40 AÑOS

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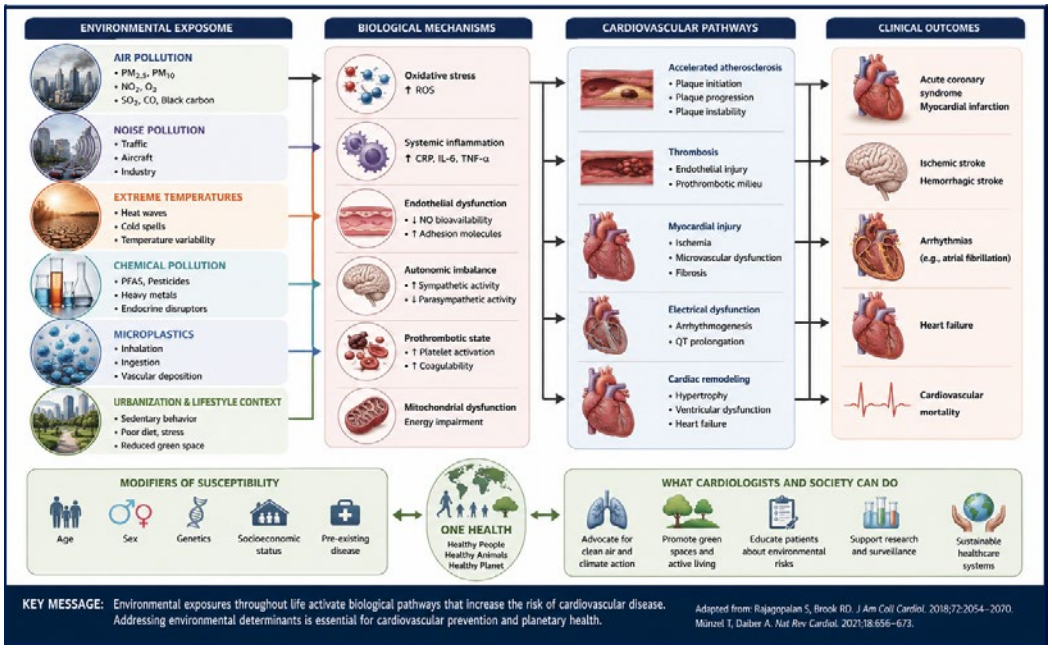

Environmental exposome and cardiovascular disease: from planetary health to cardiovascular prevention. Jannes Buelvas and Miguel A. Urina-Triana. Environmental health and cardiovascular disease: a new frontier for cardiovascular prevention. *This figure was generated with the help of generative artificial intelligence and subsequently underwent critical review, editing, and scientific validation by the authors, who guarantee its accuracy and accept total responsibility for the final content.*

- **Environmental health and cardiovascular disease**
- **Adverse outcomes of heart failure-COVID-19**
- **Aortic coarctation: percutaneous experience**
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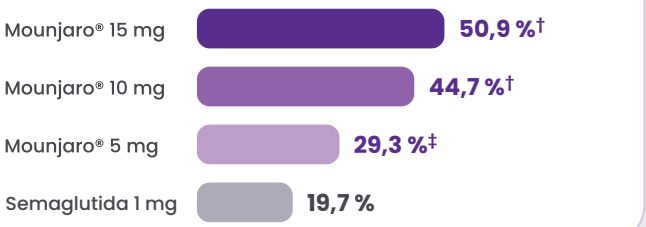
NORMOGLUCEMIA · HbA1c <5,7 % A 40 SEMANAS (SURPASS-2)[2]



ALBUMINURIA · REDUCCIÓN DEL RAC VS COMPARADORES (SURPASS-1 A 5)[7]

Análisis post hoc agrupado, exploratorio (ref. 7). Comparadores: placebo, semaglutida 1 mg, insulina degludec e insulina glargina

Consenso ADA/EASD: eficacia muy alta en la reducción de HbA1c y del peso corporal[6]

JUNTOS, ES POSIBLE ALCANZAR LAS METAS

Los números en superíndice remiten a la lista de referencias; los símbolos (*, †, ‡) remiten a estas notas metodológicas. *El rango 81 %-97 % agrupa cinco estudios con diseños, poblaciones, terapias de fondo y comparadores distintos; no establece comparabilidad clínica entre ellos ni permite una comparación directa de sus resultados. †p<0,001 vs comparador. ‡El logro de HbA1c <5,7 % con 5 mg no fue controlado para error tipo 1, por lo que no se presenta valor de p. Los datos de RAC provienen de un análisis post hoc y deben considerarse exploratorios: los ensayos SURPASS-1 a 5 no fueron diseñados para evaluar efectos sobre el RAC. En el programa de desarrollo clínico en DT2, el cambio de peso fue un desenlace secundario; MOUNJARO® no está indicado para el manejo del peso. Población mITT; valores faltantes predichos mediante MMRM. MOUNJARO® está indicado para el tratamiento de la Diabetes mellitus tipo 2 cuando la dieta y el ejercicio no proveen control glicémico adecuado: 1. Para pacientes con diabetes mellitus tipo 2 en terapia combinada, cuando metformina no logra el control glicémico bien sea sola o con otros medicamentos antidiabéticos, incluyendo insulina. 2. Para pacientes con diabetes mellitus tipo 2 en quienes metformina está contraindicada o no se tolera.

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MOUNJARO® no está indicado para el uso en pacientes con diabetes mellitus tipo 1.

Referencias: 1. Rosenstock J, et al. Lancet. 2021;398(10295):143-155. **2.** Frías JP, et al. N Engl J Med. 2021;385(6):503-515. **3.** Ludvik B, et al. Lancet. 2021;398(10300):583-598. **4.** Del Prato S, et al. Lancet. 2021;398(10313):1811-1824. **5.** Dahl D, et al. JAMA. 2022;327(6):534-545. **6.** Davies MJ, et al. Diabetes Care. 2022;45(11):2753-2786. **7.** Apperloo EM, Tuttle KR, Pavo I, Haupt A, Taylor R, Wiese RJ, Hemmingway A, Cherney DZI, Sattar N, Heerspink HJL. Tirzepatide Associated With Reduced Albuminuria in Participants With Type 2 Diabetes: Pooled Post Hoc Analysis From the Randomized Active- and Placebo-Controlled SURPASS-1-5 Clinical Trials. Diabetes Care. 2025 Mar 1;48(3):430-436. doi:10.2337/dc24-1773. PMID: 39746157; PMCID: PMC11870291. **8.** Coskun T, et al. Mol Metab. 2018;18:3-14.

ADA = American Diabetes Association; **DT2** = diabetes mellitus tipo 2; **EASD** = European Association for the Study of Diabetes; **GIP** = polipéptido insulinotrópico dependiente de glucosa; **GLP-1** = péptido similar al glucagón-1; **HbA1c** = hemoglobina glicosilada; **mITT** = intención de tratar modificada; **MMRM** = modelo mixto de medidas repetidas; **RAC** = cociente albúmina/creatinina en orina.

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EDITORIAL

Environmental health and cardiovascular disease: a new frontier for cardiovascular prevention

Salud ambiental y enfermedad cardiovascular: una nueva frontera para la prevención cardiovascular

*Jannes Buelvas[1,2] and Miguel A. Urina-Triana[2,3,4]**

[1]President of Sociedad Colombiana de Cardiología y Cirugía Cardiovascular; [2]Cardiology Specialization Program, Health Sciences Department, Universidad Simón Bolívar; [3]Revista Colombiana de Cardiología; [4]Fundación del Caribe para la Investigación Biomédica (Fundación BIOS). Barranquilla, D.C. Colombia

Cardiovascular health depends not only on biological and behavioral factors but also on the physical, social, and environmental milieu in which people are born, live, work, and grow old. In an age marked by climate change, accelerated urbanization, and growing environmental degradation, understanding the interaction between the environment and the cardiovascular system has become a scientific and public health priority.

Cardiovascular disease continues to be the main cause of death and disability worldwide. Traditionally, cardiovascular prevention has focused its efforts on controlling classical risk factors like blood pressure, diabetes mellitus, dyslipidemia, obesity, smoking, and sedentarism. However, the evidence gathered over the last decades has helped recognize that environmental exposures exert a decisive effect on cardiovascular health. In this context, environmental health emerges as one of the new frontiers of preventive cardiology and global cardiovascular health.[1-3]

Environmental contamination contributes significantly to the global burden of cardiovascular disease and is estimated to cause close to seven million premature deaths every year, most of which are attributable to cardiovascular diseases.[4] This impact has led to air pollution being considered one of the main modifiable cardiovascular disease risk factors, with a burden comparable to that of other traditional risk factors.[5]

This new paradigm has spurred the development of the exposome concept, defined as the conjunction of cumulative lifetime environmental exposures and their interactions with biological and genetic factors.[6] This perspective helps transcend the conventional model focused exclusively on the individual and incorporate the environment's effect on the pathophysiological processes responsible for cardiovascular disease.

Among the environmental factors, air pollution has been the most studied environmental determinant. Prolonged exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide, ozone, and other contaminants is associated with a significant increase in the risk of coronary disease, stroke, heart failure, arrhythmias, and cardiovascular death.[2,5,7] In a state-of-the-art review published in the *Journal of the American College of Cardiology*, Rajagopalan et al.[5] described $PM_{2.5}$ contamination as the environmental factor with the highest contribution to global cardiovascular mortality.[5]

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There are multiple pathophysiological mechanisms involved, including oxidative stress, systemic inflammation, endothelial dysfunction, sympathetic activation, coagulation disorders, and an accelerated atherosclerotic process.[2,7,8] Interestingly, many of these mechanisms are the same as those of the traditional cardiometabolic risk factors, suggesting additive and synergistic effects on global cardiovascular risk.

The climate crisis is another relevant dimension of environmental health. The progressive rise in temperatures and heightened frequency of extreme weather phenomena have been associated with increased cardiovascular mortality and hospitalizations for heart failure, coronary disease, and stroke.[3,9] Heat waves foster dehydration, neurohormonal activation, hemoconcentration, and increased metabolic demands, which are capable of triggering acute cardiovascular events, especially in older people and patients with chronic illnesses.

Forest fires, droughts, flooding, and other climate change-related events also substantially increase the levels of air pollution and contribute to deepening social and health inequalities.[10] Consequently, cardiovascular health and planetary health have become closely interrelated concepts.

Another emergent environmental determinant is noise pollution. Chronic exposure to traffic, aircraft, or industrial noise has been associated with hypertension, coronary disease, and stroke.[2,3] The pathophysiological mechanisms involve hypothalamic-pituitary-adrenal axis activation, increased sympathetic activity, sleep disorders, and endothelial dysfunction[2]. Although it often receives less attention than air pollution, noise is a significant public health problem in large cities.

Accelerated urbanization has also modified the interaction between human beings and natural environments. Various studies have shown that access to green spaces is related to lower stress levels, lower blood pressure, greater physical activity, and less cardiovascular mortality.[11] These findings have promoted the development of the planetary health concept, defined as the simultaneous pursuit of human well-being and the preservation of natural life-sustaining systems.[12]

In recent years, chemical pollution and exposure to microplastics have aroused growing interest. The presence of plastic particles in human atherosclerotic plaques and their relationship to a growing incidence of major cardiovascular events have opened a new line of investigation with potential public health implications.[13] These findings suggest that exposure to microplastics could be a new environmental determinant of cardiovascular risk and open a promising field of research in environmental cardiology. Likewise, the so-called "eternal chemicals" or perfluoroalkyl substances (PFASs) have been related to metabolic disorders and increased cardiovascular mortality.[14] Figure 1 (Main Figure) summarizes the interactions between the main environmental exposures, the biological mechanisms involved, the cardiovascular pathophysiological pathways, and their clinical consequences, incorporating the exposome and planetary health concepts.

Implications for Latin America and Colombia

These challenges take on special relevance in Latin America and Colombia. Rapid urbanization, socioeconomic inequalities, the growing automotive fleet, and vulnerability to extreme weather events constitute a scenario that requires comprehensive answers. However, the evidence from middle-income countries continues to be scarce, and a large part of the available knowledge comes from North America and Europe.[11] This underscores the need to strengthen regional research and generate our own evidence to help us understand the environmental and epidemiological idiosyncrasies of our countries.

Comprehensive cardiovascular risk assessment should progressively incorporate environmental factors within a broader perspective of patients and their context. Medical education, promoting sustainable healthy lifestyles, and supporting public policies aimed at improving air quality and reducing harmful environmental exposures are essential components of a modern preventive strategy.[3,15]

Likewise, scientific societies have a growing responsibility. In addition to developing clinical practice guidelines, they are called upon to promote research, education, and policymaking aimed at constructing healthier environments. In this regard, the recent joint statement by several international cardiovascular societies marks an important step toward recognizing environmental determinants as an essential component of cardiovascular health.[15]

Latin America is one of the most urbanized regions of the world and has significant social and environmental inequalities. Urban air pollution, forest fires, high temperatures, and extreme weather phenomena are growing threats to the population's cardiovascular

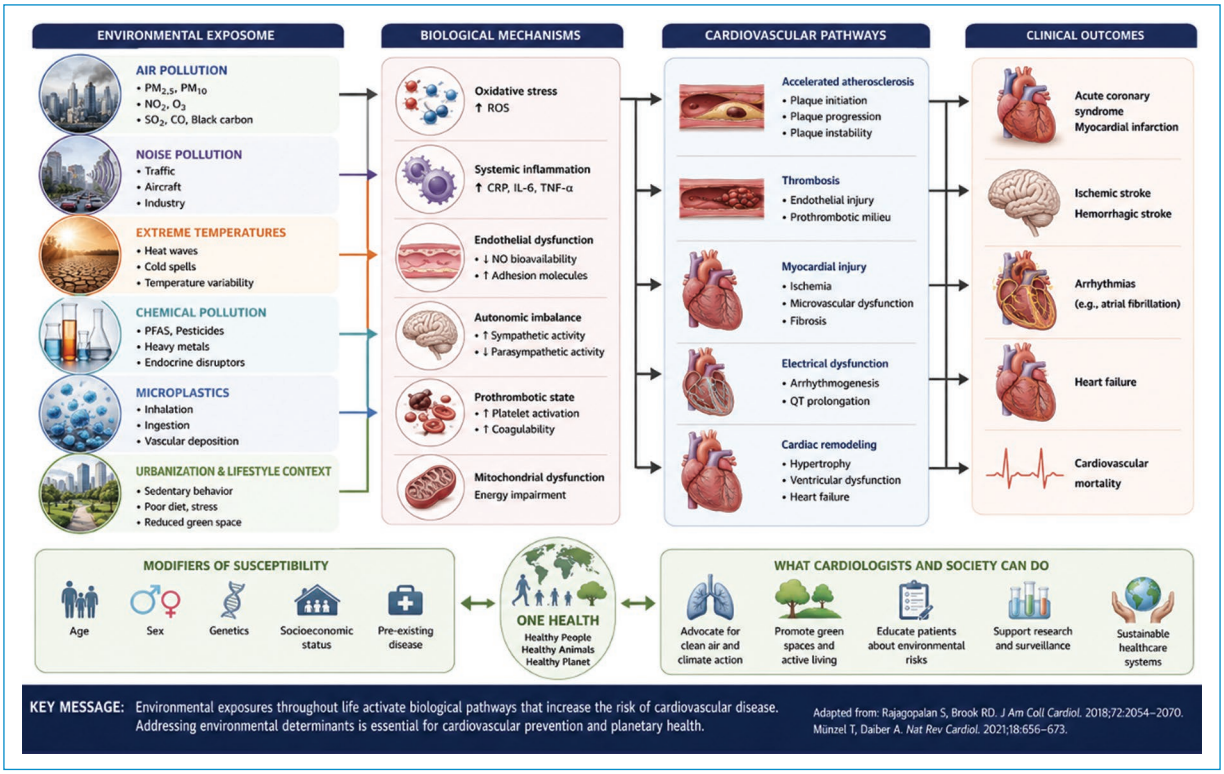

Figure 1. Main figure. Environmental exposome and cardiovascular disease: from planetary health to cardiovascular prevention. This figure was generated with the help of generative artificial intelligence and subsequently underwent critical review, editing, and scientific validation by the authors, who guarantee its accuracy and accept total responsibility for the final content.

health. However, evidence produced in the region remains limited, making collaborative research and strengthened environmental epidemiological surveillance essential.

We are facing a paradigm shift. Just as hypertension, smoking, and hypercholesterolemia redefined cardiovascular prevention in the 20th century, so environmental pollution and climate change are destined to become some of the great cardiovascular challenges of the 21st century. Modern cardiology must transcend a vision focused solely on the individual to incorporate environmental determinants within a broader and more integrative approach.

Planetary health and heart health are inseparable. Recognizing this interdependence provides the opportunity to develop more effective, equitable, and sustainable preventive strategies. Environmental health is not only an ecological concern; it is a growing cardiovascular priority and an imperative for contemporary cardiology. Incorporating the planetary health perspective could represent one of the most momentous conceptual changes for cardiology in the future.

Sociedad Colombiana de Cardiología y Cirugía Cardiovascular has the opportunity to spearhead the incorporation of planetary health and environmental cardiology concepts into cardiovascular prevention strategies, medical education, and clinical research in Latin America. The growing scientific evidence forces us to broaden our view of cardiovascular risk and integrate environmental determinants into a more sustainable and equitable healthcare agenda. Environmental cardiology is no longer an emergent discipline; it has become an essential component of this century's preventive cardiology. The future of cardiovascular prevention will largely depend on our ability to integrate planetary health with heart health.

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ORIGINAL ARTICLE

Factors associated with adverse outcomes in patients with chronic heart failure hospitalized for SARS-CoV-2/COVID-19

Factores asociados a desenlaces adversos en pacientes con falla cardiaca crónica hospitalizados por SARS-CoV-2/COVID-19

Rodrigo Castro-París[1,2], Ángel A. García-Pena[1,2], Ricardo Bohórquez[1,2], Alejandra Cañas-Arboleda[1], Melissa Díaz[3], and Óscar Muñoz-Velandia[1]*

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Abstract

Introduction: *SARS-CoV-2 infection has led to worse outcomes in patients with heart disease.* **Objective:** *To identify factors at hospital admission that are associated with ICU, mechanical ventilation, and death in patients with a history of heart failure who are hospitalized for SARS-CoV-2/COVID-19.* **Methods:** *This was a retrospective, observational, analytical cohort study of patients hospitalized for SARS-CoV-2/COVID-19 at a university hospital in Bogotá, Colombia, between March 2020 and July 2021.* **Results:** *A total of 241 patients with a history of heart failure were hospitalized for SARS-CoV-2/COVID-19, 81 (33.6%) of whom were admitted to the ICU, 62 (25.7%) required mechanical ventilation, and 99 (41.1%) died. The multivariate analysis showed an association between the composite outcome and NEWS 5-6 (OR: 8.54; 95% CI: 2.23-32.78; p = 0.002), NEWS ≥ 7 (OR: 8.174; 95% CI: 1.37-48.6; p = 0.021), CRP > 10 mg/dl (OR: 6.47; 95% CI: 1.76-23.77; p = 0.005), and elevated BNP or proBNP (OR: 5.75; 95% CI: 1.49-22.14; p = 0.011). There was also an association between mortality and age (OR: 1.04; 95% CI: 1.01-1.07; p = 0.006), NEWS ≥ 7 (OR: 3.01; 95% CI: 1.28-7.10; p = 0.012), and LDH > 350 U/L (OR: 2.68; 95% CI: 1.48-4.85; p = 0.001).* **Conclusions:** *Patients hospitalized for SARS-CoV-2/COVID-19 who had a history of heart failure had a higher proportion of ICU admissions, need for mechanical ventilation, and in-hospital mortality. The best independent predictors of adverse outcomes were age, moderate- to high-risk NEWS, and elevated LDH, CRP, and natriuretic peptides. This suggests that older age, comorbidities, and inflammation were more decisive in the adverse outcomes than heart failure etiology, functional class, and initial troponin levels or LVEF.*

Keywords: *SARS-CoV-2. COVID-19. Mortality. Intensive care unit. Respiratory failure. Heart failure.*

Resumen

Introducción: *La infección por SARS-CoV-2 ha llevado a peores desenlaces en pacientes con cardiopatías.* **Objetivo:** *Identificar factores al ingreso hospitalario asociados a UCI, ventilación mecánica y muerte en pacientes con antecedente de falla cardiaca hospitalizados por SARS-CoV-2/COVID-19.* **Métodos:** *Estudio observacional analítico de cohorte retrospectiva en pacientes hospitalizados por SARS-CoV-2/COVID-19, en un Hospital Universitario en Bogotá, Colombia, entre marzo de 2020 y julio de 2021.* **Resultados:** *Se identificaron 241 pacientes con antecedente de falla cardiaca hospitalizados por*

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SARS-CoV-2/COVID-19, 81 (33.6%) de los cuales ingresaron a UCI, 62 (25.7%) requirieron ventilación mecánica y 99 (41.1%) fallecieron. El análisis multivariado demostró asociación del desenlace compuesto con la escala NEWS 5-6 (OR: 8.54; IC 95%: 2.23-32.78; p = 0.002), NEWS ≥ 7 (OR: 8.174; IC 95%: 1.37-48.6; p = 0.021), PCR > 10 mg/dl (OR: 6.47; IC 95%: 1.76-23.77; p = 0.005) y elevación de BNP o proBNP (OR: 5.75; IC 95%: 1.49-22.14; p = 0.011); para mortalidad con edad (OR: 1.04; IC 95%: 1.01-1.07; p = 0.006), NEWS ≥ 7 (OR: 3.01; IC 95%: 1.28-7.10; p = 0.012) y LDH > 350 U/L (OR: 2.68; IC 95%: 1.48-4.85; p = 0.001). **Conclusiones:** *Se encontró mayor proporción de ingreso a UCI, requerimiento de ventilación mecánica y mortalidad intrahospitalaria en pacientes hospitalizados por SARS-CoV-2/COVID-19 al tener el antecedente de falla cardiaca. Los mejores predictores independientes de desenlaces adversos fueron: edad, NEWS entre moderado a alto riesgo, y elevación de LDH, PCR y péptidos natriuréticos. Esto sugiere que presentar mayor edad, comorbilidades e inflamación fueron más determinantes en desenlaces adversos que la etiología de la falla cardiaca, la clase funcional, el valor de la troponina o la FEVI inicial.*

Palabras clave: *SARS-CoV-2. COVID-19. Mortalidad. Unidad de Cuidados Intensivos. Insuficiencia respiratoria. Falla cardíaca.*

Introduction

During the SARS-CoV-2/COVD-19 pandemic, more than 676 million cases and more than 6.8 million deaths were reported up to the first week of October 2023[1]. SARS-CoV-2/COVID-19 has a multimodal interaction with the cardiovascular system, causing myocardial injury and dysfunction by increasing adrenergic activity and generating endothelial dysfunction along with inflammatory and prothrombotic activity. This fosters stress cardiomyopathy and leads to exacerbation of chronic conditions like ischemic heart disease and heart failure[2,3]. All the above results in worsening clinical outcomes, including intensive care unit (ICU) admission, the need for mechanical ventilation, and death[2,4-8].

Heart failure patients are a high-prevalence group (1 to 3% of the adult population[8]) with a higher SARS-CoV-2/COVID-19 risk due to immunodeficiency, frailty, and reduced hemodynamic ability to respond to serious infections[3,9-11]. Intensive care unit admissions and the need for orotracheal intubation have been reported in 23% of those hospitalized, along with an in-hospital mortality rate of up to 40% in tertiary care facilities[12-14], representing a challenge for inpatient treatment of the viral infection.

Therefore, we need a better description of this population in our region to optimize risk stratification and implement timely treatment strategies for patients with heart failure and SARS-CoV-2/COVID-19, considering the characteristics of our healthcare system and differential sociodemographic factors.

The objective of this study was to identify factors detectable on admission that were associated with adverse outcomes (ICU admission, the need for mechanical ventilation, or death) in patients with a history of heart failure who were hospitalized for SARS-CoV-2/COVID-19 at a referral hospital in Bogotá, Colombia.

Methods

This was an observational, analytical study based on a retrospective cohort from the institutional database of patients hospitalized for SARS-CoV-2/COVID-19 at Hospital Universitario San Ignacio, in Bogotá, Colombia. Patients over the age of 18 who were hospitalized for SARS-CoV-2/COVID-19 between March 19, 2020, and July 31, 2021; had PCR-confirmed infection; and met the universal definition of heart failure[15] on hospital admission were included. Those who requested voluntary discharge or were referred to other healthcare facilities were excluded.

The data regarding demographic characteristics, the variables of interest, and outcomes were extracted from the SARS-CoV-2/COVID-19 database at the hospital mentioned above, which included all patients with that diagnosis treated at the healthcare facility. The database was constructed based on a primary data source (the electronic medical chart system). The extracted data were recorded in the RedCap®[16,17] application, which certifies the safety and confidentiality of the information, using a standardized form. To ensure data quality, the rate of missing data was monitored, and information was verified in the event of extreme data.

To identify patients in the database who had heart failure, we initially selected those who reported a history of heart failure or some type of heart disease (e.g., ischemic, valvular, hypertensive, Chagas), those who were receiving pharmacological treatment related to heart failure, and those who had an echocardiogram available. We then verified whether they met the universal definition of heart failure[15]. Once patients

were included, the remaining data required was obtained directly from the electronic medical charts.

The ethics and research committees at Pontificia Universidad Javeriana and Hospital Universitario San Ignacio approved the study (approval code: FM-CIE-1052-21).

Additionally, the primary outcome was a composite of ICU admission, the need for mechanical ventilation, or in-hospital death. Secondary outcomes were ICU admission, the need for mechanical ventilation, or in-hospital death evaluated individually.

The descriptive analysis of categorical variables described data using absolute and relative frequencies. Continuous variables were presented as mean (SD) or median (interquartile range), depending on whether they met the assumption of normality. Categorical variables were described as numbers and percentages. The Shapiro-Wilks test was used to evaluate the assumption of normality. The relationship between the variables of interest and the primary outcome was initially explored using a univariate model. After this, a multivariate regression was conducted, including the variables that were significant on the univariate test and those reported in previous studies, using the backward stepwise method, looking for the most parsimonious model. Variables with a $p < 0.05$ were considered statistically significant. All statistical analyses were done using the 2019 StataCorp statistical package. (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

Out of a total of 3,793 patients hospitalized for SARS-CoV-2/COVID-19, 368 with a medical or pharmacological history or echocardiographic findings suggestive of heart failure were selected. Of these, 241 met the universal definition of heart failure[15]. Table 1 describes the demographic characteristics, comorbidities, and prior treatment of the included patients. The median age was 77 years, the majority were males (68%), and 70.9% had a high burden of comorbidities, defined as a Charlson index ≥ 5. The most frequent comorbidity was hypertension, and the most prevalent heart failure etiology was ischemia. Most were admitted in functional class (FC) II/IV according to the New York Heart Association (NYHA) scale[18], and 58.3% had a previously preserved left ventricular ejection fraction (LVEF). Altogether, 69.7% were taking a renin-angiotensin-aldosterone system (RAAS) inhibitor, and 2.9% had received at least one dose of the SARS-CoV-2/COVID-19 vaccine.

Table 1. Demographic characteristics, comorbidities, and prior treatment of patients with a history of heart failure hospitalized for SARS-CoV-2/COVID-19

Variable	Total (n = 241)
Age, years, median (IQR)	77 (68,83)
Male sex, n (%)	141 (58.5)
Comorbidities, n (%)	
Hypertension	187 (77.6)
Hypothyroidism	73 (30.4)
Atrial fibrillation/flutter	47 (19.5)
Diabetes mellitus	66 (27.4)
Kidney disease	57 (23.6)
COPD	73 (30.3)
Peripheral artery disease	27 (11.2)
Cerebrovascular disease	22 (9.1)
Cancer	43 (17.8)
Active smoking, n (%)	9 (3.7)
Charlson index ≥ 5	171 (70.9)
Heart failure etiology, n (%)	
Ischemia	92 (38.2)
Hypertension	94 (39.0)
Valve disease	21 (8.7)
Chagas	8 (3.3)
Congenital	3 (1.2)
Other	13 (5.4)
Unknown	10 (4.1)
NYHA functional class, n (%)	
I	18 (7.5)
II	120 (49.8)
III	42 (17.4)
IV	17 (7.1)
Not reported	44 (18.3)
Prior LVEF ** n (%)	
> 50%	56 (58.3)
40-50%	18 (18.8)
< 40%	22 (22.9)
Treatment on admission, n (%)	
ACE inhibitors	28 (11.6)
ARBs	126 (52.3)
ARNIs	14 (5.8)
Beta blockers	150 (62.2)
MRAs	47 (19.5)
SGLT2 inhibitors	12 (5.0)
Quadruple therapy*	3 (1.3)
Loop diuretics	95 (39.4)
DOACs	39 (16.2)
Warfarin	8 (3.3)
SARS-CoV-2 vaccination, n (%)	7 (2.9)

*Optimal heart failure therapy that includes an ARNI/ACE inhibitor/ARB, beta blocker, MRA, and SGLT2 inhibitor.
**Left ventricular ejection fraction (LVEF) evaluated by echocardiography in the last two years.
IQR: interquartile range; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; MRAs: mineralocorticoid receptor antagonists; SGLT2 inhibitors: sodium-glucose cotransporter-2 inhibitors; DOACs: direct oral anticoagulants.

Table 2 describes the vital signs and laboratory tests of patients with a history of heart failure on hospital admission; 69% of the cases were admitted with a National Early Warning Score (NEWS)[19] ≥ 5, 50% had lymphopenia, and 71% had some degree of abnormal oxygenation. Lactate dehydrogenase (LDH) and C-reactive protein (CRP) were elevated in 44.8 and 46.2% of the cases, respectively. Troponin was elevated in 46% of cases, and the median brain natriuretic peptide (BNP) level was 210 ng/L.

A total of 142 (58.9%) developed the composite outcome, 81 (33.6%) were admitted to the ICU, 62 (25.7%) required mechanical ventilation, and 99 (41.1%) died.

The univariate analysis showed that the composite outcome (ICU admission, need for mechanical ventilation, or in-hospital death) was associated with NEWS 5-6 (OR: 2.46; 95% CI: 1.35-4.49; p = 0.003), NEWS ≥ 7 (OR: 5.19; 95% CI: 2.23-12.09; p < 0.001), LDH levels > 350 U/L (OR: 3.73; 95% CI: 2.09-6.67; p < 0.001), CRP > 10 mg/dl (OR: 4.08; 95% CI: 2.29-7.27; p < 0.001), and elevated BNP or proBNP (OR: 3.15; 95% CI: 1.11-8.92; p = 0.031). For the same outcome, the multivariate analysis found a significant association with NEWS 5-6 (OR: 8.54; 95% CI: 2.23-32.78, p = 0.002), NEWS ≥ 7 (OR: 8.174; 95% CI: 1.37-48.6; p = 0.021), CRP > 10 mg/dl (OR: 6.47; 95% CI: 1.76-23.77; p = 0.005), and elevated BNP or proBNP levels (OR: 5.75; 95% CI: 1.49-22.14; p = 0.011) (Table 3).

For in-hospital mortality, the univariate analysis revealed an association with age (OR: 1.04; 95% CI: 1.01; 1.07; p = 0.003), a Charlson index ≥ 5 (OR: 1.14; 95% CI: 1.01-1.28; p = 0.0027), NEWS 5-6 (OR: 2.01; 95% CI: 1.06-3.81; p = 0.0032), NEWS ≥ 7 (OR 4.59; 95% CI 2.07-10.21, p < 0.001), LDH > 350 U/L (OR: 2.81; 95% CI: 1.62-4.87; p < 0.001), and CRP levels > 10 mg/dL (OR: 3.39; 95% CI: 1.94-5.91; p < 0.001) (Table 4). The multivariate analysis found an association with age (OR: 1.04; 95% CI: 1.01-1.07; p = 0.006), NEWS ≥ 7 (OR: 3.01; 95% CI: 1.28-7.10; p = 0.012), and LDH > 350 U/L (OR: 2.68; 95% CI: 1.48-4.85; p = 0.001) (Table 4).

Table 2. Vital signs and laboratories on admission of patients with heart failure hospitalized for SARS-CoV-2/COVID-19

Variable	Total (n = 241)
HR on admission, median (IQR)	83 (71,94)
Systolic BP, mean (SD)	123 (26)
Diastolic BP, mean (SD)	70 (13)
NEWS, n (%)	
1-4	74 (30.7)
5-6	120 (50.0)
≥ 7	46 (19.3)
Admission laboratories	
Leukocytes, median (IQR)	7,400 (5,600;10,500)
Lymphocytes < 1000, n (%)	120 (50.0)
$PaFiO_2$, n (%)	
< 100.	32 (13.3)
100-200	53 (21.9)
200-300	88 (36.5)
> 300	68 (28.4)
LDH > 350, U/L,	108 (44.8)
CRP > 10, mg/dl,	111 (46.2)
D-dimer > 1,000, n (%)	139 (58.0)
US Troponin I > 26, n (%)	111 (46)
BNP, median (IQR)	210 (88, 943)
Creatinine, median (IQR)	1.1 (0.83,1.7)

IQR: interquartile range; SD: standard deviation; HR: heart rate; BP: blood pressure; NEWS: National Early Warning Score; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Discussion

Publications on SARS-CoV-2/COVID-19 have increased steadily since 2020, with different registries and cohorts in Latin America and Colombia[20-23] suggesting worse outcomes in patients with cardiovascular disease. Our results show that patients with heart failure had a higher proportion of ICU admissions, greater need for mechanical ventilation, and more in-hospital mortality compared to the proportions reported in the general population of patients hospitalized for SARS-CoV-2/COVID-19. Even comparing previously reported data from our institution, in-hospital mortality was more than double (41.1 vs. 17%)[24]. In addition, we found that the best independent predictors of the composite outcome (ICU admission, the need for mechanical ventilation, and in-hospital death) detectable on admission were moderate- to high-risk NEWS and elevated CRP and BNP or proBNP levels. The independent predictors for mortality were age, NEWS ≥ 7, and LDH.

The study population had high comorbidity rates and frequently elevated biomarkers. The findings suggest that older age and comorbidities, coupled with the degree of inflammation and BNP elevation, were more determinant in serious outcomes than the heart failure etiology, functional class, troponin level, or LVEF at hospital admission.

We believe that these results can be explained from a pathophysiological perspective as a direct or indirect

Table 3. Univariate and multivariate analysis of the composite outcome (ICU admission, need for mechanical ventilation, and in-hospital death) in patients with a history of heart failure hospitalized for SARS-CoV-2/COVID-19

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.01 (0.99-1.04)	0.155		
Male sex	1.41 (0.84-2.38)	0.192		
Comorbidities				
Diabetes mellitus	1.72 (0.948-3.13)	0.074		
Kidney disease	1.26 (0.68-2.33)	0.457		
COPD	1.08 (0.62-1.90)	0.778		
Charlson index ≥ 5	1.02 (0.58-1.80)	0.944		
Ischemic heart failure etiology	0.64 (0.38-1.08)	0.095		
NYHA functional class III-IV/IV	1.31 (0.70-2.47)	0.399		
NEWS				
1-4	Reference		Reference	
5-6	2.46 (1.35-4.49)	**0.003**	8.54 (2.23-32.78)	**0.002**
≥ 7	5.19 (2.23-12.09)	**< 0.001**	8.174 (1.37-48.6)	**0.021**
Quadruple therapy	1.15 (0.09-14.30)	0.909		
Anticoagulation	1.01 (0.54-1.92)	0.967		
Admission laboratories				**0.005**
Positive LDH (> 350 U/L)	3.73 (2.09-6.67)	**< 0.001**	6.47 (1.76-23.77)	**0.011**
Positive CRP (> 10 mg/dl)	4.08 (2.29-7.27)	**< 0.001**	5.75 (1.49-22.14)	
Elevated BNP or proBNP	3.15 (1.11-8.92)	**0.031**		
Troponin (+ 26)	1.81 (0.79-4.17)	0.162		
Prior LVEF < 50%	1.52 (0.41-5.60)	0.526		

Values in bold type are results with p values less than 0.05.
*Optimal heart failure therapy that includes an ARNI/ACE inhibitor/ARB, beta blocker, MRA, and SGLT2 inhibitor.
**History of anticoagulant treatment with warfarin or direct oral anticoagulants.
***Left ventricular ejection fraction (LVEF) evaluated by echocardiography in the last two years.
ICU: intensive care unit; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; NEWS: National Early Warning Score; LDH: lactate dehydrogenase; CRP: C-reactive protein.

viral impact on the heart. The viral infection causes multimodal heart function abnormalities through systemic proliferation and local infiltration of inflammatory cells and cytokines. This fosters infiltrative and restrictive cardiomyopathy, as well as endothelial injury, micro-thrombosis, and increased cardiac workload, all within a setting of hypoxia, coronary thrombotic occlusion, and cardiac fibrosis and necrosis[25-29]. The above, coupled with fever, tachycardia, large intravenous fluid infusions, and pulmonary hypertension due to the onset of adult respiratory distress syndrome or associated pulmonary embolism, worsen the situation of a previously diseased heart[30,31].

The reported need for mechanical ventilation in patients with a history of heart failure ranges from 23 to 42% in different cohorts[14,32], and our study population falls within this range. It should be noted that our mortality results also concur with those described by Álvarez-García et al.[14] in hospitals within the Mount Sinai healthcare system in New York, United States. These authors found a 40% mortality rate in patients with a history of heart failure compared to 24.9% in patients without. Our results further concur with those of Salinas-Botrán et al.[33] in Spain and Bektas-Murat et al.[32] in Eskisehir, Turkey, who found 47.6 and 39.2% in-hospital mortality rates in patients with a history of heart failure. Another study in Brazil, whose study population had a mean age of 58, reported a lower mortality rate (12.3%) in patients with heart failure[21].

Previous studies have also identified age as an independent predictor of mortality due to increased frailty, geriatric syndromes, lower biological and functional reserves, and a higher frequency of comorbidities[34-36]. Águila-Gordo D et al.[36] found a 47.6% mortality rate in a geriatric population, with higher risk in more advanced ages, along with more elevated inflammatory

Table 4. Univariate and multivariate analysis of mortality in patients with a history of heart failure hospitalized for SARS-CoV-2/COVID-19

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.04 (1.01-1.07)	**0.003**	1.04 (1.01-1.07)	**0.006**
Male sex	1.66 (0.97-2.82)	0.06		
Comorbidities				
Diabetes mellitus	1.39 (0.79-2.47)	0.255		
Kidney disease	1.85 (1.02-3.37)	0.044		
COPD	1.38 (0.79-2.41)	0.254		
Charlson index 5	1.14 (0.01-1.28)	**0.027**		
Ischemic heart failure etiology	0.81 (0.48-1.39)	0.452		
NYHA functional class III-IV/IV	1.61 (0.87-2.97)	0.129		
NEWS				
1-4	Reference		Reference	
5-6	2.01 (1.06-3.81)	**0.032**	1.56 (0.77-3.14)	0.209
≥ 7	4.59 (2.07-10.21)	**< 0.001**	3.01 (1.28-7.10)	**0.012**
Quadruple therapy*	0.92 (0.69-1.22)	0.594		
Anticoagulation**	0.79 (0.42-1.52)	0.489		
Admission laboratories				
Positive LDH (> 350 U/L)	2.81 (1.62-4.87)	**< 0.001**	2.68 (1.48-4.85)	**0.001**
Positive CRP (> 10 mg/dl)	3.39 (1.94-5.91)	**< 0.001**		
Elevated BNP or proBNP	2.05 (0.69-6.02)	0.192		
Troponin	1.89 (0.84-4.26)	0.125		
Prior LVEF < 50%***	2.11 (0.80-5.58)	0.129		

Values in bold type are results with p values less than 0.05.
*Optimal heart failure treatment that includes an ARNI/ACE inhibitor/ARB, beta blocker, MRA, and SGLT2 inhibitor.
** History of anticoagulation treatment with warfarin or direct oral anticoagulants.
***Left ventricular ejection fraction (LVEF) evaluated by echocardiography in the last two years.
NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; NEWS: National Early Warning Score; LDH: lactate dehydrogenase; CRP: C-reactive protein.

parameters (leukocytes, lymphopenia, CRP, LDH) and more severe ARDS.

Vital sign-based scales, like NEWS, and biomarkers like troponin and natriuretic peptides have proven useful for early detection of patients with a higher risk of death and severe disease in different studies in both Europe and Latin America[20,37]. These scales have been useful for patients both with and without a history of cardiovascular disease[37-39]. In our study, troponin was positive in 46% of the cases; however, it did not prove to be an independent predictor of mortality. In addition, we found that elevated LDH was useful as an independent factor for predicting mortality and worse outcomes, which could be explained by the fact that it is a marker for acute pulmonary injury and acute or chronic tissue damage. It remained useful in patients with a history of heart failure, similar to what was described in the general population of patients hospitalized for SARS-CoV-2/COVID-19[40-42].

It should be noted that we found a very low frequency of patients on quadruple therapy (1.3 of 22.9% of patients with heart failure with reduced ejection fraction), which could be due to conditions inherent to the healthcare system in our country. In fact, it has been reported that, due to social distancing orders in Argentina, Italy, Poland, and the United Kingdom, follow-up appointments and procedures were postponed, affecting medication prescriptions and patients' ambulatory treatment plans[43-46].

One of the main strengths of this study is its sample size, as it is one of the largest studies in Latin America, providing an accurate perspective of the impact of COVID-19 on patients with a history of heart failure. However, there are several limitations that should be recognized:

– The retrospective nature of the analysis and lack of a concurrent group of patients with heart failure without COVID infection limits the ability to determine causality. Furthermore, the generalizability of the outcomes to other clinical settings is limited, as this study was conducted at a single tertiary care facility. Therefore, prospective studies will be needed that include patients treated in other clinical settings, in different regions, and with a different level of care, to confirm our findings.
– This same design has a risk of information bias due to missing data, either because laboratory tests are not ordered or because the necessary clinical information is not gathered. However, it is notable that the rate of missing data in the medical charts was less than 5% for most of the exposure variables, and we had no significant data losses for evaluating the outcomes of interest, which minimizes the risk of bias.
– Few patients had inpatient echocardiographic assessment due to the biological risk for the healthcare staff. Our method of identifying patients with heart failure may also have prevented the detection of patients in early stages or with mild disease. However, this method is very sensitive for detecting patients with a more serious clinical condition, who are precisely those who could have worse outcomes and benefit more from earlier and more targeted treatment.
– Our study did not consider the impact of variations in the treatment measures implemented to manage heart failure, including the lack of resources during the most critical times of the pandemic, which may have affected the clinical outcomes of these patients. Future studies should provide a more detailed analysis of the potential impact of early interventions, both for heart failure and inflammation control in this specific population.

Conclusions

Our data suggest that patients with a history of heart failure hospitalized for SARS-CoV-2/COVID-19 have worse outcomes than the general population, with higher ICU admission rates, more need for mechanical ventilation, and higher mortality rates. The factors best associated with worse outcomes are age, multiple comorbidities, abnormal vital signs on admission (yielding moderate- to high-risk NEWS), elevated acute phase reactants like LDH and CRP, as well as biomarkers like BNP and proBNP (which are more important than the heart failure etiology), and functional class or LVEF on hospital admission. These findings suggest that patients with a history of heart failure hospitalized for COVID-19 should be carefully evaluated on admission, using tools like NEWS and laboratory tests for CRP and LDH, and those with high scores should be considered for invasive monitoring and possible early ICU admission. Furthermore, our findings suggest that inflammation is a key predictor of worse clinical outcomes, and therefore inflammation management strategies should be considered for these patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the ethics committee for the analysis of routinely obtained and anonymized clinical data. Due to the nature of the study, individual informed consent was not required. The pertinent ethical guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing or creating content for this article.

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ORIGINAL ARTICLE

Retrospective descriptive study of the management of aortic coarctation

Estudio descriptivo retrospectivo de la experiencia del tratamiento de la coartación de aorta

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Abstract

Introduction: *Aortic coarctation (CoA) can be treated with balloon angioplasty and/or stenting, yet local evidence on immediate outcomes is limited.* **Objective:** *To assess the immediate hemodynamic effectiveness and procedural safety of percutaneous CoA treatment at a referral center in Cundinamarca.* **Methods:** *This was a retrospective descriptive study of a consecutive cohort. We included 40 patients with CoA who underwent balloon angioplasty and/or stent implantation. Effectiveness was evaluated with the catheterization peak-to-peak gradient before and after the procedure and the proportion with a residual gradient < 20 mmHg. Safety included intraprocedural/inpatient adverse events and reinterventions. A paired t-test was used when appropriate (α = 0.05).* **Results:** *Forty patients were included (70% male); ductal-type CoA predominated (77.5%). Procedural success was 97.5% with 5.0% complications. In 30 cases with paired measurements, the gradient decreased from 40.3 ± 23.7 to 18.5 ± 27.8 mmHg (Δ 21.8 ± 25.7; p = 0.0001); 73.3% achieved a residual gradient < 20 mmHg. Documented reintervention was 34.2% (13/38). The CP and Palmaz platforms were widely used; covered stents accounted for 12.5%.* **Conclusions:** *Percutaneous treatment of CoA showed high acute effectiveness and low complication rates. Technical optimization and structured follow-up may further increase the share with very low residual gradients and potentially reduce reinterventions.*

Keywords: *Aortic coarctation. Balloon angioplasty. Stents. Cardiac catheterization. Treatment outcome.*

Resumen

Introducción: *La coartación de la aorta (CoA) puede tratarse con angioplastia con balón, stent, o ambos, pero la evidencia local de resultados inmediatos es limitada.* **Objetivo:** *Evaluar la efectividad hemodinámica inmediata y la seguridad del tratamiento percutáneo de la CoA en un centro de referencia de Cundinamarca.* **Métodos:** *Estudio descriptivo retrospectivo de cohorte consecutiva, en el que se incluyeron 40 pacientes con CoA sometidos a angioplastia con balón, implante de stent, o ambos. La efectividad se midió con el gradiente pico-a-pico por cateterismo antes/después y la proporción con gradiente residual < 20 mmHg. La seguridad consideró eventos adversos intraprocedimiento/intrahospitalarios y reintervenciones. Se aplicó t pareada cuando correspondió (α = 0.05).* **Resultados:** *Se incluyeron 40 pacientes (70% hombres); predominó la CoA*

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ductal (77.5%). El éxito procedimental fue del 97.5% y las complicaciones del 5%. En 30 casos con medidas pareadas, el gradiente disminuyó de 40.3 ± 23.7 a 18.5 ± 27.8 mmHg (Δ 21.8 ± 25.7; p = 0.0001); 73.3% alcanzó gradiente residual < 20 mmHg. La reintervención documentada fue 34.2% (13/38). Se emplearon con frecuencia plataformas CP y Palmaz; los stents cubiertos representaron el 12.5%. **Conclusiones:** *El abordaje percutáneo de la CoA mostró alta efectividad aguda y baja tasa de complicaciones. Persisten oportunidades de optimización técnica y de seguimiento estructurado para aumentar la proporción con gradientes muy bajos y, potencialmente, reducir reintervenciones.*

Palabras clave: *Coartación aórtica. Angioplastia con balón. Stents. Cateterismo cardíaco. Resultado del tratamiento.*

Introduction

Coarctation of the aorta (CoA) is a congenital heart defect defined by segmental narrowing of the aorta, usually the aortic isthmus. It accounts for approximately 5 to 8% of congenital heart defects, and its clinical significance lies in the fact that, without prompt diagnosis and treatment, it can cause hypertension, heart failure, premature vascular disease, and early death.[1-5]

Treatment has evolved from surgical repair to percutaneous alternatives like balloon angioplasty and stent implantation, especially in older children, adolescents, and adults. However, local evidence regarding its immediate hemodynamic effectiveness, safety, reinterventions, and follow-up is limited. Therefore, this study describes the experience with the percutaneous treatment of CoA at a referral center in Cundinamarca.[1,6-8]

The problem

Aortic coarctation continues to be a clinical challenge because its presentation may vary from neonatal shock to hypertension in older children or young adults. Although screening and surveillance have improved in Colombia, late diagnoses persist, and there are gaps in the local description of outcomes[5].

In practice, the treatment selected depends on age, anatomy, gradient, the presence of associated lesions, and the healthcare facility's level of experience. One relevant dimension is differentiating between isolated CoA and CoA associated with other structural heart defects. This information was reviewed in this cohort, but the consolidated database did not include it in a standard, verifiable fashion[1,3,6,8].

Therefore, the problem addressed in this study is the lack of a systematic description of local percutaneous outcomes, including success, residual gradient, complications, reintervention, and the availability of complementary anatomical variables. These data can guide improvements in the institutional database, device selection, and structured follow-up of patients with CoA[5].

Methods

This was a retrospective descriptive study based on a consecutive cohort of patients with CoA who received percutaneous treatment at a referral center in Cundinamarca.

We consecutively included all patients with a CoA diagnosis who underwent percutaneous treatment (balloon angioplasty and/or stent implantation) and were recorded in the institution's system during the study period. The cases were identified in the institutional database and medical charts, forming a consecutive sample of 40 patients treated at the referral center.

The main outcomes were defined as the immediate effectiveness and safety of the procedure. Effectiveness was evaluated using the trans-coarctation gradient measured by catheterization before and after the intervention, the absolute change in gradient, and the proportion of patients who achieved a residual gradient < 20 mmHg. Safety was evaluated through the presence of adverse events or intraprocedural and inpatient complications, and the need for reintervention recorded during the observation period. We described the demographic (age, sex), anthropometric (weight, height, body surface area), anatomical (type of coarctation), and procedural (type of device and stent category, including the distinction between a coated or uncoated stent) variables. Procedural success was interpreted using the institutional database's coding. In addition, we verified whether the CoA was recorded as isolated or associated with other structural heart defects. We also sought to describe cases that did not respond to treatment as well as major complications using age, sex, anatomical type, pre- and post-procedural gradients, device used, adverse events, and the need for additional interventions. When these fields were not individually and verifiably available, the missing data was explicitly reported[2-4,8].

Moreover, data were extracted from the institutional procedural records and the clinical charts. Baseline and post-procedural trans-coarctation gradients were measured invasively during catheterization. The anatomical

characteristics, demographic and anthropometric variables, and details of the devices employed were extracted from the clinical reports and the database. Reinterventions and complications were verified with the database and inpatient documentation. The classification of isolated/associated CoA, details of patients without procedural success, and assignment of major complications were sought in the same sources; data that were not recorded in the analytical file or the consolidated database available for this study were not allocated.

Consecutive case sampling was used, which reduced the risk of selection bias. Using standardized invasive measurements of the gradient during catheterization reduced information bias in evaluating immediate effectiveness. Given the study's descriptive goal, adjustment for confounders was not planned for causal inference, and the interpretation of associations was limited to describing the center's experience. The report followed the STROBE guidelines to foster transparency and comprehensiveness in communicating the methods and results.

We did not calculate a sample size *a priori*; all consecutive cases available in the institution's records during the study period were included, constituting a final sample of 40 patients.

Continuous variables were described using means and standard deviation or medians and interquartile ranges, depending on their distribution. The Shapiro-Wilk test was used to evaluate the normality of the absolute change in gradient (pre-post). Student's t-test for paired samples was employed for comparison of the trans-coarctation gradient before and after the procedure, when the change met the assumption of normality. Categorical variables were summarized as counts and proportions, which included the procedural success rate, frequency of complications, and proportion of patients with a residual gradient < 20 mmHg. A two-tailed significance threshold of 0.05 was used for the hypothesis tests.

Results

A total of 40 patients were included. The age was 9.5 years (SD 13.1), with a median of 3.5 [0.3-14.0]; weight was 25.6 kg (SD 23.7), with a median of 15.8 [4.5-45.5]; height was 91.9 cm (SD 55.8), with a median of 75.5 [51.8-158.2]; and body surface area was 1.3 m² (SD 0.5), with a median of 1.0 [1.0-2.0]. The baseline catheterization gradient was available for 33/40 patients, with a mean of 40.8 mmHg (SD 23.1) and a median of 30.0 [22.0-60.0] (Table 1). Seventy percent were males (28/40), and 30% were females (12/40). Regarding the anatomical type of coarctation, the ductal type predominated (77.5%, 31/40), followed by the post-ductal/isthmic (12.5%, 5/40) and hypoplastic (10.0%, 4/40) (Table 1 and Fig. 1. Main Figure). A review of the consolidated database did not reliably differentiate between isolated CoA and that associated with other structural heart defects; therefore, this variable was not quantified and was marked as a priority point for institutional record-keeping improvement.

Table 1. Baseline characteristics

Variable	n	Mean (SD)	Median [IQR]
Age (years)	40	9.5 (13.1)	3.5 [0.3-14.0]
Weight (kg)	40	25.6 (23.7)	15.8 [4.5-45.5]
Height (cm)	40	91.9 (55.8)	75.5 [51.8-158.2]
Body surface area	40	1.3 (0.5)	1.0 [1.0-2.0]
Baseline pressure gradient (mmHg)	33	40.8 (23.1)	30.0 [22.0-60.0]
Variable	**Category**	**n**	**%**
Sex	Male Female	28 12	70 30
Type of coarctation	Ductal Post-ductal/ Isthmic Hypoplasia	31 5 4	77.5 12.5 10

The procedural success rate was 97.5% (39/40). The rate of intraprocedural or inpatient adverse events/complications was 5.0% (2/40). During the observation period, reintervention (re-coarctation) was documented in 34.2% (13/38 cases had information) (Table 2). The distribution of devices showed greater use of the CP stent (22.5%), with similar proportions for the Palmaz (17.5%), other/unspecified (17.5%), and NA (17.5%) categories. Coated stents accounted for 12.5%, medicated stents for 10.0%, and Andra stents for 2.5% (Table 2). The only case with an unsuccessful procedure represented 1/40 patients (2.5%). The available analytical file did not have enough individualized variables to verifiably describe age, weight, anatomical type, residual gradient, device, or specific cause of non-response; therefore, undocumented characteristics were not added. Similarly, complications were reported using overall frequency, as the consolidated database did not

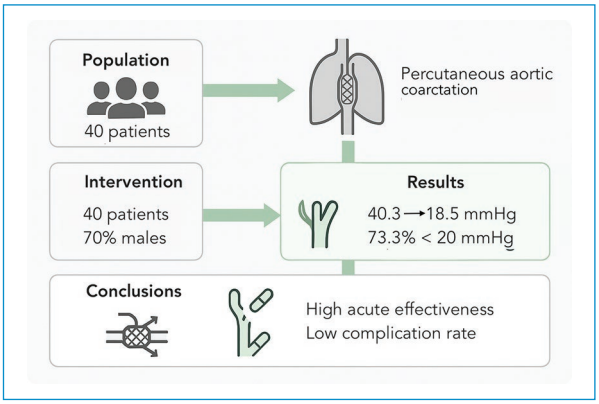

Figure 1. Main Figure. Graphic summary of the retrospective descriptive study of CoA treated percutaneously at a referral center in Cundinamarca: (n = 40); 70% males; predominantly ductal anatomy (77.5%). Intervention with balloon angioplasty or stent or both (CP/Palmaz platforms; coated stents: 12.5%). Immediate effectiveness: peak-to-peak gradient 40.3→18.5 mmHg (Δ 21.8 mmHg; p = 0.0001); 73.3% with a residual gradient < 20 mmHg. Safety: complications in 5.0%. Follow-up: reintervention documented in 34.2%. The available database did not allow uniform classification of isolated/associated CoA nor assignment of major complications by type.

Table 2. Procedural indicators and complementary information requested on review

Indicator	n/N	%
Procedural success	39/40	97.5
Adverse events/complications	2/40	5
Reintervention (recoarctation)	13/38	34.2
Stent category	n	%
CP stent	9	22.5
NA	7	17.5
Other/unspecified	7	17.5
Palmaz	7	17.5
Coated	5	12.5
Medicated	4	10
Andra	1	2.5
Failed/no response to the procedure	1/40	2.5
Isolated CoA vs. association with other heart defects	Not available in the structured database	NA
Major complications assigned by type/severity	Not available in the structured database	NA

include standardized attribution by type or severity of the major complication.

Immediate hemodynamic effectiveness was evaluated in 30 patients, using paired measurements. The baseline gradient was 40.3 mmHg (SD 23.7) (median: 30.0 [22.0-58.8]), and the post-catheterization gradient was 18.5 mmHg (SD 27.8) (median: 8.5 [3.5-20.0]). The absolute reduction in gradient (pre-post Δ) was 21.8 mmHg (SD 25.7) (median: 21.0 [11.2-37.2]). The Δ distribution did not deviate from normality (Shapiro-Wilk p = 0.6718), and therefore Student's paired t-test was applied, showing a significant reduction in gradient (p = 0.0001). In addition, 73.3% (22/30) achieved a residual gradient < 20 mmHg immediately after the procedure (Table 3).

Table 3. Effectiveness (pressure gradient)

Measure	Value
Paired n	30
Baseline pressure gradient (mmHg) (mean, SD)	40.3 (23.7)
Baseline pressure gradient (mmHg) (median, IQR)	30.0 [22.0-58.8]
Post-catheterization pressure gradient (mmHg) (mean, SD)	18.5 (27.8)
Post-catheterization pressure gradient (mmHg) (median, IQR)	8.5 [3.5-20.0]
Δ (pre-post) (mean, SD)	21.8 (25.7)
Δ (median, IQR)	21.0 [11.2-37.2]
Paired test	Paired Student's t-test
p	0.0001
Shapiro's p (normality of the Δ)	0.6718
Proportion with a post-catheterization gradient <20 mmHg	22/30 (73.3%)

Discussion

The validity of this study lies in its observational design with consecutive inclusion and standardized invasive hemodynamic evaluation that allowed accurate calculation of the immediate performance of percutaneous interventions for CoA. Out of 40 patients, technical success was achieved in 97.5%, with a mean peak-to-peak gradient reduction from 40.3 to 18.5 mmHg (Δ: 21.8 mmHg), and 73.3% achieving a residual gradient < 20 mmHg. Overall adverse events/complications were infrequent (5%), and 34.2% required reintervention during follow-up. These results synthesize a

relevant clinical and hemodynamic benefit in a cohort with a wide variety of ages and anatomical differences.

Our findings essentially concur with multicenter studies and trials that have established stents as the treatment of choice in older children and adults. In the multicenter study by Forbes et al.[7], the rate of technical complications reduced from 16.3 to 6.1% in the modern era, with improvements in balloons and stent platforms; our 5% is within the current safety range. Furthermore, the literature shows immediate gradient reductions to low double-digits after implantation, consistent with the guideline-recommended clinical goal of significant obstruction relief. Within this framework, our achievement of a residual gradient < 20 mmHg in 73.3% is congruent with the hemodynamic threshold used by the ESC 2020 guidelines for determining severity, treatment, and re-intervention, although our average residual of 18.5 mmHg suggests room for optimizing post-dilation and the final stent diameter in some cases[7,8].

Mid-term comparisons are also informative. In the COAST program (and its extension), Cheatham-Platinum stent implants maintained obstruction relief for up to 60 months, with a reduction in the use of antihypertensives from 53 to 29%. However, cumulative stent fractures amounted to 24.4%, and re-interventions increased between the intermediate and late follow-up. In very long follow-ups, other studies have reported infrequent aneurysms (~ 6%) and reinterventions in adults (~ 10%), suggesting that age and the anatomical profile modulate the risk of late events. Compared to these patterns, our reintervention rate of 34.2% appears higher, probably affected by the higher proportion of young patients with the potential for body growth, complex ductal anatomy, and the need for planned re-expansions. Altogether, the acute efficacy we found is consistent with the state of the art, and the differences in reinterventions are plausible due to the mix of ages and follow-up strategies[9,10].

As far as blood pressure burden, the evidence indicates that hypertension persists in 20 to 50% of patients even after anatomically successful repair, with an impact on ventricular remodeling and events. In repaired adults, persistent hypertension was associated with suboptimal regression of the left ventricular mass index and more cardiovascular events; recent systematic reviews also estimate mean prevalence rates of close to 47% in the long term. Our residual gradients and the need for additional treatments should be interpreted in the light of this data, since even "mild" gradients may not be benign in terms of blood pressure control and remodeling. Current studies suggest that residual gradients in the 10-20 mmHg range are associated with worse intermediate outcomes, which reinforces the goal of achieving more complete relief and conducting close monitoring[11-14].

This study had some limitations inherent to its design and context: a moderate sample size, potential selection bias since it is the experience of a single institution, heterogeneity in age and anatomy (which conditions the indication for a coated or uncoated stent and the probability of re-expansion), and the lack of systematic evaluation of blood pressure parameters with ABPM and uniform long-term imaging surveillance (e.g., tomography for aneurysms and fractures). Furthermore, while we tried to cover the need to describe whether CoA was isolated or associated, the characteristics of unresponsive cases, and major complications, these fields were not coded in an individual, consistent, and verifiable way in the available database. This limitation prevents a detailed clinical characterization of the single unsuccessful case and the two adverse events and should be corrected in future versions of the database. The study's strengths include consecutive inclusion, invasive hemodynamic attribution with hard figures, and "real-world" applicability in a population with a wide spectrum of coarctation.

The practical implications are clear. First, optimizing the technique to further reduce the immediate gradient (selecting a final diameter aligned with the healthy isthmus and having a scheduled re-expansion plan for growing patients) can improve subsequent blood pressure control and reduce the need for reintervention. Second, selecting a coated stent for high-risk anatomies (critical stenoses, calcified walls, or aortic lesions) is consistent with the observational data and guidelines and could mitigate wall complications. Third, standardizing follow-up according to guidelines (with gradient goals of < 20 mmHg, strict blood pressure control, periodic ABPM, and serial magnetic resonance imaging/computed tomography) is crucial for early detection of aneurysms, fractures, and restenosis. Finally, integrating adult congenital heart disease clinics facilitates lifelong surveillance in accordance with the residual risk. As an operational improvement, the institutional database should include mandatory fields for associated heart defects, the reason for non-response, major complications by type and severity, and blood pressure figures so that future studies can answer these questions more precisely[8-10,12-14].

In conclusion, the percutaneous intervention in our cohort showed high immediate efficacy and safety, with a significant gradient reduction and low complication

profile, aligned with international evidence. The proportion of residual gradients < 20 mmHg was acceptable, although there is room for improvement, and the rate of reintervention underscores the importance of technical and follow-up strategies aimed at achieving a more complete and sustained relief. The additional review requested helped show that the consolidated database requires more detail for classifying isolated/associated CoA, describing unresponsive cases, and attributing major complications. Looking forward, multicenter studies with standardized follow-up are needed to determine risk-based reintervention thresholds and optimize the choice of devices and expansion sizes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent, and ethical approval. The authors received approval from the ethics committee for analyzing routinely obtained anonymized data, and therefore informed consent was not required. The pertinent guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for writing this article.

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REVIEW ARTICLE

Current perspectives on mineralocorticoid receptor antagonists in the treatment of heart failure across the entire spectrum of ejection fraction

Perspectivas actuales de los antagonistas del receptor de mineralocorticoide en el tratamiento de la insuficiencia cardiaca en todo el espectro de la fracción de eyección

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Abstract

Heart failure (HF) is a clinical syndrome with high prevalence and mortality, classified according to left ventricular ejection fraction (LVEF) as HF with reduced (HFrEF), mildly reduced (HFmrEF), or preserved (HFpEF) ejection fraction. Activation of the renin-angiotensin-aldosterone system promotes inflammation, fibrosis, and myocardial remodeling that can be mitigated using mineralocorticoid receptor antagonists (MRAs). These are divided into steroidal (spironolactone and eplerenone) and nonsteroidal (finerenone) medications, with different selectivity and safety. This article describes the available evidence on the use of MRAs across the entire LVEF spectrum. A narrative review was performed using a search in PubMed, Embase, Scopus, and the Cochrane Library between 1999 and 2025. In HFrEF, steroidal MRAs have demonstrated tangible benefits. The RALES study showed a 30% reduction in total mortality with spironolactone, while EPHESUS and EMPHASIS-HF confirmed that eplerenone reduces mortality and hospitalizations for HF. However, these drugs increase the risk of hyperkalemia, especially in patients with chronic kidney disease. In HFmrEF and HFpEF, the evidence for spironolactone has been mixed; although TOPCAT did not significantly reduce the primary outcome, it did reduce hospitalizations for HF. FINEARTS-HF indicated that finerenone significantly reduces HF worsening in patients with LVEF ≥ 40%. Mineralocorticoid receptor antagonists continue to be essential for HF, and finerenone expands treatment options for HFmrEF and HFpEF, with clinical efficacy and a favorable safety profile.

Keywords: *Heart failure. Mineralocorticoid receptor antagonists. Spironolactone. Eplerenone. Finerenone. Mortality. Hospitalization.*

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Resumen

La insuficiencia cardíaca (IC) es un síndrome clínico de alta prevalencia y mortalidad, clasificado según la fracción de eyección del ventrículo izquierdo (FEVI) en IC con FE reducida (IC-FEr), levemente reducida (IC-FElr) y preservada (IC-FEp). La activación del sistema renina–angiotensina–aldosterona favorece inflamación, fibrosis y remodelado miocárdico, procesos que pueden atenuarse mediante antagonistas del receptor mineralocorticoide (ARM). Estos se dividen en esteroideos (espironolactona y eplerenona) y no esteroideos (finerenona), con diferencias en selectividad y seguridad. Se describió la evidencia disponible sobre el uso de los ARM en todo el espectro de la FEVI. Se realizó una revisión narrativa mediante búsqueda en PubMed, Embase, Scopus y Cochrane Library entre 1999 y 2025. En IC-FEr, los ARM esteroideos han demostrado beneficios tangibles. El estudio RALES evidenció una reducción del 30% de la mortalidad total con espironolactona, mientras EPHESUS y EMPHASIS-HF confirmaron que la eplerenona disminuye la mortalidad y las hospitalizaciones por IC. Sin embargo, estos fármacos incrementan el riesgo de hipercalemia, especialmente en pacientes con enfermedad renal crónica. En IC-FElr e IC-FEp, la evidencia con espironolactona ha sido heterogénea; aunque TOPCAT no redujo significativamente el desenlace primario, sí disminuyó las hospitalizaciones por IC. FINEARTS-HF mostró que la finerenona reduce significativamente los eventos de empeoramiento de IC en pacientes con FEVI ≥ 40%. Los ARM continúan siendo fundamentales en IC, y la finerenona amplía las opciones terapéuticas en IC-FElr e IC-FEp, con eficacia clínica y un perfil de seguridad favorable.

Palabras clave: *Insuficiencia cardíaca. Antagonistas de los receptores de mineralocorticoides. Espironolacton. Eplerenona. Finerenona. Mortalidad. Hospitalización.*

Introduction

Heart failure (HF) is a clinical syndrome characterized by signs and symptoms caused by a structural or functional heart anomaly that produces elevated intracardiac pressures or insufficient cardiac output at rest or during exercise[1,2]. Heart failure affects more than 64 million people worldwide, and its incidence is expected to increase with population aging and improved diagnosis. It is also one of the main causes of global morbidity and mortality[3,4].

Heart failure is classified into three groups according to left ventricular ejection fraction (LVEF):

– HF with reduced ejection fraction (HFrEF): LVEF equal to or less than 40%.
– HF with mildly reduced ejection fraction (HFmrEF): LVEF 41-49%.
– HF with preserved ejection fraction (HFpEF): LVEF equal to or greater than 50%.

The AMERICCAASS registry, a large acute and chronic HF registry that includes more than 60 institutions in 20 countries across the American continent, found a mean age of 66 years, 59.7% male patients, and ischemic heart disease as the most common HF etiology. Altogether, 60.7% of hospitalized patients and 58.5% of ambulatory patients in this registry had HFrEF, while 19.2% of hospitalized patients and 17.2% of ambulatory patients had HFpEF[5,6]. Meanwhile, the RECOLFACA registry included patients with a history of hospitalization for HF in the 12 months prior to recruitment. A total of 3,268 patients from 60 institutions in 24 departments in Colombia were enrolled, with a median age of 69 years. This registry reported that 75.5% of patients had HFrEF and 15% had HFpEF, with an average of 1.4 hospitalizations per year for decompensated HF and a one-year mortality rate of 6.7%[7].

Over the last few years, great strides have been made in treating patients with this disease, and there is evidence of new pharmacological treatments that reduce mortality and hospitalizations due to HF. Consequently, the objective of this article is to present the current state of the art in the use of mineralocorticoid receptor antagonists (MRAs) across the entire LVEF spectrum in patients with HF[1,2].

Methods

This was a state-of-the-art narrative review of the use of MRAs in HF. Databases like PubMed, Embase, Scopus, and Cochrane Library (1999–2025) were searched using the following MeSH terms and keywords: “heart failure,” mineralocorticoid receptor antagonists,” “spironolactone,” “eplerenone,” “finerenone,” “mortality,” and “hospitalization.” Clinical trials, meta-analyses, and literature review articles were included, while pediatric studies and case reports were excluded. A qualitative analysis was done, prioritizing high-quality evidence and considering clinical outcomes and safety. Since this was a literature review, ethics committee approval was not required. The principles of scientific integrity and proper source citation were respected.

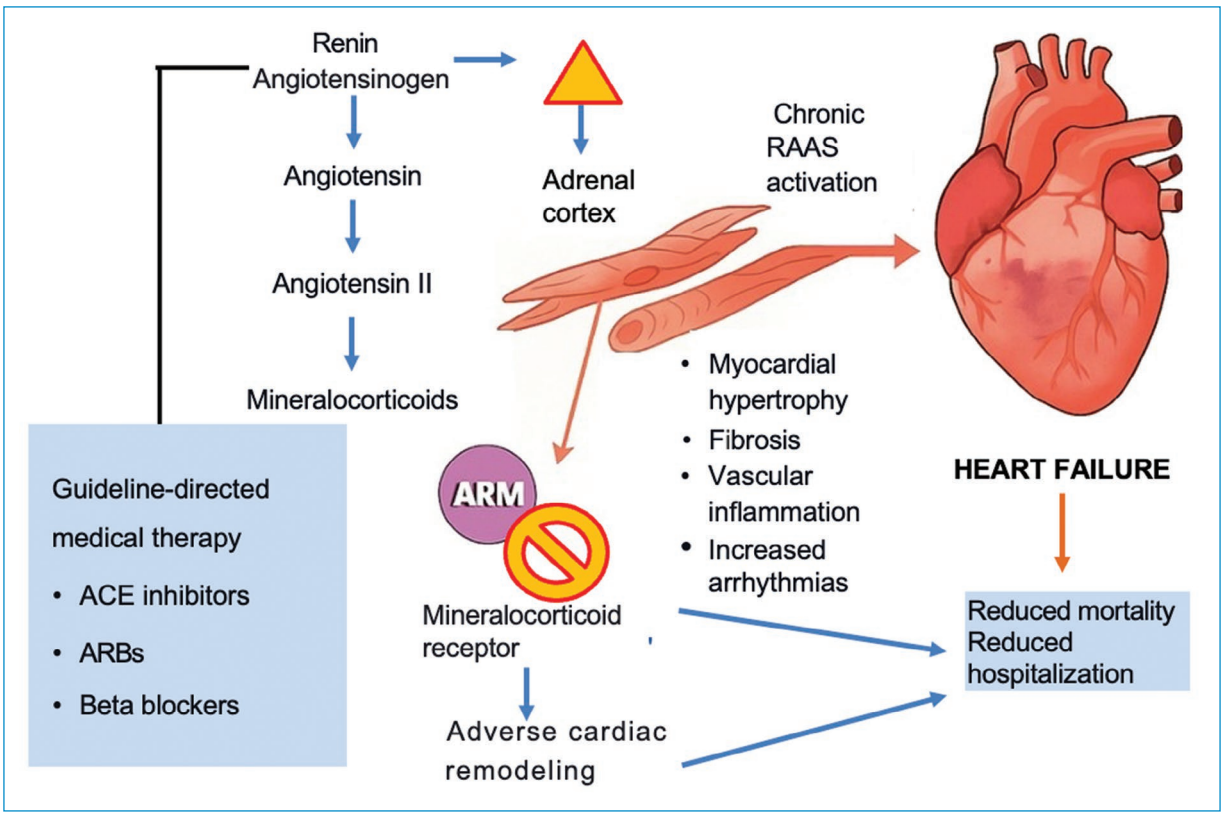

Figure 1. Mechanism of action of MRAs in HF. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; RAAS: renin-angiotensin-aldosterone system. *Adapted from: Carlino I, Pirrotta F, Gennari L, Palazzuoli A. Current Application of Mineralocorticoid Antagonist (MRA) in Heart Failure and CKD: Does Non-Steroidal Drug Add Novel Insights. Biomedicines. 2025 Jul 10;13(7):1693. doi: 10.3390/biomedicines13071693.*

Rational use of mineralocorticoid receptor antagonists in heart failure

Aldosterone is a mineralocorticoid hormone produced mainly by the adrenal cortex in response to angiotensin II secretion, hyperkalemia, and corticotropin. Aldosterone binds to mineralocorticoid receptors (MRs) in the kidney's collecting duct, stimulates gene expression of serum and glucocorticoid-regulated kinase (SGK1), and activates epithelial sodium channels (ENaCs) to regulate salt excretion, extracellular volume, and blood pressure[8].

Mineralocorticoid receptor antagonists directly bind to and block MRs, inhibiting aldosterone or 11-deoxycorticosterone activation, which reduces the degree of inflammation, endothelial dysfunction, and cardiac remodeling (Fig. 1)[9]. These medications (MRAs) are classified into two groups:

– Steroidal MRAs (sMRAs): spironolactone and eplerenone
– Nonsteroidal MRAs (nsMRAs): finerenone

Comparison between nsMRAs (finerenone) and sMRAs

Mineralocorticoid receptor antagonists are classified as (Table 1):

– Steroidal (spironolactone and eplerenone): act as competitive aldosterone antagonists, blocking its receptors in the distal convoluted tubules. This causes greater sodium and water excretion and less potassium excretion. These MRAs reduce myocardial fibrosis and inflammation, improving left ventricular function. They are more effective in controlling blood pressure due to their central action but are associated with a higher risk of sexual side effects[10].
– Nonsteroidal (finerenone): blocks MR overactivation, reducing proinflammatory and profibrotic signaling, oxidative stress, and Na+/K+-ATPase delocalization. These effects lead to improved glomerular integrity, less tubulointerstitial fibrosis, and slower diabetic kidney disease progression. In the heart,

Table 1. Differences between steroidal and nonsteroidal MRAs

Category	sMRA (spironolactone, eplerenone)	nsMRA (finerenone)
Main structure	Based on steroids	Based on dihydropyridines
Receptor selectivity	Binds to multiple hormone receptors (androgen, progesterone, glucocorticoid)	Highly selective for the mineralocorticoid receptor alone; greater antagonism
Transcriptional activity	High	Reduced activation of proinflammatory and profibrotic genes
Size	-	More bulky (finerenone)
Side effects	Gynecomastia, menstrual irregularities, sexual dysfunction, hyperglycemia	Minimal hormonal side effects
Half-life	Long (spironolactone: 13.8-16.5 h; eplerenone: 4-6 h)	Short (finerenone: 2-3 h)
Metabolism	Produces active metabolites (spironolactone)	Does not have active metabolites
Risk of hyperkalemia (PK/PD)	Higher (due to accumulation in the kidneys)	Lower (due to more balanced tissue distribution)
Organ distribution	Mainly in the kidneys	Balanced between the heart and the kidneys
Risk of hyperkalemia (safety)	High (especially in patients with CKD)	Lower
Antifibrotic and anti-inflammatory effects	Present, but with side effects	Possibly stronger, with fewer side effects
Clinical implications	Effective, but with hormonal side effects and the risk of hyperkalemia	More selective, safer in patients with CKD, and better for cardiorenal protection
Function	Block the effects of aldosterone to reduce inflammation, fibrosis, and fluid retention	-
Use	For treating heart failure and chronic kidney disease	-

CKD: chronic kidney disease; nsMRA: nonsteroidal mineralocorticoid receptor antagonist; PD: pharmacodynamic; PK: pharmacokinetic; sMRA: steroidal mineralocorticoid receptor antagonist.

finerenone mitigates inflammation, fibrosis, and oxidative stress, contributing to improved cardiac function and a lower risk of arrhythmia. It has a better renal safety and tolerance profile. Given its high affinity for the receptor and rapid elimination in the kidney without active metabolites, common side effects associated with sMRAs, like gynecomastia and sexual dysfunction, can be avoided, making it ideal for people with chronic kidney disease[10,11].

Molecular modeling studies of the finerenone-MR complex suggest that fineronone blocks the MR as a bulky, passive antagonist. This mechanism differs from that of sMRAs, which explains the different clinical responses[10]. Finerenone's unique way of binding determines the potency, selectivity, and recruitment of nuclear cofactors, while its physicochemical properties, including lipophilia and polarity, determine tissue penetration and distribution, which, together, offer a novel MRA pharmacology with marked antifibrotic efficacy in animal models[11]. Compared to other MRAs, finerenone is more selective for the MR than eplerenone and spironolactone and is at least as potent as spironolactone. In preclinical studies, finerenone was distributed evenly between the kidneys and the heart. This fact could contribute to spironolactone and eplerenone's greater effect on sodium and potassium balance; furthermore, finerenone does not cross the blood-brain barrier. Compared to sMRAs, finerenone is six to ten times less lipophilic, has minimal kidney excretion, a short half-life in patients with kidney disease (two to three hours), and no active metabolites. Meanwhile, spironolactone is a pro-drug with active metabolites like canrenone and 7α-thiomethyl spironolactone and a long half-life, which can accumulate and be detected in patients with estimated glomerular filtration rates (eGFRs) of 25-45 mL/min/1.73 m^2 for up to three weeks after stopping treatment[12-14].

Clinical evidence of MRAs in heart failure (Table 2)

a. HFrEF MRAs

The results of the Randomized Aldactone Evaluation Study (RALES; n = 1,663) demonstrated that spironolactone (~ 25 mg/day) lowered the risk of death by 30% compared to placebo in patients with HFrEF in New York Heart Association (NYHA) class III-IV (< 35%). The effects were so robust that the trial ended early due to its efficacy. The incidence of progressive HF and sudden death reduced, and the NYHA class improved. However, side effects like gynecomastia were higher in the treatment group (10% with spironolactone versus 1% with placebo)[15].

The main limitation of spironolactone's aldosterone blocking was hyperkalemia. In 2004, a study found an increased incidence of hyperkalemia after RALES was published, which was also correlated with increased spironolactone prescription. The rise in the incidence of hyperkalemia was probably related to the use of spironolactone in patients who would have been excluded from RALES (that is, in those with low eGFR) and higher spironolactone doses than those used in RALES[16,17].

Subsequently, the eplerenone development program appeared. Eplerenone is a more selective aldosterone antagonist whose efficacy was proven in the EPHESUS study, which included patients with myocardial infarction (MI), LVEF ≤ 40%, and symptomatic HF. The EPHESUS study results revealed that eplerenone was associated with a 15% relative risk reduction for all-cause mortality, compared to placebo, and a 13% relative risk reduction for cardiovascular (CV) mortality or hospitalization, compared to placebo[18].

A study published in 2011 evaluated the efficacy and safety of eplerenone in the hospitalization and survival of patients with HF (EMPHASIS-HF). This study showed that, compared to placebo, eplerenone substantially reduced the risk of death, as well as the risk of hospitalization for any cause, in patients with an LVEF ≤ 30%, a history of recent hospitalization, and NYHA functional class II[19]. Although the rate of hyperkalemia was higher with eplerenone than with placebo, no sexual adverse events were reported, unlike those found with spironolactone in RALES. Despite eplerenone's proven efficacy and safety, its use in daily clinical practice with chronic kidney disease (CKD) patients is limited. This may be due to the associated risk of hyperkalemia, as well as the data sheet's contraindications for use in patients with hypertension and type 2 diabetes mellitus (T2DM) with microalbuminuria[20].

The Phase 2 study known as ARTS included 2,000 patients and was designed to test the safety and tolerability of finerenone vs. eplerenone in patients with HFrEF and mild to moderate kidney disease. The study's primary objective was to evaluate N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction at 90 days, which was comparable in both groups. However, potassium was less elevated in the finerenone group, and there was less kidney function deterioration. In addition, the exploratory objective of evaluating reductions in hospitalizations, death, and emergency room visits was nominally lower in the group assigned to finerenone. These results are only exploratory and hypothesis-generating, as the study was not planned to evaluate the impact on clinical outcomes[21,22].

The clinical guidelines for diagnosing and treating patients with HFrEF give sMRAs a 1a recommendation, with no specific recommendation for choosing between spironolactone and eplerenone[2].

b. MRAs in HFmrEF and HFpEF

Spironolactone was evaluated in patients with HFpEF in the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial. This study included 422 patients (213 on spironolactone and 209 on placebo) with LVEF ≥ 50% to evaluate the effect of spironolactone (25 mg/day) on diastolic function and maximum exercise capacity at 12 months. Spironolactone improved cardiac remodeling and lowered NT-proBNP levels without significantly changing VO_2 max[23].

After these results, spironolactone was evaluated in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial that recruited 3,445 patients (1,722 on spironolactone and 1,723 on placebo) with HFmrEF or HFpEF (LVEF ≥ 45%). During a mean follow-up of 3.3 years, spironolactone did not significantly reduce the main composite outcome of time to cardiovascular death, cardiac arrest with resuscitation, or hospitalization for HF. However, it reduced HF hospitalizations by 17%[24]. It should be noted that TOPCAT had marked geographic differences: patients from the Americas (Canada, USA, Argentina, and Brazil) responded to spironolactone (a 26% relative risk reduction in primary outcome events), while patients recruited in Eastern European countries (Russia and Georgia) did not benefit from treatment. The lack of treatment benefits may have been because patients did not have natriuretic peptide measurements to confirm the HF diagnosis and may have had problems with adherence to the study

Table 2. Summary of MRA studies in HF

Study name	n	Treatment arms	Length of follow-up (years)	Primary efficacy outcome	NNT	Safety outcomes
sMRAs in HFrEF						
RALES	1,663	Spironolactone vs. placebo	2	All-cause mortality (RR: 0.70; 95% CI: 0.60-0.82)	9	Increased mean creatinine (0.05–0.10 mg/dL) and potassium (0.30 mmol/L) in the spironolactone group ($p < 0.001$)
EPHESUS (post MI)	6,642	Eplerenone vs. placebo	1.3	All-cause mortality (RR: 0.85; 95% CI: 0.75-0.96) and cardiovascular mortality, hospitalization for HF (RR: 0.87; 95% CI: 0.79-0.95)	44	Increased mean creatinine (0.06 vs. 0.02 mg/dL) ($p < 0.001$) and potassium (0.3 vs. 0.2 mmol/L) ($p < 0.001$)
EMPHASIS-HF	2,737	Eplerenone vs. placebo	1.75	All-cause mortality and hospitalizations for HF (HR: 0.63; 95% CI: 0.54-0.74])	19-21	Increased creatinine (0.09 vs. 0.04 mg/dL) and potassium (0.16 vs. 0.05 mmol/L) ($p < 0.001$)
sMRAs in HFmrEF or HFpEF						
TOPCAT	**3,445**	Spironolactone vs. placebo	3.3	Cardiovascular death, HF, and reversed cardiac arrest (HR: 0.89; 95% CI: 0.77-1.04)	~ 45-50*	Hyperkalemia rates (18.7 vs. 9.1%) and doubled creatinine (10.2 vs. 7.0%)
nsMRA in HFmrEF						
FINEARTS-HF (nsMRA, HFpEF and HFmrEF)	6,001	Finerenone vs. placebo	2.7	Cardiovascular death and worsening heart failure (RR: 0.84; 95% CI: 0.74-0.95)	~ 30-35	Hyperkalemia (> 6 mmol/L) 3.0 vs. 1.4%
Ongoing studies	**Inclusion criteria**	**Expected sample size**	**Treatment arms**	**Primary outcome**		
nsMRA-HF						
REDEFINE-HF nsMRA (NCT06080197)	HF EF ≤ 40% and recent hospitalization for HF	5,200	Finerenone vs. placebo	Cardiovascular death and total HF events		
CONFIRMATION-HF nsMRA (NCT06024746)	HF (any EF) and recent hospitalization for HF	1,500	Early initiation of finerenone and placebo vs. usual care (open)	Composite outcome of HF, HF events, and a > 5-point change in KCCQ-TSS at 7 months		
FINALITY-HF nsMRA (NCT06033950)	HF EF < 40% and ineligible for or intolerant of MRAs	2600	Finerenone vs. placebo	Time to CV death or HF event		

CI: confidence interval; CV: cardiovascular; EF: ejection fraction; HF: heart failure; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; MRA: mineralocorticoid receptor antagonist; NNT: number needed to treat; nsMRA: nonsteroidal mineralocorticoid receptor antagonist; PD: pharmacodynamics; PK: pharmacokinetics; RR: relative risk; sMRA: steroidal mineralocorticoid receptor antagonist.

Table 3. Scenarios for using MRAs in HF

Condition	Preferred MRA	Recommendations
HFrEF	Eplerenone/ spironolactone	Eplerenone 25 mg/day for patients with eGFR < 50 and 50 mg/day for patients with eGFR ≥ 50 ml/min/1.73m². Spironolactone 12.5 to 50 mg/day if eplerenone is not available, the patient/insurance/government cannot cover the costs, or the patient tolerates spironolactone well.
HFp/mrEF	Finerenone	Finerenone 10-20 mg/day for patients with eGFR≤60 and 20-40 mg/day for patients with eGFR > 60 mL/min/1.73m².
HF prevention	Finerenone/ eplerenone	Finerenone 10-20 mg/day in patients with diabetes and CKD with microalbuminuria. Eplerenone (preferred) or spironolactone for patients with hypertension or high cardiovascular risk.
Acute HF	Eplerenone	Eplerenone 25-50 mg/day, indicated for patients with acute HF and reduced EF after myocardial infarction, to reduce congestive signs and symptoms.

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; MRA: mineralocorticoid receptor antagonist; r/p/mrEF: reduced/preserved/mildly reduced ejection fraction.

medication, as they did not experience elevated potassium and only a small proportion had detectable spironolactone metabolites in their blood[25].

Finerenone is an nsMRA recommended by the clinical practice guidelines for treating diabetic kidney disease[2] due to its preventive effect on kidney disease progression and reduction of cardiovascular events[26,27]. The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) is an international, multicenter, parallel, randomized, double-blind study that included patients with HFmrEF or HFpEF (LVEF ≥ 40%) who were randomized in a 1:1 ratio to finerenone (maximum doses of 20 mg or 40 mg once a day) vs. placebo, along with their usual treatment. The primary objective was a composite of total HF worsening events (unplanned hospitalizations or emergency visits for HF) and death from cardiovascular causes. Each component was also evaluated individually. Follow-up lasted 32 months. As far as results, 1,083 primary objective events were recorded in 624 of the 3,003 patients in the finerenone group, compared to 1,283 events in 719 of the 2,998 patients in the placebo group (RR: 0.84; 95% CI: 0.74-0.95; p = 0.007). The total number of HF worsening events was lower in the finerenone group than in the placebo group (842 vs. 1,024 events) (RR 0.82; 95% CI: 0.71-0.94; p = 0.006). The cardiovascular mortality rate was 8.1% in the finerenone group and 8.7% in the placebo group (RR: 0.93; 95% CI: 0.78-1.11). Finerenone was associated with a higher risk of hyperkalemia vs. placebo but a lower risk of hypokalemia. This study concluded that, in patients with HFpEF or HFmrEF, the use of finerenone was associated with a significantly lower rate of the composite primary objective of total HF worsening events and cardiovascular mortality versus placebo[28,29].

The Finerenone in Heart Failure and Chronic Kidney Disease with Type 2 Diabetes (FINE-HEART) trial performed a pooled analysis of two studies of patients with CKD and T2DM (FIGARO-DKD and FIDELIO-DKD)[26,27] and one study of patients with HF (FINEARTS-HF)[29]. The three studies included 18,991 patients (mean age 67 ± 10 years; 35% females) with a follow-up of 2.9 years. The primary outcome of cardiovascular death occurred in 421 patients (4.4%) assigned to finerenone and 471 participants (5%) assigned to placebo (HR: 0.89; 95% CI: 0.78-1.01; p = 0.076). Death from any cause occurred in 1,042 patients (11%) in the finerenone group and 1,136 patients (12%) in the placebo group (HR: 0.91; 95% CI: 0.84-0.99; p = 0.027). Finerenone reduced the risk of hospitalization for HF even further (HR: 0.83; 95% CI: 0.75-0.92; p < 0.001), along with the composite renal outcome (HR: 0.80; 95% CI: 0.72-0.90; p < 0.001). This pooled analysis found no difference in cardiovascular death reduction; however, finerenone lowered the risk of death from any cause, cardiovascular events, and renal outcomes[30].

Scenarios for using MRAs in HF (Table 3) Practical use of MRAs (for finerenone)

Kidney function and serum potassium levels are key for safe MRA use. Therefore, creatinine and potassium levels must be measured before beginning treatment and four weeks after starting. Patients who are already taking the medication chronically should have their creatinine and potassium measured at least every three months. Nonsteroidal MRAs (finerenone) should not be

started if the eGFR is less than 25 mL/min/1.73 m² or potassium is higher than 5 mmol/L. The dose should be titrated every four weeks, and treatment should be suspended if the eGFR decreases more than 30% or potassium is greater than 6 mmol/L[2].

The starting dose for patients with an eGFR higher than 60 mL/min/1.73 m² is 12.5 to 25 mg/day for spironolactone, 25 mg/day for eplerenone, and 20 mg/day for finerenone. If the eGFR is between 30 and 59, the recommended dose for spironolactone or eplerenone is 12.5 mg/day, and 10 mg/day for finerenone. The target or maximum dose for spironolactone is 25 to 50 mg/day; for eplerenone it is 50 mg/day, and for finerenone it is 40 mg/day in patients with an eGFR greater than 60 mL/min/1.73 m²; in addition, the finerenone dose is lowered to 20 mg/day if the eGFR is between 30 and 59 mL/min/1.73 m². Finally, finerenone is the only aldosterone antagonist that has been evaluated in patients with eGFRs between 25 and 30 mL/min/1.73 m² [31].

Conclusions

Mineralocorticoid receptor antagonists are an essential pillar of HF treatment. There are differences between sMRAs (spironolactone and eplerenone) and nsMRAs (finerenone), mainly related to their renal and cardiac selectivity, half-life, and antiandrogenic effects. The efficacy and safety of MRAs have been evaluated in studies of spironolactone and eplerenone in patients with HFrEF (with a reduction in mortality and hospitalizations for HF) and of finerenone in patients with HFmrEF and HFpEF.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. Does not apply (nonexperimental study).

Confidentiality, informed consent, and ethical approval. This study did not involve personal data, medical charts, or human biological samples, and therefore did not require ethical approval. The SAGER guidelines did not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing or creating content for this article.

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REVIEW ARTICLE

Adaptations in functional evaluation and exercise prescription in wheelchair users within cardiac rehabilitation. A scoping review

Adaptaciones en la evaluación funcional y prescripción del ejercicio en usuarios de silla de ruedas en rehabilitación cardíaca. Una revisión de alcance

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Abstract

Wheelchair users present a distinct cardiometabolic profile characterized by reduced cardiorespiratory fitness, altered body composition, and increased cardiovascular risk. However, evidence regarding their integration into cardiac rehabilitation program assessments remains limited and heterogeneous. The available evidence on adaptations to functional assessment and exercise prescription for wheelchair users within the context of cardiac rehabilitation was mapped. A scoping review was conducted following the Joanna Briggs Institute methodology and PRISMA-ScR guidelines. A systematic search was performed in PubMed, Scopus, and Web of Science without restrictions on language or publication date. Original studies involving adult wheelchair users that assessed cardiorespiratory fitness, muscular strength, body composition, or exercise prescription characteristics were included. Seventeen studies were included. Functional evaluation was primarily based on upper-body exercise testing using arm crank ergometry and oxygen uptake measurement. Muscular strength was assessed using repetition maximums and handgrip dynamometry, while body composition was evaluated using bioimpedance, densitometry, and waist circumference. Exercise interventions included aerobic training, high-intensity interval training, and resistance training, typically performed 3 to 5 times per week over 4 to 16 weeks, showing improvements in cardiorespiratory fitness. Functional assessment and exercise prescription in wheelchair users require specific adaptations but can be effectively integrated into cardiac rehabilitation programs, promoting inclusion and enabling a comprehensive approach to cardiovascular risk.

Keywords: *Wheelchair. Cardiac rehabilitation. Cardiovascular risk. Exercise prescription. Scoping review.*

Resumen

Los usuarios de silla de ruedas tienen un perfil cardiometabólico distintivo asociado a menor capacidad cardiorrespiratoria, cambios en la composición corporal y mayor riesgo cardiovascular. Sin embargo, la evidencia sobre su integración en programas de rehabilitación cardíaca es limitada y heterogénea. Se Mapeó la evidencia disponible sobre las adaptaciones en la evaluación funcional y en la prescripción del ejercicio en personas usuarias de silla de ruedas dentro del contexto de la rehabilitación cardíaca. Se efectuó una búsqueda sistemática en PubMed, Scopus y Web of Science sin restricción de fecha o idioma. Se incluyeron estudios originales en adultos usuarios de silla de ruedas que evaluaran capacidad cardiorrespiratoria, fuerza muscular, composición corporal y características de la prescripción del ejercicio. Se incluyeron diecisiete estudios. La evaluación funcional se basó principalmente en pruebas de ejercicio en miembros superiores mediante cicloergometría

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de brazos y medición del consumo de oxígeno. La fuerza muscular se evaluó mediante repeticiones máximas y dinamometría de agarre, mientras que la composición corporal se valoró con bioimpedancia, densitometría y circunferencia abdominal. Las intervenciones de ejercicio incluyeron entrenamiento aeróbico, interválico de alta intensidad y entrenamiento de fuerza, con frecuencias de tres a cinco sesiones por semana y duración de cuatro a dieciséis semanas, mostrando mejoras en la capacidad cardiorrespiratoria. La evaluación funcional y la prescripción del ejercicio en personas usuarias de silla de ruedas requieren adaptaciones específicas, pero pueden integrarse de manera efectiva en programas de rehabilitación cardíaca, favoreciendo la inclusión y el abordaje integral del riesgo cardiovascular.

Palabras clave: *Silla de ruedas. Rehabilitación cardíaca. Riesgo cardiovascular. Prescripción del ejercicio. Revisión de alcance.*

Introduction

Wheelchair use is essential for the functional mobility of people with motor disabilities caused by different etiologies including spinal cord injuries, cerebral palsy, neuromuscular diseases, and amputations. It is estimated that approximately 1 in 100 people worldwide need a wheelchair to move around, and in countries like the United States, more than three million individuals depend on this device for daily mobility[1]. Beyond its functional impact, wheelchair dependence is associated with profound changes in the physiology of movement, energy expenditure, and body composition, factors that are closely related to cardiovascular risk. The evidence suggests that people with disabilities are more likely to experience less healthy lifestyles, which, coupled with barriers to accessing preventive medical care, adds another cardiovascular risk factor to the traditional ones[2].

Cardiovascular diseases remain the main cause of morbidity and mortality worldwide[3]. Meta-analyses indicate that people with physical disabilities have a higher prevalence of cardiovascular risk factors and greater all-cause mortality compared to the general population. However, this excess risk does not appear to be explained solely by the coexistence of traditional factors like hypertension, diabetes mellitus, or dyslipidemia, but also by a particular pathophysiological profile derived from chronically reduced active muscle mass, cardiorespiratory deconditioning, and altered autonomic control[4].

For wheelchair users, especially those with spinal cord injuries or neuromuscular disorders, diminished muscle recruitment in their lower limbs significantly reduces maximal oxygen consumption, venous return, and peripheral oxidative capacity. This condition fosters central adiposity accumulation, insulin resistance, atherogenic dyslipidemia, and low-grade systemic inflammation. Together, these elements make up a differentiated cardiometabolic phenotype that could place this population at moderate to high cardiovascular risk, even without established coronary disease[5].

Exercise-based cardiac rehabilitation is a multimodal secondary prevention intervention with solid evidence, associated with significantly reduced cardiovascular mortality, hospitalizations, and recurrent ischemic events, along with improved quality of life[6]. Its structural components have been clearly defined, including comprehensive initial assessment, supervised physical training, education, risk factor control, and psychosocial support[7]. However, the development and implementation of cardiovascular risk prevention and cardiac rehabilitation programs for wheelchair users are not clearly standardized, and the available literature differs in regard to the populations, interventions, and outcomes evaluated[5].

Given the coexistence of a distinctive cardiovascular profile and limited access to cardiac prevention and rehabilitation programs among wheelchair users, the evidence regarding developing and adapting cardiac rehabilitation interventions aimed at improving cardiovascular risk and functional capacity must be expanded. Therefore, the objective of this scoping review is to map the available evidence regarding functional assessment and exercise prescription adaptations for wheelchair users in the context of cardiac rehabilitation.

Methods

This scoping review followed the Joanna Briggs Institute methodological guidelines for scoping reviews[8] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist[9]. The protocol was registered in the Open Science Framework.

Eligibility criteria

The Population, Concept, and Context (PCC) model was used to determine the eligibility criteria for the

review, and studies that met the following criteria were included:

- Population: wheelchair-using adults (≥ 18 years old), including those with spinal cord injuries, cerebral palsy, neuromuscular diseases, or other conditions that involved functional wheelchair dependence.
- Concept: studies that described adaptations of physical-functional assessment (cardiorespiratory capacity, muscular strength, and body composition) or exercise prescriptions for wheelchair users.
- Context: exercise interventions or exercise-based rehabilitation programs conducted in clinical, community, or research settings.
- Type of studies: original, experimental, and observational studies (randomized and nonrandomized clinical trials, quasi-experimental studies, cohorts, and cross-sectional studies).
- Language and time period: no language or publication date restrictions were applied.

Study identification

Search strategy

We conducted a systematic search on MEDLINE (through PubMed), Scopus, and Web of Science. The search strategy was structured by combining terms related to three conceptual domains: a) wheelchair use or motor disability, b) exercise or exercise-based rehabilitation, and c) functional assessment and cardiorespiratory capacity. We used MeSH terms and keywords combined with Boolean operators (AND/OR) were used. The strategy was adapted to each database, as follows: (wheelchair* OR "spinal cord injury" OR parapleg* OR quadripleg*) AND ("exercise therapy"[Mesh] OR "exercise training" OR "cardiac rehabilitation" OR "physical rehabilitation") AND ("cardiorespiratory fitness" OR "functional capacity" OR "VO2peak" OR "exercise test*" OR assessment).

The reference lists of the selected studies were also reviewed manually to identify any additional studies that would meet the inclusion criteria.

Data extraction and synthesis

The references found were imported to Rayyan, a web tool for screening and managing reviews. Two reviewers (NG and AR) independently reviewed the titles and abstracts and then conducted a full-text review of eligible studies. Disagreements were resolved by consensus between the two reviewers or, when necessary, by the intervention of a third reviewer (CA).

A standardized data extraction matrix was set up on Microsoft Excel (Microsoft Corporation, 2021). The following variables were collected for each included study: author and year of publication, country, study design, population characteristics (primary diagnosis), sample size, and mean age or age range. Data related to the methods used for the functional assessment was also extracted, including cardiorespiratory capacity, muscular strength, and body composition assessment. In addition, the characteristics of the exercise interventions were recorded, such as the type, intensity, frequency, duration, and progression of the exercise, as well as the main results related to functional capacity or the physiological response to exercise. After extracting the data, the results were reviewed and discussed among the authors to ensure coherence and consistency in categorization.

Given the exploratory nature of the review, the findings were synthesized using descriptive analysis and topical mapping, organizing the evidence into two principal domains: a) functional assessment adaptations, including methods for evaluating cardiorespiratory capacity, muscular strength, and body composition; and b) exercise prescription adaptations, including the type of exercise, intensity, frequency, duration, and progression in the context of exercise interventions. There was no formal assessment of the risk of bias, in accordance with the scoping review methodology.

Results

The database searches identified 1,186 records (PubMed = 750, Scopus = 244, and Web of Science = 192). After eliminating 427 duplicate records, 759 were evaluated through title and abstract screening. Subsequently, 31 articles underwent full-text evaluation to determine their eligibility, 17 of which met the scoping review's inclusion criteria.

Characteristics of the included studies

The 17 studies included were published between 1997 and 2025, and most were in North America (n = 6) and Europe (n = 5), with other regions less represented (n = 7). In South America, Brazil was the only country with publications (n = 2). As far as methodological design, there were clinical trials (n = 13) and observational studies (n = 4). Clinical trials accounted for a

significant proportion of the available evidence, especially for exercise-based interventions.

The study population consisted mainly of wheelchair users with spinal cord injuries. The study sample sizes varied but were generally small, ranging from approximately 5 to 46 participants.

The exercise interventions included aerobic upper body training, high-intensity interval training, and functional electrical stimulation, with varying intensity, frequency, and duration of the programs. The detailed characteristics of the included studies are presented in table 1.

Characteristics of the functional assessment

Functional assessment of wheelchair users focused on evaluating their cardiorespiratory capacity using arm exercise tests. Most of the studies used incremental protocols with arm ergometers to determine peak oxygen consumption (VO_2 peak). Only three studies used other methods, like the distance traveled in six minutes[10-12].

In addition, some studies sought to provide a more detailed description of the physiological response to exercise, using variables like ventilatory threshold, substrate oxidation, and mechanical efficiency. They showed differences in wheelchair users' energy metabolism and substrate use during exercise compared to people without disability[13,14].

As far as muscular strength assessment, upper limb repetition maximum measurements (1RM) predominated, adapted for the population[14-17]. In addition, some studies used handgrip dynamometry as a complementary measure of muscular strength[18,19]. For body composition, studies included techniques like bioelectrical impedance analysis (BIA), dual x-ray absorptiometry (DXA), or anthropometric measurements like waist circumference[10,11,20-22].

Exercise prescription characteristics

Exercise interventions for wheelchair users were based on upper body training modalities, aiming to improve cardiorespiratory capacity and muscle function. Aerobic exercise using arm ergometers was the most frequently used modality, followed by high-intensity interval training and functional electrical stimulation.

As far as exercise intensity, the studies used different prescription methods, including the percentage of maximal oxygen consumption, maximum heart rate or heart rate reserve, and perceived exertion scales. Generally, the protocol intensities ranged from moderate to vigorous, with some studies showing adequate tolerance of vigorous interventions.

The training frequency was usually reported as three to five sessions per week, with each session lasting 20 to 60 minutes. The total duration of the interventions ranged from 4 to 16 weeks, with improved cardiorespiratory capacity even in short-term interventions.

On the other hand, strength training-based interventions used different modalities like free weights, machines, and elastic bands, often prescribed with a certain number of series and repetitions[15,16]. In general, the protocols included two to four series per exercise, with a range of eight to fifteen repetitions, adjusting the load according to each individual's tolerance. Specifically, interventions that involved a larger number of muscle groups tended to show greater benefits.

Altogether, the above findings suggest that exercise prescriptions for wheelchair users require specific adaptations in terms of modality, intensity, and progression, privileging personalized strategies to optimize cardiorespiratory capacity and muscular strength.

Discussion

The objective of this study was to explore and synthesize the available evidence on functional assessment and exercise prescription adaptations for wheelchair users participating in cardiac rehabilitation. The findings show that, while the evidence in this field has grown over the last few years, its clinical application is still limited and variable. The studies included here identify feasible adaptations for functional assessment and exercise prescription that provide a basis to encourage the inclusion of this population in cardiac rehabilitation programs.

Regarding functional assessment, cardiorespiratory capacity was the most frequently evaluated component in the included studies. The cardiopulmonary exercise test (CPET) using arm ergometry, measuring maximal oxygen consumption (VO_2max), was identified as the reference method. The healthcare team should consider that this test requires specialized equipment and trained staff while keeping in mind the differences with lower limb ergometry, such as 25 to 40% lower VO_2max levels, mainly due to lower muscle mass involved in exercise[23,24].

In settings with limited access to exercise testing with gas analysis (a common situation in low- and middle-income countries), the six-minute wheelchair push test

Table 1. Description of the primary studies included

Study, author, and design	Country	Physical assessment	Exercise intervention	Results
Alrashidi A, et al.[37]	Canada	Ergospirometry	Bodyweight training or UBE for 30 to 60 minutes, three times per week for 24 weeks	Improved VO_2. No differences in arterial stiffness or cardiometabolic health
Hansen R, et al.[20]	Denmark	Ergospirometry Body mass and waist circumference	Rowing for 30 minutes at moderate to vigorous intensity, three times per week for 12 weeks	Improved VO_2 and brachial artery diameter. Modest effects on traditional cardiometabolic risk factors
Martín-Manjarrés S, et al.[13]	Spain	Ergospirometry Anthropometry using BIA	Analysis of fat burning zone (Fatmax) during exercise	The Fatmax zone is found at a higher VO_2 percentage in men with SCI
Nash et al.[15]	United States	Ergospirometry 1RM 30-second Wingate	High-speed, low-load strength training for four weeks	50% improvement in strength, 10% improvement in VO_2, and 6% improvement in anaerobic power
Hansen R, et al.[38]	Denmark	Ergospirometry Body mass and waist circumference	Rowing, 30 minutes at moderate to vigorous intensity, three sessions per week for 12 weeks	VO_2 improvement persists for at least six months after the intervention
Williams A, et al.[39]	Canada	Ergospirometry	Cycle ergometer for 60 minutes, three times per week for five weeks	An average 16% improvement in VO_2
Farkas G, et al.[21]	United States	Ergospirometry DXA and waist circumference	UBE sessions, five days per week, intensity at 75% MHR, for 16 weeks	10 to 20% improvement in VO_2
Alves Rodrigues J, et al.[11]	Brazil	Medicine ball toss, Wingate. DXA	Circuit strength training, twice a week for 12 weeks	Improved strength and agility, maintaining lean muscle mass and bone density
Valent L, et al. [18]	Netherlands	Ergospirometry, treadmill Handgrip dynamometry	Cycle ergometer for 35 to 45 minutes, twice a week, RPE 4-7/10, with 16 to 31 sessions	20% improvement in VO_2 and peak strength
Pelletier C, et al.[14]	Canada	Ergospirometry Adapted 1RM	Moderate to vigorous aerobic and strength training twice a week for 16 weeks	17% improvement in VO_2, and 12 and 39% improvement in strength
Bresnahan J, et al.[22]	United States	Ergospirometry DXA	Cycle ergometer three days a week, 30 minutes at 70% VO_2 for 10 weeks	5 to 10% improvement in VO_2. No changes in body composition
Tørhaug T, et al.[16]	Norway	Ergospirometry 1RM	Strength training three days/week for six weeks, at 85 to 95% of 1RM	17% improvement in strength and wheelchair propulsion
Graham K, et al.[17]	United States	Ergospirometry 1RM 30-second Wingate DXA	HIIT exercise two days per week for 20 minutes vs. 30 minutes of moderate exercise three days a week, both for six weeks	Both HIIT and moderate exercise improved insulin sensitivity, VO_2, and strength
Kim et al.[19]	Korea	Ergospirometry Handgrip dynamometry BIA	Cycle ergometer for 60 minutes at 70 to 80% MHR, for six weeks	Increased VO_2 and shoulder and elbow strength
El-Sayed M, et al.[40]	United Kingdom	Ergospirometry	UBE sessions at an intensity of 60-65% VO_2 for 30 minutes, for 12 weeks	Improved VO_2, peak strength, and HDL cholesterol. No changes in total cholesterol or triglycerides

(Continues)

Table 1. Description of the primary studies included *(continued)*

Study, author, and design	Country	Physical assessment	Exercise intervention	Results
Kim S, et al.[10]	Korea	6MPT Ergospirometry nRM DXA	High-intensity strength training (70% of 1RM) vs. moderate intensity (45% of 1RM) for eight weeks	High-intensity resistance training was more effective for improving lean mass and physical fitness
Haddad S, et al.[12]	Brazil	Indirect VO_2 by formula	Cycle ergometer at an intensity of 65 to 85% of HRR, for 12 weeks	Improved VO_2 and resting and exercise blood pressure

CPET: cardiopulmonary exercise test; UBE: upper body ergometer; SCI: spinal cord injury; BIA: bioelectrical impedance analysis; MHR: maximum heart rate; 1RM: one repetition maximum; VO_2 peak: oxygen consumption; DXA: dual X-ray absorptiometry; RPE: rate of perceived exertion; ULs: upper limbs; HIIT: high-intensity interval training; HRR: heart rate reserve.

(6MPT) may be a useful and cost-effective alternative for functional assessment[10]. Since this test is an adaptation of the traditional six-minute walk test, it is practical to implement in cardiac rehabilitation programs, allowing objective functional assessment when cardiopulmonary exercise testing is not available.

Another relevant component of functional assessment is upper limb muscular strength evaluation, which can be done using handgrip dynamometry or adapted one-repetition maximum (1RM) testing[15,17,19]. In this context, handgrip dynamometry is an accessible, low-cost, easy-to-use tool that is very useful in limited-resource settings. This measurement has also been associated with relevant clinical outcomes like functional capacity, nutritional status, and cardiovascular prognosis, and its assessment should therefore be considered an essential component of the initial evaluation and follow-up in cardiac rehabilitation[25-27].

Body composition is another relevant component of the assessment. This population is characterized by reduced muscle mass and increased adipose tissue[28]. The most frequently used techniques include bioelectrical impedance analysis and dual x-ray absorptiometry (DXA). However, waist circumference is especially relevant as a clinical indicator for evaluating cardiometabolic risk, as it allows a more direct estimate of central adiposity, compared to body mass index, which may underestimate body composition abnormalities in this population[19,20]. Its easy use, low cost, and availability favor its incorporation into clinical practice within cardiac rehabilitation programs[29].

As far as exercise prescription, the included studies showed predominantly aerobic exercise interventions using modalities like arm ergometry and rowing. As a whole, these strategies proved to be safe and effective for improving cardiorespiratory and functional capacity, factors that are key predictors of cardiovascular morbidity and mortality[20,30]. The most common training frequency was three to five sessions a week, lasting 20 to 60 minutes per session. These characteristics are in line with the amount of exercise usually employed in cardiac rehabilitation programs, which generally include three one-hour sessions per week. The above suggests that the exercise prescription principles traditionally used in cardiac rehabilitation can be applied to wheelchair users[31,32].

As far as exercise intensity is concerned, most of the included studies used a moderate to vigorous intensity, suggesting that higher training loads could lead to greater cardiorespiratory adaptations. However, the intensity must be personalized, considering the level and severity of the injury as well as the patient's functional capacity[33].

Moreover, strength training using modalities like free weights, machines, and elastic bands, prescribed with a given number of sets and repetitions, is also safe in this population[15,16]. Strength training was essential for overall functional capacity and mobility, as it improved wheelchair propulsion[34]. In this regard, combined aerobic and strength exercise programs are a key strategy within cardiac rehabilitation for wheelchair users[35].

Finally, although exercise-based interventions proved to be beneficial for cardiorespiratory capacity and physical function, metabolic profile changes were less consistent or significant. This finding suggests that, while exercise is an essential component, cardiac rehabilitation for wheelchair users should adopt a comprehensive approach, using other risk factor control strategies like education in lifestyle modification, adherence to medications, and periodic clinical follow-up[36].

Limitations

This review has a few limitations that should be considered when interpreting its findings. First, most of the

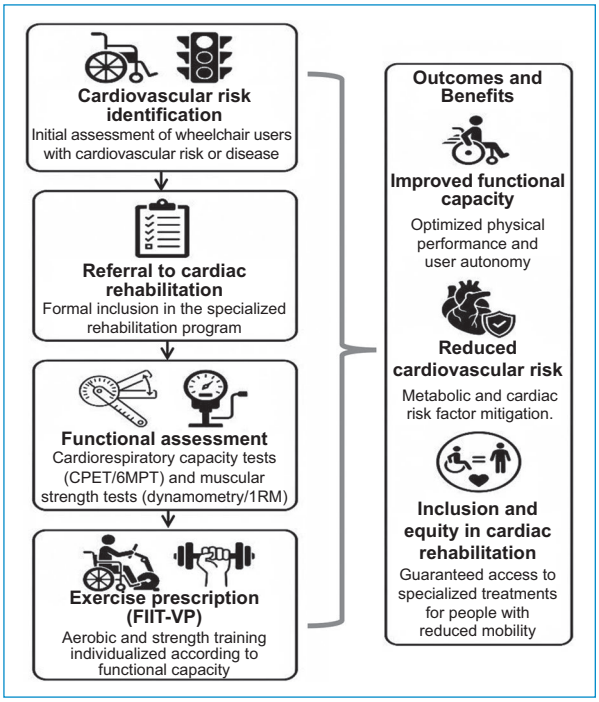

Figure 1. Main Figure. Conceptual algorithm for including wheelchair users in cardiac rehabilitation programs. The proposal integrates cardiovascular risk identification, functional assessment using accessible tools, and personalized exercise prescription to improve functional capacity, contribute to cardiovascular risk management, and foster more inclusive and equitable care.

studies included were conducted in high-income countries, which may limit the applicability of the results to low- and middle-income settings, where wheelchair users face additional barriers to accessing cardiac rehabilitation programs.

Second, the study designs, population characteristics, and intervention protocols varied significantly, making it difficult to compare studies directly and draft standardized recommendations. Also, the sample size was small, which is a common situation in this population but can affect the solidity of the available evidence.

Finally, while we conducted a broad search on multiple databases and followed recognized scoping review methodologies, the omission of some potentially relevant studies cannot be ruled out. Also, we did not perform a formal risk of bias evaluation on the included studies; therefore, the results should be interpreted bearing in mind the inherent methodological limitations of the available evidence.

Clinical implications

Wheelchair users have a higher risk of developing early and accelerated cardiometabolic disease while also facing limited access to cardiovascular prevention, detection, and management strategies. This combination constitutes a significant healthcare gap that could contribute to a higher burden of disease and worse health outcomes. In this context, cardiac rehabilitation provides an opportunity to improve cardiovascular risk stratification, promote healthy lifestyles, and optimize functional capacity through exercise-based interventions.

Closing this gap requires strengthening referral processes, access, and adherence to adapted cardiac rehabilitation programs, fostering more equitable and inclusive care for wheelchair users.

In low- and middle-income countries with potentially limited access to advanced technologies, we propose a practical approach for wheelchair users' medical care and inclusion in cardiac rehabilitation programs. This model may be supported by accessible functional assessment tools, like the adapted six-minute push test, handgrip dynamometry, and waist circumference, complemented by exercise programs prescribed according to the functional and clinical characteristics of each patient. This proposal, which is summarized in figure 1, main figure, could facilitate early identification of cardiovascular risk, broaden access to exercise-based interventions, and promote more equitable and inclusive care for this population.

Conclusions

The available evidence indicates that functional assessments and exercise prescriptions for wheelchair users require specific adaptations but may feasibly be integrated into cardiac rehabilitation programs. Using accessible assessment strategies and adapted exercise programs favors inclusion of this population and is an opportunity to improve functional capacity, optimize cardiovascular risk management, and promote more equitable care.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent, and ethical approval. The study did not involve personal data, medical charts, or human biological samples, and therefore did not require ethical approval. The SAGER guidelines did not apply.

Declaration on the use of artificial intelligence. The authors declare that ChatGPT was used to create the main figure.

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SPECIAL ARTICLE

Colombian consensus on cardiopulmonary risk in patients with chronic obstructive pulmonary disease (COPD) from the Colombian Association of Pulmonology and Thoracic Surgery and the Colombian Society of Cardiology and Cardiovascular Surgery

Consenso colombiano de riesgo cardiopulmonar en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) de la Asociación Colombiana de Neumología y Cirugía de Tórax y la Sociedad Colombiana de Cardiología y Cirugía Cardiovascular

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Abstract

Introduction: *Chronic obstructive pulmonary disease (COPD) is associated with higher cardiovascular risk, especially after exacerbations. However, cardiopulmonary and mortality risk stratification continue to be heterogeneous in clinical practice.* **Objective:** *To develop evidence-based guidelines, adapted to the Colombian healthcare system, for providing multidisciplinary evaluation, stratification, and management of cardiopulmonary risk in COPD patients.* **Methods:** *The Colombian Association of Pulmonology and Thoracic Surgery and the Colombian Society of Cardiology and Cardiovascular Surgery convened a multidisciplinary panel of 19 experts. Six questions were posed, and systematic literature reviews were conducted. The certainty of the evidence was evaluated with GRADE, and the recommendations were developed using an Evidence-to-Decision framework. A modified Delphi process was applied, along with formal voting using a nine-point Likert scale; ≥ 70% agreement was required to approve each recommendation.* **Results:** *The consensus developed recommendations for identifying high-risk subgroups, determining the prognostic value of exacerbations, and integrating clinical and functional variables with a selective use of biomarkers. It included considerations for pharmacological and nonpharmacological treatment, emphasizing cardiovascular safety, and recommended targeted cardiovascular disease evaluation in the event of disproportionate symptoms, as*

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well as tailored follow-up according to the individual risk profile. **Conclusion:** *This consensus provides an evidence-based framework for evaluating and stratifying cardiopulmonary risk in COPD patients in Colombia, emphasizing early high-risk detection and comprehensive multidisciplinary treatment.*

Keywords: *COPD. Cardiovascular risk. Consensus. Colombia. Exacerbation. Mortality.*

Resumen

Introducción: *La enfermedad pulmonar obstructiva crónica (EPOC) se asocia con mayor riesgo cardiovascular, particularmente después de las exacerbaciones. Sin embargo, la estratificación del riesgo cardiopulmonar y de la mortalidad continúa siendo heterogénea en la práctica clínica.* **Objetivo:** *Desarrollar y adaptar al sistema de salud colombiano recomendaciones basadas en la evidencia para evaluar, estratificar y tratar de manera multidisciplinaria el riesgo cardiopulmonar en pacientes con EPOC.* **Métodos:** *La Asociación Colombiana de Neumología y Cirugía de Tórax y la Sociedad Colombiana de Cardiología y Cirugía Cardiovascular convocaron un panel multidisciplinario de diecinueve expertos. Se formularon seis preguntas y se realizaron revisiones sistemáticas de la literatura. La certeza de la evidencia se evaluó mediante GRADE y las recomendaciones se elaboraron utilizando el marco Evidence-to-Decision. Se aplicó un Delphi modificado y una votación formal con escala Likert de nueve puntos; se requirió un acuerdo ≥ 70% para aprobar cada recomendación.* **Resultados:** *Se desarrollaron recomendaciones sobre la identificación de subgrupos de alto riesgo, el valor pronóstico de las exacerbaciones y la integración de variables clínicas y funcionales, con uso selectivo de biomarcadores. Se incluyeron consideraciones para el tratamiento farmacológico y no farmacológico, con énfasis en la seguridad cardiovascular. También se recomendó evaluar de manera dirigida la enfermedad cardiovascular ante síntomas desproporcionados y ajustar el seguimiento al perfil individual de riesgo.* **Conclusión:** *Este consenso proporciona un marco basado en evidencia para la evaluación y estratificación del riesgo cardiopulmonar en pacientes con EPOC en Colombia, enfatizando la identificación temprana del alto riesgo y el manejo integral y multidisciplinario.*

Palabras clave: *EPOC. Riesgo cardiovascular. Consenso. Colombia. Exacerbación. Mortalidad.*

Introduction

Chronic pulmonary obstructive disease (COPD) is a chronic respiratory disease and one of the main causes of morbidity and mortality worldwide. In 2021, there were an estimated 213 million people with COPD in the world, with an age-standardized mortality rate of approximately 45 per 100,000 inhabitants, which is equivalent to close to 3.7 million deaths attributable to this disease every year.[1] While standardized mortality rates have decreased slightly compared to previous decades, the absolute burden continues to increase due to population growth and aging, and COPD remains one of the main causes of death in many countries.[2]

Chronic obstructive pulmonary disease is consistently associated with a higher risk of cardiovascular disease compared to the risk of people without COPD. In a recent systematic review that included more than 3.4 million patients, people with COPD had a higher risk of overall cardiovascular disease, myocardial infarction, heart failure, and arrhythmias, than controls without COPD.[3] Likewise, large-scale population-based cohort studies have demonstrated that its coexistence with other risk factors like metabolic syndrome is associated with a significant increase in cardiovascular events and cardiovascular mortality.[4]

This excess risk could be partially explained by shared pathophysiological mechanisms, including persistent systemic inflammation, oxidative stress, endothelial dysfunction, chronic hypoxemia, and sympathetic nervous system activation, which contribute to both pulmonary deterioration and the occurrence of cardiovascular events.[5]

Exacerbations constitute a critical point in the course of the disease and are associated with a substantial increase in the risk of cardiovascular events and death. In a systematic review and meta-analysis that included over 1.8 million participants, exacerbations were associated with a higher risk of acute cardiovascular events, including acute coronary syndrome, heart failure, strokes, and arrhythmias, with the highest risk occurring 1 to 30 days after the episode and persistent excess risk in subsequent periods.[6] Similarly, in a retrospective cohort in Spain (n = 24,393; median follow-up: 3.03 years), the onset of a moderate or severe exacerbation was associated with a marked increase in the risk of the composite outcome of serious cardiovascular events or death from any cause, with the

highest increase during days 1-7 (HR: 10.10; 95% CI: 9.29-10.97). Although the effect lessened with time, the risk remained high even after one year (> 365 days: HR, 1.65; 95% CI: 1.49-1.82).[7]

Overall, the period immediately following an exacerbation constitutes a heightened window of vulnerability to adverse cardiovascular events, underscoring the need for clinical strategies to integrate exacerbation prevention, early identification of cardiopulmonary risk, and multidisciplinary management of COPD patients.

Despite growing evidence, cardiopulmonary and mortality risk stratification continue to be heterogeneous in clinical practice. The international guidelines recognize that cardiovascular diseases are a significant cause of morbidity and mortality in people with COPD, especially in those with frequent exacerbations, advanced functional deterioration, or a high burden of comorbidities. However, a standardized approach for comprehensive and reproducible cardiovascular risk stratification in this population is lacking.[8] Furthermore, studies and reviews have indicated that cardiovascular events may be underdiagnosed in this population, partly due to symptom overlap and diagnostic difficulties, contributing to delayed treatment, suboptimal implementation of preventive strategies, and, ultimately, worse clinical outcomes.[5,9]

In Colombia, an analysis based on administrative data from 2020-2023 estimated a national COPD prevalence (adjusted for underdetection) of 2.22% (adults ≥ 40 years old), with significant geographic variability. This suggests persistent gaps in diagnosis, access to spirometry, and clinical characterization of the disease.[10]

Within this context, this consensus, developed by the Colombian Association of Pulmonology and Thoracic Surgery and the Colombian Society of Cardiology and Cardiovascular Surgery, seeks to help specialists and primary care professionals understand the relationship between COPD and cardiovascular risk, and enable its application in different clinical settings, both ambulatory and inpatient. Likewise, it intends to provide recommendations based on the best available evidence to reduce practice variability and give structured guidance for stratification and comprehensive management of cardiopulmonary risk in people with COPD, adapted to the Colombian healthcare system.

Methods

Scope

This consensus establishes recommendations and statements for evaluating and stratifying cardiopulmonary and mortality risk in people with COPD, as well as their follow-up and comprehensive treatment within the Colombian healthcare system. The recommendations and statements are aimed at supporting clinical and prognostic decision-making within the Colombian healthcare system; they do not replace individual clinical judgment and should be interpreted as a complement for decision-making.

Target population

The target population consists of adult patients with a confirmed COPD diagnosis, in all stages of the disease, and treated at any level of care within the general social security healthcare system in Colombia.

Consensus users

This document is aimed at healthcare professionals involved in caring for people with COPD, including pulmonologists, cardiologists, internists, family doctors, and other related specialists in different care settings, both ambulatory and inpatient.

Clinical aspects addressed

The consensus focuses on comprehensively evaluating and stratifying cardiopulmonary and mortality risk in people with COPD, emphasizing the identification of high-risk subgroups and an evaluation that integrates clinical and functional variables, biomarkers, and the history and prognostic impact of exacerbations. It also develops considerations for the diagnostic approach, follow-up, and pharmacological and non-pharmacological treatment, addressing the cardiovascular safety profile, clinical surveillance of cardiovascular events, and secondary prevention.

Ethical aspects

Ethics committee approval was not required for developing this consensus, as no interventions were performed on, nor data collected from, human or animal subjects.

Methods

This consensus was developed following a formal evidence-based expert consensus methodology, integrating a modified Delphi method[11-13] and using the GRADE methodology.[14,15] The process involved

convening a multidisciplinary expert panel, posing structured clinical questions, searching and synthesizing the available evidence, and engaging in structured discussion of the recommendations using an explicit decision-making framework based on GRADE's Evidence-to-Decision (EtD).[16,17]

Composition of the development team

Nineteen clinical experts with extensive experience in managing COPD and the cardiovascular risk associated with this disease participated in the consensus (16 pulmonologists and three cardiologists). The panel's composition was established to ensure a multidisciplinary focus, incorporating pulmonology's experience as the lead specialty in comprehensive COPD management and clinical cardiology to strengthen the evaluation of aspects related to the stratification and prevention of cardiovascular risk, including major cardiovascular events, heart failure, and arrhythmias.

The clinical cardiology experts actively participated in all stages of the consensus process. This included discussion of the clinical scope of the questions, review and critical interpretation of the evidence, evaluation of the pertinence and clinical applicability of cardiovascular risk recommendations, and deliberation and approval of the final recommendations, on the same level as the rest of the panel members.

The process was methodologically coordinated by an independent group of five methodologists with expertise in evidence-based consensus processes (ODDS Epidemiology). All participants declared their possible conflicts of interest; the methodological coordination group's review of these statements established that none of the declared conflicts affected independent judgment in drafting the recommendations. The complete list of participants and their detailed declarations are available in the supplementary material (Annex 1: https://doi.org/10.17605/OSF.IO/BX9Z5).

The preliminary questions were drafted by the consensus leaders and methodological team and subsequently submitted for discussion and review by the entire multidisciplinary panel. After this deliberation, six final questions were established, for which corresponding recommendations were issued through a structured consensus process.

Literature search

Once the questions were established, a rigorous systematic search was conducted following the Cochrane methodological standards[18] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] Searches for the six questions (structured in a PICO/PECO format) were conducted in PubMed, Embase, and the Cochrane Library in May 2025, restricted to the previous five years and with no language restriction. After a pilot test, two reviewers independently evaluated titles and abstracts according to the predetermined eligibility criteria. The full text of potentially relevant studies was reviewed, and disagreements were resolved by consensus.

Evidence was selected using a hierarchical approach, prioritizing systematic reviews, clinical practice guidelines, formal consensuses, and, when necessary, relevant primary studies. Detailed search strategies and the results of the selection process (PRISMA flowchart) are presented in the supplementary material (https://doi.org/10.17605/OSF.IO/BX9Z5).

Evaluating the quality and certainty of the evidence

The methodological quality of the included studies was evaluated independently by two reviewers using validated tools according to the design of the data sources: AMSTAR 2 for systematic reviews,[20] AGREE II for clinical practice guidelines,[21] RoB 2 for randomized clinical trials (RCTs),[22] and JBI tools for observational studies.[23] The quality assessment is presented in the supplementary material (https://doi.org/10.17605/OSF.IO/BX9Z5).

The evidence from the included studies was synthesized on GRADEpro, which was used to develop evidence profiles and score the certainty of the effect estimates. Certainty was evaluated and classified according to the GRADE approach as high, moderate, low, or very low, considering the risk of bias, imprecision, inconsistency, indirect evidence, and publication bias (Table 1).[24] The GRADE framework specific to prognostic studies was applied to the prognostic questions, following the respective methods for each effect measure evaluated[25,26] (https://doi.org/10.17605/OSF.IO/BX9Z5).

Recommendation and statement drafting

Recommendations were generated considering items like the availability and type of evidence, the balance of desirable/undesirable effects, the patients' values and preferences, the availability of resources for implementation, and acceptability. In clinical settings where it was feasible, the EtD frameworks proposed by the GRADE

Table 1. Certainty of the evidence (GRADE)

High certainty	Very confident that the true effect is close to the estimated effect.
Moderate certainty	Moderately confident in the estimated effect: the true effect may be close to the estimated effect but may be substantially different.
Low certainty	Limited confidence in the estimated effect: the true effect may be substantially different from the estimate.
Very low certainty	There is very little confidence in the estimated effect: the true effect is very likely to be different from the estimate.

Adapted from Schünemann H, et al.[27].

Table 2. Strength and direction of the recommendations (GRADE)

Recommendation	Clinical implication
Strongly in favor	The benefits of the intervention exceed the undesirable effects
Strongly against	The undesirable effects exceed the benefits of the intervention
Conditionally in favor	The benefits of the intervention probably exceed the undesirable effects
Conditionally against	The undesirable effects probably exceed the benefits of the intervention

Adapted from Schünemann H, et al.[27].

collaboration were constructed.[16,17] Strong or conditional recommendations for or against the intervention of interest were drafted (Table 2). When there was little or no evidence to directly answer a question, recommendations were drafted based on ungraded expert consensus.[28] At the discretion of the expert panel, statements were also produced to expand the results obtained in the evidence synthesis. The information is reported in the OSF (https://doi.org/10.17605/OSF.IO/BX9Z5).

Voting process and consensus establishment

Deliberations were conducted through three virtual meetings. Prior to each meeting, a specific technical file for each clinical question was distributed to each panelist, which included a preliminary recommendation/statement and its justification, based on the synthesis of the available evidence.

Both the recommendations and the statements were put to a vote using a nine-point Likert scale: (1: totally disagree; 9: totally agree). A consensus was required for recommendations to be approved, which was defined as having at least 70% of the eligible panel member's votes concentrated in categories 7 to 9. If the consensus threshold was not reached, the recommendation was revised and submitted to a new round of discussion and voting. The detailed results of the voting process are presented in the supplementary material (https://doi.org/10.17605/OSF.IO/BX9Z5).

Results

Below, we present the questions organized by topics, along with the corresponding recommendations and synthesis of the evidence used to answer each question (Tables 3 and 4).

Clinical question 1

In adult patients with either an exacerbator or non-exacerbator COPD phenotype, is there an association between moderate to severe exacerbations in the previous year, compared to no exacerbations in the same period, and a higher risk of the following events?:

- Major adverse cardiovascular events (MACE) including coronary disease, stroke, cardiovascular death, non-fatal myocardial infarction (MI), and hospitalization for unstable angina.
- Arrhythmias like atrial fibrillation, ventricular tachyarrhythmias, or other clinically significant arrhythmias.
- Acutely decompensated heart failure, defined as hospitalization for or death from heart failure (defined as right and/or left ventricular dysfunction, with both reduced and preserved ejection fraction).

Panel statement

- We suggest considering COPD patients with moderate or severe exacerbations to be a high cardiovascular risk subgroup, especially during the first 90 days following the exacerbation.

Recommendation

- Establish strategies for diagnosing and treating cardiovascular risk factors (dyslipidemia, hypertension, diabetes, and smoking) in this subgroup, as well as strengthening the inpatient-to-outpatient care transition to reduce morbidity and mortality. In patients with

Table 3. Panel statements

Statement
In adults with stable, high-risk COPD, with an indication for triple inhaled therapy (LAMA/LABA/ICS), the available evidence suggests that the use of this therapy is associated with lower cardiovascular mortality compared to the LABA/LAMA combination.
Currently, there is no evidence indicating a reduction in the incidence of specific cardiovascular events (fatal and non-fatal MI, stroke, or heart failure) with the use of triple inhaled therapy.
Patients with COPD and appropriate therapy who have disproportionate dyspnea, chest pain, and/or palpitations will require a differential diagnosis and, therefore, a search for cardiovascular and pulmonary vascular disease, among others, personalizing each case.

established atherosclerotic cardiovascular disease, achieve the secondary prevention goals suggested in the guidelines (*recommendation based on expert consensus, without grading the quality of the evidence).*

Evidence synthesis

Moderate or severe exacerbations in adults with COPD have been associated with an increased risk of MACE, clinically significant arrhythmias, and decompensated acute heart failure, compared to no exacerbations, according to reports in recent systematic reviews.[6,29]

A systematic review and meta-analysis published in 2025 included 16 observational studies (cohort, case-control, paired cases, and case series) with more than 1.8 million participants, most with stable COPD at the time of presentation.[6] Exacerbations were classified as moderate (treated as outpatients with corticosteroids or antibiotics) or severe (those that required hospitalization). The analysis evaluated cardiovascular risk during specific time periods after the exacerbation and found the highest risk of cardiovascular events during the first 30 days. Individual outcomes were evaluated: acute coronary syndrome, acute cerebrovascular events, arrhythmias, and acute heart failure.

Significantly elevated risks were found during the first 30 days after an exacerbation:

– Acute coronary syndrome (HR: 3.74; 95% CI: 2.35-5.95).
– Acute cerebrovascular events (HR: 2.46; 95% CI: 1.65-3.68).
– Heart failure (HR: 6.81; 95% CI: 1.80-25.82).

Table 4. COPD and cardiopulmonary risk consensus recommendations

Recommendations	Strength of the recommendation
Consider COPD patients with moderate or severe exacerbations to be a high cardiovascular risk subgroup, especially during the first 90 days after the exacerbation.	Conditionally in favor
Establish strategies for diagnosing and treating cardiovascular risk factors (dyslipidemia, hypertension, diabetes, and smoking) in this subgroup, as well as strengthening the inpatient-to-outpatient care transition to reduce morbidity and mortality.	Expert consensus
In patients with established atherosclerotic cardiovascular disease, achieve the secondary prevention goals suggested in the guidelines.	Expert consensus
Conduct close surveillance of cardiovascular events in patients with COPD at high risk of adverse outcomes.	Expert consensus
Offer pulmonary rehabilitation programs to patients with COPD who have had an exacerbation, with evidence showing a greater potential benefit when these programs begin within the first four weeks after the exacerbation. *Certainty of the evidence: moderate*	Strongly in favor
Assess the nutritional status and correct malnutrition in patients with COPD.	Expert consensus
Immunization is strongly recommended as part of the comprehensive care of patients with COPD. *Certainty of the evidence: low*	Strongly in favor
In adults with stable high-risk COPD with an indication for triple inhaled therapy (LAMA/LABA/ICS), the available evidence suggests that its use is associated with lower cardiovascular mortality compared to the LABA/LAMA combination. *Certainty of the evidence: moderate*	Strongly in favor
Consider that, as the pulmonary function evaluated by FEV_1 diminishes, the risk of adverse cardiovascular outcomes, including MI, stroke, and congestive heart failure, increases. This association justifies prioritizing these patients' assessment, comprehensive management of their cardiovascular risk, and achieving the established treatment goals.	Expert consensus
NT proBNP measurement is suggested as a useful tool for detecting cardiac dysfunction in patients with COPD and an $FEV_1 \leq 50\%$.	Expert consensus

(Continued)

Table 4. COPD and cardiopulmonary risk consensus recommendations *(continued)*

Recommendations	Strength of the recommendation
Use long-acting bronchodilators (LAMA or a combination of LAMA+LABA) as first-line maintenance treatment in patients with stable COPD and high cardiovascular risk. These medications are safe for the cardiovascular system, improve pulmonary function, and reduce the number of exacerbations. *Certainty of the evidence: low*	Strongly in favor

– Arrhythmias (HR: 3.93; 95% CI: 1.94-7.95).

The risks diminished between days 31 and 180 but remained elevated. The risk of acute myocardial infarction persisted up to more than one year after the exacerbation (HR: > 365 days: 1.43; 95% CI: 1.09-1.88). The risk of heart failure was the highest of all outcomes in the first seven days after the exacerbation (HR 17.43; 95% CI: 4.49-67.63). Despite high heterogeneity (I^2 > 90%), the sensitivity analyses, meta-regressions, and use of random effects models reinforce the robustness of the findings.[6]

Another systematic review with meta-analysis published in 2021,[29] which included seven observational studies, evaluated the association between COPD exacerbations and the risk of MACE (acute myocardial infarction, stroke, and cardiovascular death). Exacerbations were classified as moderate or severe, and the comparator was exacerbation-free periods. In the first and third months after an exacerbation, there were significant increases in the risk of:

– Acute myocardial infarction (AMI) (RR = 2.43; 95% CI: 1.40-4.20).
– Stroke (RR = 1.68; 95% CI: 1.19-2.38).

During the first one to three days after the exacerbation, the risk of AMI was almost double for moderate exacerbations (IRR = 1.96) and up to eight times greater for severe exacerbations. One cohort included in this review reported that the risk of cardiovascular death was almost four times greater after an exacerbation compared to exacerbation-free periods. This review did not specify whether the exacerbations had occurred within the previous year, as the follow-up intervals varied from study to study (one to three days to more than 12 months).[29]

The methodological quality of the included studies varied, and the evidence was derived exclusively from observational studies. Both meta-analyses have a limited level of certainty due to the risk of bias inherent in the primary designs, as well as the clinical and methodological heterogeneity between the studies. The certainty of this evidence, evaluated with GRADE for prognostic factors, is rated as low to moderate.

Clinical question 2

In adult patients with stable COPD, does triple therapy (including inhaled corticosteroids, a long-acting β2-agonist, and a long-acting muscarinic antagonist), compared to treatment without triple therapy, reduce the risk of developing MACEs, like heart failure or arrhythmias?

Recommendations

– In adults with high-risk, stable COPD, with an indication for triple inhaled therapy (LAMA/LABA/ICS), the available evidence suggests that this therapy is associated with lower cardiovascular mortality compared to a LABA/LAMA combination *(conditional recommendation in favor, based on moderate certainty of the evidence)*.
– Maintain close surveillance of cardiovascular events for COPD patients at high risk of adverse outcomes *(recommendation based on expert consensus, without grading the quality of the evidence)*.

Panel statement

– Triple inhaled therapy (LAMA/LABA/ICS) is safe, as it does not generate greater cardiovascular risk.
– There is currently no evidence indicating a reduction in the specific incidence of cardiovascular events (fatal and nonfatal MI, stroke, or heart failure) with the use of triple inhaled therapy.

Evidence synthesis

In a recent Cochrane systematic review, van Geffen et al.[29] included four large randomized clinical trials (n = 15,412) that compared triple therapy (ICS/LABA/LAMA) to LABA/LAMA in patients with severe or very severe COPD and at least one exacerbation in the previous year. This review is the source with the highest methodological level available, with an exhaustive database search, independent selection by reviewers, and formal evaluation of the risk of bias, generally classified as low.

Its results indicated that triple therapy is associated with a significant reduction in all-cause mortality (OR: 0.70; 95% CI: 0.54-0.90; n = 15,397) and specific cardiovascular mortality (OR: 0.51; 95% CI: 0.34-0.77; n = 13,865), which provides direct evidence regarding benefits and serious cardiovascular outcomes. Although the review did not disaggregate other MACE components (like arrhythmias or heart failure, individually), the finding of lower cardiovascular mortality confers great clinical weight to the potential benefits of triple therapy. The authors also highlight that, despite an increased risk of pneumonia (OR: 1.74; 95% CI: 1.39-2.18), the overall balance favors its use in this population at high risk for exacerbations.[30]

Other studies, of the systematic review with meta-analysis variety, show heterogeneous results regarding the effect of triple inhaled therapy (ICS/LABA/LAMA) on the incidence of MACE, heart failure, or arrhythmias, compared to treatments that do not include this combination.[30-34]

A recent systematic review and meta-analysis (Hammadi et al., 2025) included 11 randomized clinical trials (n = 25,774) that compared triple inhaled therapy (ICS/LABA/LAMA) with dual therapy (LABA/LAMA or ICS/LABA) or monotherapy in patients with stable COPD diagnosed via spirometry (FEV_1/FVC <0.70 after bronchodilator use).[31] The primary outcome was all-cause mortality, and the following cardiovascular outcomes were evaluated as secondary outcomes: cardiovascular mortality, acute myocardial infarction, acute coronary syndrome, stroke, heart failure, and atrial fibrillation. Compared to LABA/LAMA, triple therapy was associated with a statistically significant reduction in the risk of cardiovascular death (HR: 0.45; 95% CI: 0.29-0.71). There were no significant differences in the risk of MACE when compared to LABA/LAMA (HR: 0.79; 95% CI: 0.54-1.15) or to ICS/LABA (HR: 1.26; 95% CI: 0.94-1.68). The global risk of bias was rated as low. The review applied explicit inclusion criteria, performed searches on multiple databases, conducted independent evaluator reviews, evaluated the risk of bias of the primary studies, and managed heterogeneity through random effects models. The meta-analysis integrated all eligible studies according to the predetermined criteria.[31]

Three of the trials included in this systematic review (IMPACT, TRIBUTE, and ETHOS) contributed relevant data on cardiovascular events, although none considered these events as primary or secondary outcomes.

The double-blind, multicenter, randomized clinical trial, TRIBUTE, compared the efficacy and safety of triple inhaled therapy (beclomethasone/formoterol/glycopyrronium) versus dual therapy (indacaterol/glycopyrronium) in 1,532 patients with stable COPD and at least one moderate or severe exacerbation in the previous year.[35] The primary objective was the rate of exacerbations, and the MACE data reported was part of the safety evaluation. The incidence of MACE-related adverse events (AEs) was similar between groups: heart failure in 15 patients (2.0%) in the triple group and 16 patients (2.1%) in the dual group, while ischemic cardiac events (myocardial infarction, chest pain, coronary disease, or myocardial ischemia) were reported in 8 patients (1.0%) in the triple group and 16 patients (2.1%) in the dual group. As far as serious adverse events (SAEs), heart failure occurred in 6 patients (0.8%) in the triple group and 7 (0.9%) in the dual group, and cardiac ischemia occurred in 2 patients (0.3%) in the triple group and 11 (1.4%) in the dual group. In addition, atrial fibrillation occurred in 7 patients (0.9%) in the dual group and none in the triple therapy group. The quality of the evidence is considered moderate to high, supported by the rigorous methodological design.[35]

The ETHOS clinical trial was a double-blind, randomized Phase 3 study with parallel groups that compared the efficacy and safety of triple inhaled therapies (budesonide at two doses [320 μg or 160 μg], glycopyrrolate, and formoterol) to dual therapies (glycopyrrolate-formoterol or budesonide-formoterol) over 52 weeks in patients with moderate to very severe COPD.[36] Although the primary outcome was the annual rate of moderate or severe COPD exacerbations, MACEs were also evaluated as adverse events. As far as the clinical question, the incidence of confirmed major cardiovascular events was lower in the groups who received triple therapy: 1.4% in the groups on 320 μg and 160 μg of budesonide, compared to 2.1% in the glycopyrrolate–formoterol group and 1.1% in the budesonide-formoterol group. The rates of cardiovascular events were 16.9, 16.4, 26.6, and 13.1 events per 1,000 patient-years, respectively. The lower incidence in the group on triple therapy with a high budesonide dose suggests a possible reduction in the risk of MACE compared to LAMA-LABA therapy. However, the study did not report specific measures of association (e.g., hazard ratios) or a direct inferential analysis of MACE as an outcome, and therefore these results should be interpreted with caution. The MACE evidence contributed by ETHOS is useful for generating hypotheses but limited for establishing

solid causal conclusions, since the cardiovascular events (MACEs) were not evaluated as primary or secondary outcomes of the study.[36]

The IMPACT randomized clinical trial was a double-blind, multicenter, Phase 3 trial that evaluated the efficacy and safety of triple inhaled therapy (fluticasone furoate, umeclidinium, and vilanterol) versus dual therapies (fluticasone furoate-vilanterol or umeclidinium-vilanterol) in 10,355 patients with symptomatic COPD and a history of exacerbations.[37] Over the 52 weeks of follow-up, cardiovascular adverse events were evaluated as part of the safety outcomes. Heart failure events were reported in 3% of the patients in each group: 138 patients in the triple therapy group, 126 in the fluticasone furoate-vilanterol group, and 68 in the umeclidinium-vilanterol group, with rates of 42.5, 42.8, and 44.8 per 1,000 person-years, respectively. The rates for arrhythmias were similar between groups: 50.9, 51.5, and 51.2 per 1,000 person-years, respectively. From a methodological perspective, the design was robust (randomized, double-blind, with blind attribution of events), with a large sample size and low risk of bias in the measurement of independently attributed cardiovascular outcomes. However, the MACE results were not primary or secondary outcomes, which limits the precision of the estimates for this specific question.[37]

Yang et al. conducted a systematic review and meta-analysis of 51 randomized clinical trials (n = 91,021) that included adults with moderate to severe COPD (GOLD 2-3).[5] The intervention was triple inhaled therapy, compared to ICS/LABA, LABA/LAMA, LAMA, or placebo. The main outcome was the incidence of MACE, defined as cardiovascular death, non-fatal acute myocardial infarction, or non-fatal stroke. There were no significant differences in the risk of cardiovascular death (RR = 0.91; 95% CI: 0.59-1.40) or myocardial infarction (RR = 1.05; 95% CI: 0.58-1.89). Specific outcomes related to heart failure or arrhythmias were not reported either. The global risk of bias was considered moderate due to limitations in the data collection and assessment domains, as well as the synthesis of results, as individual participant data was not available and the included clinical trials were not specifically designed to evaluate MACE. This limited the ability to adjust for variables like smoking, age, or comorbidities.[32]

In an online systematic review and meta-analysis, Rogliani et al.[33] included four clinical trials with a total of 21,809 participants with moderate to severe COPD (post-bronchodilator FEV_1 < 65%) and compared triple therapy (the same device) with dual therapy (ICS/LABA or LABA/LAMA) over at least 24 weeks. They evaluated cardiovascular serious adverse events (CV SAEs) as a safety outcome. Triple therapy was associated with a higher risk of CV SAEs compared to ICS/LABA (RR = 1.29; 95% CI: 1.10-1.51) but not compared to LABA/LAMA (RR = 1.03; 95% CI: 0.98-1.08). In a sensitivity analysis (excluding heterogeneous studies), they found fewer CV SAEs compared to LABA/LAMA (RR = 0.66; 95% CI: 0.53-0.80), and all-cause mortality was also lower with triple therapy (RR = 0.75; 95% CI: 0.58-0.96). Cardiovascular events were analyzed as a composite outcome without specifically disaggregating heart failure or arrhythmias. The overall risk of bias was moderate (specifically due to the data collection and evaluation domains and synthesis of results). The certainty of the evidence was considered moderate due to methodological variability and the focus on composite outcomes.[33]

As far as clinical consensuses, the Delphi consensus by Solidoro et al.[38] included 104 experts and a formal methodology (Estimate-Talk-Estimate). Recommendation 10 is based on a systematic review of clinical trials that concludes that triple therapy is not associated with higher cardiovascular risk compared to dual therapy, although it does not specifically evaluate outcomes like arrhythmias or heart failure. The quality of the evidence was not explicitly evaluated in the consensus.[38] Other consensuses (Kaplan et al.; Dhar et al.[39,40]) did not apply systematic and transparent evidence search, selection, and synthesis methods, which limited their usefulness for answering this question.

An observational cohort study based on the regional prospective coronary interventionism registry (REAL) in Emilia-Romagna, Italy, included patients with ST-elevation acute myocardial infarction (STEMI) from 2003 to 2009.[41] From this registry, a cohort of COPD patients was identified, defined by a combination of three criteria: COPD recorded as a comorbidity in the database, a documented history of hospitalization for COPD, or the use of pharmacological treatment specific to COPD (inhaled corticosteroids plus long-acting bronchodilators, inhaled anticholinergic drugs, inhaled β-agonists, or theophylline). The hospitalization for COPD criterion implies that part of the cohort may have had moderate or severe exacerbations in the past, and therefore the study indirectly includes patients with a history of exacerbations. However, it did not select the population based on a recent exacerbation or analyze the temporal relationship between the exacerbation and cardiovascular outcomes. The patients were classified according to exposure to prior treatment with ICS plus

a long-acting bronchodilator (LABA or LAMA) (defined as at least two prescriptions in the six months prior to the event), and followed to evaluate inpatient and long-term outcomes, including pulmonary edema, cardiogenic shock, the need for a counter-pulsation balloon, and mortality.[41] This design is considered a retrospective cohort with prospectively collected data, allowing exploration of associations but not the establishment of causality. In this case, it does not directly evaluate the effect of triple therapy in stable COPD nor the incidence of MACE, and therefore its findings constitute indirect evidence for the clinical question posed.

A retrospective cohort study that included adults with COPD aged 40 or above who were hospitalized for a severe exacerbation evaluated whether early initiation of triple inhaled therapy (inhaled corticosteroid, long-acting β2-agonist, and long-acting muscarinic antagonist) after a severe COPD exacerbation was associated with a lower risk of subsequent exacerbations as well as less use of healthcare services and lower costs. It also estimated the effects of each 30-day delay in beginning treatment.[42] Patients were classified according to whether they initiated triple therapy early (≤ 30 days), late (31-180 days), or very late (181-365 days). The multivariate analysis adjusted for demographic characteristics, comorbidities (including cardiovascular disease and pre-existing heart failure), prior use of medications, and the use of healthcare services. It is relevant to note that the study did not evaluate MACEs as main outcomes and therefore does not completely answer the clinical question posed. The results showed that, for every 30-day delay in beginning triple therapy, the likelihood of developing any COPD exacerbation increased (OR: 1.13; 95% CI: 1.11-1.15), as did that of developing severe exacerbations (OR: 1.10; 95% CI: 1.08-1.12). Likewise, the risk of hospitalization for any cause increased (OR: 1.09; 95% CI: 1.075-1.107), as did the risk of emergency room visits for any cause (OR: 1.06; 95% CI: 1.04-1.07), and the risk of COPD-related emergency room visits (OR: 1.07; 95% CI: 1.05-1.08).[42] The evidence presented helps estimate the association between the timing of triple therapy initiation and exacerbations or the use of services but does not provide specific data regarding the relationship between this treatment and the onset of major cardiovascular events.

Clinical question 3

In adult patients with stable COPD, does non-pharmacological treatment, including pulmonary rehabilitation, immunization, and nutritional optimization, reduce the risk of MACE compared to standard treatment?

Recommendations

- Offer pulmonary rehabilitation programs to COPD patients who have experienced an exacerbation, with evidence of greater potential benefits when these programs are started within the first four weeks after the exacerbation *(strong recommendation in favor, based on moderate certainty of the evidence, indirect evidence)*.
- Conduct nutritional assessment and malnutrition correction in COPD patients *(recommendation based on expert consensus, without grading the quality of the evidence)*.
- Provide immunization as part of the comprehensive treatment of COPD patients *(strong recommendation in favor, based on low certainty of the evidence; indirect evidence)*.

Evidence synthesis

The available evidence does not establish a direct relationship between non-pharmacological interventions (pulmonary rehabilitation, immunization, and nutritional optimization) and the reduction of MACE in patients with stable COPD. The NICE guidelines (2018, updated in 2019) recommend pulmonary rehabilitation, especially after an exacerbation, for its beneficial effects on symptoms, functional capacity, and quality of life, but do not report specific data on myocardial infarction, stroke, arrhythmias, or cardiovascular death.[43] These guidelines recognize the high prevalence of cardiovascular comorbidities and establish contraindications for pulmonary rehabilitation in the event of unstable angina or recent infarction, reflecting a consideration of cardiovascular risk without direct evidence regarding MACE outcomes. Nor do they offer recommendations linked to the impact of immunization or nutritional optimization on cardiovascular risk.[43] The EtD from the clinical practice guidelines for the diagnosis, management, and follow-up of chronic obstructive pulmonary disease in Colombia (2023) was used to issue the recommendation for pulmonary rehabilitation, to inform the direction and strength of the recommendation.[44]

The available systematic reviews reinforce this limitation. Souto et al.[45] found 267 studies on pulmonary rehabilitation, but only one reported cardiovascular events, with no group analysis, which limits its ability

to answer the question. On the other hand, Pereira et al.[46] demonstrated that malnutrition is associated with more mortality (RR = 1.97, 95% CI: 1.55-2.50) and exacerbations (RR = 1.73, 95% CI: 1.03-2.91), which suggests a possible indirect benefit of nutritional optimization, although without data on MACE. In a complementary fashion, the RCT by Maltais et al.[47] that included 252 patients with moderate to severe COPD demonstrated that pulmonary rehabilitation improved dyspnea (mean difference: 0.62; 95% CI: 0.43-0.80 in the home-based group and 0.46; 95% CI: 0.28-0.64 in the ambulatory group), functional capacity (6MWT), and quality of life, but did not evaluate cardiovascular outcomes as the primary objective. Adverse cardiovascular events were only reported descriptively, with no statistical analysis, and none were attributed to the intervention.[47] As far as immunization, a recent meta-analysis by Yedlapati et al.[48] that specifically evaluated the influenza vaccine in patients with established cardiovascular disease showed a significant reduction in the risk of MACE (RR: 0.87; 95% CI: 0.80-0.94). This finding provides indirect evidence that supports the cardiovascular benefit of immunization in high-risk populations like COPD patients.

The evidence as a whole is still insufficient and too low-quality to fully answer clinical question 3, and therefore specific research must be done to evaluate cardiovascular outcomes in the context of comprehensive nonpharmacological interventions.

However, the panel recognizes that there is low certainty in the immunization-related reduction in mortality from cardiovascular events. There are other supporting factors, like the patients' preference for interventions that improve both mortality and hospitalization and exacerbation outcomes; the wide acceptability of immunization among healthcare professionals and decision makers within the healthcare system; and, finally, the feasibility of implementation, as influenza immunization is included in the Expanded Program on Immunization for people over the age of 60 and is recommended for COPD patients by the Ministry of Health in its technical and operational guidelines for seasonal influenza vaccination[49] and in the evidence-based clinical practice guideline for the prevention, diagnosis, treatment, and follow-up of adults with COPD.[50] Therefore, the panel has decided to issue a strong recommendation in favor.

Clinical question 4

In adult patients with stable COPD, is more deteriorated pulmonary function ($FEV_1 \leq 50\%$) or lower functional capacity (walk test distance ≤ 300 meters) associated with a higher risk of MACE, including MI, stroke, cardiovascular death, and acutely decompensated heart failure (differentiating between right- and left-sided heart failure) compared to better pulmonary function ($FEV_1 > 50\%$) or greater functional capacity (walk test distance > 300 meters)?

Recommendations

- Consider that, as pulmonary function evaluated by FEV_1 reduces, the risk of adverse cardiovascular outcomes (including MI, stroke, and congestive heart failure) increases. This association justifies prioritizing the evaluation of these patients, comprehensive management of their cardiovascular risk, and meeting the established treatment goals *(recommendation based on expert consensus, without grading the quality of the evidence).*
- NT proBNP measurement is suggested as a useful tool for identifying cardiac dysfunction in patients with COPD and $FEV_1 \leq 50\%$ *(recommendation based on expert consensus, without grading the quality of the evidence).*
- There was no evidence that covering ≤ 300 m on the six-minute walk test is a sole criterion for predicting cardiovascular outcomes in COPD patients.

Synthesis of the evidence

The available evidence from four systematic reviews suggests a possible association between greater pulmonary function deterioration ($FEV_1 \leq 50\%$) and an increased risk of MACE, although this association is mainly based on indirect analyses. Based on 29 observational studies, Orlowski et al.[51] found that patients with COPD and $FEV_1 < 50\%$ had a higher risk of coronary disease (HR = 1.8; 95% CI: 1.4-2.3) and heart failure (HR = 2.9; 95% CI: 2.2-3.9) than those with better pulmonary function. While these findings did not directly evaluate MACE or distinguish between right- or left-sided heart failure, they support a relationship between pulmonary dysfunction and cardiovascular comorbidity in this population.

Furthermore, Hammadi et al.[31] documented a high burden of cardiovascular events in patients with advanced COPD (average FEV_1 between 34.5 and 52.4%), with no clear modification of the risk of MACE according to the inhaler plan used.

In addition, Su et al.[52] reported significantly higher levels of NT-proBNP, a biomarker of cardiac stress, in

patients with FEV_1 < 50% compared to those with better pulmonary function (SMD = 0.17; 95% CI: 0.05-0.29; I^2 = 0%), suggesting a higher subclinical cardiovascular burden in this group. However, this review did not evaluate clinical outcomes like MACE or analyze functional capacity. Altogether, the available evidence consistently indicates that more deteriorated pulmonary function could be associated with a higher cardiovascular risk in COPD patients, although the direct relationship with MACE and the role of functional capacity measured by a walk test distance of ≤ 300 m have yet to be clearly established.

Clinical question 5

In patients with stable COPD and high cardiovascular risk, what is the impact of β-agonist bronchodilators and long-acting anticholinergics on pulmonary function, exacerbation frequency, and cardiovascular outcomes?

Recommendation

– Use long-acting bronchodilators (LAMA or a LAMA + LABA combination) as first-line maintenance treatment for patients with stable COPD and high cardiovascular risk. These drugs are safe for the cardiovascular system, improve pulmonary function, and reduce the number of exacerbations *(strong recommendation in favor, based on low certainty of the evidence).*

Evidence synthesis

In patients with stable COPD and high cardiovascular risk, long-acting bronchodilators show consistent and clinically significant benefits in pulmonary function and exacerbation frequency. Monotherapy with LAMA improves FEV by 0.12 L (95% CI: 0.10-0.14) compared to placebo and lowers the risk of exacerbations by approximately 15% (27). Dual LAMA/LABA therapy, on the other hand, provides additional 0.11 L FEV_1 increments (95% CI: 0.10-0.13) compared to monotherapies and reduces the frequency of moderate to severe exacerbations, with an RR of 0.82 (95% CI: 0.70-0.95) compared to placebo.[53,54]

Regarding cardiovascular outcomes, the available evidence is solid in showing that long-acting bronchodilators do not significantly increase serious cardiovascular events. In 23 RCTs with 24,987 participants, LAMAs did not increase the risk of expanded MACE compared to placebo (RR = 0.98; 95% CI: 0.88-1.09).[55] Nor did studies on LAMA/LABA combinations like indacaterol/glycopyrronium (21,238 participants) show an increased risk of myocardial infarction, atrial fibrillation, or heart failure, compared to monotherapies.[54]

It is important to point out that most of the clinical trials did not specifically select patients with high cardiovascular risk, which limits direct generalization of the results. However, the consistency of the effects on pulmonary function and exacerbations, coupled with the lack of signs of significant cardiovascular risk, strongly supports the efficacy and safety of LAMA and LAMA/LABA in this population. According to the 2024 GOLD Global Strategy, long-acting bronchodilators provide benefits for symptom control, pulmonary function, and exacerbation prevention, and caution is recommended in patients with cardiovascular comorbidities, without advising against their use in high-risk patients.[53]

Clinical question 6

In patients with stable COPD who have disproportionate dyspnea, persistent tachycardia, and high cardiovascular risk, do structured assessment and follow-up using specific diagnostic tests contribute to a reduction in cardiovascular events, fewer exacerbations, and improved quality of life?

Recommendation

– Patients with properly treated COPD and disproportionate dyspnea, chest pain, and/or palpitations will need to undergo a differential diagnosis and therefore a search for cardiovascular or pulmonary vascular disease, among others, individualizing each case *(expert consensus, without grading the quality of the evidence).*

Evidence synthesis

Various recent systematic reviews have suggested that structured assessment using specific diagnostic tests and biomarkers can contribute additional prognostic value to patients with stable COPD, especially those with disproportionate symptoms such as dyspnea or persistent tachycardia. The evidence of coronary calcium (CC) on chest computed tomography (CT) has been identified as an independent predictor of ischemic cardiovascular events and death. In a meta-analysis of three cohort studies with 4,135 participants, Jiménez-Gómez et al.[56] found that the presence of CC was associated with a significant increase in the risk of ischemic cardiovascular events (HR

= 1.44; 95% CI: 1.22-1.70), while another meta-analysis of four studies with 7,473 participants reported that CC is related to increased overall mortality during follow-up (HR = 1.57; 95% CI: 1.35-1.83).

Likewise, pulmonary artery dilatation (PAD) on chest CT has been related to worse respiratory and cardiovascular clinical outcomes. In a meta-analysis of four studies with 444 patients, Chen et al.[57] showed that PAD was associated with a significant increase in mortality (OR = 3.06; 95% CI: 1.76-5.32). Also, in six studies with 4,017 patients, PAD was related to marked functional deterioration, reflected in a -67.53-meter reduction in the distance walked in six minutes (95% CI: -85.98 to -49.08).

Biomarkers like NT-proBNP also have prognostic value in COPD. In a meta-analysis of three studies with 744 patients hospitalized for COPD exacerbations, Su et al.[52] reported that NT-proBNP levels were significantly higher in non-survivors than in survivors (SMD = 1.67; 95% CI: 0.47-2.88), which suggests that this biomarker may be useful for identifying patients at risk of heart failure or pulmonary hypertension.

Clinical implications

The evidence reviewed and expert consensus highlight the fact that COPD must be understood as a systemic disease in which cardiovascular risk and mortality do not depend exclusively on respiratory involvement but rather on the interaction between chronic inflammation, the burden of comorbidities, functional deterioration, and exacerbation frequency. In this context, cardiopulmonary risk stratification cannot be limited to isolated spirometric parameters but rather requires comprehensive evaluation that incorporates clinical and functional variables, biomarkers, and the exacerbation history.

In addition, the period following exacerbations is a window in which patients are highly vulnerable to adverse cardiovascular events, which reinforces the need for a multidisciplinary approach and structured follow-up strategies that integrate the pulmonology and cardiovascular perspectives. These consensus recommendations seek to contribute to a more homogenous and risk-based clinical practice, adapted to the context of the Colombian healthcare system.

Conclusions

The recommendations drafted in this consensus provide a structured framework for evaluating and stratifying the cardiopulmonary and mortality risk of COPD patients, integrating the best available evidence with the clinical experience of national experts. Their implementation may facilitate earlier identification of high-risk patients, optimize treatment of cardiovascular comorbidities, and promote a more comprehensive and multidisciplinary approach to care.

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Conflicts of interest

All members of the developing group and participants in the consensus filled out their declaration of conflicts of interest at the beginning of the process and before the structured discussion sessions.

The conflicts of interest identified were evaluated and managed according to the policies of Asoneumocito and current editorial recommendations in order to ensure transparency, academic independence, and the scientific integrity of the process.

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Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent, and ethical approval. The study did not involve personal data, medical charts, or human biological samples, and therefore did not require ethical approval. The SAGER guidelines did not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing or creating content for this article.

Supplementary Material

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CASE PRESENTATION

Acute lower limb ischemia as an atypical manifestation of acute aortic syndrome

Isquemia aguda de miembros inferiores como manifestación atípica del síndrome aórtico agudo

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Abstract

Acute aortic syndrome comprises a group of cardiovascular conditions associated with high morbidity and mortality, among which aortic dissection is particularly significant. Its prognosis depends on timely diagnosis and appropriate management. Although sudden, severe, tearing chest pain is considered the hallmark symptom, up to one-third of patients may present with atypical clinical manifestations, leading to diagnostic delays and increased mortality. We report the case of a patient with a history of chronic arterial hypertension, advanced chronic kidney disease, and active cocaine use, who presented without the classic symptoms of aortic dissection. The initial presentation consisted of severe pain and acute ischemia of the left lower limb, without chest or abdominal pain. Lower-limb computed tomography angiography revealed an intimal flap involving both common and external iliac arteries, associated with thrombosis of the left false lumen and limb malperfusion. Due to the patient's sudden and fatal clinical deterioration, further imaging characterization of the proximal extent of the dissection by thoracoabdominal computed tomography angiography or echocardiography could not be completed. This case highlights the importance of considering acute aortic syndrome in the differential diagnosis of high-risk patients, even in the absence of typical symptoms, to avoid delays in the management of a potentially fatal condition.

Keywords: *Aortic dissection. Hypertension. Renal insufficiency. Cocaine. Limb ischemia.*

Resumen

El síndrome aórtico agudo comprende un grupo de entidades cardiovasculares de alta morbimortalidad, entre las que se destaca la disección aórtica, cuyo pronóstico depende de un diagnóstico y tratamiento oportunos. Aunque el dolor torácico súbito, intenso y desgarrador constituye el síntoma cardinal, hasta un tercio de los pacientes puede presentar manifestaciones clínicas atípicas, lo que conlleva retrasos diagnósticos y aumento de la mortalidad. Se presenta el caso de un paciente con antecedentes de hipertensión arterial crónica, enfermedad renal crónica avanzada y consumo activo de cocaína, quien debutó sin la sintomatología clásica de disección aórtica, con dolor intenso e isquemia aguda del miembro inferior izquierdo, sin dolor torácico ni abdominal. La angiotomografía de extremidades inferiores evidenció un colgajo de disección con compromiso de ambas arterias ilíacas comunes e ilíacas externas, asociado a luz falsa trombosada izquierda y malperfusión de la extremidad. Debido al deterioro clínico súbito y fatal, no fue posible completar la caracterización imagenológica de la

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extensión proximal mediante angiotomografía toracoabdominal ni ecocardiografía. Este caso resalta la importancia de considerar el síndrome aórtico agudo en el diagnóstico diferencial de pacientes de alto riesgo, incluso en ausencia de síntomas típicos, para evitar demoras en el abordaje de una condición potencialmente fatal.

Palabras clave: *Disección aórtica. Hipertensión. Insuficiencia renal. Cocaína. Isquemia crítica.*

Introduction

Acute aortic syndrome (AAS) comprises a group of potentially fatal diseases that share similar clinical characteristics including aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. These conditions are characterized by rapid progression and a high risk of death and therefore require prompt diagnosis and treatment. [1] Aortic dissection, specifically, is the most common and severe form of AAS, present in up to 90% of cases. Generally, AAS is more common in men than in women, and its prevalence increases with age, with a mean age at onset of approximately 63 years. In young patients, generally under the age of 40, genetics plays an important role and is related to connective tissue diseases and bicuspid aortic valve. Acquired risk factors must also be considered, including chronic and active use of sympathomimetic substances like cocaine[2,3].

The diagnosis and treatment of aortic dissection depend mainly on the location of the lesion, its anatomic extension, and the presence of complications. The Stanford classification, widely used in clinical practice, divides dissections into type A (when the ascending aorta is involved, with or without affecting the descending aorta) and type B (when they are limited to the descending aorta, distal to the origin of the left subclavian artery). This classification has essential prognostic and treatment implications, since type A dissections typically require urgent surgical intervention due to their high early mortality. On the other hand, the DeBakey system describes the site of origin and longitudinal extension of the dissection in greater detail: type I, when it originates in the ascending aorta and extends distally; type II, when it is limited to the ascending aorta; and type III, when it originates in the descending aorta[4,5] (Fig. 1). However, the traditional Stanford and DeBakey systems fall short in their ability to describe more complex anatomical and pathophysiological scenarios. Therefore, current classifications like the clinically oriented classification proposed by Qanadli et al. (Fig. 2), which incorporates aortic arch involvement and malperfusion patterns, and the type-entry-malperfusion (TEM) classification (Fig. 3) that includes the type of dissection, location of the entry site, and presence of malperfusion, have sought to complement the classic anatomical description with elements with prognostic and treatment relevance. These classifications also recognize non-A-non-B scenarios, especially when the aortic arch is involved without affecting the ascending aorta.[6,7]

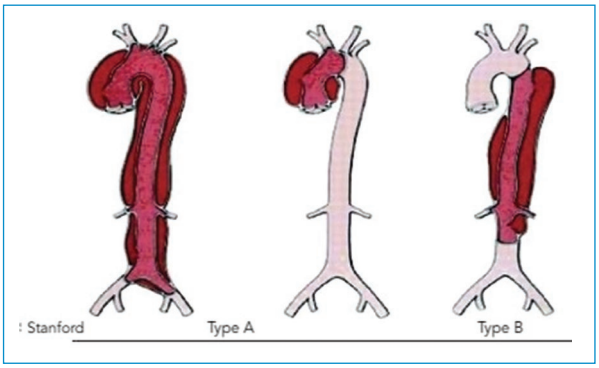
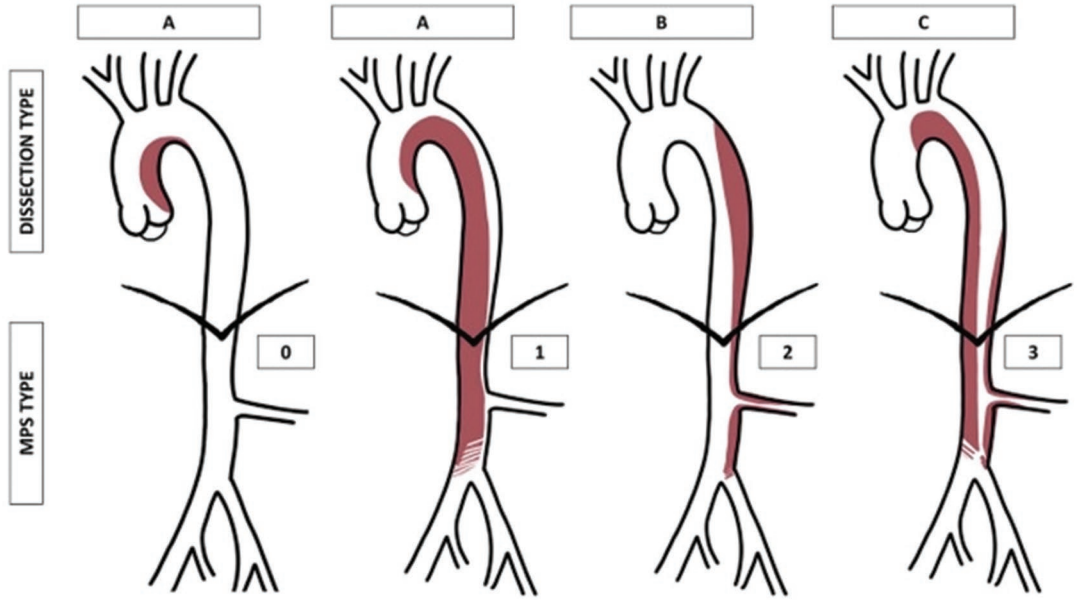


Figure 1. Stanford classification for acute aortic dissection. **Type A:** dissections affecting the ascending aorta, regardless of the site of origin. **Type B:** dissections that do not affect the ascending aorta. *Source: Ince H, et al.*[5].

Clinically, sudden-onset intense, tearing chest pain is considered the cardinal symptom of aortic dissection. However, 10 to 30% of cases may present atypical symptoms, making early detection difficult and delaying treatment[8,9]. These presentations may mimic other conditions like heart failure, acute kidney failure, neurological events, or peripheral vascular syndromes. Lower limb ischemia, reported in up to 9.7% of cases, is a rare but relevant manifestation of AAS. In this context, diminished or absent distal pulses, coolness, changes in color, and peripheral neurological deficit should alert to the possibility of malperfusion associated with aortic dissection[10].

The following case describes an atypical presentation of AAS, with acute left lower limb ischemia as the initial manifestation. The coexistence of well-established risk factors, coupled with the lack of an evident embolic cause, directed suspicion to an aortic etiology. This case manifests the importance of maintaining a high index of suspicion when faced with unusual presentations, especially in patients with comorbidities that



Graphic representation of the classification proposed for aortic dissection (type A, B, or C) and subtypes of malperfusion syndrome (MPS) (grade 0, 1, 2, or 3). Grade 1 MPS is shown as compression of the true lumen in the abdominal aorta, grade 2 as an extension of the dissection to the left renal artery, and grade 3 as a combination of both.

Figure 2. Clinically oriented classification of acute aortic dissection proposed by Qanadli et al. that integrates anatomical aortic involvement and the degrees of malperfusion. *Adapted from Qanadli et al.*[6]

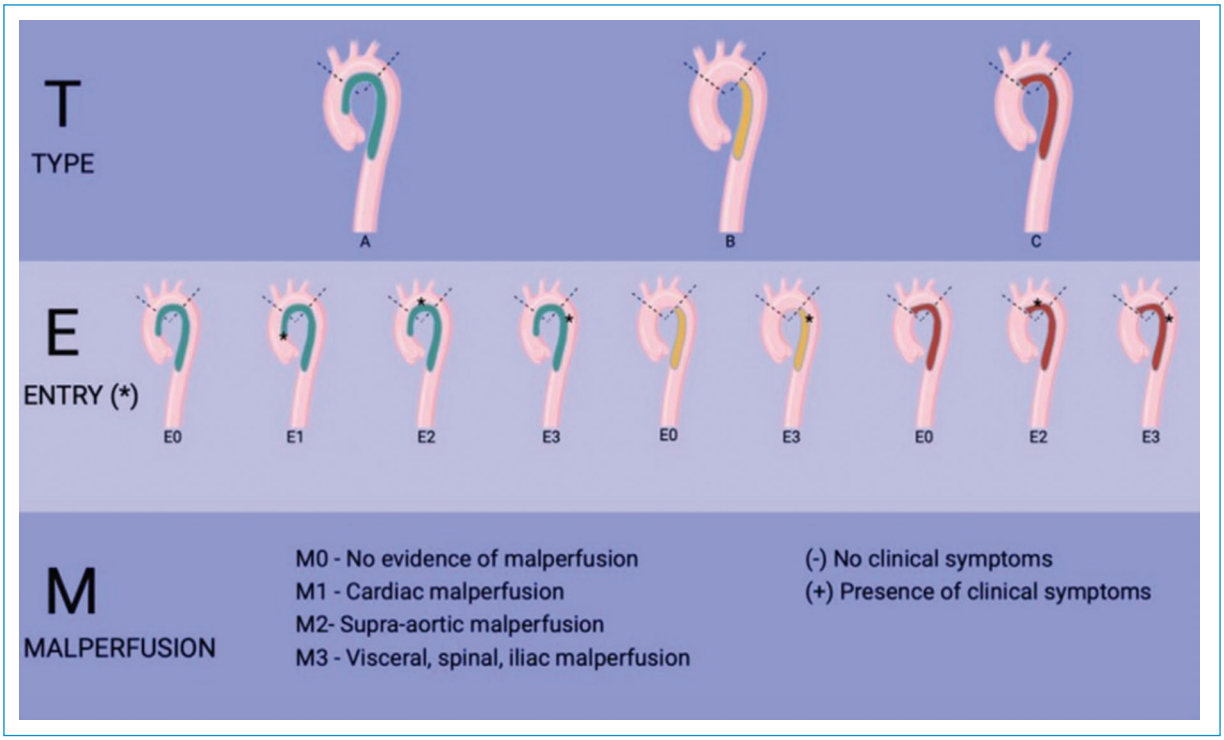


Figure 3. Type-entry-malperfusion (TEM) classification for aortic dissection that integrates the type of dissection, location of the entry site, and presence of malperfusion. *Adapted from Ramesh et al.*[7]

could modify or mask the classic manifestations of AAS[10,11].

Clinical case

We present the case of a 41-year-old male patient with a history of hypertension and stage IV chronic kidney disease, secondary to focal and segmental glomerulosclerosis, being followed by nephrology and internal medicine, with no recent appointments or beginning of renal replacement therapy. He was being treated with atorvastatin, calcitriol, metoprolol, and nifedipine. He reported chronic *Cannabis sativa* and cocaine use and had ingested high doses of both substances two days prior to the onset of symptoms.

The clinical picture began suddenly with intense pain in his left lower limb, along with paresthesia and difficulty walking, and he therefore consulted at a local hospital. On the initial exam, he had signs of acute limb ischemia, with cyanosis, distal coolness, and motor involvement. An electrocardiogram showed sinus rhythm with no ST segment abnormalities or atrial fibrillation. Given the suspicion of acute arterial occlusion, he was urgently referred to our institution for testing and treatment by vascular surgery.

On admission, he was alert and anxious due to the intense pain and had a blood pressure of 140/90 mmHg, heart rate of 100 bpm, oxygen saturation of 94% on room air, and a Glasgow score of 15/15. On physical exam, he had no chest pain, abdominal pain, or relevant pulmonary findings. His left lower limb exhibited color changes with distal cyanosis, coolness, absent pedal and posterior tibial pulses, and distal paresthesia, findings compatible with acute limb ischemia (Fig. 4). Analgesia was optimized, continuous monitoring was prescribed, and a computed tomography angiography with contrast of the lower limbs was ordered.

The tomography revealed a dissection flap involving both common and external iliac arteries. There was a thrombosed false lumen on the left, with marked reduction of the true lumen and filiform contrast flow, although there was adequate distal patency of the femoral segments and most distal branches (Fig. 5). Since the scan was of the pelvis and lower limbs, the report recommended completing the evaluation with computed tomography angiography of the thoracic and abdominal aorta to determine the proximal extension of the dissection.

During monitoring in critical care after the test, the patient experienced sudden clinical deterioration with loss of consciousness, cyanosis, and no carotid pulse.

Figure 4. The left lower limb (LLL) shows changes in color, pallor, and distal coolness evident in the ankle, dorsum, and plantar surface of the foot, compared to the right lower limb (RLL). Findings compatible with critical limb ischemia. *Source: image published with the patient's informed consent for academic and scientific purposes, ensuring confidentiality and anonymity.*

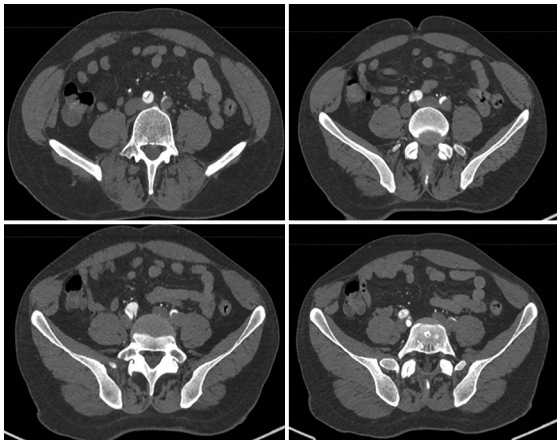


Figure 5. Computed tomography angiography of the lower limbs: dissection involving both common and external iliac arteries, with thrombosis of the false left lumen causing marked reduction of the true lumen at this level. *Source: Diagnostic Imaging Service, Clínica SOMER, Rionegro, Antioquia, Colombia.*

Advanced cardiopulmonary resuscitation was started due to pulseless electrical activity. Due to the patient's extreme instability and a rapid fatal outcome, neither echocardiography nor complementary computed tomography angiography of the thoracic and abdominal aorta was able to be performed. Despite advanced resuscitation maneuvers, spontaneous circulation was not restored. The case was interpreted as an atypical presentation of AAS with aorto-iliac involvement and malperfusion of the lower limb in a young patient with

hypertension, advanced chronic kidney disease, and active cocaine use.

Discussion

Acute aortic syndrome, which includes aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer, constitutes a cardiovascular emergency with high morbidity and mortality when not identified promptly. Aortic dissection is the most common and serious condition within this spectrum, with a risk of rapid deterioration, especially when coupled with malperfusion, rupture, or hemodynamic disorders[8,11].

The case we presented was of a young adult with hypertension, stage IV chronic kidney disease, and active cocaine use, which increase vascular vulnerability and the risk of acute aortic events. Hypertension fosters increased wall stress, while chronic kidney disease is associated with vascular stiffness, chronic inflammation, oxidative stress, and endothelial dysfunction[12]. Cocaine, in turn, has sympathomimetic and vasoconstrictive effects, capable of inducing hypertensive spikes, tachycardia, and abrupt pressure increases on the aortic wall, which can foster intimal rupture and dissection progression[13,14].

The case's peculiarity lies in its presentation. The patient did not complain of chest pain, abdominal pain, or central nervous system symptoms but of intense pain in the left lower limb associated with cyanosis, distal coolness, absent pulses, and sensorimotor abnormalities. This manifestation initially oriented the diagnosis toward a peripheral arterial occlusive disorder. However, given the patient's clinical context, an aortic etiology also needed to be considered. The literature reports that up to 30% of patients with aortic dissection may show atypical signs and symptoms like isolated abdominal pain, absent or asymmetric pulses, syncope, neurological deficits, migrating pain, heart failure, cardiac tamponade, limb ischemia, or sudden death[8,9,15]. These presentations make early recognition of an acute aortic disorder difficult[16,17]. Table 1 presents the reported frequency of these atypical manifestations and their relationship to the findings in this case.

Computed tomography angiography of the lower limbs reported a dissection flap involving both common and external iliac arteries, coupled with a thrombosed left false lumen and marked reduction of the true lumen. These findings explain the predominant malperfusion of the left lower limb. Acute limb ischemia, while uncommon, may be the initial manifestation of aortic dissection and has been reported in up to 9.7% of cases[16].

Table 1. Atypical signs and symptoms of acute aortic syndrome (AAS) as they relate to the patient's clinical presentation

Atypical AAS manifestation	Reported frequency	Relationship to the case presented
Isolated abdominal pain	30%	Not present
Absent or diminished pulses	22-30%	Present: absent left pedal and posterior tibial pulses
Congestive heart failure	20%	Not recorded
Syncope or sudden loss of consciousness	19%	Present during the hospital stay
Migrating pain	19%	Not reported
Hypotension	18%	Not present on admission
Cardiogenic shock	18%	Not recorded as a specific diagnosis
Cardiac tamponade	18%	Not documented; neither echocardiography nor thoracic computed tomography angiography could be performed, but this was suspected due to the patient's signs and symptoms and acute deterioration
Neurological deficit	12%	Not recorded on admission; Glasgow 15/15
Stroke	11%	Not recorded
Acute limb ischemia	9.7%	Present: initial clinical manifestation of the case
Limb pain	7.9%	Present: intense left lower limb pain
Sudden death	4%	Outcome after sudden clinical deterioration

This finding is relevant in light of current classifications like the one proposed by Qanadli et al. and the TEM classification, which complement the traditional systems by incorporating malperfusion as an essential anatomical, clinical, and prognostic element[6,7].

A relevant aspect of this case is that the initial diagnostic approach was determined by the dominant clinical manifestation: acute lower limb ischemia. In this context, computed tomography angiography of the pelvis and lower limbs was pertinent and helped document a key finding: dissection with bilateral involvement of the iliac arteries and malperfusion, predominantly of the left lower limb. The need to complete the study with

computed tomography angiography of the thoracic and abdominal aorta was recognized in the radiology report. However, the patient's sudden clinical deterioration did not allow complementary studies or echocardiography to be performed. This limitation does not invalidate the documented diagnosis but rather accurately delineates its scope: aortoiliac dissection was confirmed, but the exact proximal extension could not be determined, nor could a definitive Stanford or DeBakey classification be assigned.

Although this report does not aim to provide in-depth coverage of treatment, the initial principles for managing AAS include close monitoring, analgesia, heart rate and blood pressure control (as the hemodynamic conditions allow), and early activation of vascular surgery, cardiovascular surgery, critical care, and diagnostic imaging teams. The definitive strategy depends on the location of the dissection, its anatomic extension, and the presence of rupture, arterial branch involvement, or malperfusion[4,11].

There are no consolidated national registers of AAS in Colombia, and the available information is mainly derived from case series at high-level healthcare facilities. This limitation makes it difficult to understand the true epidemiological burden and establish systematic strategies for early diagnosis[17,18]. Therefore, reporting atypical presentations like this one is relevant: acute limb ischemia should not be interpreted in isolation when it occurs in a patient with significant risk factors. In these scenarios, AAS should be included in the differential diagnosis from the onset, even without chest pain.

Conclusions

Acute aortic syndrome continues to be a devastating cardiovascular emergency, which, despite its high lethality, still faces significant diagnostic and care gaps, especially in countries like Colombia, where the lack of national registries, limited access to timely imaging studies, and low clinical suspicion with atypical presentations perpetuate unfavorable outcomes. This clinical case, documenting an unusual debut with acute lower limb ischemia in a young patient with multiple risk factors, contributes evidence to the medical literature regarding the clinical variability of AAS and highlights the importance of considering an aortic etiology, even in the absence of chest pain or classic signs and symptoms.

Although the dissection's proximal extension could not be described due to the patient's rapid clinical deterioration, the initial computed tomography angiography was able to document aorto-iliac dissection with malperfusion of the lower limb, a finding that explains the clinical presentation and is the academic focus of this report. This circumstance does not invalidate the documented diagnosis but rather delineates its scope and highlights the real difficulties in handling fulminant aortic disorders in the emergency room.

As a clinical and academic team, reporting this case is an act of scientific and social responsibility; it seeks to raise awareness of the need to strengthen staff training in recognizing non-classic presentations, promote appropriate diagnostic pathways adapted to the local context, and encourage the creation of national AAS registries that will help grasp its true epidemiological burden in Colombia. Only a comprehensive approach combining clinical suspicion, continuing medical education, imaging availability, and interdisciplinary work will help transform tragic outcomes into concrete opportunities for improvement in cardiovascular health.

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Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Confidentiality, informed consent, and ethical approval. The authors followed their institution's confidentiality protocols and obtained informed consent from the patients and approval from the ethics committee. They followed the SAGER guidelines according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in writing this article.

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LETTER TO THE EDITOR

Limitations and scope of the main contemporary measuring instruments of cardiovascular risk

Limitaciones y alcances de los principales medidores contemporáneos del riesgo cardiovascular

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Dear Editor,

Cardiovascular risk (CVR) assessment is one of the most relevant pillars of primary and secondary cardiovascular disease (CVD) prevention. From the classical to the most recent models, cardiovascular risk calculators have helped guide therapeutic decisions, determine control targets, and establish public health policies. However, the proliferation of tools like the Framingham Risk Score (FRS), ASCVD Risk Estimator, PREVENT calculator, and SCORE-2OP has raised questions regarding their applicability, external validity, and ability to adapt to different populations, particularly in Latin American countries, where local calibration data are limited.

The FRS, developed from the historic Framingham Heart Study, was the first prediction tool to be extensively validated in clinical practice. Its main strength lies in the simplicity and availability of the variables it uses (age, sex, blood pressure, total cholesterol, HDL, and smoking), which helps estimate the 10-year absolute risk of a major coronary event and has served as the basis of other derived scores. However, the model was constructed based on a predominantly white, middle-aged, United States cohort, which limits its validity in populations with a different genetic or epidemiological structure, such as Latin American or Asian populations. Furthermore, it tends to overestimate risk in populations with a low CVD risk and underestimate it in settings with a high prevalence of metabolic or inflammatory factors. In addition, emergent markers like abdominal obesity, chronic inflammation, or insulin resistance, which are very relevant in today's epidemiological transition, are not incorporated.[1,2] Despite its limitations, it continues to have great historical and educational value by consolidating the concept of multifactorial risk and laying the foundations for modern preventive medicine, although its local recalibration underscores an urgent need.

The SCVD Risk Estimator Plus, promoted by the American College of Cardiology and American Heart Association, represents a progression of the Framingham model. It broadens the spectrum of atherosclerotic events considered (acute myocardial infarction, fatal and non-fatal stroke) and helps estimate 10-year risk, while also considering ongoing treatments like the use of statins, antihypertensives, and preventive aspirin. Its most important advantages include digital accessibility, its capacity for dynamic updating, and the inclusion of racial categories, which seeks to refine its predictive accuracy. However, its dependence on racial categories introduces significant clinical bias. Various studies have demonstrated risk overestimation in people of African descent and underestimation in Hispanics, limiting its

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usefulness in multiethnic populations, such as those in Latin America.[3] Although it is remarkably easy to use, its performance decreases in older adults, patients with autoimmune or endocrine comorbidities, or under unfavorable socioeconomic conditions that alter the burden of cardiovascular risk.

In 2023, the American Heart Association presented the PREVENT Risk Calculator as a next-generation tool whose design is based on more than 6.5 million clinical charts, incorporating contemporary factors like obesity, chronic kidney disease, and statin treatment. This model differentiates between the risk of atherosclerosis and heart failure and extends the predictive horizon to 30 years. Its main strength lies in the use of a massive amount of data and its automated updating through electronic clinical charts. It has proven to have a better predictive fit for women and those over the age of 65.[4] However, its algorithmic complexity and the obscurity of its calculations make its direct clinical interpretation difficult. In addition, its calibration is based exclusively on the United States healthcare system, which restricts its applicability in countries with different epidemiological infrastructures. Even so, it marks the beginning of an era in which artificial intelligence and dynamic models may transform personalized preventive medicine.

Meanwhile, SCORE2 and its SCORE2-OP version, updated by the European Society of Cardiology in 2021, are reference tools in Europe. These models estimate the 10-year risk of fatal and non-fatal cardiovascular events, adjusting the weight of age using non-linear curves and calibrating risk according to European regions with different CVD incidences. Their strength lies in their geographic stratification and the simplicity of their variables: age, sex, blood pressure, total cholesterol, HDL cholesterol, and smoking, making them reproducible even in limited resource settings. However, they have a significant limitation, which is the underestimation of risk in regions with a high prevalence of metabolic syndrome or chronic inflammatory diseases. They also lack key metabolic variables like glycemia or central obesity, and their validity in non-Caucasian populations is still uncertain.[5]

Comparing these predictive models reveals a constant tension between simplicity and accuracy. Classical designs like Framingham or SCORE2-OP are practical and accessible but show low sensitivity in identifying new cardiometabolic and inflammatory events associated with cardiovascular risk. On the other hand, more recent tools like ASCVD or PREVENT offer greater precision, although at the expense of growing complexity, technological dependence, and less applicability outside of the United States or Europe. In Latin America, the lack of locally calibrated models continues to be a critical limitation. Comparative studies in Colombia, Chile, and Mexico have shown discrepancies of up to 40% in risk classification between Framingham and SCORE2-OP, evidencing the need for regional adjustments and internal validation.[6-10]

Consequently, the future of cardiovascular risk stratification should combine the statistical solidity of contemporary models with adaptability to different population contexts. Integrating inflammatory biomarkers, social determinants, family history, artificial intelligence, and actual longitudinal data could facilitate a more personalized and equitable prediction.

Progress in cardiovascular risk estimation reflects the evolution of modern epidemiology but also highlights the need to contextualize information beyond the algorithms. No model, by itself, replaces clinical judgment. Therefore, the results should be interpreted critically and individually for each patient, adjusted to the demographic need and local healthcare context. Encouraging national validations and the development of hybrid pilot models to integrate clinical, genetic, and behavioral information will help advance toward a more accurate and humanized predictive medicine.

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LETTER TO THE EDITOR

Respiratory therapists in cardiovascular intensive care units: clinical impact and challenges in Colombia

El terapeuta respiratorio en las unidades de cuidado intensivo cardiovascular: impacto clínico y desafíos en Colombia

Jhojan S. Herrera-Vargas[1-3] and Luisa F. Méndez[1]*

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Editor:

Cardiovascular intensive care units (CICUs) are one of the most complex settings in modern hospital care. They are characterized by a high technological burden, critically ill patients, and the need for prompt and coordinated decision-making[1]. The sustained increase in patients requiring mechanical ventilation (both invasive and noninvasive), coupled with the growing complexity of cardiovascular critical care, has revealed the urgent need for professionals highly trained in handling advanced respiratory support[1,2]. In this context, the role of respiratory therapists (RTs) in the CICU has evolved considerably: it has gone from being a historically technical job to becoming a strategic clinical position within the multidisciplinary team.

The available evidence indicates that actively incorporating RTs into CICUs favors adherence to mechanical ventilation and weaning protocols, reduces the number of days on ventilatory support, and can decrease both hospital stays and readmissions for cardiothoracic patients[2,3]. Likewise, their participation in respiratory monitoring strategies, extracorporeal support, and clinical decision-making reflects an impact beyond the performance of isolated procedures[4,5].

Despite these advances at an international level, there are still significant barriers in Colombia to consolidating RT in the CICU. Among the most significant barriers are the limited number of respiratory therapy academic programs, scant availability of graduate training aimed at cardiovascular critical care, and little RT-led scientific production. This situation restricts not only the discipline's strengthening but also the visibility of its contribution within the modern cardiovascular critical care models.

In view of this, we believe that further RT integration into the Colombian CICUs must be encouraged, not only in clinical care, but also by fostering advanced training, research, and clinical leadership. Recognizing and potentiating their role in these scenarios is a priceless opportunity to strengthen the quality, safety, and sustainability of cardiovascular critical care in this country.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

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