ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 93 N° 5 OCTOBER 2025
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar
web site: www.sac.org.ar / http://ppct.caicyt.gov.ar/index.php/rac
Editorial and graphic production
Graphic design - digital edition
CF Brand Design & Communication - e-mail: estanislao@cfdisenografico.com.ar / www.cfdisenografico.com.ar

VOL 93 Nº 5
OCTOBER 2025

Summary

EDITORIAL

The Only Truth is Post-Truth: Reluctance to Use Statins

La única verdad es la post-verdad: reticencia al uso de estatinas

MARIANO A. GIORGI[1, MTSAC]

In this issue, the Argentine Journal of Cardiology highlights an important health concern explored by Lucía Helguera et al.: (1) patients' reluctance to take statins.

The authors, from the Argentine Society of Cardiology, conducted the study through a digital and anonymous survey of healthcare professionals (predominantly cardiology specialists) in our country. The survey results indicate that 40.9% of respondents reported receiving an express refusal from their patients to take statins. Among the main reasons given by patients for their refusal, two stand out: "adverse events" indicated by 53.4% of respondents and "the influence of negative information from digital media" by 50.5%.

The issue of "adverse events" is noteworthy, not only because of its frequency, but also because of the sociological complexity of this phenomenon. An adverse event includes not only tangible signs and/or symptoms, but also patients' perceptions and beliefs, as evidenced by the ASCOT-LLA substudy, which identified the nocebo effect as a determinant of the reporting of adverse muscle events only when patients (and their physicians) were aware that a statin was being used and not during the double-blind period of the study. (2) Healthcare professionals have an important role to play here, as we cannot declare a patient intolerant to statins without a rational evaluation process, as the SAC proposed in its position statement on the Appropriate Use of Statins. (3) This assignment of attributability can, for example, be facilitated by the system proposed by Rosenson et al. (4), which requires an alliance with the patient due to the time and patience it demands. However, this approach enables the identification of "false intolerants," who may have the opportunity to continue treatment. Not all pains are caused by statins.

The second reason given for refusing to take statins is perhaps the most alarming, as it confronts us with the immense complexity of the simultaneous interaction between the scientific system, patients, the mass media, industry, and the healthcare system. When faced with an issue relevant to their areas of interest, all of them will probably express an opinion, but they can only do so based on their worldview. They only see what they can see, but they do not see what they cannot. Post-truth and "tailored lies" (5) lurk just one click away as useful resources for simulating solutions to issues of ignorance. As German sociologist Niklas Luhmann points out — and special thanks to sociologist Luis Costa for contributing to this section — the absence of an explanatory center of the world is the underlying condition for this to be feasible. This is a consequence of the proliferation of viewpoints resulting from these systems.

The media should prioritize reporting news, industry should focus on achieving higher sales, and those who spread false information should concentrate on gaining more followers on social media. As doctors, we communicate within these same tensions and viewpoints. Thus, each system communicates and the other understands in its own code, only what is relevant to it. Given the current state of modern society, no one should expect anything other than the meaning of the term "adverse event" to differ among those involved. In an era when everyone wants to share their "point of view," the "adverse event" becomes just another topic of conversation.

That is why, from the perspective of healthcare professionals, it is important to know (and be able to communicate effectively) the best estimate of the prevalence of statin intolerance, 9.1% according to the meta-analysis by Bytyçi et al., (7) and to counterbalance what is reported in the media. In particular, it is important to bear in mind that the influence of "statin-negative" publications has been associated with discontinuation of therapy and a 26% increase in the risk of cardiovascular death and an 18% increase

Rev Argent Cardiol 2025;93:321-322. https://doi.org/10.7775/rac.v93.i5.20939

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:362-365. https://doi.org/10.7775/rac.v93.i5.20933

[1] Cardiology Section. CEMIC. Associate Professor of Pharmacology. Medicine Degree. CEMIC University Institute. Director, Center for Technology Assessment and Health Decision Analysis. CEMIC University Institute

in the risk of myocardial infarction, as demonstrated in a cohort study of nearly 675 000 people conducted in Denmark in 2015. (8) These results warn us about the dangers of the diverse interpretations of medical news, even among healthcare professionals. (9)

This study becomes even more relevant when viewed in the context of providing local evidence on a social phenomenon that, as noted, transcends the scientific system. As with the results of clinical trials, which vary greatly depending on the country or region where they are conducted, the same is true for statin reluctance. A study by Xie et al., (10), conducted at Mass General Brigham in the United States, reveals that the primary reasons for refusal are a preference for lifestyle changes (51.9%) and fear of adverse events (10.9%).

We live with multiple "truths," and the information provided by the authors gives us more elements to contribute to our evidence-based perspective.

Conflicts of interest

None declared

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

REFERENCES

1. Helguera L, Carrero C, Giunta G, Lerech E, Costabel JP, Stutzbach P. Reluctance to Use Statins in Secondary Prevention: Worrying Results in the Age of Digital Misinformation SAC 2025 Statin Experience – Argentine Society of Cardiology. Rev Argent Cardiol 2025;93: 362-5 https://doi.org/10.7775/rac.v93.i5.20933

2. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al; ASCOT Investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2017;389:2473-81. https://doi.org/10.1016/S0140-6736(17)31075-9

3. Sociedad Argentina de Cardiología. Área de Consensos y Normas. Uso apropiado de estatinas en Argentina: documento de posición. Rev Argent Cardiol. 2018; 86(Sup.1): 1-13

4. Rosenson RS, Miller K, Bayliss M, Sanchez RJ, Baccara-Dinet MT, Chibedi-De-Roche D, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for Clinical Use, Content Validation, and Inter-rater Reliability. Cardiovasc Drugs Ther 2017;31:179-86. https://doi.org/10.1007/s10557-017-6723-4

5. Amat M D. Coronavirus y posverdad: Mentiras a medida. Universidad Nacional de José C. Paz. Bordes 2021;6:9-17.

6. Luhmann, Niklas (1996). Introducción a la teoría de sistemas. Lecciones publicadas por Javier Torres Nafarrate. Barcelona / México: Anthropos – Universidad Iberoamericana – ITESO. Lección 13:pp233-249.

7. Bytyçi I, Penson PE, Mikhailidis DP, Wong ND, Hernandez AV, Sahebkar A, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J 2022;43:3213-23. https://doi.org/10.1093/eurheartj/ehac015

8. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J 2016;37:908-16. https://doi.org/10.1093/eurheartj/ehv641

9. Buhse S, Rahn AC, Bock M, Mühlhauser I. Causal interpretation of correlational studies - Analysis of medical news on the website of the official journal for German physicians. PLoS One 2018;13:e0196833. https://doi.org/10.1371/journal.pone.0196833

10. Xie M, Martin SS, Turchin A. Reasons for non-acceptance of statin therapy by patients at high cardiovascular risk. Sci Rep 2025;15:17014. https://doi.org/10.1038/s41598-025-01930-2

EDITORIAL

The Epicardium as a Mirror of Metabolism: from Visceral Fat to Heart Failure with Preserved Ejection Fraction

El epicardio como espejo del metabolismo: de la grasa visceral a la insuficiencia cardíaca con fracción de eyección preservada

PAULA PÉREZ TERNS[1, MTSAC]

For a long time, adipose tissue was considered a passive energy store. Today we know that it is a highly dynamic endocrine and paracrine organ, capable of communicating with multiple tissues through a complex molecular language. In the heart, this conversation occurs in close proximity: epicardial adipose tissue (EAT), which rests directly on the myocardium without an intermediate anatomical barrier shares its blood supply, oxygenation, and metabolic fate. (1,2)

The study published in this issue of the Argentine Journal of Cardiology, "Epicardial Fat and Its Relationship with Cardiac Morphological Alterations and Markers of Diastolic Dysfunction," provides valuable local evidence. (3) In a cohort of patients with type 2 diabetes without overt cardiovascular disease, the authors demonstrate that increased EAT thickness—as measured by echocardiography—is associated with a higher prevalence of diastolic dysfunction criteria. This finding transforms the epicardium: it ceases to be an anatomical curiosity to become an accessible biomarker of early cardiometabolic risk. (1,4)

In essence, EAT is visceral fat, sharing its embryological origin and its inflammatory and hormonal circuits. Under overeating, insulin resistance, and mitochondrial dysfunction conditions, EAT expands, infiltrates, and loses its anti-inflammatory profile, releasing proatherogenic cytokines, leptin, angiotensinogen, and microRNAs. (5,6) Thus, the heart is literally surrounded—and affected—by its own metabolic environment. (7)

In line with this evidence, Milton Packer has in recent years proposed a transformative pathophysiological model . In his most recent work, "The Adipokine Hypothesis of Heart Failure with a Preserved Ejection Fraction: A Novel Framework to Explain Pathogenesis and Guide Treatment", (8) he postulates that the expansion of visceral adipose tissue is not only a marker but also the upstream trigger that drives a cascade of endothelial dysfunction, systemic inflammation, and myocardial stiffness. (8-11) According to this hypothesis, alterations in the secretion of proinflammatory and antifibrotic adipokines modify nitric oxide signaling and the myocyte´s ability to sustain oxidative phosphorylation. Consequently, heart failure with preserved ejection fraction (HFpEF) emerges as a systemic disease whose epicenter is not in the heart, but in adipose tissue. (8,11)

In this context, the epicardium acts as a local messenger of this global disorder. Its expansion exerts a mechanical compressive effect on the ventricle, and also releases mediators that interfere with myocardial bioenergetics, reduce mitochondrial biogenesis, and stimulate the activation of cardiac fibroblasts. (2,6) Clinical observation and molecular physiology are intertwined: the hypertrophied epicardium becomes a visible mirror of altered metabolism, anticipating the transition from silent metabolic phenotype to overt heart failure. (5,7,8)

This metabolic process also interacts with classical hemodynamic mechanisms. Hypertension and activation of the renin-angiotensin-aldosterone axis perpetuate wall stress, inflammation, and myocardial fibrosis. (7,9) In HFpEF, aldosterone not only retains sodium but also induces mitochondrial dysfunction and epicardial remodeling, integrating the hormonal component into the inflammatory and metabolic framework that defines this entity. (7,11)

One of the great merits of the Argentine study

Rev Argent Cardiol 2025;93:323-324. https://doi.org/10.7775/rac.v93.i5.20932

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:366-369. https://doi.org/10.7775/rac.v93.i5.20931

[1] Cardiometabolism Council – Argentine Society of Cardiology

lies in restoring the value of echocardiography as a practical tool for quantifying EAT. Although magnetic resonance imaging or computed tomography allow for more accurate volumetric characterization, epicardial thickness measured in the right parasternal long axis correlates strongly with total EAT burden and myocardial stiffness. (1,4) In this study, a threshold of 5 mm was associated with a sharp increase in the prevalence of diastolic dysfunction and multiple adverse echocardiographic criteria. (1,3) It could be said that the heart receives inflammation before symptoms.

Perhaps the most encouraging message from this line of research is its potential for reversibility. Epicardial fat is a dynamic tissue that responds to metabolic changes. Trials with GLP-1 (glucagon-like peptide-1) receptor agonists and SGLT2 (sodium-glucose cotransporter 2) inhibitors have shown significant reductions in epicardial volume within a few months, accompanied by improvements in diastolic function and functional capacity. (6,7) Therefore, EAT could become a dynamic therapeutic biomarker, sensitive to the impact of pharmacological and lifestyle interventions. (5,7,8)

The study here discussed marks a milestone in local research. Beyond its limitations—small sample size and cross-sectional design—it demonstrates that it is possible to generate robust evidence on cardiometabolic pathophysiology from our own centers. According to Packer´s hypothesis HFpEF is not a disease of the heart, but of the metabolism that the heart suffers from.

In this new cardiology of the tissue, the epicardium emerges as a witness of and participant in metabolic imbalance. Measuring, understanding, and modifying it could be one of the keys to preventing HFpEF in the 21st century. (7-9,11)

Conflicts of interest

None declared

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

REFERENCES

1. Packer M. Do most patients with preserved ejection fraction have an unrecognized hypertensive heart disease? Eur J Heart Fail 2018;20:1559-72. https://doi.org/10.1002/ejhf.1293

2. Packer M. Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium. J Am Coll Cardiol 2018;71:2360-72. https://doi.org/10.1016/j.jacc.2018.02.074

3. Forte E, Becerra P, Buso C, Calzia V Chicote F, Lynch S, et al. Epicardial fat and its relationship with cardiac morphological alterations and markers of diastolic dysfunction. Rev Argent Cardiol. 2025;93:366-9. https://doi.org/10.7775/rac.v93.i5.20931

4. Packer M. Role of epicardial fat in the pathogenesis of heart failure with preserved ejection fraction. Eur Heart J 2021;42:1671-7. https://doi.org/10.1093/eurheartj/ehaa1072

5. Packer M. The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction: A Novel Framework to Explain Pathogenesis and Guide Treatment. J Am Coll Cardiol 2025;86:1269-373. https://doi.org/10.1016/j.jacc.2025.06.055.

6. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 2009;22:1311-9. https://doi.org/10.1016/j.echo.2009.10.013

7. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? Am Heart J 2007;153:907-17. https://doi.org/10.1016/j.ahj.2007.03.019

8. Mahabadi AA, Berg MH, Lehmann N, Kälsch H, Bauer M, Kara K, et al. Association of epicardial fat with cardiovascular risk factors and subclinical atherosclerosis: the Heinz Nixdorf Recall Study. J Am Coll Cardiol 2013;61:1388–95. https://doi.org/10.1016/j.jacc.2012.11.062

9. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol 2022;19:593-606. https://doi.org/10.1038/s41569-022-00679-9

10. Dutour A, et al. Visceral and epicardial fat have different impacts on cardiometabolic risk and glucose metabolism: the ABOS cohort study. J Clin Endocrinol Metab 2016;101:151–8. https://doi.org/10.1210/jc.2015-2828

11. Packer M, Anker SD. Cardiorenal metabolic disease as a systemic disorder of energy utilization. Cardiovasc Diabetol 2022;21:56. https://doi.org/10.1186/s12933-022-01498-2

ORIGINAL ARTICLE

Results from the Argentine Registry of Cardiovascular Surgery ARGEN-CCV

Resultados del Registro Argentino de Cirugía Cardiovascular ARGEN-CCV

ESTEBAN ROMEO[1], JAVIER FERRARI[2], ADRIÁN LESCANO[1, MTSAC], HERNÁN DEL PERCIO[2], YANINA CASTILLO COSTA[1, MTSAC], HERALDO D'IMPERIO[1, MTSAC], MAURO J. GARCÍA AURELIO[1], HERNÁN COHEN ARAZI[1, MTSAC]

ABSTRACT

Background: Cardiovascular surgery (CVS) is an essential tool in the treatment of heart disease, and its practice has undergone changes in recent years. In our setting, we have registries on CVS, but they date back more than 10 years. For this reason, a new study was required to understand the reality of CVS in Argentina.
Objective: The aim of this study was to evaluate the preoperative and operative characteristics and in-hospital course of patients undergoing CVS.
Methods: We conducted a prospective, multicenter cross-sectional study over a 13-month period (from July 2021 to August 2022), including consecutive patients > 18 years who underwent central CVS.
Results: A total 1515 patients were analyzed; 79% underwent elective surgery, 19% underwent urgent surgery, and 2% underwent emergency surgery. The types of surgery performed were coronary artery bypass grafting (CABG) in 46% of cases, heart valve surgery in 32%, combined surgeries in 19%, and ascending aorta surgeries in 3%. Mean age of patients was 64 ± 11 years, and 75% were male. Most (75%) surgeries used cardiopulmonary bypass (CPB); median (interquartile range, IQR) CPB time was 100 minutes (75-123) and median aortic cross- clamp time was 71 minutes (50-94). Compared with previous registries, there was a higher proportion of left main coronary artery disease, heart valve surgeries and combined procedures, in addition to the inclusion of aorta surgeries. The most common complications were atrial fibrillation (24%), low cardiac output syndrome (16%), renal failure (13%), and postoperative bleeding (10%). Overall mortality was 9.1%.
Conclusion: The ARGEN-CCV registry included more complex cases than previous registries. Overall in-hospital mortality was high, probably due to the level of complexity and the atypical context of the COVID-19 pandemic.

Key words: Cardiovascular surgery - Registry - Surgical outcomes

RESUMEN

Introducción: La cirugía cardiovascular (CCV) es una herramienta fundamental en el tratamiento de las enfermedades cardíacas y su práctica ha experimentado cambios en los últimos años. En nuestro medio tenemos registros sobre CCV pero de hace más de 10 años. Por ese motivo surgió la necesidad de realizar un nuevo estudio para conocer la realidad de la CCV en Argentina.
Objetivo: El objetivo de este trabajo fue evaluar las características prequirúrgicas, quirúrgicas y la evolución intrahospitalaria de pacientes que fueron sometidos a una CCV .
Material y métodos: Se realizó un estudio multicéntrico de corte transversal de 13 meses de duración (julio 2021 a agosto 2022) prospectivo, en que pacientes mayores de 18 años que se realizaron una CCV central fueron incluidos de manera consecutiva. Quedaron excluidas del registro las cirugías para reparación de cardiopatías congénitas y procedimientos periféricos, como así los casos de cirugías cardiovasculares debidas a trauma.
Resultados: Se analizaron 1515 pacientes de los cuales el 79 % recibieron cirugía programada, 19 % fueron de urgencia y 2 % de emergencia. Los tipos de cirugías practicadas fueron cirugía de revascularización miocárdica (CRM) 46 %, cirugía valvular 32 %, cirugías combinadas 19 % y un 3 % de cirugías de aorta ascendente. La edad media de los pacientes fue de 64 ± 11 años y el 75 % de los pacientes fue de género masculino. La mayoría (75 %) de las cirugías utilizaron circulación extracorpórea (CEC), la mediana (rango intercuartilo, RIC) del tiempo de CEC fue de 100 minutos (75-123) y la mediana del tiempo de clampeo aórtico fue de 71 minutos (50-94). En comparación con registros previos hubo mayor proporción de lesión de tronco de coronaria izquierda, cirugías valvulares y combinadas, y fueron incluidas cirugías de aorta. Las complicaciones más frecuentes fueron la necesidad de vasoactivos (72 %), la fibrilación auricular (24 %), el síndrome de bajo gasto cardíaco (16 %), la insuficiencia renal (13 %) y la hemorragia posoperatoria (10 %). La mortalidad global fue del 9,1 %.
Conclusión: En el registro ARGEN CCV se observaron casos más complejos que en los registros previos .La mortalidad general intrahospitalaria fue elevada, probablemente por el nivel de complejidad y el contexto atípico de la pandemia de COVID-19.

Palabras clave: Cirugía cardiovascular - Registro - Resultados quirùrgicos

Rev Argent Cardiol 2025;93:325-332. https://doi.org/10.7775/rac.v93.i5.20940

Received: 05/22/2025 – *Accepted:* 08/21/2025

Correspondence: Esteban Romeo. E-mail: romeo.esteban@gmail.com

[1] Research Area of the Argentine Society of Cardiology
[2] Argentine College of Cardiovascular Surgeons

INTRODUCTION

Cardiac surgery is an area of medicine that has undergone remarkable development over recent decades, and Argentina is no exception. Cardiovascular surgery (CVS) and its postoperative care hold an outstanding position in clinical cardiology. This is because advances in surgical techniques, whether exclusively surgical, hybrid techniques (using percutaneous and surgical approaches), or minimally invasive procedures, require detailed knowledge of the processes involved in proper postoperative recovery. (1,2)

Over the last decade, percutaneous techniques have experienced significant progress, particularly in the field of aortic stenosis, opening the door to treating other conditions in a similar manner, which indicates a promising future. (3-5) Despite this, CVS is the procedure of choice in many clinical situations and the only possible approach in different clinical scenarios. Based on this, the characteristics of patients eligible for surgical techniques, the maneuvers, and the materials used vary over the years, and clinical registries are conducive to publicizing and analyzing these aspects. Furthermore, they help us understand the outcomes of interventions in real-life settings, as clinical trials often lack representativeness of the population, and their applicability to different populations is therefore unknown. Another important point is that results may vary within the same city, within a country, and, of course, in relation to other countries. Another important aspect is that the results may vary within the same city, within a country, and, obviously, in relation to other countries. Therefore, it is essential to have local records to understand the reality of cardiovascular surgery in areas of particular interest, such as in-hospital outcomes and mortality, among others, which permit comparison with data published in previous and international registries. Finally, they enable the development of risk prediction scores such as the EuroSCORE and the Society of Thoracic Surgeons (STS) score. (6,7) Argentina followed suit with the development of the ArgenSCORE, which was made possible by the history of national CVS records. (8,9)

It is well known that percutaneous coronary interventions have gained ground as a revascularization technique. For this reason, patients who are not candidates for these procedures, either due to their anatomical characteristics or difficulty of approach, currently undergo surgery in a more complex context. This advancement raises questions about the contemporary characteristics of patients undergoing CVS surgery and their outcomes. (10)

It is important to highlight that the registry period encompassed part of the SARS-CoV-2 pandemic, including the conclusion of the lockdown phase.

In this context, the Argentine Society of Cardiology, in conjunction with the Argentine College of Cardiovascular Surgeons, conducted a new study on cardiovascular surgery with the aim of determining the characteristics of patients undergoing central cardiovascular surgery and their in-hospital outcome based on the National Registry of Cardiovascular Surgery in Argentina (ARGEN-CCV).

Objectives

The aim of this study was to evaluate the preoperative and operative characteristics and in-hospital course of patients who underwent central cardiovascular surgery.

METHODS

The Argentine National Registry of Cardiovascular Surgery (ARGEN-CCV) was a cross-sectional, multicenter study conducted over 13 months, from July 2021 to August 2022. Patients were recruited from 48 public and private centers. Institutions with central cardiovascular surgery capabilities were invited to voluntarily participate. Data were collected on the REDCap platform, and the audit was performed using pre-established parameters on the platform to evaluate consistency and avoid missing data. No financial compensation was provided to the participating centers or researchers. The inclusion criteria were patients > 18 years admitted to the institution on an elective, urgent, or emergency basis for central cardiovascular surgery. These included coronary artery bypass grafting (CABG) surgery, heart valve surgery, combined surgery, and ascending aorta surgery. Surgeries for congenital heart defects, peripheral vascular surgery, and surgery due to trauma were excluded from the registry. Preoperative, operative, and postoperative data were obtained during the hospitalization period. The study was registered at ClinicalTrials.gov NCT0519916.

Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard deviation, and those with non-Gaussian distribution as median and interquartile range (IQR 25-75). Qualitative variables were expressed as percentages. Comparisons between groups were performed using Student's t-test or Wilcoxon test according to the distribution for continuous data, and 2x2 tables were used, as well as the chi-square test with Yates's correction for continuity for categorical variables. A p-value < 0.05 was considered statistically significant. The analysis was performed in R.

Ethical considerations

The ARGEN-CCV registry protocol was approved by the ethics committee of the Argentine Society of Cardiology.

RESULTS

A total of 1515 patients were enrolled in the registry, of whom 1202 underwent elective surgery (79%), 282 (19%) underwent urgent surgery, and 27 (2%) underwent emergency surgery. The types of surgeries performed were CABG in 700 cases (46%), heart valve surgery in 480 (32%), aorta surgery in 48 (3%), and combined procedures in 287 (19%). The mean age of the patients was 64 ± 11 years, and 75% were male. The risk factors included 77% of patients with hypertension, 29% with diabetes mellitus, 54% with dyslipidemia, and 16% who were active smokers. The body mass index was 28 kg/m² (IQR 23–33). In terms of clinical history, 13% had a previous heart attack, 15%

had heart failure, and 16% had moderate to severe ventricular dysfunction. Regarding prior CVS, 5% of patients had a history of CABG surgery, and 6% reported heart valve surgery. Regarding the assessment of surgical risk, the EuroScore predicted a median mortality of 1.5% (IQR 0.9–2.9), while the ArgenScore predicted a median mortality of 2.33% (IQR 1.1–4.7) (Table 1).

Cardiopulmonary bypass (CPB) was used in 75% of cases (Table 2). Median CPB time was 100 minutes (IQR 75-123) and median aortic cross-clamp time was 71 minutes (IQR 50-94).

The median duration of mechanical ventilation was 4 days, which had an inevitable impact on the median length of hospital stay (8 days; IQR 6-13). There were no significant differences in the outcomes of patients extubated within the first 6 hours compared to those who remained on mechanical ventilation beyond that time.

The most common postoperative complications found were atrial fibrillation (24%), low cardiac output syndrome (16%), renal failure (13%) (of which about one-third required dialysis), and postoperative bleeding (10%), most commonly due to clinical conditions. (See supplementary material)

Overall mortality was 9.1% (Table 3). Mortality by type of surgery was 6.8% after CABG, 7.9% after heart valve surgery, 30.4% after ascending aorta interventions, and 13% after combined procedures. Finally, when mortality was explored according to the urgency of the intervention, mortality rates for elective, urgent and emergency procedures were 7.9%, 11.3%, and 38.5%, respectively ($p<0.001$) (Table 4).

DISCUSSION

The ARGEN-CCV registry presents the results of cardiovascular surgery in Argentina after more than a decade since the last available data on the subject.

Our previous local registries were CONAREC III, which collected data of 1293 patients from 41 healthcare centers in Argentina in 1993, ESMUCICA, which recruited 2125 patients from four institutions in Buenos Aires between 1996 and 1997, and CONAREC XVI, which was carried out in 49 centers and recorded 2553 cases between 2007 and 2008. (11-13)

The distinctive feature of this project was that it took place during the unexpected SARS-CoV-2 pandemic. IIt should be noted that conducting the study during this period was not the objective; it was merely a coincidence. Therefore, the information was not collected for the purpose of analyzing the results of CVS in this particular context.

Nevertheless, 85 centers from 17 provinces were registered, though only about half actively participated by including at least one case (see supplementary material). In this study, nearly 80% of cases were elective surgeries. The remaining cases were urgent or emergency surgeries due to critical cardiac conditions.

Table 1. General preoperative characteristics

	n= 1515
Age, mean (SD)	64 (±11,4)
Male gender, %	74,6
Hypertension, %	77,2
Diabetes mellitus, %	29,3
Dyslipidemia, %	54,4
Current smoking, %	16,1
Chronic stable angina, %	11,7
History of myocardial infarction, %	12,7
History of heart failure, %	15,1
History of percutaneous coronary intervention, %	12,2
History of CABG surgery	4,6
History of heart valve surgery, %	5,6
History of stroke, %	4,8
History of moderate-severe COPD, %	8
History of peripheral vascular disease, %	9,5
History of left ventricular dysfunction, %	16,3
Mortality calculated by EuroSCORE, median (IQR)	1,5 (0,9-2,9)
Mortality calculated by ArgenSCORE, median (IQR)	2,33 (1,1-4,7)

CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SD: standard deviation

Compared to previous records, the prevalence of diabetes mellitus has steadily increased, which is consistent with other sources, such as the national household survey. (14-16) In addition, we have observed a high percentage of patients undergoing CABG with left main coronary artery disease (38.1%), as previously published. (17) This observation contrasts with rates of 28.4% in the CONAREC XVI registry, 19% in the ESMUCICA registry, and 17.1% in the CONAREC III registry.

When the operative characteristics were analyzed, the procedures requiring CPB exhibited shorter times compared to those reported by previous registries. In the ARGEN-CCV registry, the CPB time was 90 minutes (IQR 70-110 minutes) during CABG surgery, compared to 98 minutes in the ESMUCICA registry and 96 minutes in the CONAREC III registry. A similar finding was observed with heart valve surgeries. (11-13)

A high rate of vasoactive drug use was observed during postoperative care, and one-third of patients entered the recovery room extubated. This latter data is available for the first time in national registries.

Atrial fibrillation was the most common postoperative complication. The incidence of low cardiac output syndrome was slightly lower than that reported in the CONAREC XVI registry, and renal failure remained at a similar incidence as in previous reports, with approximately 30% requiring dialysis. Postoperative bleeding requiring transfusions occurred in around 10% of patients, which appears to remain at historical levels.

Table 2. Operative data

	n= 1515
Need for surgery, % -Elective -Urgent -Emergency	 79,5 18,7 1,8
Type of surgery, % -CABG surgery -Valve surgery -Aortic surgery -Combined surgery	 46,2 31,7 3,2 18,9
Use of CPB, %	74,9
CPB time, median (IQR)	100 (75-123)
Aortic cross-clamp time, median (IQR)	71 (50-94)

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IQR: interquartile range

Table 3. Postoperative complications

	n= 1515
Intubation duration in days, median (IQR)	4 (2-10)
Atrial fibrillation, %	24,0
Postoperative myocardial infarction, %	3,3
Low output syndrome, %	15,7
Renal failure , %	13,4
Bleeding, % -Medical bleeding -Surgical bleeding	10,6 62,7 37,3
Mediastinitis, %	0,9
Sepsis, %	6,0
Stroke, %	3,3
Length of hospital stay, median (IQR)	8 (6-13)
Mortality, %	9,1

IQR: interquartile range

Table 4. Mortality according to type and necessity of surgery

	Elective	Urgent	Emergency	p-value
Type of surgery, %				
-CABG	40,8	70,6	33,3	
-Heart valve	36,4	14,2	7,4	
-Aorta	2,5	2,5	40,7	
-Combined	20,5	13,5	18,5	
Mortality, %	7.9	11.3	38.5	<0.001

CABG: coronary artery bypass graft

Table 5. Comparison of Argentine cardiovascular surgery registries

	Argen-CCV n = 1515 (2021-22)	CONAREC XVI n = 2553 (2007-08)	ESMUCICA n = 2125 (1996-97)	CONAREC III n = 1293 (1992-93)
Age, mean (SD)	64 (±11)	63 (±11)	-	
Male, %	1130 (74,6)	1912 (74,9)	1558 (73)	1045 (80,8)
Hypertension, n (%)	1168 (77,2)	1948 (76,3)		754 (58,3)
Smoking habits, n (%)	235(15,5)	987 (38,3)		720 (55,7)
Dyslipidemia, n (%)	821 (54,4)	1443 (56,5)		744 (57,5)
Diabetes, n (%)	442 (29,3)	635 (24,9)	354 (16,6)	272 (21)
History of CHF, n (%)	229 (15,1)	453 (17)		64 (5)
COPD, n (%)	124 (8)	240 (9,4)		
CABG surgery, n (%)	700 (46,2)	1465 (57,4)	1493 (70)	1293 (100)
Heart valve surgery, n (%)	480 (31,7)	528 (20,7)	395 (18,6)	
Combined surgery, n (%)	287 (18,9)	312 (12,2)	176 (8,3)	
Moderate/severe left ventricular dysfunction, n (%)	246 (16,3)	607 (23,8)	275 (13)	541 (42)
Overall mortality, n (%)	134 (9,1)	196 (7,7)	110 (5,1)	152 (11,7)

CABG: coronary artery bypass grafting; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease

The mortality rate by type of surgery was 6.8% for CABG (previously published), while aorta surgeries had the highest mortality rate at 30.4%. This is the first national registry to report on these types of procedures, which are characterized by their technical complexity. Most of these surgeries were performed in an emergency context, which could explain the high mortality rate. Heart valve procedures had a mortality rate of 7.9%, while combined surgeries had a rate of 13%. Compared with previous studies, our registry included a higher proportion of heart valve and combined surgeries (Table 5). In this context, the overall mortality rate was 9.1%. This figure is higher than that of the last registry, the CONAREC XVI, conducted more than ten years ago. Several factors should be discussed in detail. As previously noted, patients in the ARGEN-CCV registry had a higher prevalence of left main coronary artery disease, diabetes, heart valve surgeries, and combined procedures. Additionally, the registry was conducted in the unique context of the COVID-19 pandemic. Specifically, part of the study population entered the registry during the period in which mandatory preventive social distancing was in effect, as decreed by the national executive branch. This had direct consequences for social behavior and affected the dynamics of the healthcare system, as documented in international and local reports (18–23). For this reason, it is difficult to assert that the characteristics of patients currently undergoing cardiac surgery are more complex than those in previous studies, because only the most complex cases could be operated on during the pandemic. A different sampling strategy might have mitigated this potential selection bias. In this registry, the cases that proceeded to surgery were more complex and were treated and recovered under atypical healthcare conditions. We cannot rule out that these factors contributed to the observed mortality.

Two of the most commonly used perioperative scores, the EuroSCORE and the ArgenSCORE, were measured in the study population. While this study

was not designed to validate these scores, the predicted mortality was clearly lower than the observed mortality. However, it has been noted in the literature that the EuroSCORE may underestimate mortality in populations other than the one for which it was developed. (24, 25).

One weakness of this registry was the lack of sampling planning in line with the circumstances of the pandemic. As previously stated, the objective was not to analyze cardiac surgery performance during the pandemic. Despite the stress on the healthcare system, the participating centers made an extra effort to contribute. However, even with voluntary participation, data collection could have been structured differently when considering these variables. As in previously published registries, variability among participating centers must also be acknowledged. Consequently, it is evident that the results do not reflect the reality of all institutions. It is reasonable to assume that a greater number of participating centers would be necessary to validate the findings of this registry.

CONCLUSIONS

The ARGEN-CCV registry included more complex patients than in previous studies, with severe left main coronary artery involvement, a higher proportion of heart valve surgeries and combined procedures, and ascending aorta surgeries (not included in previous registries). The overall in-hospital mortality was high, probably due to the level of complexity already described and the atypical context of the COVID-19 pandemic The ARGEN-CCV registry included more complex patients than in previous studies, with more frequent left main coronary artery involvement, a higher proportion of heart valve surgeries and combined procedures, and ascending aorta surgeries (not included in previous registries). The overall in-hospital mortality was high, probably due to the level of complexity already described and the atypical context of the COVID-19 pandemic.

Conflicts of interest

None declared.

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

Acknowledgments

The authors thank all the participating centers that contributed to the development of this registry during the COVID-19 pandemic.

REFERENCES

1. Chong JL, Pillai R, Fisher A, Grebenik C, Sinclair M, Westaby S. Cardiac surgery: moving away from intensive care. Heart 1992;68:430-3. https://doi.org/10.1136/hrt.68.10.430

2. Westaby S, Pillai R, Parry A, O'Regan D, Giannopoulos N, Grebenik K, et al. Does modern cardiac surgery require conventional intensive care? Eur J Cardiothorac Surg 1993;7:313-8. https://doi.org/10.1016/1010-7940(93)90173-9

3. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32:198-204. https://doi.org/10.1093/eurheartj/ehq339

4. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020;76:2492-16. https://doi.org/10.1016/j.jacc.2020.09.595

5. Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. Eur Hear J 2010;31:1382-89. https://doi.org/10.1093/eurheartj/ehq051

6. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41:734-44. https://doi.org/10.1093/ejcts/ezs043

7. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC Jr, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. Ann Thorac Surg 2018;105:1411-8. https://doi.org/10.1016/j.athoracsur.2018.03.002

8. Carosella VC, Navia JL, Al-Ruzzeh S, Grancelli H, Rodriguez W, Cardenas C, et al. The first Latin-American risk stratification system for cardiac surgery: can be used as a graphic pocket-card score. Interact CardioVasc Thorac Surg 2009;9:203-8. https://doi.org/10.1510/icvts.2008.199083

9. Carosella V, Grancelli H, Stutzbach P, Sigal A, Lerech E, Morcos L, y cols. Estimación del riesgo en cirugía cardiaca en el "Mundo Real": ArgenSCORE ajustado al centro. Rev Argent Cardiol 2021;89:3-12. https://doi.org/10.7775/rac.v89.i1.19185

10. Harris WO, Mock MB, Orszulak TA, Schaff HV, Holmes DR. Use of Coronary Artery Bypass Surgical Procedure and Coronary Angioplasty in Treatment of Coronary Artery Disease: Changes During a 10-Year Period at Mayo Clinic Rochester. Mayo Clinic Proceedings 1996;71:927-35. https://doi.org/10.1016/S0025-6196(11)63765-8

11. Ciruzzi M, Henquin R, Aranda G, Bozovich G, Heredia P, Rodriguez R, y cols. CONAREC III. Evolución de los pacientes sometidos a cirugía coronaria. Esudio multicéntrico. Rev Argent Cardiol 1996;64:91-100.

12. Investigadores Esmucica. Estudio Multicéntrico de cirugía cardíaca. Pacientes coronarios. Rev Argent Cardiol 1999;5:605-16.

13. Lowenstein Hber D, Guardiani F, Pieroni P, Pfister L, Carrizo L, Villegas E, y cols. Realidad de la cirugía cardíaca en la República Argentina. Registro CONAREC XVI. Rev Argent Cardiol 2010;78:228-37.

14. Ferrante D, Linetzky B, Konfino J, King Ana, Virgolini M, Lapiur S. Encuesta Nacional de Factores de Riesgo 2009: Epidemia de Enfermedad Crónicas no Transmisibles en Argentina. Estudio de Corte Transversal. Rev Argent Salud Pública. 2011;2:34-41.

15. Galante M, Konfino J, Ondarsuhu D, Goldberg L, O'Donnell V, Begue C, y cols. Principales Resultados de la Tercera Encuesta de Nacional de Factores de Riesgo de EnfermedadesTransmisibles en Argentina. Rev Argent Salud Pública 2015;6:22-9.

16. Instituto Nacional de Estadísticas y Censos. 2019. 4 Encuesta Nacional de Factores de Riesgo. Resultados Definitivos. "https://www.indec.gob.ar/ftp/cuadros/publicaciones/enfr_2018_resultados_definitivos.pdf"

17. Alustiza W, Carli N, Romeo E, Ferrari J, Lescano A, Cáceres L, y cols. Cirugía de revascularización miocárdica en Argentina. Subanálisis del Registro ARGEN-CCV. Rev Argent Cardiol 2024;92:361-66. https://doi.org/10.7775/rac.es.v92.i5.20825

18. Fernández R. Occupancy of the Departments of Intensive Care Medicine in Catalonia (Spain): A Prospective, Analytical Cohort Study. Med Intensiva 2015;39:537-42. https://doi.org/10.1016/j.medin.2014.11.002

19. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, et al; Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020;41:2083-8. https://doi.org/10.1093/eurheartj/ehaa409

20. Abdelaziz HK, Abdelrahman A, Nabi A, Debski M, Mentias A, Choudhury T, et al. Impact of covid-19 pandemic on patients with ST-segment elevation myocardial infarction: insights from a British cardiac center. Am Heart J 2020;226:45-8. https://doi.org/10.1016/j.ahj.2020.04.022

21. Wong LE, Hawkins JE, Langness S, Murrell KL, Iris P, Sammann

A, et al. Where are all the patients? Addressing covid-19 fear to encourage sick patients to seek emergency care. NEJM Catalyst 2020
22. D´Imperio H, Gagliardi J, Zoni R, Charask A, Castillo Costa Y, Marturano MP, y cols. Resultados de la Encuesta COVID-19. Impacto en la atención cardiovascular del Registro Nacional de Infarto ARGEN IAM-ST. Rev Argent Cardiol 2020;88:222–30. https://doi.org/10.7775/rac.es.v88.i4.18658
23. D'Imperio H, Gagliardi J, Charask A, Zoni C, Castillo Costa Y, Quiroga W. Internación por Infarto Agudo de Miocardio con Elevación del Segmento ST Durante el Aislamiento Obligatorio: Reporte del Registro Continuo de Infarto ARGEN IAM-ST. Rev Arg Med 2020;8:127-30. https://doi.org/10.7775/rac.es.v88.i4.18658
24. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13. https://doi.org/10.1016/S1010-7940(99)00134-7
25. Rodríguez-Chávez LL, Figueroa-Solano J, Muñoz-Consuegra CE, Avila-Vanzzini N, Kuri-Alfaro J. EuroSCORE subestima el riesgo de mortalidad en cirugía cardiaca valvular de población mexicana [EuroSCORE underestimate the mortality risk in cardiac valve surgery of Mexican population]. Arch Cardiol Mex 2017;87:18-25. https://doi.org/10.1016/j.acmx.2016.07.001

SUPPLEMENTARY MATERIAL. Complications

Definitions	
Postoperative bleeding	500 mL in the first hour or > 400 mL in the second hour or > 300 mL in the third hour or > 200 mL in the fourth hour or > 100 mL in the fifth hour
Right ventricular dysfunction	Persistent hypotension, elevated (right atrium) ventricular filling pressures, low cardiac output requiring pharmacological and possibly mechanical intervention (TAPSE <17 mm or visually assessed RV dysfunction on echocardiography)
Low cardiac output syndrome	Systolic blood pressure < 90 mmHg, pale and cold skin, poor capillary refill, clouding of consciousness and oliguria, cardiac index < 2.2 L/min/m^2, pulmonary capillary pressure > 18 mmHg requiring inotropic agents and/or intra-aortic balloon pump (IABP)
Renal failure	Increase in creatinine levels > 50% of baseline value and/or requirement for hemodialysis
Stroke	Focal and/or diffuse brain injury confirmed by clinical findings and/or computed tomography scan with motor or sensory deficits at patient discharge
Psychiatric disorders	Any of the following: delirium, hallucinations, psychomotor agitation
Respiratory distress syndrome	Infiltrate in 4 quadrants - wedge < 18 mm Hg - PA/FI ratio < 200
Sepsis	Suspected or documented infection with target organ dysfunction and at least two of the following criteria: temperature > 38 °C°C or < 36 °C, white blood cell count greater than 12,000 uL or less than 4000 uL, tachycardia, tachypnea > 30 bpm, altered mental status, positive culture from primary site of infection, mean arterial blood pressure less than 70 mm Hg for at least two hours, poor distal perfusion

Participanting Ccnters

CEMIC, Autonomous City of Buenos Aires
Centro Gallego, Autonomous City of Buenos Aires
Clínica Bazterrica, Autonomous City of Buenos Aires
Clínica Colón, Mar del Plata, Province of Buenos Aires
Clínica Pasteur, Province of Neuquén
Clínica San Jorge, Province of Tierra del Fuego
Clínica Santa Clara, Province of Mendoza
Clínica Santa Isabel, Autonomous City of Buenos Aires
Clínica Zabala, Autonomous City of Buenos Aires
Fundación Favaloro, Autonomous City of Buenos Aires
Fundación para la Salud / Sanatorio San Roque de Salta / Hospital Privado Santa Clara de Asís, Province of Salta
HIEAYC San Juan de Dios, La Plata, Autonomous City of Buenos Aires
Hospital Alemán, Autonomous City of Buenos Aires
Hospital Británico, Autonomous City of Buenos Aires
Hospital Churruca, Autonomous City of Buenos Aires
Hospital Cosme Argerich, Autonomous City of Buenos Aires
Hospital de Clínicas José de San Martín, Autonomous City of Buenos Aires
Hospital Dr. Alberto Duhau, Autonomous City of Buenos Aires
Hospital Dr. César Milstein, Autonomous City of Buenos Aires
Hospital Italiano de Mendoza, Province of Mendoza
Hospital Privado de Mar del Plata, Mar del Plata, Autonomous City of Buenos Aires
Hospital Público descentralizado Dr. Guillermo Rawson, Province of San Juan
Hospital Santojanni, Autonomous City of Buenos Aires
Hospital Sirio Libanés, Autonomous City of Buenos Aires
Hospital Universitario Austral, Pilar, Autonomous City of Buenos Aires
Instituto Cardiovascular de San Luis, Province of San Luis
Instituto de Cardiología de Corrientes, Province of Corrientes
Instituto de Cardiología de Rosario "Dr. Luis González Sabathie", Rosario, Province of Santa Fe
Instituto Modelo de Cardiología Privado, Province of Córdoba
Leben Salud, Cipolletti, Province of Rio Negro
Policlínico Bancario, Autonomous City of Buenos Aires
Sanatorio Adventista del Plata, Province of Entre Ríos
Sanatorio Allende, Province of Córdoba
Sanatorio Anchorena San Martín, Autonomous City of Buenos Aires
Sanatorio Británico, Rosario, Province of Santa Fe
Sanatorio de la Cañada, Province of Córdoba
Sanatorio de la Trinidad Mitre,
Sanatorio de la Trinidad Quilmes, Province of Buenos Aires
Sanatorio de la Trinidad Ramos Mejía, Autonomous City of Buenos Aires
Sanatorio del Salvador, Province of Córdoba
Sanatorio Delta, Province of Santa Fe
Sanatorio Güemes ACE, Province of Chaco
Sanatorio Juan XXIII, Gral. Roca, Province of Río Negro
Sanatorio Dr. Julio Méndez, Avellaneda, Autonomous City of Buenos Aires
Sanatorio Pasteur, Province of Catamarca
Sanatorio Sagrado Corazón, Autonomous City of Buenos Aires
Sanatorio San Martín, Venado Tuerto, Province of Santa Fe

ORIGINAL ARTICLE

Ventricular Arrhythmia Alerts and Survival in Patients with Implantable Defibrillators under Remote Monitoring

Alertas de arritmias ventriculares y supervivencia en pacientes con desfibriladores implantables bajo monitorización remota

JUAN P GUZMAN[1], PEDRO DIAZ UBERTI[1], FRANCISCO TOSCANO[1], VALERIA PIAZZA[1], DAMIAN LONGO[1], FIORELLA MANCUSI[1], JUAN MANUEL VILLALBA[2], RODOLFO DANIEL LA GRECA[2, MTSAC]

ABSTRACT

Background: Patients with implantable cardioverter defibrillators (ICDs) or cardiac resynchronization therapy with defibrillator (CRT-D) can be followed-up with remote monitoring (RM), which allows the evaluation of complex and serious arrhythmias.
Objectives: The aim of this study was to evaluate the prognostic value of ventricular arrhythmia alerts on mortality in patients with implantable devices.
Methods: A retrospective cohort study was conducted in 62 patients, analyzing demographic and clinical data and RM alerts: non-sustained ventricular tachycardia (NSVT), ventricular tachycardia (VT), or ventricular fibrillation (VF)and its prognostic value for mortality.
Results: 35.5% of patients presented alerts for ventricular arrhythmias. They had worse left ventricular ejection fraction and a higher prevalence of heart failure. During follow-up, they had higher all-cause mortality (40.9% in the group with alerts vs. 7.5% in the group without alerts; p=0.003). Survival analysis confirmed that these patients had a significantly lower probability of survival (Log-Rank test, p=0.006).
Conclusion: The occurrence of alerts for ventricular arrhythmias detected by RM was a significant prognostic marker of lower survival, underscoring the value of this technology for risk stratification and clinical decision-making. A larger patient cohort and longer follow-up are needed to confirm its independent prognostic value.

Key words: Implantable Defibrillators - Cardiac Arrhythmias - Remote Monitoring - Mortality - Prognosis

RESUMEN

Introducción: Los pacientes con desfibrilador automático implantable (DAI) o terapia de resincronización cardíaca con desfibrilador (TRC-D) pueden ser seguidos con monitorización remota (MR) que permite definir la incidencia de arritmias complejas y graves.
Objetivos: Evaluar el valor pronóstico de las alertas por arritmias ventriculares en pacientes con dispositivos implantables sobre la mortalidad.
Materiales y métodos: Se realizó un estudio de cohorte retrospectivo en 62 pacientes, analizando datos demográficos, clínicos y de las alertas de MR: taquicardia ventricular no sostenida (TVNS), taquicardia ventricular (TV) o fibrilación ventricular (FV), y su valor pronóstico sobre mortalidad.
Resultados: El 35,5 % de los pacientes presentaron alertas por arritmias ventriculares. Tenían peor fracción de eyección ventricular izquierda y mayor prevalencia de insuficiencia cardíaca. En el seguimiento tuvieron mayor mortalidad por todas las causas (40,9% en el grupo con alertas vs. 7,5% en el grupo sin alertas; p=0,003). El análisis de supervivencia confirmó que estos pacientes tuvieron una probabilidad de supervivencia significativamente menor (prueba de Log-Rank, p=0,006).
Conclusión: La aparición de alertas por arritmias ventriculares detectadas por MR fue un marcador pronóstico significativo de menor supervivencia, subrayando el valor de esta tecnología para la estratificación de riesgo y la toma de decisiones clínicas.Un análisis con mayor cantidad de pacientes y seguimiento es necesario para confirmar su valor pronóstico independiente.

Palabras clave: Desfibriladores Implantables - Arritmias Cardíacas - Monitorización Remota - Mortalidad - Pronóstico

Rev Argent Cardiol 2025;93:333-339. https://doi.org/10.7775/rac.v93.i5.20938

Received: 07/14/2025 – *Accepted:* 09/28/2025

Correspondence: Juan Pablo Guzman – email: jpguzman1988@gmail.com
Financing: None

[1] Arrhythmias and Pacemakers Section, Cardiology Department, Hospital Churruca Visca, Autonomous City of Buenos Aires
Cardiology Department, Hospital Churruca Visca, Autonomous City of Buenos Aires

INTRODUCTION

Cardiac implantable electronic devices (CIEDs), such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with defibrillator (CRT-D), are a cornerstone in the treatment of patients at risk of sudden cardiac death and those with advanced heart failure. (1) These devices not only deliver life-saving therapies, but also function as sophisticated diagnostic tools that allow continuous collection of large amounts of data on the patient's heart rhythm and physiological parameters.

Over the last decade, remote monitoring (RM) has transformed the follow-up of this patient population, evolving from a complementary technology to a standard of care recommended by leading international clinical practice guidelines. (2-4) Remote monitoring enables the automatic and scheduled transmission of data from the patient's device to a monitoring center, facilitating continuous and proactive surveillance, which has consistently shown to reduce the time to detection of actionable clinical and technical events, such as atrial and ventricular arrhythmias or electrode malfunctions.(5-7) In addition, it has proved to be effective in reducing the incidence of inappropriate ICD shocks and decreasing the need for routine in-person visits, thereby optimizing clinical workflows and improving patient convenience. (8-9)

Despite these established benefits, the impact of RM on "hard" clinical outcomes, such as all-cause mortality and hospitalizations, has been an area of intense debate with heterogeneous results in the literature. While some observational studies and clinical trials have suggested an association between RM and improved survival (10-12), other large-scale randomized controlled trials and meta-analyses have reported neutral findings, failing to demonstrate a clear benefit on these primary endpoints. (13-15) This discrepancy highlights the importance of evidence generated in the "real world," which reflects routine clinical practice in patient populations that are more diverse and complex than those typically included in clinical trials.

Ventricular arrhythmias, ranging from non-sustained ventricular tachycardia (NSVT) to sustained ventricular tachycardia (VT) and ventricular fibrillation (VF), are events frequently detected by RM in patients with ICD/CRT-D. The occurrence of these arrhythmias not only triggers device therapies, but may also be a marker of progression of the underlying heart disease and an indicator of poor prognosis. (16) Therefore, understanding the incidence of these alerts and their association with long-term outcomes such as survival is of utmost clinical importance.

The aim of this study was twofold: first, to characterize demographically and clinically our cohort of patients with ICD and CRT-D followed-up with RM in a routine practice setting in Argentina; and second, to evaluate the prognostic value of ventricular arrhythmia alerts (VT, VF, or NSVT) on all-cause survival in this population.

METHODS

A descriptive, retrospective cohort study was conducted in a closed-population hospital of the Autonomous City of Buenos Aires. A database was built from the records of patients with CIEDs. For the present analysis, all patients with an ICD or CRT-D implanted between August 2018 and January 2025 and with an active RM system were selected. The exclusion criteria were: 1) patients with devices other than ICDs or CRT-Ds, 2) documented follow-up of less than 6 months, and 3) incomplete data on key variables such as the date of implantation or vital status at the end of follow-up. The final cohort who met all the criteria for analysis consisted of 62 patients.

Data were obtained from two main sources, linked through a unique patient identifier: a patient management database and a systematic record of alerts received through RM platforms.

The following baseline variables were collected: age at the time of implantation, gender, device type (ICD vs. CRT-D), history of atrial fibrillation prior to implantation, use of baseline anticoagulation, and comorbidities such as hypertension, diabetes mellitus, diagnosis of heart failure, and chronic kidney disease. Drugs such as sodium-glucose cotransporter 2 inhibitors were not analyzed, since a significant number of patients began follow-up in the cohort prior to the publication of the studies that established their use as standard of care. Dual angiotensin-nepril ysin inhibitors were also not included in the baseline analysis, as these data were not systematically collected in the retrospective database.

The date of device implantation, the date of the last check-up or death, and vital status were recorded during follow-up. Based on these dates, the follow-up time and survival time in days were calculated for each patient.

All alerts transmitted and classified by the device as NSVT, VT, or VF were analyzed. Each alert documented whether the event was symptomatic and whether it generated an unscheduled visit. The device response to the alert was categorized as "Monitor", "ATP" (anti-tachycardia pacing therapy), or "Shock." Subsequent clinical management was categorized as "Pharmacological Adjustment", "Inappropriate Shock Programming Adjustment", or other. A dichotomous variable was created to classify patients into two groups: those who had at least one of these alerts during follow-up and those who did not.

The standard baseline programming used for alerts followed the recommendations of international guidelines for reducing inappropriate therapies. (17) A VT monitoring zone was established, with a detection threshold of 340 ms (> 176 bpm) and a counter of 28 intervals for detection. In this zone, sudden onset (Onset 20%), Stability (48 ms), and morphology discriminators were programmed as active. The therapy zone (VF) was programmed with an interval of 320 ms (> 188 bpm) and a counter of 18 out of 24 intervals for detection, with ATP (Burst) therapies followed by shocks.

It should be noted that this was the baseline programming; in secondary prevention patients or after an episode, this programming could be individualized. However, these values were used as the minimum criteria for defining events.

With this programming, the 40 alerts analyzed were classified as: NSVT alerts (n=4), defined as non-sustained episodes (e.g., duration less than 28 beats) that only generated a "Monitor" alert; and VT/VF alerts (n=36), defined as sustained episodes that reached the detection counter in the therapy zone and received ATP or shock.

All 40 alerts analyzed were manually confirmed by a staff electrophysiologist to validate their ventricular origin and exclude artifacts or supraventricular tachycardias.

Statistical analysis

Descriptive statistics were used to summarize the cohort characteristics. Continuous variables were presented as mean±standard deviation (SD) or median and interquartile range and categorical variables were expressed as absolute frequencies (n) and percentages (%).

Baseline characteristics between the group of patients with alerts and those without alerts, were compared with Fisher's exact test for all categorical variables, and for the continuous variable "Age at Implantation," with a non- normal distribution, the Mann-Whitney U test was used.

For survival analysis, the event of interest was defined as all-cause mortality. The time to event was calculated from the device implantation date to the date of death or the date of the last follow-up. The Kaplan-Meier method was used to estimate and visualize survival probabilities over time for each group. The Log-Rank test was used to formally compare the survival curves.

A value of $p < 0.05$ was considered statistically significant. All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. (18) Data confidentiality was ensured by anonymizing the final database. All patients had given an informed consent at the start of remote monitoring, authorizing the use of their data for research purposes. Given the retrospective and anonymized nature of the analysis, the need for specific approval by the institutional ethics committee was waived from the study.

RESULTS

Baseline Cohort Characteristics

A total of 62 patients with ICD or CRT-D were included in the analysis. The baseline demographic and clinical characteristics of the cohort are summarized in Table 1. Mean age at implantation was 61.8 years (median 64; range 16-87). The population was predominantly male (47 patients, 75.8%). The mean follow-up time was 2.61 years (median 2.2 years; range 0.6-7.2).

Table 1. Baseline characteristics of the cohort of patients with ICD/CRT-D (N= 62)

Characteristic	Variable
Age at Implantation (years)	
- Median (IQR)	64.8 (55.8-73.8)
- Range (Min-Max)	16-87
Gender, n (%)	
- Male	47 (75.8%)
- Female	15 (24.2%)
Type of device, n (%)	
- ICD only	49 (79.0%)
- CRT-D	13 (21.0%)
Baseline Comorbidities, n (%)	
- AF Prior to Implantation	7 (11.3%)
- Baseline Anticoagulation	13 (21.0%)
- Heart Failure	41 (66.1%)
- Hypertension	53 (85.5%)
- Diabetes Mellitus	19 (30.6%)
- Chronic Kidney Disease	16 (25.8%)
LVEF (median, IQR)	30.0% (22-34)
Etiology, n (%)	
- Ischemic	19 (30.6%)
- Non-ischemic	42 (67.7%)
Functional class (NYHA), n (%)	
- NYHA I	45 (72.6%)
- NYHA II-IV	17 (27.4%)
Baseline Medication, n (%)	
- Beta-blockers	55 (88.7%)
- RAAS blockade	49 (79.0%)
- MRA	39 (62.9%)
- Amiodarone	31 (50.0%)
Follow-up time (years)	
- Median (IQR)	2.2 (1.2 – 3.6)
- Range (Min-Max)	0.6-7.2

AF: Atrial fibrillation; CRT-D: Cardiac resynchronization therapy with defibrillator; ICD: Implantable cardioverter defibrillator; IQR: interquartile range; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Heart Association; RAAS: Renin-angiotensin-aldosterone system

Incidence and Management of Ventricular Arrhythmia Alerts

During the follow-up period, 22 of the 62 patients (35.5%) presented a total of 40 alerts for ventricular arrhythmias (VT, VF, or NSVT). Of these 40 alerts, 15 (37.5%) were symptomatic and 17 (42.5%) led to an unscheduled consultation.

The device response associated with these alerts was: only monitoring in 4 cases (10%), anti-tachycardia pacing (ATP) therapy in 11 (27.5%), and shock therapy in 25 (62.5%). The documented clinical management following the alerts consisted of no change in 24 cases (60%), pharmacological adjustment in 11 (27.5%), programming adjustment in 4 (10%), and referral for ablation in 1 (2.5%). It should be noted that, of the 25 shocks, 3 (12%) were followed by reprogramming because they were considered inappropriate. Details of management according to device response are summarized in Table 2.

Comparative Subgroup Analysis

The baseline characteristics of patients who presented ventricular arrhythmia alerts (n=22) were compared with those who did not (n=40), as detailed in Table 3. There was a trend toward older age (median 67 vs.

62 years; p=0.063) and a higher prevalence of hypertension (95.5% vs. 77.5%; p=0.082) in the group with alerts. Left ventricular ejection fraction (LVEF) was significantly lower in the subgroup with alerts, and the prevalence of major heart failure (Table 3) The most relevant finding was the statistically significant association between the occurrence of ventricular alerts and higher all-cause mortality (40.9% vs. 7.5%; p=0.003), with an odds ratio of 8.54 (95% CI 2.05-41.5, p=0.003).

Survival Analysis

To assess the prognostic impact of ventricular arrhythmia alerts on all-cause mortality, a survival analysis was performed using the Kaplan-Meier method. Survival over time was compared between the group of patients who had at least one VT, VF, or NSVT alert (n=22) and the group who did not have such alerts (n=40).

Figure 1 shows the survival curves for both groups. A clear and early separation of the curves was observed, with a consistently lower probability of survival over time in the group of patients with alerts compared with the group without alerts.

The Log-Rank test confirmed that this difference in survival was highly statistically significant (p= 0.006). To adjust for heterogeneous follow-up duration (range 0.6–7.2 years), annualized mortality was calculated by group. This was markedly higher in the alert group (18.33 deaths per 100 person-years) compared with the no-alert group (2.74 deaths per 100 person-years).

Table 2. Clinical management according to device response to ventricular arrhythmia alerts (N=40 alerts)

Device Response	Pharmacological Adjustment	Programming Adjustment	Ablation	No Change	Total Alerts
Monitor	0	0	0	4	4
ATP	2	1	0	8	11
Shock	9	3*	1	12	25
Total	11	4	1	24	40

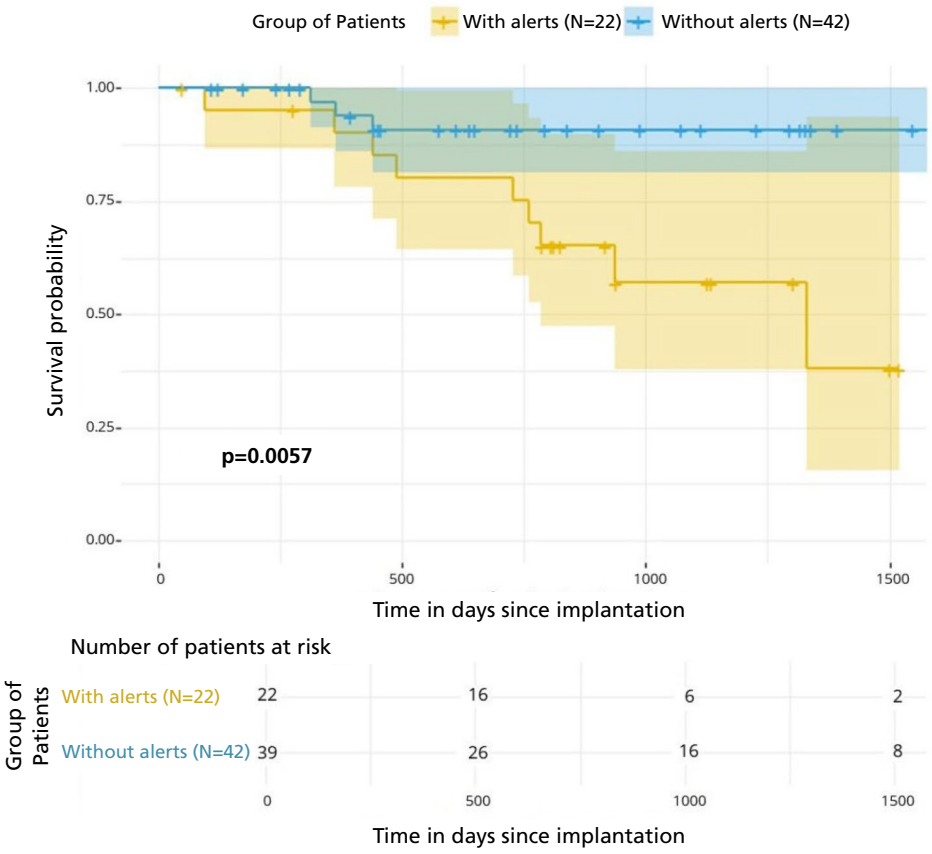
ATP: anti-tachycardia pacing
*Corresponds to "Inappropriate Shock Programming Adjustment"

Table 3. Comparison of baseline characteristics between patients with and without ventricular arrhythmia alerts

Baseline Characteristic	Patients with alerts (N=22)	Patients without alerts (N=40)	Ratio (95% CI)	p-value
Age at Implantation (years, median)	67	62	-	0.063
Male gender	86.4 %	70.0 %		0.218
CRT-D	31.8 %	15.0 %		0.191
AF prior to implantation	13.6 %	10.0 %		0.691
Heart failure	77.3 %	60.0 %		0.262
Hypertension	95.5 %	77.5 %		0.082
Diabetes Mellitus	22.7 %	35.0 %		0.395
Chronic kidney disease ( )	31.8 %	22.5 %		0.546
LVEF (median)	28.5 %	38%	-	0.003
Ischemic etiology	45.5 %	22.5 %		0.085
NYHA II-IV	54.5 %	12.5 %		0.005
Beta blockers	95.5 %	85.0 %		0.371
RAAS blockade	100 %	67.5 %		0.002
MRA	86.4 %	50.0 %		0.005
Amiodarone	50.0 %	50.0 %		1.000

AF: atrial fibrillation; CRT-D: cardiac resynchronization therapy with defibrillator; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; NYHA: New York Heart Association; RAAS: renin-angiotensin-aldosterone system

Fig. 1. Kaplan-Meier survival curve according to the presence of ventricular arrhythmia alerts



These findings indicate that the occurrence of ventricular arrhythmia alerts, detected by remote monitoring, was a strong predictor of increased mortality in our cohort of patients with ICD/CRT-D.

DISCUSSION

This real-world study characterizes a cohort of patients with ICD/CRT-D and demonstrates that the occurrence of ventricular arrhythmia alerts detected by RM is a powerful marker of poor prognosis. The main finding of our study is the statistically significant association between the presence of VT, VF, or NSVT alerts and an increase in all-cause mortality. The Kaplan-Meier survival analysis not only confirms this finding but also allows us to visualize how risk diverges over time, with a notable separation of the curves after 500 days.

This result aligns our experience with that of other studies that have identified ventricular arrhythmias as an independent risk factor for mortality in this population. (16,19) The ability of RM for the early detection of these events is therefore crucial not only for the immediate management of the arrhythmia but also for long-term risk stratification. It is important to contextualize our findings with those of large international studies, although with differences in their objectives. Unlike randomized trials such as REM-HF (9) or studies as REMOTE-CIED, (14) which reported neutral findings on the impact of RM on all-cause mortality, our study does not evaluate RM per se, but rather the prognostic value of the alerts detected. In this sense, our results are in line with those of large observational registries, such as the ALTITUDE study (11), which did suggest an association between RM and improved survival. (20) The nearly sevenfold difference in the exposure-adjusted mortality rate reinforces the Kaplan-Meier curve finding and suggests that the association between ventricular alerts and worse prognosis is robust, rather than a mere artifact of differential follow-up. (21)

The ability of RM for the early identification of high-risk patients, such as those with ventricular ar-

rhythmias, remains of fundamental clinical value. A patient presenting with these alerts may be a candidate for intensification of heart failure therapy, reevaluation of antiarrhythmic therapy, or consideration of more advanced therapies such as ablation.

We are aware of the limitations of our study. Its retrospective and observational design does not allow us to establish causality but only association, and the modest cohort size (n=62) limits statistical power.

The main limitation is the absence of multivariate analysis (e.g., Cox regression) to adjust for obvious confounding factors. As shown in the comparative analysis (Table 3), the group that presented alerts had a significantly higher baseline risk profile: a markedly lower median left ventricular ejection fraction (LVEF), a greater prevalence of ischemic etiology, a much higher proportion of symptomatic patients according to the New York Heart Association (NYHA II-IV) functional classification and a greater use of heart failure medication (such as mineralocorticoid receptor antagonists and renin-angiotensin-aldosterone system blockade).

Although a Cox analysis was considered, because of the low number of mortality events in the cohort (n=12), attempting to adjust for multiple confounders would result in overfitting of the model, generating statistically unstable and unreliable results. Therefore, the reported odds ratio for mortality probably overestimates the actual association, as it is an unadjusted calculation.

DISCUSSION

In conclusion, in our cohort, the occurrence of remote monitoring alerts for ventricular arrhythmias was a frequent finding and was significantly associated as a prognostic marker of lower survival. This finding underscores the prognostic value of information obtained through RM and its importance for risk stratification and clinical decision-making in patients with implantable defibrillators.

Conflicts of interest

None declared.

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

REFERENCES

1. Priori SG, Blomström-Lundqvist C. 2015 European Society of Car diology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. Eur Heart J 2015;36:2757-9. https://doi.org/10.1093/ eurheartj/ehv445.

2. Slotwiner D, Varma N, Akar JG, Annas G, Beardsall M, Fogel RI, et al. 2015 HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular electronic implantable devices. Heart Rhythm 2015;12:e69-e100. https://doi.org/10.1016/j.hrthm.2015.05.008

3. Ferrick AM, Raj SR, Deneke T, Kojodjojo P, Lopez-Cabanillas N, Abe H, et al. 2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on remote monitoring and management of cardiovascular implantable electronic devices. Heart Rhythm 2023;20:e3-e49. https://doi.org/10.1016/j.hrthm.2023.03.1525

4. Klersy C, De Silvestri A, Gabutti G, Regoli F, Auricchio A. A meta-analysis of remote monitoring of heart failure patients. J Am Coll Cardiol 2009;54:1683 94. https://doi.org/10.1016/j.jacc.2009.08.017

5. Varma N, Piccini JP, Snell J, Fischer A, Dalal N, Mittal S. The relationship between level of adherence to automatic wireless remote monitoring and survival in pacemaker and defibrillator pa tients. J Am Coll Cardiol 2015;65:2601-10. https://doi.org/10.1016/j.jacc.2015.04.033

6. Mabo P, Victor F, Bazin P, Ahres S, Babuty D, Da Costa A, et al. A randomized trial of long-term remote monitoring of pacemaker recipients (the COMPAS trial). Eur Heart J 2012;33:1105-11. https://doi.org/10.1093/eurheartj/ehr419

7. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH ; CONNECT Investigators The CONNECT (Clini cal Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with auto matic clinician alerts. J Am Coll Cardiol 2011;57:1181-9. https://doi.org/10.1016/j.jacc.2010.12.012

8. Guédon-Moreau L, Lacroix D, Sadoul N, Clémenty J, Kouakam C, Hermida JS, et al. A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial. Eur Heart J 2013;34:605-12. https://doi.org/10.1093/eurheartj/ehs425

9. Landolina M, Perego GB, Lunati M, Curnis A, Guenzati G, Vicentini A, et al. Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of manage ment strategies of heart failure patients with implantable defibril lators (EVATEL) trial. Circulation 2012;125:2985-92. https://doi.org/10.1161/CIRCULATIONAHA.111.088971

10. Varma N, Epstein AE, Irimpen A, Schweikert R, Love C, et al; TRUST Investigators. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Reduces Routine Office Device Follow-up (TRUST) trial. Circulation 2010;122:325-32. https://doi.org/10.1161/CIRCULATIONAHA.110.937409

11. Saxon LA, Hayes DL, Gilliam FR, et al. Long-Term Outcome After ICD and CRT Implantation and Influence of Remote Device Follow Up: the ALTITUDE survival study. Circulation 2010;122:2359-67. https://doi.org/10.1161/CIRCULATIONAHA.110.960633

12. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multi parameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet 2014;384:583-90. https://doi.org/10.1016/S0140-6736(14)61176-4

13. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J, et al. Remote-managed follow-up of implantable cardioverter-defibrillators: the REM-HF study. Eur Heart J 2017;38:3017-26. https://doi.org/10.1093/eurheartj/ehx227

14. Versteeg H, Timmermans I, Widdershoven J, Kimman GJ, Prevot S, Rauwolf T, et al. Effect of remote monitoring on patient-reported outcomes in European heart failure patients with an implantable cardioverter-defibrillator: primary results of the REMOTE-CIED randomized trial. Europace 2019;21:1360-8. https://doi.org/10.1093/europace/euz140

15. Boriani G, Da Costa A, Quesada A, Ricci RP, Favale S, Boscolo G, et al. Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial. Eur J Heart Fail 2017;19:416-25. https://doi.org/10.1002/ejhf.626

16. Powell BD, Saxon LA, Boehmer JP, Day JD, Gilliam FR 3rd, Heidenreich PA, et al. Survival after shock therapy in ICD and CRTD recipients according to rhythm shocked: the ALTITUDE Survival by Rhythm study. J Am Coll Cardiol 2013;62:1674-9. https://doi.org/10.1016/j.jacc.2013.04.083

17. Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm 2016;13:e50-86. https://doi.org/10.1016/j.hrthm.2015.11.018

18. World Medical Association. World Medical Association Declara-

tion of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA 2013;310:2191-4. https://doi.org/10.1001/jama.2013.281053

19. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med. 2008;359:1009-1017. https://doi.org/10.1056/NEJMoa071098

20. Parthiban N, Esterman A, Mahajan R, Twomey DJ, Pathak RK, Lau DH, et al. Remote Monitoring of Implantable Cardioverter-Defibrillators: A Systematic Review and Meta-Analysis of Clinical Outcomes. J Am Coll Cardiol 2015;65:2591- 600. https://doi.org/10.1016/j.jacc.2015.04.029

21. Hindricks G, Varma N, Kappenberger L, Lewalter T, Søgaard P, Guédon-Moreau L, et al. Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST). Eur Heart J 2017;38:1749-55. https:// doi.org/10.1093/eurheartj/ehx015

ORIGINAL ARTICLE

Development of the Hemodynamic Instability Index in Acute Kidney Injury and its Association with In-Hospital Mortality

Desarrollo del Índice de Inestabilidad Hemodinámica en insuficiencia renal aguda y su asociación con la mortalidad hospitalaria

ALBERTO GUEVARA TIRADO[1]

ABSTRACT

Background: Hemodynamic instability increases the risk of in-hospital mortality in patients with acute kidney injury (AKI), but there is no specific tool to quantify this risk.
Objective: The aim of the present study was to develop the Hemodynamic Instability Index in Acute Kidney Injury (IIH-AKI), analyze its association with in-hospital mortality in patients hospitalized for AKI and compare its discriminatory ability with other established prognostic scores.
Methods: We conducted an analytical study based on a secondary database derived from a clinical record of 5060 patients hospitalized with AKI. The outcome analyzed was in-hospital mortality. Principal component analysis (PCA) was used to develop the HII-AKI model based on five key parameters: pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, and oxygen saturation. The HII-AKI performance was evaluated using the area under the ROC curve (AUC-ROC), Kaplan-Meier curves, and Cox regression analysis.
Results: The HII-AKI prsented an AUC-ROC of 0.742 (95% CI 0.722-0.762; p<0.001) for predicting in-hospital mortality, surpassing the SOFA score (AUC-ROC=0.723) and the Elixhauser comorbidity index (AUC-ROC=0.465). Patients with high HII-AKI were younger and had a longer hospital stay. They also had more acidosis, lower bicarbonate levels, higher urea nitrogen levels, and lower creatinine levels. In Cox regression analysis, a high HII-AKI was associated with higher in-hospital mortality (HR=2.394; 95% CI 2.008-2.855; p<0.001).
Conclusion: A high HII-AKI is associated with greater hemodynamic instability, inflammation, metabolic disturbances, and prolonged length of hospital stay, supporting its usefulness as a prognostic marker of mortality in AKI. Its implementation in clinical practice could improve risk stratification and optimize the therapeutic decisions. Further studies are necessary for external validation.

Key words: Hemodynamic Monitoring - Acute Kidney Injury - In-Hospital Mortality - Survival Analysis - Disease Severity Index

RESUMEN

Introducción: La inestabilidad hemodinámica en la insuficiencia renal aguda (IRA) aumenta el riesgo de mortalidad hospitalaria, pero carece de una herramienta específica para cuantificarla.
Objetivo: Desarrollar el Índice de Inestabilidad Hemodinámica en Insuficiencia Renal Aguda (IIH-IRA), evaluar su asociación con la mortalidad intrahospitalaria y comparar su capacidad discriminativa frente a escalas pronósticas establecidas.
Material y métodos: Estudio analítico de datos secundarios de un registro clínico de 5060 pacientes hospitalizados con IRA. La variable de desenlace fue la mortalidad intrahospitalaria. Se aplicó análisis de componentes principales (ACP) para construir el IIH-IRA utilizando cinco parámetros clave: pulso, presión arterial sistólica, presión arterial diastólica, frecuencia respiratoria y saturación de oxígeno. Se evaluó su rendimiento con el análisis del área bajo la curva ROC (ABC ROC), curvas de Kaplan-Meier y regresión de Cox.
Resultados: El IIH-IRA mostró un ABC ROC de 0,742(IC95% 0,722-0,762;p<0,001) para predecir mortalidad hospitalaria, superando al índice SOFA (ABC ROC=0,723), y a la clasificación Elixhauser (ABC ROC=0,465). Los pacientes con IIH-IRA elevado fueron más jóvenes, con estadía hospitalaria más prolongada, más acidosis, bicarbonato más bajo, nitrógeno ureico más alto y creatinina más baja. En la regresión de Cox, un IIH-IRA elevado se asoció con mayor mortalidad hospitalaria (HR=2,394; IC95%:2,008 -2,855; p<0,001).
Conclusión: El IIH-IRA elevado se asocia con inestabilidad hemodinámica, inflamación, alteraciones metabólicas y mayor estadía hospitalaria. Ello respalda su utilidad como marcador pronóstico de mortalidad en IRA. Su aplicación podría mejorar la estratificación del riesgo y las decisiones terapéuticas.Se requieren más estudios para validar su uso externo.

Palabras clave: Monitorización Hemodinámica - Lesión Renal Aguda - Mortalidad Hospitalaria - Análisis de Supervivencia - Índice de Severidad de la Enfermedad

Rev Argent Cardiol 2025;93:340-34. https://doi.org/10.7775/rac.v93.i5.20936

Received: 03/19/2025 – *Accepted:* 08/27/2025

Correspondence: Alberto Guevara Tirado. E-mail: albertoguevara1986@gmail.com

[1] Scientific University of the South, Lima, Peru

INTRODUCTION

Acute kidney injury (AKI) is the sudden loss of renal function that causes retention of nitrogenous wastes and alterations in fluid, electrolyte, and acid–base balance. It can be differentiated into prerenal, intrarenal, and postrenal etiologies, which affect patients' outcomes. (1) Acute kidney injury is a predictor of poor prognosis in hospitalized patients, especially those in critical condition, where its association with hemodynamic instability increases the risk of multiple organ dysfunction and death. (2)

Hemodynamic instability in AKI is related to a decrease in effective intravascular volume, endothelial dysfunction, release of mediators of inflammation, and neurohormonal activation. These factors lead to tissue hypoperfusion, which perpetuates renal damage and affects other vital organs, producing a state of hemodynamic dysfunction condition is characterized by hypotension, tachycardia, and alterations in systemic vascular resistance. (3)

There are various tools for assessing the prognosis and mortality of hospitalized patients, such as the SOFA (Sequential Organ Failure Assessment) score and the Elixhauser Comorbidity Index. The SOFA score is a widely used metric in intensive care units to predict mortality based on multiple organ dysfunction. Its calculation is complex and requires the combination of numerous clinical and laboratory parameters. (4) Conversely, the Elixhauser Comorbidity Index enables the stratification of mortality risk based on patients' comorbidities. (5) However, these systems have not been specifically designed to assess hemodynamic instability in patients with AKI, which may limit their applicability in this population.

The assessment of hemodynamic instability in patients with AKI is essential to guide therapeutic interventions and stratify the risk of complications. However, there is currently no standardized index that quantifies hemodynamic instability and its association with in-hospital mortality, allowing for an objective assessment of the hemodynamic status of these patients.

The aim of the present study was to develop the Hemodynamic Instability Index in Acute Kidney Injury (HII-AKI) and analyze its association with in-hospital mortality in patients hospitalized for AKI. This novel index could allow for the early identification of patients at higher risk of death using less extensive clinical data than, for example, the SOFA score. Consequently, this will facilitate the optimization of clinical decisions and management strategies for this vulnerable population.

METHODS

Study design and population

We conducted an analytical study based on a secondary database derived from a clinical registry of patients hospitalized with AKI. (6) The original database included a total of 5,060 hospitalized adult patients; only those with complete information on in-hospital mortality were selected. Of these, 721 patients (14.2%) died during hospitalization, while 4339 (85.8%) survived. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which includes an increase in serum creatinine to 1.5 times or more than the baseline of the prior 7 days or an increase in serum creatinine by 0.3 mg/dL or more (26.5 μmol/L or more) within 48 hours. (7) This study was conducted in accordance with the RECORD (Reporting of Studies Conducted using Observational Routinely Collected Health Data) guideline, thereby ensuring transparency and methodological rigor in the management of routinely collected observational data.

Variables and measurements

The dependent variable was in-hospital mortality, defined as the death from any cause during hospitalization. This variable was recorded dichotomously (yes/no) and used as an outcome variable in the regression models to assess its association with the clinical and hemodynamic factors analyzed.

The independent variables used in this study were classified as continuous or categorical, depending on their nature and implementation in the different analyses. Continuous variables included clinical and hemodynamic parameters and laboratory test results. The following variables were analyzed: age (years), anion gap (mEq/L), serum bicarbonate (mEq/L), blood urea nitrogen (BUN, mg/dL), serum chloride (mEq/L), glomerular filtration rate (GFR, mL/min/1.73 m^2), creatinine levels on admission (mg/dL), hemoglobin (g/dL), platelet count ($\times 10^3/\mu$L), serum potassium (mEq/L), serum sodium (mEq/L), white blood cell count (WBC, $\times 10^3/\mu$L), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), pulse (beats per minute), respiratory rate (breaths per minute), oxygen saturation (%), body temperature (°F), and length of hospital stay. These variables were analyzed using descriptive statistics and were used in the construction of indices and predictive models.

Categorical variables included the presence of previous diseases and clinical conditions. These included chronic kidney disease, heart failure, lung disease, diabetes, hypertension, cancer, and liver disease and recorded as dichotomous variables (present or absent). In addition, the Elixhauser Comorbidity Index and the SOFA score were considered and categorized into specific ranges to assess disease burden and organ dysfunction.

The principal component analysis (PCA) identified the variables that contributed most to the clinical variability of acute kidney injury. The principal component analysis (PCA) identified the variables that contributed most to the clinical variability of acute kidney injury. These included age, serum bicarbonate, BUN, serum chloride, GFR, hemoglobin, platelet count, serum potassium, serum sodium, WBC, SBP, DBP, pulse, respiratory rate, oxygen saturation, temperature, length of hospital stay, and creatinine levels at different times prior to hospitalization.

The Hemodynamic Instability Index in Acute Kidney Injury (HII-AKI) was constructed using five key variables: pulse, SBP, DBP, respiratory rate, and oxygen saturation. The index was then calculated using a specific formula, with an adjustment made to avoid negative values. Then, the clinical parameters were analyzed according to the HII-AKI and their association with in-hospital mortality using the Kaplan-Meier method and Cox regression analysis, which included variables such as HII-AKI, SOFA score, Elixhauser Comorbidity Index, creatinine level on admission, anion gap,

serum bicarbonate, BUN, serum chloride, GFR, hemoglobin, platelet count, serum potassium, serum sodium, WBC, and blood temperature. These variables were used in regression models to evaluate their association with in-hospital mortality and the relative risk of adverse events in patients with acute kidney injury.

The cohort included 51.5% of men (n = 2607) and 48.5% of women (n = 2453). Given the absence of statistically significant differences in in-hospital mortality based on sex ($p > 0.05$), this variable was not incorporated as a covariate in the multivariate models. However, it was maintained in the description of the study population for the purpose of reporting sex-disaggregated data.

Statistical analysis

Qualitative variables are presented as percentages and were compared using the chi-square test or Fisher's test, as appropriate. Quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate and were compared using the t-test for normally distributed data and the Mann-Whitney U test for non-normal distributions.

To explore the internal structure of clinical and hemodynamic variables, principal component analysis (PCA) was applied. Sample adequacy was evaluated using the KMO test and Bartlett's sphericity test. Components with eigenvalues >1 were identified, and the five variables with the highest factor loadings (respiratory rate, oxygen saturation, pulse, systolic blood pressure, and diastolic blood pressure) were selected to construct the Hemodynamic Instability Index in Acute Kidney Injury (HII-AKI).

The discriminatory capacity of the HII-AKI to predict in-hospital mortality was evaluated by calculating the area under the ROC curve (AUC-ROC) and its 95% confidence interval (95% CI). This performance was compared with prognostic scales and relevant clinical parameters, including the SOFA score, Elixhauser Comorbidity Index, age, GFR, anion gap, serum creatinine, and white blood cell count, in order to determine the discriminatory capacity of the HII-AKI compared to conventional indicators.

The optimal cutoff point for HII-AKI was determined in 72.20 using the Youden index (J = sensitivity + specificity - 1), using the ROC curve for in-hospital mortality as a reference. Based on this value, patients were classified into two categories: low HII-AKI (<72.20) and high HII-AKI (≥72.20). Kaplan-Meier curves were constructed stratified by the cutoff point obtained (low vs. high HII-AKI) to analyze the association between the index and in-hospital survival. The curves were then compared using the log-rank test.

Finally, a Cox proportional hazards model was applied to estimate the hazard ratio (HR) of the HII-AKI, adjusted for clinical variables and significant prognostic scales (SOFA, Elixhauser, GFR, creatinine levels, anion gap, WBC). All the analyses were performed using a specialized statistical software package (SPSS 25), considering a level of significance of 0.05.

Ethical considerations

The secondary database was uploaded by the authors to Dryad, an open-access repository (https://datadryad.org/) under a Creative Commons (CC) license, allowing unrestricted use, distribution, and reuse of the data. To ensure the privacy of participants, the data were anonymized and numerically coded, in compliance with the ethical principles established in the Declaration of Helsinki for research on human subjects. (9) This process ensures that the database can be used in future research without compromising the confidentiality of the subjects. The information is available at the following link: https://datadryad.org/stash/dataset/doi:10.5061/dryad.kh189327p#citations.

RESULTS

A total of 5060 patients hospitalized for AKI were analyzed; mean age was 68.25 ± 15.50 years and the distribution by sex was balanced (51.5% were men and 48.50% were women). The patients exhibited the following metabolic and hemodynamic abnormalities: anion gap 12.01 ± 3.87 mEq/L, serum bicarbonate 23.42 ± 4.92 mEq/L, BUN 33.24 ± 19.39 mg/dL, GFR 63.49 ± 30.21 mL/min/1.73 m^2, and creatinine levels on admission 1.34 ± 0.72 mg/dL. Mean hemoglobin levels were 10.77 ± 2.43 g/dL, platelet count 227.33 ± 115.40 $\times 10^3/\mu L$, and WBC 11.32 ± 17.23 $\times 10^3/\mu L$. Mean systolic and diastolic blood pressure were 120.57 ± 22.25 mmHg and 67.74 ± 13.04 mmHg, respectively. The comorbidities recorded included chronic renal disease (25.4%), heart failure (31.8%), lung disease (30.4%), diabetes mellitus (37.5%), and hypertension (67.9%). The median SOFA score on admission was 2 points (IQR: 1–3) and the median length of hospital stay was 7 days (IQR: 4–13), reflecting a population with a high burden of comorbidities and physiological instability (Table 1)

Principal component analysis (PCA) identified seven pathophysiological components with eigenvalues > 1, which explained 62% of the total variance, with acceptable sample adequacy (KMO = 0.591; Bartlett $p < 0.001$). The first component encompassed renal function markers (creatinine, BUN, and GFR). The second component captured respiratory and acid–base parameters (respiratory rate, oxygen saturation, and bicarbonate). The third component represented hemodynamic measures (systolic and diastolic blood pressure, and pulse pressure). The remaining components reflected metabolic and hematological axes. Based on the factor loadings of the hemodynamic axis, the five variables with the greatest direct contribution to cardiovascular instability were selected—respiratory rate, oxygen saturation, pulse, systolic blood pressure, and diastolic blood pressure—and used to construct the Hemodynamic Instability Index in Acute Kidney Injury (HII-AKI) (Table 2)

PCA identified five key variables of hemodynamic instability in acute kidney injury: respiratory rate, oxygen saturation, pulse, systolic blood pressure, and diastolic blood pressure. These variables were weighted according to their factor loadings to construct the Acute Renal Failure Hemodynamic Instability Index (AKI-HII) formula. Pulse and respiratory rate had a positive contribution, while oxygen saturation and systolic and diastolic blood pressures had a negative influence. Before adjustment, HII-AKI values ranged from -129.21 to 22.49 (mean -60.81, standard deviation 19.22). To avoid negative values and facilitate clinical interpretation, 129.21 was added to all values.

Table 1. Clinical characteristics of the total population in the database of patients hospitalized for acute kidney injury (n = 5060)

Variable	
Age (years)	68.25 ± 15.50
Men (%)	51.50 (2607)
Women (%)	48.50 (2453)
Anion gap (mEq/L)	12.01 ± 3.87
Serum bicarbonate (mEq/L)	23.42 ± 4.92
BUN (mg/dL)	33.24 ± 19.39
GFR (mL/min/1.73 m²)	63.49 ± 30.21
Creatinine (mg/dL)	1.34 ± 0.72
Hemoglobin (g/dL)	10.77 ± 2.43
Platelet count (×10³/µL)	227.33 ± 115.40
White blood cells (×10³/µL)	11.32 ± 17.23
SBP (mmHg)	120.57 ± 22.25
DBP (mmHg)	67.74 ± 13.04
Chronic kidney disease (%)	25.4 (1285)
Heart failure (%)	31.80 (1607)
Lung disease (%)	30.40 (1539)
Diabetes mellitus (%)	37.50 (1898)
Hypertension (%)	67.90 (3438)
SOFA score	2 (1–3)
Length of hospital stay (days)	7 (4–13)

BUN: blood urea nitrogen; DBP: diastolic blood pressure; GFR: glomerular filtration rate; SBP: systolic blood pressure (mmHg); SOFA: Sequential Organ Failure Assessment.
Qualitative variables are presented as % (n) and quantitative variables as mean ± SD or median (IQR)

This adjustment resulted in an adjusted index with a range of 0 to 151.70, maintaining the same standard deviation, and with an adjusted mean of 68.39

The HII-AKI demonstrated effective performance in discriminating in-hospital mortality, with an AUC-ROC of 0.742 (95% CI 0.722 - 0.762; $p < 0.001$), surpassing the performance of other scales and biomarkers evaluated. The SOFA score exhibited an AUC-ROC of 0.723 (95% CI 0.702–0.744; $p < 0.001$), with a similar though slightly lower performance while the AUC-ROC of the Elixhauser Comorbidity Index was 0.465 (95% CI 0.442–0.489; $p = 0.003$), suggesting a limited discriminatory ability. Other clinical parameters, such as anion gap (AUC-ROC = 0.658), WBC count (AUC-ROC = 0.672), and age (AUC-ROC = 0.527) showed moderate to low performance. Oxygen saturation exhibited the lowest performance, with an AUC-ROC of 0.348 (95% CI 0.323–0.374; $p < 0.001$), indicating an inverse association with in-hospital mortality.

Patients with elevated HII-AKI (≥72.20) had significant differences in multiple clinical parameters. They were younger, and median length of hospital stay was longer [10 (IQR 5-19) days vs. 6 (IQR 4-12) days; $p < 0.001$]. These patients demonstrated elevated anion gap levels, reduced bicarbonate levels, and elevated BUN, findings that reflect greater severity of metabolic acidosis. In addition, hemoglobin concentration and blood pressure were significantly lower. Heart rate and respiratory rate were also higher, as well as white blood cell count. Oxygen saturation was reduced, reflecting significant cardiovascular and respiratory instability (Table 4)

Kaplan-Meier survival analysis showed significant differences in survival between patients with high HII-AKI (≥72.2) and those with a lower index. Median survival was significantly lower in the group with high HII-AKI (46.36 vs. 81.56 days). The log rank (Mantel-Cox) test demostrated a statistically significant difference between the two groups ($p < 0.001$). In the Cox regression analysis, HII-AKI emerged as the strongest predictor of in-hospital mortality, with a hazard ratio (HR) of 2.394 (95% CI 2.008 - 2.855). Compared to other severity scales, the SOFA score also showed a significant association with mortality (HR = 1.559; 95% CI 1.308 - 1.858), although the impact was lower than that of the HII-AKI. The Elixhauser Comorbidity Index did not demonstrate a significant association with mortality (Table 5).

DISCUSSION

This study employed principal component analysis (PCA) to identify the pathophysiological axes of AKI, with seven components explaining 62% of the total variance. These components reflect the dynamic interaction between renal function, acid-base balance, electrolytes, hemodynamics, metabolism, and age. The results, supported by an acceptable sample adequacy (KMO = 0.591) and a significant Bartlett's test ($p < 0.001$), showed that the first component grouped renal variables, creatinine levels, and BUN as the primary determinants. This finding is consistent with previous evidence that positions kidney dysfunction and the retention of nitrogenous wastes as independent predictors of hospital mortality, reflecting reduced glomerular filtration that contributes to systemic toxicity. (10,11) Furthermore, components associated with respiratory function and acid-base status were identified. These components influence tissue oxygenation and the risk of multiple organ dysfunction. (12, 13)

Based on this factor structure, five key variables associated with hemodynamic instability were identified: respiratory rate, oxygen saturation, pulse, SBP and DBP, which were used to construct the HII-AKI. The reduction in SBP and DBP, along with the compensatory increase in heart rate and respiratory rate, reflects a physiological response to hypoperfusion and circulatory compromise characteristic of AKI. In this context, the HII-AKI demonstrated a strong discriminatory ability to predict in-hospital mortality (AUC-ROC = 0.742), surpassing general scales such as the

Table 2. Principal component matrix of clinical variables and laboratory test results in acute kidney injury

Variable	C1	C2	C3	C4	C5	C6	C7
Age	0.295	-0.234	0.121	-0.370	0.200	0.518	-0.232
Serum bicarbonate	-0.293	-0.470	0.221	-0.336	0.573	-0.200	-0.063
BUN	0.708	0.086	-0.018	-0.121	0.223	0.170	-0.057
Serum chloride	0.081	0.218	0.823	0.134	-0.365	0.201	0.165
Glomerular filtration rate	-0.850	0.151	-0.095	0.077	-0.116	-0.080	0.049
Hemoglobin	-0.183	-0.207	-0.177	0.338	0.222	0.290	-0.258
Platelet count	-0.138	-0.072	-0.137	0.222	0.384	0.287	0.300
Serum potassium	0.263	0.186	-0.201	-0.069	-0.036	0.326	0.605
Serum sodium	0.018	0.131	0.866	0.108	-0.003	0.195	-0.173
White blood cells	0.011	0.244	-0.062	0.034	0.223	0.331	0.242
SBP	0.036	-0.494	0.208	0.568	0.129	0.020	0.052
DBP	-0.131	-0.421	0.047	0.750	0.069	-0.061	0.060
Pulse	-0.133	0.577	-0.035	0.334	0.153	-0.169	0.054
RR	0.027	0.465	0.000	0.160	0.345	0.172	-0.219
SpO_2	-0.007	-0.432	-0.166	0.060	-0.243	0.053	0.183
Temperature	-0.075	0.369	0.217	0.101	0.379	-0.294	0.172
Days of hospitalization	0.024	0.313	0.107	-0.067	0.289	-0.286	0.057
Creatinine on admission	0.901	-0.070	0.059	0.070	0.057	-0.126	0.045
Creatinine	0.909	0.007	-0.049	0.085	-0.002	-0.140	0.020
Min. creatinine 48 hours prior	0.944	-0.056	-0.018	0.077	0.007	-0.154	0.019
Min. creatinine 7 days prior	0.938	-0.086	0.004	0.083	0.005	-0.140	0.026
Anion gap	0.265	0.431	-0.405	0.362	-0.161	0.192	-0.431
AKI duration	0.002	-0.037	0.046	0.009	-0.086	-0.182	-0.201
KMO: 0.591; Bartlett's test: $\chi^2 = 68435.935$; $p < 0.001$; Explained variance: 62% (7 components)							

AKI: acute kidney injury; BUN: blood urea nitrogen; C: principal component; DBP: diastolic blood pressure; RR: respiratory rate; SaO_2: arterial oxygen saturation; SBP: systolic blood pressure

Table 3. Development of the HII-AKI

Variable	Load	Components in the HII-AKI formula
RR	0.46	0.465 × Respiratory rate
SaO_2	-0.432	(-0.432) × Oxygen saturation
Pulse	0.577	0.577 × Pulse
SBP	-0.494	(-0.494) × Systolic blood pressure
DBP	-0.421	(-0.421) × Diastolic blood pressure
HII-AKI formula		0.577 * Pulse + (- 0.494) * SBP + (- 0.421) * DBP + 0.465 * RR - 0.432 * SaO_2
Descriptive statistics of HII-AKI before adjustment		Minimum: -129.21, Maximum: 22.49, Mean: -60.81, SD: 19.22
Adjusted HII-AKI		HII-ARI+129.21
Descriptive statistics of HII-AKI after adjustment		Minimum: 0, Maximum: 151.70, Mean: 68.39, SD: 19.22

C: principal component; DBP: diastolic blood pressure; HII-AKI: Hemodynamic Instability Index in Acute Kidney Injury; RR: respiratory rate; SaO_2: arterial oxygen saturation; SBP: systolic blood pressure

Table 4. Clinical parameters according to the Hemodynamic Instability Index in Acute Kidney Injury (HII-AKI)

Parameter	Low HII-ARI (<72.2)	High HII-ARI (≥72.2)	p
Age (years)	69.46 ± 15.10	66.45 ± 15.89	<0.001
Length of hospital stay (days)	6 (4–12)	10 (5–19)	<0.001
Creatinine levels (mg/dL)	1.36 ± 0.71	1.28 ± 0.70	<0.001
Anion gap (mEq/L)	11.50 ± 3.30	12.79 ± 4.52	<0.001
Bicarbonate levels (mEq/L)	23.91 ± 4.42	22.67 ± 5.51	<0.001
BUN (mg/dL)	32.37 ± 18.74	34.54 ± 20.27	<0.001
Chloride levels (mEq/L)	102.25 ± 5.93	102.51 ± 6.63	0.147
GFR (mL/min/1.73 m²)	61.32 ± 29.56	66.99 ± 30.79	<0.001
Hemoglobin (g/dL)	11.02 ± 2.33	10.38 ± 2.52	<0.001
Platelet count (×10³/µL)	102	102	0.002
Potassium (mEq/L)	102	102	<0.001
Sodium (mEq/L)	102	102	0.043
WBC (×10³/µL)	102	102	<0.001
SBP (mmHg)	102	102	<0.001
DBP (mmHg)	102	102	<0.001
Pulse (bpm)	102	102	<0.001
Respiratory rate (rpm)	102	102	<0.001
Oxygen saturation (%)	102	102	<0.001

BUN: blood urea nitrogen; DBP: diastolic blood pressure (mmHg); GFR: glomerular filtration rate; HII-AKI: Index of Hemodynamic Instability in Acute Kidney Injury; SBP: systolic blood pressure (mmHg); WBC: white blood cells
Quantitative variables are presented as mean ± SD or median (IQR).

Table 5. Survival analysis

Variable	HR	95% CI	p
HII-AKI	2.394	2.008 - 2.855	<0.001
SOFA score	1,559	1,308 - 1,858	<0.001
Elixhauser comorbity index	1,154	0.904 - 1.474	0.251
Creatinine on admission	0.818	0.670 - 1.000	0.050
Anion gap	1.005	0.913 - 1.107	0.919
Bicarbonate	0.920	0.836 - 1.013	0.091
BUN	1.012	1.009 - 1.015	<0.001
Chloride	0.939	0.852 - 1.034	0.201
GFR	0.996	0.991 - 1.001	0.128
Hemoglobin	1.015	0.986 - 1.046	0.306
Platelet count	0.999	0.999 - 1.000	0.099
Potassium	1.268	1.126 - 1.428	<0.001
Sodium	1.094	0.992 - 1.206	0.072
WBC	1.002	1.001 - 1.004	<0.001

BUN: blood urea nitrogen; DBP: diastolic blood pressure (mmHg); GFR: glomerular filtration rate; HII-AKI: Index of Hemodynamic Instability in Acute Kidney Injury; SBP: systolic blood pressure (mmHg); WBC: white blood cells
Quantitative variables are presented as mean ± SD or median (IQR).

SOFA score or the Elixhauser Comorbidity Index, as well as isolated parameters such as the anion gap level or white blood cell count.

Compared to the SOFA score, the HII-AKI offers significant advantages, as it is based on basic, noninvasive, and easily reproducible hemodynamic monitoring parameters, making it particularly useful in resource-limited settings. While the SOFA score assesses multiple physiological systems, the IHII-AKI focuses on cardiovascular instability, a prognostic axis that is often underestimated for AKI progression. (14,15) This specificity explains its greater discriminatory power, suggesting that it could become a practical tool for risk stratification and therapeutic prioritization within general and critical care units.

Patients with elevated IHII-AKI (≥ 72.2) presented greater metabolic and inflammatory instability, elevated anion gap level, lower bicarbonate, higher BUN, and leukocytosis, along with clear signs of cardiovascular impairment: hypotension, tachycardia, tachypnea, and hypoxemia. They also had a longer length of hospital stay and a lower mean age, which could reflect more aggressive forms of hemodynamic dysfunction in young patients. These results are consistent with studies that have associated early circulatory instability with adverse outcomes and mortality in AKI. (16-18) By integrating these objective variables, the HII-AKI quantitatively synthesizes the impact of hemodynamic imbalance on prognosis, providing a clinical tool that can be immediately applied and validated in different healthcare settings.

Likewise, Kaplan–Meier survival analysis showed that patients with elevated HII-AKI had a lower probability of in-hospital survival, a difference that was statistically significant. In accordance with these findings, the Cox proportional hazards model revealed that a high HII-AKI was associated with an elevated risk of in-hospital mortality, even after adjusting for clinical variables and prognostic scales such as the SOFA score, the Elixhauser Comorbidity Index, and GFR, confirming the independent value of the tool as a prognostic predictor. This finding reinforces the role of the HII-AKI as a prognostic marker and suggests that acute cardiovascular impairment plays a central role in the progression and mortality associated with AKI, consistent with the mechanisms of systemic hypoperfusion and dysregulated inflammation described in recent literature. (19, 20)

The HII-AKI could have relevant implications for the clinical management of patients with acute kidney injury. By integrating simple hemodynamic parameters, this index could contribute to estimating the risk of in-hospital mortality and the early identification of patients with a higher probability of adverse outcomes. It could also facilitate more accurate risk stratification and guide monitoring or interventions according to individual clinical profiles. The use of this tool in intensive care units could help prioritize the allocation of resources to cases requiring close monitoring or adjustments in hemodynamic support. In addition, its prospective use could facilitate the evaluation of the clinical course and therapeutic response in real-time settings. Finally, the HII-AKI has the potential to serve as a valuable research instrument in examining the association between hemodynamic instability and clinical outcomes in acute kidney injury. However, external validation is necessary before its implementation in routine clinical practice.

Among the limitations of this study, despite the amount of data available, the retrospective analysis of a hospital cohort could restrict the generalizability of the findings to other settings. Additionally, while PCA enabled the identification of key pathophysiological axes, the selection of variables and the methodology may influence the interpretation of results. Further research is necessary to externally validate the HII-AKI and explore its usefulness for the early management of AKI.

In conclusion, a high HII-AKI is associated with greater hemodynamic instability, inflammation, metabolic disturbances, and prolonged length of hospital stay, supporting its usefulness as a prognostic marker. This index represents an innovative tool for assessing hemodynamic instability in AKI, with a discriminatory ability superior to other scores and biomarkers. Its implementation in clinical practice could improve risk stratification and optimize the therapeutic management of this vulnerable population. It is imperative to conduct further research in diverse cohorts to evaluate the generalizability of these findings.

Conflicts of interest

None declared.

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

REFERENCES

1. Goyal A, Daneshpajouhnejad P, Hashmi MF, Bashir K. Acute kidney injury. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [citado 19 de marzo de 2025]. Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK441896/

2. Asim M, Amin F, El-Menyar A. Multiple organ dysfunction syndrome: Contemporary insights on the clinicopathological spectrum. Qatar Med J 2020;2020:22. http://dx.doi.org/10.5339/qmj.2020.22

3. Villa G, Husain-Syed F, Saitta T, Degl'Innocenti D, Barbani F, Resta M, et al. Hemodynamic instability during acute kidney injury and acute renal replacement therapy: Pathophysiology and clinical implications. Blood Purif 2021;50:729-39. http://dx.doi.org/10.1159/000513942

4. Reddy V, Reddy H, Gemnani R, Kumar S, Acharya S. Navigating the complexity of scoring systems in sepsis management: A comprehensive review. Cureus 2024;16:e54030. https://doi.org/10.7759/cureus.54030

5. Mehta HB, Li S, An H, Goodwin JS, Alexander GC, Segal JB. Development and validation of the summary Elixhauser comorbidity score for use with ICD-10-CM-coded data among older adults. Ann Intern Med 2022;175:1423-30. https://doi.org/10.7326/M21-4204

6. Wilson FP, Yamamoto Y, Martin M, Coronel-Moreno C, Li F, Cheng C, et al. A randomized clinical trial assessing the effect of automated medication-targeted alerts on acute kidney injury outcomes. Nat

Commun 2023 2024;14:1–10. https://doi.org/10.1038/s41467-023-38532-3
7. Bollenbecker S, Czaya B, Gutiérrez OM, Krick S. Lung-kidney interactions and their role in chronic kidney disease-associated pulmonary diseases. Am J Physiol Lung Cell Mol Physiol 2022;322:L625–40. https://doi.org/10.1152/ajplung.00152.2021
8. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [Internet]. Equator-network.org. [citado 29 de mayo de 2024]. Disponible en: https://www.equator-network.org/reporting-guidelines/record/
9. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310 :2191–2194. doi:10.1001/jama.2013.281053
10. Balkrishna A, Sinha S, Kumar A, Arya V, Gautam AK, Valis M, et al. Sepsis-mediated renal dysfunction: Pathophysiology, biomarkers and role of phytoconstituents in its management. Biomed Pharmacother 2023;165:115183. https://doi.org/10.1016/j.biopha.2023.115183
11. Blanco VE, Hernandorena CV, Scibona P, Belloso W, Musso CG. Acute kidney injury pharmacokinetic changes and its impact on drug prescription. Healthcare (Basel) 2019;7(1). https://doi.org/10.3390/healthcare7010010
12. Srdić T, Đurašević S, Lakić I, Ružičić A, Vujović P, Jevđović T, et al. From molecular mechanisms to clinical therapy: Understanding sepsis-induced multiple organ dysfunction. Int J Mol Sci 2024;25:7770. https://doi.org/10.3390/ijms25147770
13. Harky A, Joshi M, Gupta S, Teoh WY, Gatta F, Snosi M. Acute kidney injury associated with cardiac surgery: A comprehensive literature review. Braz J Cardiovasc Surg 2020;35:211–24. https://doi.org/10.21470/1678-9741-2019-0122
14. Poukkanen M, Wilkman E, Vaara ST, Pettilä V, Kaukonen K-M, Korhonen A-M, et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care 2013;17(6):R295. https://doi.org/10.1186/cc13161
15. Griva P, Griva V, Samara D, Talliou C, Panagouli K, Roungeris L. Central venous pressure as a predictor of acute kidney injury in cardiac surgery: A systematic review of observational studies. Diagnostics (Basel) [Internet]. 2025;15(5). https://doi.org/10.3390/diagnostics15050530
16. Douvris A, Zeid K, Hiremath S, Bagshaw SM, Wald R, Beaubien-Souligny W, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. Intensive Care Med 2019;45:1333–46. https://doi.org/10.1007/s00134-019-05707-w
17. Villa G, Husain-Syed F, Saitta T, Degl'Innocenti D, Barbani F, Resta M, et al. Hemodynamic instability during acute kidney injury and acute renal replacement therapy: Pathophysiology and clinical implications. Blood Purif 2021;50:729–39. https://doi.org/10.1159/000513942
18. Douvris A, Zeid K, Hiremath S, Bagshaw SM, Wald R, Beaubien-Souligny W, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. Intensive Care Med 2019;45:1333–46. https://doi.org/10.1007/s00134-019-05707-w
19. Voicehovska JG, Trumpika D, Voicehovskis VV, Bormane E, Bušmane I, Grigane A, et al. Cardiovascular consequences of acute kidney injury: Treatment options. Biomedicines 2023;11:2364. https://doi.org/10.3390/biomedicines11092364
20. Tang WH, Bakitas MA, Cheng XS, Fang JC, Fedson SE, Fiedler AG, et al. Evaluation and management of kidney dysfunction in advanced heart failure: A scientific statement from the American heart association. Circulation 2024;150:e280–95. https://doi.org/10.1161/CIR.0000000000001273

ORIGINAL ARTICLE

Reduction in Contrast Use through the Application of the *Dynamic Coronary Roadmap* in Coronary Angioplasty

Reducción en el uso de contraste mediante la aplicación del Dynamic Coronary Roadmap en la angioplastia coronaria

MARCELO A. ABUD[1], FACUNDO VILLA[1], IGNACIO L. PAGANINI[1], JAVIER CÓGGIOLA[1], JUAN P. DE BRAHI[1]
INSTITUTO CARDIOVASCULAR SAN GERÓNIMO - ENDOVASCULAR THERAPY SERVICE

ABSTRACT

Background: Contrast-induced nephropathy is a significant complication of percutaneous coronary intervention (PCI), especially in patients with comorbidities. Dynamic Coronary Roadmap (DCR) is an innovative tool that optimizes intravascular navigation and could reduce contrast consumption without compromising the safety of the procedure.
Objective: The aim of this study was to evaluate the impact of DCR use on contrast volume reduction during PCI at a center in Argentina.
Methods: A single-center retrospective study was conducted including 480 consecutive patients undergoing PCI between January 2024 and December 2024. Two groups were compared: DCR-guided PCI (n=201) and conventional angiography-guided PCI (n=279). The total volume of contrast used, radiation exposure, and serum creatinine variation were evaluated.
Results: The DCR group showed a significant reduction in contrast volume used compared with the control group: median (interquartile range, IQR) of 120 ml (90-158) vs. 140 ml (100-200), p=0.007. The average reduction, adjusted for age, sex, and procedure complexity, was 37.3 mL per patient (95% CI 24.3-50.5 mL; p<0.001). No significant differences were observed in post-procedure renal function or radiation exposure.
Conclusions: The use of DCR during PCI was associated with a significant reduction in contrast volume without affecting the safety of the procedure. These findings, which are relevant in the regional context, could have a positive impact on patient safety and cost optimization in interventional cardiology.

Key words: Percutaneous coronary intervention - Contrast-induced nephropathy - Contrast media exposure - Dynamic Coronary Roadmap - Ionizing radiation - Patient safety

RESUMEN

Introducción: La nefropatía inducida por contraste es una complicación relevante de la intervención coronaria percutánea (ICP), especialmente en pacientes con comorbilidades. El Dynamic Coronary Roadmap (DCR) es una herramienta innovadora que optimiza la navegación intravascular y podría reducir el consumo de contraste sin comprometer la seguridad del procedimiento.
Objetivos: Evaluar el impacto del uso de DCR en la reducción del volumen de contraste durante la ICP en un centro de Argentina.
Materiales y métodos: Se realizó un estudio retrospectivo unicéntrico que incluyó 480 pacientes consecutivos entre enero de 2024 y diciembre de 2024 sometidos a ICP. Se compararon dos grupos: ICP guiada por DCR (n=201) e ICP guiada por angiografía convencional (n=279). Se evaluó el volumen total de contraste utilizado, la exposición a radiación y la variación de creatinina sérica.
Resultados: El grupo DCR presentó una reducción significativa en el volumen de contraste utilizado en comparación con el grupo control: mediana (rango intercuartílico, RIC) de 120 ml (90-158) vs. 140 ml (100-200), p=0,007. La reducción promedio, ajustada por edad, sexo y complejidad del procedimiento, fue de 37,3 ml por paciente (IC95% 24,3 a 50,5 ml; p<0,001). No se observaron diferencias significativas en la función renal post procedimiento ni en la exposición a radiación.
Conclusiones: El uso de DCR durante la ICP se asoció con una reducción significativa en el volumen de contraste sin afectar la seguridad del procedimiento. Estos hallazgos, relevantes en el contexto regional, podrían tener un impacto positivo en la seguridad del paciente y en la optimización de costos en cardiología intervencionista.

Palabras clave: Intervención coronaria percutánea - Nefropatía inducida por contraste - Exposición a medios de contraste - Dynamic Coronary Roadmap - Radiación ionizante - Seguridad del paciente.

Rev Argent Cardiol 2025;93:348-353. https://doi.org/10.7775/rac.v93.i5.20941

Received: 08/24/2025 – *Accepted:* 10/05/2025

Correspondence: Marcelo A. Abud. Email: abudmarceloangel@gmail.com

[1] Endovascular Therapy Service San Gerónimo Cardiovascular Institute

INTRODUCTION

Over the last decade, the profile of patients undergoing percutaneous coronary intervention (PCI) has changed considerably. It is increasingly common to treat patients with advanced atherosclerosis, previous coronary revascularization, and more complex coronary anatomy. In addition, these patients often have systemic comorbidities, such as chronic renal dysfunction or diabetes, which increase the complexity of the procedure and raise the risk of associated complications.

In this context, the need to optimize the use of iodinated contrast has become particularly relevant, given that high doses can cause acute renal injury, known as contrast-induced nephropathy (CIN). This condition is associated with higher morbidity and mortality, longer hospital stays, and a significant increase in healthcare costs. Although CIN is a multifactorial phenomenon, the amount of contrast used during PCI has been identified as one of the main risk factors, leading to the search for new strategies to minimize its use without compromising the diagnostic and therapeutic efficacy of the procedure.

To address this issue, tools have been developed to optimize contrast use during PCI. Among them, the *Dynamic Coronary Roadmap (DCR)* appears to be an innovative solution. This software projects a real-time reference image of the coronary anatomy onto the fluoroscopy. In this way, the DCR generates a dynamic and automated map of the coronary arteries, superimposed on the live fluoroscopy image, allowing devices (guides, balloons, and stents) to be guided more efficiently and safely with less contrast use. The technical feasibility of the DCR has already been evaluated in previous studies. In an analysis of 936 cases, the quality of anatomical superimposition with angiography was considered "fit for use" in 99.5% of cases, with low inter- and intra-observer variability. These findings support the reliability of the technology for integration into clinical practice. (1)

The present study aims to evaluate the impact of DCR use on contrast utilization during PCI at a center of Argentina. Despite international evidence supporting its efficacy, the reported local experience is limited, which justifies the need to generate specific data for our healthcare reality. The findings of this study could facilitate the adoption of this technology in interventional cardiology centers in the country, with direct implications in patient safety, operational efficiency, and resource optimizatio.

METHODS

This single-center, retrospective study analyzed the database of the Endovascular Therapy Service at Instituto Cardiovascular San Gerónimo (Santa Fe, Santa Fe), which has been collecting information since 2017. The database allows for systematic 30-day and annual follow-up, with monitoring of population characteristics and technical and clinical outcomes. Demographic data, cardiovascular history, procedures performed, and clinical evolution are analyzed. Contrast consumption, recorded in the Radiology Report prepared for each patient admitted to the Hemodynamics Room, includes the amount used and radiation doses. In procedures that combine cine coronary angiography and PCI, contrast and radiation consumption are reported separately for each intervention.

Study population

The analysis included consecutive patients undergoing PCI between January and December 2024, who were classified according to whether the procedure was guided by DCR (DCR group) or conventional angiography (control group). In all cases, at least 25 mL of contrast was injected manually. Only cases with cardiogenic shock on admission (systolic blood pressure <100 mmHg, heart rate >100 bpm, poor distal perfusion requiring inotropic drugs or mechanical circulatory support devices) or those in whom only lateral branch lesions were treated without involvement of the main coronary arteries were excluded. No other exclusion criteria were applied.

All procedures were performed by the same team of operators with experience in coronary intervention, in the same catheterization laboratory and using the same angiographic system (Azurion 3 M15, Philips).

Definitions

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

Outcomes

The primary objective of this study was to evaluate whether the use of DCR reduces the total contrast volume in PCI. The secondary objectives were to analyze the total amount of radiation used by PCI in each group, as well as post-PCI renal function evaluation according to the use or non-use of DCR.

Statistical analysis

Qualitative variables are expressed as percentages and were evaluated using the chi-square test. Quantitative variables were subjected to normality tests (Kolmogorov-Smirnov test or Shapiro-Wilk test, as appropriate) and histogram parameter measurements were used: skewness and kurtosis. Those variables that met the criteria for normality were expressed as mean ± standard deviation (SD), and otherwise as median and interquartile range (IQR).

Baseline demographic, clinical, and procedural characteristics were compared using Student's t-test or the Mann-Whitney U test for continuous variables according to their distribution, and the chi-square test or Fisher's exact test for categorical variables. A two-tailed significance level of 0.05 was set for all analyses.

Differences in the primary outcome (total contrast consumption) as well as in the secondary outcome were evaluated using Student's t-test or the Mann-Whitney U test

depending on their distribution and variance. Linear regression was used to evaluate the impact of DCR use adjusted for confounding variables: age, sex, vessel treated, and PCKI complexity.

RESULTS

This analysis included 480 cases of patients treated with PTCI between January and December 2024, of which 201 were guided by DCR (41.8%) and 279 by angiography (58.2%).

Demographic variables are detailed in Table 1. No significant differences were observed in terms of age and sex, although patients in the DCR group had a higher prevalence of dyslipidemia.

Table 2 reports the procedure data. There were no significant differences between the two groups in terms of type of procedure (ad hoc PCI vs. scheduled PCI) or the vessel treated. There was a significant difference in the proportion of complex PCI in the DCR branch compared with the control group (39.6% vs. 17.6%, p < 0.001).

Contrast consumption

A significant reduction in contrast use was observed in the DCR group (median of 120 mL vs. 140 mL, p = 0.007) (Figure 1). As detailed in Table 3, this difference remains even when stratifying the data according to procedure type and PCI complexity. These findings, adjusted for sex, age, and procedure complexity using a linear regression model, confirm an average reduction of 37.3 mL (95% CI 24.3 -50.5 mL; p <0.0001) of contrast per patient in the DCR group.

Secondary outcomes

Radiation exposure during each procedure was analyzed, expressed in terms of Kerma (an indicator of the amount of radiation emitted and received in the working field, measured in Gy) and Dose-area prod-

Table 1. Baseline variables

Variable	DCR group (n= 201)	Control group (n= 279)	p
Age, years	69 (62-75)	68 (60 - 75)	0.507
Male gender	78.8	75	0.819
BMI, kg/m^2	28 (23 – 31)	28 (22 - 31)	0.653
Diabetes mellitus	23.8	21.6	0.596
Dyslipidemia	79.7	67.3	0.006
HTN	84.9	86.1	0.723
Previous PTCA	32.1	30.7	0.779
LVEF < 30%	2	2.6	0.951
Baseline creatinine, mg/dL	0.88 (0.78 – 1.0)	0,90 (0.73 – 1.0)	0.896

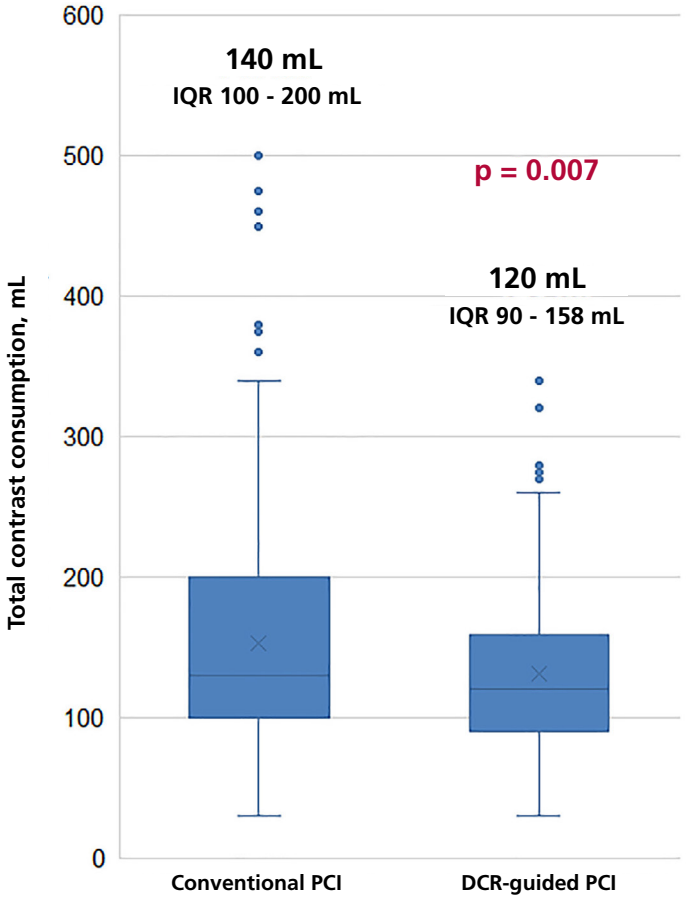
BMI: body mass index; DCR: Dynamic Coronary Roadmap; HTN: hypertension; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention;
Continuous variables are presented as median (interquartile range) and categorical variables as percentage.

Table 2. Type of procedure and vessel treated

Variable	DCR group (n= 201)	Control group (n= 279)	p
Type of procedure			
Ad hoc PCI	58.1	53.1	0.306
Scheduled PCI	41.9	46.9	
Treated vessel			
LMCA	4.1	7.6	0.195
LAD	41.9	37.1	
Cx	25.6	33.1	
RCA	25	25.7	
Complex PCI	39.6	17.6	< 0.001

Cx: circumflex artery; DCR: Dynamic Coronary Roadmap; LAD: left anterior descending artery; LMCA: left main coronary artery; PCI: percutaneous coronary coronary intervention; RCA: right coronary artery
Categorical variables are presented as percentage.

Fig. 1. Contrast consumption according to the use of DCR



DCR: Dynamic Coronary Roadmap; IQR: interquartile range; PCI: percutaneous coronary intervention

Table 3. Radiation, contrast dose, and renal function evolution according to the use or non-use of DCR

	DCR group (n= 201)	Control group (n= 279)	p
Total contrast, mL	120 (90-158)	140 (100-200)	0.007
Contrast in PCI, mL	100 (70-140)	120 (80-180)	0.001
DAP, Gy.cm^2	41.7 (25.3-68)	45.5 (27.7-69.7)	0.846
Kerma, mGy	517 (299-824)	514 (315-801)	0.567
Cr delta, mg/dL	0.10 (0-0.02)	0.10 (0.01-0.2)	0.813

Cr: creatinine; DAP: dose area product; DCR: Dynamic Coronary Roadmap; PCI: percutaneous coronary intervention. Variables are expressed as median (interquartile range).

uct (DAP; a dosimetric quantity that expresses the total amount of radiation emitted to the patient and is usually measured in Gy·cm^2), with no significant differences observed between the two groups (Table 3). With regard to renal function, given its direct relationship with the use of contrast medium, the variation in serum creatinine (ΔCr) was evaluated, comparing the values prior to the procedure with those recorded before discharge. No significant differences were found between the groups.

DISCUSSION

To our knowledge, this is the first study in our region to evaluate the impact of using the DCR on the reduction of contrast volume in PCI procedures. Our findings provide relevant evidence on the applicability of this technology in an unselected population with significant comorbidities and complex coronary anatomies.

The main observations were: a) a significant reduction in contrast use in the DCR group (median of

120 mL vs. 140 mL; p=0.007); b) adjusting for age, sex, type of procedure, and PCI complexity, an average reduction of 37.3 mL per patient was observed; c) no significant differences were observed in post-procedural renal function or radiation exposure.

Performing complex procedures in patients with comorbidities and challenging anatomies involves risks that must be minimized. Among these, CIN is a major concern, with an incidence of ≤1% in patients without risk factors, (1,2) but which can rise to 10–30% in patients with diabetes and/or chronic kidney disease after angiography. (3,4) In addition, recent reviews and international guidelines confirm the relevance of this complication and emphasize the need for preventive strategies. (16-18) In this context, any tool that reduces contrast exposure without compromising the effectiveness of the procedure becomes clinically relevant.

The finding of a reduction in contrast requirements with the use of DCR is consistent with other reports in the literature. (5-8) The multicenter randomized trial DCR4Contrast demonstrated significant reductions in contrast volume and number of angiographic acquisitions. (9,10) Similarly, two recent meta-analyses confirmed that the use of DCR is associated with lower contrast volume and fluoroscopy time, without compromising the success rate of the procedure. (11,12)

Recent studies on low-contrast PTCA techniques highlight the integration of DCR as part of broader strategies to minimize nephrotoxicity. (13,14) Furthermore, recent reviews and international guidelines confirm the relevance of NIC and emphasize the need for preventive strategies. (15-18)

Although no significant differences in serum creatinine variation were observed in our cohort, the reduction in contrast supports the potential of DCR to mitigate adverse effects. A meta-analysis of seven studies (2020–2024) reported a lower incidence of CIN in patients undergoing DCR-guided PCI (OR 0.50; 95% CI 0.27–0.93). (11) Likewise, complementary technologies, such as contrast modulation systems, have been shown to reduce contrast use and the incidence of AKI. (19)

In resource-limited settings, the implementation of DCR may represent an initial challenge in terms of technological investment. However, its potential to reduce contrast consumption, improve procedural efficiency, and decrease renal complications could offset these costs in the mid-term. The progressive availability of consoles integrated into modern angiography systems could favor its regional adoption, especially in centers with a high volume of procedures.

Our study has limitations: being observational, the risk of bias persists despite multivariable adjustment, limiting a definitive causal relationship; in addition, the sample size may not be sufficient to detect differences in rare outcomes such as CIN.

Despite these limitations, our results provide useful evidence in a regional context, where population characteristics and access to advanced technologies can condition the implementation of innovations. In addition to its clinical implications, reducing contrast volume has potential economic benefits, as CIN is associated with higher hospital costs. (20) Resource optimization and improved patient safety are aligned with public health policies aimed at reducing catheterization-related morbidity and improving the efficiency of cardiovascular care.

It is worth mentioning that the adoption of DCR in our center occurred progressively during the first quarter of 2024. No significant differences in contrast volumes were observed over time, suggesting a rapid learning curve for the team and stable integration of the tool into daily practice.

CONCLUSIONS

The use of DCR during PCI was associated with a significant reduction in contrast volume without affecting renal function or increasing radiation exposure. These findings, consistent with previous literature, provide relevant local evidence in a context where socioeconomic variability and access to advanced technologies can influence clinical practice. The reduction in contrast consumption not only has implications for patient safety, but also for the optimization of healthcare costs and resources, aligning with public health strategies aimed at improving efficiency and reducing the morbidity associated with catheterization.

Conflicts of interest

None declared.

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

Funding

None.

REFERENCES

1. Piayda K, Kleinebrecht L, Afzal S, Bullens R, Ter Horst I, Polzin A, et al. Dynamic coronary roadmapping during percutaneous coronary intervention: a feasibility study. Eur J Med Res 2018;23:36. https://doi.org/10.1186/s40001-018-0333-x

2. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol 2017;28:653-9. https://doi.org/10.1681/ASN.2016010021

3. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003;348:491-9. https://doi.org/10.1056/NEJMoa021833

4. Rudnick MR, Davidson C, Laskey W, Stafford JL, Sherwin PF; VALOR Trial Investigators. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) trial. Am Heart J 2008;156:776-82. https://doi.org/10.1016/j.ahj.2008.05.023

5. Hong WY, Kabach M, Feldman G, Jovin IS. Intravenous fluids for the prevention of contrast-induced nephropathy in patients undergoing coronary angiography and cardiac catheterization. Expert Rev Cardiovasc Ther 2020;18:33-9. https://doi.org/10.1080/14779072.2020.1724537

6. Yabe T, Muramatsu T, Tsukahara R, Nakano M, Takimura H, Kawano M, et al. The impact of percutaneous coronary intervention using the novel dynamic coronary roadmap system. Heart Vessels 2020;35:323-30. https://doi.org/10.1007/s00380-019-01502-1
7. Bendary A, Mahmoud D, Attia A, Elrabbat K. Value of the new dynamic coronary roadmap system in percutaneous coronary intervention for patients with chronic coronary syndrome. Iran Heart J 2023;24:34-41.
8. Hirano S, Yabe T, Oka Y, Kojima Y, Aikawa H, Noike R, et al. Clinical outcomes of patients with chronic kidney disease undergoing percutaneous coronary interventions with a novel Dynamic Coronary Roadmap system. Int Heart J 2023;64:823-31. https://doi.org/10.1536/ihj.23-213
9. Quast C, Phinicarides R, Afzal S, Veulemans V, Klein K, Berisha N, et al. Roadmap fusion imaging in percutaneous coronary intervention reduces contrast medium exposure irrespective of investigator's experience level. J Invasive Cardiol 2024;36:1-8. https://doi.org/10.25270/jic/23.00203
10. Hennessey B, Danenberg H, De Vroey F, Kirtane AJ, Parikh M, Karmpaliotis D, et al. Dynamic Coronary Roadmap versus standard angiography for percutaneous coronary intervention: the randomised, multicentre DCR4Contrast trial. EuroIntervention 2024;20:e198-206. https://doi.org/10.4244/EIJ-D-23-00460
11. Behnoush AH, Ramandi A, Mahajan S, Altibi A, Samavarchitehrani S, Gupta R. Dynamic coronary roadmap in percutaneous coronary intervention: a systematic review and meta-analysis. BMC Cardiovasc Disord 2024;24:681. https://doi.org/10.1186/s12872-024-04350-8
12. Hennessey B, Messenger JC, Kirtane AJ, Parikh M, Danenberg H, De Vroey F, et al. Rationale and design of the Dynamic Coronary Roadmap for Contrast Reduction (DCR4Contrast) randomized controlled trial. Am Heart J 2023;263:151-8. https://doi.org/10.1016/j.ahj.2023.04.004
13. Al Hayek M, Beshr IA, Beshr MS. Dynamic coronary roadmap-guided PTCA reduces contrast volume and radiation time: a meta-analysis. Heliyon 2025;11:e41557. https://doi.org/10.1016/j.heliyon.2024.e41557
14. Shabbir A, Ali Z, Colletti G, Dudek D, Garbo R, Hellig F, et al. Ultra-low-contrast PTCA: structured approach including DCR. JACC Cardiovasc Interv 2025;18:123-34. https://doi.org/10.1016/j.jcin.2024.11.043
15. Azzalini L, Kalra S. Contrast-Induced Acute Kidney Injury—Definitions, Epidemiology, and Implications. Interv Cardiol Clin 2020;9:299-309. https://doi.org/10.1016/j.iccl.2020.02.001
16. American College of Radiology. ACR Manual on Contrast Media. Version 2024. Reston, VA: ACR; 2024.
17. European Society of Urogenital Radiology (ESUR). ESUR Guidelines on Contrast Agents. Version 10.0. 2018.
18. Mehran R, Faggioni M, Chandrasekhar J, Angiolillo DJ, Bertolet B, Jobe RL, et al. Effect of a Contrast Modulation System on contrast use and AKI after coronary angiography. JACC Cardiovasc Interv 2018;11:1601-10. https://doi.org/10.1016/j.jcin.2018.04.007
19. Modi K, Hennessey T. Contrast-Induced Nephropathy. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2024].
20. Sůva M, Kala P, Poloczek M, Kaňovský J, Štípal R, Radvan M, et al. Contrast-induced acute kidney injury and its contemporary prevention. Front Cardiovasc Med. 2022;9:1073072. https://doi.org/10.3389/fcvm.2022.1073072

ORIGINAL ARTICLE

The 21-Day Plan: Anthropometric, Biochemical, and Cardiovascular Risk Assessment After a Lifestyle Intervention in Entre Ríos, Argentina

El Plan de 21 días: evaluación antropométrica, bioquímica y del riesgo cardiovascular luego de una intervención de estilo de vida en Entre Ríos, Argentina

DAIANA MARIEL PICCINI[1], ELSA VALERIA BRODER[1], LUIS MANTILLA[1]

ABSTRACT

Background: The development of chronic noncommunicable diseases (NCDs) is largely associated with modifiable behavioral risk factors such as unhealthy diets, physical inactivity, smoking, excessive alcohol consumption, inadequate restorative sleep, poor stress management, and low social connectivity. Lifestyle programs that promote the systematic incorporation of healthy habits are essential to prevent and control NCDs in Latin America.
Objective: To determine the impact on anthropometric and biochemical parameters, and overall cardiovascular risk before and after a 21-Day Plan consisting of a prescribed plant-based diet and regular and personalized physical activity.
Methods: The 21-Day Plan consisted of a 21-day prescription of a plant-based diet combined with personalized physical activity, as well as psychological and spiritual support. It aimed to assess whether this intervention could modify the aforementioned parameters in the short term to confirm its benefits and potentially incorporate it as a long-term lifestyle. Data were collected from patients enrolled between March 2020 and October 2023, including body mass index (BMI) and laboratory parameters measured pre- and post-intervention.
Results: Fifty-nine patients were included in the study (mean age, 47.5±12.6 years), 72.8% women. After 21 days of lifestyle intervention, BMI significantly decreased from 36.3 to 35.5 kg/m² (p<0.001), total cholesterol from 191.5 to 163.6 mg/dL (p<0.001), low-density lipoprotein cholesterol (LDL-C) from 130.4 to 107.6 mg/dL (p<0.001), triglycerides from 145.5 to 112.5 mg/dL (p<0.001), atherogenic index from 4.2 to 3.7 mg/L (p<0.001), high-sensitivity C-reactive protein (hs-CRP) from 4.2 to 2.3 mg/dL (p<0.001). Overall 10-year cardiovascular risk did not show statistically significant changes.
Conclusion: This lifestyle intervention was effective in significantly reducing anthropometric and biochemical parameters in the short term. A larger sample size, longer intervention duration, and longer follow-up are needed to demonstrate a significant reduction in long-term cardiovascular risk.

Key words: Cardiovascular risk – Lifestyle Medicine – Cholesterol – High-sensitivity CRP - Atherogenic index

RESUMEN

Introducción: El desarrollo de enfermedades crónicas no transmisibles (ECNT) está asociado en gran parte a factores de riesgo conductuales modificables como dietas poco saludables, inactividad física, tabaquismo, consumo excesivo de alcohol, falta de sueño reparador, bajo control del estrés y pobre conectividad social. Programas de estilo de vida que fomenten la incorporación sistemática de hábitos saludables son necesarios para ayudar en la prevención y control de las ENT en Latinoamérica.
Objetivo: Determinar el impacto a nivel antropométrico, de parámetros bioquímicos y del riesgo cardiovascular global, antes y después de un plan de 21 días consistente en la prescripción de dieta basada en plantas y actividad física regular y personalizada.
Material y métodos: El "Plan de 21 días" constó de 21 días de prescripción de dieta basada en plantas, más actividad física personalizada junto con apoyo psicológico y espiritual, y buscó comprobar si dicha prescripción lograba modificar los parámetros antes mencionados a corto plazo, con el objetivo de corroborar sus beneficios y poder incorporarlo como estilo de vida definitivo. Se recopilaron datos de pacientes inscriptos entre marzo de 2020 y octubre de 2023, relativos al índice de masa corporal (IMC) y parámetros de laboratorio medidos antes y después de la intervención.
Resultados: Se incluyeron 59 pacientes con una media de edad de 47,5±12,6 años, 72,8 % mujeres. Luego de 21 días de intervención de estilo de vida se redujeron significativamente el IMC de 36,3 a 35,5 kg/m² (p<0,001), el colesterol total de 191,5 a 163,6 mg/dL (p<0,001), el colesterol LDL de 130,4 a 107,6 mg/dL (p<0,001), los triglicéridos de 145,5 a 112,5 mg/dL (p<0,001), el índice aterogénico de 4,2 a 3,7 (p<0,001), y la proteína C reactiva (PCR) ultrasensible de 4,2 a 2,3 mg/dL (p<0,001). El riesgo cardiovascular global a 10 años no experimentó cambios significativos.

Rev Argent Cardiol 2025;93:354-361. https://doi.org/10.7775/rac.v93.i5.20926

Received: 04/16/2025 – *Accepted:* 06/23/2025

Correspondence: Luis Mantilla: E-mail: luisemanti@gmail.com

[1] Adventist Sanatorium of the River, Libertador San Martín, Entre Ríos, Argentina

Conclusión: Esta intervención de estilo de vida fue favorable para reducir significativamente a corto plazo los parámetros antropométricos y bioquímicos estudiados. Son necesarios más pacientes, duración de la intervención y tiempo de seguimiento para demostrar una reducción significativa del riesgo cardiovascular a largo plazo.

Palabras clave: Riesgo cardiovascular - Medicina de Estilo de Vida - Colesterol - PCR ultrasensible - Índice aterogénico

INTRODUCTION

Chronic noncommunicable diseases (NCDs) are the leading cause of death and disability worldwide. In the Americas, they account for approximately 5.5 million deaths annually, about 50% of which occur in people aged 30-69 years. (1)

NCDs are associated with modifiable behavioral risk factors such as unhealthy diets, physical inactivity, smoking, excessive alcohol consumption, inadequate restorative sleep, poor stress management, and low social connectivity, which contribute to the development of obesity, fatty liver, hypertension, dyslipidemia, and insulin resistance. (2)

Lifestyle Medicine (LM) is a discipline that promotes, based on scientific evidence, the prescription of healthy habits aimed at the prevention and management of NCDs. It includes interventions that encourage healthy eating, regular physical activity, stress management, restorative sleep, avoidance of risky substances, and positive social connections. (3)

Among the most effective LM interventions are plant-based diets, characterized by the predominance of plant-based foods and the partial or total exclusion of animal products, with proven benefits in type 2 diabetes, hypertension, dyslipidemia, and obesity. (4)

Several studies have evaluated these effects: the Adventist Health Study 2 reported lower cardiovascular mortality in vegetarians and vegans in comparison with omnivores, (5) while the Atherosclerosis Risk in Communities (ARIC) study showed that higher adherence to an overall plant-based diet index is associated with lower cardiovascular risk. (6) The EPIC-Oxford study found a lower incidence of coronary artery disease in vegetarians compared to omnivores, (7) and the BROAD study demonstrated significant reductions in body mass index (BMI), lipid profile, and glycated hemoglobin in patients with obesity or cardiovascular disease. (8)

Chronic stress, defined as sustained neurohormonal activation in response to adverse situations, is a significant cardiovascular risk factor that promotes low-grade chronic inflammation, endothelial dysfunction, and progression of atherosclerosis. (9)

Regular physical activity not only improves cardiovascular and metabolic health but also promotes mental well-being, cognitive function, sleep quality, and social interaction; it encourages healthy coping mechanisms and enhanced self-perception. Physical exercise has been shown to reduce blood pressure, improve the lipid profile, increase insulin sensitivity, and decrease low-grade systemic inflammation. (10) In addition, prospective studies such as the Harvard Alumni Health Study and the Aerobics Center Longitudinal Study have confirmed that sufficient physical activity is associated with a lower incidence of coronary artery disease, stroke, type 2 diabetes, and all-cause mortality. (11,12)

Insufficient or poor-quality sleep is associated with an increased risk of hypertension, obesity, insulin resistance, and cardiovascular disease. Improving sleep duration and quality has demonstrated beneficial effects on the immune system, hormonal balance, and appetite regulation. (13)

Likewise, positive social connections are protective factors against cardiovascular disease, cognitive impairment, and premature mortality. Social isolation and loneliness have been shown to exert a negative impact comparable to that of traditional risk factors such as hypertension or obesity. (14)

Furthermore, within a framework of spirituality that transcends religiosity and involves a set of moral, emotional, and behavioral values and attitudes toward the world, there is growing evidence of its benefits in terms of cardiovascular risk, mortality, and, in particular, blood pressure control. (15)

New community health programs are needed to promote the adoption of healthy habits. Therefore, the objective of this study was to determine the impact of a lifestyle intervention, referred to as the "21-Day Plan" on the anthropometric and biochemical parameters as well as cardiovascular risk in a group of patients who regularly attended a private healthcare facility in Entre Ríos between March 2020 and October 2023.

METHODS

This study was conducted in the province of Entre Ríos, Argentina, over a period of 3 years and 6 months. Patients referred from different medical specialties were invited to participate. After being duly informed about the project, they voluntarily decided to enroll in the 21-Day Plan, which involved a specific cost paid by each participant. The identity and personal information of participants were kept confidential throughout the process.

Adults aged 18 years or older were invited to participate in the research by signing an informed consent form included in the admission document. All activities related to the development and implementation of the study complied with the principles of the Declaration of Helsinki. (16)

A total of 171 people registered, of whom 59 met the inclusion criteria, regardless of nationality, race, sex, religion, age, pre-existing conditions, or treatments. All participants were from Argentina and Uruguay.

Inclusion criteria required participants to have at least one modifiable and measurable risk factor (hypertension, dyslipidemia, type II diabetes, obesity), acceptable func-

tional capacity (FC I and FC II according to the New York Heart Association scale) to carry out the physical activities involved in the plan, and adequate cognitive ability to understand the tasks to be performed.

A subgroup of patients not covered by the cardiovascular risk score used in this study was excluded, based on standardized variables within the score (age between 40 and 79 years, total cholesterol between 155 and 309 mg/dL). Due to the virtual format adopted partly because of the COVID-19 pandemic and partly due to the geographical origin of some participants as well as the impossibility of collecting complete laboratory and clinical data, an additional 110 patients were excluded.

A quasi-experimental, pre- and post-, single-group, analytical and descriptive study was conducted in both face-to-face and virtual formats, involving a multidisciplinary team of professionals from Cardiology, Nutrition, Psychology, Chaplaincy, and Physical Education.

Data collection was performed between March 2020 and October 2023, following both face-to-face and virtual interviews with the Lifestyle Medicine team. (17) BMI was calculated as weight in kilograms divided by height in meters squared. Based on BMI, patients were classified into three categories: normal weight (<25 kg/m^2), overweight (≥25 and <30 kg/m^2) and obesity (≥30 kg/m^2), which was further divided into grade 1 (≥30 and < 35 kg/m^2), grade 2 (≥35 and <40 kg/m^2) and grade 3 (≥ 40 kg/m^2).

Fasting blood samples were collected before starting the plan and immediately after its completion, using Abbott Alinity automated analyzers. (18) The following parameters were measured: lipid profile and atherogenic index, complete blood count, blood glucose, insulin, and glycated hemoglobin, renal function (urea and creatinine), vitamin D, vitamin B12, homocysteine, and high-sensitivity C-reactive protein (hs-CRP).

The World Health Organization (WHO) cardiovascular risk chart was used to estimate the overall 10-year cardiovascular risk. (19)

The 21-Day Plan consisted of 21-day prescription of a plant-based diet combined with personalized physical activity, as well as psychological and spiritual support. It aimed to assess whether this intervention could modify the aforementioned parameters in the short term to confirm its benefits and potentially incorporate it as a long-term lifestyle. Participants received a schedule of appointments assigned by time slots and for the same day, and a roadmap designed by the Lifestyle Medicine team (see Annex 1).

The cardiologist took each patient's case history, including, personal data, personal and family history, previously diagnosed conditions, and current treatment, as well as a physical examination and identification of any symptoms that might contraindicate physical activity. The cardiologist also ordered blood tests and any other preliminary studies necessary according to each patient's risk.

Physical trainer provided a personalized and progressive exercise program, specifying frequency and intensity, according to each patient's characteristics and ability to perform the prescribed activities, and based on the cardiologist's prior assessment. Nutrition Department provided a plant-based diet plan with various food options and daily guidelines (see Annex 2), as well as a weekly virtual workshop.

The psychologist and the team chaplain provided psychological and spiritual support during the intervention, with face-to-face or virtual follow-up (via video call or WhatsApp group). In addition, virtual workshops were held via Zoom, each addressing specific topics presented by the corresponding professional and offering space for questions and experience sharing.

Data was entered and analyzed using JASP statistical package, version 0.95.0 for Windows. For univariate analysis, frequencies, means, and standard deviations were calculated according to the type of variable. For bivariate analysis, paired t-test or Wilcoxon signed-rank sum test was performed, depending on the variable normality, with a 95% confidence level.

RESULTS

Of the 171 enrolled participants, 59 were included in the study (mean age, 47.5±12.6 years); 43 were women (72.8%). Eighteen patients (30.5%) had hypertension, and 17 (28.8%) had dyslipidemia.

Ten patients (16.9%) had type 2 diabetes mellitus. Among included participants, 18.6% were overweight and 62.6% had some degree of obesity (23.7% had grade 1 obesity). Seventeen patients had hypothyroidism (28.8%). Table 1 shows baseline characteristics of the study participants

After implementation of the 21-Day Plan, a significant reduction was observed in the following parameters: body mass index from 36.3 to 35.5 kg/m^2 (p<0.001), total cholesterol from 191.5 to 163.6 mg/dL (p<0.001), LDL-C from 130.7 to 107.6 mg/dL (p<0.001), triglycerides from 145.5 to 112.5 mg/dL (p<0.001), the atherogenic index from 4.2 to 3.7 (p<0.001), and hs-CRP from 4.2 to 2.3 mg/dL (p<0.001). Anthropometry and laboratory measurements are shown in Table 2.

Among the 41 participants with complete measurements pre- and post-intervention, cardiovascular risk according to the WHO risk score was low in 68.3%, moderate in 4.9%, high in 19.5%, and very high in 7.3% before implementation of the 21-Day Plan. After implementation of the plan, 4 patients moved from high to moderate risk: the high-risk category decreased to 9.8%, and moderate risk increased to 14.6%; these changes were not statistically significant (p=0.351). Table 3 summarizes cardiovascular risk classification.

DISCUSSION

In light of the study objectives and of previous research conducted by pioneers and organizations in the field of LM (20)), based on the results obtained, we can state that a plant-based diet combined with regular physical activity positively impacts on physical health. (21)

Specific macro- and micronutrients within a predominantly plant-based dietary pattern help reduce low-density lipoprotein cholesterol (LDL-C). It has been shown that, with appropriate diet and lifestyle changes, approximately 80% of premature cardiovascular mortality may be prevented. (22)

Despite the ongoing controversy regarding the role of elevated triglycerides as an independent cardiovascular risk factor, epidemiological, clinical, and

Table 1. Baseline characteristics of the study participants (n=59)

Variable	n	%
Female sex	43	72.88
Age, years (mean ±SD)	47.5±12.6	
Overweight	11	18.6
Grade 1 obesity	14	23.7
Grade 2 obesity	11	18.6
Grade 3 obesity	12	20.3
Type 2 diabetes mellitus	10	16.9
Smoking	1	1.7
Dyslipidemia	17	28.8
Hypertension	18	30.5
Peripheral arterial or venous disease	5	8.5
Pacemaker	3	5.08
Hypothyroidism	17	28.8
Cancer	4	6.8
Bariatric surgery	2	3.4
Depression	10	16.9
Hematologic disease	3	5.1
Neurologic disease	5	8.5
Rheumatic disease	4	6.8
Regular medication		
Beta-blockers	9	15.3
Oral antidiabetic agents	10	16.9
Antihypertensive agents	15	25.4
Lipid-lowering agents	16	27.1
Hormone replacement therapy and/or vitamins	22	37.3
Antidepressant agents	11	18.6
Benzodiazepines	6	10.2
Antiplatelet agents	2	3.4
Diuretics	4	6.8

SD: standard deviation

pathophysiological evidence indicate that, particularly in patients with insulin resistance, triglycerides are a key etiopathogenic factor in the process related to the development of atherosclerosis and cardiovascular disease. (23)

Regarding the atherogenic index, a recent clinical study published in January 2024 demonstrated that it may serve as an effective marker of future cardiovascular events in the general population, including patients with and without diabetes, and that its monitoring and management may provide additional cardiovascular benefits even in individuals without traditional risk factors. (24)

Obesity has been associated with alterations in hemodynamic, autonomic, and hormonal pathways, resulting in a spectrum of cardiovascular changes, from subclinical structural heart abnormalities to overt heart failure. (25)

A major study collected individual-level data from 1 518 028 subjects from 112 cohort studies conducted in eight geographic regions, and assessed five cardiovascular risk factors: body mass index, systolic blood pressure, non-HDL cholesterol, current smoking, and diabetes, because of their impact on cardiovascular disease (CVD) and all-cause mortality. The five modifiable risk factors accounted for a population-attributable fraction of CVD of 57.2% in women and 52.6% in men and a population-attributable fraction of all-cause mortality of 22.2% in women and 19.1% in men, with elevated systolic blood pressure being the leading contributing factor. (26)

Among the available inflammatory biomarkers, hs-CRP is an independent and significant risk marker of ischemic cardiovascular disease, as it plays a vital role in atherogenesis. Inhibition of hs-CRP might be an innovative, effective, and safe therapy for the treatment of ischemia and myocardial and cerebral infarctions (27,28) .

Finally, regarding the close relationship between psychological health, well-being, and the mind-heart-

Table 2. Anthropometric and laboratory parameters of participants pre- and post-intervention

	Pre-intervention			Post-intervention			
	n	Mean	SD	n	Mean	SD	p-value
Body mass index, kg/m^2	49	36.3	8.9	43	35.5	8.3	<0.001
Uric acid, mg/dL	33	5.5	1.9	22	5.0	1.4	0.057
hs-CRP, mg/dL	40	4.2	3.3	39	2.3	2.1	<0.001
Hematocrit, %	56	41.0	3.7	52	40.9	3.5	0.257
Hemoglobin, g/dL	56	13.3	1.5	52	13.4	1.2	0.127
Leukocytes, thousand/µL	56	6.6	1.5	52	6.5	1.7	0.113
Total cholesterol, mg/dL	59	191.5	43.4	58	163.6	33.6	<0.001
HDL cholesterol, mg/dL	57	46.5	9.9	58	44.5	9.3	0.020
LDL cholesterol, mg/dL	59	130.7	45.0	59	107.6	35.0	<0.001
Triglycerides, mg/dL	58	145.5	74.7	59	112.5	54.9	<0.001
Triglyceride/HDL ratio	57	3.4	2.2	57	2.6	1.5	0.029
Atherogenic index	57	4.2	1.2	57	3.7	0.9	<0.001
Blood glucose, mg/dL	56	100.5	27.9	55	96.4	15.6	0.041
Creatinine, mg/dL	52	0.78	0.20	51	0.7	0.13	0.187
Urea, mg/dL	41	29.2	11.3	46	25.2	9.6	0.016
Vitamin B12, pg/mL	43	632.5	622.8	9	365.5	252.8	0.813
Vitamin D, ng/mL	45	28.8	11.2	9	24.1	6.4	0.877
Homocysteine, µmol/L	29	7.9	2.5	14	9.2	1.9	1.000
Glycated hemoglobin, %	27	5.7	1.15	19	5.9	1.2	0.030
Insulin, IU/mL	29	18.9	12.07	23	24.9	19.2	0.646

hs-CRP = high-sensitivity C-reactive protein

Table 3. Cardiovascular risk of participants according to WHO classification

	Pre-intervention		Post-intervention	
	n	%	n	%
Low risk	28	68.3	28	68.3
Moderate risk	2	4.9	6	14.6
High risk	8	19.5	4	9.8
Very high risk	3	7.3	3	7.3

WHO: World Health Organization

body connection, this topic warranted a specific 2021 AHA statement, which emphasized the importance of considering psychological health in the assessment and management of patients with or at risk for CVD. (29)

Based on the scientific evidence and the results obtained regarding reductions in BMI, total and LDL cholesterol, triglycerides, atherogenic index, hs-CRP, and overall cardiovascular risk, we highlight the strengths of this study and its potential for systemic and long-term application.

As main limitations, we should note that not all blood pressure and laboratory measurements were obtained both pre- and post-intervention, partly because some consultations were virtual and some patients without medical coverage were unable to complete the laboratory tests. The intervention lasted 21 days, which may have influenced the absence of statistical significance in the variation of estimated long-term cardiovascular risk. An extended follow-up methodology has not yet been developed to verify adherence to lifestyle changes and the persistence of these outcomes.

CONCLUSIONS

The 21-Day Plan demonstrated the short-term benefit of a plant-based diet and the implementation of regular physical activity, psychological and spiritual support for stress management and emotional sup-

port on the studied anthropometric and laboratory parameters, which directly impacted on overall cardiovascular risk.

Conflicts of interest

None declared.

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

REFERENCES

1. OPS. Enfermedades no transmisibles. Organización Panamericana de la Salud. 2021. Disponible en: https://www.paho.org/es/temas/enfermedades-no-transmisibles

2. OMS. Factores de riesgo de las enfermedades no transmisibles. Organización Mundial de la Salud, 2022. Disponible en: https://iris.who.int/bitstream/handle/10665/356888/9789240050105-spa.pdf?sequence=1

3. American College of Lifestyle Medicine. Lifestyle Medicine Core Competencies, 2023. Disponible en: https://portal.lifestylemedicine.org/Portal/ACLM/Education/LMCC/LMCC.aspx

4. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, et al. Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. J Am Coll Cardiol 2017;70:411-22. https://doi.org/10.1016/j.jacc.2017.05.047.

5. Orlich MJ, Singh PN, Sabaté J, Jaceldo-Siegl K, Fan J, Knutsen S, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA Intern Med 2013;173:1230-8. https://doi.org/10.1001/jamainternmed.2013.6473.

6. Kim H, Caulfield LE, Garcia-Larsen V, Steffen LM, Coresh J, Rebholz CM. Plant-Based Diets Are Associated With a Lower Risk of Incident Cardiovascular Disease, Cardiovascular Disease Mortality, and All-Cause Mortality in a General Population of Middle-Aged Adults. J Am Heart Assoc 2019;8:e012865. https://doi.org/10.1161/JAHA.119.012865.

7. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr 2016;103:218-30. https://doi.org/10.3945/ajcn.115.119461.

8. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: A randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. Nutr Diabetes 2017;7:e256. https://doi.org/10.1038/nutd.2017.3.

9. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012;9:360–70. https://doi.org/10.1038/nrcardio.2012.45

10. Pedersen BK, Saltin B, Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;25 Suppl 3:1–72. https://doi.org/10.1111/sms.12581.

11. Paffenbarger RS, Hyde RT, Wing AL, Hsieh CC, Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med 1986;314:605–13. https://doi.org/10.1056/NEJM198603063141003

12. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996;276:205-10. https://doi.org/10.1001/jama.1996.03540030039029

13. St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, et al; American Heart Association Obesity, Behavior Change, Diabetes, and Nutrition Committees of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart Association. Circulation 2016;134:e367-e386. https://doi.org/10.1161/CIR.0000000000000444.

14. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D, et al, Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci, 2015;10:227–37. https://doi.org/10.1177/1745691614568352

15. VanderWeele TJ, Balboni TA, Koh HK, Health and Spirituality. JAMA. 2017;318:519-20. https://doi.org/10.1001/jama.2017.8136

16. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310 :2191–2194. doi:10.1001/jama.2013.281053

17. Sanatorio Adventista del Plata [Internet], [citado 24 de octubre de 2023], Medicina del Estilo de Vida. Disponible en: https://sanatorioadventista.org.ar/servicios_medicos/Medicina-del-Estilo-de-Vida-19

18. Alinity | Core Laboratory at Abbott [Internet]. [citado 22 de octubre de 2023]. Disponible en: https://www.corelaboratory.abbott/int/es/offerings/brands/alinity,html

19. Calculadora de riesgo cardiovascular de la OMS. Disponible en: https://www.paho.org/es/hearts-americas/calculadora-riesgo-cardiovascular

20. SAMEV | Nosotros [Internet]. SAMEV, [citado 27 de septiembre de 2024]. Disponible en: https://samev.org/nosotros/

21. Haghighatdoost F, Mahdavi A, Mohammadifard N, Hassannejad R, Najafi F, Farshidi H, et al, The relationship between a plant-based diet and mental health: Evidence from a cross-sectional multicentric community trial (LIPOKAP study). PloS One, 2023;18:e0284446. https://doi.org/10.1371/journal.pone.0284446

22. Trautwein EA, McKay S, The Role of Specific Components of a Plant-Based Diet in Management of Dyslipidemia and the Impact on Cardiovascular Risk. Nutrients [Internet], 1 de septiembre de 2020 [citado 27 de septiembre de 2024];12(9):2671. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7551487/ DOI: 10.3390/nu12092671

23. Ponte DCI, Redescubriendo los triglicéridos como factor de riesgo cardiovascular Avances Cardiol 2009;29:367-76. Disponible en: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.sscardio.org/wp-content/uploads/10trigliceridos.pdf

24. Zhi YW, Chen RG, Zhao JW, Zhou SX, He ZJ, Association Between Atherogenic Index of Plasma and Risk of Incident Major Adverse Cardiovascular Events. Int Heart J 2024;65:39-46. https://doi.org/10.1536/ihj.23-406

25. Chen HHL, Bhat A, Gan GC, Khanna S, Ahlenstiel G, Negishi K, et al, The impact of body mass index on cardiac structure and function in a cohort of obese patients without traditional cardiovascular risk factors. Int J Cardiol Cardiovasc Risk Prev 2023;19:200211. https://doi.org/10.1016/j.ijcrp.2023.200211

26. Magnussen C, Ojeda FM, Leong DP, Alegre-Diaz J, Amouyel P, Aviles-Santa L, et al, Global Impact of Modifiable Risk Factors on Cardiovascular Disease and Mortality. N Engl J Med [Internet], 2023;389:1273-85. https://doi.org/10.1056/NEJMoa2206916

27. Banait T, Wanjari A, Danade V, Banait S, Jain J, Role of High-Sensitivity C-reactive Protein (Hs-CRP) in Non-communicable Diseases: A Review. Cureus [Internet], 2023;14:e30225. https://doi.org/10.7759/cureus.30225

28. Sociedad Argentina de Cardiología (SAC), Consenso de Prevención Cardiovascular. Rev Argent Cardiol 2023;91(Supl 3), http://dx.doi.org/10.7775/rac.es.v91.s3

29. Levine GN, Cohen BE, Commodore-Mensah Y, Fleury J, Huffman JC, Khalid U et al. Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. Circulation 2021;143:e763-e783. https://doi.org/10.1161/CIR.0000000000000947

SUPPLEMENTARY MATERIAL

Annex 1. 21-Day Plan: Roadmap – October 2023

Friday, September 28	You will be added to a WhatsApp group created for the 21-Day Plan. Additional information will be shared there, and professionals will be available to answer questions.
Monday, October 2	**Face-to-face interviews at the private healthcare facility, or virtual interviews via video call.** The meal plan and shopping list will be provided. The following days will be spent familiarizing yourself with the plan and obtaining the ingredients. meal plan and a shopping list. The following days are intended to get familiar with the meal plan and gather the necessary ingredients.
Monday, October 2 to Wednesday, October 4	**Preparation:** Purchase the ingredients for the meal plan and clarify any questions with the nutritionists. Begin implementing habits related to physical activity, hydration, sleep, and stress management
Thursdays, October 5-26	**Virtual workshops via Zoom at 8 p.m.** This space will provide opportunities to share experiences and ask questions. Each professional involved in the Plan will present a specific topic. • Thursday, October 5: "Eating with Calm" – Psychology Workshop. • Thursday, October 12: "Preparing a Healthy Plate" –Nutrition Workshop • Thursday, October 19: "In Search of Lost Muscle" – Physical Activity Workshop • Thursday, October 26: "Let's Face It, We're a Walking Zoo" – Cardiometabolic Workshop
WhatsApp group	Originally, the Plan was designed for individual participation, but after more than 20 editions, we have confirmed the value of making lifestyle changes together. Thus, a WhatsApp group was created to share experiences, photos of daily activities and meals, and to encourage one another throughout the program. Participation is recommended but optional. We understand that group chats can sometimes be overwhelming due to the volume of shared messages, and some participants may be more comfortable than others. Therefore, we encourage everyone to keep the group balanced by sharing content that contributes and enriches the collective experience without overloading the space. Proposed times for group interaction: • 8-10 a.m.: Share your experience, ask questions, encourage your peers, and receive guidance from professionals in spiritual, nutritional, and physical activity fields. • 6-9 p.m.: Share your experience, ask questions, encourage your peers and receive guidance from professionals in psychological and medical fields.
Monday, October 30	Evaluation and closing interviews with each professional. Maintenance goals will be based on what was achieved during the 21-Day Plan. These interviews will take place at the same time as the initial ones. If you have any issues attending them, please contact us: estilodevida@sanatorioadventista.org.ar **Note:** Body composition assessments and laboratory tests will also be repeated on this date.
Tuesday, November 5	Closure of the WhatsApp group. A link to the *21-Day Plan Alumni WhatsApp group* will be sent to those who wish to stay in touch with the professionals and other participants from previous editions.

Recommendations:

- If possible, get a juicer or blender to prepare the recipes for the first few days of the Plan.
- Find a "buddy" to accompany you in adopting the 21-Day Plan habits (family member, friend, partner, etc.). Throughout the many plan editions, we have observed that making these changes alongside someone close greatly facilitates their implementation.

ANNEX 2

Lifestyle Medicine: 21-Day Plan. Nutrition Guide

Plan Summary

Day 1	Juices and supplements
Day 2	Juices, fruits, vegetables, whole grains, nuts, and seeds
Day 3	Same as day 2 + cooked vegetables and legume-based dressings
Day 4 Day 5	Raw and cooked vegetables, whole grains, and fruit
Day 6	Same as day 4 + legumes
Day 7 to 21	Varied menu
Day 22 onwards	New lifestyle applying what you have learned

General Recommendations

Rest schedule: never after 11 p.m. Ideally, bedtime should be between **9 p.m. and 10 p.m.**, without screen exposure.

Hydration: drink at least 2 liters of water per day, including the recommended homemade flavored waters.

Physical activity: commit to exercising at least **30-45 minutes** every day.

Foods to avoid: all types of meat and meat products, dairy products and eggs, white (refined) flour, sugar in any form, and processed foods.

Eating habits: chew food thoroughly, avoid snacking between meals, eat at regular times, and do so without distractions and in a pleasant environment

Food portions: these will be defined according to each person's caloric and nutritional requirements. Please note how the quantities are indicated, either in the table below or as specified by the professional. Follow the recommended amounts of food and preparations.

BRIEF ARTICLE

Reluctance to Use Statins in Secondary Prevention: Worrying Results in the Age of Digital Misinformation. SAC 2025 Statin Experience – Argentine Society of Cardiology

Reticencia al uso de estatinas en prevención secundaria: preocupantes resultados en la era de la desinformación digital. Experiencia Estatinas SAC 2025 – Sociedad Argentina de Cardiología

LUCÍA HELGUERA[1], CELESTE CARRERO[2], GUSTAVO GIUNTA[2], EZEQUIEL LERECH[1], JUAN PABLO COSTABEL[2], PABLO STUTZBACH[2]

ABSTRACT

Background: Adherence to statin therapy in secondary cardiovascular prevention remains a clinical challenge. Medical misinformation, especially through digital media, has been identified as a possible contributing factor to this problem.
Objective: To describe the reasons for patients' reluctance to use statins in secondary prevention., according to the perception of health professionals in Argentina.
Methods: An anonymous and voluntary survey was conducted between March and April 2025, distributed through the Argentine Society of Cardiology, with the participation of 638 health professionals. Data were collected on the frequency and reasons for statin refusal, perception of recent changes, and acceptance of other therapies.
Results: A total of 40.9% of respondents reported recent rejection of statins. The main reasons were adverse events (53.4%) and the influence of negative digital information (50.5%). Other factors included advice from third parties, controversial medical indications, economic reasons, and autonomous decisions. Other therapies were accepted by 74% of patients who rejected statins, and 66.6% of professionals noted an increase in this trend.
Conclusions: Reluctance to use statins represents a growing threat to cardiovascular prevention in Argentina. The results highlight the impact of medical misinformation on therapeutic decisions. It is essential to implement educational and communication strategies aimed at professionals and patients to reverse this trend.

Keywords: Statins - Secondary prevention - Treatment adherence - Medical misinformation - Nocebo effect - Cardiovascular diseases

RESUMEN

Introducción: La adherencia al tratamiento con estatinas en prevención secundaria cardiovascular sigue siendo un desafío clínico. La desinformación médica, especialmente a través de medios digitales, ha sido identificada como un posible factor que contribuye a esta problemática.
Objetivo: Describir las razones de la reticencia al uso de estatinas por parte de pacientes en prevención secundaria, según la percepción de los profesionales de la salud en Argentina.
Material y métodos: Se realizó una encuesta anónima y voluntaria entre marzo y abril de 2025, distribuida mediante la Sociedad Argentina de Cardiología. Participaron 638 profesionales de la salud. Se relevaron datos sobre frecuencia y motivos de rechazo a estatinas, percepción de cambios recientes, y aceptación de otras terapias.
Resultados: El 40,9% de los encuestados reportó rechazo reciente a estatinas. Los motivos principales fueron: eventos adversos (53,4%) e influencia de información digital negativa (50,5%). Otros factores incluyeron consejos de terceros, indicaciones médicas contrarias, motivos económicos y decisiones autónomas. El 74% de los pacientes que rechazaron estatinas aceptaban otras terapias. El 66,6% de los profesionales notó un aumento en esta tendencia.
Conclusiones: La reticencia al uso de estatinas representa una amenaza creciente para la prevención cardiovascular en Argentina. Los resultados destacan el impacto de la desinformación médica en decisiones terapéuticas. Es esencial implementar estrategias educativas y comunicacionales dirigidas a profesionales y pacientes para revertir esta tendencia.

Palabras clave: Estatinas - Prevención secundaria - Adherencia al tratamiento - Desinformación médica - Efecto nocebo - Enfermedades cardiovasculares

Rev Argent Cardiol 2025;93:362-365. http://dx.doi.org/10.7775/rac.v93.i5.20933
SEE RELATED ARTICLE: Rev Argen Cardiol 2025:93:331-332. http://dx.doi.org/10.7775/rac.v93.i5.20939

Received: 08/08/2025 – *Accepted:* 09/27/2025

Correspondence: Lucía Helguera - luu.helguera@gmail.com

[1] Young SAC Area, Argentine Society of Cardiology
[2] Research Area of the Argentine Society of Cardiology

INTRODUCTION

Adherence to statin therapy in secondary prevention of cardiovascular events remains a significant clinical challenge. Several international studies have reported a growing proportion of patients who refuse or discontinue statins, even when their medical indication is clear. This phenomenon is developing in a context where the increasing dissemination of unverified medical information further complicates this picture, particularly through social media and digital platforms. (1)

The Argentine Society of Cardiology (SAC) designed a national survey to explore the frequency and reasons for refusing statin treatment in patients with an indication for secondary prevention, according to the perception of healthcare professionals. The objective of this study is to identify the most relevant factors linked to therapeutic reluctance.

METHODS

Study design and population

A national, anonymous, voluntary survey was conducted between March and April 2025. It was distributed through the SAC's institutional registry and social media networks. The REDCap platform (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) was used to support the survey. (2)

Healthcare professionals from across the country were invited to participate, including physicians who treated patients in the context of secondary cardiovascular prevention. The survey consisted of closed-ended multiple-choice questions aimed at identifying the frequency, causes, and perception of changes in patient behavior.

Variables surveyed

Demographic variables were collected from respondents (specialty, region), frequency of recent refusal (last 2 months), and causes attributed to it. Respondents were also asked whether patients who refused to use statins accepted other cardiovascular therapies, and whether physicians perceived an increase in this trend.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed in absolute and relative frequencies (percentage). No statistical comparisons or inferences between groups were made, given the exploratory nature of the study and the absence of a formal prior hypothesis.

Ethical considerations

The study was conducted under the ethical principles of the Declaration of Helsinki.(3) Since it was an anonymous survey, with no collection of sensitive patient data or direct intervention, formal informed consent or evaluation by an ethics committee was not necessary. Participation was completely voluntary, with no financial compensation.

RESULTS

A total of 638 healthcare professionals from all regions of the country, with the exception of the province of La Pampa, responded to the survey. The majority were cardiologists (84.4%; n=538). Forty-point-nine percent (n=261) reported having received explicit refusal to use statins from patients in secondary prevention during the previous two months. The reasons most frequently cited by these 261 physicians were the occurrence of adverse events (53.4%; n=135) and the influence of negative information from digital media (50.5%; n=132). Other reasons included recommendations from family or friends (46.7%; n=122), controversial advice from another professional (28.3%; n=74), economic reasons (21.8%; n=57), and autonomous decisions without apparent cause (15.7%; n=41). A total of 6.5% (n=17) reported that the patient had consulted artificial intelligence tools as the reason for discontinuation. (Figure 1)

A noteworthy finding was that, within this 40.9% who reported having received a refusal to use statins, 74% (n=193) described having received acceptance of other cardiovascular medications. Furthermore, within that same group, 66.6% (n=174) perceived a recent increase in the frequency of treatment refusal.

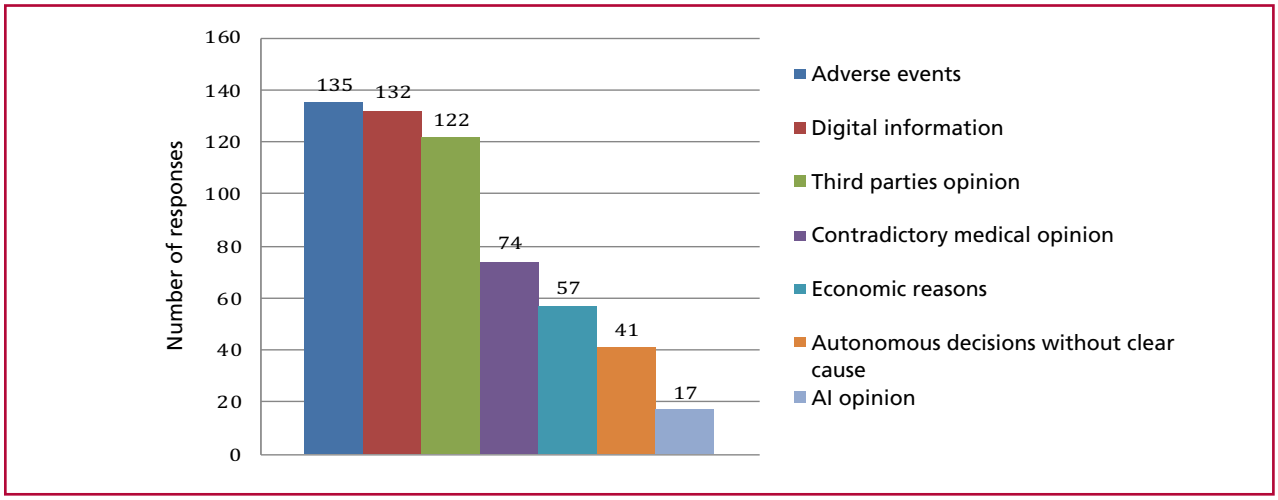
DISCUSSION

The survey results reflect a worrying trend: a considerable proportion of patients with a formal indication for statins in secondary prevention refuse to start or continue treatment. Furthermore, this problem seems to be specific to this pharmacological group, as we could see that patients did not refuse the use of other drugs indicated for cardiovascular prevention in the same proportion. This behavior is often attributed to the occurrence of mild adverse events, or the fear that they will occur, and the influence of discouraging content on social media, a combination that reflects the growing digital misinformation in health.

The situation observed in Argentina is in line with international reports. In the PALM registry in the United States, 26.5% of patients with statin indication were not undergoing treatment. Within this group, 10.1% had refused to start therapy and 30.7% had discontinued it, with fear of adverse effects and perceived lack of safety being the most common reasons. (1) In Europe, studies such as EUROASPIRE V and SANTORINI reveal that less than 30–50% of patients achieved the recommended low density lipoprotein cholesterol (LDL-C) targets, despite being on treatment, (4,5) suggesting both underprescription by healthcare personnel and poor adherence by patients. In Argentina, the registry carried out by CONAREC (National Council of Cardiology Residents) in 2020 already showed that only 85.9% of patients received statins for secondary prevention, and only 30% achieved therapeutic LDL-C targets. Once again, we find the main causes in this registry to be adverse effects, fear of experiencing them, and underprescription by physicians. (6)

Despite extensive evidence on the safety of statins, there remains a marked discrepancy between perceived adverse effects and those actually observed in clinical trials. In randomized, double-blind studies,

Figure 1. Reasons for statins rejection in secondary prevention



AI: artificial intelligence

the rates of myalgia and other reported adverse effects are similar between statins and placebo, indicating that a significant proportion of symptoms attributed to treatment are not directly caused by the drug. (7) Severe myopathies with marked elevation of creatine phosphokinase (CPK) (>10 times the upper normal limit) are a rare event, with an estimated incidence of between 1 per 1000 and 1 per 10 000 patients/year, depending on the dose and predisposing factors. (8)

In contrast, in both clinical practice and observational studies, between 7% and 29% of patients report nonspecific muscle symptoms with normal or minimally elevated CPK, which contributes significantly to treatment discontinuation. (8-10) This discrepancy has been linked to the nocebo effect, demonstrated in trials such as SAMSON and StatinWISE, where more than 90% of reported muscle symptoms also appeared with placebo, reinforcing the role of expectations in the perception of adverse effects. (11,12)

On the other hand, suboptimal adherence to statins is directly associated with increased mortality and adverse cardiovascular events. In a cohort study of more than 300 000 patients, an inverse relationship between adherence and all-cause mortality was evident, reinforcing the clinical impact of therapeutic persistence. (13)

Given this scenario, it is essential to develop strategies to rebuild confidence in statins as a pillar of cardiovascular prevention. Evidence shows that multifaceted interventions, combining clinical support, personalized education, contextual adaptation, and interactive assistance, improve adherence, increase appropriate prescribing, and are associated with greater reductions in LDL-C when applied concurrently.(14) Likewise, shared decision-making, together with the use of clear and understandable visual tools, has been shown to promote a better perception of cardiovascular risk and a greater willingness to initiate and sustain therapy, an approach that is emphasized by the 2019 ACC/AHA guidelines for cardiovascular prevention. (15)

On the other hand, it is necessary to recognize the role that the digital environment plays in the construction of meanings. Evidence suggests that misinformation related to statins circulates widely on social media, where subjective experiences and negative narratives gain disproportionate visibility. Qualitative studies show that digital discourse around statins is highly polarized, with reports of perceived adverse effects influencing therapeutic decision-making. (16) In this regard, digital health literacy and the development of accessible and consistent communication tools are essential to counteract misperceptions and promote evidence-based decisions.

CONCLUSIONS

The therapeutic reluctance observed in this survey poses a real challenge for cardiovascular prevention in Argentina. Overcoming it requires a coordinated response: strengthening doctor-patient communication, promoting sustained educational interventions, using reliable digital resources, and encouraging shared decision-making. The Argentine Society of Cardiology emphasizes the need to promote actions aimed at both professionals and the community to restore confidence in essential therapies such as statins and promote informed, rational clinical decisions oriented toward comprehensive cardiovascular health care.

Conflicts of interest

Lerech Ezequiel declares an employment relationship with the companies Novartis and Gador..

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

REFERENCES

1. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, et al. Patient-reported reasons for declining or discontinuing statin therapy: Insights from the PALM registry. J Am Heart Assoc 2019;8:e011765. https://doi.org/10.1161/JAHA.118.011765

2. https://project-redcap.org

3. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA 2013;310:2191-4. https://doi.org/10.1001/jama.2013.281053

4. Kotseva K, De Bacquer D, De Backer G, Ryden L, Jennings C, Gyberg V, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the EUROASPIRE V registry. Eur J Prev Cardiol 2019;0:1-12. https://doi.org/10.1177/2047487318825350.

5. Ray KK, Müller-Wieland D, Sattar N, Schunkert H, Zeymer U, Brudi P, et al. Lipid management in patients with coronary heart disease: Results from the SANTORINI study. Eur J Prev Cardiol 2023;30:250-63. https://doi.org/10.1016/j.lanepe.2023.100624

6. Sigal AR, Antonioli M, Lopez Santi P, Aquino N, Lerech E, Botto F, et al. Use of lipid-lowering agents and achievement of therapeutic goals in patients at high cardiovascular risk in Argentina. Rev Argent Cardiol 2021;89:390-6. https://doi.org/10.7775/rac.es.v89.i5.204092.

7. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61. https://doi.org/10.1016/S0140-6736(16)31357-5.

8. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: EAS Consensus Panel statement. Eur Heart J 2015;36:1012-22. https://doi.org/10.1093/eurheartj/ehv043

9. Moon J, Sedgh RC, Jackevicius C. Examining the Nocebo Effect of Statins Through Statin Adverse Events Reported in the Food and Drug Administration Adverse Event Reporting System. Circ Cardiovasc Qual Outcomes 2021;14:e007480. https://doi.org/10.1161/CIRCOUTCOMES.120.007480

10. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the ASCOT-LLA. Eur Heart J 2017;38:3562-72. https://doi.org/10.1016/S0140-6736(17)31075-9

11. Wood FA, Howard JP, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects (SAMSON). N Engl J Med 2020;383:2182-4. https://doi.org/10.1056/NEJMc2031173

12. Herrett E, Williamson E, Brack J, Beaumont D, Perkinset A, Thayne A, et al. StatinWISE trial: Effect of statins on muscle symptoms in statin users. BMJ 2021;372:n135. https://doi.org/10.1136/bmj.n135

13. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in atherosclerotic cardiovascular disease. JAMA Cardiol 2019;4:206-13. https://doi.org/10.1001/jamacardio.2018.4936

14. Desai NR, Farbaniec M, Karalis DG. Nonadherence to lipid-lowering therapy and strategies to improve adherence in patients with atherosclerotic cardiovascular disease. Clin Cardiol 2021;44:206-13. https://doi.org/10.1002/clc.23935

15. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation. 2019;140:e596-e646. https://doi.org/10.1161/CIR.0000000000000006

16. Golder S, O'Connor K, Hennessy S, Gross R, Gonzalez-Hernandez G. Assessment of beliefs and attitudes about statins posted on Twitter: a qualitative study. JAMA Netw Open. 2020;3(6):e208953. https://doi.org/10.1001/jamanetworkopen.2020.8953

BRIEF ARTICLE

Epicardial Adipose Tissue and its Association with Cardiac Morphological Abnormalities and Markers of Diastolic Dysfunction

Grasa epicárdica y su relación con alteraciones morfológicas cardíacas y marcadores de disfunción diastólica

EZEQUIEL FORTE[1], PEDRO BECERRA[1], CARLOS BUSO[1], VALERIA CALZIA[1], FIORELLA CHICOTE[1], SANTIAGO LYNCH[1], JUAN NAVARRO[1], HUGO SANABRIA[1]

ABSTRACT

Background: Epicardial adipose tissue (EAT) is a layer of visceral fat located between the myocardium and the visceral pericardium. Increased EAT functions as a metabolically active organ and has been linked to heart failure with preserved ejection fraction (HFpEF).
Objective: The aim of this study was to assess EAT thickness measured by echocardiography in a group of patients with type 2 diabetes mellitus (T2DM) and to evaluate its relationship with parameters of diastolic dysfunction (DD) as an early marker of HFpEF.
Methods: EAT was evaluated in 86 patients with T2DM and no cardiovascular disease (mean age 56 years; 53% women; 63% obesity; 67% hypertension).
Results: Mean EAT thickness was 7.07 ± 3.09 mm; 65% had EAT > 5 mm and 45% > 7 mm. Patients with EAT > 5 mm showed significantly > 2 DD criteria (42.9% vs. 6.7%, p = 0.001). Increased EAT was associated with higher left atrial volume and septal e´ velocity < 7 cm/s. A progressive increase in mean EAT thickness was observed with the number of DD criteria (8.56 mm with two criteria; 9.8 mm with three criteria).
Conclusion: EAT is associated with subclinical structural and functional cardiac abnormalities and may serve as an early marker of DD and HFpEF in patients with T2DM.

Keywords: Epicardial adipose tissue - Diastolic dysfunction - Heart failure with preserved ejection fraction - Type 2 diabetes

RESUMEN

Introducción: El tejido adiposo epicárdico (TAE), es una capa de grasa visceral que se encuentra entre el miocardio y el pericardio visceral. El TAE incrementado funciona como un órgano metabólicamente activo y se ha relacionado insuficiencia cardíaca con función preservada (ICFEp).
Objetivo: El objetivo de este estudio fue evaluar el monto de TAE medido por ecocardiograma en un grupo de pacientes con diabetes tipo 2 (DM2) y relacionarlo con la presencia de parámetros de disfunción diastólica (DD) como marcador precoz de ICFEp.
Material y métodos: El estudio evaluó el TAE en 86 pacientes con DM2 sin enfermedad cardiovascular (edad media 56 años, 53 % mujeres, 63 % obesidad y 67 % hipertensión).
Resultados: El grosor medio del TAE fue 7,07 ± 3,09 mm; el 65 % presentó TAE > 5 mm y el 45 % > 7 mm. Los pacientes con TAE > 5 mm mostraron significativamente > 2 criterios de DD (42,9 % vs 6,7 %, p = 0,001). En particular, el TAE incrementado se asoció con mayor volumen auricular izquierdo, relación E/A<0,8 y velocidades e´septal <7 cm/s y e´lateral <10 cm/s. Observamos que a mayor número de criterios de DD, mayor espesor medio de TAE (8,56 mm con 2 criterios; 9,8 mm con 3 criterios).
Conclusión: Como conclusión observamos que el TAE se asocia con alteraciones estructurales y funcionales cardíacas subclínicas, y podría ser un marcador temprano DD e ICFEp en pacientes con DM2.

Palabras clave: Grasa epicárdica - Disfunción diastólica - Diabetes - ICFEp

Epicardial adipose tissue (EAT) is a layer of visceral fat found between the myocardium and the visceral pericardium. EAT is more than just an energy depot. It has important paracrine and endocrine activity, and its proximity to the myocardium has pathophysiological implications. In conditions like obesity, EAT increases and has been identified as a metabolically active organ capable of releasing proinflammatory and

Rev Argent Cardiol 2025;93:366-369. https://doi.org/10.7775/rac.v93.i5.20931

SEE RELATED ARTICLE: Rev Argen Cardiol 2025:93:323-324. http://dx.doi.org/10.7775/rac.v93.i5.20932

Received: 07/30/2025 – *Accepted:* 09/04/2025

Correspondence: Ezequiel Forte. E-mail: ezeforte@yahoo.com

[1] Council on Cardiometabolism, Argentine Society of Cardiology

proatherogenic molecules including tumor necrosis factor-alpha, interleukins 1 and 6, leptin, and angiotensinogen. (1)

Current evidence shows that increased EAT volume or thickness correlates with a higher prevalence of diastolic dysfunction, independent of other factors of general or visceral adiposity. (2) Patients with obesity-related heart failure with preserved ejection fraction (HFpEF) often exhibit significant symptoms, physical limitations, and a high risk of cardiovascular death. (3) In this context, EAT appears to play a relevant pathogenic role, as its expansion and remodeling are associated with increased myocardial stiffness, endothelial dysfunction, and fibrosis, which exacerbate diastolic dysfunction. (4) Diastolic dysfunction, an early and core marker in the pathophysiology of HFpEF, is characterized by impaired ventricular relaxation and filling, usually precedes the development of clinical symptoms of HFpEF, and can be detected before symptomatic heart failure develops. (5) Observational and cohort studies have demonstrated that the presence of diastolic dysfunction, as determined by echocardiographic parameters such as the E/e' ratio, septal and lateral e' wave velocity, left atrial volume, and filling pressure, is associated with an increased future risk of developing HFpEF and related cardiovascular events.

EAT can be measured using two-dimensional echocardiography, a technique that requires minimal operator training (6) and correlates well with measurements obtained by computed tomography (CT) or nuclear magnetic resonance imaging (MRI). The aim of this study was to assess EAT thickness by echocardiography in a group of patients with type 2 diabetes without cardiovascular disease and to examine its association with parameters of diastolic dysfunction as a potential risk marker for the development of HFpEF.

METHODS

The registry of diastolic dysfunction in patients with type 2 diabetes (T2DM) of the Council on Cardiometabolism of the Argentine Society of Cardiology included 229 patients < 65 years without cardiovascular disease and adequate ultrasound window, evaluated on an outpatient basis with transthoracic color Doppler echocardiography and tissue Doppler echocardiography. Patients with clinically established cardiovascular disease, blood pressure >140/90 mmHg during Doppler echocardiography, atrial fibrillation, or kidney disease were excluded from the study. The registry had a pre-specified (but non-mandatory) option to measure EAT. Therefore, EAT was measured in 86 non-correlative patients, with measurements taken at convenience. The protocol specified the methodology for assessing epicardial fat with images and a training video. Images were obtained from standard parasternal long-axis and short-axis 2D views to allow for the most accurate measurement of epicardial fat thickness in the right ventricle with optimal cursor beam orientation in each view. On echocardiography, epicardial fat is generally identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. Its thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles at the point on the free wall of the right ventricle along the midline of the ultrasound beam perpendicular to the aortic annulus which was used as an anatomic landmark.

Although there is no cutoff point for defining increased EAT, thickness values > 4-5 mm or >7 mm were considered abnormal in different epidemiological studies. (7) In our study, a value > 5 mm was considered increased EAT thickness. Mean values were compared with the different functional or structural abnormalities related to the possibility of diastolic dysfunction according to 6 evaluation criteria recommended by the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging: left atrium (LA) ≥ 34 mL/m2, E/A ratio <0.8, E/e' ratio >14, septal e' <7 and lateral e' <10, tricuspid regurgitation velocity >2.8 m/s. (8)

Informed consent was obtained prior to inclusion in the protocol. The protocol was submitted to the Computerized Registration Platform for Health Research (PRIISA) of the City of Buenos Aires and was approved by the Research Area of the Argentine Society of Cardiology. The study was conducted following the ethical principles of the Declaration of Helsinki. (9)

All the statistical calculations were performed using Jamovi 2.6.24.0 software package. Statistical methods included univariate descriptive statistics (mean, median, and frequency) and chi-square test, Student's t-test, and correlation and linear regression tests. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Of the 229 patients, EAT was measured in 86, who were included in this analysis. Mean age was 56 ± 8.8 years, 53.2% were women, 62.8% were obese, defined as body mass index (BMI) ≥ 30, mean BMI was 31.2 ± 5.3 kg/m^2 and 67.1% had hypertension. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were 129 ± 11 and 79.5 ± 7.4 mmHg, respectively. Regarding treatment with cardioprotective antidiabetic drugs, 10 patients (11.6%) were taking sodium-glucose cotransporter 2 (SGLT2) inhibitors and 8 patients (9.3%) were on glucagon-like peptide-1 receptor agonists (GLP-1RAs). None of the patients had wall motion abnormalities, left ventricular hypertrophy, or significant valvular heart disease. Table 1 shows the morphological and functional abnormalities evaluated by echocardiography according to the presence of increased EAT thickness Mean EAT was 7.07 mm ± 3.09 mm; 65.1% (n = 56) presented EAT thickness >5 mm and 45.5% (n = 39) had EAT thickness >7 mm.

In patients with EAT > 5 mm, 42.9% had > 2 criteria for diastolic dysfunction, vs. 6.7% of those with EAT ≤ 5 mm (p = 0.001).

When there were 0 criteria for diastolic dysfunction, mean EAT was 6.8 mm; with 1 criterion, mean EAT was 8.3 mm (p < 0.001 vs. 0 criteria), with 2 criteria mean EAT was 8.5 mm (p < 0.001 vs. 0), and with 3 criteria mean EAT was 9.8 mm (p < 0.001 vs. 0) (Figure 1). There were no patients with a combination of 4, 5, or 6 criteria.

DISCUSSION

In our study, we analyzed a group of patients with T2DM without cardiovascular disease and observed an association between structural and functional abnormalities on echocardiography and increased EAT thickness. Most of our patients with EAT thickness > 5 mm had some form of functional or structural abnormality on echocardiography.

Like any other fat depot, EAT consists of adipocytes, preadipocytes, stromal-vascular cells, nerve cells, and immune cells, with the unique feature of sharing microcirculation and being in close contact with the myocardium. Dysfunctional EAT releases hypoxia-inducible factor-1α (HIF-1α), which increases myocardial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and reactive oxygen species (ROS) production. This promotes hypertrophy through Akt / mammalian target of rapamycin (mTOR) / nuclear factor kappa B (NFkB) pathways, which are related to the development of HFpEF. (10)

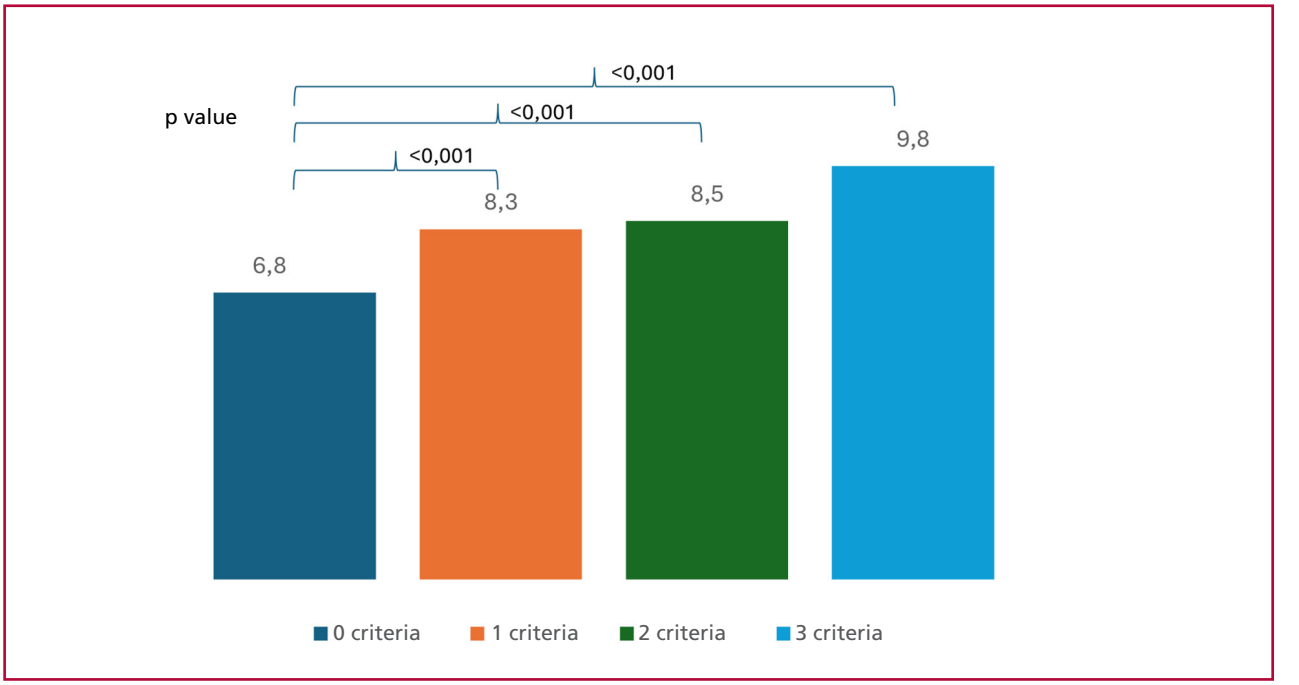
EAT tissue assessed by echocardiography has been shown to be an early marker of subclinical cardiac dysfunction, even in obese subjects without overt cardiovascular disease. Interstitial fibrosis, myocardial stiffness, extracellular matrix expansion, and vascular function are key components in the pathogenesis of HFpEF. (11) Increased EAT predicts the onset of diastolic dysfunction before advanced clinical or structural abnormalities become apparent. (12) Cross-sectional studies and meta-analyses have shown that increased EAT thickness or volume correlates with echocardiographic parameters of diastolic dysfunction, such as decreased mitral annular e' velocity and increased E/e' ratio. (13) Furthermore, EAT thickness appears to have prognostic value and could be useful for monitoring therapeutic response in patients with HFpEF

Table 1. Echocardiographic abnormalities by increased epicardial adipose tissue (EAT) thickness

	n	%	EAT ≤ 5 mm (n=30)	EAT > 5 mm (n=56)	p-value
LA ≥34 mL/m²	25	29.7	3.3% (1)	42.8% (24)	<0.001
E/A < 0.8	56	65.1	60% (18)	67.8% (38)	0.485
E/e'> 14	2	2.3	3.3% (1)	1.8% (1)	1
Septal E' < 7 cm/s	56	65.1	80% (24)	57.1% (32)	0.034
Lateral E' < 10 cm/s	45	52.3	50% (15)	53.6% (30)	0.822
Tricuspid regurgitation velocity > 2.8 m/s	2	2.3	0% (0)	3.6% (2)	0.540

LA: Left atrium

Figure 1. Association of epicardial adipose tissue thickness (in mm) with the criteria for diastolic dysfunction



and obesity. (14) In patients with severe obesity, an EAT thickness > 5.4 mm measured by echocardiography was independently associated with subclinical cardiac dysfunction. This threshold was identified as a predictor of early functional dysfunction, even in the absence of overt cardiovascular disease. (6) Elevated epicardial fat values, especially > 5–7 mm on echocardiography, should be considered a marker of increased risk for diastolic dysfunction and cardiac functional abnormalities, regardless of other risk factors. (15) In our study, mean EAT thickness was 7.07 mm, with EAT > 5 mm in 65.1% and EAT > 7 mm in 45.5%.

The association between EAT and diastolic dysfunction is particularly relevant in the population of diabetic patients, where it not only functions as a risk marker but may also contribute directly to functional impairment through inflammation, fibrosis, and myocardial stiffness. (16) In our study, patients with EAT >5 mm had a higher prevalence of criteria for diastolic dysfunction. Current clinical evidence demonstrates a correlation between epicardial adiposity and LV diastolic filling or contractility, LV hypertrophy, or atrial remodeling. These findings reflect the clinical manifestation of increased EAT on cardiac metabolism, oxidative stress, inflammation, and fibrosis and, ultimately, the presence of HFpEF. (17) In our study, where the entire population was under 65 years of age and had no established CVD, the presence of significant diastolic dysfunction with three criteria or greater was too rare to draw conclusions in this regard.

Left atrial volume is one of the strongest structural markers for determining diastolic dysfunction. There is a positive and independent relationship between left atrial volume and pericardial fat thickness, and it correlates with greater adverse structural remodeling. (18) In our study, most patients with increased left atrial volume had increased ETT thickness.

CONCLUSIONS

In a group of patients with T2DM without heart disease or significant medical history, the presence of structural or functional abnormalities on echocardiography was associated with increased EAT thickness.

Conflicts of interest

None declared. .

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

REFERENCES

1. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inà ammatory mediators. Circulation 2003;108:2460-6.

2. Nerlekar N, Muthalaly RG, Wong N, Thakur U, Wong DT, Brown AJ, et al. Association of Volumetric Epicardial Adipose Tissue Quantification and Cardiac Structure and Function. J Am Heart Assoc 2018;7:e009975. https://doi.org/10.1161/JAHA.118.009975.

3. Kosiborod MN, Deanfield J, Pratley R, Borlaug BA, Butler J, Davies MJ, et al. SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM Trial. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet 2024;404:949-61. https://doi.org/10.1016/S0140-6736(24)01643-X.

4. Janssen-Telders C, Eringa EC, de Groot JR, de Man FS, Handoko ML. The role of epicardial adipose tissue remodelling in heart failure with preserved ejection fraction. Cardiovasc Res 2025;121:860-70. https://doi.org/10.1093/cvr/cvaf056.

5. Redfield MM. Heart Failure with Preserved Ejection Fraction. N Engl J Med 2016;375:1868-77. https://doi.org/10.1056/NEJMcp1511175.

6. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alesi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.

7. Gustafsson B, Rovio SP, Ruohonen S, Hutri-Kähönen N, Kähönen M, Viikari JS, et al. Determinants of echocardiographic epicardial adipose tissue in a general middle-aged population - The Cardiovascular Risk in Young Finns Study. Sci Rep 2024;14:11982. https://doi.org/10.1038/s41598-024-61727-7.

8. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. , Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277-314. doi: 10.1016/j.echo.2016.01.011. PMID: 27037982.

9. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310 :2191–2194. doi:10.1001/jama.2013.281053

10. Antonopoulos A, Papastamos C, Cokkinos D, Tsioufis K, Tousoulis D. Epicardial Adipose Tissue in Myocardial Disease: From Physiology to Heart Failure Phenotypes. Curr Probl Cardiol 2023;48:10184. https://doi.org/10.1016/j.cpcardiol.2023.101841

11. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. New Engl J Med 2024:391:1475-85. https://doi.org/10.1056/NEJMoa2407107.

12. Yao F, Zeng L, Hua M, Zhang S, Liang J, Gao Y, et al. Association of epicardial and visceral adipose tissue in relation to subclinical cardiac dysfunction in Chinese: Danyang study. BMJ Open 2023;13:e075576. https://doi.org/10.1136/bmjopen-2023-075576.

13. Nerlekar N, Muthalaly RG, Wong N, Thakur U, Wong DT, Brown AJ, et al. Association of Volumetric Epicardial Adipose Tissue Quantification and Cardiac Structure and Function. J Am Heart Assoc 2018;7:e009975. https://doi.org/10.1161/JAHA.118.009975.

14. Dhore-Patil A, Urina-Jassir D, Samson R, Le Jemtel TH, Oparil S. Epicardial Adipose Tissue Thickness and Preserved Ejection Fraction Heart Failure. Curr Hypertens Rep 2024;26:381-8. https://doi.org/10.1007/s11906-024-01302-7.

15. Christensen RH, Hansen CS, von Scholten BJ, Jensen MT, Pedersen BK, Schnohr P, et al. Epicardial and pericardial adipose tissues are associated with reduced diastolic and systolic function in type 2 diabetes. Diabetes Obes Metab 2019;21:2006-11. https://doi.org/10.1111/dom.13758.

16. Mancio J, Azevedo D, Fragao-Marques M, Falcao-Pires I, Leite-Moreira A, Lunet N, et al. Meta-Analysis of Relation of Epicardial Adipose Tissue Volume to Left Atrial Dilation and to Left Ventricular Hypertrophy and Functions. Am J Cardiol 2019;123:523-31. https://doi.org/10.1016/j.amjcard.2018.10.020.

17. Christensen RH, Hansen CS, von Scholten BJ, Jensen MT, Pedersen BK, Schnohr P, et al. Epicardial and pericardial adipose tissues are associated with reduced diastolic and systolic function in type 2 diabetes. Diabetes Obes Metab 2019;21:2006-11. https://doi.org/10.1111/dom.13758.

18. Greif M, von Ziegler F, Wakili R, et al. Clinical Research in Cardiology : Official Journal of the German Cardiac Society. 2013;102(8):555-62. doi:10.1007/s00392-013-0566-1.

Imaging Diagnosis of Posterior Medial Papillary Muscle Infarction

Infarto de músculo papilar posteromedial, diagnóstico por imagen

DIEGO VÁZQUEZ ALLER[1], UXUE IDIAZABAL RODRÍGUEZ[1], NORA GARCÍA IBARROND[1]

We present the case of a 55-year-old man who consulted for episodes of chest pain radiating to his left arm and neck of one-week duration. For the past 72 hours, he had been experiencing the same pain, with greater intensity, associated with general malaise and paleness. Physical examination revealed blood pressure of 172/118 mm Hg, with symmetrical pulses in the upper and lower limbs. Given the persistent chest pain and high blood pressure, a computed tomography angiography (CTA) of the aorta was initially performed, which ruled out acute aortic syndrome, but revealed a hypodense nodular image in the left ventricle (Figure A, red arrow).

The electrocardiogram revealed inferolateral ST-segment depression with slight troponin T elevation, and the echocardiogram only showed an increase in the papillary muscle size (Figure B, green arrow), with no intracavitary thrombi or valve involvement. Emergency catheterization was decided due to persistent pain, revealing a critical distal lesion in the circumflex artery and posterolateral branch.

Finally, to complete the study, a cardiac magnetic resonance imaging (MRI) scan was performed, confirming involvement of the posteromedial papillary muscle, which was enlarged due to edema, presenting a no-reflow area at the head of the medial zone corresponding to the intracavitary hypodense image seen on computed tomography (Figure C).

This case shows the finding of an edematous and prominent papillary muscle in the context of acute coronary syndrome, which can pose an initial diagnostic challenge when making the differential diagnosis of an intraventricular mass. (1-3)

Conflicts of interest

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

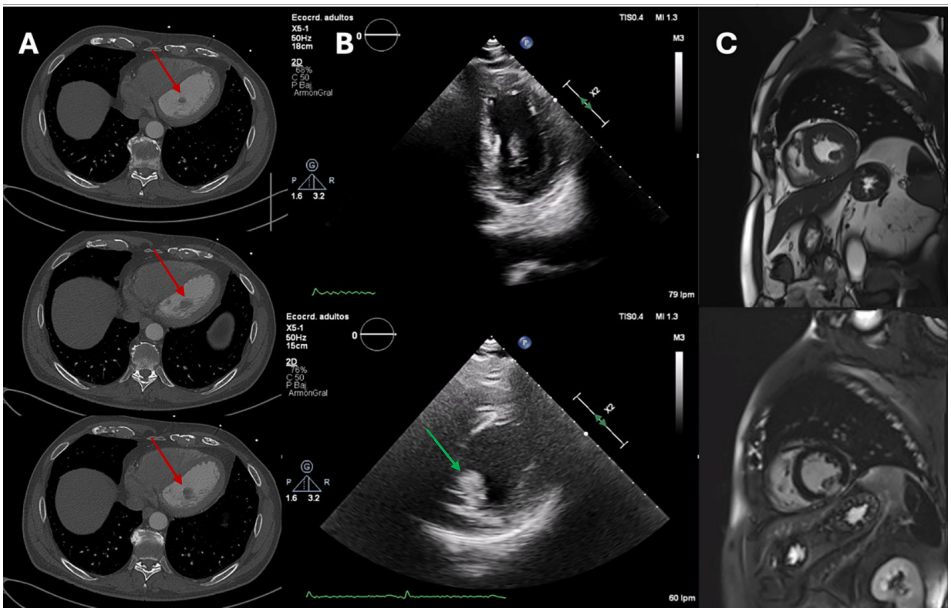


Fig. 1. Column **A** (CT angiography slices). Column **B** (apical 2-chamber and short-axis echocardiogram images at mid-level). Column **C**. (short-axis T1 and late enhancement sequences).

Rev Argent Cardiol 2025;93:370-371. https://doi.org/10.7775.rac.93.i5.20935

Correspondence: digovaller@gmail.com

[1] Hospital Universitario Basurto: Cardiology Department, Inpatient ward. Osakidetza. Bilbao, Spain

REFERENCES

1. Restrepo CS, Largoza A, Lemos DF, Diethelm L, Koshy P, Castillo P, et al. CT and MR imaging findings of benign cardiac tumors. Curr Probl Diagn Radiol 2005;34:12-21. https://doi.org/10.1067/j.cpradiol.2004.10.002.
2. Motwani M, Kidambi A, Herzog BA, Uddin A, Greenwood JP, Plein S. MR imaging of cardiac tumors and masses: a review of methods and clinical applications. Radiology 2013;268:26-43. https://doi.org/10.1148/radiol.13121239.
3. Kirkpatrick JN, Wong T, Bednarz JE, Spencer KT, Sugeng L, Ward RP, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol. 2004;43:1412-9. https://doi.org/10.1016/j.jacc.2003.09.065.

REVIEW ARTICLE

Role of Myosin Inhibitors in Hypertrophic Cardiomyopathy: Evidence Review and Clinical Application

Rol de los inhibidores de miosina en miocardiopatía hipertrófica: revisión de la evidencia y aplicación clínica

SANTIAGO DECOTTO[1*], ANA SPACCAVENTO[2*], ROCIO BLANCO[1], DIEGO PÉREZ DE ARENAZA[1, MTSAC], JUAN PABLO COSTABEL[2, MTSAC]

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a complex genetic disease that can lead to serious complications, such as heart failure and potentially fatal arrhythmias. There are several widely used therapeutic options, such as beta-blockers, calcium channel blockers, and disopyramide. However, a significant proportion of patients with HCM remain refractory to pharmacological treatment, which may lead to invasive procedures, such as septal reduction therapies.
In this scenario, myosin inhibitors have emerged as an innovative strategy targeting the underlying pathophysiological mechanisms of the disease. By inhibiting cardiac myosin ATPase, these drugs reduce hypercontractility, improve myocardial relaxation, and lead to significant symptom relief, with a positive impact on the quality of life of patients with obstructive HCM.
This review article details the mechanisms of action of myosin inhibitors, the available clinical evidence, the therapeutic indications, and forms of use of these drugs.

Keywords: Hypertrophic cardiomyopathy - Mavacamten - Aficamten.

RESUMEN

La miocardiopatía hipertrófica (MCH) es una enfermedad genética compleja que puede provocar complicaciones graves, como insuficiencia cardíaca y arritmias potencialmente mortales. Existen diversas opciones terapéuticas ampliamente utilizadas, como los betabloqueantes, los bloqueantes cálcicos y la disopiramida. Sin embargo, una proporción significativa de pacientes con MCH persiste con síntomas refractarios a pesar del tratamiento farmacológico, lo que puede llevar a la necesidad de procedimientos invasivos, como las terapias de reducción septal.
En este escenario, los inhibidores de miosina han surgido como una estrategia innovadora dirigida a los mecanismos fisiopatológicos subyacentes de la enfermedad. Al inhibir la ATPasa de la miosina cardíaca, estos fármacos reducen la hipercontractilidad, mejoran la relajación miocárdica y conducen a un alivio significativo de los síntomas, con un impacto positivo en la calidad de vida de los pacientes con MCH obstructiva
Este artículo de revisión detalla los mecanismos de acción de los inhibidores de miosina, la evidencia clínica disponible, las indicaciones terapéuticas y las formas de uso de estos fármacos.

Palabras claves: Miocardiopatía hipertrófica - Mavacamten - Aficamten.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common and heterogeneous genetic disease, with an estimated prevalence of 1 in 200 to 1 in 500 people. It can present with variable symptoms and serious complications such as heart failure, arrhythmias, and sudden death. (1) It is classified as obstructive HCM (OHCM), characterized by dynamic obstruction of the left ventricular outflow tract (LVOT), and non-obstructive HCM (NOHCM). Although conventional treatments exist, some patients have refractory symptoms or require invasive procedures. In this context, myosin inhibitors have emerged as a new therapeutic strategy to address the underlying pathophysiological mechanisms of the disease. (2,3). This article will review their mechanism of action, the available evidence, in-

Rev Argent Cardiol 2025;93:372-379. https://doi.org/10.7775/rac.v93.i5.20924

Received: 09/16/2025 – *Accepted:* 10/18/2025

Correspondence: Juan Pablo Costabel - e-mail: jpcostabel@icba.com.ar

[1] Department of Cardiology. Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina
[2] Cardiomyopathy Clinic, Instituto Cardiovascular de Buenos Aires, Autonomous City of Buenos Aires, Argentina.
*Both authors contributed equally to this work.

dications and forms of use, as well as the associated adverse effects.

MECHANISMS OF ACTION

Myocardial hypercontractility is one of the central characteristics of HCM. This phenomenon results from alterations in actin-myosin interaction, often caused by mutations in sarcomeric genes. In addition to contributing to dynamic obstruction of the LVOT, hypercontractility promotes the development of myofibrillar disorders and myocardial fibrosis. (4,5)

Myosin antagonists, such as mavacamten and aficamten, act by directly modulating actin-myosin interaction, reducing the force of contraction and attenuating the chronic hypercontractile state of myocytes. These drugs selectively inhibit cardiac myosin ATPase, decreasing the formation of cross-bridges between actin and myosin, which results in lower myocardial contractility. In addition, they stabilize the super-relaxed state of myosin, reduce the release of inorganic phosphate, and limit the interaction of myosin with actin, counteracting the hypercontractility observed in HCM. (6) (Figure 1)

These agents increase the proportion of myosin molecules in a super-relaxed state and promote the kinetics of cross-bridge detachment, stimulate the release of adenosine diphosphate (ADP) from myosin, and promote the binding of adenosine triphosphate (ATP) to myosin. As a result, they not only decrease contractile force but also improve cardiac muscle relaxation, simultaneously addressing hypercontractility and diastolic dysfunction, two of the main pathophysiological mechanisms of HCM. (7-9)

PHARMACOLOGY

Mavacamten is a selective and reversible inhibitor of cardiac myosin ATPase, developed to modulate myocardial contractility. It is administered orally, in doses of 2.5 to 15 mg, with adequate bioavailability and a half-life of approximately 9 days, allowing once-daily dosing. Its metabolism is predominantly hepatic, mediated by CYP2C19 and, to a lesser extent, by CYP3A4 and CYP2C9. This makes it susceptible to interactions with inhibitors and inducers of these enzymes, which can affect its plasma concentration and efficacy. (10)

Aficamten is a second-generation inhibitor of cardiac myosin ATPase. Its dose is 5 to 20 mg, and its half-life is shorter than that of mavacamten (28 to 40 hours), allowing for faster dosage adjustments and a lower risk of accumulation. It is also administered orally and is metabolized in the liver, mainly by CYP3A4, with a lesser contribution from other cytochrome P450 enzymes. Compared with mavacamten, it has fewer relevant drug interactions and a more predictable safety profile, with no need for dose adjustment based on CYP2C19. (10,11)

Available studies suggest that neither drug is significantly excreted renally. However, the pharmacokinetics in patients with severe kidney impairment is not fully characterized. In the presence of moderate to severe hepatic impairment, drug accumulation may occur, although clinical data in these patients are limited.

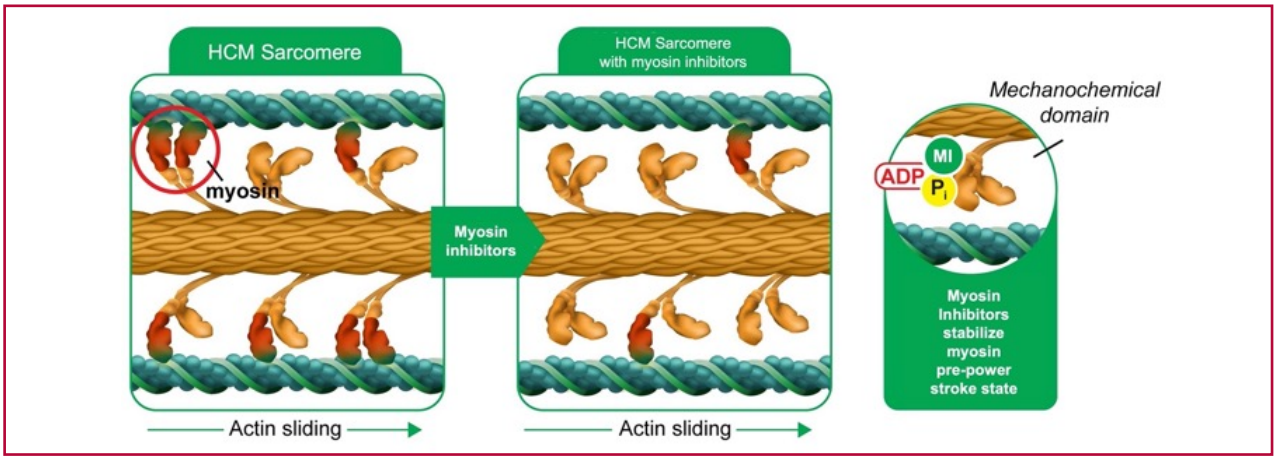
Mavacamten and aficamten are contraindicated during pregnancy due to their mechanism of action, which may affect fetal cardiovascular development. Therefore, effective contraceptive methods are recommended for women of childbearing age during treatment and for at least four months after discontinuation.

EVIDENCE IN PATIENTS WITH OHCM

Clinical trials

The clinical development of mavacamten began with the phase 2 PIONEER-HCM study, which demonstrated a significant reduction in LVOT obstruction gradient, both at rest and after exercise in patients with symptomatic OHCM. Patients treated with ma-

Fig. 1. Mecanism of action of aficamten and mavacamten



ADP: adenosine diphosphate; HCM: Hypertrophic cardiomyopathy; MI: myosin inhibitors; Pi: inorganic phosphate

vacamten experienced improvement in NYHA functional class and a reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP). In addition, peak oxygen consumption (peak VO_2) increased by an average of 1.5 mL/kg/min, reflecting an enhanced functional capacity. (12)

These results led to the phase 3 EXPLORER-HCM trial, which confirmed the efficacy of mavacamten in reducing LVOT gradient, with an average decrease of 40 mmHg.

In addition, 65% of treated patients showed improvement in at least one NYHA functional class, and peak VO_2 increased by 1.4 mL/kg/min compared with placebo. (13) In echocardiographic terms, 80.9% of patients in the mavacamten arm achieved complete resolution of systolic anterior mitral valve motion at 30 weeks, suggesting a significant impact on the pathophysiology of the disease. (14)

The phase 3 VALOR-HCM study evaluated mavacamten in patients with severe OHCM with an indication for septal reduction therapy. After 16 weeks of treatment, 82% of patients in the mavacamten arm no longer met criteria for intervention, compared with only 23% in the placebo group. A reduction in LVOT gradient from 51 mmHg to 14 mmHg was observed, with improvement in NYHA functional class and an increase in peak VO_2 of 1.7 mL/kg/min. (15)

Long-term data emerge from the MAVA-LTE study, which included patients previously treated in the EXPLORER-HCM trial, with 80-week follow-up. The results confirmed a progressive and sustained reduction in the LVOT gradients, from 48 mmHg to 10 mmHg, as well as a significant decrease in NT-proBNP from 783 ng/L to 123 ng/L. In addition, 60.2% of patients preserved improvement in their functional class. These findings suggest that mavacamten not only has a short-term symptomatic effect but may also modify disease progression. (16)

In turn, aficamten has shown a similar efficacy profile. In the REDWOOD-HCM phase 2 trial, treatment with aficamten resulted in a significant reduction in the obstructive gradient of 36 mmHg, accompanied by an improvement in NYHA functional class and a decrease in NT-proBNP. (17) In the phase 3 SEQUOIA-HCM study, aficamten achieved enhanced peak VO_2 of 1.9 mL/kg/min, with a favorable safety profile and a low incidence of left ventricular ejection fraction (LVEF) reduction. (18) A recently published key study is the MAPLE-HCM trial, the first to compare a myosin inhibitor with standard therapy. This phase 3 trial randomized patients with symptomatic OHCM to receive aficamten or metoprolol. At 24 weeks, aficamten achieved a significant reduction in LVOT gradient (-40.7 mmHg) in contrast to the modest reduction observed with metoprolol (-3.8 mmHg; $p<0.001$). Moreover, superior improvements were documented with aficamten in functional capacity (peak VO2: +1.1 vs. -1.2 ml/kg/min; $p=0.001$) and quality of life (KCCQ-CSS score: +15.8 vs. +8.7 points, $p=0.002$). In contrast, treatment with metoprolol was not associated with significant improvement in functional or symptomatic parameters. The safety profile of aficamten was favorable, with transient reductions in LVEF below 50% in 1% of patients, all of which were reversible. These findings reinforce the hypothesis that, unlike beta-blockers, myosin inhibitors such as aficamten act directly on the pathophysiological mechanism of obstruction and could redefine the initial treatment of OHCM. (19)

Table 1 summarizes the clinical trials conducted with mavacamten and aficamten.

Safety

In terms of safety, both drugs have been well tolerated. Between 6% and 7% of patients treated with mavacamten developed LVEF <50%, leading to temporal treatment suspension in some cases. However, this dysfunction was reversible upon drug discontinuation. In the case of aficamten, less than 2% of patients had an LVEF <50%, and in most cases ventricular function normalized after dose reduction. (13,18)

Hard events

Despite the benefits observed in terms of symptoms, oxygen consumption, and biomarkers, to date there is no clear evidence that mavacamten or aficamten reduce mortality or the incidence of ventricular arrhythmia in patients with OCHM. No reductions in mortality have been demonstrated, as clinical trials have been designed with functional and quality-of-life endpoints, without specifically evaluating long-term survival. There is also no conclusive evidence that these drugs reduce the arrhythmic burden or the risk of ventricular tachycardia and fibrillation, which are the main causes of sudden death in this population. It has been hypothesized that reducing wall stress with these agents could decrease the arrhythmic burden, but so far this has not been demonstrated in clinical trials. Regarding the need for implantable cardioverter-defibrillators, no changes in the current indication criteria have been reported.

Although studies with longer follow-up are still needed, myosin inhibitors currently represent a non-invasive alternative for the treatment of patients with OHCM who require septal intervention, such as septal myectomy and alcohol ablation. Both myectomy and septal ablation are invasive procedures associated with a very low risk of periprocedural mortality, (20,21) a risk that has not been observed with the use of myosin inhibitors.

Real-world evidence

Mavacamten has been approved by major regulatory agencies worldwide. However, to reduce the risk of left ventricular systolic dysfunction, heart failure, and drug interactions, its approval is subject to a risk evaluation and mitigation strategy (REMS) program. This program establishes education and continuous

Table 1. Main complete and published clinical trials of myosin inhibitors in adult patients with OHCM

Study (drug)	Study type	Endpoints	Results
PIONEER-HCM (mavacamten*) 2019 (12)	Phase II, multicenter, open label, non-randomized, n=21 Cohort A (n=11): Initial dose 10 or 15 mg Cohort B: (n=10): slow titration from 2 to 5 mg	Reduction of exercise LVOT gradients at 12 weeks. PeakVO2 assessment	Cohort A: mean change of –89.5 mmHg and 3.5 mL/kg/min Cohort B: mean change of 25 mmHg and 1.7 mL/kg/min
EXPLORER-HCM (mavacamten) 2020 (13)	Phase III, multicenter, randomized, double blind, controlled with placebo, n=251 Active group n=128 Placebo n=123	Increase of 1.5 mL/kg/min or more in peak VO2, plus 1 point reduction in NYHA FC or Increase > 3 mL/kg/min in peak VO2 without NYHA FC worsening at 30 weeks	37% mavacamten group vs. 17% placebo (p = 0.0005) PeakVO2: + 1.4 mL/kg/min in the mavacamten group vs. +0.1 mL/kg/min in the placebo group (p = 0.0006) Gradient: –35.6 mm Hg, p < 0.0001
VALOR-HCM (mavacamten) 2022 (15)	Phase III, multicenter, randomized, double blind, controlled with placebo, n=112.	Improvement implying abandoning the indication of septal reduction at 16 week	Continue with the indication: 18% with mavacamten vs. 77% with placebo, p<0.001 Gradient: –37.2 mm Hg vs. placebo, p < 0.001
REDWOOD (aficamten**) 2023 (17)	Phase II, multicenter Patients with LVOT gradients at rest ≥30 mmHg or provoked ≥50 mmHg. Assignment 2:1 aficamten/ placebo 10 weeks	Gradient changes in LVOT, LVEF and NYHA FC	-40 mmHg in the LVOT gradient at rest and - 36 mmHg in Valsalva in Cohort 1, and -43 mmHg at rest and - -53 mmHg during Valsalva in Cohort 2
SEQUOIA-HCM (aficamten) 2024 (18)	Phase III, multicenter, randomized, double blind, controlled with placebo n=282 Active group n=142 Placebo n=140	Change in peak oxygen consumption at 24 weeks Quality of life	Increase of 1.8mL/kg/min in the aficamten group vs. 0.0 mL/kg/min in placebo. ≥20 points in KCCQ-CSS: 29.7% vs. 12.4% in placebo
MAPLE -HCM (aficamten) 2025 (19)	Phase III, multicenter, randomized, double blind, aficamten vs metoprolol Aficamten n=87 Metoprolol n=88	Change in oxygen consumption at 24 weeks Quality of life	Peak VO2: 1.1 mL/kg/min in aficamten and -1.2 mL in metoprolol; p=0.001 LVOT gradient: –40.7 mmHg vs. –3.8 mmHg; p<0.001 KCCQ-CSS: +15.8 vs. +8.7 points p=0.002.

Mavacamten approved by Food Drug Administration (FDA), European Medicines Agency (EMA), and National Administration of Drugs, Food and Medical Technology (ANMAT).
** Aficamten not yet approved by FDA, EMA or ANMAT.

KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF: left ventricular ejection fraction; LVOT: Left ventricular outflow tract; NYHA FC: New York Heart Association functional class; OHCM: obstructive hypertrophic cardiomyopathy.

monitoring strategies, including mandatory training for healthcare professionals and periodic echocardiograms during follow-up.

In this context, Desai et al. published the results of the first 22 months of the REMS program at the end of 2024, providing data on the use of this drug in the United States. (22) Among a total of 5573 patients who received at least one dose of the drug and submitted the corresponding forms, 4.6% had a decline in LVEF, 1.3% were hospitalized for heart failure, and only 0.3% developed both complications jointly. The values were very similar in those patients who received the medication for at least one year. (22)

The drug dose used was 5 or 10 mg at six months of follow-up in most patients (74%), and only 5% required the maximum dose of 15 mg at that time. The main reason for dose reduction (95% of cases) was therapeutic adequacy, due to the achievement of a LVOT gradient < 20 mmHg. Finally, with regard to LVOT gradients, 42% persisted with resting gradients above 30 mmHg at 3 months after starting the drug, and only 29% at 6 months of treatment. As limita-

tions, this program is designed to ensure that the conditions for safe use of the drug are met (patients with LVEF > 50% and no interactions with other drugs), without evaluating the clinical criteria for the indication, the reason for discontinuation, the evolution of symptoms, or the requirement for septal reduction therapies. The latter was evaluated in some real-world cohorts with fewer patients, also with good results. (23-25) Concerning safety strategies, the regulatory agency in Europe (EMA) requires the analysis of polymorphisms in the cytochromes responsible for its metabolism prior to treatment initiation in order to adjust the initial dose. In Argentina, the evaluation of these polymorphisms is not necessary, and monitoring depends on clinical and echocardiographic variables.

EVIDENCE IN PATIENTS WITH NOHCM

The clinical development of mavacamten in NOHCM began with the phase 2 MAVERICK-HCM study, which included symptomatic patients with LVEF ≥ 55% and no significant LVOT obstruction. At 16 weeks, a significant reduction in NT-proBNP levels was observed in the mavacamten-treated group compared with placebo, suggesting an improvement in pressure overload and diastolic function. In addition, a reduction in ventricular stiffness, measured by the E/e' index, was observed, although without significant changes in LVEF or functional capacity as measured by peak VO2. (26)

These findings led to the design of the phase 3 ODYSSEY-HCM study, which evaluated the effects of mavacamten in a population of 580 patients with symptomatic NOHCM. At 48 weeks, the drug did not meet the primary endpoint of peak VO2 improvement (+1.0 mL/kg/min with mavacamten vs. +1.3 mL/kg/min with placebo; p=NS). However, benefits were observed in secondary parameters, including significant reductions in NT-proBNP (–50% vs. –10%; p<0.01) and ultrasensitive troponin T (–22% vs. placebo; p<0.05), as well as a favorable trend in the KCCQ-CSS score (+7 vs. +5 points). In terms of safety, a relevant finding was that 21.5% of patients treated with mavacamten developed LVEF <50%, which was reversible in most cases after treatment discontinuation.

These results suggest that, although mavacamten reduces hemodynamic load and biomarkers of myocardial stress, its effect on overall functional capacity is limited. One possible explanation is that the dose used could have been excessive and the exposure time relatively short, which could have attenuated the net clinical benefit observed in this population. (27)

In the case of aficamten, the phase 2 FOREST-HCM trial has shown encouraging preliminary results, with a reduction in NTproBNP and improved echocardiographic parameters of diastolic dysfunction. (28) The phase 3 ACACIA-HCM study is currently underway, evaluating the efficacy and safety of aficamten in a large cohort of patients with NOHCM, and will provide key evidence on its impact on cardiac function and symptoms.

MEDICATION TITRATION

Mavacamten is administered orally in 2.5 mg, 5 mg, 10 mg, and 15 mg capsules. The method of use, dosage, and titration are based on the regimen used in the EXPLORER-HCM study. (13)

The recommended starting dose is 5 mg once daily. Dose adjustment is suggested every 4 weeks, with a maximum daily dose of 15 mg. Strict clinical monitoring is essential to identify possible signs of heart failure, supplemented by echocardiographic monitoring focused mainly on the evaluation of LVEF and LVOT gradient, both before the start of treatment and during the subsequent follow-up. Treatment initiation is not recommended in patients with LVEF < 50%. Once initiated, it is advised to follow the scheme in Figure 2. (adapted from 29)

In the case of aficamten, the initial dose is 5 mg once daily with adjustments every 2 weeks due to its shorter half-life. Figure 3 outlines the titration algorithm used in the phase III SEQUOIA-HCM study. (18)

Clinically relevant and frequent drug interactions

Given its metabolism through the cytochrome system (mainly CYP2C19), the use of mavacamten should be avoided with drugs such as certain antifungals, certain macrolide antibiotics, some antidepressants, and protease inhibitors, among others, as well as grapefruit juice. CYP2C19 inhibitors and strong CYP3A4 inhibitors should be discontinued for at least 14 days before starting mavacamten. Aficamten does not interact with the cytochrome system, so there would be no such interaction and no further precautions would be necessary. Table 2 summarizes some of the relevant pharmacologic interactions for mavacamten.

COST-EFFECTIVENESS

The high cost of mavacamten raises questions about its cost-effectiveness compared with other therapeutic strategies. While it offers significant clinical benefits, its current price could place it outside the generally cost-effectiveness threshold accepted in some healthcare systems.

An analysis conducted in the United States by the Institute for Clinical and Economic Review (ICER) established that, for mavacamten to be considered cost-effective according to the thresholds used in that country, its annual price would need to be less than $15 000 (far from the current $85 000). (30) However, these conclusions are not directly applicable to other health systems, as the costs of treatments and procedures vary considerably between countries.

While mavacamten could reduce the need for invasive procedures and improve patients' quality of life, the cost remains a challenge for its widespread implementation. Its economic viability will depend on access strategies, price negotiations, and additional studies to assess its impact in real-world clinical practice.

As for aficamten, it is not yet commercially avail-

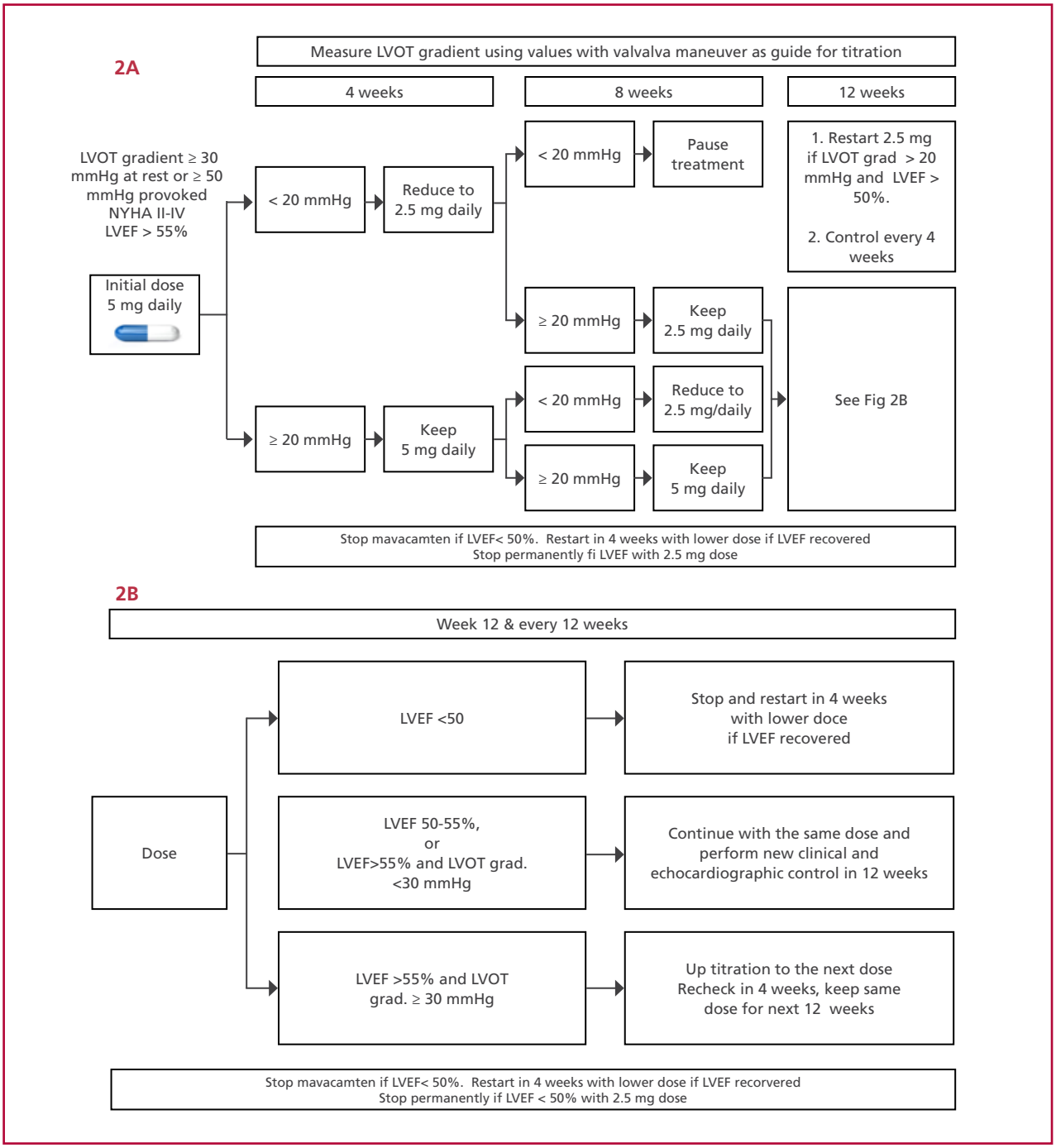
able, so it is not possible to analyze its cost-effectiveness at this moment.

CONCLUSION

Myosin inhibitors have proven to be a safe and effective option in the treatment of OCHD, currently positioning them as a second-line alternative. However, more evidence is still needed to consider them as a first-line treatment, especially in terms of their structural impact and their long-term effect on hard clinical events, such as mortality, arrhythmias, and need for devices. Their potential to modulate disease progression is a key aspect to investigate, particularly in relation to the regression of hypertrophy and the reduction of myocardial fibrosis.

On the other hand, their high cost and difficulty

Fig. 2. Mavacamtem titration algorithm. Adapted from (29)



LVEF: left ventricular ejection fraction; grad: gradient; LVOT: left ventricular outflow tract

Fig. 3. Titration of aficamten in SEQUOIA-HCM and MAPLE trials

LVOT gradient ≥ 30 mmHg at rest or ≥ 50 mmHg provoked
NYHA II-IV
LVEF > 55%

Initial Dose 5 mg/day

Control every 15 days (week 2 – week 4 – week 6)

LVEF	&	LVOT gradient with Valsalva maneuver	Action
≥ 55%	+	≥ 30 mmHg	Up titrate dose
≥ 55%	+	< 30 mmHg	Keep dose
< 55 % and ≥ 50 %		NA	Keep dose
< 50 % and ≥ 40 %		NA	Down titrate dose (Stop if dose was 5 mg)
< 40 %		NA	Stop for at least 7 days and consider restart only if last dose was ≥ 10 mg

LVEF: left ventricular ejection fraction; LVOT: Left ventricular outflow tract; NA: not available; NYHA FC: New York Heart Association functional class

Table 2. Relevant pharmacological interactions for mavacamten

Group	Effect	Example	Recomendation
Strong 2C19 inhibitors	Increase mavacamten plasma concentration	Fluoxetine, modafinil, ritonavir	Do not combine
Strong 3A4 inhibitors	Increase mavacamten plasma concentration	Clarithromycin, itraconazol, ritonavir, lopinavir, loperamide, efavirenz	Do not combine
Moderate 2C19 inhibitors	Slightly increase mavacamten plasma concentration	Sertraline, efavirenz, pantoprazole, lansoprazole, omeprazole, clarithromycin	Lower dose to 2.5 mg when starting any of these drugs
Moderate 3A4 inhibitors	Slightly increase mavacamten plasma concentration	Erythromycin, fluconazole, amiodarone, diltiazem, verapamil, grapefruit juice	Lower dose to 2.5 mg when starting any of these drugs
3A4 and 2C19 inducers	Decrease mavacamtem concentration and increase it when discontinued	Rifampicin, phenytoin, dexamethasone, modafinil, efavirenz	Precaution when suspending any of these drugs

of access in many healthcare systems, including ours, limit their availability and underscore the importance of careful selection of patients who can benefit most. Despite these challenges, their use in nonobstructive forms and in asymptomatic patients is promising, opening new perspectives in the management and possible modification of the natural course of HCM.

Conflicts of interest

None declared.

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

REFERENCES

1. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Management of Hypertrophic Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2022;79:390-414. https://doi.org/10.1016/j.jacc.2021.11.021

2. Gill R, Siddiqui A, Yee B, DiCaro MV, Houshmand N, Tak T. Advancements in the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Comprehensive Review. J Cardiovasc Dev Dis [Internet] 2024;11;290. http://dx.doi.org/10.3390/jcdd11090290

3. Kalinski JK, Xu B, Boyd R, Tasseff N, Rutkowski K, Ospina S, et al. Novel Cardiac Myosin Inhibitor Therapy for Hypertrophic Cardiomyopathy in Adults: A Contemporary Review. Am J Cardiovasc Drugs 2024;24:591-602. https://doi.org/10.1007/s40256-024-00667-z.

4. Sequeira V, Bertero E, Maack C. Energetic drain driving hypertrophic cardiomyopathy. FEBS Lett 2019;593:1616–26. https://doi.org/10.1002/1873-3468.13496

5. Toepfer CN, Garfinkel AC, Venturini G, Wakimoto H, Repetti G, Alamo L, et al. Myosin Sequestration Regulates Sarcomere Function, Cardiomyocyte Energetics, and Metabolism, Informing the Pathogenesis of Hypertrophic Cardiomyopathy. Circulation 2020;141:828-42. https://doi.org/10.1161/CIRCULATIONAHA.119.042339.

6. Rohde JA, Roopnarine O, Thomas DD, Muretta JM. Mavacamten stabilizes an autoinhibited state of two-headed cardiac myosin. Proc Natl Acad Sci U S A 2018;115:E7486–94. https://doi.org/10.1073/pnas.1720342115

7. Anderson RL, Trivedi DV, Sarkar SS, Henze M, Ma W, Gong H, et al. Deciphering the super relaxed state of human β-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A 2018;115:E8143-E8152. https://doi.org/10.1073/pnas.1809540115.

8. Lehman SJ, Crocini C, Leinwand LA. Targeting the sarcomere in inherited cardiomyopathies. Nat Rev Cardiol 2022;19:353-63. https://doi.org/10.1038/s41569-022-00682-0
9. Sykuta A, Yoon CH, Baldwin S, Rine NI, Young M, Smith A. Cardiac Myosin Inhibitors: Expanding the Horizon for Hypertrophic Cardiomyopathy Management. Ann Pharmacother 2024;58:273–85. https://doi.org/10.1177/10600280231180000
10. Lancellotti P, de Marneffe N, Scheen A. [Mavacamten (Camzyos ®) : first myosin modulator for obstructive hypertrophic cardiomyopathy treatment]. Rev Med Liege 2024;79:120–8.
11. Chuang C, Collibee S, Ashcraft L, Wang W, Vander Wal M, Wang X, et al. Discovery of Aficamten (CK-274), a Next-Generation Cardiac Myosin Inhibitor for the Treatment of Hypertrophic Cardiomyopathy. J Med Chem 2021;64:14142-52. https://doi.org/10.1021/acs.jmedchem.1c01290.
12. Heitner SB, Jacoby D, Lester SJ, Owens A, Wang A, Zhang D, et al. Mavacamten Treatment for Obstructive Hypertrophic Cardiomyopathy: A Clinical Trial. Ann Intern Med 2019;170:741-8. https://doi.org/10.7326/M18-3016..
13. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, et al; EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69. https://doi.org/10.1016/S0140-6736(20)31792-X.
14. Hegde SM, Lester SJ, Solomon SD, Michels M, Elliott PM, Nagueh SF, et al. Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2021;78:2518-32. https://doi.org/10.1016/j.jacc.2021.09.1381..
15. Desai MY, Owens A, Geske JB, Wolski K, Naidu SS, Smedira NG, et al. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. J Am Coll Cardiol 2022;80:95-108. https://doi.org/10.1016/j.jacc.2022.04.048.
16. Garcia-Pavia P, Oręziak A, Masri A, Barriales-Villa R, Abraham TP, Owens AT, et al. Long-term effect of mavacamten in obstructive hypertrophic cardiomyopathy. Eur Heart J 2024;45:5071-83. https://doi.org/10.1093/eurheartj/ehae579.
17. Maron MS, Masri A, Choudhury L, Olivotto I, Saberi S, Wang A, et al; REDWOOD-HCM Steering Committee and Investigators. Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2023;81:34-45. https://doi.org/10.1016/j.jacc.2022.10.020.
18. Maron MS, Masri A, Nassif ME, Barriales-Villa R, Arad M, Cardim N, et al; SEQUOIA-HCM Investigators. Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy. N Engl J Med 2024;390:1849-61. https://doi.org/10.1056/NEJMoa2401424.
19. Garcia-Pavia P, Maron MS, Masri A, Merkely B, Nassif ME, Peña-Peña ML, et al; MAPLE-HCM Investigators. Aficamten or Metoprolol Monotherapy for Obstructive Hypertrophic Cardiomyopathy. N Engl J Med 2025;393:949-60. https://doi.org/10.1056/NEJMoa2504654.
20. Maron MS, Rastegar H, Dolan N, Carpino P, Koethe B, Maron BJ, et al. Outcomes Over Follow-up ≥10 Years After Surgical Myectomy for Symptomatic Obstructive Hypertrophic Cardiomyopathy. Am J Cardiol 2022;163:91-7. https://doi.org/10.1016/j.amjcard.2021.09.040.
21. Batzner A, Pfeiffer B, Neugebauer A, Aicha D, Blank C, Seggewiss H. Survival After Alcohol Septal Ablation in Patients With Hypertrophic Obstructive Cardiomyopathy. J Am Coll Cardiol 2018;72:3087–94. https://doi.org/10.1016/j.jacc.2018.09.064
22. Desai MY, Seto D, Cheung M, Afsari S, Patel N, Bastien A, et al. Mavacamten: Real-World Experience From 22 Months of the Risk Evaluation and Mitigation Strategy (REMS) Program. Circ Heart Fail 202518:e012441. https://doi.org/10.1161/CIRCHEARTFAILURE.124.012441.
23. Abdelfattah OM, Lander B, Demarco K, Richards K, Dubose D, Martinez MW. Mavacamten Short-Term Hemodynamic, Functional, and Electrocardiographic Outcomes: Initial Real-World Post-Trial Experience. JACC Adv 2023;2:100710. https://doi.org/10.1016/j.jacadv.2023.100710
24. Desai MY, Hajj-Ali A, Rutkowski K, Ospina S, Gaballa A, Emery M, et al. Real-world experience with mavacamten in obstructive hypertrophic cardiomyopathy: Observations from a tertiary care center. Prog Cardiovasc Dis 2024;86:62-68. https://doi.org/10.1016/j.pcad.2024.02.001.
25. Reza N, Dubey A, Carattini T, Marzolf A, Hornsby N, de Feria A, et al. Real-World Experience and 36-Week Outcomes of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy Treated With Mavacamten. JACC Heart Fail 2024;12:1123-5. https://doi.org/10.1016/j.jchf.2024.03.009.
26. Ho CY, Mealiffe ME, Bach RG, Bhattacharya M, Choudhury L, Edelberg JM, et al. Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2020;75:2649-60. https://doi.org/10.1016/j.jacc.2020.03.064.
27. Desai MY, Owens AT, Abraham T, Olivotto I, Garcia-Pavia P, Lopes RD, et al; ODYSSEY-HCM Investigators. Mavacamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy. N Engl J Med 2025;393:961-72. https://doi.org/10.1056/NEJMoa2505927.
28. Masri A, Barriales-Villa R, Elliott P, Nassif ME, Oreziak A, Owens AT, et al; on behalf of the FOREST-HCM Investigators. Safety and efficacy of aficamten in patients with non-obstructive hypertrophic cardiomyopathy: A 36-week analysis from FOREST-HCM. Eur J Heart Fail 2024;26:1993-8. https://doi.org/10.1002/ejhf.3372.
29. Bello J, Pellegrini MV. Mavacamten. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
30. Beinfeld M, Wasfy JH, Walton S, Sarker J, Nhan E, Rind DM, et al. Mavacamten for hypertrophic cardiomyopathy: effectiveness and value. J Manag Care Spec Pharm 2022;28:369-75. https://doi.org/10.18553/jmcp.2022.28.3.369

SCIENTIFIC LETTER

Acute Myeloid Leukemia Presenting as Acute Lower Limb Ischemia: A Case Report

Presentación de leucemia mieloide aguda como isquemia aguda de miembro inferior. Reporte de un caso

IGNACIO PEPE[1], FRANCO IMBROGNIO[1], ROCIO GAU[2], PABLO SALVADORES[2], DIEGO HERRERA VEGAS[2]

INTRODUCTION

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by the infiltration of bone marrow, peripheral blood and, occasionally, other tissues by aberrant and abnormally differentiated clones of the myeloid lineage. (1) It accounts for 80% of acute leukemia cases in adults, and its incidence increases with age. (2)

From a clinical perspective, AML typically presents with symptoms of bone marrow failure, such as anemia, recurrent infections, or bleeding, reflecting pancytopenia. In other cases, it may present with marked leukocytosis, which can lead to hyperviscosity and leukostasis-related complications. (3)

Although initial thrombotic manifestations are uncommon, they may occur in cases of hyperleukocytosis, presenting as neurological, pulmonary, or microvascular events. (3,4) Large-vessel arterial thromboembolic complications, such as acute lower-limb ischemia, are infrequent initial manifestations and present diagnostic and therapeutic challenges. (5,6)

The case we describe involves a patient with no significant medical history who presented with acute arterial ischemia as the initial manifestation of AML. This clinical presentation is exceptional and recognizing it is crucial for an early diagnosis and appropriate treatment.

The patient was a previously healthy 70-year-old man, who presented with a sudden onset of severe (intensity 9/10) pain in the right calf, accompanied by sensory impairment and fever. On physical examination, the right lower limb was cold and pale, and no distal pulses were present. These findings were consistent with acute arterial ischemia.

Arterial and venous Doppler ultrasound and computed tomography (CT) angiography revealed thrombosis in the distal popliteal artery extending to the posterior tibial artery, with no evidence of deep venous thrombosis.

Laboratory tests on admission revealed leukocytosis (white blood cell count 64 370/mm^3, with 86% immature cells, consistent with blasts), thrombocytopenia (platelet count 47 000/mm^3), mild anemia (hemoglobin 12.4 g/dL, hematocrit 37.4%), and elevated creatine phosphokinase (CPK) (1331 U/L), with no evidence of renal failure or elevated transaminases.

Given the suspicion of AML, consultation with hematology experts was sought, who ordered a bone marrow aspiration and biopsy. As the condition progressed, an initial hybrid therapy was performed. This consisted of fluoroscopy-guided thrombectomy using a Fogarty catheter and balloon angioplasty in the popliteal artery, where an atherosclerotic plaque was identified. Intraoperative angiography (Figure 1) showed the following:

- Occlusion of the popliteal artery.
- Occlusion of the anterior tibial artery, not suitable for revascularization.
- Occlusion of the peroneal artery with poor distal blood flow.
- Occlusion of the posterior tibial artery with inadequate recanalization.

Thromboembolectomy was performed on the femoropopliteal and tibial axes, achieving satisfactory technical outcomes and initial clinical improvement. However, due to early reocclusion, a repeat procedure involving multilevel arteriotomy and extensive thromboembolectomy was necessary.

The following day, the patient suffered an ischemic stroke, as confirmed by magnetic resonance angiography. This was attributed to AML. Meanwhile, the affected limb progressed to necrosis with recurrent

Rev Argent Cardiol 2025;93:380-382. http://doi.org/10.7775/rac.v93.i5.20922

Correspondence: Ignacio Pepe. E-mail: ignaciopepe.ip@gmail.com

[1] CEMIC University Institute, Autonomous City of Buenos Aires, Argentina
[2] Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Autonomous City of Buenos Aires, Argentina

Fig. 1. Angiography showing arterial thrombosis of the right lower limb.

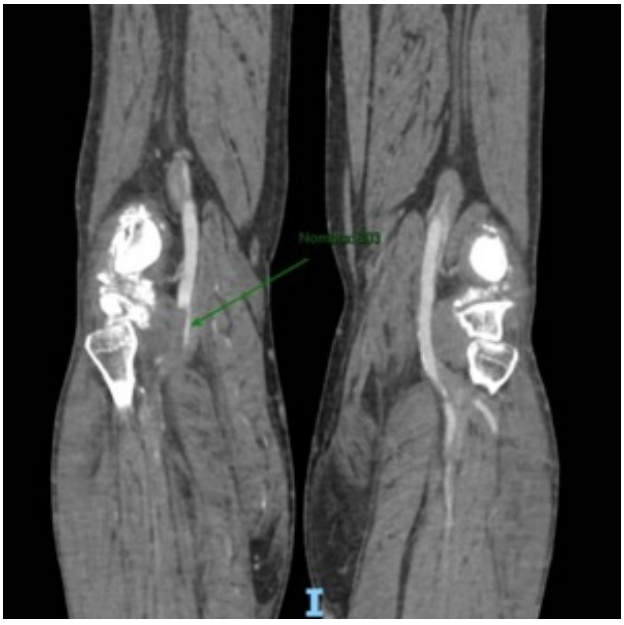
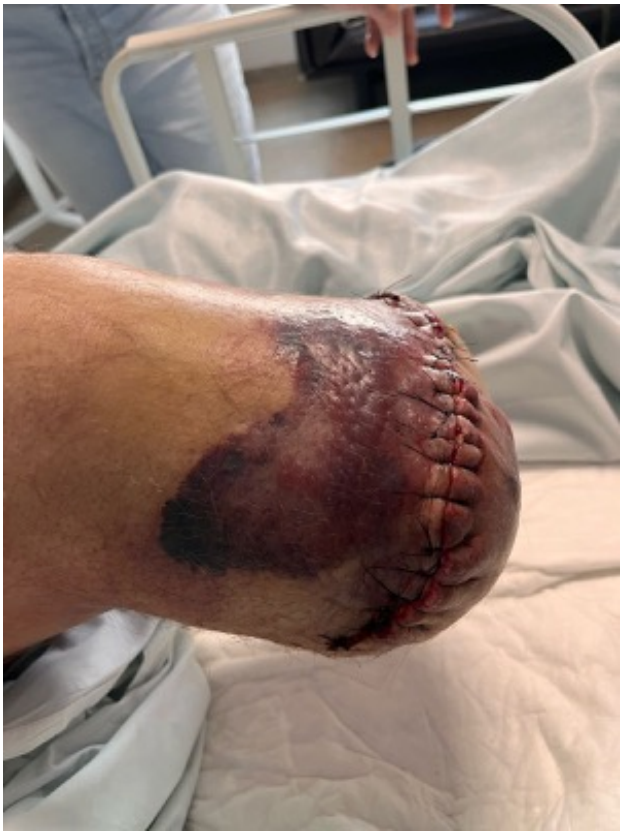


Fig. 2. Infracondylar amputation of the right lower limb



obstruction on Doppler ultrasound, so an infracondylar amputation was performed (Figure 2).

In the immediate postoperative period, the patient remained stable. However, 48 hours later, he developed a surgical wound infection and was treated with piperacillin-tazobactam and vancomycin. Seventy-two hours after the onset of symptoms, the patient suffered a cardiorespiratory arrest and died.

The case was interpreted as AML with multiple arterial thrombotic events mediated by hyperleukocytosis and leukostasis, resulting in a fatal outcome despite the multidisciplinary approach.

Arterial ischemia at the onset of AML is rare and has only been documented in isolated reports. (5,6) The disease usually presents insidiously with constitutional symptoms, hemorrhages or pancytopenia. (1,2)

The pathophysiology is multifactorial. Leukostasis involves microvascular obstruction caused by the accumulation of blasts, resulting in hypoperfusion and secondary thrombosis. (3) Although it is classically associated with a leukocyte count >100 000/mm^3, cellular adhesion and the interaction with the endothelium allow it to occur even at lower counts. (3) In this case, with a leukocyte count of 64 370/ mm^3 and 86% blasts, the "microleukostasis phenomenon" (leukostasis in microvessels) likely occurred.

In addition, AML induces a systemic prothrombotic state through multiple mechanisms, including tissue factor expression in blasts, cytokine release, endothelial activation, and platelet dysfunction. This leads to arterial and venous thrombosis, which is a different phenomenon from atherothrombosis or cardiogenic embolism. There are reports of thrombi predominantly composed of blasts. (4)

The literature reflects the uncommon and severe nature of this condition. A systematic review identified 26 cases of arterial ischemia in acute leukemia over four decades, with approximately half occurring in AML. Amputation rates were 30%, and 30-day mortality was high. (5) Case reports, such as that of Kafetzakis et al., have documented femoral thrombosis without underlying atherosclerosis, attributing it to leukostasis and the intrinsic hypercoagulability of the disease. (6)

Management requires an emergency multidisciplinary approach. Alongside vascular surgery, immediate measures to treat hematologic malignancies, such as leukapheresis and induction chemotherapy, must be promptly initiated to reduce the tumor burden and improve perfusion. (3)

In conclusion, AML may initially present with atypical symptoms, such as acute arterial ischemia of a lower limb. This case emphasizes the importance of considering a wide range of potential diagnoses in cases of sudden ischemia in previously healthy patients with no cardiovascular risk factors. Identifying AML as an underlying cause of arterial events enables timely referral to hematology specialists and the initiation of specific treatment. The case also highlights the importance of interdisciplinary collaboration among different departments, such as Emergency, Vascular

Surgery, Intensive Care, and Hematology, to achieve an accurate diagnosis and optimize therapy.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

REFERENCES

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2022 ELN recommendations from an international expert panel. Blood 2022;140:1345-77. https://doi.org/10.1182/blood.2022016867

2. Tallman MS, Gilliland DG, Rowe JM. Drug therapy for acute myeloid leukemia. Blood 2005;106:1154-63. https://doi.org/10.1182/blood-2005-01-0178

3. Porcu P, Cripe LD, Ng EW, et al. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. Leuk Lymphoma 2000;39:1-18. https://doi.org/10.3109/10428190009053534

4. Novotny JR, Müller-Beissenhirtz H, Herget-Rosenthal S, et al. Arterial thrombotic events as a first manifestation of acute promyelocytic leukemia. Haematologica 2008;93:e25-7.

5. Bontinis A, Bontinis V, Koutsoumpelis A, Perifanis V, Kaiafa G, Giannopoulos A, et al. Acute leukemia presenting as acute lower limb ischemia. Vasa 2022;51:37-45. https://doi.org/10.1024/0301-1526/a000977

6. Kafetzakis A, Foundoulakis A, Ioannou CV, Stavroulaki E, Koutsopoulos A, Katsamouris AN. Acute lower limb ischemia as the initial symptom of acute myeloid leukemia. Vasc Med 2007;12:199-202. https://doi.org/10.1177/1358863X07080630

SCIENTIFIC LETTER

Left Bundle Branch Pacing in a Patient with Orthotopic Heart Transplantation and Pacemaker-Induced Cardiomyopathy: First Case in Argentina

Estimulación de la rama izquierda en paciente con trasplante cardíaco ortotópico con miocardiopatía inducida por marcapasos: primer caso en Argentina

MARIEL ÁLVAREZ CORREA[1], NÉSTOR GALIZIO[1], GUILLERMO CARNERO[1], MAURICIO MYSUTA[1], VANESA AUDIL[1], JOSÉ LUIS GONZÁLEZ[1]

Sinus node dysfunction (SND) and atrioventricular block may require pacemaker (PM) implantation in patients with orthotopic heart transplantation (OHT). This is a case of a female patient with post-OHT SND who underwent DDR PM implantation and developed pacemaker-induced cardiomyopathy and left ventricular systolic dysfunction, which required an upgrade to left bundle-branch pacing (LBBP).

The patient was a 26-year-old female, who underwent an OHT in 2012 due to dilated cardiomyopathy requiring extracorporeal membrane oxygenation (ECMO) support for 14 days. In 2019, a dual-chamber pacemaker was implanted due to SND, and during the last year, she was hospitalized for dengue and infectious endocarditis. She required explantation and reimplantation of the pacemaker. An endomyocardial biopsy (EMB) was indicated in the context of acute dengue because of a drop in left ventricular ejection fraction (LVEF). The biopsy showed mild, grade 1R rejection (ISHLT 2005), pAMR1 (+). The patient did not receive treatment; the subsequent EMB showed no rejection and a LVEF of 52%. She showed an increase in the percentage of ventricular pacing (VP 92%) and a deterioration in LVEF, so the following studies were performed:

- Cardiac Doppler ultrasound: Left ventricular dilatation with left ventricular diastolic diameter (LVDD) of 54 mm, indexed 33.5 mm/m². LVEF 40%. Akinesia of the basal inferoseptal, inferior, and basal and mid inferolateral walls. Abnormal interventricular septum motion. Right ventricle (RV) normal. Moderate mitral regurgitation (MR) due to restrictive closure of the posterior leaflet. Moderate tricuspid regurgitation (TR) with central jet. Systolic pulmonary artery pressure (sPAP) 30 mmHg. E-wave deceleration time 91 ms. Pulmonary acceleration time 148 ms. Isovolumic relaxation time 83 msec.
- Holter electrocardiography (ECG): PM rhythm (atrial sensing (AS)-ventricular pacing (VP) at 80 bpm (60-88); 655 premature supraventricular beats (PSVBs) with no runs of tachycardia (<1%). No pauses.
- ECG: atrial sensing and ventricular pacing at 60 bpm with isolated PSVBs (Figure 1A).
- Cine-coronary angiography (cine-CAG): no significant angiographic lesions. Mild lesion in the mid-segment of the circumflex artery.
- Intervalometer data: DDD mode (60-130 bpm). ECG AS/VP (AP 23%, VP 92.4%). Battery 10A/3.02 V. AV interval 180-150 ms. Sensing: P wave 0.4 mV, R wave dependent. Outputs: RA 3.5V/0.4 ms, RV 2.5 V/0.4 ms. Thresholds: RA NR (AT/AF), RV 0.5 V/0.4 ms. Impedances: RA 361 Ω, RV 380 Ω. From September 20 to September 27: AT/AF episodes with RA lead sensing failure.
- Endomyocardial biopsy: EM G0 ISHLT.

Current treatment: tacrolimus, meprednisone, rapamycin, acetylsalicylic acid, bisoprolol, B complex, rosuvastatin, folic acid, ferrous sulfate, magnesium, potassium, lamotrigine,brivaracetam, trimetoprime, sulfametoxazol, warfarin.

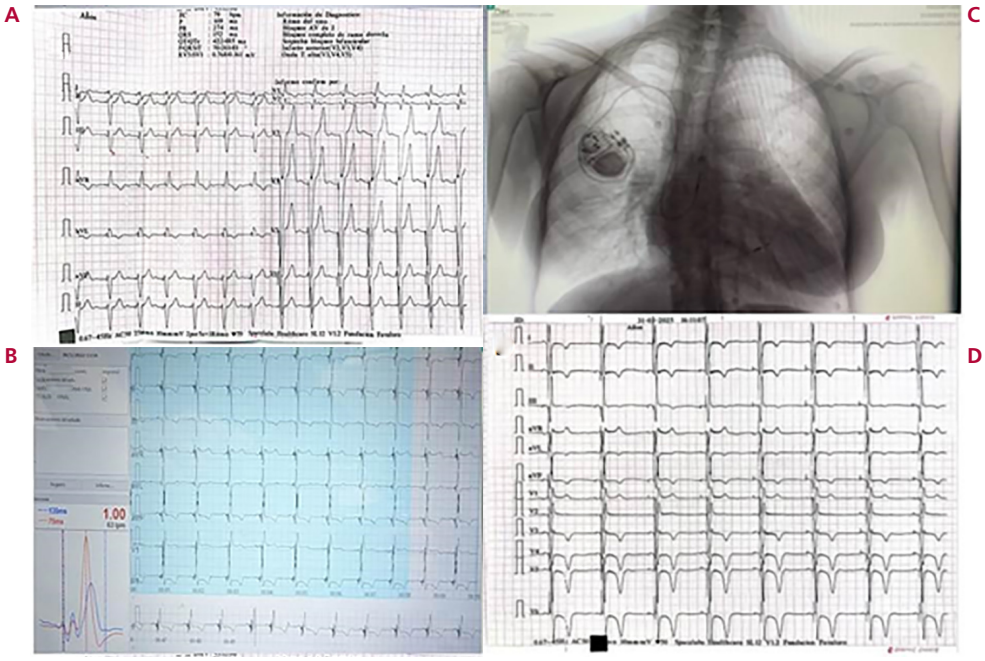
Progression to left ventricular systolic dysfunction was interpreted as pacemaker-induced cardiomyopathy due to the high percentage of ventricular pacing. It was decided to upgrade to physiological left bundle-branch pacing and to reposition the RA lead. A right deltopectoral incision was made, the generator was exposed, and the RA lead was extracted by simple traction. A right jugular puncture was performed, and

Rev Argent Cardiol 2025;93:383-385. http://doi.org/10.7775/rac.v93.i5.20923

Correspondence: Mariel Alvarez Correa. Fundación Favaloro, University Hospital. E-mail: marielalvarez1126@gmail.com

[1] Department of Electrophysiology and Arrhythmias. Fundación Favaloro University Hospital.

Fig. 1. A. Pre-implantation ECG: dual-chamber pacemaker rhythm with a pattern consistent with complete left bundle-branch block (LBBB). **B.** ECG during implantation showing QRS duration of 135 ms and a patent rSR' pattern in lead V1. **C.** Post-implantation chest X-ray. **D.** Post-implantation ECG showing QRS duration of 135 ms and negative T waves in the anterolateral leads (electrotonic modulation).



a 7 Fr introducer was advanced. A curved sheath was inserted into the right ventricle and positioned in the interventricular septum. An active fixation lead (Select Secure MRI Surescan, Medtronic) was advanced and fixed to the septum to achieve left bundle- branch. An 8 Fr introducer sheath was then inserted via the right subclavian puncture under the clavicle, and the lead was advanced and secured in the right atrium with an adequate threshold. It was connected to the DR generator in the pectoral pocket. The previous right ventricular lead was removed by simple traction without complications.

Post-implantation electrocardiography: Sinus rhythm 60 bpm, QRS 135 ms with rSR' pattern in V1 (Figures 1B and 1D).

Chest X-ray: Normally positioned leads without complications (Figure 1C).

The most common conduction abnormality following heart transplantation is right bundle-branch block. (1-2) In this case, the patient developed SND requiring permanent cardiac pacing and subsequently progressed to increased ventricular pacing requirements, leading to left ventricular systolic dysfunction (LVSD). (3) Common etiologies of LVSD were ruled out through cine-CAG and EMB. Although mild cellular rejection cannot be completely ruled out as the cause of late graft failure, the lack of improvement in LVEF with immunosuppression argues against it being the cause of LVSD. A pacemaker with LBBP was then implanted.

To our knowledge, this is the first case reported in Argentina of LVSD due to a high percentage of ventricular pacing in a transplanted heart treated with LBBP. We believe that the temporal relationship between the high percentage of pacing and the development of LVSD, followed by an adequate response, would demonstrate pacing-induced cardiomyopathy. (4-5) LBBP corrected the pacing-induced pseudo-left bundle branch block (LBBB), thus overcoming the electrical dyssinchrony caused by the pacemaker. Six months later, new echocardiographic measurements of LV function will be performed to assess its progression.

Acknowledgments
Carlos Perona (Proctor).

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

Ethical considerations
Not applicable

REFERENCES

1. Golshayan D, Seydoux C, Berguer DG, Stumpe F, Hurni M, Ruchat P, et al. Incidence and prognostic value of electrocardiographic abnormalities after heart transplantation. Clin Cardiol. 1998;21:680-4.

https://doi.org/10.1002/clc.4960210914.
2. Ferretto S, Tafciu E, Giuliani I, Feltrin G, Bottio T, Gambino A, et al. Interventricular conduction disorders after orthotopic heart transplantation: risk factors and clinical relevance. Ann Noninvasic Electrocardiol. 2017;22:e12402. https://doi.org/10.1111/anec.12402.
3. Vaillant C, Martins RP, Donal E, Leclercq C, Thébault C, Behar N, et al. Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. J Am Coll Cardiol. 2013;61:1089–95. https://doi.org/10.1016/j.jacc.2012.10.053.
4. Sze E, Dunning A, Loring Z, Atwater BD, Chiswell K, Daubert JP, et al. Comparison of incidence of left ventricular systolic dysfunction among patients with left bundle branch block versus those with normal QRS duration. Am J Cardiol 2017;120:1900–7. https://doi.org/10.1016/j.amjcard.2017.08.003.
5. Do DH, Bailey KL, Beyer R, Neubuerger S, Bradfield J, Shivkumar K, et al. Outcomes in orthotopic heart transplantation following pacemaker implantation. Pacing Clin Electrophysiol 2023;46:583-91. https://doi.org/10.1111/pace.14716.

OPINION ARTICLE

Two Views on Congestion

Dos visiones sobre la congestión

Is It Time to Incorporate Urinary Sodium as a Therapeutic Guideline in Heart Failure?

CRISTHIAN EMMANUEL SCATULARO[1, MTSAC], JORGE THIERER[2, MTSAC]

Acute heart failure (AHF) is one of the leading causes of hospitalization in people over 65 years of age worldwide, with an in-hospital mortality rate of up to 7%. Despite notable advances in pharmacological and device-based management, optimizing diuretic treatment remains one of the most complex and least standardized clinical aspects. (1-3)

For decades, the evaluation of diuretic response has been based on indirect parameters such as body weight, total diuresis, water balance, and clinical assessment of congestion. However, these indicators have low sensitivity and specificity, especially in patients with advanced HF, refractory congestion, or impaired renal function. (1-3) In this context, urinary sodium measurement emerges as a tool both for assessing diuretic efficiency (4-11) and for guiding decongestive treatment. (12-16)

The recent position paper "*Urinary sodium analysis: The key to effective diuretic titration?*", published by Meekers et al. in the European Journal of Heart Failure, (17) presents a detailed and critical review of the renal mechanisms involved in water and salt retention in patients with AHF, therapeutic options in cases of diuretic resistance (DR), and the role of urinary sodium in monitoring and therapeutic guidance in these patients.

Patients with significant neurohormonal activation, chronic or acute renal impairment due to congestion and reduced renal perfusion, as well as those with hypoalbuminemia and chronic use of furosemide, experience greater water and salt retention and less effective diuretic treatment. (15,16) This condition, known as DR, can occur in up to 40% of cases of AHF and undoubtedly constitutes a therapeutic challenge. In these patients, a combination of diuretics to block sodium reabsorption in different sectors of the nephron could be beneficial, requiring careful and individualized evaluation of congestion and diuretic response. (15,16) It is then when multiparametric assessment of congestion and measurement of diuretic efficacy expressed by natriuresis become essential.

The document provides a review of the main studies that demonstrated benefits in terms of decongestion from the combination of diuretics in patients with DR.

The ADVOR (intravenous acetazolamide 500 mg/day vs. placebo) and CLOROTIC (hydrochlorothiazide 25-100 mg/day adjusted for renal function vs. placebo) studies have shown that adding these drugs to intravenous furosemide in patients with DR is associated with increased diuresis, natriuresis, weight loss, and successful clinical decongestion, with no impact on mortality or readmissions for HF, and with increased risk of worsening renal function and hypokalemia with hydrochlorothiazide. (18,19)

Mineralocorticoid receptor antagonists could be useful in patients with acute HF and DR, as demonstrated by the ATHENA study, (20) although they have a slower onset of action and are therefore probably not useful in patients who require aggressive and rapid decongestion due to the clinical severity of their condition. The possibility of using gliflozins in patients with acute HF is also noteworthy, as they have demonstrated an adequate safety and efficacy profile in various studies, (21-24) although their diuretic action also begins at approximately 48 hours. (25) Although dapagliflozin was not superior to metazolone in patients with AHF and DR in the DAPA-RESIST study, (26) it should be noted that gliflozins provide additional modest diuresis and have long-term cardio- and nephroprotective effects. (27) It is possible that both drugs, antialdosterone agents and gliflozins, will be reserved for patients with AHF and DR with a certain degree of compensation or possibly close to discharge.

Given the complexity of decongestive treatment,

Rev Argent Cardiol 2025;93:386-390. https://doi.org/10.7775/rac.v93.i5.20908

Correspondence: Cristhian Emmanuel Scatularo. Email: emmanuelscatularo@gmail.com

[1] Coronary Care Unit – Sanatorio de la Trinidad de Palermo – Buenos Aires, Argentina.
[2] Heart Failure Unit – Sanatorio CEMIC – Buenos Aires, Argentina

urinary sodium measurement emerges as a direct, quantifiable, and dynamic tool for assessing the actual natriuretic effect of intravenous diuretics, allowing for objective evaluation of the therapeutic response in the first hours after administration. In addition, there is significant evidence supporting the association between natriuresis in patients with AHF and in-hospital evolution and outpatient follow-up at 6 months after the event. (4-11)

The use of urinary sodium in spot samples, generally 2 hours after diuretic administration, is an early marker of response and may allow for more agile and personalized treatment titration, thus reducing clinical variability in congestion management, medical inertia, and risk of failure during decongestion. (15,16) Diuretic titration is recommended if the urinary sodium concentration is <70 mmol/L, bearing in mind that other cut-off points such as 50 meq/L are less sensitive in detecting patients with DR, and of course taking into account a urinary volume of less than 100-150 mL/h. (17) In a recently published study in Argentina, a single measurement of natriuresis 2 hours after a 40 mg intravenous bolus of furosemide upon hospital admission, with a cutoff point of 70 meq/L, was associated with worse in-hospital outcomes (DR, persistent congestion, use of more aggressive decongestion therapies and inotropes, and cardiovascular death). (11)

Finally, Meekers et al. present a possible algorithm for the therapeutic management of diuretics based on urinary sodium in patients with acute HF and DR, which attempts to summarize the evidence on the benefits of using tubular blockade and of three important studies that demonstrated significant improvements in natriuresis and diuresis when following therapeutic guidelines based on urinary sodium (ENACT-HF, PUSH-AHF, and EASY-HF). (28-30)

This is a pragmatic algorithm for managing diuretic therapy and assessing congestion, with fewer urinary sodium measurements but a more aggressive and early approach to tubular blockade than other previously proposed algorithms. (15,16) Although this would possibly reduce hospital stay and achieve greater success in decongestion, it necessarily implies closer control of blood volume status, tissue congestion, and the possible adverse effects of these drugs. In addition, the greater benefit of combining acetazolamide with thiazides is emphasized due to its better renal safety profile, as evidenced in the ADVOR and CLOROTIC trials, (18,19) although the choice must undoubtedly be personalized based on renal function and electrolyte and acid-base imbalances.

It is important to recognize that the available evidence, while promising, still lacks randomized clinical trials demonstrating a direct impact of this strategy on hard clinical outcomes such as mortality or readmissions. Furthermore, the usefulness of measuring natriuresis after 24-48 hours has not yet been demonstrated, so this strategy would be limited to the first day of hospitalization. Finally, serial measurement of natriuresis as a routine tool presents logistical and educational challenges, especially in centers with limited resources or no experience with standardized monitoring protocols. Therefore an institutional strategy including interdisciplinary training and adaptation of laboratory systems is required. to enable rapid and reliable analyses

Clinical trials are underway to evaluate the influence of dietary sodium and fluid intake on urinary sodium concentration and the role of urinary sodium concentration in later stages of decongestion.

In conclusion, Meekers et al.'s work reevaluates an underutilized tool in clinical practice that will potentially transform the management of congestion in patients with acute HF. We are facing a potential paradigm change, in which basic physiology returns to the center of clinical decision-making. The challenge now is to validate this strategy in prospective studies and facilitate its adoption in a safe and cost-effective manner. The remaining question is when and how to systematically integrate natriuresis measurement into our therapeutic algorithms.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material).

Ethical considerations

Not applicable

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023;44:3627-39. https://doi.org/10.1093/eurheartj/ehad195.

2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al; 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032. https://doi.org/10.1161/CIR.0000000000001063

3. Fernández A, Thierer J, Fairman E, Giordanino E, Soricetti J, Belziti C, et al. Heart Failure Consensus 2022. Rev Argent Cardiol 2023;91:1-80. http://dx.doi.org/10.7775/rac.es.v91.s2

4. Hodson DZ, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J, et al. Natriuretic response is highly variable and associated with 6-month survival: insights from the ROSE-AHF trial. JACC Heart Fail 2019;7:383-91. https://doi.org/10.1016/j.jchf.2019.01.007.

5. Biegus J, Zymlinski R, Sokolski M, Todd J, Cotter G, Metra M, et al. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. Eur J Heart Fail 2019;21:624-33. https://doi.org/10.1002/ejhf.1428.

6. Honda S, Nagai T, Nishimura K, Nakai M, Honda Y, Nakano H, et al. Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure. Int J Cardiol 2018;254:189-94. https://doi.org/10.1016/j.ijcard.2017.08.053

7. Collins S, Jenkins C, Baughman A, Miller K, Storrow AB, Han JH, et al. Early urine electrolyte patterns in patients with acute heart failure. ESC Heart Fail 2019;6:80-8. https://doi.org/10.1002/ehf2.12368

8. Cobo-Marcos M, Zegri-Reiriz I, Remior-Perez P, Garcia-Gomez S, Garcia-Rodriguez D, Dominguez-Rodriguez F, et al. Usefulness of natriuresis to predict in-hospital diuretic resistance. Am J Cardio-

vasc Dis. 2020;10:350-5
9. Luk A, Groarke JD, Desai AS, Mahmood SS, Gopal DM, Joyce E, et al. First spot urine sodium after initial diuretic identifies patients at high risk for adverse outcome after heart failure hospitalization. Am Heart J 2018;203:95-100. https://doi.org/10.1016/j.ahj.2018.01.013
10. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. J Card Fail 2014;20:392–9. https://doi.org/10.1016/j.cardfail.2014.03.006.
11. Scatularo CE, Battioni L, Guazzone A, Esperón G, Corsico L, Grancelli HO. Basal natriuresis as a predictor of diuretic resistance and clinical evolution in acute heart failure. Curr Probl Cardiol 2024;49:102674. https://doi.org/10.1016/j.cpcardiol.2024.
12. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, et al. Protocolized natriuresis-guided decongestion improves diuretic response: The multicenter ENACT-HF study. Circ Heart Fail 2024;17:e011105. https://doi.org/10.1161/CIRCHEARTFAILURE.123.011105
13. Ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Postmus D, Coster JE, et al. Natriuresis-guided diuretic therapy in acute heart failure: A pragmatic randomized trial. Nat Med 2023;29:2625–32. https://doi.org/10.1038/s41591-023-02532
14. Meekers E, Martens P, Dauw J, Gruwez H, Dhont S, Nijst P, et al. Nurse-led diuretic titration via a point-of-care urinary sodium sensor in patients with acute decompensated heart failure (EASY-HF): A single-center, randomized, open-label study. Eur J Heart Fail 2024;26:2129–39. https://doi.org/10.1002/ejhf.3429.
15. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1178-95. https://doi.org/10.1016/j.jacc.2019.12.059
16. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:137-55. https://doi.org/10.1002/ejhf.1369.
17. Meekers E, Dauw J, Ter Maaten JM, Martens P, Nijst P, Verbrugge FH, et al. Urinary sodium analysis: The key to effective diuretic titration? European Journal of Heart Failure expert consensus document. Eur J Heart Fail 2025; 27:940-9.https://doi.org/10.1002/ejhf.3632.
18. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, et al.; CLOROTIC Trial Investigators. Combining loop with thiazide diuretics for decompensated heart failure: The CLOROTIC trial. Eur Heart J 2023;44:411–21. https://doi.org/10.1093/eurheartj/ehac689
19. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. Eur J Heart Fail 2019;21:1415–22. https://doi.org/10.1002/ejhf.1478.
20. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al.; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: The ATHENA-HF randomized clinical trial. JAMA Cardiol 2017;2:950–8. https://doi.org/10.1001/jamacardio.2017.2198
21. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail 2020;22:713-22. https://doi.org/10.1002/ejhf.1713
22. Schulze PC, Bogoviku J, Westphal J, Aftanski P, Haertel F, Grund S, et al. Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). Circulation 2022;146:289-98. https://doi.org/10.1161/CIRCULATIONAHA.122.059038.
23. Cox ZL, Collins SP, Hernandez GA, McRae AT, Davidson BT, Adams K, et al. Efficacy and Safety of Dapagliflozin in Patients With Acute Heart Failure. J Am Coll Cardiol 2024;83:1295-306. https://doi.org/10.1016/j.jacc.2024.02.009.
24. Berg DD, Patel SM, Haller PM, Cange AL, Palazzolo MG, Bellavia A et al. ,DAPA ACT HF-TIMI 68 Trial Committees and Investigators. Dapagliflozin in Patients Hospitalized for Heart Failure: Primary Results of the DAPA ACT HF-TIMI 68 Randomized Clinical Trial and Meta-Analysis of Sodium-Glucose Cotransporter-2 Inhibitors in Patients Hospitalized for Heart Failure. Circulation. 2025 Aug 29. doi: 10.1161/CIRCULATIONAHA.125.076575. Epub ahead of print.
25. Marton A, Saffari SE, Rauh M, Sun RN, Nagel AM, Linz P, et al. Water Conservation Overrides Osmotic Diuresis During SGLT2 Inhibition in Patients With Heart Failure. J Am Coll Cardiol 2024;83:1386-98. https://doi.org/10.1016/j.jacc.2024.02.020
26. Ern Yeoh S, Osmanska J, Petrie MC, Brooksbank KJM, Clark AL, Docherty KF, et al. Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. Eur Heart J 2023;44:2966–77. https://doi.org/10.1093/eurheartj/ehad341
27. Delanaye P, Scheen AJ. The diuretic effects of SGLT2 inhibitors: A comprehensive review of their specificities and their role in renal protection. Diabetes Metab 2021;47:101285. https://doi.org/10.1016/j.diabet.2021.101285
28. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, et al. Protocolized natriuresis-guided decongestion improves diuretic response: The multicenter ENACT-HF study. Circ Heart Fail 2024;17:e011105. https://doi.org/10.1161/CIRCHEARTFAILURE.123.011105
29. Ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Postmus D, Coster JE, et al. Natriuresis-guided diuretic therapy in acute heart failure: A pragmatic randomized trial. Nat Med 2023;29:2625–32. https://doi.org/10.1038/s41591-023-02532
30. Meekers E, Martens P, Dauw J, Gruwez H, Dhont S, Nijst P, et al. Nurse-led diuretic titration via a point-of-care urinary sodium sensor in patients with acute decompensated heart failure (EASY-HF): A single-center, randomized, open-label study. Eur J Heart Fail 2024;26:2129–39. https://doi.org/10.1002/ejhf.3429.

Decompensated heart failure: diuretics are necessary, but not sufficient

LUCRECIA MARÍA BURGOS[1], NICOLE GOULD[1], ENRIQUE FAIRMAN[1]

Congestion is a constant feature in the clinical course of patients with heart failure (HF). Its presence not only marks the onset of acute symptoms, but also persists—clinically or subclinically—during stable phases and even after hospitalization. This chronicity of the congestive state has consolidated the role of diuretics as a mainstay of treatment for decades. However, recent advances in understanding the pathophysiology of HF compel us to question whether we are treating the consequence rather than the cause.

FROM PATHOPHYSIOLOGY TO CLINICAL PRACTICE: THE CENTRAL ROLE OF SODIUM APPETITE

Congestion, far from being a purely hemodynamic or volume phenomenon, is the clinical manifestation of a renal sodium appetite condition which is mediated by

[1] Members of the Heart Failure and Pulmonary Hypertension Council of the Argentine Society of Cardiology

multiple interrelated mechanisms: activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic stimulation, non-osmotic vasopressin secretion, resistance to natriuretic peptides, and a persistent proinflammatory environment. These processes not only perpetuate water and salt retention but also promote disease progression.

In this context, the administration of diuretics—especially loop diuretics—provides rapid symptomatic relief through forced excretion of sodium and water. However, it does not modify the underlying pathophysiological mechanisms and may even exacerbate them by inducing compensatory neurohormonal activation. The stimulation of renin secretion by hypovolemia or by chloride transport blockade in the macula densa is a clear example of this response. In the long term, this activation promotes diuretic resistance, creating a vicious cycle of increasing doses and decreasing efficacy.

Clinical evidence supports this view. Trials such as DOSE-AHF (*Diuretic strategies in patients with acute decompensated heart failure*), (1) ADVOR (*Acetazolamide in acute decompensated heart failure with overload*), (2) and CLOROTIC (*Combining loop with thiazide diuretics for decompensated heart failure*), (3) have shown that, although diuretic intensification improves symptoms and volume, it is not associated with a reduction in mortality or rehospitalization rates. Moreover, strategies such as ultrafiltration have not shown sustained benefits and may be associated with adverse renal events, as observed in the CARRESS-HF study (*Ultrafiltration in decompensated heart failure with cardiorenal syndrome*).(4) In parallel, urinary sodium has emerged as a useful tool to guide treatment response, as shown in the PUSH-AHF (*Pragmatic urinary sodium-based algorithm in acute heart failure*) (5) and ENACT-HF (*Protocolized natriuresis guided decongestion improves diuretic response: the multicenter ENACT-HF study*) studies. (6) Strategies focused exclusively on volume removal have failed to improve mid-term clinical outcomes.

A PARADIGM SHIFT: TREATING THE CAUSE, NOT JUST THE SYMPTOMS

The new approach proposed by Biegus et al. (7) is based on a simple but disruptive idea: decongestion should focus on correcting the mechanisms that cause it. In this model, diuretics are necessary for acute volume control, but their use must be accompanied—and ideally followed—by the rapid implementation and escalation of disease-modifying treatment or *Guideline Directed Medical Therapy (GDMT)*.

Recent studies support this paradigm. The STRONG-HF trial (*Safety, tolerability, and efficacy of up titration of guideline directed medical therapies for acute heart failure*) (8) demonstrated that an intensive strategy of early titration of angiotensin II receptor blockers and neprilysin inhibitors (ARNI), beta-blockers, and mineralocorticoid antagonists in the post-discharge period significantly reduced clinical events at 90 days, with a lower requirement for diuretics. Similar findings were observed in the EMPULSE (*Empagliflozin in patients hospitalized for acute heart failure*) study with empagliflozin, (9) and PIONEER (*Angiotensin Neprilysin inhibition in acute decompensated heart failure*) (10) studies, and the PARAGLIDE-HF (*Out-of-Hospital Initiation of Sacubitril/Valsartan Versus Valsartan in patients with mildly reduced or preserved ejection fraction and worsening heart failure*) study with sacubitril/valsartan. (11) These treatments not only improved congestion in a more sustained manner, but also reduced hospitalization and the need for subsequent symptomatic intervention. (Table)

THE VULNERABLE PHASE: AN OPPORTUNITY TO INTERVENE

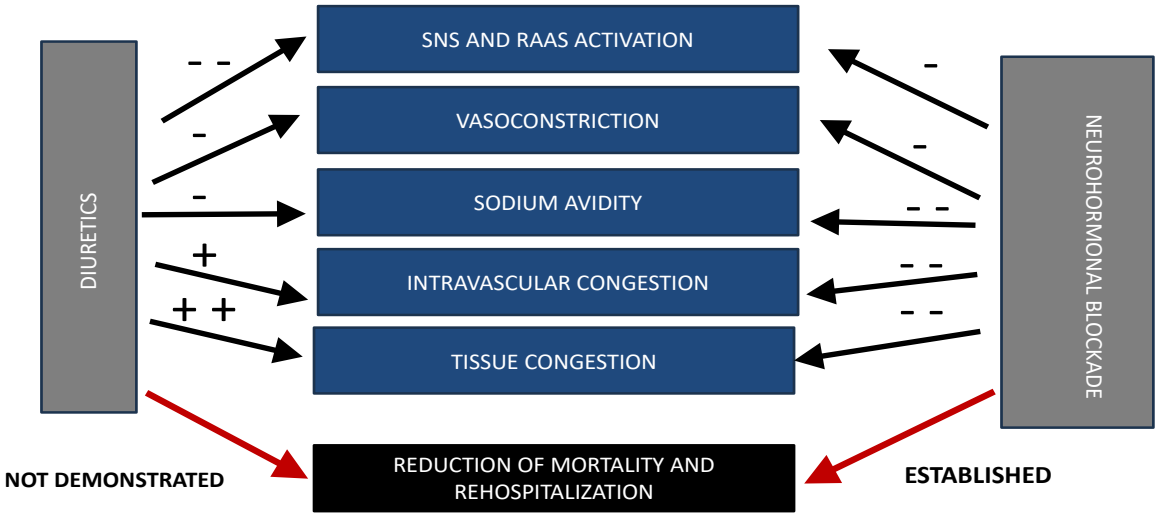
Three key stages in the evolution of HF may be considered: the stable phase, acute decompensation, and the vulnerable phase after discharge. The latter, historically neglected, is where the greatest risk of events is concentrated. It is also a critical therapeutic window for consolidating decongestion and modifying the course of the disease. At this point, intensification of *GDMT* is more effective than any diuretic combination.

The message is clear: it is not enough to "remove water." Just as in myocardial infarction we do not limit ourselves to treating pain, in HF we should not be satisfied with treating edema. The future of treatment for decompensated HF is moving toward integrating decongestion as a necessary goal, but subordinate to a strategy that prioritizes intervention on pathophysiology. In this way, we can achieve more lasting control, with fewer events and a better prognosis. (Figure)

Table. Paradigms in the treatment of congestion

	Classic paradigm (focused on diuretics)	Current paradigm (focused on pathophysiology)
Objective	Rapid relief of symptoms	Modify the course of the disease
Strategy	Scale up diuretic doses	Early GDMT initiation and tritration
Effect	Transient natriuresis	Sustained reduction in Na^+ appetite
Outcome	No change in events	Lower risk of hospitalization and death

GDMT: guideline directed medical treatment



RAAS: renin angiotensin aldosterone system; SNS: sympathetic nervous system

Figure. Mechanisms of action and effects of diuretic treatment versus neurohormonal blockade

REFERENCES

1. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805. https://doi.org/10.1056/NEJMoa1005419

2. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E et al. ADVOR Study Group. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med 2022;387:1185-95. https://doi.org/10.1056/NEJMoa2203094

3. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A. CLOROTIC trial investigators. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J 2023; 44:411-21. https://doi.org/10.1093/eurheartj/ehac689

4. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA et al. Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367: 2296-304. https://doi.org/10.1056/NEJMoa1210357

5. Ter Maaten JM, Beldhuis IE, Van der Meer P, Krikken JA, Coster JE, Nieuwland W. Natriuresis-guided therapy in acute heart failure: rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) trial. Eur J Heart Fail 2022; 2:385-92. https://doi.org/10.1002/ejhf.2385

6. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP. Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study. Circ Heart Fail 2024;17:e011105. https://doi.org/10.1161/CIRCHEARTFAILURE.124.011695

7. Biegus J, Cotter G, Metra M, Ponikowski P. Decongestion in acute heart failure: Is it time to change diuretic-centred paradigm? Eur J Heart Fail 2024;26:2094-106. https://doi.org/10.1002/ejhf.3423

8. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022;400:1938-52. https://doi.org/10.1016/S0140-6736(22)02076-1

9. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. Eur Heart J 2023;44:41-50. https://doi.org/10.1093/eurheartj/ehac530

10. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K et al. PIONEER-HF Investigators. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med 2019;380:539-48. https://doi.org/10.1056/NEJMoa1812851

11. Nouhravesh N, Cyr D, Hernandez AF, Morrow DA, Velazquez EJ, Ward J. In-Hospital or Out-of-Hospital Initiation of Sacubitril/Valsartan Versus Valsartan in Patients With Mildly Reduced or Preserved Ejection Fraction After A Worsening Heart Failure Event: The PARAGLIDE-HF Trial. J Am Heart Assoc 2025;14:e037899. https://doi.org/10.1161/JAHA.124.037899

Addressing Residual Risk in Type 2 Diabetes

Abordaje del riesgo residual en Diabetes tipo 2

RODRIGO ESPARZA IRAOLA[1]

Type 2 diabetes mellitus (T2DM) represents a global public health challenge. In 2022, it affected 830 million people, with a higher prevalence in low-income countries (1). This disease is linked to an elevated risk of cardiovascular complications such as coronary heart disease, heart failure, stroke, atrial fibrillation, peripheral vascular disease, and chronic kidney disease. In 2021, it was directly responsible for 1.6 million deaths, almost half of which occurred before the age of 70. (1)

Intensive control of classic risk factors -blood glucose, blood pressure, and LDL-C- has been shown to reduce mortality and cardiovascular events. However, a residual risk remains, with hypertriglyceridemia as an independent risk marker. Elevated triglyceride levels are associated with increased mortality in patients with coronary artery disease, reinforcing the need for complementary strategies. (2)

In this context, the REDUCE-IT trial showed that icosapent ethyl (IPE) reduces cardiovascular events by 25% in patients with atherosclerotic disease or T2DM with risk factors, leading to its inclusion in international guidelines. (3, 4)

The study published in the Argentine Journal of Cardiology, "*Eligibility for icosapent ethyl in a real-world population of patients with type 2 diabetes in the Argentine Republic,*" provides relevant local evidence. (5) Analyzing data from the registry of the Cardiometabolic Council of the Argentine Society of Cardiology, the authors observed that one in five patients with T2DM would meet the criteria for receiving IPE, with a higher proportion in secondary prevention (22.8%) than in primary prevention (15.5%). This finding underscores the importance of identifying residual risk in clinical practice and considering specific interventions to reduce it.

A striking finding is that only 25.9% of patients were receiving hypoglycemic drugs with proven cardiovascular benefits, which shows marked therapeutic inertia. This widely documented phenomenon delays the implementation of effective treatments and contributes to a worse prognosis in patients. The causes are multiple and complex: from professional factors (lack of time, lack of knowledge, fear of adverse effects) and patient factors (low adherence, low perception of risk) to healthcare system barriers (access and coverage). There is need to investigate the causes of undertreatment in T2DM and other cardiovascular diseases, as therapeutic inertia compromises the effectiveness of preventive strategies and results in unfavorable clinical outcomes.

In conclusion, this study not only estimates how many patients with T2DM in an Argentine population would be candidates for IPE, but also alerts us to the need to actively address therapeutic inertia and optimize the use of therapies with proven benefits. Recognizing and treating residual risk is essential for advances in scientific evidence to translate into actual benefits for patients.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. World Health Organization. Diabetes [Internet]. Geneva: World Health Organization; November 14, 2024. https://www.who.int/news-room/fact-sheets/detail/diabetes.

2. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman EZ, Kopel E, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes 2016;9:100-8. https://doi.org/10.1161/CIRCOUTCOMES.115.002104.

3. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22. https://doi.org/10.1056/NEJMoa1812792.

Rev Argent Cardiol 2025;93:391-392. https://doi.org/10.7775/rac.v93.i5.20921

Correspondence: Rodrigo Esparza Iraola. Email: resparza@ffavaloro.org

[1] Cardiologist, Metabolic Unit, Favaloro University Hospital, Buenos Aires.

4. Marx N, Federici M, Schütt K, Ajjan RA, Antunes MJ, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44:4043-40. https://doi.org/10.1093/eurheartj/ehad192.
5. Lavalle Cobo AM, Destaville J, Salmeri E, Forte E, Harwicz P, Corral P. Eligibility for icosapent ethyl in a real-world population of patients with type 2 diabetes in Argentina. Rev Argent Cardiol 2025;93:213-6. https://doi.org/10.7775/rac.v93.i3.20898.

AUTHORS' REPLY

We would like to thank Dr. Rodrigo Esparza Iraola for his observations and comments regarding our recently published article.

We agree with his reflection on the importance of identifying residual risk in daily practice in order to implement interventions aimed at reducing it, ethyl icosapentenoate being one possible strategy for this purpose.

When discussing residual risk in diabetes, Lawler et al. propose the use of drugs with proven cardiovascular benefits (GLP-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors) as a strategy to reduce it. 1. In this regard, we agree with Dr. Esparza Iraola that 3 out of 4 patients did not receive these groups of drugs and that inertia might be its cause. However, it is important to note that we used data from a cohort of patients evaluated between May and July 2019 to carry out this work. 2. We consider this factor to be important since this date coincides with the publication of cardiovascular safety studies of different molecules in populations with lower cardiovascular risk than those included in the first studies Moreover, it precedes the publication of international and national guidelines with the participation of scientific cardiology societies in which these drugs are included as part of the recommendations for reducing cardiovascular risk. On the other hand, as Dr. Esparza Iraola rightly points out, there are related issues that we must consider as barriers in the healthcare system. In this regard, Resolution 2820/2002 updated Annex I on the "Rules for the Provision of Medicines and Supplies for People with Diabetes," included the first of the two groups of drugs with proven cardiovascular benefits (SGLT2 inhibitors) as medications covered by the healhtcasre system for certain patients with type 2 diabetes. 3. We would like to thank you once again for the contributions highlighted in your letter, as they enrich the debate on such an important issue as the underuse of strategies with evidence of reducing cardiovascular risk.

Augusto Lavalle Cobo MTSAC

REFERENCES

1. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;42:113-31. https://doi.org/10.1093/eurheartj/ehaa099
2. Forte E, Buso C, Duczynski P, Lavalle Cobo A, Harwicz P, Giorgi M, y cols. Clinical Characteristics and Cardiometabolic Control of Persons with Diabetes in the Cardiology Office in Argentina. Rev Argent Cardiol 2020;99:517-24. https://doi.org/10.7775/rac.es.v88.i6.18201
3. https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-2820-2022-375042/texto

Genetic Testing in Hypertrophic Cardiomyopathy, Beyond the Initial Result

Estudio genético en miocardiopatía hipertrófica, más allá del resultado inicial

GUIDO ANTONIUTTI[1]

Understanding the clinical characteristics of our population enables the optimal allocation of healthcare resources, ensuring that the greatest number of patients benefit from the available means according to their clinical impact. Hypertrophic cardiomyopathy (HCM) is a clear example of a disease that must be analyzed from the workup process to the therapeutic approach, both of which are expensive. This analysis should be conducted with the aim of predicting and preventing the most serious outcomes, such as sudden

Rev Argent Cardiol 2025;93:392-393. https://doi.org/10.7775/rac.v93.i5.20930

Correspondence: E-mail:guidoantoniutti@hotmail.com

[1] Unit of Familial Heart Diseases, Quironsalud Mallorca, Hospital Quironsalud Palmaplanas, Palma, Spain

cardiac death and progression to heart failure, with the greatest possible specificity, while maintaining sensitivity.

The study by Parodi JB et al. (1) is a highly relevant population-based analysis that aligns with previous studies that have attempted to predict which patients with HCM will have a pathogenic (P) or likely pathogenic (LP) variant in genetic testing, such as that of Bos JM et al. (2), which led to the development of the Mayo Clinic score in 2014. Both studies agree, even though they involve different populations, that the reverse septal curvature pattern is associated with a higher probability of a positive genetic test with P or LP variants.

Hypertrophic cardiomyopathy has traditionally been considered a monogenic disease caused by variants in sarcomeric genes. While this assessment is not false, it is incomplete. A detailed analysis of sarcomeric genes can identify the genetic cause in 30 to 60% of cases, according to the series reported. If we only consider this pathogenesis, we would be leaving 40-70% of diagnosed patients without a genetic explanation for their disease. The constant analysis of variants found necessitates periodic reviews of genetic tests to assess the potential reclassification of those previously designated as negative as positive. One such example is the p.Arg652Lys variant in MYH7 (3) in a region of Spain, which was previously considered a variant of uncertain significance (VUS) and is currently P. In this context, the recent identification of non-sarcomeric genes associated with HCM, such as FHOD3, (4) has expanded the genetic spectrum of the disease. An analysis of intermediate-effect variants (IEVs) has recently been published. While these variants do not reach the category of P or LP, they influence the development of the disease. According to García Hernández S et al., (5) these IEVs account for 4.8% of HCM cases and modulate both the phenotype and clinical events when found in combination with P or LP variants.

Given the aforementioned reasons, it is imperative to ascertain the population to which patients with HCM belong and, following the results of a genetic test, to carry out a detailed analysis of the variants found. This analysis should consider the possibility of finding VUS or IEVs as the ultimate causes of the disease. A thorough understanding of HCM genetics improves diagnostic accuracy, facilitates optimized risk stratification, and allows for personalized therapeutic decisions)

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

REFERENCES

1. Parodi JB, Carosella L, Mando F, Munin M, Salamé M, Guetta J, et al. Correlation Between Genetic Testing and Phenotype in a Cohort of Patients with Hypertrophic Cardiomyopathy. Rev Argent Cardiol 2025;93:295-301. https://doi.org/10.7775/rac.v93.i4.20915

2. Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2014;89:727-37. https://doi.org/10.1016/j.mayocp.2014.01.025.

3. Antoniutti G, Caimi-Martinez FG, Álvarez-Rubio J, Morlanes-Gracia P, Pons-Llinares J, Rodríguez-Picón B, et al. Genotype-Phenotype Correlation in Hypertrophic Cardiomyopathy: New Variant p.Arg652Lys in MYH7. Genes (Basel) 2022;13:320. https://doi.org/10.3390/genes13020320.

4. Ochoa JP, Sabater-Molina M, García-Pinilla JM, Mogensen J, Restrepo-Córdoba A, Palomino-Doza J, et al. Formin Homology 2 Domain Containing 3 (FHOD3) Is a Genetic Basis for Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2018;72:2457-67. https://doi.org/10.1016/j.jacc.2018.10.001.

5. García Hernandez S, de la Higuera Romero L, Fernandez A, Luisa Peña Peña M, Mora-Ayestaran N, Basurte-Elorz MT, et al. Redefining the Genetic Architecture of Hypertrophic Cardiomyopathy: Role of Intermediate-Effect Variants. Circulation 2025;152:1060-75. https://doi.org/10.1161/CIRCULATIONAHA.125.074529

JACC Scientific Statement. J Am Coll Cardiol. 2023;9;81:1810-34. https://doi.org/10.1016/j.jacc.2023.01.049

AUTHORS' REPLY

We thank Dr. Guido Antoniutti for his valuable comments on our study and fully agree with his assessments.

Hypertrophic cardiomyopathy (HCM) is essentially a genetic disease, and advances in molecular research continue to refine our understanding. While a significant proportion of cases can be explained by pathogenic variants in sarcomeric, structural, or regulatory genes, usually with an autosomal dominant pattern of inheritance, we already know that this monogenic model does not encompass the full complexity of the disease. After a thorough analysis of the genetic test results, some patients remain genetically elusive. This can comprise 30 to 60% of cases, depending on the series, and could be explained by the combined contribution of rare intermediate-effect variants (oligogenic model) or the cumulative impact of common low-effect variants (polygenic model). The characterization of these intermediate-effect variants, as Dr. Antoniutti has correctly pointed out, represents a significant advance for a better understanding of the genetic origin of HCM.

We also recognize the importance of regularly reviewing genetic test results, taking into account the potential for reclassifying variants and identifying additional implicated genes.

We would like to thank Dr Antoniutti for his comments again, which enhance the interpretation of genetic research in HCM and promote a comprehensive understanding of this complex disease.

Josefina Parodi
On behalf of the authors

Impact and Significance of the SONQO-CALCHAQUÍ Program on Cardiovascular Health in Indigenous Communities

Impacto y significado del Programa SONQO-CALCHAQUÍ en la salud cardiovascular de las comunidades originarias

MARÍA GABRIELA AGUIRRE MAJUL[1]

The SONQO-CALCHAQUÍ Program (1-4) exemplifies efforts to promote cardiovascular health in indigenous communities in northern Argentina, particularly in the Calchaquí Valleys. In my view, this project not only offers a comprehensive medical approach, but also reflects a deep commitment to cultural preservation and respect for the unique characteristics of high-altitude populations.

First, it is essential to emphasize the significance of this initiative in terms of healthcare accessibility. The populations of Cachi, Coranzulí, and Quilmes live in isolated environments with extremely limited access to specialized medical care. SONQO-CALCHAQUÍ offers a comprehensive evaluation in a few hours encompassing laboratory tests, electrocardiogram, echocardiogram, vascular tests, and physical endurance tests. This enables hundreds of people to receive crucial information for the prevention and monitoring of cardiovascular diseases in a single day, which would otherwise require years of fragmented care.

The program also demonstrates a remarkable balance between science and cultural sensitivity. The evaluation takes into account the population's diet, which combines indigenous elements, such as llama meat and local vegetables, with processed products. Recommendations are contextualized without imposing urban models that may be impractical or foreign. By measuring physical activity, sleep, and lifestyle habits, professionals can take a comprehensive approach that respects local identity.

However, this effort also highlights a critical challenge: the increasing westernization. The presence of overweight, obesity, and waist circumference alterations indicates that changes in eating habits and lifestyle could affect the long-term cardiovascular health of these communities. Therefore, I believe it is crucial for future programs to keep on promoting early detection and educating people about healthy habits, adapted to the local worldview and resources.

Finally, SONQO-CALCHAQUÍ serves as a replicable model for other rural and isolated territories, demonstrating that the combination of technology, professional training, and cultural respect can generate a real and sustained impact.

This program demonstrates how preventive medicine can be effective and become more humane. It provides medical data and raises awareness about the overall health of historically marginalized communities.

In summary, SONQO-CALCHAQUÍ is more than just a cardiovascular study; it is a commitment to life, culture, and health equity. Projects of this magnitude deserve attention, ongoing support and replicability because they demonstrate how science can serve those in need in a direct and respectful manner.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. Galdeano RS, Mauro SO, Abregú D, Flores L, Zeballos GS, Fiszman L, et al. SONQO-CALCHAQUÍ Program 4th Edition 2024. Evaluation of cardiovascular variables in a native high mountain community. Rev Argent Cardiol 2025;93:287-94. https://doi.org/10.7775/rac.es.v93.i4.20914

2. Galdeano RS, Vogelmann OA, Mauro SO, Scattini G, Alderete R, Pastore FA, et al. 2023 SONQO-CALCHAQUÍ III Program: Evaluation of Cardiovascular Variables in Native Communities of the Calchaqui Valleys (Northwest Argentina). Rev Argent Cardiol 2024;92:429-36. https://doi.org/10.7775/rac.es.v92.i6.20847

3. Galdeano RS, Holownia D, Palavecino DO, Abregú JD, Benger J, Alderete R, et al. 2022 SONQO-CALCHAQUÍ Program: Evaluation of Cardiovascular Variables in a Mid- and High Mountain Calchaquí Population of Tucumán. Rev Argent Cardiol 2024;92:287-94. https://doi.org/10.7775/rac.es.v93.i4.20914

4. Galdeano RS, Holownia D, Palavecino DO, Abregú JD, Rivas Jordan MS, Frías Silva M, et al. 2022 SONQO-CALCHAQUÍ Program: Evaluation of Cardiovascular Variables in a Mid- and High Mountain Calchaquí Population of Tucumán. Rev Argent Cardiol 2021;89:20-6. https://doi.org/10.7775/rac.es.v89.i1.19095

Rev Argent Cardiol 2025;93:394-395. https://doi.org/10.7775/rac.v93.i5.20929

Correspondence: M. Gabriela Aguirre Majul. E-mail: gabiaguirrem@gmail.com

[1] Cardiology, Hospital Juan A. Fernández, Ciudad de Buenos Aires.

AUTHORS' REPLY

We appreciate the summary made by Dr. María Gabriela Aguirre Majul of the different editions of the SONQO Calchaquí Program. As the doctor indicates, the idea behind this program is to conduct cardiovascular assessments of the indigenous populations in the valleys of northwestern Argentina and to study their lifestyle within its sociocultural context. Although the communities studied share similar characteristics in several respects, each community has distinctive features that must be addressed specifically. In this regard, the most recent edition, completed in early October of this year in Susques (Jujuy, at 3,890 meters above sea level), included researchers in the social sciences. We share the reader's concern about the westernization of lifestyles that is being observed. To that end, joint actions by scientific societies, universities, and health systems are necessary to support these communities in maintaining healthy lifestyles and modifying those that are not.

Yours sincerely,

Claudio Joo Turoni MTSAC
on behalf of the authors

A Functional Look at Transthyretin Cardiac Amyloidosis Beyond Deposition

Más allá del depósito, una mirada funcional a la amiloidosis cardíaca por transtiretina

JULIO NÁPOLI[1], JONATHAN COLAIACOVO[2], MARÍA BEATRIZ SOLA Y PAZ GARCILASO DE LA VEGA[2]

Cardiac transthyretin amyloidosis (ATTR-CA) is no longer a rare and silent entity but has rather become a diagnostic and therapeutic challenge for modern cardiology. We know that the extracellular deposition of misfolded amyloid protein in cardiac tissue has a significant impact on ventricular function. The article by Carvelli MV et al. invites us to look beyond amyloid deposition and explore its relationship with myocardial flow reserve (MFR) and global longitudinal strain, thereby evaluating the functional dimension that could predict ventricular deterioration. (1)

Previous literature has documented microvascular dysfunction in amyloidosis and other infiltrative cardiomyopathies using various noninvasive techniques, including positron emission tomography, the gold standard, (2,3) cardiac magnetic resonance imaging, transthoracic Doppler echocardiography, and contrast-enhanced echocardiography.

Using cadmium-zinc-tellurium (CZT-SPECT) detectors, the authors achieved simultaneous assessment of perfusion and amyloid distribution with a resolution that redefines the limits of nuclear imaging. The finding of reduced MFR in patients with ATTR-CA, even in the absence of epicardial coronary artery disease, supports the hypothesis that microvascular dysfunction is a key pathophysiological mechanism. (4) However, the most striking aspect of the study is what was not found: no correlation between the magnitude of amyloid deposition, global longitudinal strain and MFR.

This result invites us to rethink the paradigm. Is amyloid deposition the only relevant factor in the functional progression of the disease? Or are we facing a more complex interaction between inflammation, extrinsic compression, and tissue toxicity? The homogeneous distribution of amyloid observed in polar maps challenges the classic "Japan flag plot pattern" and suggests that functional deterioration may precede or even be independent of structural compromise.

The study also introduces a methodological innovation: the measurement of MFR using CZT-SPECT, an accessible, reproducible, and noninvasive technique. In this context, MFR emerges not only as a physiological marker but also as a potential tool to inform prognostic stratification and therapeutic follow-up. A reduction in MFR could anticipate symptoms of angina and functional deterioration or guide the initiation of specific therapies such as tafamidis.

Rev Argent Cardiol 2025;93:395-396. https://doi.org/10.7775/rac.v93.i5.20928

Correspondence: Jonathan Colaiacovo. E-mail: colaiacovo.cristian@hospitalposadas.gob.ar

[1] Department of Nuclear Medicine, Hospital Posadas, El Palomar.
[2] Cardiology, Hospital Posadas, El Palomar.

In line with this perspective, it is worth mentioning the AMYTRE protocol, (5) conducted by Bastien Vançon et al., which aims to confirm coronary microvascular dysfunction and evaluate the effect of tafamidis on it. The primary outcome will be the variation of stress and rest myocardial blood flow and MFR between baseline and 24 months after tafamidis treatment.

In conclusion, this study marks a turning point in ATTR-CA research, despite its limited sample size. It reminds us that seeing the deposition is not enough; we must also understand its functional impact. The future of cardiology will combine diagnostic accuracy with physiological sensitivity. This paper is a significant step in that direction, inviting further exploration of the heart beyond its anatomy.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

REFERENCES

1. Carvelli MV, Meretta A, Gobbo M, Corneli M, Spaccavento A, del Rosario Rodríguez M, et al. Analysis of Myocardial Flow Reserve in Patients with Transthyretin Cardiac Amyloidosis. Its Relationship with Cardiac Amyloid Distribution and Global Longitudinal Strain. Rev Argent Cardiol 2025;93:279-86. https://doi.org/10.7775/rac.v93.i4.20906

2. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. Heart Fail Rev 2017;22:455-64. https://doi.org/10.1007/s10741-017-9628-1.

3. Kourek C, Briasoulis A, Magouliotis DE, Georgoulias P, Giamouzis G, Triposkiadis F, et al. Recent advances in the diagnostic methods and therapeutic strategies of transthyretin cardiac amyloidosis. World J Cardiol 2024;16:370-9. https://doi.org/10.4330/wjc.v16.i7.370.

4. Dorbala S, Vangala D, Bruyere J Jr, Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Heart Fail 2014;2:358-67. https://doi.org/10.1016/j.jchf.2014.03.009.

5. Vançon B, Bisson A, Courtehoux M, Bernard A, Bailly M. A study protocol for an observational cohort investigating cardiac transthyretin amyloidosis flow reserve before and after Tafamidis treatment: The AMYTRE study. Front Med (Lausanne). 2022;9:978293. https://doi.org/10.3389/fmed.2022.978293.

AUTHORS' REPLY

We sincerely thank Dr. Nápolí, Dr. Colaiacovo, Dr. Solá, and Dr. Garcilaso de la Vega for their interest and valuable comments on our paper "Analysis of Myocardial Flow Reserve in Patients with Transthyretin Cardiac Amyloidosis. Its Relationship with Cardiac Amyloid Distribution and Global Longitudinal Strain."

We fully agree that transthyretin cardiac amyloidosis (ATTR-CA) should be approached from a comprehensive perspective that considers not only the burden of amyloid deposition but also its functional impact. In this regard, the assessment of myocardial flow reserve (MFR) provides relevant pathophysiological information, even in the absence of epicardial coronary artery disease, and could play a prognostic and therapeutic role in monitoring these patients.

We particularly appreciate the authors' view of microvascular dysfunction as a key mechanism and their mention of ongoing studies such as the AMYTRE protocol, which will help elucidate the relationship between MFR and response to treatment with tafamidis.

We agree that the future challenge will be to integrate structural, functional, and molecular findings for a better understanding of disease progression and optimization of clinical management.

We would like to express our gratitude once again for this academic exchange, which enriches the discussion and stimulates scientific collaboration in this field.

María Victoria Carvelli [MTSAC]
on behalf of the authors

A Three-year Strategic Plan and a Historic SAC Congress

Un plan estratégico por 3 años y un Congreso SAC histórico

The Strategic Plan (SP) was presented at the 25th SAC Congress, which was reflected in the design of the event: organization, aesthetics, academic activities, communication, and scientific program. The congress placed the patient at the center and recalled the history and *raison d'être* of our Society.

WHAT IS THE STRATEGIC PLAN (SP)?

The SP is a general framework or guide to orient the decisions of the Argentine Society of Cardiology (SAC), with the aim of ensuring its coherent and sustainable development over time. It serves to guide actions and investments (in capabilities, time, and funds) and does not condition the initiatives of each member or limit the exercise of the roles assigned to managers in the performance of their duties.

The SP is based on a management consensus aimed at improving decision-making, increasing organizational efficiency, and enhancing the SAC's contribution to cardiovascular health in the country. A participatory approach was chosen for its implementation, convened by the Presidency and composed of members of the Board of Directors and leaders from different functions within the SAC. Workshops and group meetings were held to gather ideas that, by consensus, should be included in the SP, with an initial time frame of three SAC government terms.

MISSION AND INSTITUTIONAL COMMITMENT

The SAC is committed to cardiovascular health in Argentina, striving for excellence in training, equity, and quality in the healthcare system. The SAC researches, teaches, and disseminates medical knowledge to promote the training of qualified professionals and to anticipate global trends in the cardiovascular field.

Pillars of the SP

Three pillars form the initial basis of the SP:

1. Education
   The central objective is the development of the Institute of Continuing Medical Education, a preliminary step towards the SAC's University Institute of Continuing Education. This movement centralizes and professionalizes the educational strategy, the generation and transmission of knowledge in medical sciences and cardiology, prioritizing professional development through continuing medical education focused on the benefit of patients. The vision is to make the SAC a leading institution in the training of health professionals, spearheading knowledge generation and technological development in cardiology at the national and international levels.
2. Research
   The aim is to generate scientific knowledge that will improve clinical practice and the training of highly qualified human resources in cardiology. The goal is to produce rigorous and ethically sustainable research, generating national data and statistics on cardiovascular health. This block aims to become the SAC's scientific methodology, representing the cardiovascular reality of the country, promoting plural and federal participation, and promoting multicenter registries and the inclusion of research centers throughout Argentina.
3. SAC Members Area
   The creation of the training program for leading cardiologists responds to the need to professionalize leadership and management within the SAC, preparing it to face technological advances, globalization, and social changes. To be sustainable over time, these guidelines must incorporate criteria of social equity, allowing the development of all people regardless of race, religion, or socioeconomic status.

STRATEGIC CHALLENGES FOR THE COMING YEARS (SUMMARY)

1. Creation of the University Institute and professionalization of the teaching area, with the aim of training human capital to take on transformative leadership in the health system.
2. Development of the SAC professional career and consolidation of the Membership Area, seeking to strengthen management and leadership practices to harmonize and optimize institutional processes. The motto remains: "Where there is unity, there is victory" (Ubi concordia, ibi victoria).
3. Formation of a National Network of Researchers that guarantees representation of the population and has continuous, high-quality records that are

Rev Argent Cardiol 2025;93:397-399. http://dx.doi.org/10.7775/rac.v93.i5.20937

representative of the reality of the healthcare system.
4. Consolidation of national, regional, and international alliances that transcend the field of cardiology.
5. Promotion of citizen participation through the community arm of the Argentine Cardiology Foundation.
6. Becoming a benchmark for cardiovascular health before the Ministry of Health of the Nation, the provinces, and the municipalities, with two concrete actions to reduce cardiovascular mortality: a program of heart attack networks and strategies for diagnosis, treatment, and blood pressure control.

ENVIRONMENT: FUTURE TRENDS AND CHALLENGES

Strategic analysis points to profound changes in cardiology worldwide and, particularly, in our country in recent years. Among these, the acceleration in the development and implementation of innovations, diagnostic and therapeutic technologies, as well as the emergence of artificial intelligence and its rapid application in clinical practice, research, and management stand out. In Argentina, these innovations coexist with challenges of infrastructure, accessibility, inequalities, and a heterogeneous, fragmented, and underfunded health system, conditions that impact healthcare and continuing education.

The SAC is not immune to this environment; therefore, it must incorporate these realities when planning and designing future projects and initiatives aimed at collaborating in the training of more competent cardiologists and in the defense of the cardiovascular health of the population. Without quality human resources, there can be no excellence in medical care.

Macro factors influencing the profession and society

The evolution of science and technology will generate significant changes, among which the following stand out:

- The integration of data and information on individuals and patients into large databases, access to which could facilitate ministerial coordination for the exclusive use of improving national health.
- Doctors could find their decisions constrained when they contradict those derived from algorithms; if these decisions are not correct, they could be exposed to litigation. Defensive medicine could shift from excessive testing to obedience to the system.
- Medicine and cardiology will move toward modalities that require emotional intelligence, communication, and shared decision-making in defense of the patient, their context, and their family.

Macroeconomic and social challenges

- Aging population.
- Advances in life-prolonging treatments.
- Economic challenges arising from high healthcare costs and inflation.
- Increased environmental pollution and its deleterious effects on cardiovascular health.

Professional societies of the future

The coming decades will demand radical changes in a world that, through science, knowledge, and innovation, will optimize patient care and outcomes. The SAC must strengthen itself to become:

- The professional home of cardiologists, with fair and transparent governance and actionable knowledge for members, focused on people-centered medical care.
- A benchmark for quality, equity, and value in cardiovascular care.
- A coordinator of centers for obtaining quality data that will enable the generation of reliable knowledge in indigenous research.
- An organization that evaluates and selects emerging technologies for best practice guidelines, with cost-effectiveness analysis and regional application.
- A leader in education that adapts to new paradigms, providing information on emerging technologies and maintaining a critical approach to evidence.
- A promoter of environmental health, nutrition, healthy habits, and mental health among the population.
- Support for cardiologists facing exhaustion and burnout, especially during health crises.
- A contingency plan to respond to cardiovascular emergencies in the event of future health crises.
- A promoter of patient schools to inform and educate the community about care and best practices in cardiology.
- An advisor and active participant in the decisions of health authorities at all levels, to defend the needs of patients, the specialty, and the working conditions of professionals.
- A program to attract and train young talent, with tutoring and mentoring to strengthen their career path.
- A promoter of decentralized and efficient healthcare networks, with referrals according to the complexity of each case.
- An articulator to reformulate training and evaluation criteria for residents in the face of rapid technological changes.
- A bridge with other scientific and medical societies and associations to harmonize healthcare practices and policies in cardiology.
- A promoter of the responsible use of artificial intelligence, with ethical and safety frameworks; the possibility of creating an AI and telemedicine laboratory applied to cardiology could facilitate the evaluation of usefulness, safety, and feasibility.
- The Argentine Journal of Cardiology (RAC) must

continue to disseminate regional knowledge and seek global expansion, complying with international standards.

CHALLENGES TO BE RESOLVED

Based on strategic initiatives (University Institute, teaching area, development of the SAC career, and promotion of research), the SAC will seek to consolidate international alliances, promote citizen participation through the Argentine Cardiology Foundation, and establish itself as a reference point for the Ministry of Health, provinces, and municipalities. Among the challenges are:

- Globalization of knowledge: ensuring the quality and relevance of information, promoting research networks, and adapting guidelines to local realities.
- Relationship with governments and institutions: maintaining constant dialogue with authorities and universities, defending evidence-based policies, and securing resources for prevention, research, and training.
- Relationship with patients: countering misinformation and promoting education and reliable resources.
- Relationship with industry and suppliers: maintaining transparency and balance between the dissemination of innovations and good practices.
- Professional commitment: strengthen leadership and management, adapt training to new technologies, and support cardiologists in the face of burnout and structural transformations.

Looking to the future

The SAC aims to consolidate its position as the professional home for cardiologists, promoting quality, equity, and value in cardiovascular care; coordinating networks that generate reliable data; rigorously evaluating emerging technologies; and maintaining ethical principles in the use of artificial intelligence. With these foundations, we seek to achieve a more accessible, efficient, and humane cardiology.

Pablo Stutzbach MTSAC,
President of the Argentine Society of Cardiology