabitants are recorded annually. (2)

The primary goals of IHD treatment are to improve symptoms, quality of life, and prognosis. In addition to optimal medical therapy (OMT) and control of cardiovascular risk factors (CVRF), myocardial revascularization,whether through percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), represents another therapeutic strategy in selected patients. (3,4)

Several studies have shown that patients with angina and severe myocardial ischemia, as evidenced by functional tests, have an unfavorable clinical course, with an increased risk of cardiovascular events and mortality. (5,6) Consequently, in clinical practice, these patients are classified as “high clinical risk”, leading to a medical decision favoring an initial invasive strategy in many cases.

Classic studies such as that of Hachamovitch et al. (7) demonstrated a benefit from revascularization in patients with myocardial ischemic burden (IB) ≥10%. However, other clinical studies, -the most recent of which was the ISCHEMIA trial (8)- did not demonstrate a significant reduction of events in patients with moderate to severe ischemia when comparing an initial invasive strategy vs. OMT. These findings imply a shift in the interpretation of IB and, in clinical practice, its value within the decision-making process is being reevaluated.

Furthermore, contemporary registries have shown that the classic threshold for high-risk ischemia may shift toward 14–15% values in populations treated with current medical therapies. (9).

In this context, the objectives: of the present study were:

Primary objective

To analize the approach adopted by treating physicians (invasive vs. conservative) in patients with a left ventricular mass IB ≥10% on a gated-SPECT myocardial perfusion (MP) study, and to determine whether higher ischemia values (cutoff point at 15%) significantly influence this decision.

Secondary objectives

To identify clinical and/ot functional variables associated with the decision to perform an initial invasive strategy, and to compare the incidence of cardiovascular events (acute myocardial infarction, unstable angina, readmission for cardiovascular causes, heart failure, arrhythmias, and cardiovascular death) during long-term follow-up between patients treated medically and those who underwent revascularization.

METHODS

Study Population

A retrospective, observational, single-center study was conducted, including consecutive patients referred for a gated-SPECT MP study between January 2021 and December 2024.

Inclusion criteria: IB ≥10% established on the SPECT study

Exclusion criteria: Inability to conduct long-term follow-up due to loss of contact via telephone or electronic records through the City of Buenos Aires hospital management system (SIGEHOS).

For the analysis, the cohort was stratified into two subgroups based on the IB:

- Ischemia 10–15%
- Ischemia ≥16%

Follow-up was conducted via telephone contact and review of electronic medical records through SIGEHOS, with a median follow-up of 18 months. Symptoms were assessed, and cardiovascular events were recorded based on the treating cardiologist’s interpretation in the medical record, including acute myocardial infarction, unstable angina, readmission for cardiovascular causes, heart failure, arrhythmias, and death from cardiovascular causes. Patients were registered as either being referred to invasive testing with coronary angiography (CA) or continuing with medical therapy alone. For those undergoing CA, the ocurrence of subsequent revascularization (PCI or CABG) was documented. Coronary angiography without lesions was defined as studies reported “without angiographically significant lesions” or with previously treated vessels that were found to be patent.

Acquisition protocol for gated-SPECT MP study

A one-day protocol was performed using technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) during stress and

at rest with a Philips Brightview XCT 882482 gamma camera. Images were acquired 30 to 45 minutes after an intravenous injection at rest, and 15 to 20 minutes after maximum exercise. The administered activity was 8–12 mCi for the first injection (at rest or during stress) and 24–36 mCi for the second injection (during stress or at rest), in accordance with the guidelines of the American Society of Nuclear Cardiology (ASNC). (10) Patients who performed exercise did so to the point of symptom onset, according to the Astrand protocol on a cycle ergometer. (11) In patients who received pharmacological stress testing, dipyridamole was administered intravenously at a dose of 0.56 mg/kg over a 4-minute period, with the radiotracer injected 3 minutes after injection, in accordance with the ASNC guidelines .

Image Analysis and Quantification

SPECT analysis was performed according to the left ventricular 17-segment model of the American Heart Association (12). Segments were scored from 0 to 4 based on tracer activity in each segment. Perfusion quantification was achieved using the sum of the stress score (SSS), the rest score (SSR) and the differential score (SD). The ischemic and necrotic volumes were estimated by dividing the differential and rest scores, respectively, by 68 for the 17-segment model. Severe myocardial ischemia was defined as a left ventricular (LV) mass IB ≥ than 10%. (7,9) The analysis was performed visually by three independent observers (OM / JH / LB), and in the event of disagreement, a consensus was reached.

Ventricular dysfunction based on left ventricular ejection fraction (LVEF), was classified as mild (49–54%), moderate (35–48%), and severe (<35%). Ventricular dilation was defined as an end-systolic volume (ESV) >45mL/m² and/or an end-diastolic volume (EDV) >70mL/m². (13). Transient ischemic dilation (TID), defined as a stress/rest volume ratio ≥1.22, was also analyzed. (14)

Statistical Analysis

Categorical variables were expressed as absolute frequencies and percentages and were compared between groups using the chi-square test and the test for difference in proportions. When the expected value in any of the cells was less than 5, the continuity correction or Fisher's exact test was used, as appropriate.

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), depending on data distribution. Continuous variables were compared using, Student's t-test or the Mann–Whitney test, as appropriate.

To identify independent variables associated with the behavior of treating physicians, a multivariate logistic regression analysis was performed, which included the variables identified in the univariate analysis.

A p-value <0.05 was considered statistically significant. Statistical calculations were performed using Epi Info™.

Ethical Considerations

This study was approved by the Institutional Ethics Committee, and patients' personal data were protected.

All procedures were conducted in accordance with the ethical principles established in the Declaration of Helsinki.(15)

RESULTS

A total of 3051 patients, of whom 177 (5.8%) had severe myocardial ischemia were analyzed.and 142 (80%) met the inclusion criteria for the final analysis. Median IB was 14% (IQR: 11.5–17%). Ninety-two patients (64.8%) had an IB between 10% and 15%, and 50 patients (35.2%) an IB ≥16%.

Baseline and stress test clinical characteristics are presented in Tables 1 and 2. In the gated-SPECT MP study, 6 patients (4,2%) showed increased ESV, and 7 (5%) increased EDV . The decrease in LVEF was mild in 28 patients (20.1%), moderate in 28 (20.1%), and severe in 10 (7.1%). Transient ischemic left ventricular dilation (TID) was detected in 14 patients (10%), and a post-stress decline in LVEF was observed in 22 (15.7%). The comparison between the two IB groups revealed no statistically significant differences.

Of 142 patients analyzed, 105 (73.9 %) underwent CA at the discretion of the treating physician. The proportion of patients studied was higher in the IB ≥16% group than in the IB 10–15% group (84% vs. 68.4%, p=0.044). (Figure 1). No statistically significant associations predicting the indication for CA were identified. However, a trend toward a higher rate of indication was observed in symptomatic patients (OR 2.18; 95% CI 0.98–4.86; p=0.056). (Figure 2)

In the angiographic analysis, 19 patients (18.1%) had no significant lesions.

Fifty-six patients (53.3%) of those studied with CA underwent revascularization via PCI or CABG. The revascularization rate was significantly higher in the group with IB ≥16% than in the group with IB 10–15% (65% vs. 32.6%, p=0.001).

Among the 142 patients, 80 (56.3%) were initially symptomatic; of these, 65 patients (81.2%) were referred for an initial invasive strategy (OR 2.22; 95% CI 1.03 to 4.79; p=0.004). Among them, 34 (52.3%) underwent revascularization and 21 remained asymptomatic after revascularization (OR 2.24; 95% CI 0.83–6.03; p=0.282).

Over a median follow-up of 18 months, major cardiovascular events were recorded in 16 patients (11.4%); 9 out of the 92 patients with IB between 10–15% (9.8%) and 7 out of the 50 patients with IB ≥ 16% (14%), p=0.476. Patients who underwent revascularization had a higher event rate compared with those in the non-invasive arm (19.6% vs. 4.3%; OR 5.43; 95% CI 1.75–16.8; p=0.015). Events occurred with a median time between revascularization and the event of 8.3 months (range: 1 day–21 months) nearly half of the time (5/11 events), and they took place within the first month following the procedure, which could be linked to periprocedural complications.

DISCUSSION

This study analyzed the therapeutic approach adopted by treating physicians in the presence of severe myocardial ischemia (≥10% of LV mass) assessed by gated-SPECT MP study, and clinical outcomes were

Table 1. Population characteristics

	IB ≤15% (n=92)	IB ≥16% (n=50)	p
Baseline variables	n (%)	n (%)	
Male sex	78 (84. 8)	44 (88)	0.784
Smoking	25 (27. 8)	8 (16)	0.194
Former smokers	37 (40.2)	29 (58)	0.064
Hypertension	69 (75)	35 (70)	0.656
Diabetes mellitus	32 (34.8)	17 (34)	1
Dyslipidemia	48 (52.2)	32 (64)	0.237
Family history	6 (6.5)	2 (4)	0.809
Kidney Failure	1 (1.1)	1 (2)	1
HIV	6 (6.5)	3 (6)	1
Autoimmune disease	4 (4.3)	1 (2)	0.803
Previous AMI	41 (44.6)	17 (34)	0.296
Previous PCI	35 (38)	14 (28)	0.308
Previous CAGB	15 (16.3)	6 (12)	0.658
ACEI	35 (38)	21 (42)	0.778
Beta-blockers	72 (78.3)	39 (78)	1
Calcium channel blockers	9 (9.7)	4 (8)	0.962
Aspirin	70 (76.1)	42 (84)	0.374
IIB IIIA inhibitors	20 (21.7)	13 (26)	0.714
Statins	66 (71.7)	34 (68)	0.784
Nitrites	8 (8.6)	2 (4)	0.483

ACEI: angiotensin-converting enzyme inhibitors; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; HIV: human immunodeficiency virus; IB: ischemic burden; MP: myocardial perfusion; PCI: percutaneous coronary intervention.

Table 2. Data from the myocardial perfusion study

	IB ≤15% (n=92)	IB ≥16% (n=50)	p
Stress characteristics	n (%)	n (%)	
Type of physical stress	68 (73.9)	44 (88)	0.080
Angina during exertion	12 (13)	11 (22)	0.252
Shortness of breath on exertion	11 (11.9)	3 (6)	0.399
ST-segment depression	12 (13)	12 (24)	0.152
ST-segment depression and angina	4 (4.3)	7 (14)	0.084
Arrhythmias	12 (13)	7 (14)	1

IB: ischemic burden

compared according to the chosen strategy (invasive vs. conservative). Our results provide insight into current clinical practice and its agreement with evidence derived from major clinical trials on stable coronary artery disease.

In this cohort, the prevalence of severe myocardial ischemia was 5.8%, a figure comparable to that reported in other series, where it ranges from 5–10%. (7) Median IB was 14%, similar to the threshold used in studies such as COURAGE (nuclear substudy) and ISCHEMIA to define high risk. (8,16) In our population, although the presence of severe ischemia was rare, its detection was clinically relevant due to its association with a greater indication for invasive testing and a higher revascularization rate.

We observed a trend in decision-making related to the extent of ischemia and the choice of invasive procedures: patients with IB ≥16% were more frequently referred for diagnostic coronary angiography (84% vs. 68.4%, p=0.044) and for revascularization

Fig. 1. Coronary angiography (CA) based on ischemic burden in the perfusión study

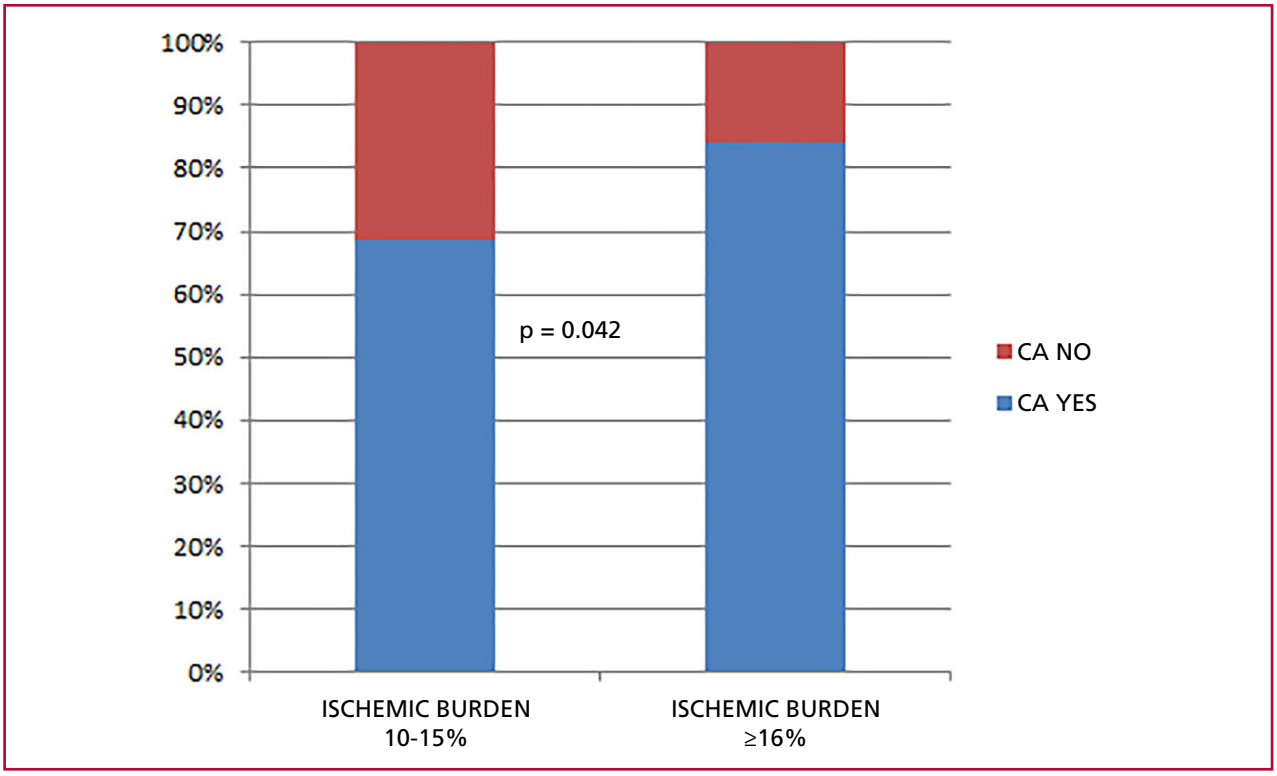
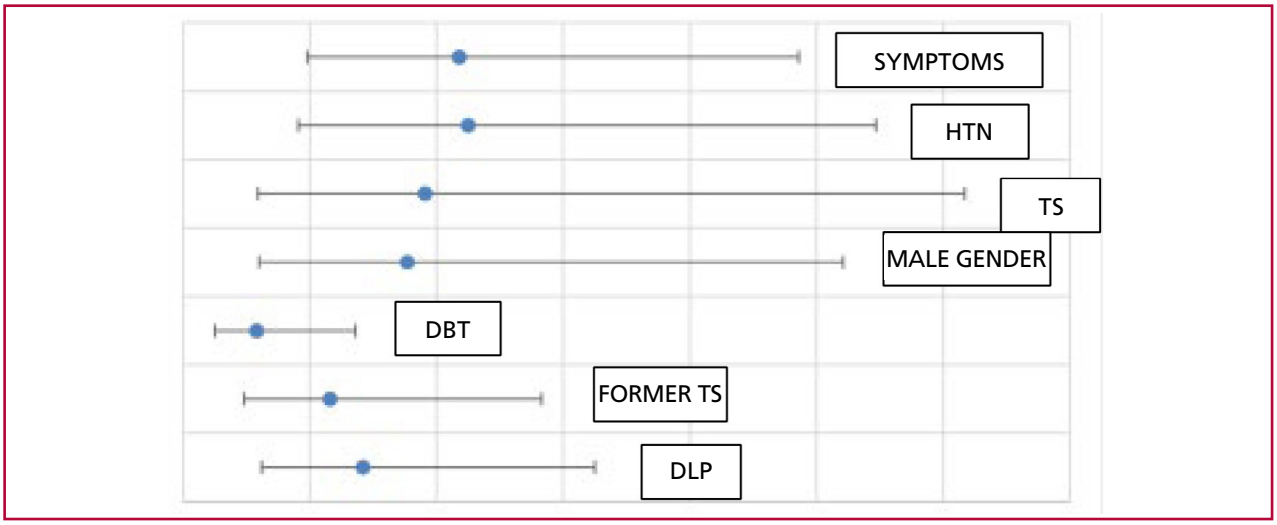


Fig. 2. Multivariate analysis of other predictor variables of initial invasive strategy- OR and 95% CI



DBT: diabetes; DLP: dyslipidemia; HTN: hypertension; TS: tobacco smoking

(65% vs. 32.6%, p=0.001) compared with those with IB 10–15%.

Another point worth noting is that clinical decisions were not based exclusively on the findings of the MP study. Symptoms, especially the presence of angina or equivalent symptoms, played a significant role in the indication for CA, as reflected in the observed trend toward greater intervention in symptomatic patients.

The ISCHEMIA study evaluated whether an initial invasive strategy in patients with moderate-severe ischemia provided additional benefit compared with OMT. In the medium term , the invasive strategy did not significantly reduce major cardiovascular

events or overall mortality, although it did improve symptoms and quality of life in the most symptomatic patients. In our population, we observed partial similarities: while IB was a factor for indicating CA and revascularization, the presence of symptoms also played an important role in decision-making. However, when we conducted a methodological analysis of the ISCHEMIA trial, we identified some differences with our population. First, patients with LVEF <30%, who are potential candidates for revascularization in the presence of myocardial viability, were excluded. On the other hand, 34% of the patients were symptomatic, unlike our cohort, in which symptomatic patients predominated at the time of the study (56.3%). Furthermore, 26% of the patients assigned to OMT were crossed over to an invasive strategy. Another aspect to consider is that in the ISCHEMIA study threre was no stratification by IB, but by a general classification of ischemia based on various criteria, including even patients with positive exercise testing without imaging, which prevented quantification of the actual IB. Conversely, in our population, only patients with ischemia ≥10% -objectively measured by gated-SPECT MP study- were included.

On the other hand, the PROMISE study provided a complementary perspective by showing that the use of anatomical angiotomography studies as an initial diagnostic tool in symptomatic patients with suspected coronary artery disease does not necessarily lead to better clinical outcomes compared with noninvasive studies. (17) In our series, all the patients included were evaluated by gated-SPECT MP study , and a significant subgroup (18.1%) had coronary arteries without angiographically significant lesions, which could reflect the presence of microvascular disease.

Regarding clinical outcomes, the incidence of major cardiovascular events was relatively low during follow-up (11.4%), which limits the ability to draw conclusions about the prognostic impact of the different strategies. However, it is noteworthy that most events (68.5%) occurred in patients who had previously undergone revascularization, and that nearly half occurred within the first month following the procedure, which likely reflects the anatomical and clinical complexity of these cases.

The absence of a significant reduction in events in the invasively treated group is consistent with the ISCHEMIA trial findings, which demonstrated that an initial invasive strategy did not reduce major events in stable patients with moderate or severe ischemia, although it was associated with symptom improvement in certain subgroups. In our cohort, symptomatic improvement was more common in patients with previous revascularization, although this did not reach statistical significance, possibly due to the sample size in the subgroup analysis.

Recently, results from the ISCHEMIA-EXTENDED study, with a follow-up of up to 7 years, showed a trend toward lower cardiovascular mortality in the invasive arm, which reopens the debate on the long-term impact of these strategies. (18) As previously noted, although our study was not designed to evaluate mortality as a primary endpoint, the incidence of major events was low and no significant differences were observed between the groups based on initial treatment.

In turn, the COURAGE study had raised similar questions years earlier, showing that in patients with stable coronary artery disease, PCI plus OMT did not offer greater benefit in preventing major events compared with OMT alone. (19) Our observation that 60% of patients with severe ischemia were not revascularized suggests that, in clinical practice, physicians have already come to recognize that revascularization does not always alter the prognosis, reserving it for more symptomatic subgroups or those with high-risk anatomical disease.

Based on our observations and in line with the results of some previous studies (7, 18, 20), the classic definition of severe ischemia (>10% of LV) may not constitute an optimal cutoff point for guiding therapeutic management. As previously mentioned, in our study, treating physicians tended to recommend an invasive strategy for patients with IB ≥16%, which could suggest the need to review and validate higher cutoff points for defining severe ischemia in gated-SPECT MP studies, this threshold probably being a more appropriate value when selecting an invasive strategy in current clinical practice.

Our results highlight the importance of contextualizing the information derived from gated-SPECT MP studies within a comprehensive clinical framework, comsidering that a high IB is associated with a stronger indication for revascularization, that there is a subgroup with angiographically normal coronary arteries that may be due to microvascular disease, and that symptoms remain a key determinant in decision-making. (21) However, the low number of recorded events calls for caution in interpreting the prognostic implications and highlights the need for larger studies with longer follow-up.

Limitations

This is a retrospective, observational, single-center study. The short follow-up period may underestimate the actual incidence of events. Twenty percent of patients were lost to follow-up.

CONCLUSION

In this population, the presence of severe myocardial ischemia with left ventricular mass IB ≥16% was associated with a higher indication for coronary angiography and revascularization. Our findings reflect that in clinical practice, therapeutic decisions tend to be individualized, considering both the IB and the patient's clinical presentation. The incidence of major events during follow-up was low, which limits the ability to draw prognostic conclusions and highlights the need

for additional studies with a larger number of patients and prolonged follow-up.

Funding

None.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Aortic Valve Replacement via Mini-Sternotomy and Rapid Deployment Valves: Are We on the Right Track?

Reemplazo valvular aórtico por miniesternotomía y válvulas de rápido implante, ¿vamos en el camino correcto?

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ABSTRACT

Background: Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its management has evolved toward techniques that reduce surgical risk and accelerate recovery, especially in elderly patients. Among these innovations are rapid deployment valves (RDV), which combine the durability of conventional surgical prostheses with anchoring mechanisms derived from transcatheter aortic valve implantation (TAVI), reducing cardiopulmonary bypass (CPB) and aortic clamping times and facilitating minimally invasive approaches such as mini sternotomy.
Objectives: The objective of this study was to evaluate 30-day and 1-year mortality following aortic valve replacement (AVR) via mini-sternotomy using INTUITY RDV. Secondary objectives included the analysis of intraoperative and postoperative complications and trans prosthesis gradients during the first 30 days after surgery.
Methods: A single-center, retrospective, observational study was conducted, including 47 patients between 50 to 85 years of age who underwent surgery for severe AS between 2018 and 2024. All patients underwent AVR with INTUITY RDV via mini sternotomy. Clinical, intraoperative, and postoperative variables were analyzed, together with pre- and post-implantation transprosthetic gradients.
Results: The procedures were successfully completed in 100% of cases, with no conversions to full sternotomy. Median CPB time was 90 minutes, and median clamping time was 65 minutes. The incidence of paravalvular leak was minimal. In the postoperative course, atrial fibrillation was the most common complication (40.4%). Median hospital length of stay was 7 days. No myocardial infarctions, pacemaker implantations, or 30-day mortality were recorded, while one-year mortality was 2.1%. The hemodynamic results were favorable: the maximum gradient decreased from 73.9 ± 21.3 mmHg to 17.2 ± 6.9 mmHg, and the mean gradient from 44.5 ± 13.3 mmHg to 8.6 ± 3.7 mmHg ($p < 0.001$ in both cases). No cases of thrombosis or moderate-to-severe paravalvular leak were observed.
Conclusion: The combination of RDV and a minimally invasive approach proved to be safe, with low morbidity and mortality and excellent short-term hemodynamic improvement.

Key words: Aortic valve stenosis – Aortic valve replacement – Minimally invasive cardiac surgery – Rapid deployment valves

RESUMEN

Introducción: La estenosis aórtica (EAo) es la valvulopatía más frecuente en países desarrollados, y su abordaje ha evolucionado en procura de técnicas que reduzcan el riesgo quirúrgico y aceleren la recuperación, especialmente en pacientes añosos. Dentro de estas innovaciones se encuentran las válvulas de rápido implante (VRI), que combinan la durabilidad de prótesis quirúrgicas convencionales con mecanismos de anclaje derivados del implante valvular aórtico transcatéter (TAVI), disminuyen los tiempos de circulación extracorpórea (CEC) y clampeo aórtico, y facilitan abordajes miniinvasivos como la miniesternotomía.
Objetivos: El objetivo del presente estudio fue evaluar la mortalidad a 30 días y al año posterior al reemplazo valvular aórtico (RVA) mediante miniesternotomía utilizando la VRI INTUITY. Como objetivos secundarios se analizaron complicaciones perioperatorias y el desempeño hemodinámico inicial.
Material y Métodos: Se realizó un estudio observacional, retrospectivo y unicéntrico que incluyó 47 pacientes entre 50 y 85 años intervenidos por EAo grave entre 2018 y 2024. Todos fueron sometidos a RVA con VRI INTUITY, mediante miniesternotomía. Se analizaron variables clínicas, operatorias y postoperatorias, además de los gradientes transprotésicos pre y posimplante.
Resultados: Los procedimientos se completaron con éxito en el 100% de los casos, sin conversiones a esternotomía completa. La mediana del tiempo de CEC fue de 90 minutos y la de clampeo de 65 minutos. La incidencia de fuga paravalvular fue mínima. En la evolución postoperatoria la fibrilación auricular fue la complicación más frecuente (40,4%). La estadía hospitalaria mediana fue de 7 días. No se registraron infartos, colocación de marcapasos ni mortalidad a 30 días, mientras que la mortalidad al año fue del 2,1%. Los resultados hemodinámicos fueron favorables: el gradiente máximo se redujo de 73,9 ±21,3 mmHg a 17,2 ±6,9 mmHg y el

Rev Argent Cardiol 2026;94:270-275. https://doi.org/10.7775/rac.v94.i4.21029

Received: 12/15/2025 – *Accepted:* 05/15/2026

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medio de 44,5 ±13,3 mmHg a 8,6 ±3,7 mmHg (p < 0,001 en ambos casos). No se observaron casos de trombosis ni leak paravalvular moderado o grave.
Conclusión: la combinación de VRI y abordaje miniinvasivo demostró ser segura, con baja morbimortalidad y excelente mejoría hemodinámica en el corto plazo.

Palabras clave: Estenosis de la válvula aórtica - Reemplazo valvular aórtico – Cirugía cardíaca mini invasiva – Válvulas de rápido implante

INTRODUCTION

The most prevalent valvular disease in developed countries frequently involves the aortic valve, and aortic stenosis (AS) is the most common condition. (1) In recent decades, due to increased life expectancy, the treatment of this condition has become increasingly important. The range of therapeutic options has evolved, and all alternatives aim to reduce surgical risk in the general population, particularly among elderly patients. Beginning with aortic valve replacement (AVR) by median sternotomy, progress was made with the development of new transcatheter aortic valve implantation (TAVI) techniques. This treatment was originally developed to provide a less invasive option for high-risk patients and is now not only the gold standard of care for that group but has also been extended to include low- and intermediate-risk patients. (2–4)

The development of rapid deployment valves (RDV) represents an innovation. This device combines the safety and long-term durability provided by the Perimount Carpentier-Edwards valve platform, with an anchoring mechanism derived from transcatheter techniques, reducing pump and aortic clamping times while ensuring a favorable hemodynamic profile. (5–10) The use of these devices facilitates the development of minimally invasive techniques (mini thoracotomy, mini sternotomy, or transaxillary approaches) which, due to their low surgical invasiveness, reduce blood loss, mechanical ventilation time, and the intensive care unit and hospital length of stay, thereby promoting a faster recovery. (11-14) In 2018, our center launched a program using RDV, and the combination of these valves with minimally invasive surgery yielded results similar to those reported in the literature. (12–15) In this study, we present our initial experience in this field at a high-volume valve surgery center.

OBJECTIVES

The primary objective of this study was to evaluate postoperative mortality at one month and one year following AVR via mini sternotomy, using INTUITY rapid-deployment valves (INTUITY Elite, Edwards Lifesciences, Irvine, CA, USA). As a secondary objective, we analyzed the incidence of intraoperative and postoperative complications, as well as pre- and postoperative transprosthetic valve gradients within the first 30 days after surgery.

METHODS

A single-center, retrospective, observational cohort study was conducted, analyzing the electronic medical records of all patients who underwent AVR in the department of cardiovascular surgery at Hospital Italiano de Buenos Aires between March 2018 and July 2024. Patients between 50 to 85 years of age with severe AS meeting diagnostic criteria established by clinical practice guidelines (1–3) were included in the study. These patients underwent surgery via J- or T-shaped mini sternotomy using the INTUITY RDV (INTUITY Elite, Edwards Lifesciences, Irvine, CA, USA), regardless of surgical risk, for both tricuspid and bicuspid valves. Patients who underwent another type of minimally invasive approach [transaxillary, right anterior thoracotomy (RAT)] or full sternotomy, those who received a prosthesis other than a RDV, or had an indication for another associated surgery, and those with infectious endocarditis were excluded from the study.

The following variables were evaluated: a) Clinical: age, sex, body mass index (BMI), cardiovascular history, chronic obstructive pulmonary disease (COPD), prior dialysis, presence of a bicuspid valve, left ventricular systolic function, usual functional class (NYHA), and STS-PROM score; b) Surgical: type of surgery, incidence of conversion to full sternotomy, valve size, prosthetic explantation and use of conventional valve, cardiopulmonary bypass (CPB) and aortic clamping times, and presence of paravalvular leak assessed by transesophageal echocardiography; c) Perioperative complications: prolonged mechanical ventilation (> 48 hours post-surgery), need for intra-aortic balloon pump (IABP), acute myocardial infarction (AMI), ischemic stroke, blood loss within 24 hours, units of red blood cells transfused, need for reoperation due to bleeding, cardiac arrhythmias, pacemaker (PM) implantation, mediastinitis, length of hospital stay, and one-month mortality. The latter was defined as death from a cardiovascular cause related to any adverse event inherent to the prosthetic implant. Finally, pre- and post-prosthetic implant valve gradient values were considered, as well as the incidence of valve thrombosis and prosthetic endocarditis within 30 days of surgery, and one-year mortality.

Statistical analysis

A consecutive sampling technique was used, so all patients who met the eligibility criteria were included. Categorical variables were expressed as frequency and percentage, and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), according to distribution. Preoperative and postoperative transvalvular gradients were compared using Student's t-test for paired samples. A p-value <0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with current national and international regulations: the World Medical Association Declaration of Helsinki, (16) the ICH E6 Guidelines for Good Clinical Practice, Resolution 1480/11 of the National Ministry of Health, and Law 3301/09 of the Government of the City of Buenos Aires (GCBA). The data required for

the study were obtained retrospectively through a review of medical records, and no sensitive data that could identify the patients were reported. All study data were treated with the utmost confidentiality and anonymized, with access restricted solely to authorized personnel for the purposes of the study, in accordance with current legal regulations (Law 25,326). Participation in the study posed no additional risk to the included patients, given its observational nature. The study protocol No. 7523 PRIISA was submitted for review by the institutional Ethics Committee.

RESULTS

The cohort included 47 patients (42.6% male) who underwent rapid deployment aortic valve procedures, with a median age of 79.4 years (IQR 74.5–82.6). Only 5 patients were under 70 years of age. Mean BMI was 27.5 ± 4.56 kg/m2. Hypertension was the most prevalent comorbidity (76.6%), followed by diabetes mellitus (21.3%) and atrial fibrillation (19.1%). In 23.4% of cases, patients had advanced functional class (NYHA III/IV), and the median STS score was 2.7 (IQR 1.83–4.32). (Table 1).

The procedures were successfully performed in 100% of cases. Most procedures were elective (93.6%), with no emergency cases or conversions to full sternotomy. The most used prosthesis sizes were 21 mm (38.3%) and 23 mm (29.8%). Median CPB time was 90 minutes (IQR 80–99), and median aortic clamping time 65 minutes (IQR 56–78.5). No valve explants or use of conventional valves were recorded, and the incidence of paravalvular leak was low, with two cases of mild leak and three cases of trivial leak. (Table 2).

In the postoperative period, the most common complication was atrial fibrillation, observed in 40.4% of patients. The only recorded reoperation for bleeding occurred in a 79-year-old patient, a few hours after admission to the intensive care unit, secondary to coagulopathy (no bleeding was observed at cannulation sites or from the aortotomy). Three cases of mediastinitis requiring subsequent mediastinal debridement were recorded. A single case of a major neurological event was recorded (hemorrhagic stroke 24 hours postoperatively in an 82-year-old patient, with no hemodynamic impact or neurological sequelae), and prolonged mechanical ventilation was rare (4.3%). No myocardial infarctions, need for IABP, or PM implantation due to AV block were reported. Median blood loss in the first 24 hours was 200 mL (IQR 142.5–252.5), and median transfusion requirement was 1 unit of red blood cells (IQR 0–2). Median hospital stay was 7 days (IQR 5–8). There were no deaths at 30 days, and only one death was recorded at one year (2.1%), corresponding to a case of septic shock secondary to prosthetic endocarditis 4 months after the initial surgery. (Table 3).

Mean preoperative valve area was 0.83 ± 0.41 cm². The maximum aortic gradient decreased from 73.9 ± 21.3 mmHg preoperatively to 17.2 ± 6.9 mmHg postoperatively (p<0.001), while mean gradient decreased from 44.5 ± 13.3 mmHg to 8.6 ± 3.7 mmHg

Table 1. Demographic and Preoperative Characteristics (n=47)

Variable	
Age, years, median (IQR)	79.4 (74.5–82.6)
Male sex, n (%)	20 (42.6)
BMI, kg/m², mean (SD)	27.5 (4.56)
Smoking, n (%)	
No	33 (70.2)
Current smoker	2 (4.3)
Former smoker	12 (25.5)
Hypertension, n (%)	36 (76.6)
Diabetes mellitus, n (%)	10 (21.3)
Atrial fibrillation, n (%)	9 (19.1)
Preoperative AMI, n (%)	1 (2.1)
Previous coronary procedure, n (%)	1 (2.1)
Peripheral arterial disease, n (%)	2 (4.3)
Previous cerebrovascular disease, n (%)	3 (6.4)
TIA	1 (2.1)
Ischemic stroke	2 (4.2)
COPD, n (%)	0 (0.0)
Previous dialysis, n (%)	0 (0.0)
Moderate/severe LV dysfunction, n (%)	1 (2.1)
NYHA Class III/IV, n (%)	11 (23.4)
Mean STS %, median (IQR)	2.7 (1.83–4.32)

AMI: acute myocardial infarction; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LV: left ventricular; NYHA: New York Heart Association; SD: standard deviation; TIA: transient ischemic attack; STS: Society of Thoracic Surgeons Risk of Mortality.

Table 2. Perioperative data (n=47)

Variables		
Preoperative status, n (%)		
Elective		44 (93.6)
Urgency		3 (6.4)
Emergency		0
Conversion from mini sternotomy to full sternotomy, n (%)		0
Valve size, n (%)		
	19	6 (12.8)
	21	18 (38.3)
	23	14 (29.8)
	25	9 (19.1)
	27	0 (0.0)
INTUITY explant, n (%)		0 (0.0)
CPB time, min, median (IQR)		90.0 (80.0–99.0)
AoCl time, min, median (IQR)		65.0 (56.0–78.5)
Mild valvular leak, n (%)		2 (4.2)

CPB: cardiopulmonary bypass; AoCl: aortic clamping

(p <0.001). No cases of prosthetic thrombosis or prosthetic endocarditis were recorded within the first postoperative month. (Table 4)

DISCUSSION

Aortic stenosis is the most prevalent valvular heart disease, and given the increase in the number of elderly patients due to higher life expectancy the therapeutic approach progressively takes into account surgical risk, life expectancy, and prosthesis durability when selecting the optimal procedure. This must combine safety, low mortality, low surgical impact, rapid recovery and functional reintegration, along with prosthetic durability and favorable long-term hemodynamic outcomes. (2,3) In the era of TAVI, minimally invasive surgery (J- or T-shaped mini-sternotomy, RAT, transaxillary), together with the use of RDV, represents the surgical alternative that is comparable in terms of minimally invasive approach.

Data from the MISSION study (10)—the only prospective, multicenter study with a 6-month follow-up focused on minimally invasive surgery and RVD—successfully assessed the safety of this combination, reporting an early cardiovascular mortality rate of 0% and a long-term rate of 4.4%. Our series showed favorable results in this regard, with zero mortality within 30 days postoperatively and 2.1% at one year.

In terms of perioperative morbidity, minimally invasive approaches offer multiple advantages, stemming primarily from reduced surgical trauma. They decrease blood loss and polytransfusion, surgical site infections, the duration of mechanical ventilation, and length of hospital stay, while also providing aesthetic benefits and enabling rapid recovery. (11–14)

Table 3. Postoperative results (n=47)

Variable	
Prolonged MRA, n (%)	2 (4.3)
IABP, n (%)	0 (0.0)
Postoperative AMI, n (%)	0 (0.0)
Postsurgical neurological event, n (%)	1 (2.1)
Hemorrhagic stroke	1 (2.1)
Ischemic stroke	0 (0.0)
TIA	0 (0.0)
24-hour bleeding in ml, median (IQR)	200.0 (142.5–252.5)
RBC units over 48 hours, median (IQR)	1.0 (0.0–2.0)
Reoperation due to bleeding n(%)	1 (2.1)
Postoperative atrial fibrillation, n(%)	19 (40.4)
AV block with permanent PM, n (%)	0 (0.0)
Mediastinitis, n (%)	3 (6.4)
Total length of stay, days, median (IQR)	7.0 (5.0–8.0)
30-day mortality, n (%)	0 (0.0)
Mortality at 1 year, n (%)	1 (2.1)

AMI: acute myocardial infarction; AV: atrioventricular; IABP: intra-aortic balloon counterpulsation; IQR: interquartile range; MRA: mechanical respiratory assistance; PM: pacemaker; RBC: red blood cells; TIA: transient ischemic attack.

Table 4. Valvular, and Prosthetic Hemodynamic Outcomes (n = 47)

Variable	
Max preoperative AoV gradient, mmHg, mean (SD)	73.89 (21.27)
Mean preoperative AoV grad, mmHg, mean (SD)	44.47 (13.31)
Preoperative AoV area, cm^2, mean (SD)	0.83 (0.41)
Max postoperative AoV grad , mmHg, mean (SD)	17.15 (6.89)
Mean postoperative AoV gradient, mmHg, mean (SD)	8.61 (3.67)
Valvular thrombosis, n (%)	0 (0.0)
Prosthetic endocarditis, n (%)	0 (0.0)

AoV: aortic valve; Grad: gradient; SD: standard deviation.

These benefits could be offset by the technical difficulty involved in implanting a conventional valve in a confined space, leading to prolonged surgical times, clamping times, and CPB times—all of which are independent predictors of morbidity and mortality. (17,18) It is at this point that RDV play a fundamental role, especially due to their rapid balloon-expandable delivery mechanism, that shortens implantation times and facilitates this type of approach. This argument was supported by Borger et al., (15) who, in a multicenter comparative study, demonstrated that patients undergoing minimally invasive surgery with RDV had 24% reduction in clamping time compared to those undergoing surgery via full sternotomy with a conventional valve.

Although our series yielded clamping and CPB times comparable to those in large-scale international studies such as the TRANSFORM study (19)—in which the mean cross-clamp time in patients undergoing AVR via mini-sternotomy was 62.3 ± 25 min—there are reports of even shorter times, such as that by Schlömicher et al. (20), who reported clamping and CPB times of 26 ± 7 min and 56 ± 16 min, respectively—one of the lowest registries recorded. Nevertheless, our results did not affect the morbidity and mortality of the cohort, which could be attributed to the initial learning curve.

A notable feature of RDV is the higher incidence of PM implantation due to atrioventricular block, reported in the literature as approximately 5% to 13%. (21,22) This is related to patient-dependent factors, such as preoperative bundle branch block, hypertrophic cardiomyopathy, excessive annular decalcification, and factors inherent to prosthesis implantation. (23) This implantation system, which extends the valve to the subannular level, causes direct compression of the conduction system, similar to the mechanism observed during TAVI. Coti et al. demonstrated in their series of 700 patients who underwent RDV that right bundle branch block was the only independent factor associated with the need for permanent PM implantation (9.5%). (24) It should be noted that in our series, there were no cases requiring permanent PM implantation within the first postoperative month. Nevertheless, we believe that careful patient selection is important, and that patients with this conduction disorder should be excluded. Additionally, prosthesis oversizing should be avoided; and in cases of uncertainty regarding whether to implant a larger or smaller prosthesis, the smaller size should be chosen.

Regarding the design of the EDWARDSINTUITY prosthesis, it combines the excellent safety and long-term durability of the Carpentier Edwards-Perimount Magna Ease prosthesis platform (25,26) with a stainless-steel expandable balloon frame that anchors the system subannularly, similarly to the structure of the Sapien transcatheter aortic valve. This has a significant hemodynamic impact, explained primarily, on the one hand, by the absence of pledget-reinforced radial points and the "tobacco pouch" effect they create, thereby optimizing the effective orifice area (EOA); (27) and, on the other hand, because the left ventricular outflow tract—where the stainless-steel frame is anchored—is widened. This has a favorable effect on transprosthetic gradients, as evidenced by the TRITON study, (21) which demonstrated a sustained reduction in gradients with a mean postoperative value of approximately 10 mmHg and an effective orifice area of approximately 1.6 cm^2 at five-year follow-up. Similarly, the TRANSFORM registry, (19) in a cohort of more than 1000 patients, confirmed a significant and stable decrease in gradients (postoperative mean ~10–12 mmHg), reinforcing the reproducibility of the hemodynamic improvement observed with this prosthesis across different clinical scenarios. On the other hand, in patients at high risk of prosthesis-patient mismatch (PPM)—such as those with a small aortic annulus, a large body surface area, or need for a prosthesis smaller than 23 mm—use of 19- or 21-mm RDV prostheses have been shown to maintain adequate transvalvular gradients. With conventional prostheses, this same situation typically requires annular enlargement techniques, which increase operative morbidity and mortality.

In this regard, Coti et al., (29) in a cohort of 217 patients with a small aortic annulus, reported an incidence of moderate and severe PPM of 33% and 10%, respectively, for 19-mm prostheses, and 23% and 9% for 21-mm prostheses. These results highlight a hemodynamic advantage of RDV over TAVI, in which the incidence of severe PPM reaches approximately 40% in patients receiving prostheses of 23 mm or smaller. (30) The long-term stability of the prosthesis, particularly at the ventriculo-aortic junction and in the left ventricular outflow tract, raises questions about the clinical relevance of paravalvular leak in this type of valve. This condition is of particular interest, given that its presence has been consistently associated with increased mortality and long-term cardiovascular events. (28) In our series, no cases of moderate or severe leak were recorded, a relevant finding given the morbidity and mortality associated with this condition following any valve replacement or transcatheter implantation procedure. (10,15,19,21,27)

Limitations

The limitations of this study are those inherent to its observational and retrospective design. That is, there may be selection bias and indication-related confounding issues that contribute to explaining the better outcomes, beyond the benefits of the valve itself. In addition, patients belong to a single center.

CONCLUSION

In our experience, the use of rapid deployment valves via a minimally invasive approach proved to be a safe technique with favorable short-term mortality outcomes and hemodynamic profile.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Prevalence of Hypotension in Elderly Patients with Hypertension Undergoing Antihypertensive Treatment

Prevalencia de hipotensión arterial en hipertensos añosos bajo tratamiento antihipertensivo

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ABSTRACT

Background: Hypotension due to antihypertensive treatment is one of the undesirable effects that can occur in elderly patients with hypertension.
Objective: The aim of this study was to assess the presence and frequency of hypotension—whether symptomatic or not—in patients over 65 years of age receiving antihypertensive therapy using 24-hour ambulatory blood pressure monitoring (ABPM).
Methods: We retrospectively analyzed ABPM data from 12 177 patients, resulting in a final sample size of 1457 studies, all conducted in subjects with isolated systolic hypertension. Fifty-nine percent were women, and mean age was 73.1 years. They were divided into three age groups: 65 to 69, 70 to 79, and over 80 years of age. Hypotension was considered present in four circumstances: daytime systolic blood pressure or 24-hour systolic blood pressure < 100 mmHg, or daytime mean blood pressure or 24-hour mean blood pressure < 73 mmHg, respectively.
Results: Among the 1457 studies analyzed, 57 reported hypotension, and in only 9 of them—15.8%—patients experienced symptoms such as dizziness and weakness. None reported syncope or falls. The mean (standard deviation) of blood pressure recordings for these 57 patients were: daytime mean systolic blood pressure: 98.9 (3.74) mmHg; 24-hour mean systolic blood pressure: 99.8 (3.44) mmHg; daytime mean blood pressure: 68.8 (4.08) mmHg; and 24-hour mean blood pressure: 73.6 (3.62) mmHg. Among the 1457 patients, 2.1 medications per patient were required for blood pressure control, with a predominance of combination therapy, whereas among the 57 patients who presented with hypotension, 43.9% were treated with a single medication and 56.1% with combination therapy. In 28.9% of cases, patients had associated comorbidities.
Conclusions: Our results demonstrated a low prevalence of hypotension in these elderly patients receiving antihypertensive treatment, as well as good blood pressure control.

Key words: Hypotension - Isolated systolic hypertension - 24-hour blood pressure monitoring - Antihypertensive treatment - Ederly hypertensive patients

RESUMEN

Introducción: La hipotensión arterial debido al tratamiento antihipertensivo es uno de los efectos indeseables que pueden ocurrir en hipertensos añosos.
Objetivo: El objetivo de nuestro trabajo fue valorar la presencia y frecuencia de hipotensión arterial ya sea sintomática o no en pacientes mayores de 65 años y bajo tratamiento antihipertensivo utilizando el Monitoreo Ambulatorio de la Presión Arterial de 24hs.
Métodos: Retrospectivamente se analizaron los MAPA de 12177 pacientes, quedando una muestra final de 1457 estudios efectuados todos en sujetos portadores de hipertensión sistólica aislada. El 59% fueron mujeres, y la edad media de 73,1 años. Se los dividió en 3 grupos etarios: de 65 a 69, de 70 a 79 y más de 80 años. Se consideró hipotensión arterial presente en estas cuatro circunstancias: presión arterial sistólica diurna o presión sistólica de 24hs < 100 mm Hg., o presión arterial media diurna o presión media de 24hs < 73 mm Hg. respectivamente.
Resultados: De los 1457 estudios analizados, 57 presentaron hipotensión y en solo 9 de ellos, el 16%, los pacientes experimentaron síntomas como mareos y debilidad. Ninguno manifestó síncopes o caídas. Las medias (desviación estándar) de los registros de presión arterial de estos 57 pacientes fueron: presión sistólica diurna: 98,9 (3,74); presión sistólica media de 24hs: 99,8 (3,44); presión media diurna: 68,8 (4,08) y presión media de 24hs: 73,6, (3,62). En los 1457 pacientes, se necesitaron 2,1 drogas por paciente para el control tensional, con predominio de uso de combinaciones, mientras que, en los 57 pacientes que presentaron hipotensión, el porcentaje de monodrogas empleadas fue del 43,9% y de combinaciones el 56,1%. El 28,9% de los pacientes tenía comorbilidades asociadas.

Rev Argent Cardiol 2026;94:276-282. https://doi.org/10.7775/rac.v94.i4.21007

Received: 03/06/2026 – *Accepted:* 06/10/2026

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Conclusiones: Nuestros resultados demostraron una escasa prevalencia de hipotensión arterial en estos pacientes añosos bajo tratamiento antihipertensivo, y un buen control de la presión arterial.

Palabras clave: Hipotensión arterial - Hipertensión sistólica aislada - Monitoreo de presión arterial de 24hs - Tratamiento antihipertensivo - Hipertensos añososica

INTRODUCTION

Hypertension has a high prevalence among adults aged 60 years or older, reaching 70 to over 80 percent after 70 years of age (1,2), with isolated systolic hypertension (ISH) being the most common form in most cases. (3,4) Isolated systolic hypertension is defined as a systolic blood pressure (SBP) above 140 mmHg with a diastolic blood pressure (DBP) below 90 mmHg. Numerous studies and meta-analyses have demonstrated the clear benefit of treating ISH in elderly patients, including those over 80 years of age. (4–6)

Hypotension caused by antihypertensive drugs, whether symptomatic or not, is one of the most concerning adverse effects in elderly patients with hypertension. It can lead, on the one hand, to the adjustment or discontinuation of medication—with its negative clinical consequences—and, on the other hand, to complications such as falls with a risk of fractures, cognitive impairment, renal dysfunction, and silent cerebral lesions. (7–10)

However, recent studies in the literature have demonstrated the safety and significant reduction in cardiovascular morbidity and mortality in patients whose systolic SBP was lowered to levels close to 120 mmHg or tolerated level through treatment; for example, the recently published Hypertension Guidelines from the European Society of Cardiology suggest a target of 120–129 mmHg for SBP, if well tolerated, for all adult patients up to 85 years of age. (11)

Twenty four-hour ambulatory blood pressure monitoring (ABPM) has demonstrated, among other things, greater accuracy in assessing blood pressure (BP) behavior during daily life and the response to specific treatment. (12,13)

The objective of our study was to assess the presence and frequency of symptomatic and asymptomatic hypotension in elderly patients over 65 years of age who were receiving antihypertensive treatment, using ABPM.

METHODS

We retrospectively analyzed ABPM recordings from 12 177 patients collected between January 2017 and July 2025 at a single center specializing in hypertension in our city. Subjects attended exclusively during the morning hours (between 8:00 a.m. and 10:00 a.m.), when the monitoring device was applied. Among the 12 177 ABPM recordings, 1327 were excluded due to technical deficiencies, leaving a total sample of 10 850 studies. Of these, 1779 (16.4%) were from patients over 65 years of age, of whom 322 were excluded because they were not currently receiving antihypertensive treatment. This left a final sample of 1457 studies for analysis. All patients had ISH and were independent, and several had associated comorbidities.

Of the final sample analyzed, 864 patients (59.3%) were women, with a mean age of 73.1 years (range 65–96). Patients were divided into three age groups: 65 to 69 years (G1, n=539, 37%), 70 to 79 years (G2, n=670, 46%), and 80 years or older (G3, n=248, 17%). (Table 1)

The ABPM studies were performed using calibrated SpaceLabs 90207 and 90217 devices (SpaceLabs Healthcare Company Headquarters: 5150 220th Ave SE, Issaquah, WA 98029, PO Box 7018), in accordance with current technical quality standards and using the normal/abnormal thresholds accepted by the various guidelines of hypertension societies, including national ones. Briefly, the studies had to have at least 70% valid recordings; the absence of only one hourly recording was accepted; and BP values obtained during the afternoon nap were not considered. Hypertension was considered uncontrolled despite treatment when the daytime average was ≥ 135 mmHg for SBP and/or ≥ 85 mmHg for DBP; or when the 24-hour average was ≥ 130 mmHg for SBP and/or ≥ 80 mmHg for DBP. Hypotension is defined as a decrease in systemic blood pressure to below 90 and 60 mmHg for systolic and diastolic blood pressure, respectively, or a mean arterial pressure (MAP) <65. .(14) As the various hypertension guidelines do not clearly define the cutoff levels for classifying hypotension based on ABPM, and given the advanced average age of our patients, we agreed to define hypotension if any of the following four conditions were observed: daytime systolic blood pressure (DSBP) or 24-hour systolic blood pressure (SBP24) <100 mmHg; or daytime mean blood pressure (DMBP) or 24-hour mean blood pressure (MBP24) <73 mmHg, based on a SBP and DBP reading of 99–60 mmHg (DBP + 1/3 of the difference) The daily study reports were analyzed to identify the symptoms reported by the patients.

Statistical analysis

Results were analyzed using descriptive statistics by means of frequencies and percentages for categorical variables and measures of central tendency and dispersion for quantitative variables. Associations between categorical variables were described using contingency tables, and associations between continuous quantitative variables using scatter plots. The chi-square test was used to evaluate associations between categorical variables. A p value <0.05 was considered statistically significant. All analyses were performed using the R software version 2.6.2 (R Core Team, 2008).

Ethical considerations

The study was approved by our institution's Ethics Committee and complied with the requirements of the Declaration of Helsinki. (15).

RESULTS

Mean (standard deviation, SD) BP values obtained in the 1457 patients were as follows: DSBP: 130.01 (12.92) mmHg and SBP24: 126.14 (12.03) mmHg; DMBP: 93.86 (8.86) mmHg; and for MBP24: 90.29 (8.45) mmHg, respectively. Mean BP values showed

statistically significant differences among the three groups, $p < 0.001$. (Table 2)

Among the 1457 studies analyzed, 57 (3.91%) met the criteria for hypotension, and in only 9 of them (16%), patients reported dizziness and weakness as the only symptoms likely attributable to hypotension. None reported more serious effects such as syncope or falls. Mean age for these 57 patients was 68.8 years (Table 1), while BP values showed no significant differences (Table 3)

Of the 57 cases of hypotension, 53.5% (n = 31) corresponded to Group 1, 30.7% (n = 17) to Group 2, and 15.8% (n = 9) to Group 3

The average number of drugs per patient in the 1457 patients were 2.1. Angiotensin II receptor blockers were the most prescribed drugs (48%), followed by calcium channel blockers, diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors, in that order. Of the 1457 patients, 445 (30.5%) were on monotherapy, while 1012 (69.5%) were on combination therapy; among them, 568 (56.1%) were on two drugs; 353 (34.9%) on three drugs; and 91 (8.9%) on three or more drugs. (Figure 1).

Among the 57 patients who suffered hypotension, 25 (43.9%) were on monotherapy, and 32 (56.1%) on combination therapy. In Group 1, 50% were on monotherapy and 50% on combination therapy; in Group 2, 33% were on monotherapy and 66% on combination therapy; and in Group 3, 50% were on monotherapy and 50% on combination therapy.

In 28.97% of cases, the study patients had associated conditions, particularly cardiometabolic disor-

Table 1. Age distribution of the total sample (n=1457) and of patients with hypotension (n=57)

Variable	Total	65 to 69 years	70 to 79 years	80 years or older
Total	1457	539 (37%)	670 (46%)	248 (17%)
Women	864	294 (34%)	400 (46,3%)	170 (19.7%)
Men	593	245 (41.3%)	270 (45,5%)	78 (13.2%)
Average age (years)	73.1			
Hypotension				
Total	57	31 (54.4%)	17 (29.8%)	9 (15.8%)
Women	35	23 (65.7%)	11 (31.4%)	1 (2.9%)
Men	22	8 (36.4%)	6 (27.3%)	8 (36.4%)
Average age (years)	69			

Table 2. Blood pressure recordings obtained in the general population studied (n=1457)

Variable	Total	65 to 69 years	70 to 79 years	80 years or older	P-value
DSBP	130.01 (12.92)	129.14 (13.67)	130.55 (11.9)	130.54 (13.92)	<0.001
SBP24	126.14 (12.03)	125.3 (12.28)	126.56 (11.41)	126.94 (13.12)	< 0.001
DMBP	93.86 (8.86)	94.32 (9.21)	93.76 (8.45)	93.1 (9.16)	< 0.001
MBP24	90.29 (8.45)	90.57 (8.77)	90.24 (8.06)	89.8 (8.77)	< 0.001

DMBP: Daytime Mean Blood Pressure; DSBP: Daytime Systolic Blood Pressure; MBP24: 24-hour Mean Blood Pressure; SBP24: 24-hour Systolic Blood Pressure. Values are presented as mean (standard deviation)

Table 3. Blood pressure values obtained in the population with hypotension (n=57)

Variable	Total	65 to 69 years	70 to 79 years	80 years or older	P-value
DSBP	94.02 (3.74)	94.52 (3.69)	93.88 (4.04)	92.56 (3.28)	0.384
SBP24	93.95 (3.44)	94 (3.71)	93.82 (3.21)	94 (3.24)	0.985
DMBP	71.05 (4.08)	71.77 (3.96)	71.12 (4.43)	68.44 (3)	0.096
MBP24	70.6 (3.62)	71.03 (3.75)	70.71 (3.75)	68.89 (2.62)	0.297

DMBP: Daytime Mean Blood Pressure; DSBP: Daytime Systolic Blood Pressure; MBP24: 24-hour Mean Blood Pressure; SBP24: 24-hour Systolic Blood Pressure. Values are presented as mean (standard deviation

ders. (Figure 2) Patients with heart failure were all hemodynamically stable (FC I–II), and patients with kidney disease had 1 to 3 stage renal failure.

DISCUSSION

Hypertension (HTN) and specially ISH is most prevalent in individuals over 60 years of age. (1,2) The demonstrated benefit in terms of reducing fatal and nonfatal cardiovascular events with the treatment of hypertension in these elderly patients, including those over 80 years of age, is clear. (4,7,16) It is accepted that SBP and other factors, such as pulse pressure, are predictors of cardiovascular events in older adults due to decreased arterial compliance. Current recommendations from various hypertension guidelines, meta-analyses, and randomized prospective studies suggest a target reduction of SBP in these patients to as low as possible or tolerated values, or at least <140 mmHg. (17, 18)

One of the most common clinically undesirable effects of antihypertensive treatment—given the need to lower SBP, especially to the newly suggested levels—is the potential to induce symptomatic or asymptomatic hypotension and cause a reduction in cerebral

Fig. 1. Distribution of antihypertensive treatment (n=1457)

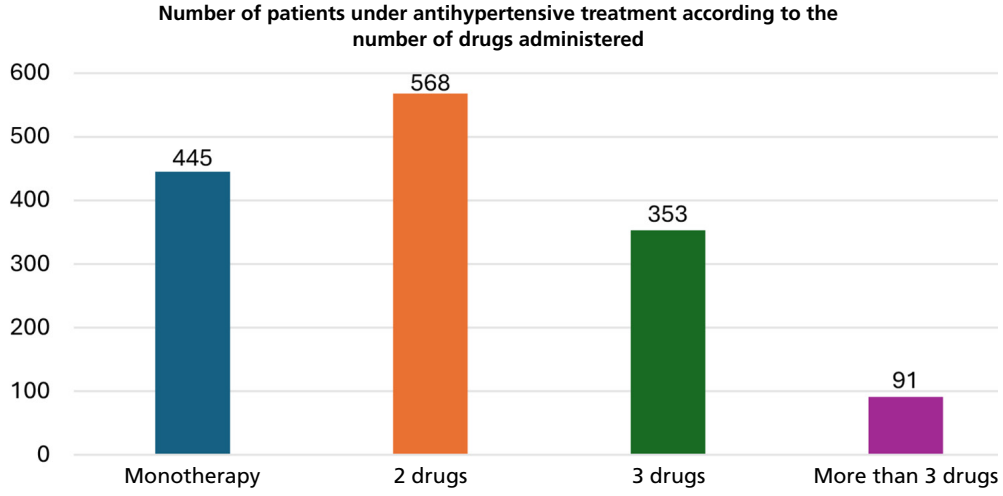
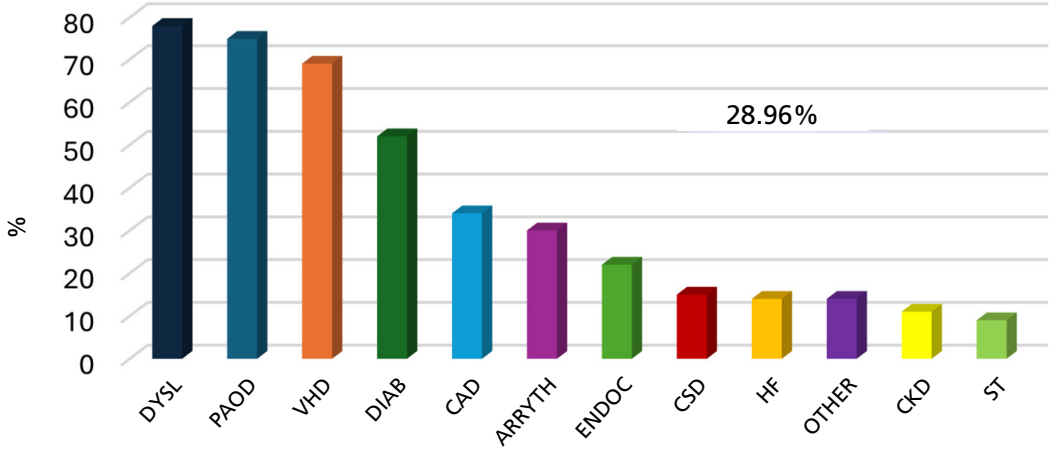


Fig. 2. Associated comorbidities



DYSL = dyslipidemia; PAOD = peripheral arterial occlusive disease; VHD = valvular heart disease; DIAB = diabetes; CAD = coronary artery disease; ARRYTH = arrhythmias; ENDOC = endocrinopathies; CSD = conduction system disease; HF = heart failure; Others: CKD = chronic kidney disease; ST = stroke

perfusion, which can lead to dizziness, orthostatic intolerance, syncope, or falls resulting in injuries of varying severity. (19) Reduced baroreflex sensitivity to hypotensive stimuli, accompanied by a minimal increase in heart rate, lower total body water and chronic conditions, such as Parkinson's disease, diabetes, etc., are some of the altered physiological mechanisms and pathologies that may contribute to the onset of hypotension in these elderly patients undergoing antihypertensive treatment. (20,21)

However, hypotension caused exclusively by antihypertensive treatment appears to be less common than expected. The ONTARGET study, conducted in 8502 patients to compare the efficacy of telmisartan versus ramipril in patients with vascular disease and a high risk of diabetes, showed that only 4.8% experienced symptoms of hypotension and only 0.3% had a syncopal episode.(10) The SPRINT study enrolled 9361 non-diabetic patients at high cardiovascular risk, with the aim of evaluating whether a SBP below 120 mm Hg, compared with under 140 mm Hg, resulted in fewer major fatal and non-fatal cardiovascular events and all-cause mortality. In that study, 2.4% of patients in the intensive treatment group developed hypotension, compared with 1.4% in the less intensive group; the incidence of syncope was 2.3% in the intensive group versus 1.7% in the less intensive group; and the incidence of falls requiring hospitalization was 2.2% in the intensive group and 2.3% in the less intensive group. Paradoxically, orthostatic hypotension was lower in the more intensive treatment group (16.6% vs. 18.3% in the other arm). (17)

The most recent Chinese STEP study enrolled 8511 patients with ISH aged 60 to 80 years—24% of whom were aged 70 to 80 years—, with the aim of evaluating whether intensive treatment (SBP 130 to <110 mm Hg) reduced cardiovascular risk compared with standard treatment (SBP 150 to <130 mm Hg). The incidence of dizziness, syncope, and fractures did not differ significantly between the two groups, although the incidence of hypotension was significantly higher in the intensive treatment group (3.4% vs. 2.6%). (18)

Consistent with the above and despite the fact that other studies have found a prevalence of 20% postural and/or postprandial hypotension in older adults with ISH (22) and others as high as 34%—albeit using daytime cutoff values for hypotension based on ABPM starting at 105 mmHg— (23), in our study, we found that only 57 patients (3.91%) had values within the hypotension range. Of these, only 9 (16%) reported symptoms such as dizziness, weakness (especially in the morning), and fatigue. Aside from those mentioned, none reported other symptoms, nor did any experience fall. Unlike other studies, the low percentage of patients with confirmed hypotension in our study has the added value of having been demonstrated using ABPM. Recognizing that the values obtained by this method correspond more accurately to actual BP values compared with those recorded in the clinic, they may more precisely represent the true prevalence of hypotension in this group of patients.

Another aspect to consider is that many older adults with hypertension have varying degrees of frailty, a condition that makes them more prone to hypotension, falls, and hip fractures. (8,22) In the SPRINT study, (17) which included 815 frail patients, the benefit of more intensive BP control was demonstrated in both older adults and frail adults, with adverse events being similar in the two treatment groups and not dependent on frailty. In our subgroup of patients, although frailty may have been present in any of them, among those over 80 years of age—and despite the fact that 50% were taking combination therapies—only 15.8% (9 patients) experienced hypotension, a finding similar to that reported in the aforementioned SPRINT study, where subjects receiving intensive treatment had lower rates of hypotension than those receiving less intensive treatment. Although our study was not designed to assess frailty, the low incidence of hypotension and symptoms once again reinforce the safety—at least from a clinical perspective—of antihypertensive treatment in this age group, which does not appear to depend on the intensity of the treatment.

Another point of interest is the very good control of SBP observed in the analysis of the studies, since the vast majority of patients had their SBP controlled by treatment to the levels recommended by the guidelines in all three groups, and only a small percentage of them had symptomatic hypotension, which once again confirms the safety of increasing the dosage of antihypertensive medications in these patients until BP reduction targets are achieved. This good BP control may corroborate what has previously been demonstrated by others, namely that elderly hypertensive patients with well-controlled BP on treatment experienced orthostatic hypotension less frequently than those whose BP was uncontrolled, supporting the notion that setting a lower BP reduction target does not appear to cause hypotension. (20,21)

Like younger hypertensive patients, most elderly patients will require two or more medications to control their BP, as demonstrated by large studies such as SHEP and Syst-Eur. (5,24) However, in elderly patients outside of urgent or emergency settings, it seems prudent to reduce SBP values gradually until the target is reached to minimize the risk of ischemic symptoms and, especially, hypotension. (25)

Our patient group was no exception regarding the number of drugs used. Analysis of ABPM data from the 1457 patients revealed that 2.1 drugs per patient were required to control BP, with drug combinations being the most used approach. Although angiotensin receptor blockers were the most frequently used drugs, all major classes of antihypertensive agents were employed without significant differences in the incidence of hypotension, which is consistent with the 2017 American College of Cardiology/American Heart

Association guidelines, which state that first-line drug classes have a low risk of causing hypotension. (12)

Among the 57 patients in whose ABPM study we confirmed hypotension, single-drug therapy was used in 43.9% (n=25) and combination therapy in 56.1% (n=32). Interestingly, when analyzing the three groups, and despite the fact that in the oldest group (G3) 50% of patients were treated with combination therapies, it was this group that recorded proportionally fewer episodes of hypotension, which confirms the current trend of using combination therapies to control SBP in the very elderly, with few side effects. Various guidelines and meta-analyses suggest that the most important factor in reducing cardiovascular risk is lowering BP in both young and elderly patients, rather than the choice of antihypertensive medication. (26) Our findings are consistent with the above and with those observed in other studies, in which the effective use of the main drug classes was well tolerated by elderly patients and associated with few side effects. (27)

In addition to frailty, elderly hypertensive patients generally have various associated comorbidities, whether cardiovascular or not, which demand the administration of different medications that may affect BP by either raising or lowering it. In our study, 28.9% of patients suffered, in addition to hypertension, from various cardiovascular, metabolic, and non-cardiovascular conditions, most under specific treatment. However, despite this, the medications administered together with antihypertensive drugs did not appear to significantly potentiate the risk of hypotension. These findings were previously observed in other studies where no significant association was found between hypotension and other comorbidities; (28) however, other studies reported an association with diabetes mellitus, dementia, and Parkinson's disease. (29)

It has been observed that an excessive decrease in DBP may be associated with an increased risk of cardiovascular events, particularly coronary events. There remains controversy regarding the minimum DBP level that should be targeted, particularly in elderly patients with ISH. Studies such as SHEP and INVEST found a significant increase in cardiovascular events when DBP was ≤60 mmHg, (30,31) as this may compromise tissue and coronary perfusion and possibly increase cardiovascular risk. However, other studies have not found this association and attribute the presence of a J-curve not to adverse effect of treatment, but rather to poor physical condition, comorbidities, and/or other medications. (32) Nevertheless, there is consensus against lowering DBP below 55–60 mmHg. In our analysis, no group average DBP fell below this figure.

Study Limitations

Although all patients were advised before and after the study of the need to record—and effectively recorded in the daily report—any symptoms they were experiencing or had experienced, we have no way of verifying actual compliance with this requirement.

Furthermore, despite having investigated the presence of other comorbidities and the use of other medications—some of which likely affect the arterial vasculature—we cannot rule out the presence of other conditions or the use of other medications not reported in the diary, a common occurrence in elderly patients, which could have influenced the SBP values.

Neither a frailty questionnaire was administered, which could have provided additional information of interest to the study.

CONCLUSION

Our study demonstrated that in elderly patients with ISH undergoing treatment, there was a low incidence of symptoms—and particularly of hypotension—when using the main classes of antihypertensive drugs.

Based on these results and in accordance with the recommendations of most current guidelines, the decision to initiate antihypertensive treatment and the treatment goals should depend less on age and more on frailty and/or associated comorbidities.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Artificial Intelligence–Driven Analysis of Infrared Thermography for Noninvasive Diagnosis of Low Cardiac Output in Critically Ill Patients

Análisis de termografía de infrarrojos mediante inteligencia artificial para diagnóstico no invasivo de bajo gasto cardíaco en pacientes críticos

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ABSTRACT

Background: Skin blood flow plays a key role in thermoregulation and is impaired in hemodynamic shock. Infrared thermography offers a noninvasive method for mapping peripheral temperature and analyzing its performance in patients with hemodynamic instability.
Objective: The aim of this study was to evaluate facial thermal behavior in critically ill patients undergoing invasive hemodynamic monitoring using an infrared camera and to establish the diagnostic value of artificial intelligence-driven analysis for diagnosing low cardiac output.
Methods: We conducted a cross-sectional study of critically ill patients undergoing pulmonary artery catheter monitoring. Facial thermal images were obtained using an infrared camera simultaneously with measurements of hemodynamic parameters obtained via invasive monitoring. Six predefined facial regions were analyzed, and individual and average temperatures and thermal gradients were calculated. Thermal data were processed using machine learning to predict a cardiac index < 2.5 L/min/m².
Results: A total of 35 monitoring sessions were performed on 18 patients (age 60 ± 14 years, 70% male). Sixty percent were in shock, and 40% were in the postoperative period following cardiovascular surgery; 54% were receiving ≥ 2 vasoactive drugs. Most infrared facial thermography analyses had a significant association with cardiac index, and the thermal gradient (TG) was the variable with the strongest correlation (r = –0.45; p = 0.010). The neural network model achieved an area under the ROC curve of 0.75 for predicting low cardiac output.
Conclusions: In this proof-of-concept study, facial thermography identified regions and gradients with a significant correlation with cardiac index. Its integration with artificial intelligence demonstrated a promising biological signal for detecting low cardiac output, emerging as an alternative to noninvasive hemodynamic monitoring in the critical care setting.

Key words: Thermography - Artificial intelligence - Hemodynamics - Critical care - Shock - Heart failure - Monitoring

RESUMEN

Introducción: El flujo sanguíneo cutáneo desempeña un papel clave en la termorregulación, y se ve alterado en estados de shock hemodinámico. La termografía infrarroja ofrece un método no invasivo para mapear la temperatura periférica y analizar su comportamiento en pacientes con inestabilidad hemodinámica.
Objetivo: Evaluar el comportamiento térmico del rostro de pacientes críticos bajo monitoreo hemodinámico invasivo, mediante el uso de cámara infrarroja. De manera secundaria, por medio de inteligencia artificial, establecer el valor diagnóstico de dicho método para bajo gasto cardíaco.
Material y métodos: Estudio transversal en pacientes críticos bajo monitoreo con catéter de arteria pulmonar. Se obtuvieron imágenes térmicas faciales con cámara infrarroja simultáneamente a la realización de mediciones hemodinámicas invasivas. Se analizaron seis regiones faciales predefinidas y se calcularon temperaturas aisladas, promedios y gradientes térmicos. Los datos fueron procesados mediante *machine learning* para predecir un índice cardíaco <2,5 L/min/m².
Resultados: Se realizaron 35 monitoreos en 18 pacientes (edad 60±14 años, 70 % hombres). El 60 % presentaba shock y el 40 % estaba en posoperatorio cardíaco; 54 % recibía ≥2 drogas vasoactivas. La mayoría de los análisis térmicos faciales mostraron correlación significativa con el índice cardíaco (mejor correlación, gradiente térmico (GT): r = –0,45; p = 0,010). El modelo de redes neuronales alcanzó un área bajo la curva ROC de 0,75 para predecir bajo gasto.

Rev Argent Cardiol 2026;94:283-288. https://doi.org/10.7775/rac.v94.i4.21036

SEE RELATED ARTICLE: Rev Argent Cardiol 2026:94:251-252. https://doi.org/10.7775/rac.v94.4.21040

Received: 11/07/2025 – *Accepted:* 03/05/2026

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This study won the Cossio Award at the 51st Argentine Congress of Cardiology

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Conclusiones: En esta prueba de concepto, la termografía facial identificó regiones y gradientes con correlación significativa con el índice cardíaco. Su integración con inteligencia artificial exhibió una señal biológica prometedora para la detección de bajo gasto cardíaco, perfilándose como una alternativa a explorar para el monitoreo hemodinámico no invasivo en el entorno crítico.

Palabras clave: Termografía - Inteligencia artificial - Hemodinamia - Cuidados críticos - Shock - Insuficiencia cardíaca - Monitoreo

INTRODUCTION

Hemodynamic monitoring is an essential component for the management of critically ill patients, and cardiac output (CO) is recognized as one of the primary indicators of circulatory status. Throughout history, Fick's method and thermodilution via a pulmonary artery catheter (PAC) have been considered the gold standard. Their invasive nature entails significant risks, including arrhythmias during insertion (ranging from 12.5% to over 70%). Clinically significant ventricular arrhythmias occur in less than 1%. Catheter-associated bacteremia is another complication occurring in approximately 1.3%–2.3% of cases. (1,2) These limitations have driven the development of less invasive or noninvasive alternatives for assessing hemodynamic status.

Among minimally invasive methods, transpulmonary thermodilution—as represented by devices such as PiCCO— (3,4) uses a central venous catheter and an arterial catheter, although it has limitations in patients undergoing extracorporeal therapies or with intracardiac shunts. Transpulmonary lithium dilution, (5,6) available in systems such as LiDCO, requires the injection of lithium chloride and an arterial sensor, which limits its use in patients undergoing lithium therapy or exposed to certain muscle relaxants. Arterial pressure waveform analysis using the FloTrac/Vigileo or MostCare systems is another alternative that estimates beat-by-beat stroke volume without requiring calibration in some systems. Nevertheless, the accuracy of this analysis may be reduced in states of vasoplegia or in the presence of ventricular assist devices. (7-9) The accuracy of these methods may be limited in patients with pacemakers, pulmonary hypertension, or severe valvular regurgitation. (10,11) Transthoracic and transesophageal Doppler echocardiography provide information on blood flow and cardiac morphology, but require specific training and exhibit interobserver variability. In addition, esCCO system, based on pulse oximetry, electrocardiography, and peripheral pulse wave analysis, has demonstrated a favorable correlation with thermodilution in selected studies. (9-12) However, the evidence regarding these techniques is characterized by significant methodological heterogeneity, small sample sizes, and limited safety information, although the incidence of adverse effects appears to be low. (12) Furthermore, costs are variable, ranging from esophageal Doppler—an affordable option—to PiCCO, one of the most expensive minimally invasive alternatives. (9-12)

In this context, infrared thermography emerges as a promising, fully noninvasive, and low-cost tool that captures infrared radiation from tissues and helps identify abnormalities in peripheral perfusion. Its clinical potential has been evaluated in heart failure, where recent studies have shown that, when combined with artificial intelligence (AI) algorithms, it can differentiate patients with acute decompensated heart failure from controls, with an interesting sensitivity and an area under the ROC curve of 0.82. (13) Similarly, ocular surface temperature, measured using thermography, has shown a correlation with core body temperature (14,15) and an association with cardiovascular outcomes, such as acute myocardial infarction and long-term prognosis in animal models. (16) This evidence suggests that infrared thermography could become a diagnostic and clinical monitoring tool applicable in critical care settings and telemedicine contexts, providing a safe and accessible alternative to current hemodynamic strategies.

METHODS

We conducted a cross-sectional study in the Critical Care Cardiology Unit of two tertiary hospitals. We included patients consecutively admitted and undergoing invasive PAC monitoring, indicated by clinical criteria independent of this protocol. Patients with a history of facial surgery or trauma, severe facial edema, active infections, ocular or facial devices, and any condition that could alter anatomy or thermal patterns were excluded from the study. The study protocol was approved by the institutional review board and complied with the Declaration of Helsinki. (17)

For each patient, three serial facial thermal images were obtained using a portable infrared camera (FLIR ONE®, FLIR Systems Inc.) with a resolution of 160 × 120 pixels and a spectral range of 8–14 μm. The photos were taken simultaneously with three hemodynamic measurements obtained using the PAC, and the values were averaged for analysis. The photos were taken in the supine position, 10 cm from the face in a room with controlled environmental temperature, avoiding the influence of external heat sources or drafts.

The images were analyzed using specialized thermography software. A blinded evaluator selected six facial regions of interest: forehead, right cheek, left cheek, nose, and the inner corners of both eyes. Three types of variables were calculated in these regions: 1) individual temperatures per region (T), 2) average temperatures across different regions (AT), and 3) thermal gradients between regions (TG) (Figure 1). Subsequently, a second blinded evaluator compared the thermal parameters with the hemodynamic variables obtained via the PAC.

Thermal data were processed using machine learning to identify the optimal predictive model for a cardiac index (CI) < 2.5 L/min/m^2, defined as low cardiac output.

Qualitative variables are expressed as numbers and percentages and quantitative variables are expressed as mean and standard deviation. The association between categorical variables was explored using the chi-square test or Fisher's test, while the Student's t test or the Wilcoxon rank sum test was used for quantitative variables. The Pearson or Spear-

man correlation coefficients were used to measure the relationship between quantitative variables. A p-value < 0.05 was considered statistically significant. Discriminative ability was evaluated using ROC curves and calculating the area under the curve (AUC), along with sensitivity, specificity, and predictive values. The study protocol was approved by an institutional review board. Patients' identities were protected because the characteristics of the thermal images do not allow for facial identification.

RESULTS

A total of 18 patients underwent 35 hemodynamic monitoring sessions, with 9 patients undergoing 2 or more monitoring sessions. Mean age was 60 ± 14 years and 70% were men. The causes of hospitalization were heart failure in 50% of cases, postoperative care following cardiovascular surgery in 39%, and non-cardiovascular causes in 11% of cases. The indication for hemodynamic monitoring was shock in 60% of cases, and postoperative complications following cardiovascular surgery in 40%. Seventeen (94.4%) patients required vasoactive drugs; 2 drugs or greater were used in 19 (54.3%) monitoring sessions. These agents included dobutamine and norepinephrine in more than 50% of cases, milrinone in 27%, and epinephrine and nitroglycerin in < 10%.

During hemodynamic monitoring with the PAC, CO was calculated using the thermodilution method in 31 measurements (88.6%). Low cardiac output occurred in 18 cases (51.4%), with the following values: mean arterial pressure (MAP), 74.5 ± 7.8 mmHg; heart rate (HR), 95.7 ± 21.2 beats/min; mean pulmonary artery pressure (MPAP), 26.2 ± 8.7 mmHg; pulmonary capillary wedge pressure (PCWP), 12.2 ± 4.9 mmHg; central venous pressure (CVP), 7.3 ± 4.2 mmHg; cardiac index (CI), 2.6 ± 0.6 L/min/m^2; systemic vascular resistance (SVR) 1123.3 ± 260.1 dyn·s cm^{-5}; and pulmonary vascular resistance (PVR), 168 ± 87.4 dyn·s·cm^{-5}. Twenty-five percent of patients were on mechanical ventilation.

A total of 105 thermographic images were obtained. The thermal data that showed the strongest correlation with the CI were, respectively: T1, 35.55 ± 1.84 °C (r = 0.42, p = 0.010); T3, 34.48 ± 2.45 °C (r= 0.37, p = 0.021), T4, 35.74 ± 1.48 °C (r = 0.41, p = 0.012), AT1 (average between T1 and T4), 34.99 ± 1.47 °C (r = 0.43, p = 0.014) and GT (gradient between T1 and AT1), 1.32 ± 0.59°C (r = −0.45, p = 0.010). There were also some significant correlations between SVR and CVP (Table 1), but not with PCWP, HR, MPAP and MAP. Except for T2, all thermal measurements correlated with CI, and the best value was obtained with TG (Figure 2).

Fig. 1. Facial thermographic image of a patient acquired with an infrared camera (FLIR ONE). The regions measured are indicated: T1 (glabellar region), T2 (inner corner of the eyes), T3 (nasal root), and T4 (alar groove). The color scale indicates temperature variations in °C.

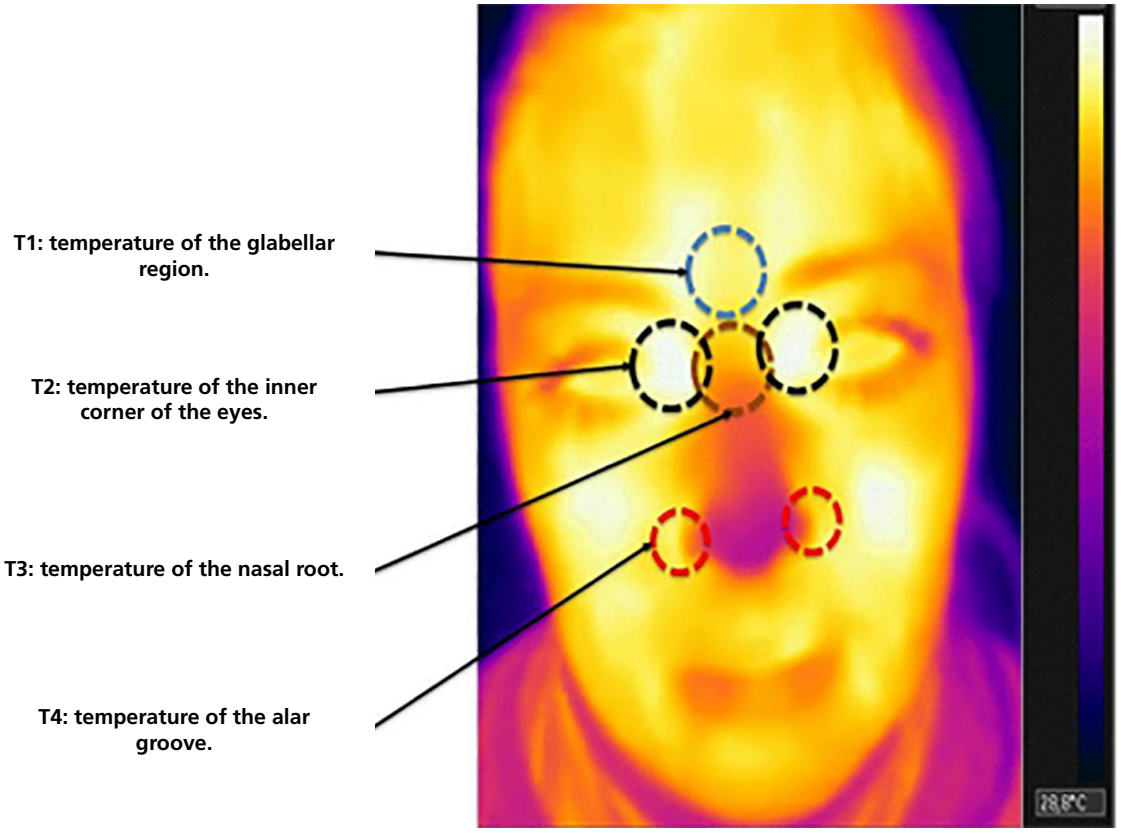
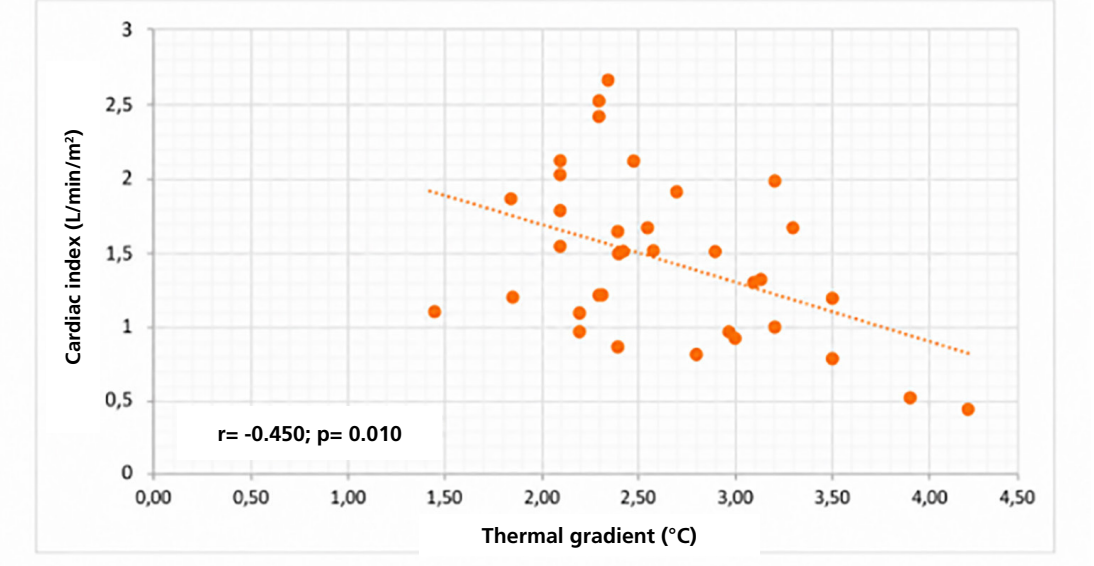


Table 1. Thermal values and their correlation with cardiac index.

Hemodynamic variable	T1	T2	T3	T4	AT=1	AT=1
CVP	r = 0.42; p = 0.010	r = 0.32; p = 0.506	r = 0.37; p = 0.020	r = 0.35; p = 0.033	r = 0.4; p = 0.010	NS
MPAP	NS	NS	NS	NS	NS	NS
PCWP	NS	NS	NS	NS	NS	NS
MAP	NS	NS	NS	NS	NS	NS
HR	NS	NS	NS	NS	NS	NS
CI	r = 0.42; p = 0.010	NS	r = 0.37; p = 0.021	r = 0.41; p = 0.012	r = 0.43; p = 0.010	r = -0.45; p = 0.010
SVR	r = -0.36; p = 0.030	NS	r = -0.35; p = 0.041	r = -0.44; p = 0.010	r = -0.41; p = 0.010	NS
PVR	NS	NS	NS	NS	NS	NS

CI: cardiac index; CVP: central venous pressure; HR: heart rate; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; NS: non-significant; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; T: individual temperature by region; TG: thermal gradient; TP: average temperature.

Fig. 2. Correlation between facial thermal gradient (TG) and cardiac index (CI). A significant inverse association is observed (r = –0.45; p = 0.01).



The best model to predict low cardiac output with the use of AI was a neural network with an AUC-ROC of 0.75 (95% CI 0.61–0.89), sensitivity of 75.0%, specificity of 60.0%, positive predictive value of 81.82%, and negative predictive value of 50.00% (Figure 3).

DISCUSSION

This study demonstrates that infrared facial thermography, integrated with AI, can identify significant correlations with CI, particularly through thermal gradients. These findings are consistent with previous evidence demonstrating that thermography had a sensitivity of 84% and a specificity of 52% to detect acute decompensated heart failure. (13) Additionally, recent studies describe how skin thermoregulation is abnormal in heart failure, with a slower and reduced thermal response during exercise, particularly in patients with reduced ejection fraction. (18,19) This thermal dysfunction reflects impaired peripheral perfusion and progression toward advanced stages of the disease.

It is worth noting that the correlation between peripheral temperature and CI is not a novel finding. (19,20) In 1969, Joly and Weil published a pioneering study demonstrating that hallux temperature was a sensitive marker of peripheral hypoperfusion and cor-

Fig. 3. ROC curve for predicting CI <2.5 L/min/m², using a neural network model based on facial thermography.

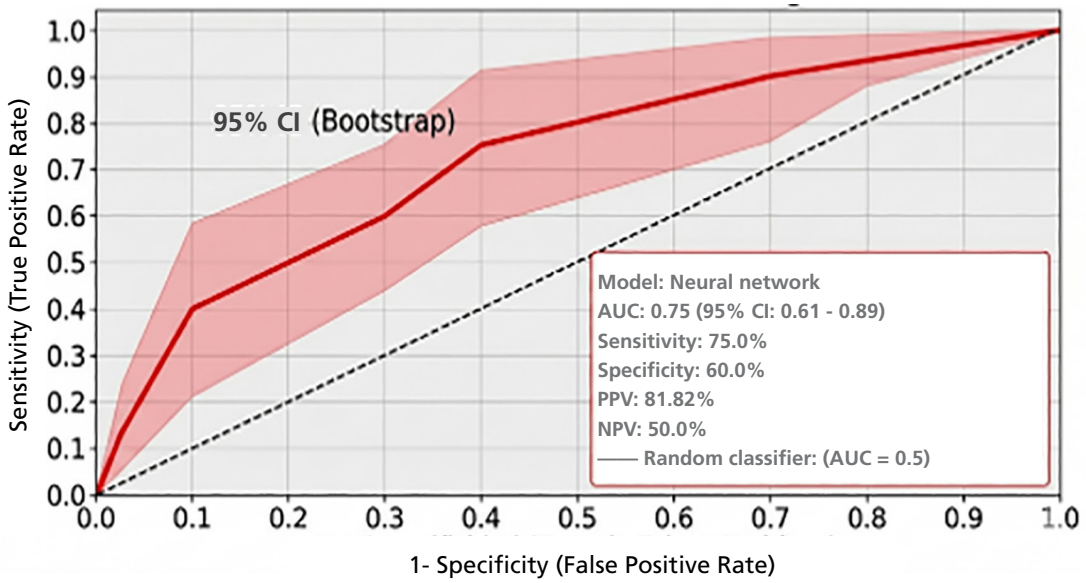
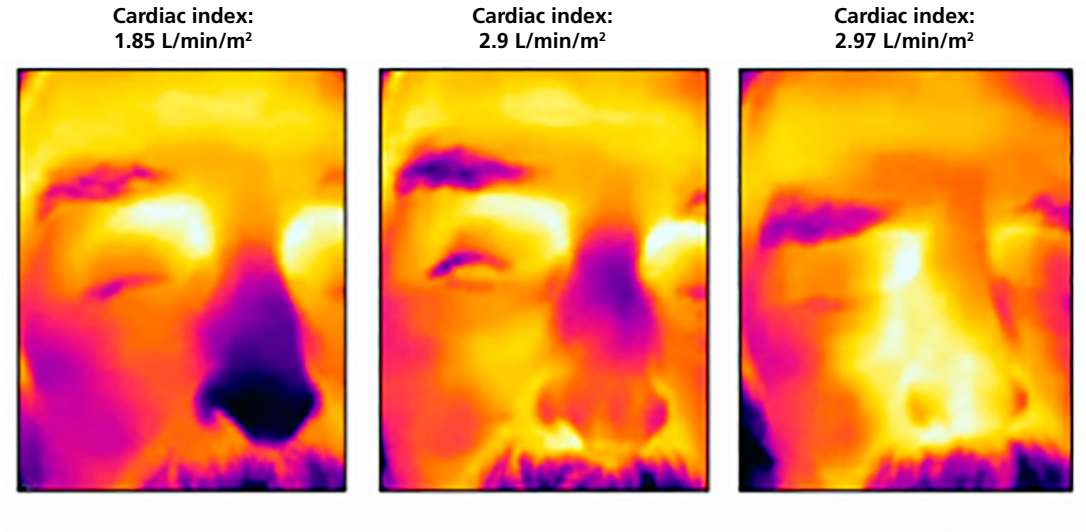


Fig. 4. Facial thermographic images of a patient with cardiogenic shock across three distinct hemodynamic states. From left to right, a progressive improvement in cardiac index (1.85, 2.9, and 2.97 L/min/m²) is observed, with the corresponding thermal changes on the color scale (white = higher temperature, black = lower temperature).



related with cardiac output in patients with shock. (21) That paper laid the physiological basis for considering skin temperature as an indirect reflection of circulatory status, predating modern applications of thermography by several decades. Our results extend this observation to facial thermal analysis, further incorporating AI algorithms to optimize diagnostic capability.

The strength of this study lies in a standardized protocol using simultaneous thermal imaging with invasive CI monitoring in critically ill patients, regional facial analysis, and AI-driven processing. This enabled robust correlations with CI, providing a novel diagnostic approach. This is the first report to combine facial thermography, simultaneous invasive monitoring, and AI-driven analysis, offering a fully noninvasive, rapid, and cost-effective tool with potential applications in telemedicine and critical care.

However, some limitations should be considered. The modest sample size and clinical heterogeneity —with a high proportion of patients presenting with

shock or post-cardiac surgery— restrict the generalizability of the results. Furthermore, the predictive ability of the AI-driven model, with an AUC of 0.75, is promising but requires external validation in larger and more homogeneous cohorts. It is not yet known whether these thermal patterns vary among specific subtypes of heart failure (based on ejection fraction, among other factors). Additionally, the temporal evolution of thermal patterns following hemodynamic interventions was not evaluated—although individual patient analyses revealed thermal–hemodynamic concordance (Figure 4)— nor was its utility explored in outpatient or remote monitoring.

In line with recent reviews, medical thermography has multiple valid applications, such as the early detection of vascular or inflammatory changes, and detection of subtle thermal variations that precede structural abnormalities. (14) However, it is essential to remember that thermography is a complementary physiological tool and does not replace conventional structural methods, such as echocardiography or cardiac catheterization, among others. As such, thermography could serve as a novel complementary diagnostic tool in critical care, and its integration with AI offers clear advantages over current alternatives due to its noninvasive, rapid, and cost-effective nature.

CONCLUSION

Infrared facial thermography showed an association with cardiac index in critically ill patients, with the thermal gradient being the variable with the strongest correlation. Integration with artificial intelligence enabled the identification of a physiological signal with potential utility for detecting low cardiac output.

Given the exploratory nature of the study, the limited sample size, and the absence of external validation, these findings should be interpreted with caution. Prospective studies with a larger number of patients and robust analytical method are needed to confirm the diagnostic value and define the applicability of this method.

Acknowledgments

We are grateful to the critical care teams at the participating hospitals.

Conflicts of interest

None declared.

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

Funding

This research did not receive any specific grant.

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ORIGINAL ARTICLE

Current Evidence on the Lipid-Lowering Efficacy and Safety of Oral PCSK9 Inhibitors: A Systematic Review and Meta-analysis.

Evidencia actual sobre la eficacia hipolipemiante y seguridad de los inhibidores orales de PCSK9: revisión sistemática y metaanálisis

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ABSTRACT

Background: Inhibition of the proprotein convertase subtilisin/kexin type 9 (PCSK9) is a well-established therapeutic strategy for significantly reducing low-density lipoprotein cholesterol (LDL-C) levels. In recent years, new oral PCSK9 inhibitors have been developed, providing emerging evidence regarding their lipid-lowering efficacy and safety profile.
Objective: The aim of this study was to update the available evidence on the efficacy and safety of oral PCSK9 inhibitors.
Methods: A systematic review and meta-analysis was conducted following the PRISMA statement guidelines. Randomized clinical trials evaluating oral PCSK9 inhibitors versus placebo or other lipid-lowering drugs were included. Percent changes in lipid parameters and the occurrence of adverse events were analyzed. Studies that could not be included in the quantitative analysis were described qualitatively.
Results: Ten randomized clinical trials were included in the qualitative analysis, of which six met the criteria for inclusion in the meta-analysis. Five oral PCSK9 inhibitors were identified. Three of them (enlicitide, laroprovstat and NNC0385-0434) provided data for the quantitative analysis, while the other two (DC371739 and CVI-LM001) were evaluated descriptively. Compared with placebo, oral PCSK9 inhibitors were associated with significant reductions in LDL-C [mean difference (MD) -57.83%; 95% confidence interval (CI) -60.48% to -5.18%; I^2 = 23%] and apolipoprotein B (MD -49.02%; 95% CI -53.61 to -44.42%; I^2 = 76.3%). Similarly, decreases were observed in non-HDL cholesterol (MD -53.48%; 95% CI -57.61% to -49.36; I^2 = 56.5%), triglycerides (MD -15.44%; 95% CI -15.96% to -14.92%; I^2 = 0.0%) and lipoprotein(a) (MD -24.86%; 95% CI -29.50% to -20.21; I^2 = 99.2%). No significant differences in the incidence of adverse events were observed between oral PCSK9 inhibitors and placebo in the included studies.
Conclusion: Oral PCSK9 inhibitors appear to offer lipid-lowering efficacy comparable to that achieved with currently approved subcutaneous therapies, without any relevant safety concerns.

Key words: Oral PCSK9 inhibitors - LDL cholesterol - Safety - Meta-analysis

RESUMEN

Introducción: La inhibición de la proproteína convertasa subtilisina/kexina tipo 9 (PCSK9) constituye una estrategia terapéutica bien establecida para reducir de manera significativa los niveles de colesterol asociado a lipoproteínas de baja densidad (C-LDL). En los últimos años han surgido nuevos inhibidores de PCSK9 de administración oral, que aportan evidencia emergente sobre su eficacia hipolipemiante y su perfil de seguridad.
Objetivo: Actualizar la evidencia disponible sobre la eficacia y seguridad de los inhibidores orales de PCSK9 .
Métodos: Se realizó una revisión sistemática con metaanálisis siguiendo las recomendaciones de la declaración PRISMA. Se incluyeron ensayos clínicos aleatorizados que evaluaron inhibidores orales de PCSK9 versus placebo u otras drogas hipolipemiantes. Se analizaron los cambios porcentuales de los parámetros lipídicos y la aparición de eventos adversos. Los estudios que no pudieron incluirse en el análisis cuantitativo se describieron de forma cualitativa.
Resultados: Se incluyeron diez ensayos clínicos aleatorizados en el análisis cualitativo, de los cuales seis cumplieron los criterios para ser incorporados en el metaanálisis. Se identificaron cinco inhibidores orales de PCSK9. Tres de ellos (enlicitide, laroprovstat y NNC0385-0434) aportaron datos para el análisis cuantitativo, mientras que los otros dos (DC371739 y CVI-LM001) fueron evaluados de forma descriptiva. En comparación con placebo, los inhibidores orales de PCSK9 se asociaron con reducciones significativas del C-LDL [diferencia de medias (DM) -57,83 %; intervalo de confianza (IC) 95% -60,48 % a -5,18 %; I^2 = 23%] y de la apolipoproteína B

Rev Argent Cardiol 2026;94:289-300. https://doi.org/10.7775/rac.v94.i4.21026

Received: 05/27/2026 – *Accepted:* 07/01/2026

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(DM -49,02 %; IC 95% -53,61% a -44,42 %; I^2 = 76,3%). Asimismo, se observaron descensos en el colesterol no-HDL (DM -53,48 %; IC 95% -57,61% a -49,36; I^2 = 56,5%), en los triglicéridos (DM -15,44 %; IC 95% -15,96% a -14,92 %; I^2 = 0,0%) y en la lipoproteína(a) (DM -24,86 %; IC 95% -29,50% a -20,21; I^2 = 99,2%). No se evidenciaron diferencias significativas en la incidencia de eventos adversos entre los inhibidores orales de PCSK9 y placebo en los estudios incluidos.
Conclusión: Los inhibidores orales de PCSK9 parecen ofrecer una eficacia hipolipemiante comparable a la alcanzada con las terapias actualmente aprobadas de administración subcutánea, sin evidenciar señales relevantes de seguridad.

Palabras clave: Inhibidores orales de PCSK9 - Colesterol LDL - Seguridad - Metaanálisis

INTRODUCTION

Elevated concentrations of lipoproteins with atherogenic potential are consistently associated with both the initial onset and recurrence of cardiovascular events. (1) The available, robust, and reproducible clinical and genetic evidence has conclusively established low-density lipoprotein cholesterol (LDL-C) as a causal factor in the development of atherosclerotic cardiovascular disease. (2)

According to current clinical practice guidelines, the initial management of dyslipidemia in patients at high cardiovascular risk is based on the use of statins at the maximum tolerated dose. (3–5) When, despite this intervention, LDL-C levels do not reach therapeutic targets—particularly in patients with established atherosclerotic cardiovascular disease or severe forms of hypercholesterolemia—it is recommended to intensify treatment by adding other lipid-lowering agents, including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid.

Pharmacological inhibition of PCSK9 has established itself as an effective strategy for achieving substantial reductions in LDL-C and lowering cardiovascular risk. Subcutaneous administration of monoclonal antibodies, such as evolocumab and alirocumab, on a biweekly or monthly strategies, has demonstrated reductions of nearly 60% in LDL-C levels, along with a significant decrease in cardiovascular events in high-risk patients on statin therapy. (6, 7) Similarly, the small interfering RNA, inclisiran, enables approximately 50% sustained reductions in LDL-C through a regimen that includes an initial dose, a second administration at 3 months, and subsequent maintenance doses every 6 months. (8, 9) Furthermore, safety assessments of these drugs (monoclonal antibodies and inclisiran) have not identified any significant signs of concern. The most common adverse events were injection-site reactions, the vast majority of mild intensity that did not require any intervention.

Although both therapeutic strategies have been shown to be capable of enabling most patients at high or very high cardiovascular risk to achieve the recommended LDL-C targets, their widespread implementation is limited by their high cost and the need for subcutaneous administration. In this context, the development of small, orally administered PCSK9 inhibitors could represent a more accessible and practical alternative for the treatment of hypercholesterolemia. (10) Although information on the price of these drugs once they are marketed is not yet available, the introduction of new therapeutic alternatives could promote greater competition in the market and, thereby, help reduce the costs of currently available treatments, regardless of their final price.

In recent years, new data have emerged providing evidence on the lipid-lowering efficacy and safety profile of these emerging agents, (11–20) and our research group published a systematic review on this topic. (21) However, given the emergence of new evidence over the past year, the objective of the present study was to provide an update through a systematic review and meta-analysis of the available evidence on the efficacy and safety of oral PCSK9 inhibitors.

OBJECTIVES

The aim of this study was to identify and reach consensus on therapeutic strategies for patients > 80 years with AF or ACS, stratified by robustness, mild frailty, and moderate frailty.

METHODS

Search and Data Collection Strategy

This systematic review was conducted in accordance with the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (22) and was registered in PROSPERO. A comprehensive literature search was conducted to identify studies evaluating oral PCSK9 inhibitors published up to April 20, 2026. Two independent reviewers searched various databases, including PubMed/MEDLINE, Scielo, Latindex, and the Cochrane Library, using both MeSH terms and relevant keywords, including “oral PCSK9 inhibitors,” “AZD0780,” “Laroprovstat,” “MK-0616,” “Enlicitide,” “CVI-LM001,” “NNC0385-0434,” and “DC371739.” In PubMed, Boolean operators were applied as follows: ("PCSK9 Inhibitors"[MeSH Terms] OR "PCSK9 inhibitor"[tiab]) AND (oral[tiab] OR orally[tiab]). In the SciELO and Latindex databases, free-text searches were conducted using terms in English and their Spanish equivalents, such as “PCSK9 inhibitors” and “inhibidores de PCSK9,” combined with the term “oral.” Subsequently, a manual review of titles and abstracts was conducted to identify relevant clinical studies. In the Cochrane Library, the search was conducted in the CENTRAL database (Cochrane Central Register of Controlled Trials), using terms such as “PCSK9 inhibitors” and “oral,” with the aim of identifying randomized clinical trials.

Grey literature was also explored, including records on ClinicalTrials.gov, congress presentations, and material available on pharmaceutical company websites. Additionally, the reference tracking (snowballing) technique was used to identify additional publications. There were no language restrictions.

Inclusion and exclusion criteria

Clinical trials in humans were considered eligible, specifically randomized studies evaluating the lipid-lowering efficacy and safety of oral PCSK9 inhibitors compared with placebo or other lipid-lowering drugs. Opinion articles, narrative or systematic reviews, and observational studies were excluded.

Outcome variables

Percent changes in lipid parameters and the incidence of clinically relevant adverse events were analyzed. The lipid markers evaluated included LDL-C, non-HDL cholesterol, apolipoprotein B (ApoB), triglycerides, and lipoprotein(a) [Lp(a)]. Safety was assessed by analyzing all reported adverse events. Additionally, serious adverse events were considered, defined as those resulting in death, being life-threatening, requiring hospitalization or prolonging hospitalization, causing significant disability, or being considered clinically relevant by the investigator.

Quality Assessment

The risk of bias was analyzed using the Cochrane Collaboration tool designed for this purpose. (23) The RoB-2 tool assesses five domains: randomization process, deviations from the planned intervention, incomplete data, outcome measurement, and selection of reported outcomes. Each domain was classified as "low risk," "high risk," or "some concerns," and an overall score was assigned to each study.

Statistical Analysis

Initially, a qualitative synthesis was performed of the studies that met the inclusion criteria. Subsequently, a meta-analysis was conducted on those studies that reported sufficient data for quantitative pooling. Regarding the doses included, the maximum reported doses were considered for NNC0385-0434 and laroprovstat (AZD0780), since the optimal dose in advanced stages has not yet been defined and both drugs demonstrated acceptable safety profiles. In the case of enlicitide (MK-0616), the 18-mg dose was selected from the study by Ballantyne et al., (11) due to its similarity to the dose used in subsequent studies [20 mg in the CorReef program and in the Johns et al. study (17)]. For each study, the percent changes in lipid parameters and the frequency of relevant adverse events were calculated. The results were expressed as mean difference (MD) or relative risk (RR), with their respective 95% confidence intervals (95% CI). When data were not reported as mean and standard deviation, conversion methods previously described in the literature were used. (24) Heterogeneity among studies was assessed using the I^2 statistic. Fixed-effect or random-effect models were used depending on the degree of heterogeneity observed. The Z-test was used to compare effects between subgroups. A p-value <0.05 (two-sided) was considered statistically significant. The analysis was performed using the R statistical software (version 3.5.1). (25)

Sensitivity Analysis

The sensitivity analysis was restricted to those lipid markers for which five or more studies were available, since, in contexts with a small number of studies, the exclusion of a single study could disproportionately alter the pooled estimates and compromise the robustness of results.

Publication bias

No formal assessment of publication bias was conducted due to the small number of included studies, which limits the validity of tools such as funnel plots or specific statistical tests, whose use is recommended only when enough studies are available.

RESULTS

The search strategy identified a total of 239 registries. After excluding 211 duplicates and irrelevant studies, 28 full-text articles were evaluated, of which 18 were excluded for failing to report the exposure or outcomes of interest. The study selection process is presented in Figure 1.

The qualitative analysis included two abstracts (11, 17) and eight full-text articles, (12-16, 18-20) and six of the latter provided sufficient information on lipid parameters to be included in the quantitative synthesis (meta-analysis) (13-15, 17–19). Table 1 summarizes the main characteristics of the studies considered in this systematic review.

The quality of the evaluated studies is shown in Figure 2. It should be noted that studies available only as abstracts were not evaluated, due to the limited information, which prevents an adequate assessment of the risk of bias. Overall, three studies were classified as having a low risk of bias, while five raised some concerns, mainly related to biases arising from deviations from the planned intervention, absence of complete data on outcomes, and the selection of reported results.

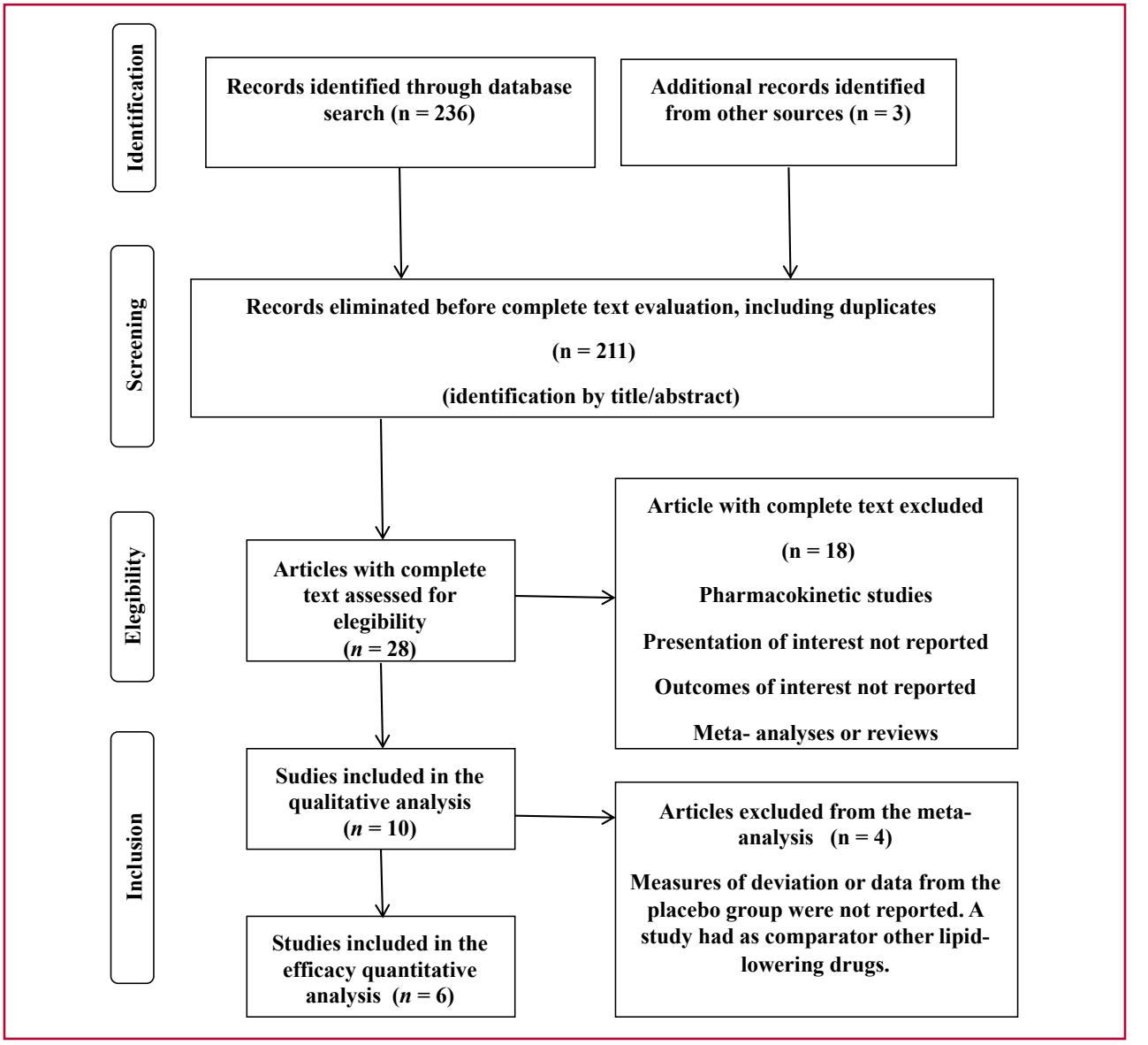
Regarding the assessment of lipid-lowering efficacy, four of the studies included in the qualitative synthesis could not be incorporated into the quantitative analysis.

One of these was a Phase 1 trial designed to evaluate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of laroprovstat, administered both as monotherapy and in combination with standard treatment (rosuvastatin). (16) In a subgroup of 35 participants with hypercholesterolemia (LDL-C between 100 and 190 mg/dL), rosuvastatin 20 mg daily was administered for 3 weeks, followed by administration of laroprovstat 30 mg or placebo for an additional period. Following this initial phase with rosuvastatin, laroprovstat 30 mg achieved a 52% reduction in LDL-C (95% CI: -57% to -45%). This study was not included in the meta-analysis because the number of patients assigned to each group was not clearly specified, nor were the percent changes in lipid levels in the placebo group reported.

The second study was a small, placebo-controlled Phase Ib clinical trial. (11) In this study, administration of CVI-LM001 at a dose of 300 mg reduced LDL-C and ApoB levels by 26.3% and 17.4%, respectively, compared with baseline values in subjects with hypercholesterolemia. However, it was not possible to include this study in the quantitative analysis due to the absence of measures of dispersion and the lack of detailed data from the placebo group.

A third study evaluated DC371739 in the context of a Phase I clinical trial. (12) In this study, LDL-C showed a significant decrease of 19.1% compared with placebo, while triglycerides and ApoB were reduced by

Fig. 1. Flowchart of the study selection process.



27.1% and 25.3%, respectively. Once again, the available information proved insufficient for quantitative analysis, which prevented its inclusion in the meta-analysis.

Finally, a fourth study was not included in the meta-analysis. (20) Unlike the previous studies, its exclusion was not due to incomplete data but rather to its specific methodological nature, as it is the only study identified comparing an oral PCSK9 inhibitor with other lipid-lowering strategies, which limited its comparability with the rest of the included evidence. This was a phase III, randomized, double-blind, active-controlled trial including adults on statin therapy with a history of atherosclerotic cardiovascular disease or high cardiovascular risk and elevated LDL-C levels. Participants were randomized to receive enlicitide, bempedoic acid, ezetimibe, or a combination of the latter two for 56 days. Enlicitide achieved a 64.6% reduction in LDL-C (95% CI: -68.3% to -60.9%), which was significantly greater than that observed with bempedoic acid (-6.3%; 95% CI: -13.5% to 0.8%), ezetimibe (-27.8%; 95% CI: -32.3% to -23.4%) or their combination (36.5%; 95% CI: -40.8% to -32.2%), with consistent results also observed for ApoB, and non-HDL cholesterol (all p <0.001). The incidence of adverse events was similar across the groups.

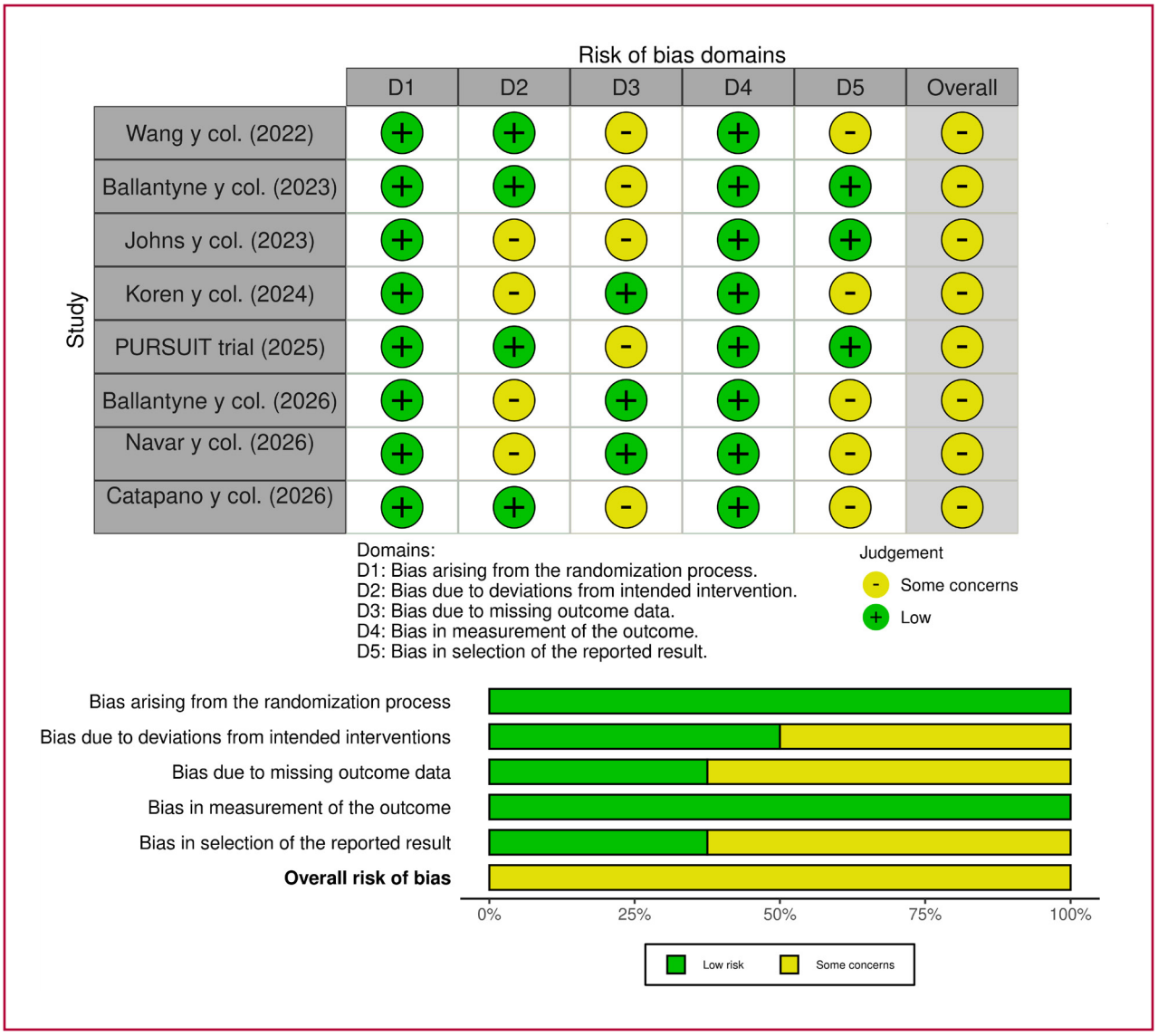
The remaining studies (n = 6) could be quantitatively assessed. In this case, our study showed that oral PCSK9 inhibitors significantly reduced LDL-C levels compared with placebo (MD -57.83%; 95% CI: -60.48% to -55.18%; I^2 = 23 .0%), as well as ApoB levels (MD -49.02%; 95% CI: -53.61% to -44.42%; I^2

Table 1. Characteristics of the studies included in the systematic review

Study (year)	Intervention	n	Population	Follow-up (weeks)
Liu et al. (2020) (11)	CVI-LM001, 200 or 300 mg/day versus placebo.	32	Chinese subjects aged 18 to 65 years with mild hypercholesterolemia (LDL-C ≥ 3.2 mmol/L and ≤ 4.88 mmol/L).	4
Wang et al. (2022) (12)	DC371739, 40 mg/day versus placebo.	20	Chinese subjects with hypercholesterolemia.	4
Johns et al. (2023) (13)	Enlicitide, 10 or 20* mg/day versus placebo.	40	Patients on statin therapy. Mean age was 57.7 years, and 67.5% were men.	2
Ballantyne et al. (2023) (14)	Enlicitide, 18 mg/day* versus placebo.	152#	Participants aged ≥18 and ≤80 years who had to fall into one of the following categories: 1) clinical atherosclerotic cardiovascular disease with LDL-C ≥70 and ≤160 mg/dL; 2) intermediate or high risk with LDL-C ≥100 and ≤200 mg/dL; or 3) borderline risk with LDL-C ≥130 and ≤250 mg/dL. Participants were also on stable lipid-lowering therapy. Mean age was 62 years, and 51% were men.	8
Koren et al. (2024) (15)	NNC0385-0434, 100 mg/day* versus placebo.	107#	Individuals with established atherosclerotic cardiovascular disease (≥40 years) or at high risk of developing it (>50 years), with LDL-C levels of at least 70 mg/dL and receiving statins at the maximum tolerated dose and stable lipid-lowering therapy. Mean age was 64.3 years, and 69% were men	12
Vega et al. (2024) (16)	Laroprovstat, 30 mg/day* versus placebo.	35	Subjects with hypercholesterolemia (LDL-C ≥100 mg/dL and ≤190 mg/dL) treated with 20 mg of rosuvastatin.	4
PURSUIT trial. (2025) (17)	Laroprovstat, 30 mg/day* versus placebo.	172#	Patients with LDL-C levels ≥70 mg/dL and <190 mg/dL, and triglycerides <400 mg/dL, on stable doses of moderate- or high-intensity statins, with or without ezetimibe at the start of the study. Mean age was 62.4 years, and 52.1% were men.	12
Ballantyne et al. (2026) (18)	Enlicitide 20 mg/day versus placebo.	303	Participants aged 18 years or older with heterozygous familial hypercholesterolemia, receiving lipid-lowering therapy (at least moderate- or high-intensity statins), and who had an LDL-C levels ≥55 mg/dL with a history of atherosclerotic cardiovascular disease, or an LDL-C level ≥70 mg/dL without a history of atherosclerotic cardiovascular disease. Mean age was 52.4 years, and 49% were men.	52
Navar et al. (2026) (19)	Enlicitide 20 mg/day versus placebo.	2,909	Adults with a history of atherosclerotic cardiovascular disease and LDL-C levels ≥55 mg/dL, as well as those with intermediate/high cardiovascular risk and LDL-C levels ≥70 mg/dL. Mean age was 62.8 years, and 60.7% were men.	52
Catapano et al. (2026) (20)	Enlicitide 20 mg/day versus ezetimibe 10 mg/day, bempedoic acid 180 mg/day, or the combination of bempedoic acid and ezetimibe at those doses.	301	Adults with a history of atherosclerotic cardiovascular disease and LDL-C levels ≥55 mg/dL, as well as those with intermediate/high cardiovascular risk and LDL-C levels ≥70 mg/dL. Mean age was 64.5 years, and 63% were men.	8

*This dose was selected for inclusion in the quantitative lipid analysis.
Sum of participants in the selected active arm and the placebo arm.

Fig. 2. Quality assessment of the studies included in the review.



= 76.3%) (Figure 3). Similarly, treatment with these drugs was associated with significant reductions in non-HDL cholesterol (DM -53.48%; 95% CI: -57.61% to -49.36%; I^2 = 56.5%), triglycerides (DM -15.44%; 95% CI: -15.96% to -14.92%; I^2 = 0 .0%), and Lp(a) (MD -24.86%; 95% CI: -29.50% to -20.21%; I^2 = 99.2%) compared with placebo. (Figure 4)

Regarding safety, of the nine studies comparing an oral PCSK9 inhibitor with placebo, six reported total adverse events and eight reported serious adverse events, allowing for a combined quantitative analysis. Our findings showed no significant differences in the outcomes assessed between oral PCSK9 inhibitors and placebo. (Figure 5)

Sensitivity analysis confirmed the robustness of the findings regarding LDL-C, ApoB and LP(a) (Figures 6 and 7).

DISCUSSION

In this systematic review and meta-analysis, treatment with oral PCSK9 inhibitors was associated with significant reductions in lipid levels, with no observed differences in the incidence of adverse events compared with placebo.

The binding of PCSK9 to the low-density lipoprotein receptor (LDLR) directs this receptor toward lysosomal degradation, preventing its recycling to the hepatocyte surface and thereby decreasing the clearance of circulating LDL-C. (26) Consequently, PCSK9 inhibition increases the availability of functional LDLRs on the cell membrane, resulting in greater removal of LDL-C from the plasma.

To date, various lipid-lowering therapeutic strategies aimed at inhibiting PCSK9 have been developed and approved. (27) All of them are administered sub-

Fig. 3. Percentage reduction in LDL-C and apolipoprotein B levels with oral PCSK9 inhibitors. Fixed- and random-effects models, mean difference (MD), 95% confidence intervals (CI), and I² statistic.

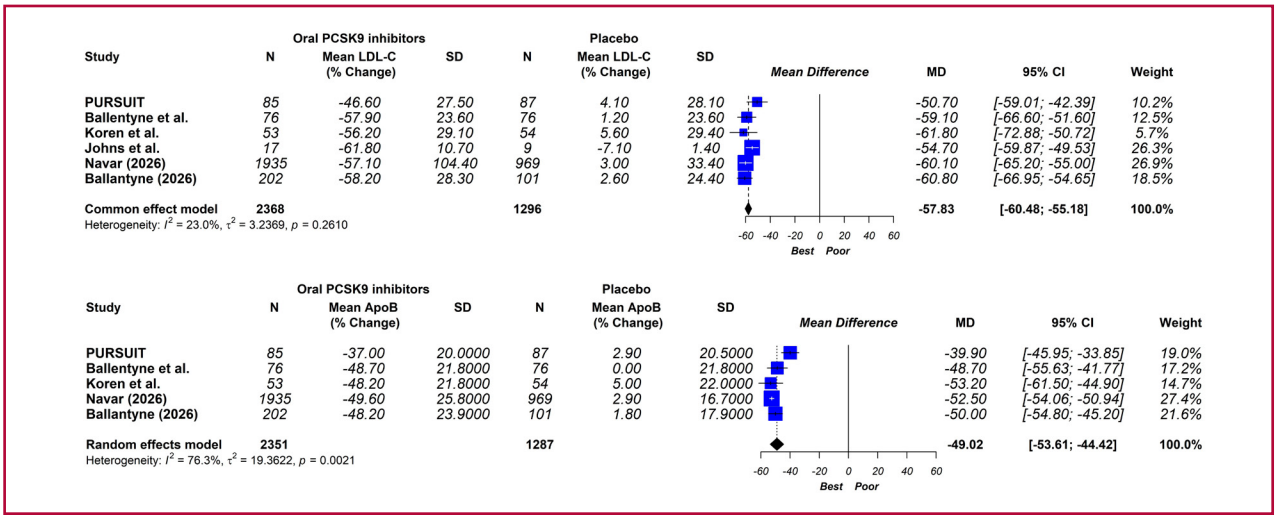
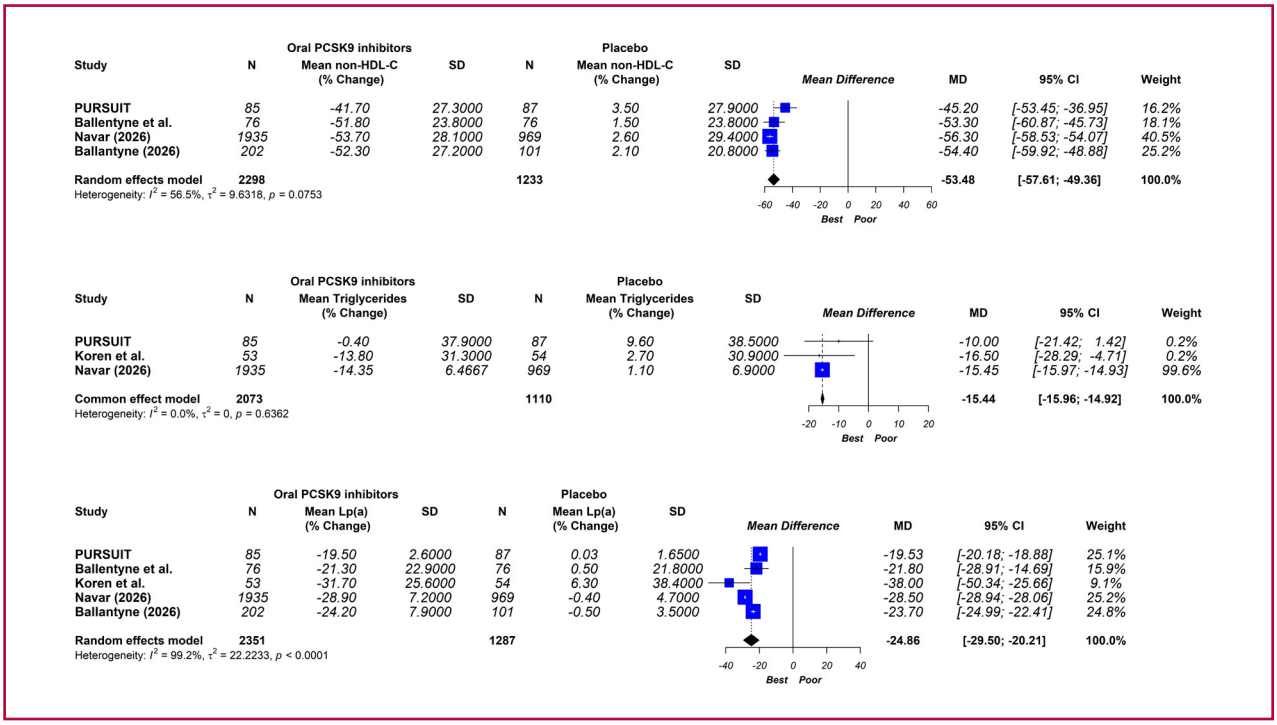


Fig. 4. Percentage reduction in non-HDL cholesterol, triglyceride, and lipoprotein(a) levels with oral PCSK9 inhibitors. Fixed- and random-effects models, mean difference (MD), 95% confidence intervals (CI), and I² statistic.



cutaneously and act through two main mechanisms: inhibition of PCSK9 functional activity in the extracellular space via monoclonal antibodies (alirocumab and evolocumab), or reduction of its hepatic synthesis at the intracellular level via a small double-stranded interfering RNA (inclisiran). Recently, an additional agent with an innovative mechanism of action has been approved: lerodalcibep, a recombinant protein engineered by fusing human serum albumin with a PCSK9-specific adnectin-like binding domain. (28) This molecule has been shown to reduce LDL-C levels by 50% in patients with heterozygous familial hypercholesterolemia, as well as in individuals with cardiovascular disease or at high cardiovascular risk. (29, 30) In addition, a fifth drug has been evaluated in two clinical trials conducted in China, which have

Fig. 5. Safety analysis. Fixed-effect and random-effects models, relative risk (RR), 95% confidence intervals (CI), and I² statistic.

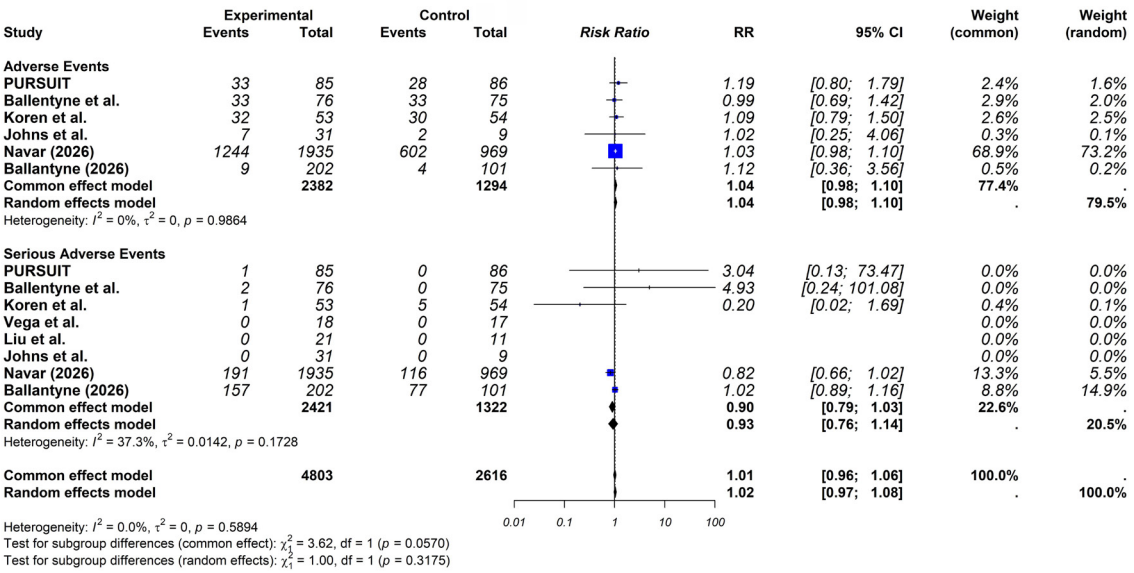
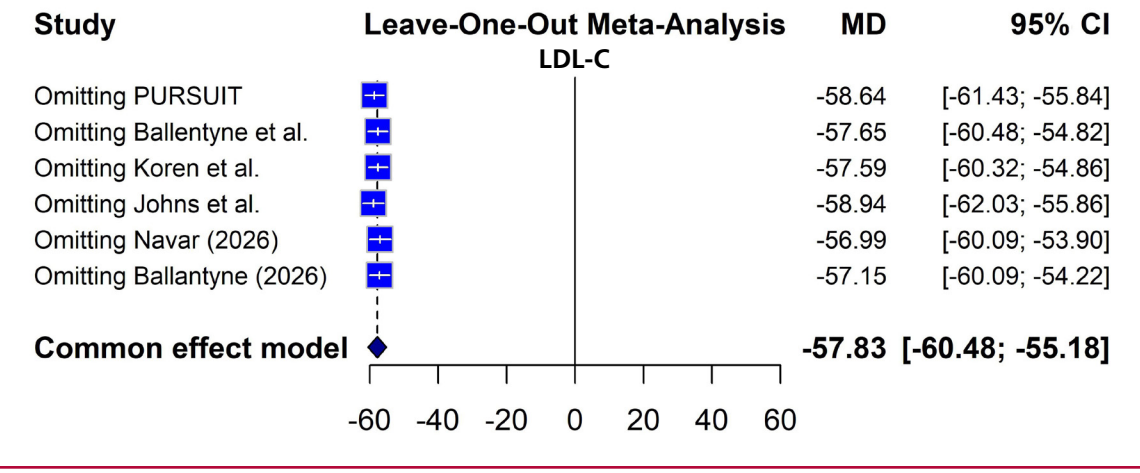


Fig. 6. Sensitivity analysis of studies evaluating the percentage reduction in LDL-C.

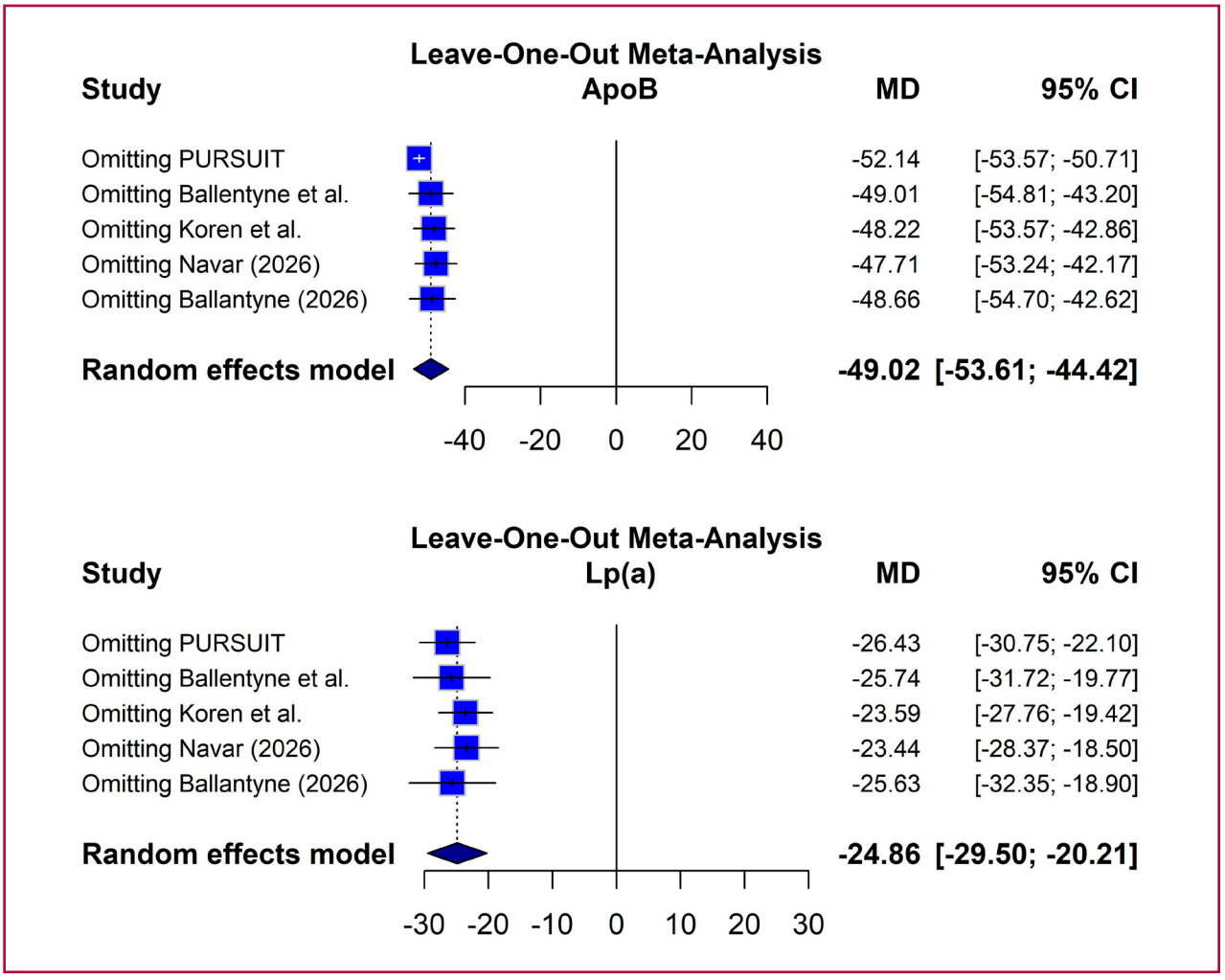


shown that recaticimab—a humanized monoclonal antibody with a prolonged half-life and less frequent dosing—reduces LDL-C levels by approximately 50% as monotherapy and by up to 62% when added to statin therapy. (31, 32)

Subcutaneous administration can be uncomfortable and poorly tolerated by many patients. Furthermore, current PCSK9-targeted therapies are considerably more expensive than other available options, particularly oral lipid-lowering agents, constituting a significant barrier for access to these treatments. (33) In this context, there has been growing interest in the development of oral PCSK9 inhibitors for reducing LDL-C. (10)

Our study evaluated the currently available evidence on five oral PCSK9 inhibitors. Three agents (enlicitide, laroprovstat, and NNC0385-0434) were included in the quantitative analysis, showing significant reductions in LDL-C and ApoB levels, consistent with those reported for injectable PCSK9 inhibitors. (34, 35) A ≥50% reduction in LDL-C levels constitute a clinically relevant outcome, as it represents a target strongly recommended by current guidelines, especially in patients at high or very high cardiovascular risk. (3–5) Moreover, the observed reduction in ApoB levels is also of great clinical importance, as this marker reflects more accurately the total number of atherogenic particles and has been proposed as an

Fig. 7. Sensitivity analysis of studies that evaluated the percentage reduction in apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)].



additional lipid target in high-risk patients who have already achieved the LDL-C target. (4, 36) While the development and research of enlicitide and laroprovstat continue to advance, it is important to note that, at the end of 2022, the development of NNC0385-0434 was discontinued by the sponsor for strategic reasons. (37) In contrast, LDL-C reduction with the other two agents (DC371739 and CVI-LM001) was more modest, ranging from approximately 19% to 26%.

The variability observed among the different drugs could be attributed, at least in part, to differences in their underlying mechanisms of action. Oral PCSK9 inhibitors comprise structurally diverse molecules that act at different levels of the PCSK9–LDLR axis. (10) Transcriptional inhibitors, such as DC371739 and CVI-LM001, reduce PCSK9 expression by interfering with transcription mediated by hepatocyte nuclear factor 1α and by stabilizing the LDLR mRNA; (38, 39) additionally, CVI-LM001 activates hepatic AMPK, reducing triglyceride synthesis and promoting fatty acid oxidation. In contrast, laroprovstat binds directly to PCSK9, while macrocyclic peptides such as enlicitide and NNC0385-0434 mimic the EGF-A domain of the LDLR or bind to the catalytic site of PCSK9, thereby blocking the interaction between PCSK9 and the LDLR. (40)

Another important finding of our meta-analysis is that oral PCSK9 inhibitors can significantly reduce Lp(a) levels by approximately 25%. This effect is consistent with what has been previously reported for other PCSK9 inhibition strategies, such as monoclonal antibodies (29%) and inclisiran (22%). (41) However, although some preliminary data suggest that the cardiovascular benefit associated with PCSK9 inhibition may be more pronounced in patients with elevated baseline Lp(a) levels, the clinical impact of this reduction on Lp(a) has not yet been fully defined. (42)

The CORALreef AddOn study demonstrated that

the PCSK9 inhibitor enlicitide achieved significantly greater reductions in LDL-C compared with standard non-statin oral therapies (bempedoic acid, ezetimibe, and their combination) in patients on statins. (20) Although this study was not included in the quantitative analysis due to the absence of a placebo group, the analysis of the arm treated with the oral PCSK9 inhibitor showed, at 8 weeks, a mean LDL-C reduction of 64.6%. This magnitude is comparable to that previously observed in studies with injectable monoclonal antibodies and is consistent with the overall findings of this meta-analysis. Similar findings are evidenced when analyzing other atherogenic markers, such as ApoB, non-HDL cholesterol, and Lp(a).

Finally, this meta-analysis did not reveal any significant safety concerns. Oral administration of these drugs eliminates the injection-site reactions typical of the subcutaneous route used by their predecessors, which constitutes a potential clinical advantage. However, the short follow-up period in many of the included studies limits the ability to fully assess long-term safety. In fact, randomized clinical trials are not the most appropriate design for detecting and evaluating rare, late-onset, and/or unexpected adverse effects related to drug safety. (43) Furthermore, the highly homogeneous populations resulting from restrictive inclusion criteria means that these studies are not suitable for comprehensively describing the safety profile of the medications.

In the context of increasingly stringent lipid-lowering targets that are often not achieved in clinical practice, (44,45) the development of new lipid-lowering therapies represents a significant advance. Future large-scale studies will be necessary to confirm their efficacy and safety, as well as to assess the cardiovascular impact of these new drugs. (46)

This meta-analysis has several limitations. First, clinical heterogeneity was observed among the studies, stemming from differences in the characteristics of the included populations, and in some cases, considerable statistical heterogeneity was also evident. Second, the lack of detailed information in some original studies limited a comprehensive assessment of their methodological quality. Third, the small number of studies included reduces the power of formal tests to detect publication bias and limits the ability to perform sensitivity analyses, which in this study were restricted to LDL-C, ApoB, and Lp(a). Finally, for some of the agents evaluated, the optimal dose has not yet been definitively established in more advanced-phase clinical trials.

CONCLUSION

According to the evidence synthesized in this systematic review, oral PCSK9 inhibitors may offer lipid-lowering efficacy comparable to that observed with other subcutaneously administered PCSK9 inhibition strategies. In addition, a randomized clinical trial demonstrated that, in patients treated with statins, these drugs are more effective than other alternatives such as ezetimibe or bempedoic acid for reducing LDL-C. In terms of safety, no relevant signals were identified. However, it is important to note that the evidence available to date remains limited and preliminary, based on a small number of studies. In this context, the clinical trials currently underway will be key to providing more robust and definitive information.

DECLARATIONS

Authorship

All authors listed meet the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE) for this article, assume responsibility for the integrity of the work as a whole and have approved the final version for publication.

Author Contributions

WM and ML participated in the conception and design of the study. WM, LB, and GG contributed to data collection. The interpretation of the results and statistical analysis were performed by WM and ML. WM, ML, JPN, and GG drafted the manuscript. All authors critically reviewed the final draft.

Funding

None.

Conflicts of interest

None declared.

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

Ethical Approval

This work is based on previously published studies and does not include research conducted by the authors on humans or animals.

Use of Artificial Intelligence

During the preparation of the manuscript, an artificial intelligence tool (ChatGPT, OpenAI) was used exclusively to improve aspects of style and writing. The tool did not intervene in the generation of scientific content, data analysis, or the interpretation of results. The authors assume full responsibility for the final content of the article.

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ORIGINAL ARTICLE

Treatment Gap in Very High-Risk Patients with Cardiorenal Disease: An Analysis of the Implementation of Evidence-Based Therapies

Brecha terapéutica en pacientes de muy alto riesgo con enfermedad cardiorrenal: análisis de la implementación de terapias basadas en la evidencia

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ABSTRACT

Background: In patients with type 2 diabetes mellitus (T2DM) and cardiorenal disease, various therapies reduce cardiovascular and renal events. However, their implementation in clinical practice remains suboptimal.
Objective: To quantify the treatment gap in patients with T2DM and very high-risk cardiorenal disease using a proportional index that differentiates between Class IA and IIA indications, and to evaluate associated clinical factors.
Methods: An observational study based on data collected prospectively from the FERICODIAB registry. The study included 367 adults with T2DM and heart failure (HF) and/or chronic kidney disease (CKD). Therapeutic eligibility criteria were established according to international guidelines, and a weighted treatment gap index (prop-TGI), ranging from 0 (no treatment gap) to 1 (complete treatment gap), was developed. Associated factors were evaluated using multivariate linear regression and, as a sensitivity analysis, beta regression was performed.
Results: The mean age was 70.0 ± 11.1 years; 61.6% were men, 80.7% had CKD, and 25.6% had HF. The mean TGI-IA was 0.491 (median: 0.483), and 45.4% had an TGI-IA >0.5. The mean TGI-IIA was 0.454 (median: 0.778), and 51.2% had an TGI-IIA >0.5. The largest gaps were observed for finerenone (98.5%), GLP-1 receptor agonists (84.4%), and the combinations of finerenone + SGLT2 inhibitors (97.7%) and SGLT2 inhibitors + GLP-1 receptor agonists (90.9%). Older age, higher body mass index, and female sex were associated with a larger treatment gap in the linear model, although the associations with age and female sex were no longer statistically significant in the beta regression model.
Conclusion: There is a significant treatment gap between recommendations and their implementation, particularly for the most recent cardiorenal therapies and recommended combination therapies. Systematic and interdisciplinary strategies are needed to optimize their use.

Key words: Type 2 diabetes mellitus - Chronic kidney disease - Heart failure - Cardiovascular disease - Treatment gap - Evidence-based treatment

RESUMEN

Introducción: En pacientes con diabetes mellitus tipo 2 (DM2) y enfermedad cardiorrenal, diversas terapias reducen los eventos cardiovasculares y renales. Sin embargo, su implementación en la práctica clínica continúa siendo subóptima.
Objetivo: Cuantificar la brecha terapéutica en pacientes con DM2 y enfermedad cardiorrenal de muy alto riesgo mediante un índice proporcional, diferenciando indicaciones de clase IA y IIA, y evaluar los factores clínicos asociados.
Material y métodos: Estudio observacional basado en datos recolectados prospectivamente del registro FERICODIAB. Se incluyeron 367 adultos con DM2 e insuficiencia cardíaca (IC) y/o enfermedad renal crónica (ERC). Se establecieron criterios de elegibilidad terapéutica según guías internacionales y se construyó un índice ponderado de brecha terapéutica (IBT-prop), comprendido entre

Rev Argent Cardiol 2026;94:301-309. https://doi.org/10.7775/rac.v94.i4.21027

Received: 12/15/2025 – *Accepted:* 05/15/2026

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0 (ausencia de brecha) y 1 (brecha completa). Los factores asociados se evaluaron mediante regresión lineal multivariada y, como análisis de sensibilidad, regresión beta.
Resultados: La edad media fue 70,0 ± 11,1 años; el 61,6 % eran hombres, el 80,7 % presentaba ERC y el 25,6 %, IC. El IBT-IA medio fue 0,491 (mediana: 0,483), y el 45,4 % presentó un valor >0,5. El IBT-IIA medio fue 0,454 (mediana: 0,778), y el 51,2% presentó un valor >0,5. Las mayores brechas correspondieron a finerenona (98,5 %), agonistas del receptor de GLP-1 GLP-1 (arGLP-1) (84,4%) y las combinaciones finerenona+iSGLT2 (97,7 %) e iSGLT2+arGLP-1 (90,9 %). Una mayor edad, mayor índice de masa corporal y sexo femenino se asociaron con mayor brecha en el modelo lineal, aunque las asociaciones de edad y sexo femenino perdieron significación en la regresión beta.
Conclusión: Existe una brecha importante entre las recomendaciones y su implementación, especialmente para las terapias cardiorrenales más recientes y las combinaciones recomendadas. Se requieren estrategias sistemáticas y transdisciplinarias para optimizar su utilización.

Palabras clave: Diabetes mellitus tipo 2 - Enfermedad renal crónica - Insuficiencia cardíaca - Enfermedad cardiovascular - Brecha terapéutica -Tratamiento basado en la evidencia

INTRODUCTION

The global burden of cardiorenal disease associated with type 2 diabetes mellitus (T2DM) has steadily increased over the past decades. (1) The coexistence of cardiovascular disease (CVD), heart failure (HF), and chronic kidney disease (CKD) constitutes a very high-risk phenotype, characterized by accelerated disease progression and a high incidence of adverse clinical outcomes. In this context, the development of novel therapies with cardiorenal benefits has substantially changed the therapeutic approach. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and, more recently, nonsteroidal mineralocorticoid receptor antagonists such as finerenone, have been shown to reduce cardiovascular events, hospitalizations for HF, and the progression of kidney disease, regardless of glycemic control. (2) Accordingly, international clinical practice guidelines have incorporated these therapies with strong recommendations supported by high-level evidence for patients with diabetes and cardiorenal disease.

However, despite the robust body of evidence, several studies have demonstrated a marked discrepancy between guideline recommendations and their implementation in routine clinical practice. In populations with T2DM and established CVD, the use of evidence-based therapies remains suboptimal, with a low proportion of patients receiving all recommended therapies. (3) This phenomenon, known as the "treatment gap," represents a significant source of potentially preventable residual risk.

The gaps in cardiometabolic management remain alarming. For example, in a population of 155 958 patients in the United States with T2DM and established atherosclerotic CVD, only 2.7% were receiving all recommended evidence-based therapies. (4)

In a 2019 study conducted in Argentina, only 12.8% of patients with T2DM and CVD were receiving SGLT2i , and 3.04% were receiving GLP-1 RA. (5)

No integrated metrics have been developed to specifically quantify this gap by stratifying treatment indications by their class of recommendation and weighting therapies by their relative clinical importance.

OBJECTIVE

This study aimed to quantify the treatment gap among patients with T2DM and very high-risk cardiorenal disease using a proportional index that differentiates therapies according to their class of recommendation (Class IA and Class IIA), and to evaluate the clinical factors associated with a greater likelihood of omission of evidence-based therapies.

METHODS

The FERICODIAB group collected data from adult patients with T2DM as part of a study on iron deficiency. Data were prospectively collected from subjects with T2DM and current or previous anemia, T2DM with HF, and/or T2DM with CKD. Of the 505 patients in the FERICODIAB registry, 4 were excluded because they did not meet the inclusion criteria and 14 were excluded due to inconsistent data. Of the remaining 487 patients, data from 367 patients with HF and/or CKD, as determined by the researchers based on patients' personal history, were included in the analysis (Figure 1).

Demographic, clinical, and biochemical variables were collected, including age, sex, body mass index (BMI), duration of diabetes, glycated hemoglobin (HbA1c), blood pressure, renal function (estimated glomerular filtration rate, eGFR), albuminuria and urine albumin-creatinine ratio (UACR), other comorbidities, and current treatment. CVD was defined as the presence of coronary artery disease, cerebrovascular disease, and/or peripheral vascular disease.

Eligibility criteria were established for each therapy and categorized according to their class of recommendation (Class IA and IIA) . The classes of recommendation were based on contemporary international guidelines (ADA/EASD, American Diabetes Association/ European Association for the Study of Diabetes, (6) KDIGO, Kidney Disease: Improving Global Outcomes, (7) and ESC, European Society of Cardiology, (8)), harmonized by consensus among the study's principal investigators, based on the primary premise that the study population consisted of patients with T2DM and a history of CKD and/or HF.

Based on the aforementioned guidelines, the following indications were defined:

Class IA indications:

1- SGLT2i for all patients with an eGFR ≥20 mL/min/1.73 m^2.
2- GLP-1 RA for all patients with a BMI ≥27 kg/m^2 and established CVD and/or CKD with an eGFR >15 mL/min/1.73 m^2.
3- Antiplatelet agents for all patients with established CVD

and hemoglobin (Hb) >12 g/dL (women) or >13 g/dL (men).
4- Statins for all patients aged between 40 and 75 years.
5- Renin-angiotensin-aldosterone system inhibitors(RAASi) for patients with hypertension (HTN) and CKD or patients with HTN and established CVD.
6- Finerenone for patients with CKD, UACR ≥30 mg/g and eGFR ≥25 mL/min/1.73 m².

Class IIA indications:

1- Combination therapy with SGLT2i and GLP-1 RA for patients with established CVD and an eGFR ≥15 mL/min/1.73 m² .
2- RAAS inhibitors for all patients with HTN.
3- Combination therapy with finerenone and SGLT2i for patients with UACR ≥100 mg/g and eGFR 30–90 mL/min/1.73 m².

Development of a treatment gap index

To quantify the treatment gap, a weighted composite index (proportional treatment gap index, prop-TGI) was developed based on the methodology used to develop composite performance measures or composite quality indicators, which integrates multiple healthcare quality indicators into a single summary measure. (9) A predefined weight was assigned to each recommended drug therapy according to its relative importance within the comprehensive management of cardiorenometabolic syndrome. The weights were assigned a priori by the research group based on the breadth and consistency of the available evidence regarding reductions in cardiovascular and renal events, the impact on multiple domains of cardiorenometabolic syndrome, and the role of each intervention in contemporary recommendations from major international guidelines. Under this framework, SGLT2i and GLP-1 RA were assigned a weight of 2.0; finerenone, a weight of 1.5; and statins, RAASi , and antiplatelet therapy, a weight of 1.0.

The prop-TGI was calculated as the sum of the weights assigned to recommended but non-prescribed therapies divided by the sum of the weights assigned to all recommended therapies for each patient, yielding a continuous index ranging from 0 (no treatment gap) to 1 (complete treatment gap).

Statistical analysis

Gaps by therapy among eligible patients, prop-TGI distributions, and subgroup comparisons were described. Independent predictors of the prop-TGI for Class IA indications (TGI-IA) and Class IIA indications (TGI-IIA) were evaluated using multivariate linear regression. The independent variables included age, sex, BMI, HbA1c, duration of diabetes, HF, CKD, CVD, HTN, dyslipidemia (DLP), and smoking. Since the prop-TGI is bounded between 0 and 1, the primary analysis was performed using linear regression because of its clinical interpretability. Beta regression was also performed as a sensitivity analysis.

Epi Info, R, and JAMOVI were used for all analyses.

Ethical considerations

The study was reviewed and approved by the Research Ethics Committee of the Argentine Society of Cardiology under registration No. 8426, in accordance with international guidelines for clinical research, including the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki and its amendments. (10)

RESULTS

Data were collected from 367 patients with a mean age of 70.0 ± 11.1 years; 226 (61.6%) were male. The prevalence of HTN was 92.1% (n = 338) and that of DLP was 86.1% (n = 316), while 6.5% (n = 24) had a history of smoking. The mean BMI was 30.9 ± 6.1 kg/m², and the mean duration of T2DM was 16.0 ± 9.9 years, reflecting a long-standing metabolic disease. Metabolic dysfunction-associated steatotic liver disease (MASLD) was present in 33.5% (n = 123). From the cardiorenal standpoint, 195 participants (53.1%) had an eGFR <60 mL/min/1.73 m². When the study definition of CKD (eGFR <60 mL/min/1.73 m² or UACR >30 mg/g) was applied, 296 participants (80.7%) met the criteria, 61 of whom also had HF. Median (IQR) UACR was 48.3 (15-201) mg/g in 309 available measurements. . A total of 94 participants (25.6%) had HF, and 61 (16.6%) had both coexisting HF and CKD. Regarding CVD, 27.5% (n = 101) had coronary artery disease, 6.8% (n = 25) had a history of cerebrovascular disease, and 14.7% (n = 54) had peripheral vascular disease. Taken together, these findings describe an elderly cohort with long-standing T2DM and a very high burden of cardiorenal comorbidities, representative of a population at very high cardiovascular and renal risk. Table 1 shows the baseline characteristics of the study population.

The mean TGI-IA was 0.491 with a median of 0.483; 45.4% of patients had an TGI-IA >0.5. The mean TGI-IIA was 0.454 with a median of 0.778, and 51.2% of patients had an TGI-IIA >0.5. (Figure 2)

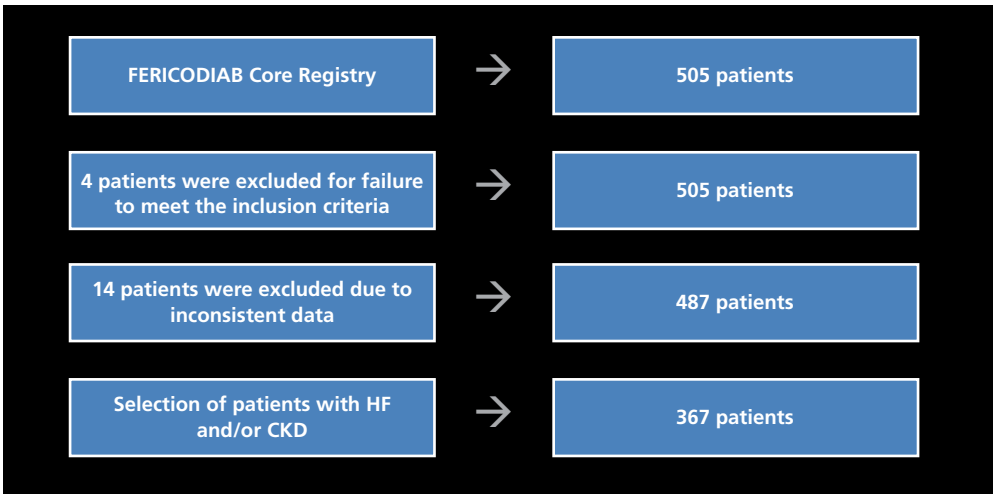
Figure 3 shows the proportion of participants eligible for each intervention, the percentage treated among eligible participants, and the resulting treatment gap. Figure 4 presents a heat map of the treatment gaps corresponding to Class IA and Class IIA indications. Table 2 presents the TGI-IA according to the presence of cardiorenal comorbidity. The index was significantly lower among participants with HF and those with established CVD. Among patients with CKD, a numerically smaller treatment gap was observed, and the difference did not reach statistical significance.

In the adjusted multivariate model, DLP, HF, CKD, and male sex were independent predictors of a smaller treatment gap for Class IA indications, whereas older age, higher BMI, and female sex were associated with a larger treatment gap (Figure 5). In the linear model, older age and female sex were associated with a higher prop-TGI; however, these associations were attenuated and were no longer statistically significant in the beta regression model and should therefore be interpreted as exploratory findings.

DISCUSSION

In this observational study, which included a cohort of patients with T2DM and a high burden of cardiorenometabolic disease, a significant treatment gap was observed in the implementation of evidence-based

Fig. 1. Flow diagram



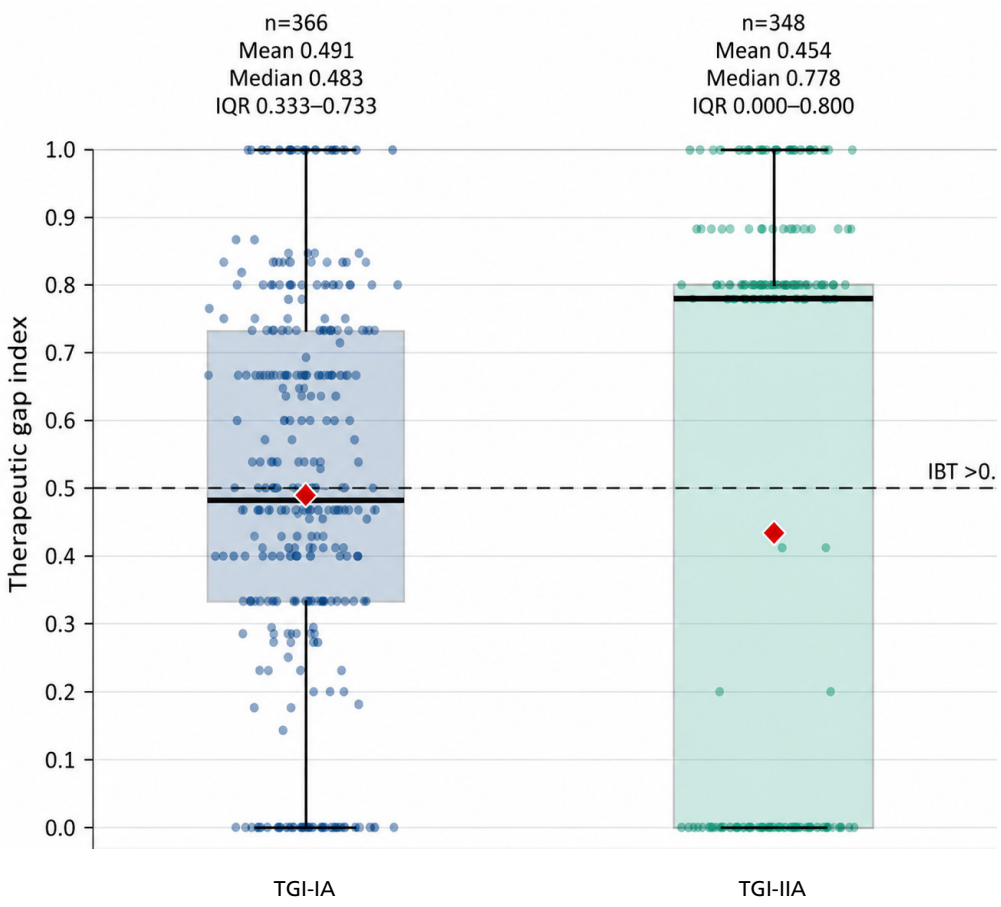
CKD: chronic kidney disease; HF: heart failure

Table 1. Demographic characteristics of the total population and by gender

Variable	Total	Men	Women	p
Age (years)	70.0 ± 11.1	70.3 ± 11.1	69.7 ± 11.3	0.618
BMI (kg/m²)	30.9 ± 6.1	31.0 ± 5.6	30.8 ± 7.1	0.884
HbA1c (%)	7.2 ± 1.5	7.1 ± 1.4	7.3 ± 1.6	0.177
eGFR (mL/min/1.73 m²)	61.5 ± 26.8	56.7 ± 24.3	69.9 ± 28.6	<0.001
Hemoglobin (g/dL)	13.0 ± 2.0	13.6 ± 2.0	12.0 ± 1.5	<0.001
HTN	338/367 (92.1%)	211/226 (93.4%)	111/124 (89.5%)	0.288
DLP	316/367 (86.1%)	200/226 (88.5%)	101/124 (81.5%)	0.098
Smoking	24/367 (6.5%)	16/226 (7.1%)	8/124 (6.5%)	0.999
eGFR <60 mL/min/1.73 m²	195/367 (53.1%)	136/226 (60.2%)	52/124 (41.9%)	0.002
UACR >30 mg/g	204/309 (66.0%)	128/188 (68.1%)	63/106 (59.4%)	0.172
HF	94/367 (25.6%)	60/226 (26.5%)	31/124 (25.0%)	0.850
Coronary CVD	101/367 (27.5%)	82/226 (36.3%)	16/124 (12.9%)	<0.001
SGLT2i	200/367 (54.5%)	140/226 (61.9%)	50/124 (40.3%)	0.001
GLP-1 RA	47/367 (12.8%)	37/226 (16.4%)	8/124 (6.5%)	0.013
Finerenone	7/367 (1.9%)	1/226 (0.4%)	6/124 (4.8%)	0.016
RAAS inhibitor	323/367 (88.0%)	197/226 (87.2%)	111/124 (89.5%)	0.635
Antiplatelet agents	155/367 (42.2%)	106/226 (46.9%)	44/124 (35.5%)	0.051

Continuous variables are expressed as mean ± standard deviation.
Categorical variables are expressed as n (%).
Student's t-test was used for continuous variables and the χ^2 test for categorical variables.
χ Differences between totals and the sums of the subgroups are due to missing data in the stratification variables.
BMI: body mass index; CVD: cardiovascular disease; DLP: dyslipidemia; eGFR: estimated glomerular filtration rate; GLP-1 RA glucagon-like peptide-1 receptor agonists; HbA1c: glycated hemoglobin; HF: heart failure; HTN: hypertension; RAAS: renin-angiotensin-aldosterone system; SGLT2i: sodium-glucose cotransporter-2 inhibitors; UACR: urine albumin-creatinine ratio.

Fig. 2. Distribution of the Therapeutic Gap Index (TGI)



Each data point represents a single patient's value. The boxes indicate the interquartile range, the central line indicates the median, the whiskers extend up to 1.5 times the interquartile range, and the red diamonds represent the mean. The dashed line indicates the TGI threshold of >0.5. TGI-IA: n=366; TGI-IIA: n=350

therapies when applying eligibility criteria aligned with current international guidelines. The principal finding was that the treatment gap was not uniform but was concentrated in the most recent disease-modifying cardiorenal therapies, whereas historically established therapies, such as RAASi and statins, have been more widely adopted in clinical practice.

Major scientific societies recommend a comorbidity-based approach for patients with T2DM and established atherosclerotic CVD, HF, or CKD. (11)

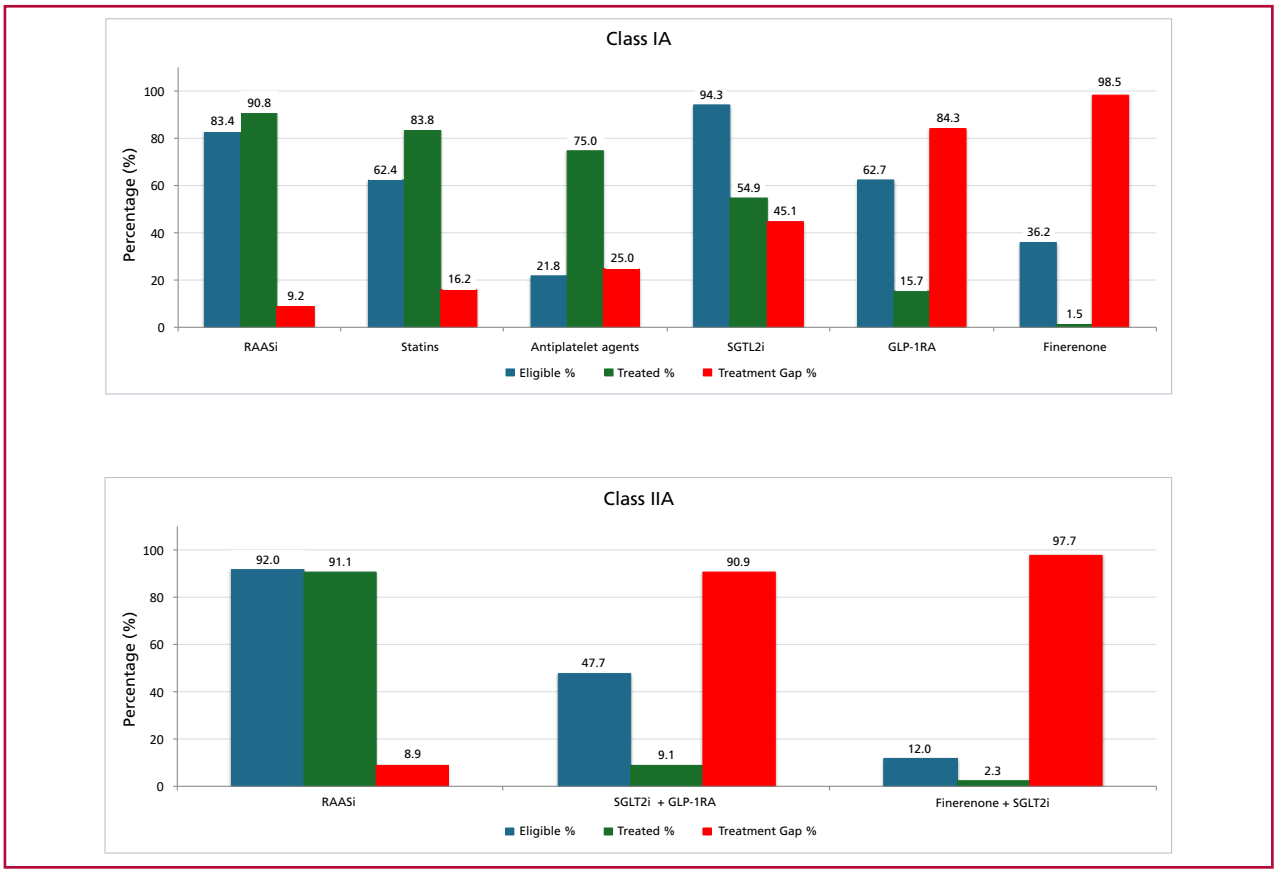
Our findings are consistent with previous reports demonstrating the low implementation of modern therapies in high-risk patients. (12) In the study by Nelson et al., only 2.7% of patients with T2DM and atherosclerotic CVD received the full combination of recommended therapies, underscoring a substantial global gap in evidence-based treatment. (4)

In the regional context, data from Argentina have shown limited use of SGLT2i (12.8%) and GLP-1 RA (3.04%) in patients with T2DM and CVD, (5) highlighting the persistence of this phenomenon across diverse healthcare systems. In our study, despite broader and more contemporary eligibility criteria, the use of GLP-1 RA (15.6%) and finerenone (1.5%) among eligible patients remained markedly low, suggesting that the treatment gap cannot be explained solely by indication restrictions but rather by more complex factors related to clinical practice.

An important finding of our study was the identification of a distinct pattern of therapy implementation. While traditional therapies such as statins and RAASi showed high rates of use, therapies with direct cardiorenal benefits—SGLT2i, GLP-1 RA, and finerenone—were used significantly less frequently.

This phenomenon may reflect an incomplete transition toward the modern cardiorenal paradigm, in which treatment is no longer based exclusively on controlling traditional risk factors but also on directly modifying the underlying pathophysiological mechanisms, including inflammation, endothelial dysfunction, hemodynamic overload, and the progression of kidney disease. (13)

Fig. 3. Percentage of patients eligible for Class IA and IIA recommendation therapies, treatment rates, and treatment gap



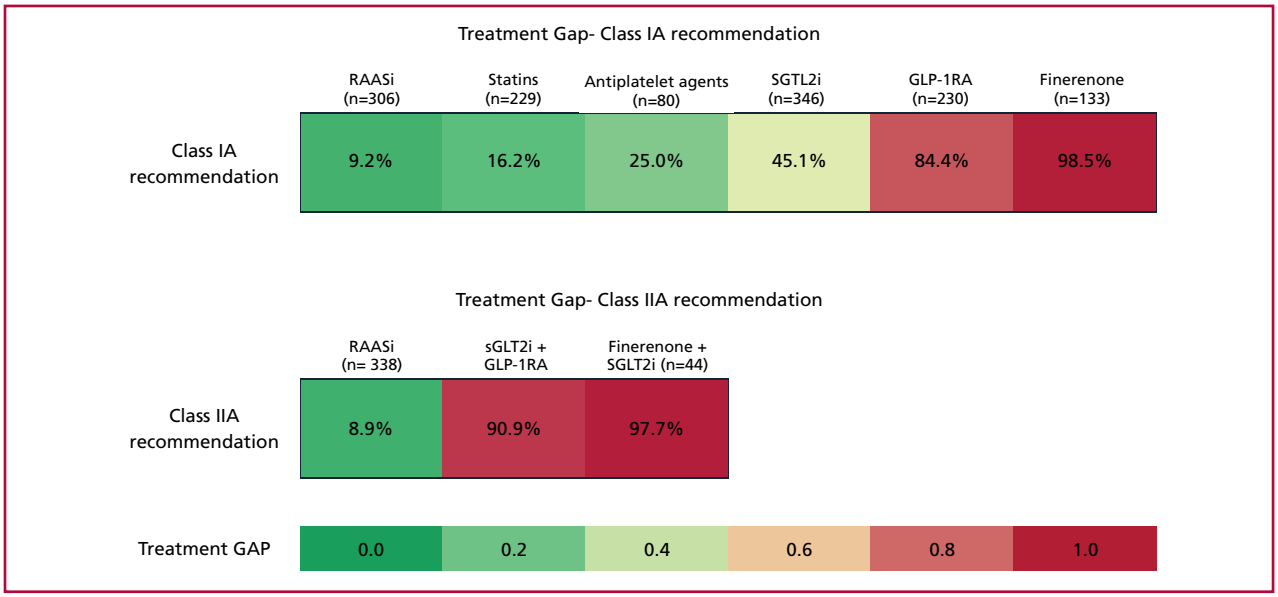
GLP-1 RA glucagon-like peptide-1 receptor agonists; RAASi: renin-angiotensin-aldosterone system inhibitors; SGLT2i: sodium-glucose cotransporter-2 inhibitors

Beyond individual clinical characteristics, the adoption of these therapies should be interpreted as a phenomenon influenced by factors operating at multiple levels of the healthcare system. In a cohort of 80 807 patients with T2DM and established CVD, those exposed to the highest out-of-pocket costs were 13% less likely to initiate treatment with a GLP-1 RA and 20% less likely to initiate treatment with an SGLT2i than those facing the lowest out-of-pocket costs. (14) Similarly, a recent study of 22 060 patients with T2DM and atherosclerotic CVD, HF, or CKD showed that only 17.4% were receiving any of these therapies and that prescription rates varied significantly according to the specialty, with lower prescription rates in cardiology practice. (15) In this context, the gap identified by the prop-TGI should not be attributed exclusively to individual practitioner decisions or therapeutic inertia but rather may also reflect economic barriers, differences in drug coverage, and fragmentation of care across specialties. Although these variables were not evaluated in our study, they should be incorporated into future research aimed at understanding and reducing the treatment gap.

Additionally, the multivariate analysis provides important insights into the variables associated with this treatment gap, namely BMI, age, and female sex. In this regard, the association between higher BMI and a higher prop-TGI suggests that patients with a greater metabolic burden—who would be expected to benefit most from therapies such as GLP-1 RA—(16) are, paradoxically, the least likely to receive them. Similarly, although there is robust evidence supporting the safety and effectiveness of these therapies in patients older than 65 years, (17) we observed systematic underuse among older adults. An analysis of older Medicare Advantage beneficiaries showed significantly lower initiation rates of SGLT2i and GLP-1 RA than among younger patients, with these gaps widening progressively with increasing age. (18) In our study, older age was an independent predictor of a wider treatment gap. This finding, which is consistent with several previous reports (19), may reflect multiple factors, including treatment inertia, ageism, or concerns regarding safety, tolerability, and socioeconomic factors.

Historically, women with T2DM and/or cardiomet-

Fig. 4. Heat map of treatment gaps for Class IA and Class IIA recommendations



GLP-1 RA glucagon-like peptide-1 receptor agonists; RAASi: renin-angiotensin-aldosterone system inhibitors; SGLT2i: sodium-glucose cotransporter-2 inhibitors

Table 2. Median TGI-IA by cardiorenal comorbidity subgroups

Subgroup	n	Present	Absent	p
HF	94	0.406	0.531	<0.001
CKD (eGFR <60 mL/min/1.73 m² or UACR >30 mg/g)	296	0.467	0.636	0.073
Established CVD	145	0.444	0.538	<0.001

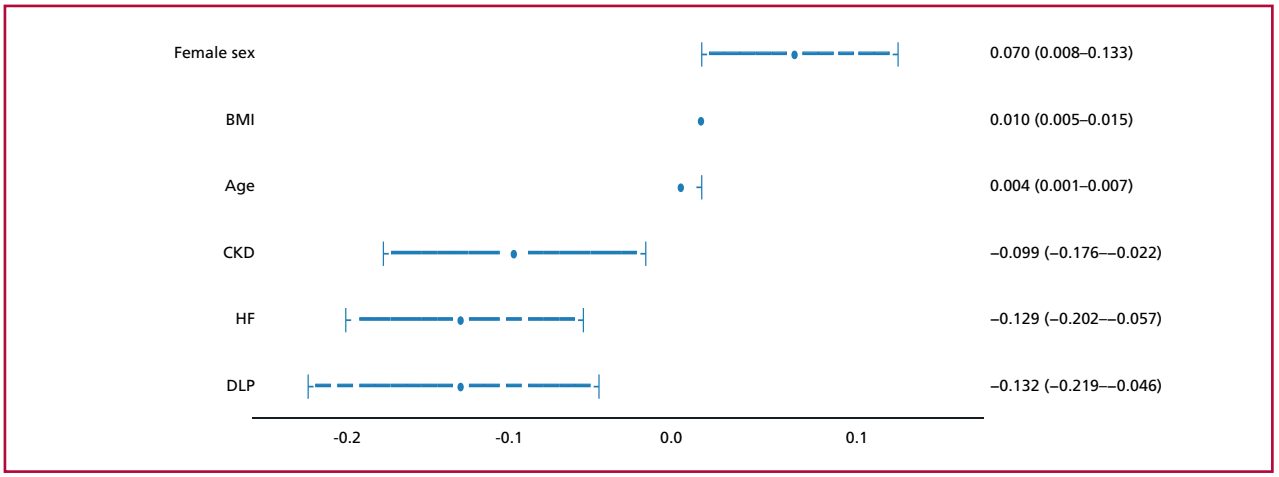
CVD: cardiovascular disease; CKD: chronic kidney disease; HF: heart failure

abolic diseases have consistently been less likely to receive guideline-recommended cardioprotective therapies. (20) A recent meta-analysis including more than 14.6 million patients confirmed that women were less likely to receive SGLT2i, although, paradoxically, they may be more likely to receive GLP-1 RA. (21) In our study, female sex was associated with a wider treatment gap. This recurring finding across multiple studies may stem from bias in cardiovascular risk assessment, whereby women are often perceived as being at lower cardiovascular risk, as well as from cultural, socioeconomic, and structural barriers. (22) The ADA/EASD consensus emphasizes that "the increase in the relative risk of CVD due to T2DM is greater in women than in men," making treatment disparities particularly concerning. (23) Conversely, the smaller treatment gap observed among patients with HF and established CVD suggests that the clinical recognition of risk has a substantial influence on therapeutic decision-making, promoting greater adherence to guideline recommendations in secondary prevention than in patients with high metabolic risk but no overt clinical events.

Limitations

This study has several limitations that should be considered. First, its observational design precludes causal inference regarding the association between the analyzed factors and the observed treatment gap. Second, although eligibility criteria were based on international guidelines, they were harmonized by consensus among the researchers, which may have introduced some variability in their interpretation. Furthermore, detailed information on specific contraindications, treatment tolerability, and adherence was not available, all of which could have influenced prescribing decisions. In addition, factors related to healthcare access, drug coverage, and socioeconomic status were not assessed, although they may play an important role in the implementation of therapies. Finally, some of the covariates included in the model, such as HF, CKD, CVD, and BMI, were also incorporated into the

Fig. 5. Predictor variables associated with the Class IA recommendation treatment gap (TGI- IA)



Forest plot of the ß coefficients and their 95% confidence intervals estimated using a multivariate linear regression model, with TGI-IA as the dependent variable. The model included age, sex, body mass index (BMI), HbA1c, duration of diabetes, heart failure (HF), chronic kidney disease (CKD), established cardiovascular disease, hypertension, dyslipidemia (DLP), and smoking (n = 343 complete cases). Positive coefficients indicate a larger treatment gap, whereas negative coefficients indicate a smaller treatment gap. The vertical line at zero represents no association. Only variables that remained statistically significant in the multivariate model are shown.

rules to determine treatment eligibility. Consequently, some of their associations with the prop-TGI may reflect the way the index was constructed rather than differences in prescribing behavior alone.

CONCLUSION

A significant treatment gap was identified in the implementation of guideline-based therapies, particularly those with a Class IA recommendation and the greatest demonstrated impact on reducing cardiovascular events and slowing progression of kidney disease. While historically established therapies, such as antiplatelet agents, RAAS inhibitors, and statins, had high rates of use, the most recent cardiorenal therapies (SGLT2i, GLP-1 RA, and finerenone) were implemented far less frequently, with particularly pronounced gaps among older patients, women, individuals with higher BMI, and especially in the use of recommended combination therapies. These findings highlight the need for systematic implementation strategies, interdisciplinary approaches, and structured treatment optimization in patients with cardiorenal disease to bridge the gap between scientific evidence and real-world clinical practice.

Conflicts of interest

None declared.

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

Acknowledgments

We thank all the researchers from the FERICODIAB registry who contributed to the collection of the data used in this study:

Roxana Abeleedo, Carina Adjiman, Florencia Aranguren, Cecilia Araya, Mauricio Arguello, Bárbara Arinovich, Judith Bendahan, José Cardozo, Yanina Castaño, Ivana Castillo, Pilar Cean, Mirta Centeno Maxzud, Alejandra Cicchitti, Jimena Conforti, Daniel Croatto, Guillermo De' Marziani, Alicia Elbert, Ezequiel Forte, Paula Gómez, Cristina Grosso, Natalia Heredia, Sonia Hermida, Andrea Laurenza, Gustavo Lavenia, Sergio Liderman, Martin Maraschio, Diego Novielli, Luciana Paganti, Bruno Payeras, Florencia Pizzatti, Andrea Prospero, Daniela Recalde, Carlos Tapia, Fiorella Tartaglione, Fabiana Vázquez, Beatriz Villarroel Parra, Rocío Zabala

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RESEARCH HYPOTHESIS

Metabolic and Cardiovascular Effects of Combined Treatment with Dapagliflozin and Zinc Supplementation in Metabolic Syndrome

Efectos metabólicos y cardiovasculares del tratamiento combinado de dapagliflozina y suplementación de zinc en el síndrome metabólico

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PATHOPHYSIOLOGICAL BASIS

Cardiovascular (CVD) and metabolic diseases are the leading cause of mortality in Western societies. Metabolic syndrome (MS) represents the combination of several risk factors, including obesity, dyslipidemia, hyperglycemia, oral glucose intolerance and hypertension, and contributes to the development of CVD and type 2 diabetes mellitus (T2DM). (1)

Feeding rats with high fat and carbohydrate diets—which mirror the Western population diet—induces the development of various components of MS. Rats fed a high-fat diet supplemented with fructose (10%) in the drinking water for 8–9 weeks exhibit increased triglyceride and cholesterol levels, as well as insulin resistance, visceral adiposity and blood pressure, in addition to ventricular hypertrophy, myocardial fibrosis, alterations in stroke volume, and remodeling of the coronary arteries. These pathophysiological changes involve increased oxidative, inflammatory and fibrotic processes, as well as mitochondrial dysfunction. (2)

On the other hand, overweight and obesity are frequently associated with mineral and vitamin deficiencies. (3) Several meta-analyses have reported low plasma zinc concentrations, hyperzincuria and redistribution of this mineral in diabetic and obese patients. (4) Furthermore, it has been shown that chronic low zinc intake is associated with reduced insulin secretion and/or tissue resistance to insulin, increased blood glucose levels, and alterations in lipid metabolism. (5) We have previously demonstrated that moderate zinc deficiency during prenatal and early postnatal development leads to renal, cardiovascular, and metabolic abnormalities in adult rats. In our experimental studies, male rats subjected to this deficiency exhibited lower birth weight, reduced renal and cardiac tissue weights, increased blood pressure, cardiorenovascular dysfunction, related to inadequate activity of the nitric oxide (NO) and renal and cardiovascular renin-angiotensin systems, as well as increased renal oxidative stress. They also exhibited hypertriglyceridemia, hyperglycemia, insulin resistance, hypertrophy, and increased oxidative state of the retroperitoneal adipose tissue. Females appear to be less sensitive to this nutritional injury. (6) In addition, zinc deficiency during fetal and postnatal life was shown to exacerbate the metabolic and retroperitoneal adipose tissue alterations induced by a high-fat diet during growth. (7)

There is an urgent need to identify new therapeutic strategies aimed at reducing the cardiovascular morbidity and mortality associated with MS. Selective sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin, dapagliflozin (DAPA), and canagliflozin, belong to a new class of drugs approved for use as antihyperglycemic therapy. SGLT2 cotransporters transport glucose and sodium in a 1:1 ratio and are located on the apical membrane of proximal tubules S1 and S2 segments. In healthy individuals, 90% of filtered glucose is reabsorbed in the renal proximal tubule by SGLT2, which has high affinity and capacity. The remaining 10% of filtered glucose is re-

Rev Argent Cardiol 2026;94:310-315. https://doi.org/10.7775/rac.v94.i4.21024

Received: 12/12/2025 – *Accepted:* 03/11/2026

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absorbed by SGLT1 transporters, which have higher affinity but lower capacity than the SGLT2 isoform. SGLT1 is located on the luminal membrane of the proximal tubule S2 and S3 segments, with a glucose-sodium coupling ratio of 1:2. When SGLT2 is blocked, SGLT1 can account for up to 50% of glucose reabsorption, since two sodium ions must be taken up for every glucose molecule absorbed. On the basolateral side, glucose leaves the intercellular space by passive diffusion through the GLUT1 and GLUT2 transporters, while sodium is expelled into the interstitium by the sodium-potassium ATPase pump. Moreover, SGLT2 transporters are physically and functionally coupled to the sodium-proton exchanger 3 (NHE3). Inhibition of SGLT2 reduces NHE3 activity, further decreasing proximal sodium reabsorption and contributing to natriuresis. (1, 8–10)

The filtered glucose load increases as plasma glucose concentration rises, with a maximum renal reabsorption capacity of approximately 375 mg/min in a healthy individual. This typically occurs at blood glucose levels between 180 and 215 mg/dL, whereas higher blood glucose levels lead to glucosuria. In people with T2DM, the threshold at which glucose appears in urine, as well as the maximum capacity for renal tubular reabsorption, increase significantly due to SGLT2 overexpression. Therefore, SGLT2i or gliflozins reduce glucose and sodium reabsorption in the proximal tubule and cause osmotic diuresis by inducing glucosuria and natriuresis. Consequently, they lower glycated hemoglobin and postprandial blood glucose levels through an insulin-independent mechanism. Their effects are not affected by impaired pancreatic islet β-cell function or by reduced insulin sensitivity. Nor are they associated with a risk of hypoglycemia, even in non-diabetic individuals. (8–10)

By lowering blood glucose levels, SGLT2i reduce cellular damage caused by advanced glycation end products, oxidative stress, inflammation, and apoptosis. They also promote the oxidation of glucose and long-chain fatty acids, regardless of insulin levels, with a modest increase in ketone body production (reflected in higher plasma levels). (1, 8)

It is important to note that, due to increased urinary glucose excretion, SGLT2i administration results in a loss of approximately 200–250 kcal per day. This leads to a reduction in visceral and subcutaneous adipose tissue, with preservation of lean body mass and a transient loss of extracellular fluid. Randomized clinical trials report a reduction of approximately 2 kg compared with placebo, an effect that stabilizes significantly after 6 months. (8–10)

SGLT2i have a wide range of beneficial effects on the kidney. Reduction of sodium reabsorption in the proximal tubule—either through direct action or via the NH3 exchanger—increases the luminal supply of sodium chloride (NaCl) to the macula densa. This leads to the restoration of tubulo-glomerular feedback through adenosine-mediated contraction of the afferent arteriole and vasodilation of the efferent arteriole mediated by reduced activity of the renin-angiotensin system. Consequently, SGLT2i can slow the progression of diabetic nephropathy by reducing glomerular hypertension, hyperfiltration, and albuminuria. In addition, by increasing glucosuria, they reduce urate reabsorption in the proximal convoluted tubule, leading to a persistent decrease in circulating uric acid. This is also a beneficial effect, as uric acid promotes inflammation, fibrosis, and apoptosis, and reduces NO levels at the vascular level. Finally, SGLT2i are associated with increased hematocrit levels, an effect that is partly due to their diuretic properties and their stimulation of erythropoietin synthesis. (1, 9–11)

Various clinical trials, including the DECLARE-TIMI 58, (12) DAPA-HF, (13) and DAPA-CKD studies, (14) have demonstrated that DAPA reduces hospitalizations for heart failure and cardiovascular mortality, even in patients without diabetes. This is because SGLT2i have been shown to improve diastolic function and myocardial contractility by reducing volume overload through a decrease in preload secondary to natriuresis and osmotic diuresis. They also help reduce afterload because the reduction in plasma volume and improvement in vascular function leads to a decrease in blood pressure. (9–11)

Despite the negligible expression of SGLT2 in the heart, SGLT2 inhibition is strongly implicated in cardiac sodium and calcium homeostasis due to its profound effects on these ions' transporters. In heart failure, the concentration of cytosolic sodium in cardiomyocytes increases significantly due to an imbalance between its influx and efflux. The concentration of cytosolic calcium also rises as a result of increased efflux from the mitochondria via the sarcolemmal sodium/calcium exchanger. The decrease in intramitochondrial calcium concentration reduces the activity of the tricarboxylic acid cycle, leading to decreased production of adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide phosphate (NADPH), as well as to an impairment of mitochondrial antioxidant defenses. Cytosolic sodium and calcium overload contributes to systolic, diastolic and mitochondrial dysfunction, as well as to arrhythmogenesis and pathological remodeling. In this regard, preclinical studies have shown that SGLT2i may help improve cardiac and vascular function by increasing NO availability, reducing oxidative stress, inflammation, fibrosis, mitochondrial dysfunction and autophagy, as well as the adipokine mass and profile of epicardial adipose tissue. (9–11)

Given this background, SGLT2i exert multifactorial cardiorenal protection that cannot be attributed solely to glycemic control, weight loss, reduced blood pressure, decreased uric acid levels, or changes in the lipid profile. Their efficacy appears to depend on a set of integrated mechanisms—metabolic, hemodynamic, and cellular—that collectively contribute to reduce heart failure morbidity and mortality, with reduced or

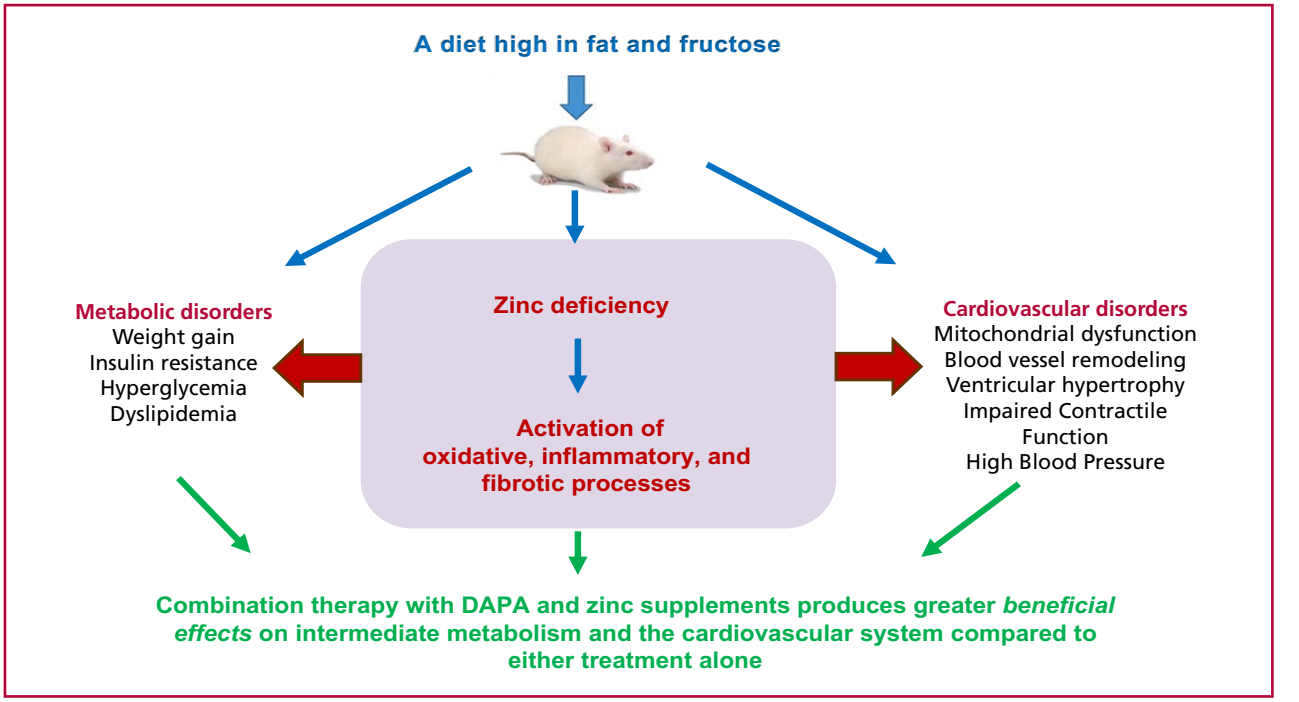
preserved ejection fraction, and diabetic kidney disease. Thus, in recent years, its use has been incorporated into clinical practice guidelines, not only those specific to T2DM but also into cardiology guidelines (cardiovascular prevention).

Moreover, given that obesity and T2DM may be associated with zinc deficiency, (4) it is of interest to analyze the effects of zinc supplementation on these conditions. The results of cross-sectional or observational studies on the associations between zinc homeostasis and the onset of MS are inconsistent. In some studies, no effects of zinc supplementation were observed on any of the MS components. However, other human studies have observed improvements in blood levels of total cholesterol, LDL cholesterol, and triglycerides, which could reduce cardiovascular morbidity and mortality. (15–17) Furthermore, in adult rats with hyperlipidemia and diabetes, zinc supplementation was shown to improve diabetic symptoms, increase serum HDL levels, and reduce markers of oxidative stress in the liver. (18) Zinc supplementation also reduced weight gain, abdominal fat, plasma insulin, leptin, and triglycerides in adult Wistar rats fed a high-fat, high-carbohydrate diet. (19)

There are several mechanisms through which zinc may help prevent the development or progression of MS and T2DM. Zinc is a trace element that plays an essential role in growth and immunity and possesses antioxidant, anti-inflammatory, and anti-apoptotic properties. It is a structural and functional component of many proteins involved in energy utilization and protein, lipid, and carbohydrate metabolism, as well as blood pressure adjustment. Zinc regulates insulin release, transport, storage, and processing, as it is concentrated in pancreatic beta cells within the dense core of insulin-secreting granules. It also possesses insulinomimetic properties by stimulating the insulin signaling pathway in adipose tissue and in skeletal and cardiac muscles. In this way, it promotes the translocation of the GLUT4 transporter to the plasma membrane, which stimulates glucose uptake, and reduces lipolysis by inhibiting hormone-sensitive lipase. These effects are mediated by zinc's inhibitory effect on protein tyrosine phosphatase (PTP1B) and a phosphatase and tensin homolog (PTEN) protein that negatively regulates PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase B) signaling. Zinc is essential for the activation of peroxisome proliferator-activated receptors (PPAR), which, in turn, can induce the expression of the GLUT1 and GLUT4 genes and regulate lipid metabolism. In terms of lipid metabolism, zinc plays a role in both the assembly and clearance of chylomicrons and lipoproteins. (6, 15)

Numerous studies indicate that zinc exerts its effects on carbohydrate and lipid metabolism through the adipokine zinc-α2-glycoprotein (ZAG), which possesses a zinc-binding site within its structure. Excess body fat reduces blood concentrations of zinc and ZAG, leading not only to the development of obesity but also to other components of MS. ZAG has been shown to play an important role in reducing obesity and improving insulin sensitivity, increasing the release of adiponectin from human adipocytes and inhibiting leptin production in vitro. (20) These actions

Fig. 1. Flow diagram



of zinc suggest a potential role in the prevention and treatment of MS.

Epidemiological studies suggest that low serum zinc levels increase the risk of developing CVD, while zinc supplementation may reduce this risk, indicating the importance of adequate zinc management for the prevention of these conditions. Additionally, the molecular mechanisms of zinc-mediated regulation of cardiac function, which include zinc transporters and calcium signaling, have been reported. (21)

Zinc can modify how a drug acts in the body through pharmacokinetic and pharmacodynamic interactions. (18,19) However, there is little evidence demonstrating how zinc may interact with DAPA. Therefore, we wondered whether zinc supplementation could enhance the efficacy of pharmacological treatment with DAPA in patients with MS.

HYPOTHESIS AND OBJECTIVES

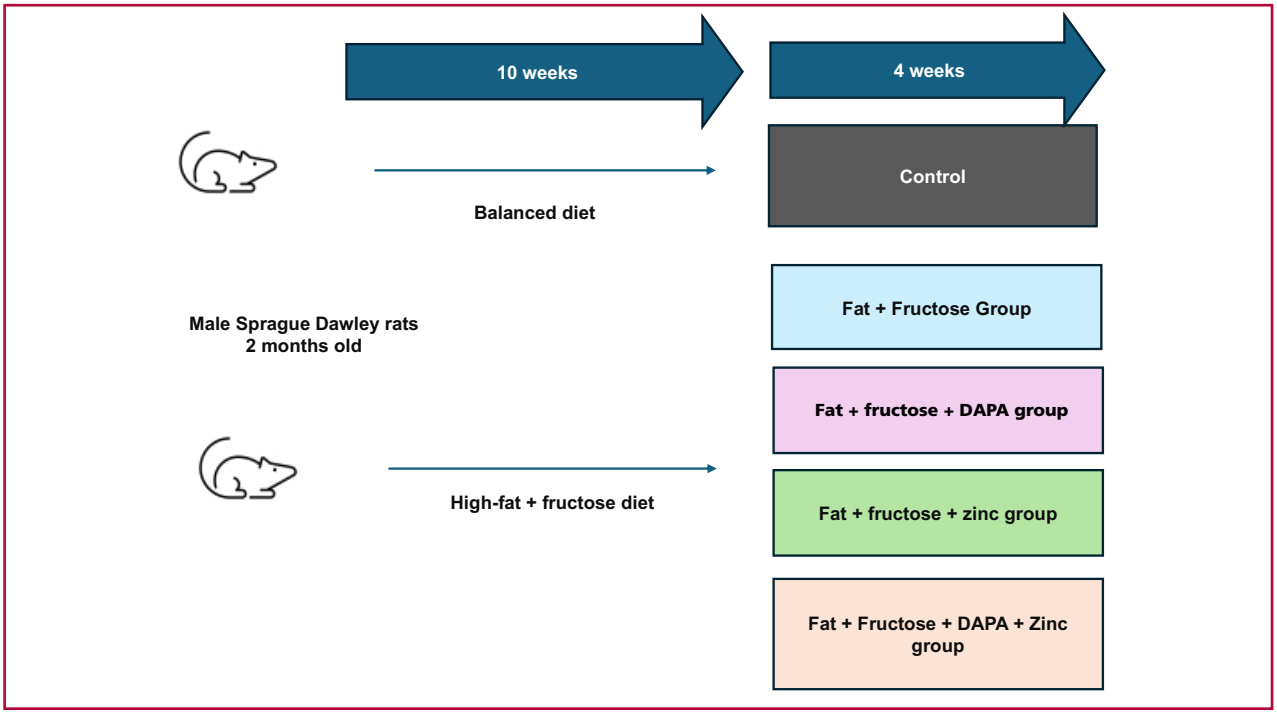
The available evidence describes the benefits of DAPA treatment and zinc supplementation separately, but there are no conclusive data on the effects of combined treatment in patients or animal models with MS.

Therefore, we hypothesize that feeding a high-fat, high-fructose diet to male rats from weaning to adulthood promotes the development of MS and CVD by causing weight gain, dyslipidemia, hyperglycemia, oral glucose intolerance, hypertension, cardiac tissue remodeling, mitochondrial dysfunction in cardiomyocytes, and cardiac dysfunction. These alterations are mediated by increased oxidative, inflammatory, and fibrotic states.

Zinc supplementation helps reduce these alterations, given its antioxidant, anti-inflammatory, and insulinomimetic properties. Treatment with DAPA improves these abnormalities by inducing antihyperglycemic effects, lowering blood pressure, reducing oxidative and inflammatory processes, and improving mitochondrial function. Combining DAPA with zinc supplementation in rats with MS would produce greater beneficial effects on the intermediate metabolism and cardiovascular system compared with either treatment alone (Figure 1).

Based on this hypothesis, the objective of this study is to investigate the mechanisms by which the combined administration of zinc and DAPA, in a rat model of MS, could produce greater beneficial effects on the cardiovascular system and intermediate metabolism compared with either treatment alone. To achieve this objective, a basic research protocol is being conducted at the Department of Physiology of the School of Pharmacy and Biochemistry at Universidad de Buenos Aires (FFyB-UBA) and at the Institute of Chemistry and Drug Metabolism (IQUIMEFA)-UBA-CONICET, which has been approved by the CICUAL ethics committee of FFyB-UBA (REDEC-2023-26-E-UBA-DCT-FFyB). For this study, male Sprague Dawley rats are fed either a balanced diet or a high fat (60% of total kcal) plus high fructose (10%) in ad libitum drinking water diet. After 10 weeks, the group fed the high-fat + fructose diet is administered orally for 4 weeks one of the following: a zinc supplement at

Fig. 2. Experimental Protocol



10 mg/kg/day; DAPA at 1 mg/kg/day; DAPA at 1 mg/kg/day plus a zinc supplement; or water (Figure 2). At the end of the experimental period, the effects on carbohydrate metabolism are assessed using an oral glucose tolerance test, and serum lipid profiles are analyzed. To evaluate the effects on the cardiovascular system, blood pressure measurements, echocardiographic studies, and morphological studies of the heart and its vessels are performed; the morphology and function of cardiac mitochondria are assessed. In addition, markers of fibrosis (transforming growth factor beta, TGF-β), inflammation (tumor necrosis factor alpha, TNF-α, and interleukin 6, IL-6), and oxidative stress (lipid peroxidation and the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase) in cardiac tissue are determined. To carry out this project, a research grant from the Argentine Society of Cardiology has been awarded in 2024 .

DISCUSSION AND CONCLUSION

The results of this research may represent a significant advance in addressing diseases of complex and multifactorial origin, such as MS. To date, there have been few basic research studies examining the relationship between DAPA and zinc. Anton I demonstrated that zinc supplementation in a rat model of diabetes—induced by streptozotocin and a high-fat diet—potentiates the effects of DAPA on metabolic conditions by producing greater reductions in blood glucose levels, improving liver function and lipid metabolism, and reducing oxidative stress compared with either treatment alone. (24) Furthermore, in a rat model of streptozotocin-induced diabetes, the combination of zinc with canagliflozin, another SGLT2i, has been shown to improve control of diabetes-related weight loss and hepatic steatosis. (25) Additionally, new DAPA-zinc complexes have demonstrated protective effects against liver damage and oxidative injury in diabetic rats. (22) Zinc plays important roles in lipid metabolism and insulin sensitivity through mechanisms involving ZAG and insulin signaling pathways, which may help enhance the effects of DAPA in MS. (11,20)

However, further basic and clinical research is needed to confirm and advance the investigation of zinc-DAPA combination effects on the various cardiovascular abnormalities associated with MS. Therefore, this study will help generate new therapeutic strategies for managing MS and preventing its progression to serious complications.

Funding

Research grant from the Argentine Society of Cardiology, Argentina, 2024–2025. Grant from Universidad de Buenos Aires, Argentina, 2023–2026, Code: 20020220100246B.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

Genetics and Clinical Cardiologist

La genética y el cardiólogo clínico

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ABSTRACT

Cardiovascular genetics has modified the traditional interpretation of numerous cardiovascular diseases. The relationship between genotype and phenotype depends on phenomena such as incomplete penetrance, variable expressivity, and the action of genetic and epigenetic modifiers, contributing to the heterogeneity of clinical manifestations observed among individuals.
While high-impact variants typically drive monogenic diseases, many common cardiovascular diseases have a polygenic architecture, in which multiple common variants with small effect sizes contribute cumulatively to individual risk.
Polygenic risk scores are designed to quantify this cumulative genetic susceptibility.
Integrating genetic information, phenotypic data, and traditional clinical variables is currently a major challenge in clinical cardiology and contemporary models of personalized medicine.

Key words: Cardiovascular genetics - Clinical cardiology - Polygenic risk - Personalized medicine.

RESUMEN

El estudio de la genética cardiovascular modificó la interpretación tradicional de numerosas enfermedades cardiovasculares. La relación entre genotipo y fenotipo depende de fenómenos como penetrancia incompleta, expresividad variable y acción de modificadores genéticos y epigenéticos, que contribuyen a la heterogeneidad clínica observada entre individuos. Mientras las enfermedades monogénicas suelen depender de variantes de alto impacto, muchas enfermedades cardiovasculares frecuentes poseen una arquitectura poligénica, donde múltiples variantes comunes de pequeño efecto contribuyen de manera acumulativa al riesgo individual. Los scores de riesgo poligénico intentan cuantificar esta susceptibilidad genética acumulativa. La integración entre información genética, fenotipo y variables clínicas tradicionales representa actualmente uno de los principales desafíos de la cardiología clínica y de los modelos contemporáneos de medicina personalizada.

Palabras clave: Genética cardiovascular - Cardiología clínica - Riesgo poligénico - Medicina personalizada

INTRODUCTION

Cardiovascular genetics is no longer limited to rare hereditary diseases but is rather being gradually integrated into daily practice. Nowadays, concepts such as genetic susceptibility, modifier variants, and polygenic risk play an increasingly important role in cardiovascular assessment. However, the association between genetics and cardiovascular disease is rarely linear. The same variant can be expressed differently among individuals, and many common diseases result from the cumulative effect of multiple variants with small effect size, combined with environmental factors.

In this context, the challenge for the clinical cardiologist is no longer the mere identification of mutations, but the understanding of how genetic information can help better interpretation of risk, phenotypic heterogeneity, and variability.

From genotype to phenotype: penetrance, expressivity, and modifiers

The presence of a genetic variant does not necessarily determine a uniform clinical expression. Patients with the same genotype may exhibit differences in penetrance, severity, age of onset, and affected organs,

Rev Argent Cardiol 2026;94:316-322. https://doi.org/10.7775/rac.v94.i4.21041

Received: 05/17/2026 – *Accepted:* 07/03/2026

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reflecting the influence of genetic, epigenetic, and environmental modifiers or conditioning factors on the final phenotype (Figure 1) (1)

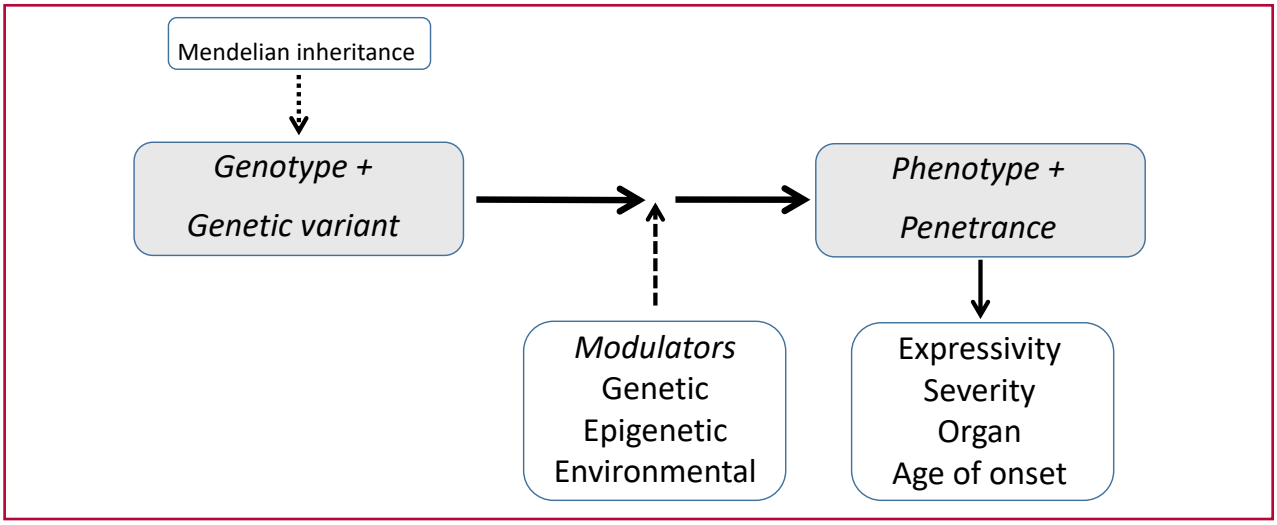
Monogenic variants are typically associated with high penetrance and lower-frequency phenotypes with larger biological effect sizes, which facilitates their clinical and familial recognition. In contrast, polygenic variants consist of multiple single-nucleotide polymorphisms (SNPs) of small individual effect sizes that are common in the general population, driving a more gradual and probabilistic phenotypic expression.

Both monogenic and polygenic variants represent extremes of a biological continuum rather than completely separate entities; thus, in clinical practice, these two mechanisms often interact. Even in diseases considered monogenic, penetrance and expressivity can be modified by polygenic variants, epigenetic mechanisms, and environmental factors. This helps explain the clinical heterogeneity observed among patients carrying the same genetic variant, including differences in severity, age of onset, and organ involvement (Figure 2). (2)

While even a single deoxyribonucleic acid (DNA) base change can cause a genetic alteration, its clinical impact is ultimately determined by the functional region involved. Variants located in critical regions of a gene can modify essential amino acids and be associated with significant structural or functional alterations in the protein. In contrast, many common SNPs have small or neutral biological effect sizes. They usually work together across many genes in a probabilistic way (Figure 3). (3)

As previously mentioned, the clinical manifestations of genetically based diseases do not follow a sin-

Fig. 1. Conceptual diagram of the relationship between genotype and phenotype in hereditary diseases



A genetic variant with a possible Mendelian pattern may be associated with a positive phenotype with variable penetrance. The final phenotypic expression may be modulated by genetic, epigenetic, and environmental factors, leading to differences in expressivity, severity, affected organ, and age of onset.

Fig. 2. Large or intermediate-effect size monogenic variants and polygenic variants associated with SNP summation

Large-effect size monogenic variant

It is a rare variant in a single gene. It may be a single-nucleotide polymorphism (SNP) with a population prevalence of <0.1% (often <0.01%) that affects a critical position, resulting in a high biological impact and a strong association with a phenotype or disease. It follows a Mendelian pattern of inheritance, often dominant, with complete penetrance and less dependence on modifiers or modulators.

Single-Nucleotide Polymorphisms (SNPs)

These are single-nucleotide polymorphisms (SNPs) distributed throughout the genome, with a high population prevalence (>1%). Each SNP represents a form of individual Mendelian genetic variability, but not the set as a whole. Individually, have no effect because affect non-critical genome regions, but multiple SNPs with minimal individual effect size generate polygenic susceptibility (PRS, or polygenic risk score). They behave as a continuous variable (the algebraic sum of SNPs) with a Gaussian population distribution, where the phenotype manifests upon exceeding a specific clinical threshold. They show high dependence on modulators that determine penetrance and expressivity.

The distinguishing characteristics of monogenic and polygenic variants are described in terms of penetrance, population frequency, magnitude of the biological effect size, and phenotypic distribution pattern.
A possible third group consists of monogenic variants with intermediate effect sizes, which exhibit characteristics that fall between those of the previous categories.

gle biological model but rather a continuous spectrum of genetic architectures. Some conditions are dominated by monogenic variants with large effect sizes and high penetrance, while others depend on the cumulative interaction of multiple variants with smaller individual impacts. Lying between these two extremes are intermediate models in which various relevant genetic alterations act together to shape the phenotype.

This heterogeneity helps explain the differences observed in age of onset, severity, progression, and organ involvement among patients with apparently similar diagnoses (Figure 4). (4)

In summary, the clinical impact of a genetic variant on diagnosis and prognosis depends on:

- inheritance pattern: dominant / recessive
- functional impact of the variant
- critical region of the gene
- type of mutation: substitution, deletion, insertion
- penetrance / expressivity: genetic, epigenetic, and environmental modifiers.

Population distribution of the genetic burden and phenotypic expression

The concept of genetic burden represents the integration of the primary variant and modifiers that influence penetrance and phenotypic expressivity; in clinical studies, it is typically an estimate derived from multiple genetic inputs rather than a single input.

For monogenic variants, the minimal overlap between genetic burden distributions in the presence and absence of the phenotype indicates strong discriminative power and high specificity. Even so, the estimated risk increases significantly only when clinical expressivity is achieved. In other words, a positive genotype with a negative phenotype is, in most cases, not a factor that by dictates intervention strategies (Figure 5).

The reduced sensitivity—typical of markers with low population prevalence—indicates that its absence does not rule out disease or clinical risk. Therefore, genetic information should be integrated with clinical variables for adequate diagnostic and prognostic stratification.

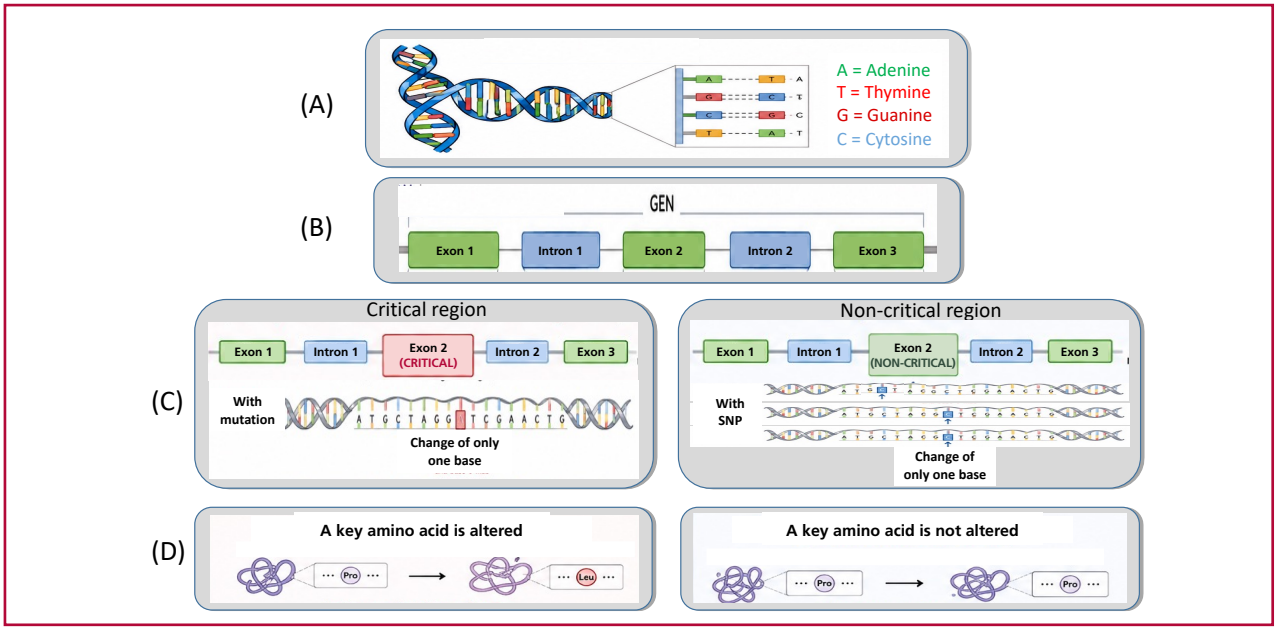
In contrast, polygenic variants resulting from multiple SNPs typically exhibit a Gaussian distribution. Dispersion, along with discrimination between negative and positive phenotypes, is substantially lower, with wider curves and increased overlap—features associated with modifiers of penetrance (Figures 5).

Unlike monogenic variants, polygenic variants allow for selecting a cutoff point with balanced specificity and sensitivity. In this case as well, the risk increases significantly with a positive phenotype, although the slope is less steep (Figure 5). (5)

Genetic prediction of subclinical and clinical phenotypes

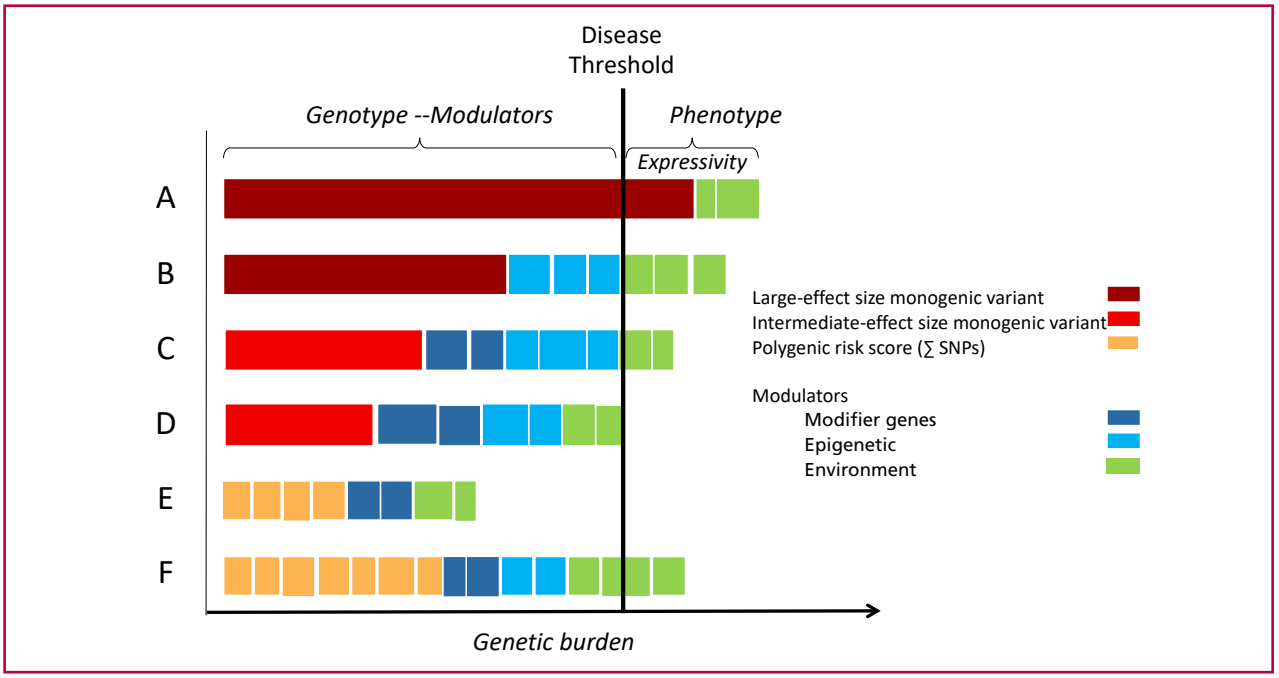
In diagnostic and prognostic trials, the genetic variant—either on its own or integrated with acquired risk factors—is the predictor variable, and the subclinical or clinical phenotype is the estimated risk. In

Fig. 3. Conceptual diagram of the structural and functional organization of DNA and genes



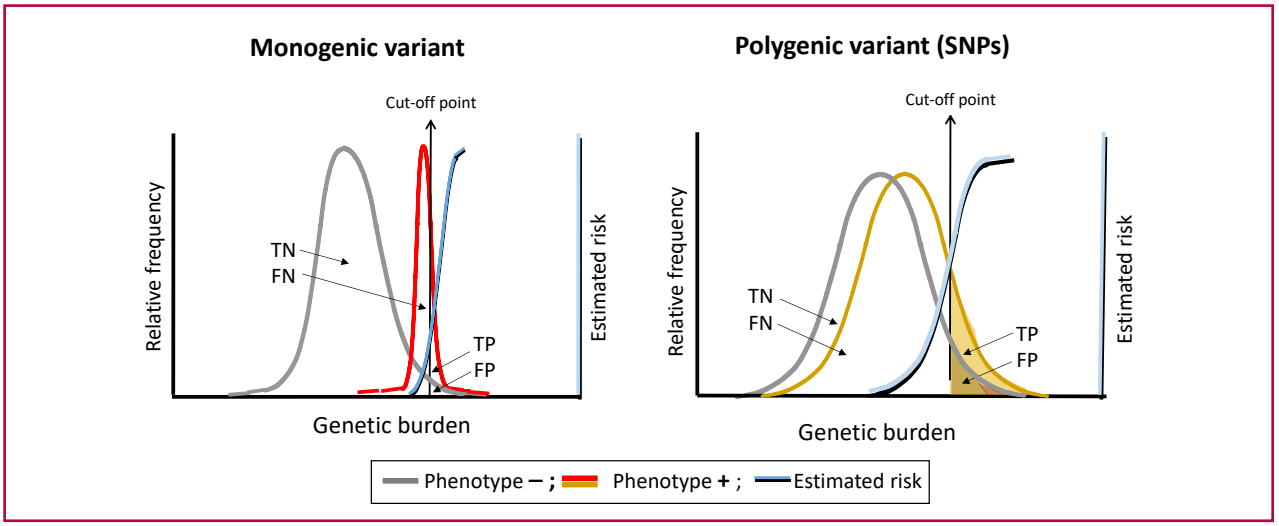
(A) DNA double-helix structure and nitrogenous base pairing: adenine (A), thymine (T), guanine (G), and cytosine (C).
(B) Schematic representation of a gene, the functional unit of DNA, composed of exons and introns.
(C) Left: Example of a single-base substitution in a critical functional region of a single gene, capable of altering a key amino acid and modifying protein structure or function.
(C) Right: Conceptual example of SNPs located in regions of lower functional impact and distributed across different genes (three are shown as examples), which individually may not produce significant alterations in the resulting protein.
(D) Structural and functional impact depending on whether a key amino acid is affected.

Fig. 4. Conceptual model of genetic burden and disease threshold



(A) Classic monogenic model, dominated by a major genetic variant with high penetrance and a large biological effect size, with little influence from genetic, epigenetic, and environmental modifiers. (B) Monogenic model, in which a major genetic variant with incomplete penetrance interacts with modifiers that determine clinical expressivity.(E and F) Polygenic model determined by the cumulative effect of numerous SNPs with small individual effect sizes distributed across different genes associated with modifiers that allow the penetrance threshold to be reached in (F), but not in (E)
(C) and (D) represent monogenic variants with intermediate effect sizes

Fig. 5. Distribution of genetic burden across monogenic and polygenic variants.



On the right, the Gaussian distribution (demonstrated for polygenic risk scores) of genetic burden is plotted in relation to a phenotypic criterion (e.g., LDL cholesterol, blood pressure, etc.) or an estimated risk (e.g., vascular event, atrial fibrillation, etc.). For comparative purposes, the theoretical distribution of high- and intermediate-penetrance monogenic variants is shown on the left.
In both panels, the distributions are schematically represented as Gaussian, based on the premise that genetic burden results from the interaction between the primary variant and multiple genetic, epigenetic, and environmental modifiers that determine penetrance and expressivity, thereby conferring the behavior of a continuous variable.
In polygenic diseases, the greater dispersion of the curve reflects the cumulative effect size of multiple small-effect size variants and their associated modifiers, while their overlap indicates a lower discriminatory capacity.
For polygenic variants, the cutoff point balances sensitivity (≈70%) and specificity (≈80%); for monogenic variants, specificity is typically high (>90%), while population-level sensitivity is lower (<25%) due to their low prevalence.
The estimated risk (represented by a sigmoidal curve derived from logistic regression) progressively increases with tge genetic burden and with the probability of exhibiting the phenotype.
TP: true positives; FP: false positives; TN: true negatives; FN: false negatives.
This figure is intended solely for conceptual purposes and does not represent exact epidemiological distributions.

other words, the genotype constitutes the input or independent variable of the model, while the phenotype represents the output or dependent variable.

Figure 6 details various phenotypes used as outputs in clinical studies of predictive genetics in cardiology. Subclinical phenotypes can be analyzed as continuous or dichotomous variables, while clinical phenotypes are typically expressed as discrete variables corresponding to diseases or complications. (2-6)

Simple association, prognostic performance, and artificial intelligence

Associations between genetic variants and phenotypes, as reported by referall centers, do not necessarily imply prognostic utility in the general population. In general, these types of studies constitute an initial step that provides insight into the prevalence or incidence of one or more mutations. Clinical applicability requires subsequent evaluation of the actual predictive ability through prospective cohorts and longitudinal follow-up (Figure 7).

From a clinical perspective, prognostic performance studies determine whether a genetic marker adequately identifies individuals who will develop the disease by estimating sensitivity, specificity, and positive and negative predictive values. This step is essential before incorporating genetic variants into risk prediction models or individual clinical decisions. (7)

Artificial intelligence enables the simultaneous integration of large volumes of genetic, biological, and clinical information, overcoming the limitations of conventional statistical models based on only a few variables (Figure 8).

However, as complexity increases, the risk of spurious associations and overfitting rises, particularly due to the high number of simultaneous comparisons.

For this reason, the clinical utility of a model depends not only on its predictive ability but also on adequate calibration, discrimination and methodological validation during training in artificial intelligence.

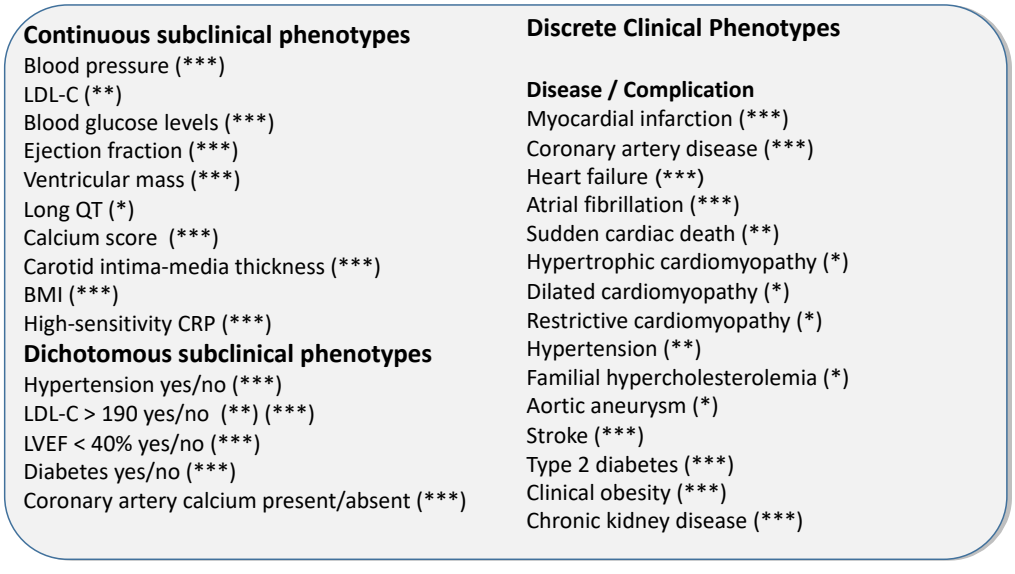
External validation is also a fundamental requirement before applying these models in clinical practice to correct potential errors resulting from multiple comparisons, but above all, to ensure reproducibility and generalizability across different populations. (8).

CONCLUSIONS

Genetic variants are often thought of as dichotomous variables (presence/absence), but this concept fails to capture the complexity of translating genetic information into clinical practice. Genetic burden is a theoretical concept that integrates multiple factors: inheritance pattern (dominant/recessive), functional impact of the variant (critical or non-critical region of the gene), and penetrance (complete/incomplete), all of which are influenced by genetic, epigenetic, and environmental modifiers.

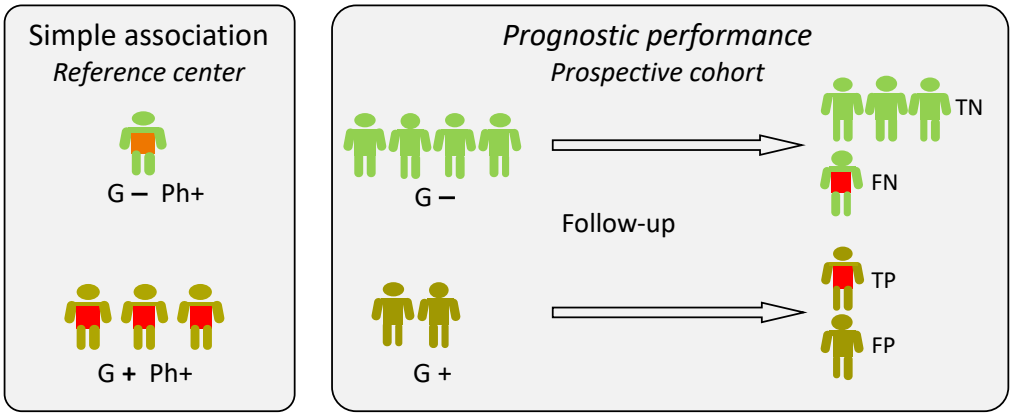
Environmental modifiers may not be within the strict concept of genetic burden and are instead considered additional factors that improve the predictive

Fig. 6. Subclinical and clinical phenotypes as outputs of genetic prediction



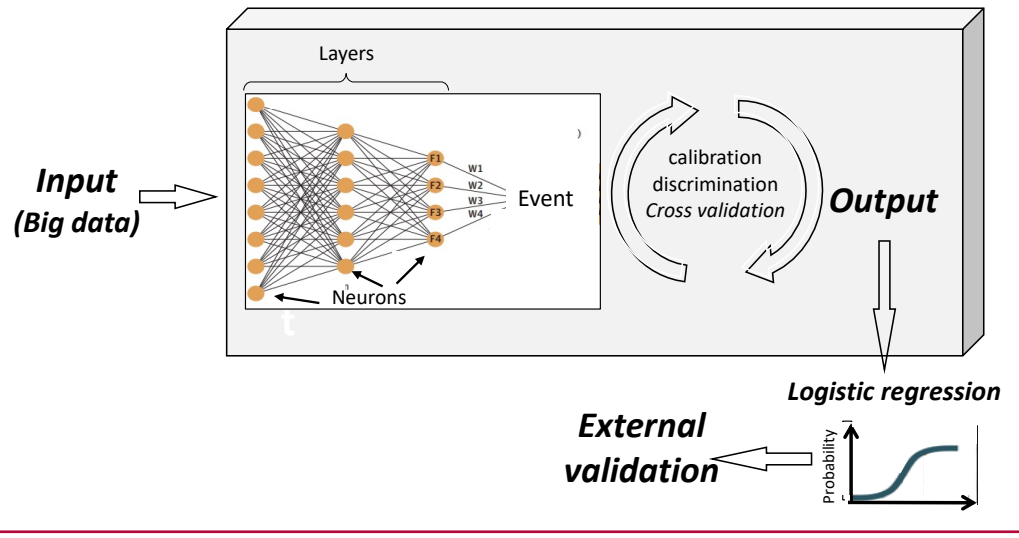
LVEF: left ventricular ejection fraction; HTN: hypertension; BMI: body mass index; LDL-C: low-density lipoprotein colesterol; CRP: C-reactive protein
The phenotypes explored in clinical trials are detailed below.
Subclinical phenotypes can be analyzed as continuous or dichotomous variables, while clinical phenotypes are typically expressed as discrete variables corresponding to diseases or their complications.
The magnitude of the relative genetic contribution across different genotypes is indicated as follows:
* large-effect size monogenic; ** monogenic and polygenic; *** polygenic.

Fig. 7. Simple association versus genetic prognostic performance



Left: The association between genetic variant (G+) and phenotype (F+) in referral centers reflects case enrichment resulting from selective referral, but without estimating predictive capacity
Right: In prospective cohorts, clinical follow-up allows for the estimation of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN), thereby enabling an evaluation of prognostic performance of the genetic variant.

Fig. 8. Conceptual diagram of an artificial intelligence model applied to clinical prediction



Multiple possible input variables are processed through interconnected layers of an artificial neural network. Each layer is represented by yellow dots, each of which represents a "neuron." Starting with approximately one million SNPs (typical range 500 000- 2 000 000) as input covariates, the AI model generates multiple regression equations in each neuron that are fitted to predict the event. In the first layers (for example, 100 equations constructed from approximately 1 million covariates each χF1 x W1) ; F2 x W2 ; F1 million x W1 million χ, where F is the SNP and W is the assigned weight). In successive layers, the information is progressively reduced until a few latent variables are obtained in the final stage (for example, 20: [F1 × W1]; F2 × W2; F20 × W20]). Integrating these functions generates a continuous score that is subsequently transformed into an estimated probability of the event or disease (output).
During this process, the model's predictive performance is assessed through internal validation, calibration, and discrimination, to reduce errors arising from multiple comparisons and improving the model's generalizability.
Final clinical applicability also requires external validation to generalize its conclusions.

capacity of clinical models.

Genetic variables basically include two major groups:

- monogenic variables with large or intermediate effect size (prevalence <1%), with a Mendelian pattern of transmission.
- polygenic variables (PRS, acronym for polygenic risk score), defined as the sum of multiple SNPs (prevalence >1%).

In monogenic diseases with a polygenic background, the inclusion of SNPs improves risk estimation.

As with any biological marker, the genetic burden for diagnostic or prognostic purposes must be inter-

preted with the general guidelines for evaluating biological tests.

In polygenic scores, sensitivity, specificity, positive predictive value, and negative predictive value are the parameters used to determine the clinical utility of genetic testing. In general, genetic information is integrated with conventional clinical scores.

In subjects with a positive genotype, the phenotypic expression significantly increases the probability of disease. Conversely, an isolated negative phenotype has limited value, a critical consideration in translating genetic information into medical decision-making.

Artificial intelligence expands and facilitates the analysis of large volumes of genetic information; however, its interpretive foundations remain based on the classical principles of statistics and probability.

Big data analysis significantly increases the risk of false positives due to multiple comparisons and statistical overfitting. Therefore, external validation is essential to confirm the consistency and reproducibility of initial findings.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

Allopurinol and Its Potential Cardioprotective Effect: A Narrative Review

Alopurinol y su potencial efecto cardioprotector: una revisión narrativa

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ABSTRACT

Allopurinol, a xanthine oxidase inhibitor traditionally used for gout and hyperuricemia, has emerged as a potential cardioprotective agent. Experimental and clinical studies suggest that its benefits extend beyond uric acid reduction and include modulation of oxidative stress, endothelial dysfunction, and myocardial remodeling. Although large, randomized trials in the general population have yielded neutral results, some exploratory analyses and studies in specific clinical subgroups have reported potentially favorable findings in patients with hyperuricemia, chronic kidney disease, or heart failure.

The cardiovascular efficacy of allopurinol appears to depend on the patient's metabolic phenotype and oxidative-inflammatory burden. Its role extends beyond urate reduction, acting as a redox and metabolic modulator. Further stratified clinical trials are needed to confirm its benefits in high-risk cardiorenometabolic populations.

Keywords: Allopurinol - Xanthine oxidase inhibition - Cardiovascular protection - Oxidative stress - Endothelial dysfunction - Heart failure.

RESUMEN

El alopurinol, un inhibidor de la xantina oxidasa utilizado tradicionalmente para la gota y la hiperuricemia, ha surgido como un potencial agente cardioprotector. Los estudios experimentales y clínicos sugieren que sus beneficios se extienden más allá de la reducción del ácido úrico, y abarcan la modulación del estrés oxidativo, la disfunción endotelial y el remodelado miocárdico. Aunque los grandes ensayos aleatorizados en la población general han tenido resultados neutros, algunos análisis exploratorios y estudios en subgrupos clínicos han mostrado hallazgos potencialmente favorables en pacientes con hiperuricemia, enfermedad renal crónica o insuficiencia cardíaca.

La eficacia cardiovascular del alopurinol parece depender del fenotipo metabólico y de la carga oxidativa–inflamatoria del paciente. Su función se extiende más allá de la reducción de urato, actuando como un modulador redox y metabólico. Se necesitan ensayos clínicos estratificados adicionales para confirmar sus beneficios en poblaciones cardiorrenometabólicas de alto riesgo.

Palabras clave: Alopurinol - Inhibición de la xantina oxidasa - Protección cardiovascular - Estrés oxidativo - Disfunción endotelial - Insuficiencia cardíaca

INTRODUCTION

Allopurinol, a competitive inhibitor of xanthine oxidase (XO), has been used for more than six decades to treat hyperuricemia and gout. However, its potential role as a cardioprotective agent has attracted increasing interest in recent years, given evidence linking serum uric acid (SUA) to endothelial dysfunction, oxidative stress, arterial stiffness, left ventricular hypertrophy (LVH), and major adverse cardiovascular events (MACE). (1–4) From a pathophysiological perspective, XO is a key source of reactive oxygen species (ROS), and its inhibition by allopurinol may improve nitric oxide bioavailability, reduce vascular inflammation, and attenuate myocardial remodeling. (5–7)

Early clinical studies suggested structural and vascular benefits of allopurinol, including improved endothelial function and reduced left ventricular mass. (5,6) However, recent randomized clinical trials, such

Rev Argent Cardiol 2026;94:323-334. https://doi.org/10.7775/rac.v94.i4.21028

Received: 11/29/2025 – *Accepted:* 05/18/2026

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as ALL-HEART, did not demonstrate a significant reduction in major adverse cardiovascular events in patients with stable ischemic heart disease. (8,9) This finding has prompted debate as to whether the potential beneficial effects of allopurinol depend on the clinical context (severe hyperuricemia, heart failure, or chronic kidney disease) rather than being universal. (1,10)

In addition, meta-analyses and cohort studies continue to show favorable associations between reductions in SUA levels and improvements in subclinical markers of cardiovascular damage. (11–15) However, recent research in patients with heart failure with preserved ejection fraction (HFpEF) did not suggest that the combination of allopurinol and verinurad may improve symptoms and functional capacity. (16)

This is further supported by evidence from large population-based cohorts. In the Swedish AMORIS study, Ding et al. found that elevated uric acid concentrations were associated with an increased risk of new-onset atrial fibrillation, broadening the spectrum of cardiovascular outcomes potentially linked to urate metabolism. (2)

In terms of causal inference, Mendelian randomization analyses and large-scale epidemiological studies suggest a possible role for uric acid in cardiovascular risk, although the magnitude of the clinical benefit associated with its pharmacological reduction remains uncertain. (4,17)

In this context, this narrative review aims to synthesize the most recent evidence on the cardiovascular effects of allopurinol, integrating pathophysiological, clinical, and epidemiological findings to discuss its potential role in the prevention and management of cardiovascular disease from an interdisciplinary perspective encompassing cardiology, internal medicine, rheumatology, and clinical epidemiology

METHODS

A narrative review was conducted to evaluate the potential cardiovascular effects of allopurinol. Publications in English and Spanish were searched in PubMed/MEDLINE, Embase, LILACS, the Cochrane Library, and Google Scholar from January 2015 to November 2025, with the last search conducted on November 1, 2025. MeSH terms, Emtree terms, and free-text terms related to allopurinol, xanthine oxidase inhibition, and cardiovascular outcomes were used; the complete search strategies are provided in the Supplementary Appendix.

Clinical trials, observational studies, systematic reviews, meta-analyses, Mendelian randomization studies, protocols, and relevant opinion articles were included, with priority given to cardiovascular outcomes, biomarkers, and pathophysiological mechanisms. Duplicate records, conference abstracts, letters without primary data, articles without full text, and studies lacking relevant cardiovascular information were excluded. The first three authors independently screened titles, abstracts, and full-text articles, with discrepancies resolved by consensus. Of the 1,316 records identified, 20 were included in the narrative synthesis (Figure 1).

RESULTS

1. Pathophysiology and cardioprotective mechanisms of allopurinol

The potential cardioprotective effect of allopurinol is based on the inhibition of XO, a key enzyme in purine metabolism that converts hypoxanthine to xanthine and subsequently to uric acid, generating superoxide radicals and hydrogen peroxide as byproducts. (1) This process contributes to vascular oxidative stress, one of the most relevant pathophysiological mechanisms in the development of endothelial dysfunction, myocardial hypertrophy, and atherosclerosis progression. (4,5,7)

a. Modulation of oxidative stress and endothelial dysfunction

Several studies have shown that XO inhibition significantly reduces ROS production, improves nitric oxide (NO) bioavailability, and restores endothelial function. (6,7) In a controlled trial, Borgi et al. evaluated the effect of urate-lowering agents on endothelial function. (6) Gaffo et al. did not observe a decrease in blood pressure with allopurinol in young adults in a crossover trial. (18) Similarly, the systematic review by Alem et al. showed consistent improvements in markers of endothelial function and arterial stiffness in patients with heart failure or chronic kidney disease (CKD). (7)

The reduction in ROS induced by allopurinol may also limit low-density lipoprotein (LDL) oxidation, reduce platelet activation, and attenuate endothelial inflammation—factors that collectively contribute to a more stable vascular microenvironment. (1)

b. Effects on ventricular hypertrophy and myocardial remodeling

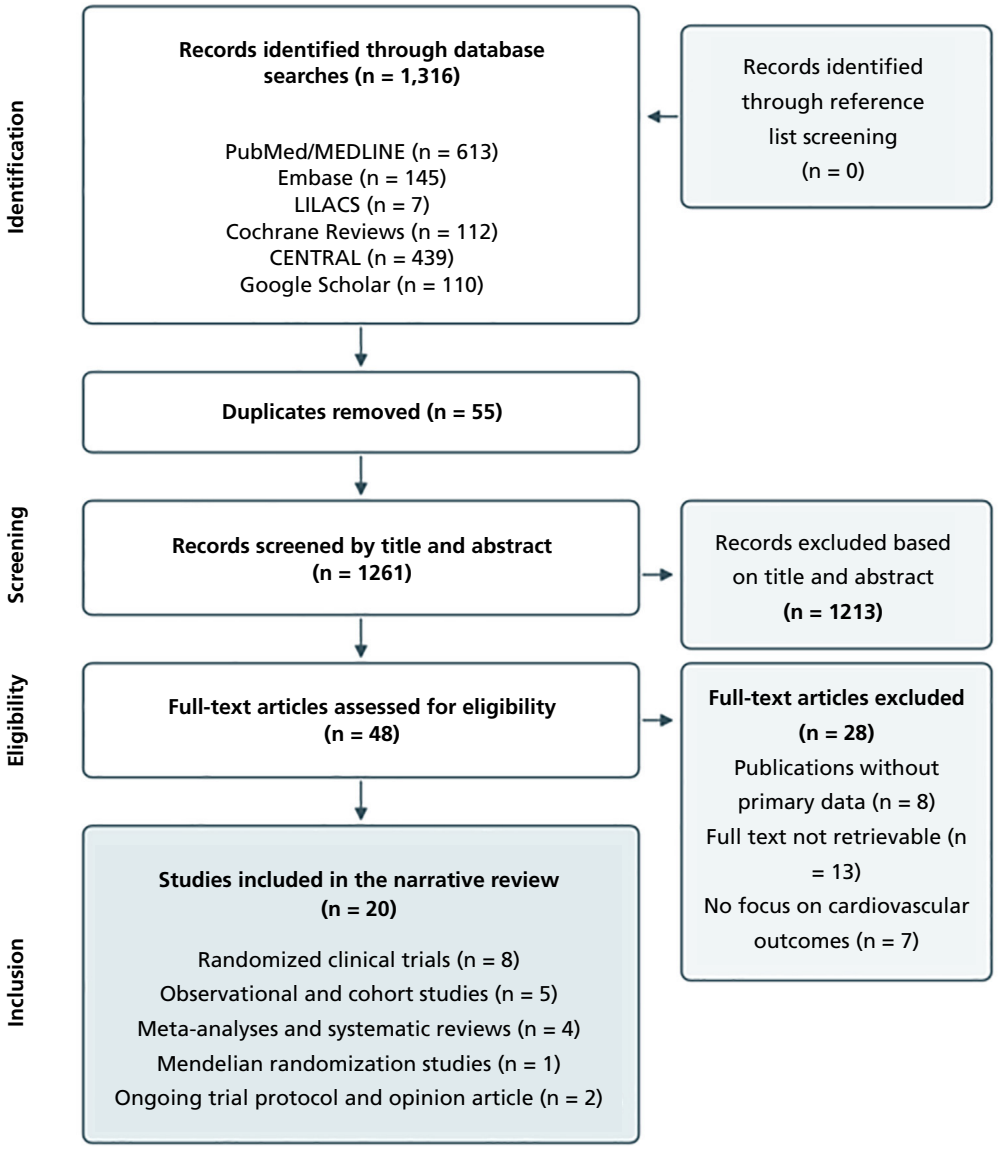
XO-derived oxidative stress contributes to prohypertrophic myocardial signaling through pathways such as mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF-κB). In the clinical setting, Rutherford et al. evaluated the effect of allopurinol on left ventricular mass index (LVMi) in hemodialysis patients. (5). These findings are consistent with the pathophysiological framework linking XO activity to interstitial fibrosis and myocardial oxidative stress. (1)

The hypothesis of reversible oxidative remodeling proposes that sustained reduction of oxidative stress with allopurinol may partially reverse left ventricular hypertrophy and improve myocardial efficiency, particularly in the early stages of heart failure. (5,7)

c. Influence on inflammation and myocardial energy metabolism

Excess uric acid and increased XO activity activate the NLRP3 inflammasome, promoting systemic and local inflammatory responses that accelerate endothelial injury and atherogenesis. (1) It has been proposed that allopurinol favorably modulates redox balance and reduces the expression of proinflammatory cy-

Fig. 1. Flow diagram of the study selection process for the narrative review



tokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). (1)

Furthermore, by limiting ROS generation, allopurinol optimizes myocardial energy metabolism, promotes oxidative phosphorylation, and reduces myocardial oxygen consumption during cardiac work. (1) This mechanism could explain the hemodynamic benefits observed in patients with heart failure with reduced ejection fraction (HFrEF) and hyperuricemia. (19)

d. Effects on metabolic and renal comorbidities

Hyperuricemia is closely associated with cardiorenometabolic syndrome, characterized by insulin resistance, low-grade inflammation, and persistent endothelial dysfunction. (4) In this context, allopurinol may exert a pleiotropic effect, improve metabolic and renal control, and reduce the progression of nephropathy and secondary cardiac overload. (5,13) These integrated mechanisms support the potential role of allopurinol in the secondary prevention of cardiovascular disease in patients with gout, CKD, or high metabolic risk.

2. Clinical evidence on the cardiovascular effects of allopurinol

The potential cardiovascular benefit of allopurinol has been investigated over the past two decades through observational studies, randomized clinical trials (RCTs), and meta-analyses with heterogeneous

results. Current evidence suggests that, although allopurinol improves intermediate parameters such as endothelial function, left ventricular mass, or functional capacity, it has not been shown to conclusively reduce MACE in the general population with established cardiovascular disease.

a. Randomized clinical trials

The ALL-HEART study remains the largest to date on this topic. It included 5721 patients aged ≥60 years with stable coronary artery disease and no history of gout, who were randomly assigned to receive allopurinol (600 mg/day) or usual care. After a median follow-up of 4.8 years, no significant difference was observed in the composite endpoint of cardiovascular death, myocardial infarction, or stroke. These results were interpreted as evidence that XO inhibition does not provide a universal cardiovascular benefit and that its effects may depend on the patient's clinical and metabolic phenotype. (8)

In the EXACT-HF trial, which included patients with heart failure with reduced ejection fraction (HFrEF) and hyperuricemia, allopurinol reduced SUA levels. However, it had a clinically neutral effect, with no significant improvement in the primary endpoint, symptoms, quality of life, or ventricular remodeling. (19) These findings suggest that, although allopurinol effectively reduces uric acid levels, its clinical effects on cardiac function may depend on specific pathophysiological conditions, such as elevated oxidative stress or severe endothelial dysfunction.

More recently, the ALL-VASCOR study was designed to evaluate whether allopurinol at doses of 200–500 mg/day in patients with high cardiovascular risk but without gout could modify markers of arterial stiffness and left ventricular mass. Although the final results have yet to be published, preliminary reports indicate a neutral effect on major clinical outcomes but modest improvements in subclinical hemodynamic parameters. (10)

Finally, in the context of HFpEF, the study by Kitzman et al. evaluated the combination of verinurad and allopurinol to enhance the reduction of uric acid and oxidative stress. A reduction in serum uric acid levels was observed, along with modest changes in certain functional parameters; however, no significant clinical benefits were demonstrated for the evaluated cardiovascular outcomes. (16) These findings call into question whether combined inhibition of urate metabolism may be more effective than isolated XO blockade.

b. Observational and cohort studies

Large population-based studies have reported associations between allopurinol use and a lower incidence of cardiovascular events, although residual confounding is possible. In the cohort by Drivelegka et al., continuous allopurinol therapy in patients with incident gout was associated with a 15–20% reduction in the incidence of acute coronary syndrome, particularly among those who achieved serum uric acid levels <6 mg/dL. (12) Similarly, Cipolletta et al. reported that patients with gout who initiated urate-lowering therapy—colchicine or allopurinol— had a lower risk of hospitalization for cardiovascular causes. (13)

Furthermore, epidemiological studies and Mendelian randomization analyses suggest a possible causal link between hyperuricemia and cardiovascular risk. Zhang et al., Ding et al., and Liu et al. reported an association between elevated uric acid levels and an increased risk of coronary artery disease, atrial fibrillation, and all-cause mortality, reinforcing the hypothesis that urate acts as a pathophysiological mediator rather than a mere epiphenomenon. (2,3,17)

c. Meta-analyses and systematic reviews

The meta-analysis by Lin et al., which included more than 20 000 patients treated with allopurinol or febuxostat, showed a trend toward a lower risk of cardiovascular mortality with allopurinol, although the difference did not reach statistical significance. (11) Similarly, Van der Pol et al. reported a neutral-to-beneficial effect on major cardiovascular events but noted substantial heterogeneity and low-quality evidence across the observational studies. (14)

These findings should be interpreted with caution. Although the available meta-analyses have reported potentially favorable associations between allopurinol use and certain cardiovascular outcomes, the results are characterized by methodological heterogeneity and are based primarily on observational studies and aggregated data, limiting the strength of the conclusions. (1,15) Furthermore, the lack of consistent findings in large-scale randomized clinical trials such as ALL-HEART and EXACT-HF makes it difficult to establish a definitive cardioprotective effect. (8,19)

d. Clinical interpretation and outlook

Overall, the evidence suggests that allopurinol has a favorable and safe pathophysiological profile, but its cardiovascular clinical benefit is not uniform. While large RCTs in the general population have yielded neutral results, studies in specific contexts—including gout, CKD, HFrEF, and cardiorenometabolic phenotypes—suggest potential effects on subclinical biomarkers and pathophysiological parameters. However, no conclusive evidence of a reduction in major cardiovascular events has been demonstrated.

From an epidemiological perspective, these discrepancies may reflect the influence of confounding biological factors such as baseline uric acid levels, inflammatory activity, or endothelial oxidative stress. Therefore, targeted trials in selected populations with high-risk cardiorenometabolic phenotypes are needed to determine whether sustained XO inhibition can indeed translate into reductions in major cardiovascular events.

DISCUSSION

The accumulated evidence on allopurinol and its potential cardioprotective effects has evolved from promising pathophysiological observations towards a more nuanced understanding of its clinical limitations. Although XO inhibition reduces oxidative stress, improves endothelial function, and attenuates myocardial hypertrophy, large clinical trials such as ALL-HEART have shown that these biological effects do not necessarily translate into a significant reduction in major cardiovascular events. (8) The apparent discrepancy between the observed pathophysiological benefits and neutral clinical outcomes may reflect differences between the effects on intermediate biomarkers and the major cardiovascular outcomes assessed in clinical studies. Although some observational studies and exploratory analyses have suggested potentially favorable associations in certain clinical subgroups, these findings should be interpreted with caution, as they have not been consistently confirmed in large-scale RCTs. (8,10)

The apparent discrepancy between pathophysiological benefits and clinical outcomes may be explained by heterogeneity among the study populations and confounding factors such as baseline uric acid levels, renal function, and systemic inflammatory burden. (10,11,16,19) In patients with stable coronary artery disease and moderate uric acid levels, XO-induced oxidative stress may not be a key determinant of cardiovascular risk. In contrast, subgroups with overt hyperuricemia, CKD, heart failure, or cardiorenometabolic syndrome exhibit significantly greater oxidative and inflammatory burdens, in which XO inhibition might play a more relevant and clinically detectable role. (12–15)

From an epidemiological and mechanistic perspective, Mendelian randomization studies suggest a possible biological link between genetically determined uric acid levels and an increased risk of coronary artery disease, atrial fibrillation, and cardiovascular mortality. (17) Such evidence suggests that uric acid acts as a marker and potentially as a pathogenic mediator within complex metabolic phenotypes. Thus, allopurinol may be considered not merely a urate-lowering agent but also a redox and metabolic modulator whose clinical impact depends on the severity of oxidative stress and the underlying inflammatory context.

In this context, the CARES trial (20) provides highly relevant complementary information. In more than 6,000 patients with gout and established cardiovascular disease, febuxostat and allopurinol showed similar rates of MACE, but higher rates of cardiovascular and all-cause mortality were observed in the febuxostat group. Although CARES was not designed to evaluate the benefits of allopurinol, its results reinforce the favorable cardiovascular safety profile of allopurinol, particularly in high-risk populations. Clinically, this finding suggests that, unlike other XO inhibitors, allopurinol does not increase cardiovascular risk and may have a neutral or even beneficial effect on overall mortality in patients with cardiovascular or renal comorbidities.

Furthermore, recent controlled studies and systematic reviews have shown that reductions in SUA levels with allopurinol are associated with improvements in subclinical parameters of arterial stiffness, endothelial function, and ventricular remodeling. (5–7,18) In patients with HFpEF, XO inhibition may improve functional capacity and reduce myocardial stress, particularly when endothelial dysfunction or persistent hyperuricemia is present. (16) Although not yet definitive, these findings align with the pathophysiological framework linking excessive ROS production to progressive hemodynamic deterioration.

From an epidemiological and public health perspective, discrepancies among experimental, clinical, and observational findings may also reflect the multifactorial nature of the determinants of cardiovascular risk in the general population. In large cohorts, hyperuricemia often coexists with obesity, insulin resistance, hypertension, and CKD, acting more as a marker of systemic metabolic dysfunction than as an isolated pathogenic factor. (4) Therefore, the clinical efficacy of allopurinol may depend not only on its ability to reduce urate levels but also on its effects on redox balance, endothelial function, and metabolic homeostasis in predisposed individuals.

Table 1 summarizes the main lines of evidence supporting the physiological plausibility of a cardioprotective role for allopurinol, integrating findings from randomized clinical trials, subgroup analyses, cohort studies, and Mendelian randomization data. Taken together, these findings suggest a consistent pattern in which allopurinol appears to exert greater benefit in phenotypes characterized by high oxidative stress and metabolic inflammation.

Taken as a whole, the available evidence suggests that the cardiovascular effects of allopurinol may vary according to the clinical context and the patient's metabolic profile. Although large RCTs have shown predominantly neutral results with respect to major cardiovascular events, some observational studies and exploratory analyses have reported potentially favorable associations in patients with hyperuricemia, CKD, or heart failure. However, these findings remain heterogeneous and do not establish a conclusive cardioprotective effect. In this context, the CARES trial (20) provides relevant information on the comparative cardiovascular safety of XO inhibitors, although it was not designed to demonstrate specific cardiovascular benefits of allopurinol.

CONCLUSIONS

Allopurinol remains the drug of choice for the management of gout and hyperuricemia; however, its potential cardiovascular role remains under investigation

Table 1. Summary of key evidence supporting the physiological plausibility of allopurinol's cardioprotective effect

Study type	Key findings	Clinical Implications	Source
ALL-HEART (large randomized clinical trial)	No significant differences in MACE were observed in patients with stable ischemic heart disease.	These findings do not support a universal cardiovascular benefit of allopurinol in stable coronary artery disease.	(8,9)
Subgroup studies (marked hyperuricemia, heart failure, chronic kidney disease)	Hemodynamic, endothelial, and structural improvements were observed. In heart failure with preserved ejection fraction (HFpEF), the combination of verinurad and allopurinol was not associated with symptomatic improvement.	These exploratory findings in clinical subgroups require confirmation in prospective studies.	(5–7,16,18,19)
Cohort studies (e.g., gout)	Continuous allopurinol therapy was associated with a 15–20% reduction in the incidence of acute coronary syndrome.	These observational associations do not establish a causal cardiovascular benefit.	(12,13)
Mendelian randomization studies	These studies suggest a possible role for uric acid in cardiovascular risk.	These findings support the biological plausibility of a potential role of uric acid in cardiovascular disease.	(2,3,17)

ICFEp: insuficiencia cardíaca con fracción de eyección preservada; MACE: eventos adversos cardiovasculares mayores

and appears to depend on the clinical and metabolic context. Current evidence suggests that:

1. In the general population with stable cardiovascular disease, allopurinol does not significantly reduce major cardiovascular events.
2. XO inhibition by allopurinol remains a biologically plausible strategy for modulating mechanisms related to oxidative stress, endothelial dysfunction, and cardiovascular remodeling; however, this pathophysiological plausibility has not consistently translated into a reduction in major cardiovascular events in the available RCTs.
3. The heterogeneity observed across mechanistic, observational, and clinical results suggests that the potential cardiovascular impact of allopurinol may depend on the patient's baseline metabolic and inflammatory profile, particularly in settings characterized by hyperuricemia, CKD, or heart failure.
4. Although some exploratory studies and subgroup analyses have shown potentially favorable effects on vascular biomarkers and functional parameters, the current evidence remains insufficient to establish a definitive cardioprotective effect or to recommend the use of allopurinol for cardiovascular prevention.
5. Future research should focus on carefully phenotyped populations and clinically relevant outcomes to determine whether sustained modulation of XO-dependent oxidative pathways could have clinically relevant therapeutic implications within the cardiorenal and metabolic spectrum.

Funding

This work has not received external funding.

Conflicts of interest

None declared.

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

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SUPPLEMENTARY APPENDIX. SEARCH STRATEGY AND SEARCH RECORD S

Allopurinol and its potential cardioprotective effect: a narrative review

Rev Argent Cardiol · Restrepo Manuscript

Databases searched: PubMed/MEDLINE, Embase, LILACS, Cochrane Library, and Google Scholar. Publication period: January 1, 2015-November 1, 2025. Languages: English and Spanish. Controlled vocabulary (MeSH, Emtree) was combined with free-text terms in titles and abstracts using Boolean operators. The search was last conducted on November 15, 2025.

1. Search structure

The search combined two conceptual blocks using the AND operator, such that each record had to address both the pharmacological intervention and a cardiovascular outcome.

Block	Terms
A. Pharmacological Intervention	allopurinol; xanthine oxidase inhibitor; urate-lowering therapy; verinurad
B. Cardiovascular Outcomes	cardiovascular diseases; major adverse cardiovascular events; myocardial infarction; heart failure; atrial fibrillation; endothelial function; flow-mediated dilation; arterial stiffness; left ventricular hypertrophy; left ventricular mass; cardiorenal syndrome

A broader strategy was initially tested by incorporating a third metabolic exposure block (uric acid, hyperuricemia, gout) combined with the block A terms using the OR operator. That version retrieved 7,648 records in PubMed and 35,346 in Embase. These figures were considered incompatible with exhaustive screening and indicative of a markedly nonspecific search, as it included literature on uric acid unrelated to the pharmacological inhibition of xanthine oxidase. The strategy was therefore narrowed to the two-block structure reported here.

2. PubMed / MEDLINE

Interface: pubmed.ncbi.nlm.nih.gov—Advanced Search Builder. The search was run as a single query.

```
("Allopurinol"[MeSH] OR allopurinol[tiab]
 OR "xanthine oxidase inhibitor*"[tiab]
 OR "urate-lowering therapy"[tiab] OR verinurad[tiab])
AND
("Cardiovascular Diseases"[MeSH]
 OR "major adverse cardiovascular event*"[tiab]
 OR "Myocardial Infarction"[MeSH]
 OR "Heart Failure"[MeSH] OR "heart failure"[tiab]
 OR "Atrial Fibrillation"[MeSH] OR "atrial fibrillation"[tiab]
 OR "Endothelium, Vascular"[MeSH] OR "endothelial function"[tiab]
 OR "flow-mediated dilation"[tiab]
 OR "Vascular Stiffness"[MeSH] OR "arterial stiffness"[tiab]
 OR "Left Ventricular Hypertrophy"[MeSH]
 OR "left ventricular mass"[tiab]
 OR "Cardio-Renal Syndrome"[MeSH] OR "cardiorenal"[tiab])
AND ("2015/01/01"[PDAT] : "2025/12/31"[PDAT])
AND (English[Filter] OR Spanish[Filter])
```

Records retrieved: 613

3. Embase

Interface: embase.com—Advanced Search, with Emtree terms enabled. The search was run as a single query.

```
('allopurinol'/exp/dd_dt,dd_ct OR allopurinol:ti
 OR 'urate lowering therapy':ti OR verinurad:ti)
AND
('cardiovascular disease'/mj
 OR 'heart infarction'/mj
 OR 'heart failure'/mj
 OR 'atrial fibrillation'/mj
 OR 'endothelial function':ti
 OR 'flow-mediated vasodilation'/mj
 OR 'arterial stiffness'/mj
 OR 'left ventricular hypertrophy'/mj
 OR 'left ventricular mass':ti
 OR 'cardiorenal syndrome'/mj)
AND [2015–2025]/py
AND ([English]/lim OR [Spanish]/lim)
AND [humans]/lim
AND ([article]/lim OR [review]/lim)
NOT ([conference abstract]/lim OR [conference paper]/lim)
```

Records retrieved: 145

3b. Progressive refinement of the strategy in Embase

The effect of each successive restriction is documented because the initial version proved to be nonspecific.

Strategy version	Records	Reduction
Three blocks, with no field or publication-type restrictions	35,346	—
Two blocks; title restriction; Emtree subheadings; human, publication-type, and conference-abstract limits	1,389	96.1%
Addition of a major topic restriction (/mj) to the cardiovascular block	145	89.6%

4. LILACS

Interface: pesquisa.bvsalud.org, with a LILACS database filter. It was included to retrieve regional Latin American literature not indexed in the previous databases, given that the manuscript is published in the Ibero-American context.

```
(alopurinol OR allopurinol OR "acido urico" OR "ácido úrico"
 OR hiperuricemia OR gota)
AND
(cardiovascular OR "insuficiencia cardiaca" OR "insuficiencia cardíaca"
 OR "fibrilacion auricular" OR "funcion endotelial"
 OR "hipertrofia ventricular" OR "estres oxidativo"
 OR cardiorrenal)
AND (year cluster:[2015 TO 2025])
```

Records retrieved: 7

The three-block strategy was retained for LILACS, with no field restrictions, given the relatively small size of the database and to maximize sensitivity for regional literature.

5. Cochrane Library

Interface: cochranelibrary.com—Advanced Search. Cochrane Database of Systematic Reviews, Issue 8 of 12, November 2025. The search was run as a single query using the Title, Abstract, and Keyword fields.

```
(allopurinol OR "xanthine oxidase inhibitor" OR "urate lowering")
AND
(cardiovascular OR "heart failure" OR "atrial fibrillation"
 OR "endothelial function" OR "arterial stiffness"
 OR "left ventricular" OR cardiorenal)
```

Library segment	Records	Screening
Cochrane Reviews	2	Yes
Trials (CENTRAL)	439	Yes
Protocols, editorials, special collections, and clinical responses	0	—

Records retrieved and included in screening: 441 (2 systematic reviews and 439 trials from the CENTRAL registry).

6. Google Scholar

Google Scholar does not support controlled vocabulary, field tags, or reliable result counts. Therefore, a predefined number of results sorted by relevance were reviewed in accordance with standard practice. Customized date range: 2015–2025; patents and citations were excluded.

```
allopurinol AND ("cardiovascular outcomes" OR "heart failure"
 OR "endothelial function" OR "left ventricular mass")
```

Screened records: 110 (first 110 results sorted by relevance). This was reported in the Methods section.

7. Search record

Google Scholar does not support controlled vocabulary, field tags, or reliable result counts. Therefore, a predefined number of results sorted by relevance were reviewed in accordance with standard practice. Customized date range: 2015–2025; patents and citations were excluded.

Database	Date	Records	Notes
PubMed/MEDLINE	December 1, 2025	613	Two-block strategy
Embase	December 1, 2025	145	Refined strategy; see Section 3b
LILACS	December 1, 2025	7	Three-block strategy, with no field restrictions
Cochrane Library— Reviews	December 1, 2025	2	Cochrane Database of Systematic Reviews
Cochrane Library— CENTRAL	December 1, 2025	439	Trial registry; included in screening
Google Scholar	December 1, 2025	110	First 110 results by relevance
A. Total identified in databases		**1,316**	
B. Identified through reference list screening		**0**	

8. Screening cascade

The values in this table should be transferred to Figure 1 of the manuscript. The three arithmetic identities must be verified before submission.

Stage	n	Check
C. Duplicates removed	55	Provisional; see note
D. Records screened by title and abstract	1,261	A + B – C
E. Excluded based on title and abstract	1,213	
F. Full-text articles assessed for eligibility F1. Excluded—publications without primary data F2. Excluded—full text not retrievable F3. Excluded—no focus on cardiovascular outcomes or pathophysiological relevance	48 8 13 7	D – E 7 conference abstracts and 1 letter
G. Total full-text articles excluded	28	F1 + F2 + F3
H. Included in the narrative synthesis	**20**	**F – G**

8b. Method used for duplicate detection

The records were exported from each database (PubMed in .nbib format and Embase in RIS format) and programmatically matched, first by Digital Object Identifier (DOI) and then by normalized title for records without a DOI.

Detection method	Identified duplicates
By Digital Object Identifier (DOI)	17
By normalized title, in records without a DOI	38
Total (provisional, PubMed vs. Embase)	55

9. Eligibility criteria applied in the full-text phase

Included	Excluded
Randomized clinical trials	Conference abstracts
Observational studies (cohort, case-control, cross-sectional)	Letters without primary data
Systematic reviews and meta-analyses	Articles without full text available
Mendelian randomization studies	Studies without cardiovascular outcomes or pathophysiological relevance
Protocols for ongoing trials of direct relevance	Publications outside the 2015–2025 period or in languages other than English and Spanish Duplicate publications

10. Reviewers and resolution of discrepancies

Role	Author
Screening—Reviewer 1	C.M.R.G. (Carlos Manuel Restrepo-Guette)
Screening—Reviewer 2	E.F. (Elías Forero)
Screening—Reviewer 3	J.C.G.D. (Juan Camilo García-Domínguez)
Procedure	The three reviewers independently screened all records, both at the title and abstract stage and at the full-text stage. Disagreements were resolved through discussion among the three reviewers until consensus was reached

11. Methodological assessment tools

The assessment guided the weight assigned to each body of evidence and was not used as an exclusion criterion, consistent with the article's narrative design.

Study design	Tool
Systematic reviews and meta-analyses	AMSTAR-2
Randomized clinical trials	Cochrane RoB 2
Observational studies	Newcastle-Ottawa Scale
Mendelian randomization studies	Core instrumental variable assumptions

12. Search limitations

- Duplicate detection was initially performed between PubMed and Embase; an update using the CENTRAL registry export is pending and will change the number of records screened by title and abstract.
- Thirteen of the forty-eight articles evaluated in the full-text phase could not be retrieved due to institutional access limitations, which constitutes a potential source of availability bias.
- The strategy applied in Embase was deliberately more restrictive than that used in PubMed, as it required the drug to appear in the title and a cardiovascular outcome to be designated as a major topic. This approach prioritized specificity over sensitivity and may have excluded relevant studies that were less precisely indexed.
- A review protocol was not registered in advance, which is a common practice in narrative reviews but should be explicitly stated.
- The restriction to English and Spanish may introduce language bias.
- The 2015-2025 time frame excludes earlier foundational literature on xanthine oxidase inhibition.
- No search was conducted in gray literature or in clinical trial registries beyond the protocols identified in the databases searched.

Angiographic Characterization of the Left Main Coronary Artery Following Surgical Repair of Anomalous Origin of the Left Main Coronary Artery from the Pulmonary Artery (ALCAPA)

Caracterización angiográfica del tronco coronario izquierdo tras corrección quirúrgica de anomalía del origen de la arteria coronaria izquierda desde la arteria pulmonar (ALCAPA)

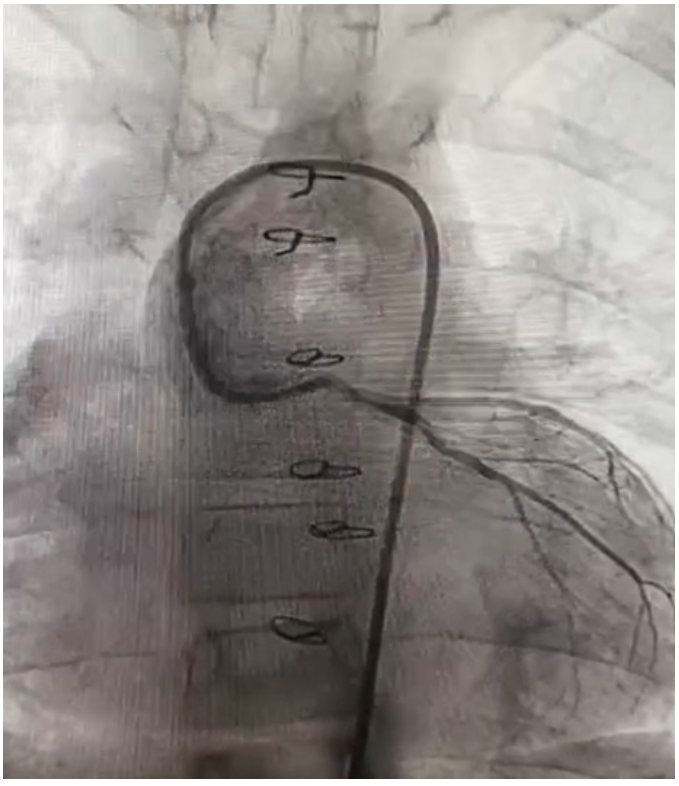
CARLOS VARGAS ECHEVERRÍA[1], RAFAEL ECHEVERRÍA[2], LUISA VARGAS ECHEVERRÍA[3]

A 10-year-old asymptomatic female patient with a history of anomalous origin of the left main coronary artery from the pulmonary artery (ALCAPA) surgically corrected during childhood (1) was referred for cardiac catheterization as part of follow-up evaluation of the previously treated congenital heart disease.

The initial aortogram showed no evidence of residual shunts or a patent ductus arteriosus (Figure 1). During the procedure, the left coronary artery territory had a smaller diameter compared to the right coronary artery territory; therefore, selective coronary angiography was performed for detailed anatomical characterization.

Selective contrast injection using a Tiger catheter demonstrated adequate reimplantation of the left main coronary artery into the aorta, associated with narrowing of the proximal segment and diffuse reduction in ves-

Fig. 1. Aortogram showing no evidence of a patent ductus arteriosus.



Rev Argent Cardiol 2026;94:335-336. https://doi.org/10.7775.rac.94.i4.21032

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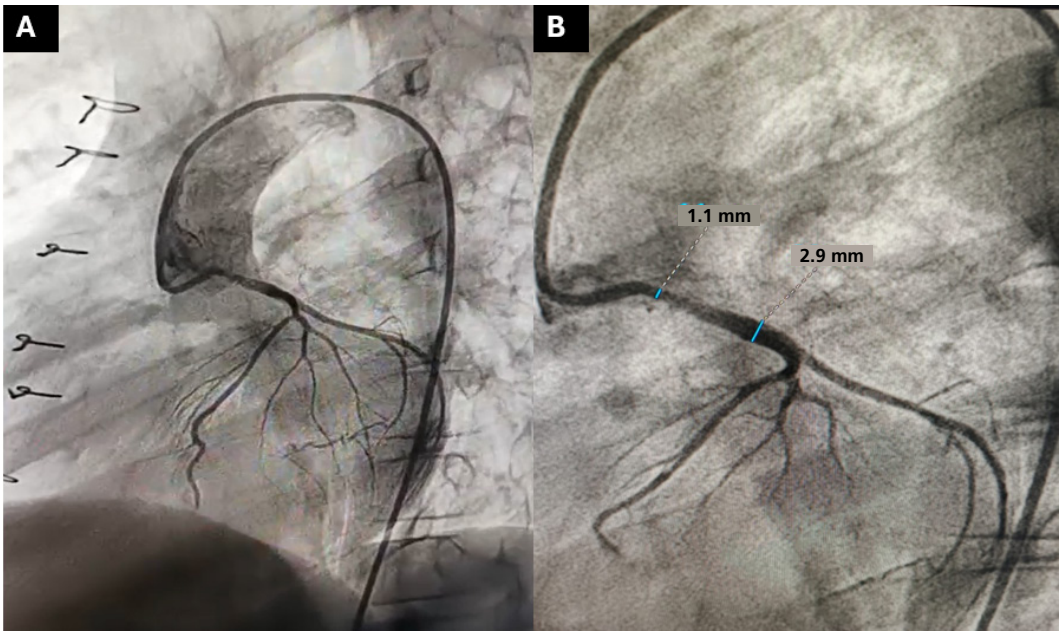
Fig. 2. Selective angiogram of the left main coronary artery. A) Reimplantation of the left main coronary artery into the aorta. B) Narrowing of the proximal segment and diffuse reduction in vessel diameter, with good distal opacification.



sel diameter (Figure 2A-B), with good distal opacification. There were no hemodynamic abnormalities during the procedure.

The angiographic findings were consistent with residual coronary changes following surgical correction of ALCAPA. In this context, assessment of coronary artery anatomy remains an important component of long-term follow-up, even in patients without clinical manifestations. (1,2)

This case highlights the utility of cardiac catheterization for characterizing the anatomy of coronary arteries in pediatric patients with corrected congenital heart diseases and identifying relevant angiographic findings during follow-up. (3)

Ethical considerations

The authors obtained informed consent from the patient.

Conflicts of interest

None declared (See authors' conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Heart Failure in a Patient with Congenital Complete Atrioventricular Block. A Metabolic Disorder Presenting as an Arrhythmia

Insuficiencia cardíaca en paciente con bloqueo auriculoventricular completo congénito. Detrás de una arritmia, una metabolopatía

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Dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by ventricular dilation and systolic dysfunction leading to heart failure (HF). Its incidence is approximately 0.57 cases per 100 000 people-year. (1,2) The etiology of DCM is multifactorial, with idiopathic cases being most common. Other causes include myocarditis, neuromuscular diseases, ischemia, genetic abnormalities, metabolic disorders, toxins, arrhythmias, and endocrine disorders, among others. (1,2)

Congenital complete atrioventricular block (CCAVB) is a rare condition with an incidence of 1 per 20 000 live births (LB). Early diagnosis is feasible with fetal echocardiography. It is well known that an inadequate heart rate (HR) leads to ventricular dysfunction in some patients with the subsequent development of DCM, which is generally reversible with permanent ventricular pacing. (3)

Among metabolic causes, very long-chain acyl-coenzyme A (acyl-CoA) dehydrogenase deficiency (VLCAD) is an extremely rare condition, with an incidence of 1 per 30 000–100 000 LB. This metabolic disorder is caused by mutations in the ACADVL gene and is categorized into three well-defined subgroups: a) the severe infantile form typically presents within the first few months of life and is characterized by cardiomyopathy, hypoglycemia, arrhythmias, and episodes of severe metabolic decompensation; b) the moderate form presents during childhood with episodes of hypoglycemia, liver involvement and less cardiac compromise; c) the late-onset form, that occurs in older children or adults and is characterized by myopathy, exercise intolerance, and recurrent rhabdomyolysis. (4) Treatment includes restricting the intake of long-chain fatty acids and supplementing with medium-chain fatty acids and carbohydrates.

We present the case of a 3-year-old female patient who was admitted to hospital in cardiac arrest which recovered following advanced resuscitation maneuvers. She had a history of prenatal diagnosis of CCAVB that was confirmed at birth, associated with maternal systemic lupus erythematosus. During follow-up at another center, the patient developed progressive left ventricular (LV) dilation associated with systolic dysfunction. For this reason, dual-chamber epicardial pacemaker (PM) was implanted at age 2. (Figure 1). Despite treatment, cardiac function worsened.

Four months before admission, the patient had experienced seizures interpreted as secondary to ischemic stroke (consistent with brain CT scan findings) and was hospitalized several times for hypoglycemia, without a definite diagnosis.

During the clinical interview, the family highlighted the occurrence of repeated episodes of sweating, tachypnea, dizziness, diaphoresis, and altered mental status, which resolved after drinking sugar-sweetened beverages.

The rapid progression of DCM with progressive impairment of left ventricular ejection fraction (LVEF) despite optimal medical treatment and pacemaker programming, along with frequent episodes of hypoglycemia, suggested an etiology of DCM other than CCAVB (Figure 2). Laboratory tests ruled out rheumatologic, endocrine, and infectious causes of DCM. A comprehensive metabolic workup performed during an episode of hypoglycemia revealed a metabolic deficiency (VLCAD), which was responsible for the unusual course of his disease.

The patient presented an atypical and severe form of VLCAD with serious cardiac involvement. The diagnosis was challenging and difficult because it occurred concurrently with CCAVB.

Rev Argent Cardiol 2026;94:337-339. http://doi.org/10.7775/rac.v94.i4.21031

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Fig. 1. 12-lead electrocardiogram showing atrial-sensed, ventricular-paced rhythm.

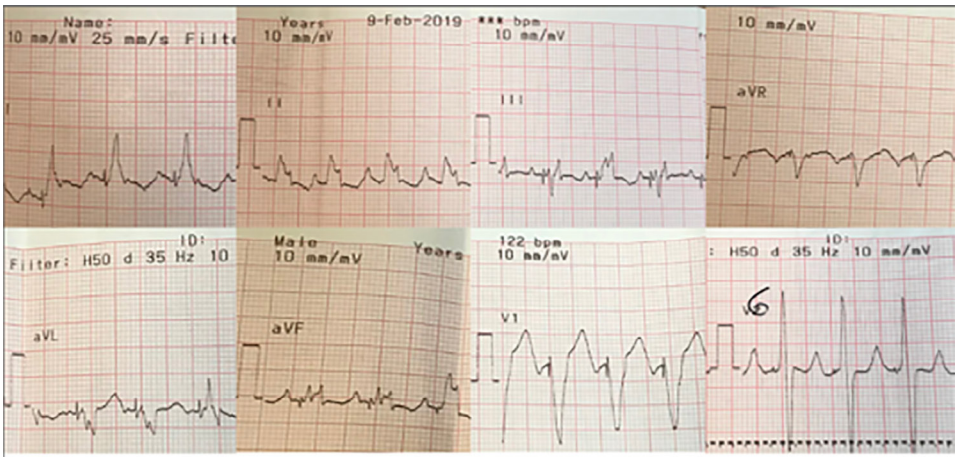
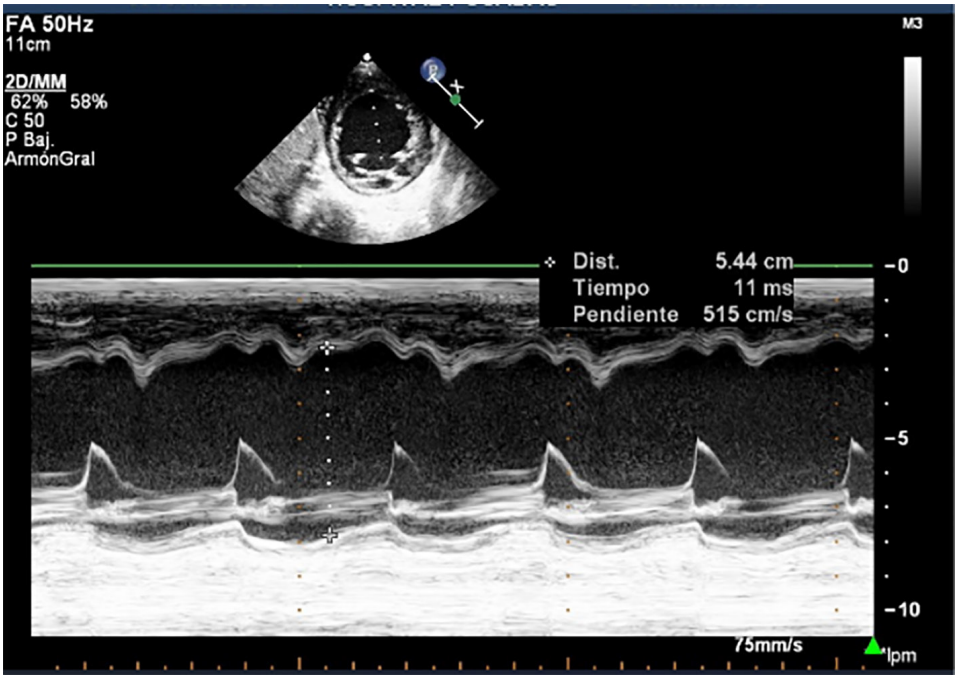


Fig. 2. Transthoracic echocardiogram, parasternal short-axis view, M-mode, showing left ventricular dilation and septal dyskinesia.



In this case, we emphasize the importance of considering other, less common causes when common diagnoses such as CAVB and DCM do not respond adequately to conventional treatment or present unexplained manifestations, such as hypoglycemia and nonketotic acidosis. A high level of clinical suspicion along with ordering metabolic tests was essential to reaching the definitive diagnosis. Therefore, we conclude that when a patient's course does not align with expectations after standard therapy, we must investigate other possible causes, including less common ones.

Once the diagnosis of VLCAD deficiency is made, early specific dietary treatment should start and be based on restriction of long-chain fatty acids, supplementation with medium-chain triglycerides, and adequate carbohydrate intake to prevent episodes of hypoglycemia. Prolonged fasting should be avoided, and individualized nutritional adjustments should be tailored according to age and metabolic needs. In

situations of metabolic stress (infections, surgeries, fever), intravenous glucose should be administered.(5)

Family genetic counseling is also an essential tool in the comprehensive management of these patients.

Ethical considerations

As the patient passed away in 2019, the healthcare professionals committed to maintaining data protection and confidentiality, in accordance with the provisions of National Law No. 25,326 (Personal Data Protection Act). A waiver of informed consent was requested. Approval has been granted by the institutional review board of Hospital Nacional Prof. Dr. Alejandro Posadas under ethics approval code: Ccari971/25.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Severe Carotid Stenosis Associated with a Persistent Hypoglossal Artery: Endovascular Treatment With Double Embolic Protection

Estenosis carotídea grave asociada a persistencia de arteria hipoglosa: resolución endovascular con doble protección embólica

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Atherosclerotic carotid disease accounts for 20% to 30% of ischemic cerebrovascular events. Its clinical presentation can range from asymptomatic disease to transient ischemic attacks or established strokes.

Persistent carotid-vertebrobasilar anastomoses are remnants of embryonic circulation, and their prevalence in the adult population is low. Among these, the persistent hypoglossal artery is a rare variant. (1) Its clinical significance increases when the vertebrobasilar circulation depends predominantly on this artery, particularly in the presence of bilateral hypoplasia of the vertebral arteries. In these cases, the coexistence of severe carotid stenosis creates a complex hemodynamic situation and poses therapeutic challenges. (2)

We present a 67-year-old male patient who was normotensive and had a history of dyslipidemia with irregular treatment. During a cardiovascular checkup, a non-significant fibrolipid plaque was detected in the left internal carotid artery (LICA), associated with bilateral hypoplasia of the vertebral arteries. Lipid-lowering therapy and clinical follow-up were prescribed.

During follow-up, he remained asymptomatic until, years later, he developed episodes of phosphenes and flashes that had been present for three months. Doppler ultrasound of the neck vessels revealed disease progression and severe stenosis of the LICA (Figure 1). Digital angiography confirmed 90% stenosis of the LICA and demonstrated a persistent hypoglossal artery originating from the internal carotid artery above the atheromatous plaque, associated with bilateral hypoplasia of the vertebral arteries (Figure 2).

Given the vascular anatomy, carotid endarterectomy presented significant technical challenges, because of the limited distal segment available for shunt placement and the potential risk of compromising the posterior circulation. Endovascular treatment was therefore performed.

Carotid angioplasty stenting was performed using double embolic protection, with filters placed in both the LICA and the persistent hypoglossal artery. The procedure was performed under conscious sedation, with no technical or neurological complications (Figure 3). Adequate stent expansion was confirmed, with no residual stenosis and preserved flow to both the anterior and posterior circulation (Figure 4). The patient had a favorable clinical course and was discharged 48 hours later, with no new neurological symptoms.

A persistent hypoglossal artery is a rare vascular anomaly that is generally asymptomatic. However, in cases in which the vertebrobasilar circulation depends on this artery, its association with severe carotid stenosis may compromise both the anterior and posterior circulations.

Conventional surgical treatment may be limited by anatomical complexity and the risk of ischemia during carotid clamping. In this context, carotid artery stenting with embolic protection devices constitutes a valid alternative. (3) The ability to protect both dependent branches is key to minimizing the risk of embolism. (4) Endovascular treatment with double embolic protection successfully addressed a complex vascular anatomy, providing a safe and effective option for selected patients.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

Rev Argent Cardiol 2026;94:340-343. http://doi.org/10.7775/rac.v94.i4.21033

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Fig. 1. Color Doppler ultrasound of neck vessels showing severe stenosis of the left internal carotid artery with turbulent blood flow and increased velocities.

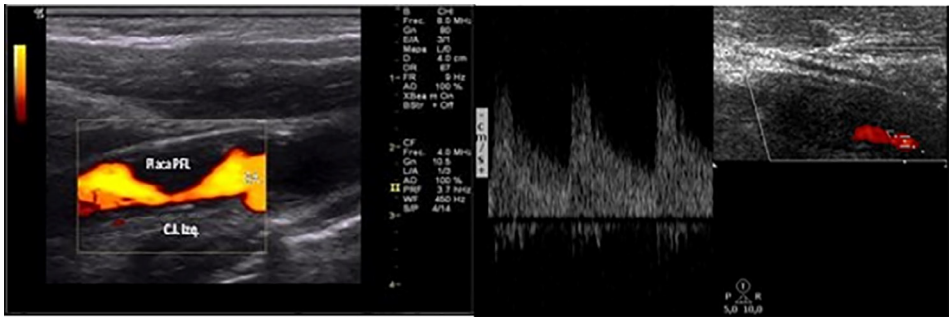

Fig. 2. Digital angiography of neck vessels showing critical stenosis (≈90%) of the left internal carotid artery, with the persistent hypoglossal artery arising above the atheromatous plaque.

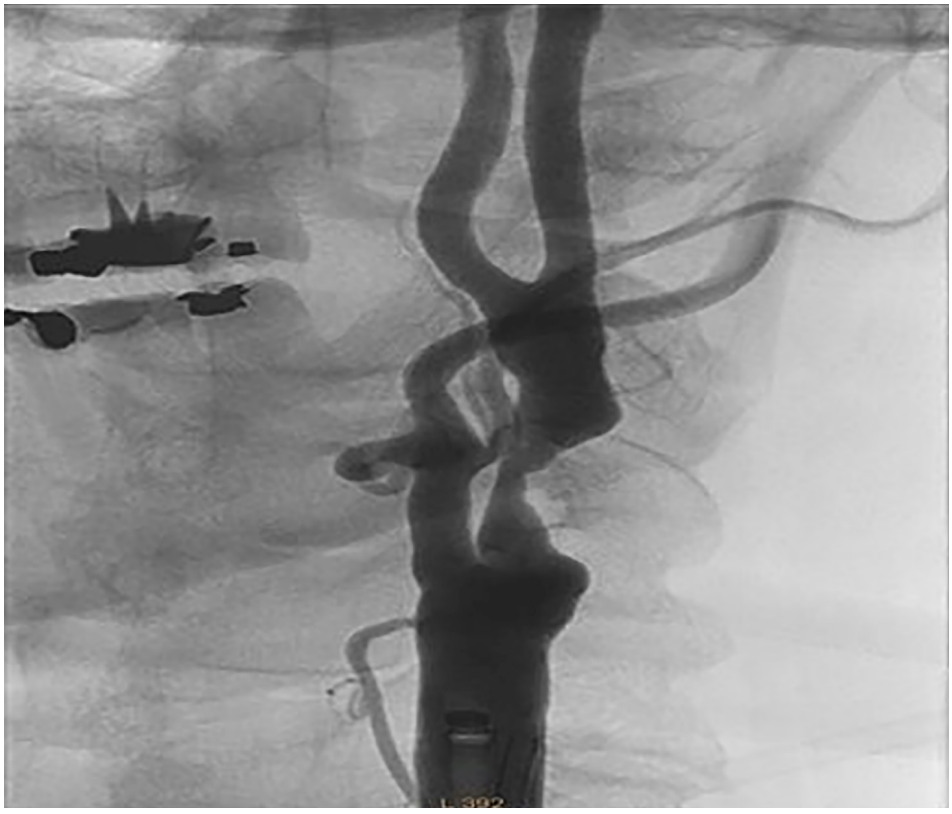

Fig. 3. Angiography during the endovascular procedure showing simultaneous placement of embolic protection devices in both the left internal carotid artery and the persistent hypoglossal artery.

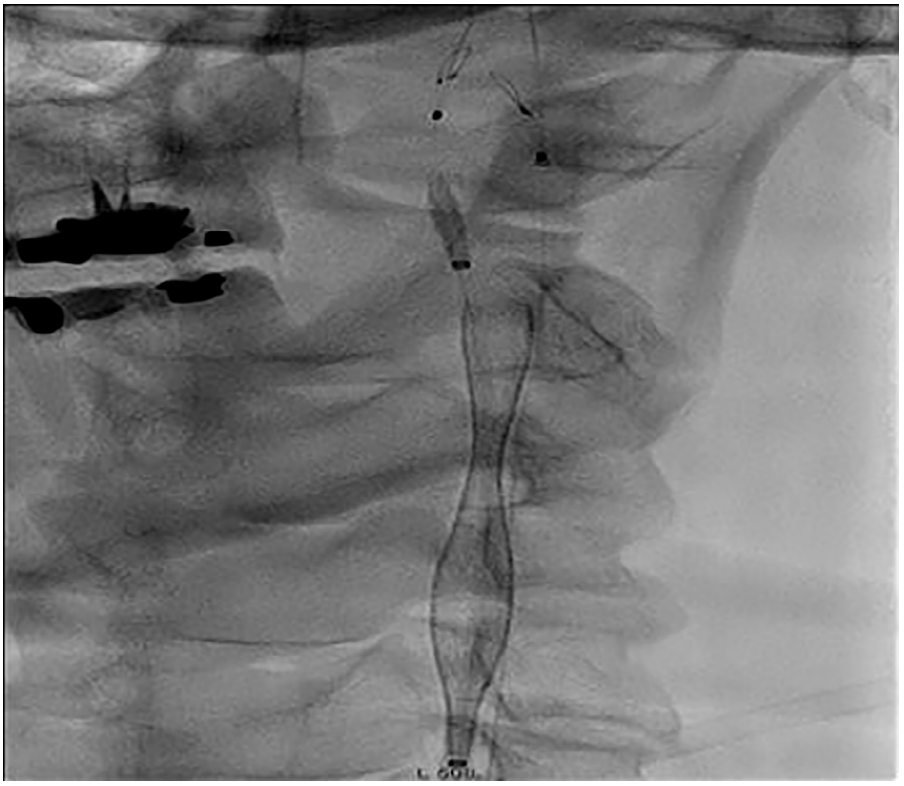

Fig. 4. Post-operative digital angiography showing a well-positioned stent, preserved blood flow and hypoplasia of the vertebral artery.

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SCIENTIFIC LETTER

Postoperative Euglycemic Ketoacidosis Associated with Sodium-Glucose Cotransporter-2 Inhibitors Following Cardiovascular Surgery: A Case Series

Cetoacidosis euglucémica por iSGLT2 en el postoperatorio cardiovascular: serie de casos

NOEL CERGNEUX[1]

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have revolutionized the treatment of diabetes mellitus and heart failure across the entire spectrum of ventricular function. However, their use has been associated with a rare but potentially life-threating complication: euglycemic ketoacidosis (EKA). This condition is characterized by metabolic acidosis and ketosis despite normal blood glucose levels. (1) The profound metabolic stress associated with cardiovascular surgery may precipitate this condition. (2)

The aim of this report is to describe four cases of EKA associated with dapagliflozin therapy in the postoperative period following cardiovascular surgery and to discuss the underlying pathophysiological mechanisms. (Table 1)

Case 1. Coronary artery bypass grafting and aortic valve replacement in a patient with insulin-dependent type 2 diabetes mellitus

A 55-year-old male patient with hypertension, dyslipidemia, obesity (body mass index [BMI], 37.2 kg/m^2), and a sedentary lifestyle had a long-standing history of insulin-dependent type 2 diabetes mellitus with poor glycemic control. He underwent combined aortic valve replacement with a 23-mm bioprosthetic valve and coronary artery bypass grafting using the left internal mammary artery (LIMA) to the left anterior descending artery (LAD) and a saphenous vein to a lateral branch of the left circumflex artery. His preoperative glycated hemoglobin (HbA1c) was 9.5%. His chronic medication included dapagliflozin 10 mg once daily, metformin, and both human insulin and insulin glulisine. The procedure was performed using cardiopulmonary bypass (CPB), with a 101-min CPB time and an 80-min aortic cross-clamp time. On postoperative day 1, the patient developed EKA (blood glucose, 179 mg/dL; pH, 7.30; bicarbonate, 8.6 mEq/L), requiring intravenous insulin infusion.

Case 2. Aortic valve replacement in a patient with non-insulin-dependent type 2 diabetes mellitus

A 60-year-old male patient, a former smoker, with overweight. His main cardiovascular condition was severe symptomatic aortic stenosis. He had non-insulin-dependent type 2 diabetes mellitus and was chronically treated with dapagliflozin and metformin 850 mg twice daily. He underwent surgical aortic valve replacement with a 25-mm bioprosthetic valve, with a 64-min CPB time and a 54-min aortic cross-clamp time. In the immediate postoperative period, he developed metabolic acidosis and his blood glucose was 189 mg/dL. The condition was interpreted as SGLT2i-associated ketoacidosis, which resolved after initiation of intravenous insulin infusion.

Case 3. Coronary artery bypass grafting (CABG) in a patient with heart failure and non-insulin-dependent type 2 diabetes mellitus

A 77-year-old female patient with a history of acute myocardial infarction (AMI), severe left ventricular dysfunction, and a 25% left ventricular ejection fraction (LVEF). She had non-insulin-dependent type 2 diabetes mellitus (HbA_{1c}, 6.2%). Her treatment regimen included dapagliflozin 10 mg, sacubitril/valsartan, and sitagliptin. She underwent off-pump CABG with a left internal mammary artery (LIMA) to the left anterior descending (LAD) artery and a saphenous vein to the right coronary artery (RCA). The patient developed postoperative EKA (blood glucose, 197 mg/dL; pH, 7.28; bicarbonate, 16.1 mEq/L) associated with surgical stress and prior SGLT2 inhibitor use.

Case 4. Aortic valve replacement in a patient with heart failure without diabetes mellitus

A 78-year-old male patient with a history of severe aortic stenosis and heart failure with preserved left ventricular ejection fraction (LVEF, 65%). Importantly, the patient did not have diabetes mellitus; he was receiving dapagliflozin 10 mg once daily for the treatment of his heart failure. He underwent a surgical aortic valve replacement with a 23-mm bioprosthetic valve using cardiopulmonary bypass, with a 69-

Rev Argent Cardiol 2026;94:344-346. http://doi.org/10.7775/rac.v94.i4.21034

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Table 1. Clinical and laboratory parameters of the 4 cases

Parameter	Case 1	Case 2	Case 3	Case 4
Age / Sex	55, M	60, M	77, F	78, M
SGLT2i indication	Insulin-dependent diabetes mellitus	Non-insulin dependent diabetes mellitus	Diabetes + HF	HF
HbA1c (%)	9.5	7.3	6.2	Not available
Creatinine (mg/dL) / ClCr	1.37 / 57	1.0 / 81.4	2.29 / 57	1.65 / 40.7
LVEF (%)	62	41–49	25	60–69
Initial blood glucose	179 mg/dL	189 mg/dL	197 mg/dL	102 mg/dL
pH	7.30	7.28	7.28	7.25
Bicarbonate (mEq/L)	8.61	16.3	16.15	16.97
BE / Anion Gap	-14.4 / Elevated	-6.9 / Elevated	-8.2 / Elevated	-10.3 / Elevated
Lactate (mEq/L)	1.7	2.8	2.57	6.42
Ketonemia	Positive	Positive	Positive	Positive

BE: base excess; CrCl: creatinine clearance; F: female; HbA1c: glycated hemoglobin; HF: Heart failure; LVEF: left ventricular ejection fraction; M: male; SGLT2i: sodium-glucose cotransporter-2 inhibitor

min CPB time and a 53-min aortic cross-clamp time. Postoperatively, he developed shock with refractory hypotension and severe metabolic acidosis (pH, 7.25; bicarbonate,16.9 mEq/L) with a normal blood glucose level (102 mg/dL). Positive ketonemia confirmed the diagnosis of EKA. (1,2)

Diabetic ketoacidosis is defined as a metabolic acidosis (pH ≤7.3; bicarbonate ≤18 mEq/L) with an increased anion gap, hyperglycemia (blood glucose level >250 mg/dL) and positive ketone bodies (beta-hydroxybutyrate ≥3 mmol/L), according to the American College of Endocrinology. (1,2)

In SGLT2i associated diabetic ketoacidosis, the criteria described above are met, with the characteristic feature of euglycemia (usually blood glucose level <250 mg/dL). (2)

Pathophysiologically, gliflozins induce persistent glycosuria by blocking glucose reabsorption in the proximal tubule, which persists even during fasting or metabolic stress. In addition, the reduction in plasma glucose levels decreases endogenous insulin secretion; at the same time, SGLT2i directly stimulate pancreatic ć-cells, increasing glucagon secretion. This hypoinsulinemic and hyperglucagonemic state promotes lipolysis and massive hepatic ketogenesis. Furthermore, SGLT2i may reduce renal ketone body clearance, exacerbating ketone accumulation in the blood. (3)

The postoperative period following cardiac surgery represents a precipitating factor, as surgical stress increases cortisol, epinephrine, and norepinephrine levels, thereby promoting insulin resistance. Additionally, cardiopulmonary bypass may perpetuate and amplify this effect through activation of the systemic inflammatory response. Preoperative fasting further reduces circulating insulin levels.

To prevent this complication, preoperative discontinuation of SGLT2i for at least 3 to 4 days before scheduled major surgery is recommended. In patients previously receiving these agents, pH and ketones (in blood or urine) should be measured in the presence of nausea, vomiting, general malaise, or persistent metabolic acidosis, regardless of whether blood glucose level is normal. Treatment requires insulin administration with glucose-containing solutions to suppress ketone production, along with aggressive fluid replacement. (1,4)

All four patients were receiving dapagliflozin 10 mg once daily. In all cases, following the metabolic stress of cardiovascular surgery, they developed high anion gap metabolic acidosis requiring insulin infusion despite the absence of hyperglycemia (blood glucose levels approximately 180–200 mg/dL). This report underscores the importance of close metabolic monitoring in patients receiving gliflozins who undergo coronary artery bypass grafting or surgical valve replacement, in accordance with the American Association of Clinical Endocrinology and the American College of Endocrinology (AACE/ACE) safety recommendations.

Importantly, patient 4 was receiving dapagliflozin for heart failure (HF) and did not have diabetes mellitus. This finding raises the question of whether postoperative EKA following cardiovascular surgery should be attributed to perioperative stress or represents a pharmacological effect of gliflozins.

Traditionally, EKA has been associated almost exclusively with absolute or relative insulin deficiency in diabetic patients. However, it may seem paradoxical that this condition can occur in non-diabetic patients, as observed in patient 4. As previously mentioned, by promoting glucosuria, these agents reduce the insulin-to-glucagon ratio even in euglycemic individuals. In the context of cardiac surgery, where counterregulatory hormones (cortisol and catecholamines) reach

peak levels, this imbalance is amplified, promoting lipolysis and hepatic ketogenesis regardless of the patient's prior insulin reserve. (5)

It could be argued that the stress of cardiac surgery (particularly with cardiopulmonary bypass) may contribute to acidosis. While a typical surgical patient may develop stress-induced hyperglycemia or lactic acidosis due to hypoperfusion, the metabolic shift toward ketone body production characteristic of EKA levels represents a specific biochemical hallmark of SGLT2 use, making it an adverse drug event triggered by surgical trauma. (6)

Finally, all four patients were referred directly for cardiac surgery without prior cardiovascular evaluation; therefore, SGLT2i therapy was not discontinued before surgery.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Left Main Coronary Artery Pseudoaneurysm in Infective Endocarditis Following Percutaneous Coronary Intervention: A Diagnostic and Therapeutic Challenge Addressed by Multimodality Imaging

Pseudoaneurisma del tronco de la arteria coronaria izquierda en endocarditis infecciosa posangioplastia. Desafío diagnóstico y terapéutico desde la multiimagen

YANINA CASTILLO COSTA[1, MTSAC], JUAN PABLO GONZÁLEZ[1, MTSAC], NICOLE GOULD[1], CAMILA FORCLAZ[1], GUSTAVO FEDERICO ANDERSEN[1], VÍCTOR MAURO[1, MTSAC]

Coronary artery pseudoaneurysms are a rare but potentially fatal complication characterized by disruption of the arterial wall with flow contained either by perivascular tissues or an organized thrombus. Most pseudoaneurysms are associated with percutaneous coronary interventions, while those due to infections are rare and typically related to bacteremia or infective endocarditis caused by *Staphylococcus aureus*. (1,2) The left main coronary artery is rarely involved and poses a diagnostic and therapeutic challenge due to high risk of rupture, thrombosis, and sudden cardiac death, with limited evidence available to guide its management. (2,3)

We present the case of a patient with infective endocarditis following a recent percutaneous coronary intervention of the left main coronary artery, who, among other clinical complications, developed a pseudoaneurysm of the left main coronary artery, diagnosed and characterized using multimodality cardiovascular imaging.

A 68-year-old male patient with a history of hypertension, type 1 diabetes mellitus, and prostate cancer treated in 2019 was admitted for persistent fever after undergoing a percutaneous coronary intervention to the distal left main coronary artery and ostium of the left circumflex artery, with the implantation of two drug-eluting stents. After cultures were taken and intravenous antibiotics were initiated, transesophageal echocardiogram revealed a 6.3 × 3.3 mm vegetation on the anterior mitral leaflet. This finding, along with blood cultures positive for methicillin-susceptible *Staphylococcus aureus*, led to the diagnosis of infective endocarditis. The patient initially presented a right pseudoaneurysm of the radial artery, which was managed with surgery, and acute kidney injury requiring temporary hemodialysis. Once fever had resolved and follow-up cultures remained negative, he developed dyspnea and hemodynamic impairment. An emergency echocardiogram was performed, revealing a new cavity adjacent to the left coronary sinus, suggestive of a pseudoaneurysm, wall motion abnormalities on the anterior wall, and a marked decrease in left ventricular ejection fraction. Coronary angiography confirmed a pseudoaneurysm of the left main coronary artery with contrast agent passage into the periarterial space (Figure 1). There was also a new severe stenosis of the proximal left anterior descending coronary artery, which required implantation of a drug-eluting stent. Coronary computed tomography angiography demonstrated a partially thrombosed pseudoaneurysm extending into the proximal segments of the left anterior descending and circumflex arteries (Figure 2).

Given the high risk of rupture and the high surgical risk, the Heart Team decided to exclude the pseudoaneurysm by implanting a covered stent in the left main coronary artery. The patient had a favorable outcome and left ventricular function showed a partial recovery.

At the 4-month follow-up, the patient experienced recurrent chest pain, and a new coronary angiography was performed. The covered stent in the left main coronary artery was patent and the pseudoaneurysm was completely excluded, but the left anterior descending and circumflex arteries presented severe stenoses. Therefore, the Heart Team indicated elective coronary artery bypass grafting, after which the patient had a favorable postoperative course.

Coronary artery pseudoaneurysms are a rare complication following percutaneous coronary interven-

Rev Argent Cardiol 2026;94:347-349. http://doi.org/10.7775/rac.v94.i4.21035

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Fig. 1. Coronary angiography showing a pseudoaneurysm of the left main coronary artery with contrast agent passage into the periarterial space.

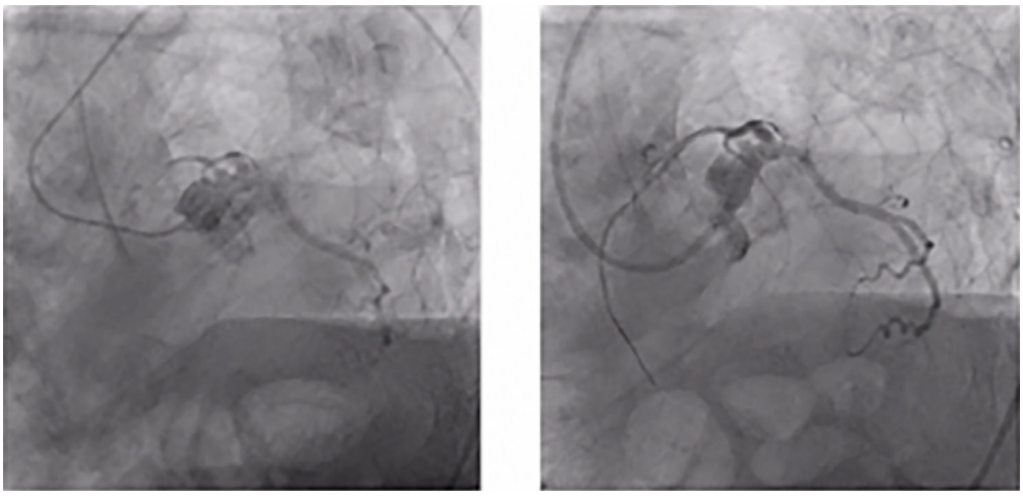
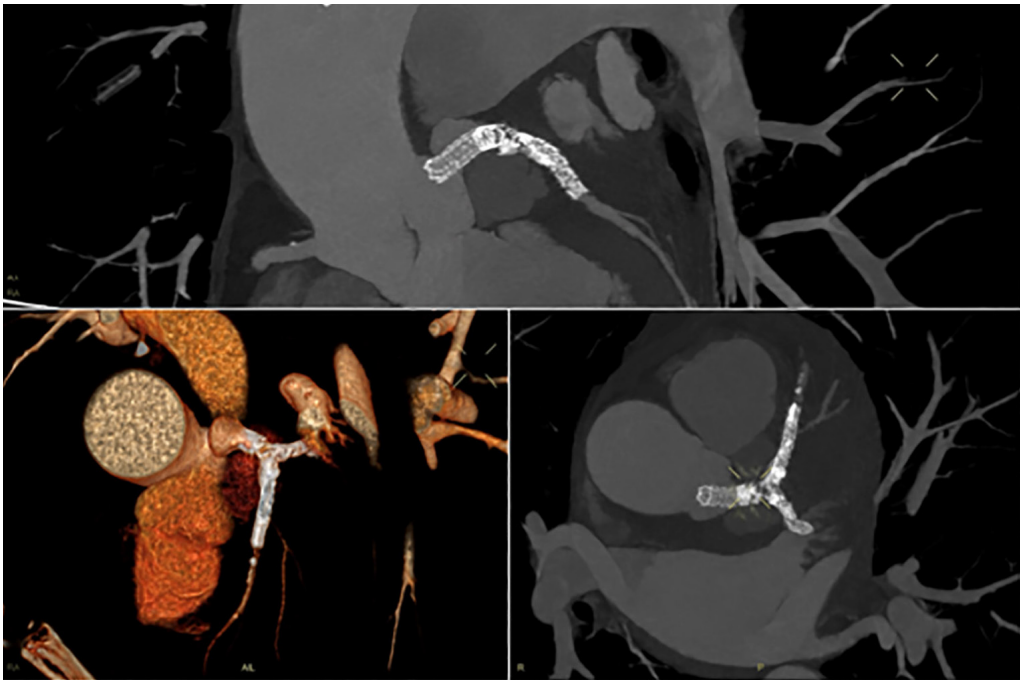


Fig. 2. Coronary computed tomography angiography confirming a partially thrombosed pseudoaneurysm extending into the proximal segments of the left anterior descending and circumflex arteries.



tions. In addition to the mechanical trauma associated with such interventions, factors such as local inflammation, delayed endothelization, and infection may contribute to their development, particularly following the implantation of drug-eluting stents. (4)

In cases of infection, *Staphylococcus aureus* is the most common causative microorganism, and the right coronary artery is the most common location. Involvement of the left main coronary artery is rare, as demonstrated by the largest published case series. (2)

The clinical presentation is often nonspecific, and the diagnosis requires a high index of suspicion, especially in patients with persistent fever or bacteremia following a coronary artery intervention. In our case, the diagnosis did not arise from the initial infection but rather from the clinical and hemodynamic impairment, which prompted a new echocardiographic assessment. The sequential integration of echocardiography, coronary angiography, and coronary computed tomography angiography confirmed the diagnosis, defined the extent of the lesion, and allowed for treatment planning, highlighting the value of multimodal-

ity cardiovascular imaging in this type of patient.

The management of coronary artery aneurysms and pseudoaneurysms should be tailored based on etiology, anatomy, and risk of complications, given the lack of comparative studies and specific recommendations. (5) Although surgery remains the treatment of choice for mycotic pseudoaneurysms, Kilic et al. reported that drug-eluting stents may constitute an alternative for treating certain types of pseudoaneurysms when the immediate surgical risk is high, as in the case of our patient. Yet the authors warned about the increased risk of thrombosis and restenosis. (3)

In addition to reporting the exceptional location of this pseudoaneurysm, we believe the primary contribution of this case is demonstrating that a strategy based on multimodality imaging and Heart Team discussion is essential for both diagnosis and treatment planning. (6)

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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Echocardiography in Diabetic Cardiomyopathy

El ecocardiograma en la miocardiopatía diabética

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Diabetic cardiomyopathy is defined as structural and functional myocardial impairment secondary to diabetes mellitus, in the absence of coronary artery disease, hypertension, or other causes of heart disease. (1) Its prevalence is uncertain, but it is estimated that approximately 12–22% of diabetic patients develop diabetic cardiomyopathy after 10 years of disease duration. (1) Therefore, it is essential to identify clinical, laboratory, and imaging markers that enable early diagnosis, allowing timely initiation of appropriate treatment and preventing disease progression.

Pathophysiologically, hyperglycemia, insulin resistance, and lipotoxicity induce oxidative stress, inflammation, cardiomyocyte apoptosis, and interstitial fibrosis, initially resulting in impaired ventricular relaxation, followed by left ventricular hypertrophy and, in advanced stages, impaired systolic function. (2)

Consequently, echocardiography is a useful, accessible, and reproducible imaging technique. It enables the identification of patients with diastolic dysfunction, an early marker of diabetic cardiomyopathy, (1) as well as patients with reduced global longitudinal strain before changes in ejection fraction occur, an early marker of systolic dysfunction. (3)

In the study entitled "*Differences in Diastolic Function and Global Longitudinal Strain on Stress Echocardiography between Elderly Diabetic and Non-diabetic Patients*" by Kufert et al., 176 diabetic patients and 771 non-diabetic patients underwent stress echocardiography. The researchers found that the group with diabetes had a higher prevalence of significant diastolic dysfunction, both at rest and during exercise, and that although left ventricular ejection fraction was normal and similar between the two groups, global longitudinal strain was significantly lower in diabetic patients. (4)

The study's strengths include the number of patients enrolled, the systematic exclusion of coronary artery disease as a potential confounder, the incorporation of conventional echocardiographic parameters alongside global longitudinal strain, and the assessment of impaired diastolic reserve during exercise, thereby unmasking an abnormality that is often not apparent at rest.

As a limitation, considering this was a cross-sectional study, the true prognostic impact of the observed abnormalities cannot be established. Although the association of diabetes with diastolic dysfunction and reduced global longitudinal strain is consistent, this does not address whether these findings identify patients at higher risk of developing heart failure with preserved ejection fraction. In this context, it would have been of interest to examine variables related to the course of diabetes, particularly whether patients were receiving SGLT2 inhibitors or GLP-1 receptor agonists, given that these therapies have been shown to modify the risk of heart failure and could influence echocardiographic parameters. (2;3)

As suggested by this study, diabetes mellitus is independently associated with a higher prevalence of diastolic dysfunction and reduced global longitudinal strain, even in the presence of preserved ejection fraction, reinforcing the concept of subclinical myocardial involvement. Awareness of these findings allows the echocardiographer to focus the examination on assessing these parameters and provides the clinical cardiologist with a broader perspective when initiating or modifying treatment in this population, rather than focusing solely on coronary or peripheral vascular disease.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

Rev Argent Cardiol 2026;94:350-351. https://doi.org/10.7775/rac.v94.i4.21038

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AUTHORS' REPLY

Dear Dr. María Eugenia Delle Donne:

We appreciate your interest in our publication and agree that understanding the prognosis of this condition, asymptomatic diabetic diastolic cardiomyopathy, is important for determining the most appropriate therapeutic approach. We are continuing our work in this area and hope to share our results with you soon.

Sincerely.

Alejandro Simón Kufert
Cardiologist, Hospital Cesar Milstein

Are There Really Sex-Related Differences in Transthyretin Amyloidosis?

¿Existen realmente diferencias de sexo en la cardiopatía amiloidótica por transtiretina?

JOSEFINA PARODI[1]

We read with great interest the study "Clinical, imaging, and disease progression sex-related differences in transthyretin cardiac amyloidosis" by Decotto et al. The authors present one of the first national registries specifically addressing this topic and report findings consistent with international experience: women represent a minority of diagnosed patients, are diagnosed at older ages, and have lower wall thickness and better-preserved ventricular function at the time of diagnosis, with no significant differences in clinical course during follow-up. (1) Far from settling the debate, these results prompt us to reconsider several questions regarding the true impact of sex on this disease.

The first question is whether the marked epidemiological difference reflects a lower true prevalence or, at least in part, underdiagnosis in women. International registries such as THAOS and other contemporary cohorts show a clear male predominance, although the magnitude of this difference varies across studies. (2–4) The SCAN-MP study, which used an active screening strategy with nuclear scintigraphy in minority populations, found that women accounted for 31.3% of the active ascertainment cohort, compared with 13.3% of referral clinical cohorts. (5) Suspicion of transthyretin cardiac amyloidosis (ATTR-CA) continues to rely heavily on increased wall thickness, with absolute cutoffs derived from predominantly male populations. In this context, it is particularly interesting that, in the cohort presented, differences in wall thickness disappear after indexing these measurements to body surface area, and that a significant proportion of women have a septal thickness <12 mm at the time of diagnosis. These findings support the need to reassess whether current echocardiographic criteria might delay clinical suspicion and, consequently, access to confirmatory testing such as scintigraphy.

However, diagnostic bias likely does not fully account for the observed difference. In hereditary ATTR-CA, penetrance is clearly influenced by sex, with lower clinical expression and later disease onset in women carrying several pathogenic variants. This difference in penetrance suggests that biological mechanisms—possibly related to hormonal factors and transthyretin tetramer stability—also contribute to the natural history of the disease. The lower representation of women is likely the result of an interaction between these biological differences and lower clinical recognition.

Another relevant aspect is prognosis. Although some early series suggested a more unfavorable course in men, contemporary analyses adjusted for disease stage, including THAOS and other recent registries, have not demonstrated consistent differences in mor-

Rev Argent Cardiol 2026;94:351-352. https://doi.org/10.7775/rac.v94.i4.21030

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tality or heart failure hospitalizations, in line with the results reported by the authors. (2,3) This suggests that the differences observed at the time of diagnosis do not necessarily translate into differences in disease course once the disease is established.

Finally, these observations should be interpreted in light of a persistent limitation in clinical research: the underrepresentation of women in pivotal ATTR-CA trials. Studies such as ATTR-ACT (6) and more recent trials of transthyretin-stabilizing or -silencing therapies included a markedly lower proportion of women, limiting the ability to perform sex-specific analyses. In this context, clinical practice registries are particularly valuable, as they provide a more precise understanding of the actual disease burden in women and help identify opportunities to optimize diagnostic and therapeutic strategies.

The study by Decotto et al. represents a valuable contribution to the regional literature. Rather than confirming that women present a different form of the disease, their findings prompt us to ask whether we are using diagnostic tools that are sufficiently sensitive to recognize a presentation that is likely to be different as well.

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 Dr. Parodi for her interest in our article, "Clinical, Imaging, and Disease Progression Sex-Related Differences in Transthyretin Cardiac Amyloidosis," and for the accompanying editorial.

We agree with the hypotheses put forward and, in particular, with her concluding reflection, which prompts us to ask whether the diagnostic tools we currently use are sufficiently sensitive to recognize a clinical presentation that likely differs in women as well.

As Dr. Parodi points out, the challenge is no longer merely to demonstrate that differences exist between men and women with transthyretin cardiac-amyloidosis, but rather to develop diagnostic strategies capable of promptly identifying these differences and ensuring earlier access to diagnosis and treatment.

Santiago Decotto and team

Specialized Heart Failure Units

Unidades especializadas de insuficiencia cardíaca

MARIANGEL SANCHEZ[1]

Heart failure (HF) units have been established to systematize the diagnosis, treatment, and clinical follow-up of patients with HF, incorporating multidisciplinary teams, standardized protocols, and structured follow-up. In developed countries, their main benefit is the reduction of hospitalizations and the op-

Rev Argent Cardiol 2026;94:352-354. https://doi.org/10.7775/rac.v94.i4.21039

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timization of guideline-based treatment. (1) In Latin America, where health care systems exhibit greater heterogeneity and structural restrictions, their implementation remains limited.

In the research study published by the Argentine Journal of Cardiology, "Impact of a Specialized Heart Failure Unit on Patients Hospitalized for Acute Heart Failure: Analysis of a Decade of Experience," 3368 hospitalizations for acute HF over a ten-year period were analyzed at a high-complexity center in Argentina, comparing an initial phase (2014–2019) with a consolidation phase (2020–2024) of the program. The most significant finding was a sustained reduction in the length of hospital stay, from 9.3 to 2.8 days, without an increase in in-hospital mortality or 30-day rehospitalization. (2) This result is clinically significant, as prolonged hospital stays for acute HF are associated with higher costs, complications, and a poorer prognosis. (3)

Although this study provides local evidence and suggests a consistent positive impact of HF units, it should be noted that the model was developed at a high-complexity, referral center. Its implementation required a considerable set of resources, such as staff specialized in HF, access to a day hospital, and telemonitoring, among others. Unfortunately, this level of resources is not typically available in most public centers or in a significant number of private centers in the region. This reality is evident in the ARGEN-IC registry, (4) a multicenter study with heterogeneous complexity, which reported longer hospital stays and reduced access to early outpatient follow-up, illustrating the gap between what has been demonstrated and what is replicable.

However, it is likely that not all components of the program have an equal impact on the observed outcomes; therefore, the real challenge for the future appears to be identifying which components are indispensable and which could be adapted for centers with fewer resources. An interesting contribution of this study was the use of the coefficient of variation (CV) as an indicator of care stability. In this regard, this methodological tool could also be applied to evaluate adapted versions of the model and thus generate local evidence to guide its gradual implementation in our setting. (5)

The study's findings encourage reconsidering the design of HF units in versions adapted to available resources, identifying those components of greater clinical impact, with the goal of expanding access to a population with increasing prevalence, as patients with HF.

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 for her careful reading and comment, which provides a valuable perspective on the implementation of HF units in heterogeneous healthcare systems. We agree that the gap between what has been demonstrated and what is replicable in the region is real, and that the ARGEN-HF registry clearly illustrates this disparity. However, we believe it is necessary to clarify one point: the commentary groups components of quite different nature under the notion of "resources," and that distinction is, in our view, central to considering the replicability of the model.

Staff specialized in HF, day hospital, and telemonitoring do indeed require institutional investment, whether in dedicated training, physical space, or technology. But a significant portion of our program's components do not depend on that type of investment: management based on critical pathways, structured discharge checklist, education with written guidelines, administrative coordination of appointments and follow-up, and multidisciplinary case conferences for complex decision-making are not merely ancillary elements of the program; rather, the available evidence suggests that they account for a significant portion of its clinical effect, and their implementation depends on systematization and organizational discipline, not on the facility's level of complexity.

This is consistent with the meta-analysis by McAlister et al., which showed that multidisciplinary strategies involving active follow-up by trained staff and access to specialized consultations reduce all-cause mortality and hospitalizations, whereas models of scheduled consultations without structured follow-up show a considerably smaller benefit. (1) Similarly, the meta-analysis by Feltner et al. on transitional care in

HF showed that programs focused on discharge education, follow-up coordination and early post-discharge contact—rather than isolated technological interventions—were the ones that significantly reduced readmissions. (2)

Something similar can be said regarding the day hospital. Its rationale does not lie in the availability of a dedicated space, but preferably in a protocol for intensive outpatient treatment and follow-up that helps prevent avoidable hospitalizations in selected low-risk patients. Strictly speaking, it is a way of working—involving explicit selection criteria, a standardized diuretic regimen, and closely spaced follow-up appointments—rather than a physical structure. In our own experience, the day hospital operated for many years using general inpatient beds, without a dedicated physical space, and it was not until 2023—toward the end of the consolidation period analyzed—that a dedicated area became available. This reinforces the fact that the protocolized approach preceded, and largely explains, the observed benefit, regardless of the infrastructure available at any given time.

It should also be noted that, within our own cohort, components such as telemonitoring were gradually incorporated only in the final years of the consolidation period, whereas the most pronounced decline in length of stay was already evident in earlier stages, limiting the ability of these technological components alone to explain the sustained improvement observed throughout the decade. This point is significant when considering local historical evidence: the DIAL study, conducted in Argentina two decades ago, showed that an intervention as simple as structured telephone follow-up by trained nurses—without any technological support—significantly reduced mortality and hospitalizations due to HF in outpatients. (3) The fact that a low-cost strategy without a technological component has demonstrated a benefit of this magnitude reinforces the idea that the critical factor is the consistency and quality of contact with the patient—and not necessarily the sophistication of the tool used to achieve it.

In short, we agree with the author that identifying the relative importance of each component is the central challenge in the future, and that the proposed coefficient of variation could be a useful tool for that assessment.

Our interpretation of the evidence suggests that these results are based on organizational components and structured follow-up—which do not require a high-complexity center for implementation—rather than on the incorporation of technology. Ultimately, we believe that a HF unit is not a matter of technological sophistication or exceptional resources, but rather of maintaining a systematic, patient-centered approach to care. It is, above all, an institutional decision: a project that relies on widely available or low-cost resources, whose true challenge lies not in availability but in sustainability—consistently applying these protocols with a care team whose goal is the continuous improvement of the quality of care for patients with HF. Standardizing care—rather than any specific resource—is what explains the observed results and what expands, instead of restricting, the real possibilities for adapting the model to other centers in the region.

The Authors

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Cardiology and Humanism in the Age of Artificial Intelligence: A Challenge to Become More Human

Cardiología y humanismo en tiempos de inteligencia artificial: un desafío para ser más humano

"The fault, dear Brutus, is not in our stars,
but in ourselves."
William Shakespeare

Modern medicine is undergoing an unprecedented transformation in which Artificial Intelligence (AI) is evolving from a mere technical tool into a proactive support system capable not only of processing language, analyzing images and movement, but also of predicting or describing clinical patterns, enabling multimodal integration, performing simulations, and supporting automation and management. The true challenge in clinical practice lies in understanding AI so that it can be guided toward the common good, transparency, and unwavering respect for human dignity.

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.

In this regard, humanism should not be seen as a hindrance to technology, but rather as its ethical compass. AI is not neutral; it reflects the values and ideology of those who create it. Therefore, the development of medical AI requires what we might call "Digital Humanism."

Integrating humanism into technological development means "educating the algorithm with values." While AI surpasses us in speed and computational power, it lacks physical embodiment, dignity, and above all, moral consciousness. It cannot distinguish between right and wrong or assume responsibility for the consequences of its decisions.

Recognizing the need to foster a more rigorous discussion on the integration of digital medicine and AI, the Digital Health Council of the Argentine Society of Cardiology (SAC) was established in 2022. In April 2026, the first Digital Health Consensus was presented. (1)

Two recent international events highlight the importance of this issue. In May 2025, Pope Leo XIV published the encyclical *Magnifica Humanitas* on safeguarding the human person in the time of artificial intelligence. (2)

Last June, G7 leaders, together with the European Union, held a landmark working session on AI at the summit in Évian-les-Bains, France. For the first time, beyond the political framework, they met with leading AI developers and chief executive officers. The discussions focused on technological sovereignty, the safe development of advanced AI models, and the protection of children.

As cardiologists, we are enthusiastic about the future of AI in medicine and firmly convinced of the importance of understanding and shaping it so that it becomes a tool that enhances the value of the human person. Furthermore, given the central role of AI together with the aspiration to transcend the limits of the human condition, we have an opportunity to discuss the future impact of emerging trends in transhumanism and posthumanism.

WHAT IS AI?

AI is a branch of computer science that develops systems capable of learning from data and performing complex tasks that normally require human intelligence. AI encompasses *machine learning*, which enables computers to learn from data without being explicitly programmed, and *deep learning*, an advanced *machine learning* technique that uses artificial neural networks inspired by the human brain. (1,3)

Machine learning works as follows:

1. Supervised learning: The system analyzes correctly labeled data and learns to identify different patterns and improve its predictions when presented with new data.
2. Unsupervised learning: The system is provided with a dataset without predefined labels and must identify patterns on its own, without requiring labeled data.

Rev Argent Cardiol 2026;96:355-358. http://dx.doi.org/10.7775/rac.v94.i4.21037

3. Reinforcement learning: Combines aspects of both supervised and unsupervised learning. The system learns through interactions with its environment, receiving rewards or penalties based on the actions it takes.

AI has advanced at an accelerating pace over the past century and has grown exponentially over the last decade. (4) Looking back, Alan Turing, in his paper Computing Machinery and Intelligence, proposed the "Turing Test" as a criterion for determining whether a machine could simulate human intelligence. (5)

In 1943, the neurophysiologist Warren McCulloch and the mathematical logician Walter Pitts introduced the artificial neuron model and proposed that neurons could be modeled as binary units (active or inactive) capable of computing any logical function. (6)

It was John McCarthy who coined the term "artificial intelligence." Together with Herbert Simon, Marvin Minsky, and Allen Newell, they laid the foundations for this discipline at the historic 1956 Dartmouth Conference.

In 1958, Frank Rosenblatt developed the perceptron, a practical implementation of an artificial neural network consisting of an input layer, a hidden layer, and an output layer. Each node computed a weighted sum of its inputs and applied an activation function to generate an output. (7)

The 1986 paper by David Rumelhart, Geoffrey Hinton, and Ronald Williams popularized the backpropagation algorithm. By implementing the chain rule, it solved the problem of updating the weights in the hidden layers of a multilayer neural network. Using a mathematical optimization method known as gradient descent, the algorithm iteratively adjusts the network's weights in the direction that minimizes the overall error, thereby improving the predictive performance of different models. (8)

The year 2012 marked the beginning of the large-scale deep learning revolution. Advances in computing infrastructure enabled machines to learn autonomously at unprecedented levels. The digital revolution was driven by several simultaneous developments: faster graphics processing units (GPUs), increased storage capacity, the availability of big data, the emergence of cloud computing, advancements in communication networks (broadband and fiber optics), the introduction of Tensor Processing Units (TPUs) and other specialized chips, and reduced energy costs per operation.

"Attention Is All You Need" was a groundbreaking scientific paper published in 2017 by Google researchers. It introduced the Transformer architecture, which dispenses with recurrent neural networks and relies exclusively on attention mechanisms to understand context and the relationships between words. (9) The architecture introduced in this paper laid the foundation for the subsequent development of large language models (LLMs), including the GPT (Generative Pre-trained Transformer) family of models, which use neural networks to generate human-like text and are capable of conversing, programming, translating, and reasoning logically.

In 2018, Google DeepMind introduced AlphaFold, a groundbreaking AI system that predicted the three-dimensional structure of proteins from their amino acid sequences. (3)

Within medicine, after medical imaging, cardiology is the second specialty in which AI has been most extensively developed. The thoughtful integration of algorithms provides invaluable tools for expanding human capabilities and optimizing medical care in the pursuit of precision, efficiency, and reproducibility. (10)

Some examples of these developments include:

- Precision diagnosis and early screening: Recent studies have shown that AI tools achieve area under the curve (AUC) values greater than 0.90 for the detection of cardiovascular diseases, demonstrating robust accuracy across a variety of modalities. AI-optimized electrocardiographic models have proven highly effective in identifying the risk of atrial fibrillation, cardiomyopathies, and asymptomatic left ventricular dysfunction. (11)
- Training and procedural guidance: Deep learning algorithms assist non-expert professionals in acquiring diagnostic images, such as echocardiograms, thereby reducing technical training requirements.
- Optimization and administrative relief: Automation of diagnostic test ordering, automated summaries of medical records, real-time transcriptions ("ambient notes"), and the generation of discharge reports substantially reduce clinician's administrative burden.
- Critical monitoring: In intensive care units, machine learning models have accurately predicted the onset of shock, enabling earlier intervention. Other potential applications include the use of facial thermography analyzed by neural networks to noninvasively detect low cardiac output in critically ill patients. (12,13)

Each of these predictive models has a greater impact on diagnosis than on the prediction of events, given the importance of time as an uncertainty variable. It is important to emphasize that most of these studies lack multicenter validation, and comparative studies evaluating different models remain scarce.

Furthermore, integrating AI into clinical workflows is a work in progress, and we are still in the early stages of digital medicine, where aspects such as connectivity, interoperability, and scalability remain major challenges. For example, in an imaging laboratory, AI could be useful in reducing measurement variability caused by intra- and inter-observer differences, assisting with the standardization of image acquisition and improving image quality, helping to optimize image interpretation and post-processing

times, shortening report turnaround times, addressing both overdiagnosis and underdiagnosis, increasing the volume of imaging studies, identifying imaging features (radiomics) imperceptible to the human eye, and, of course, optimizing workflows, scheduling, billing, and the management of relevant information. (10,14)

CLINICAL, ETHICAL, AND EPISTEMIC RISKS

Alongside its benefits, the unregulated use of AI poses critical risks that must be actively identified and mitigated: (1,11,14,15)

- Epistemic opacity: Many algorithms operate as a "black box," where the decision-making process is not transparent, hindering clinical validation and raising ethical and legal questions regarding liability.
- Diagnostic and interpretive failures: Biases inherent in training data, algorithmic hallucinations (false information presented as factual), and sycophancy (the tendency of AI systems to conform to users' assumptions) pose direct risks to patient safety.
- The illusion of knowledge: Research has shown that current LLMs lack the ability to distinguish between belief, factual knowledge, and objective truth, leading to critical errors when processing false information.
- Loss of professional skills (deskilling): There is a risk that clinicians may relinquish their independent clinical judgment in favor of the convenience of allowing machines to make decisions for them. Adapting Hegel's "master-slave dialectic," there is a risk that physicians, by delegating complex tasks to AI, may become dependent on these systems and lose their practical skills and critical judgment.
- Dehumanization and disconnection: Replacing human conversation and therapeutic contact with mere digital connectivity and computational efficiency distances us from the true essence of healing.

THE POTENTIAL RISKS OF UNREGULATED AI. BEYOND MEDICINE

There are other aspects of AI that could affect the future of humanity. (14) Broadly speaking, transhumanism advocates the enhancement of human beings through technology with the goal of optimizing human performance and capabilities. Likewise, posthumanism, at its most extreme, criticizes anthropocentrism and proposes a form of hybridization between humans, machines, and the environment, ushering in a new evolutionary stage for humanity. (2) The decisions made over the coming decades will shape not only the future of AI but also our future as a species. From this perspective, leaving the evolution of AI in the hands of a few could have several negative consequences:

- Dehumanization in decision-making
- Concentration of power and global imbalance
- Threat to truth and democracy
- Impact on employment and new forms of exploitation
- Psychological and educational risks
- Arms race and impersonal warfare
- Environmental degradation

In *The Wealth of Nations*, Adam Smith established that labor is the true source of wealth and that capital is the engine that allows wealth to multiply. The division of labor and the accumulation of capital are the fundamental pillars that drive a country's economic growth. (16) With the advent of AI, a third factor has emerged: the management of both global data and individual citizens' data.

Currently, the development of AI is driven predominantly by competition among the United States, China, and Russia, as well as by private transnational actors with resources surpassing those of many governments, creating concentrations of power that are often opaque, difficult to regulate, and prone to generating new forms of domination and inequality.

In this regard, AI can act as a powerful multiplier of disinformation by enabling the manipulation of images, videos, and narratives that distort reality. This undermines social trust and the foundations of democracy, which depend on fidelity to the facts.

Likewise, automation can lead to mass unemployment and relegate workers to rigid, repetitive tasks, eroding their capacity for innovation.

Among young people, the early and unsupervised use of these tools can affect attention and emotional regulation and encourage reliance on immediate answers—a tendency that undermines critical thinking and the desire to patiently seek the truth.

Access to personal data poses the risk of creating a digital panopticon that raises serious dilemmas regarding individual privacy and freedom, and where human experience could become the raw material for commercially driven predictions.

Beyond speculative theoretical positions, transhumanism and posthumanism are two perspectives that will gradually shape the collective imagination and, consequently, guide social, economic, and political decisions. In this regard, an amoral AI that does not recognize the value of human life is at risk of contributing not only to a culture of waste but also to a loss of recognition of the human person as an ontological being.

TOWARD A CONSTRUCTIVE DIGITAL HUMANISM

To build a future where technology is a pillar rather than a threat, the medical community must guide its practice by adhering to several fundamental principles.

- Validation as a human act: AI processes and analyzes data at extraordinary speed, but it lacks moral consciousness, physicality, the ability to distinguish between right and wrong, and the ca-

pacity to feel empathy or establish a genuine therapeutic friendship. Ethical judgment, ultimate responsibility, and clinical decision-making remain exclusively the physician's .

- Critical training and leadership: it is imperative to actively prepare for this transition. Medical education must prepare physicians to continuously guide and audit AI algorithms according to sound ethical values.
- Prioritizing human dignity: technology must be implemented in an equitable, transparent, and thoughtful manner so that it becomes an agent of inclusion that brings physicians closer to the patient rather than creating technological barriers between them.
- Restoring conversation: following Sherry Turkle's reflections, we must not sacrifice deep conversation for mere digital connection. Technology should free time to strengthen the physician-patient bond. (17)
- Empowered clinical judgment: AI can detect patterns that were previously invisible, but its success depends on thoughtful and equitable deployment. AI can process data, but only physicians can give it meaning within each patient's unique life story. (18) The kind of attention we give to the world changes the world to which we give our attention. If our attention is merely technical, we will dehumanize the patient; if AI free our attention for genuine openness to others and active listening, we will elevate medical practice.

AI is not an inevitable fate to which we must resign ourselves, but a historic opportunity to rediscover what defines us as physicians. Therefore, the future of cardiology depends not only on the sophistication of its machines, but on the physician's ability to remain the guardians of our humanity. The ultimate goal is a model of clinical practice in which technology enhances precision, while physicians preserve judgment, ethics, and empathy.

The present and future of medical practice lie in our hands, and AI may challenge us to become more human, rather than allowing us to fall into the gravest existential risk of "treating the disease better and the person worse."

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