ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 94 N° 1 FEBRUARY 2026
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Graphic design - digital edition
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VOL 94 Nº 1
FEBRUARY 2026

Summary

EDITORIAL

"Everything Changes," Except for Mortality from Acute Myocardial Infarction

"Cambia todo cambia", menos la mortalidad del infarto agudo de miocardio

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The lyrics, composed by songwriter Julio Numhauser and exquisitely performed by Mercedes Sosa, tell us that people, things, and the world change over time; everything can change except love for one's homeland. To some extent, this poetic expression is repeated in Argentina. Although changes occur constantly and rapidly, the history and serious consequences of myocardial infarction remain unchanged. Nothing has changed; everything remains invariably the same.

This statement is supported by the results of the ARGEN-IAM-ST registry, in a timeline spanning 10 uninterrupted years, where the most striking data were the high in-hospital mortality rates, which remained persistent and unchanged throughout the decade. (1)

Going back to previous experiences, in 2010 the mortality rate of the 705 patients with STEMI admitted to centers with medical residency programs was also similar, close to 8%. (2)

International records, similar to national data in terms of reperfusion times and percentages, show lower mortality rates, ranging from 4.4% to 5.6%, even in Latin American countries with similar socio-cultural characteristics. (3-5)

The epidemiological reality in Argentina is, in fact, even more alarming than these figures suggest, as the available data largely come from institutions with academic training. Unfortunately, there are few population-based surveys available. (6,7)

The dilemma is interpreting why, despite a high reperfusion rate and acceptable in-hospital times, there is no impact on mortality.

In general, this problem has multiple causes, which can be attributed to factors such as a paucity of hospital resources, a reduced availability of cardiac catheterization laboratories in low-income regions, and the presence of untrained and unmotivated staff.

Among the main reasons, the authors highlight "the long time to presentation, with a delay at least 50% longer than observed in other registries."

Total ischemic time, measured from the onset of symptoms to balloon inflation, was independently associated with all-cause in-hospital mortality.

In another registry, in patients with a time from the onset of symptoms to balloon inflation ≥ 361 minutes, the risk of mortality increased by 50% compared to those with a time from the onset of symptoms to balloon inflation ≤120 minutes. (8)

Furthermore, the high incidence of heart failure is related to a greater degree of myocardial injury due to prolonged ischemia. (9,10)

This reality clearly indicates the decline of the national healthcare system—or rather the lack of a system. It falls far short of the World Health Organization's (WHO) definition of a health system as "all organizations, people, and actions whose primary intent is to promote, restore, or maintain health. This includes medical services (hospitals, clinics), community-based actions, health policies, funding, and the health workforce." (11)

There is a consensus that ensuring the health of the population is a responsibility that extends beyond the direct actions of the health sector. It is the State as a whole that must serve as the guarantor of health through its comprehensive policies. (12)

This underscores the importance of implementing more efficient care networks in countries with limited resources and prioritizing health policies that ensure equitable and timely access to high-quality reperfusion strategies. (13)

In the contemporary context, the phrase "Argentines, attend to the realities!" articulated by the Spanish philosopher and essayist José Ortega y Gasset holds particular pertinence. It urges Argentines to set

Rev Argent Cardiol 2026;94:1-2. https://doi.org/10.7775/rac.v94.i1.20980

SEE RELATED ARTICLE: Rev Argent Cardiol 2026;94:5-11. https://doi.org/10.7775/rac.v94.i1.20967

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aside complacency, narcissism, and personal conflicts, thereby redirecting their focus towards the objective and tangible development of the country. (14)

Conflicts of interest

None declared

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

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EDITORIAL

Illuminating the Myocardium: Cardiac Magnetic Resonance Imaging as an Ally in the Cardiologist's Daily Practice

Iluminando el miocardio: la resonancia magnética cardíaca como aliada en la práctica diaria del cardiólogo

MARÍA DE LA PAZ RICAPITO[1, MTSAC]

Since the acquisition of the first cardiac images in the 1980s, cardiac magnetic resonance imaging (CMR) has evolved from a technical curiosity to become the "gold standard" for non-invasive morphological and functional assessment and tissue characterization. (1) Currently, the technique transcends mere anatomical description to become a precision phenotyping tool, where Artificial Intelligence (AI) is no longer a future promise but a reality that optimizes everything from accelerated image acquisition to automated post-processing, enabling more personalized medicine. (2) This progress is reflected in the global expansion of the method, although, as Sierra-Galán et al. aptly describe, CMR practice shows significant variations worldwide, depending on the size of the centers and regional technological disparities. (3)

In this scenario of constant innovation, tissue characterization has taken a qualitative leap. Beyond the detection of focal fibrosis evidenced by the presence of late gadolinium enhancement, the development of T1 and T2 parametric mapping techniques, along with extracellular volume (ECV) quantification, now allows the identification of diffuse myocardial alterations and subclinical inflammation that were previously unvisualizable. (4) These metrics provide essential biological information in the field of cardiomyopathies and allow a transition from a static diagnosis to a dynamic understanding of the myocardial interstitium. This evolution is complemented by the analysis of ventricular mechanics, evaluating strain using feature tracking, a tool that has proven to be a robust predictor of events. However, the clinical implementation of strain measurement faces the challenge of standardization; recent meta-analyses underscore the complexity of establishing normal values, which vary significantly according to age, sex, and, fundamentally, the software provider used, necessitating a cautious and contextualized interpretation of the results. (5, 6)

The relevance of these metrics is evident in this issue of the Journal through the work of Cantora et al., which analyzes the association between the deterioration of global longitudinal strain and functional capacity—measured by peak oxygen consumption—in patients with hypertrophic cardiomyopathy (HCM). (7) In this pathology, cardiac magnetic resonance (CMR) has become indispensable for risk stratification of sudden death, integrating ventricular mechanics with fibrosis findings. Such is its importance that the 2025 Argentine Consensus on the Diagnosis and Treatment of Hypertrophic Cardiomyopathy of the Argentine Society of Cardiology assigns it a central role in the management algorithm, reflecting how technique guides the clinical cardiologist's conduct in the daily practice. (8) In Argentina, although disparities in access persist depending on the region, cardiac magnetic resonance (CMR) is an increasingly incorporated tool, serving as the link between clinical suspicion and the definitive therapeutic decision.

Alongside these cutting-edge technologies, the originality of local research also focuses on the optimization of fundamental measurements with accessible resources. The work of Jaimovich et al. on the quantification of left atrial volume (LAV) is a paradigmatic example. By proposing a cylindrical model with an irregular base, the authors achieve superior geometric precision compared to traditional methods, with the enormous advantage of being applicable in routine practice without requiring more time, sophisticated post-processing software, or expensive licenses. (9) This ability to generate accurate and reproducible data with basic tools is vital for the generalization of

Rev Argent Cardiol 2026;94:3-4. https://doi.org/10.7775/rac.v94.i1.20981

SEE RELATED ARTICLE: Rev Argent Cardiol 2026;94:25-31. https://doi.org/10.7775/rac.v94.i1.20971. Rev Argent Cardiol 2026;94:20-24. https://doi.org10.7775/rac.v94.i1.20979

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the method in our centers, allowing such a sensitive marker of diastolic dysfunction and atrial fibrillation risk to be available to all operators. (10)

In conclusion, CMR imaging has reached a point of maturity where the sophistication of AI and tissue mapping coexist with the need to standardize processes and simplify critical measurements. The integration of these advances, supported by local guidelines and growing international evidence, ensures that the technique continues to illuminate the path toward precision cardiology. (11) The original works presented in this issue not only contribute to the scientific body of knowledge but also demonstrate that, beyond the complexity of the software, excellence in interpretation and the adaptation of methods to our clinical reality are the true drivers of medical progress in our country.

Conflicts of interest

None declared

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

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ORIGINAL ARTICLE

Mortality Patterns in ST-Segment Elevation Myocardial Infarction Over 10 Years in Argentina. ARGEN-IAM-ST Registry

Evolución de la mortalidad en el infarto agudo de miocardio con elevación del segmento ST durante 10 años en Argentina. Registro ARGEN-IAM-ST

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ABSTRACT

Background: Acute myocardial infarction (AMI) is the leading cause of preventable death in Argentina and in most developing countries. Publications evaluating cardiovascular mortality have shown a downward trend over the last 20 years, attributable to significant advancements in care.
Objective: The aim of this study is to evaluate mortality of ST-segment elevation MI (STEMI) in Argentina, time from symptom onset to presentation, and time to reperfusion over a 10-year period.
Methods: Cases registered in the ARGEN-IAM-ST registry with a date of chest pain onset between January 1, 2015, and December 31, 2024, were analyzed. The characteristics of the population, times to presentation, in-hospital mortality, and complications during hospitalization due to STEMI were explored.
Results: A total of 7690 cases were analyzed from 209 institutions. Mean age was 61.1 ± 12 years, and 79% were male. The median time from the onset of pain to presentation was 120 minutes (interquartile range, IQR, 59-243), door-to-needle time was 55 minutes (IQR 30-120), total ischemic time for fibrinolytic therapy was 180 minutes (IQR 108-300), door-to-balloon time was 79 minutes (IQR 45-137), and total ischemic time for percutaneous coronary intervention was 315 minutes (IQR 190-607). These values did not present significant variations when compared individually over time. In-hospital mortality was 8.6%, over 10 years with no statistically significant variations when comparing annual periods (p = 0.927), despite reperfusion rate was > 90% in 8 of the 10 years evaluated.
Conclusion: Over the past 10 years, the ARGEN-IAM-ST registry showed absence of significant changes in in-hospital mortality, time to presentation and time to treatment. It is necessary to take specific actions to change the reality of STEMI in Argentina.

Key words: Myocardial infarction - Percutaneous coronary intervention - Mortality-Registry

RESUMEN

Introducción: El infarto agudo de miocardio (IAM) es la principal causa de muerte prevenible en Argentina, así como en la mayoría de los países en desarrollo. Las publicaciones que evalúan la mortalidad de causa cardiovascular muestran una tendencia decreciente en los últimos 20 años gracias a los avances en la atención.
Objetivo: Evaluar la mortalidad del IAM con elevación del segmento ST en la Argentina durante 10 años. Evaluar los tiempos desde el inicio del dolor a la consulta y la reperfusión en el mismo período.
Material y métodos: Se analizaron los casos ingresados con fecha de inicio del dolor desde el 1ero de enero de 2015 hasta el 31 de diciembre de 2024 en el registro ARGEN-IAM-ST. Se exploró las características de la población, los tiempos de consulta, mortalidad intrahospitalaria y complicaciones durante la internación por IAM.
Resultados: Se analizaron 7690 casos en 209 instituciones. La media de edad fue de 61,1 ±12 años, el 79 % era de sexo masculino. La mediana (rango intercuartílico, RIC) desde el inicio del dolor a la consulta fue de 120 minutos (59-243); el tiempo puerta-aguja fue 55 minutos (RIC 30-120), el tiempo total de isquemia para fibrinolíticos fue de 180 minutos (RIC 108-300), el tiempo puerta-balón 79 minutos (RIC 45-137) y el tiempo total de isquemia en angioplastia 315 minutos (RIC 190-607). Éstos valores no sufrieron variaciones significativas cuando se los comparó de forma individual a lo largo del tiempo. La mortalidad intrahospitalaria fue del 8,6 %, sin variaciones estadísticamente significativas cuando se compararon períodos anuales (p = 0,927), a pesar de que la tasa de reperfusión fue mayor del 90 % en 8 de los 10 años.

Rev Argent Cardiol 2026;94:5-11. https://doi.org/10.7775/rac.v94.i1.20967

Received: 11/14/2025 – *Accepted:* 01/06/2026

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Conclusión: En 10 años del registro ARGEN IAM-ST no se evidenciaron variaciones significativas en la mortalidad intrahospitalaria ni los tiempos de consulta y atención. Resulta necesario realizar acciones concretas que permitan cambiar la realidad del IAM en Argentina.

Palabras clave: Infarto de miocardio - Intervención coronaria percutánea - Mortalidad - Registro

INTRODUCTION

Acute myocardial infarction (AMI) is the leading cause of preventable death in Argentina and in most developing countries. Timely treatment has a positive impact on short- and long-term prognosis. Therefore, it is of utmost importance to understand how treatment patterns and their outcomes evolve in the local population. To this end, various tools allow for the observation of how indicators evolve over successive periods, the evaluation of advances in care, and the identification of barriers and opportunities for improvement. (1)

Prevalent disease registries are effective tools for monitoring clinical care and its outcomes because they are inexpensive and simple to use. There are multiple publications of AMI registries from Europe, the United States, Asia, and Oceania. These publications provide insight into clinical evolution, the effects of treatments, and issues arising from delays in medical interventions. (2-5)

The ARGEN-IAM-ST registry is the only registry on ST-segment elevation MI (STEMI) in Argentina that has been active for more than a decade. In previous publications, the registry has been a reference for understanding the reality of STEMI nationwide. (6-9) It is important to create a timeline for summarizing information for a given period and, at the same time, defining how the most important parameters related to care, treatment, and prognosis have evolved.

OBJECTIVE

The aim of this study is to evaluate mortality associated with STEMI in Argentina over recent years using data from the ARGEN-IAM-ST registry, and to evaluate time to presentation and time to reperfusion.

METHODS

The ARGEN-IAM-ST registry is a prospective, multicenter, and nationwide study with voluntary participation, conducted in collaboration between the Argentine Society of Cardiology and the Argentine Federation of Cardiology. The protocol had been previously published. (6) The target population was made up of STEMI patients admitted within the first 36 hours of the event. Non-STEMI cases, secondary infarctions, aortic dissection, pericarditis, and myocarditis were excluded. Cases registered with a date of chest pain onset between January 1, 2015, and December 31, 2024, were analyzed. Centers that reported at least one case during the specified period were considered participants in the study.

The most relevant data collected included coronary risk factors, cardiovascular history, and comorbidities; clinical picture, treatment used (antiplatelet agents, reperfusion, and treatment at discharge), and in-hospital clinical outcome. Data related to delays until effective treatment were achieved was also obtained.

The following times and delays were considered:

1) Time to presentation: time elapsed between the onset of symptoms suggestive of myocardial ischemia and first medical contact.
2) Time to reperfusion: time elapsed between arrival at a medical center and initiation of reperfusion treatment.
   a) In case of fibrinolytic therapy:
      - Time window: time interval in minutes from the onset of symptoms to the start of infusion.
      - Door-to-needle time: time interval in minutes from arrival at the institution to the start of infusion.
   b) In case of percutaneous coronary intervention:
      - Time window: time interval in minutes from the onset of symptoms to balloon inflation.
      - Door-to-balloon time: time interval in minutes from arrival at the institution to balloon inflation.

Data were collected on the REDCap platform. The protocol was registered in ClinicalTrials.gov with the number NCT2458885.

Ethical considerations

The protocol design of the ARGEN-IAM-ST registry was approved by the Committee on Ethics of the Argentine Society of Cardiology.

Statistical analysis

Qualitative variables are presented as frequencies and percentages. Quantitative variables are expressed as mean ± standard deviation (SD), or median and interquartile range (IQR), according to their distribution.

A logistic regression analysis was performed to explore mortality during the analyzed periods (which were annual) and to identify statistical differences. A p value < 0.05 was considered statistically significant. The analysis was performed using R statistical package.

RESULTS

A total of 7690 cases were analyzed from 209 institutions; 42% of the participating centers corresponded to public institutions. Mean age was 61.1 ± 12 years, and 78.8% were male. Fifty-four percent had hypertension, 27.2% had diabetes, 10.8% were active smokers, and 37.5% had dyslipidemia (Table 1). Over the past 10 years, the median time from the onset of chest pain to presentation was 120 minutes (IQR 59-243), door-to-needle time was 55 minutes (IQR 30-120), total ischemic time for fibrinolytic therapy was 180 minutes (IQR 108-300), door-to-balloon time was 79 minutes (IQR 45-137), and total ischemic time for percutaneous coronary intervention was 315 minutes (IQR 190-607). These values did not present significant interannual variations (Table 2).

In-hospital mortality was 8.6% over 10 years with

no statistically significant variations when comparing annual periods (p = 0.927) (Figure 1). Reperfusion therapy was utilized in at least 90% of cases in 8 of the 10 years analyzed, except for 2015 (84.2%). There were no significant variations in the use of reperfusion therapy or in mortality (Figure 2).

Anterior wall MI was the most common presentation, accounting for 39.7% of cases. Cardiogenic shock was present on admission in 7.4% of patients, 11.5% had cardiopulmonary arrest at the time of presentation, and heart failure was the most common in-hospital complication, occurring in 13.2% of cases. With respect to a key safety indicator, 4.1% of patients experienced bleeding complications during hospitalization.

Participating physicians were asked to complete a brief survey about their perceptions of the causes of delayed reperfusion in MI. They reported the following causes: delays in medical consultation (38.4%); delays in referral to another center for percutaneous coronary intervention (20.5%); delays in transportation (19.3%); and delays in the emergency department (13.5%) (Table 4).

DISCUSSION

This study presents data from 10 years of uninterrupted activity of the ARGEN-IAM-ST registry. This is the longest-running study on STEMI in Argentina. Despite the voluntary nature of registry participation and the absence of funding for on-site auditing and sampling planning, the registry has been widely accepted by institutions, with 42% being public hospitals and 58% being private institutions or managed by social security funds. Since its inception, subsequent papers have been published on the reality of STEMI. In this publication, a timeline is presented to offer an overview of the most important aspects regarding STEMI care and outcomes, such as time to presentation, time to treatment, time to reperfusion, and overall in-hospital mortality. These are important indicators that help evaluate the management of STEMI cases. (6-9) Although the number of participating centers and the number of cases entered into the registry have declined over time, as seen in Table 2 (1699 cases in 2015 and 393 cases in 2024), there have been no significant variations in the most important indicators. This suggests that the decline in cases did not affect these indicators, possibly because the centers contributing the most records have remained constant over time.

Table 1. Baseline characteristics

Variables	n = 7690
Age (years)	61.1 ± 12
Male	6059 (78.8%)
Hypertension	4153 (54.0%)
Diabetes mellitus	2092 (27.2%)
Current smoking	831 (10.8%)
Dyslipidemia	2882 (37.5%)
Family history	1129 (14.7%)
Previous coronary artery disease	955 (12.4%)
Previous heart failure	149 (1.9%)
COPD	232 (3.0%)
Chronic kidney disease	68 (0.9%)
Previous atrial fibrillation/atrial flutter	30 (0.4%)
Previous stroke	111 (1.4%)
Peripheral vascular disease	86 (1.1%)

Qualitative variables are presented as frequency and percentage and quantitative variables are expressed as mean and standard deviation
COPD: chronic obstructive pulmonary disease

Despite the high volume of cases achieving reperfusion, we have not observed a variation in in-hospital mortality. This is noteworthy because mortality is higher than in other registries, such as that of the European Society of Cardiology, where the 30-day mortality rate is 4.4%. The highest mortality rate was observed in Middle Eastern centers, which are not affiliated with the Society (5.9%). (5) In the ACI-SEC Infarction Code Registry conducted in Spain in 2019, Oriol Rodriguez-Leor et al. analyzed data from 5401 patients, reporting in-hospital mortality and 30-day mortality rates of 5.5% and 7.9%, respectively. The reperfusion therapy rate was 91.9%, and reperfusion was performed within 120 minutes of the first medical contact in more than half of these cases. (10) In our registry, despite times to fibrinolytic therapy or percutaneous coronary intervention being shorter, in-hospital mortality was higher. This could be explained by the fact that the time to presentation was 50% longer compared to the Spanish registry. In the ACI-SEC Infarction Code Registry, the median time to presentation was 60 minutes. In the ARGEN-IAM-ST Registry, the lowest median time to presentation was 90 minutes in 2016 and the overall median time doubled after 10 years of follow-up. This contributes to an extended total ischemic time, a crucial indicator that may be associated with this excess mortality.

Amini et al. investigated the trend in cardiovascular disease mortality from 1990 to 2017 and concluded that, with a few exceptions, there was an overall downward trend. (11) Conversely, the prevalence and incidence of cardiovascular disease are increasing globally, as evidenced by the publication by Khan et al., who also explored the period between 1990 and 2017 as a reference. This suggests that despite the rise in the prevalence and incidence of cardiovascular disease, different health systems have found ways to effectively treat this significant challenge. (12)

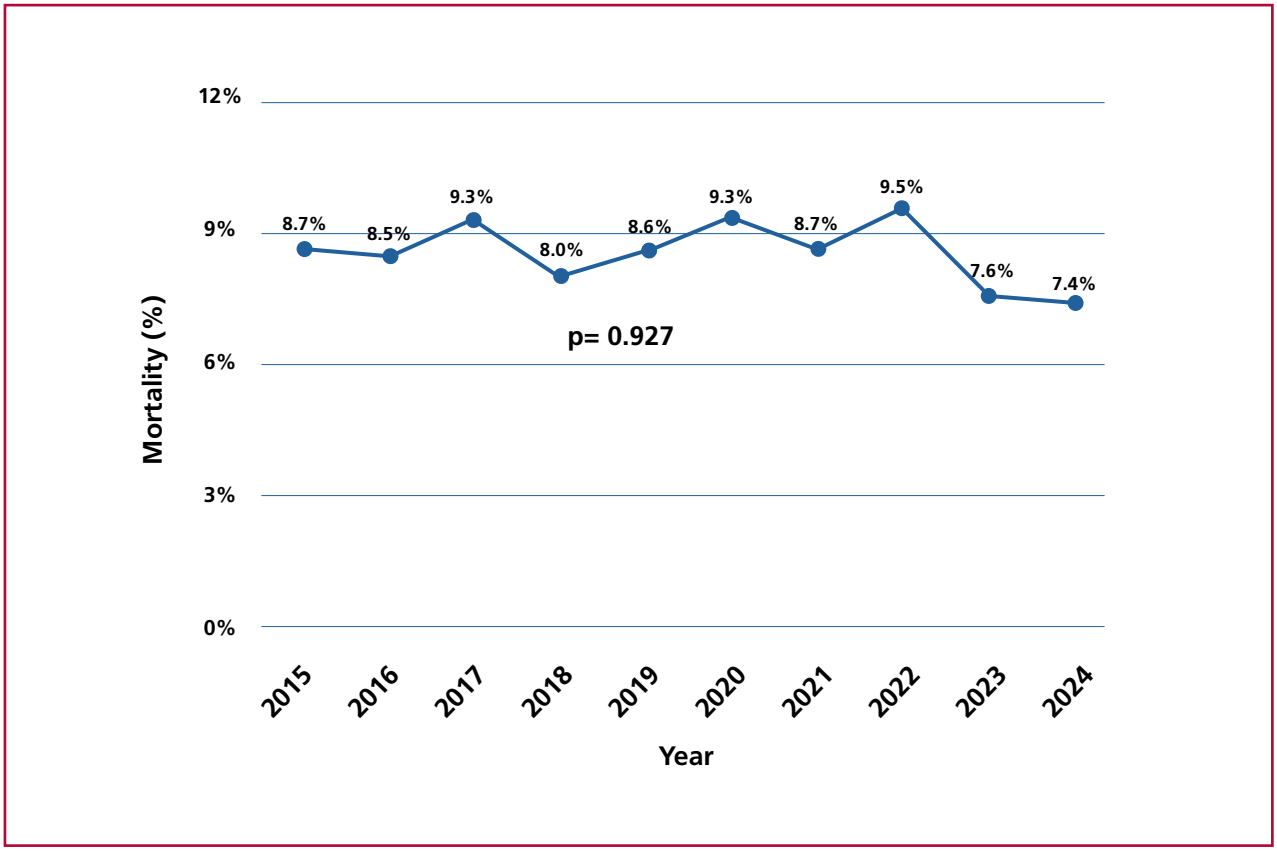
Over the past decade, there has been no significant progress in care times. When professionals were asked about this issue, their response was that they perceive delays in time to presentation, time to referral to another center, and in ambulance arrival as the main barriers to improving reperfusion times. This

Table 2. Time intervals (in minutes) of the ARGEN-IAM-ST Registry [median (IQR)]

Year	N	Chest pain to presentation	Door-to needle time	Time window to fibrinolysis	Door-to-balloon time	Time window to PCI
2015	1699	130 (60- 300)	49 (30- 90)	165(114- 297)	85 (53- 139)	301(190- 570)
2016	307	90 (40- 180)	45 (30- 120)	185(149- 315)	86 (53- 166)	280 (180- 533)
2017	688	97 (45- 190)	72 (30- 131)	200(124- 292)	88 (50- 150)	300(185- 571)
2018	911	102 (40- 240)	60 (30- 129)	190(120- 330)	75 (40- 140)	323(191- 616)
2019	1045	120 (60- 240)	60 (30- 101)	160 (110- 260)	74 (43- 135)	310(190- 600)
2020	674	120 (59- 240)	61 (40- 128)	180 (107- 295)	74 (38- 140)	315(190- 600)
2021	688	120 (56- 270)	45 (30- 177)	223 (133- 328)	70 (40- 120)	365 (190- 695)
2022	696	120 (60-270)	52 (30- 150)	200 (120- 300)	82 (45- 135)	335 (203- 679)
2023	488	112 (60- 240)	45 (15- 158)	185 (98- 271)	75 (40- 128)	325(192- 559)
2024	393	100 (48- 200)	40 (29- 105)	150 (90- 260)	70 (38- 120)	322(180- 646)
Total	7589	120 (59- 243)	55 (30- 120)	180 (108- 300)	79 (45- 137)	315(190- 607)

IQR: interquartile range; PCI: percutaneous coronary intervention

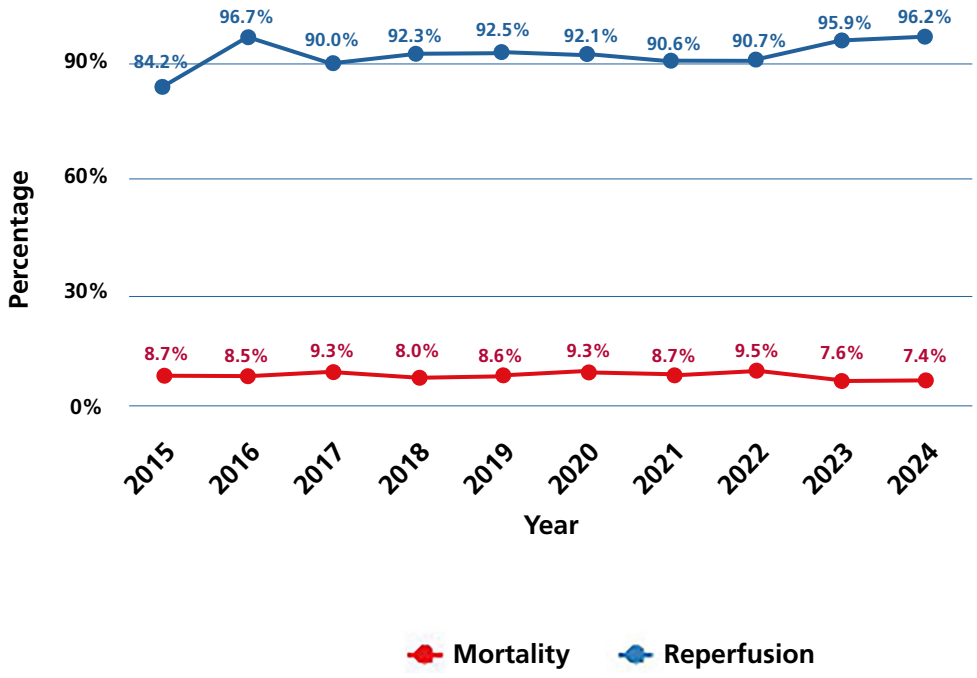
Fig. 1. STEMI mortality by year



has been a recurring issue in previous publications by the ARGEN-IAM-ST group, yet the issue remains unresolved. (6,7)

The most significant complication that occurred during hospitalization was heart failure, with an incidence of 13.2%, compared to 7.4% with cardiogenic shock and 11.5% with cardiac arrest on presentation. The incidence of heart failure during hospitalization is higher than in other registries. For example, the GRACE registry reported a rate of 5.6% in 13 707 cases, Spencer et al. recorded a rate of 8.6% in 123,938 patients, and the US ACTION registry reported a rate

Fig. 2. Reperfusion and mortality from STEMI by year



of 3.6%. (13-15). Given that heart failure rates in this registry are more than double those in other registries, the prolonged total ischemic time could be the cause of this phenomenon despite the high reperfusion rates, as it was previously mentioned. (16)

The most significant indicators show an impact on in-hospital morbidity and mortality. As is well known, these indicators also suggest that the impact will occur during mid- and long-term follow-up, particularly for patients who develop heart failure. (17-20)

This exploratory analysis shows prolonged times to presentation, which is consistent with physicians' perceptions. Issues related to the organization of resources (delays in referral, ambulance arrival, and emergency care) are also reported. It is widely recognized that the logistics of transfers can lead to delays in reperfusion times. Therefore, the implementation of effective strategies in both prehospital and hospital settings is strongly recommended. (21)

Based on this information, it is necessary to educate and promote awareness among the population to prevent delays in cases of chest pain. Additionally, health systems must be organized to prevent delays in care and optimize human and technological resources. Implementing protocols and creating networks for AMI care could improve current outcomes and avoid another decade of stagnation. This approach would avoid the economic and social impacts of being left behind by the improvements seen in other health systems.

In the case of Argentina, a country with a fragmented health system and different districts with their own demographic, geographic, and climatic characteristics, it is imperative to develop policies tailored to each reality.

CONCLUSION

Over the past 10 years, the ARGEN IAM-ST registry shows absence of significant changes in STEMI mortality despite high reperfusion rates. This could be due to prolonged times to presentation and treatment, which have not shown significant reductions. Analysis of delays suggests that logistics could be improved. It is imperative to implement policies designed to change the reality of AMI in Argentina to reduce the time between symptom onset and patient presentation, improve medical care, and optimize referral logistics. This will optimize both public and private healthcare resources.

Study limitations

The ARGEN IAM-ST registry is a voluntary registry, with no financial incentives and no data auditing at each institution. Data quality control is performed

Table 3. Characteristics and complications of STEMI

Characteristicistic	n=7690
ECG location (n = 7538)	
Anterior wall (V1-V6)	2989 (39.7%)
Inferior wall (LI - LII - VF)	2828 (37.5%)
Lateral wall (LI and VL or V5-V6 only)	256 (3.4%)
Anterolateral wall	710 (9.4%)
Anterior and inferior wall	81 (1.1%)
Inferolateral wall	626 (8.3%)
Undetermined (LBBB or cannot be located)	48 (0.6%)
Infarct-related artery (n= 6407)	
LMCA	85 (1.3%)
LAD	3052 (47.6%)
Diagonal	126 (2.0%)
LCx	830 (13%)
RCA	2201 (34.4%)
Venous graft	33 (0.5%)
Arterial graft	16 (0.2%)
None	47 (0.7%)
Unidentified	17 (0.3%)
Killip and Kimball class (n= 7533)	
KK I	5798 (77%)
KK II	1068 (14.2%)
KK III	113 (1.5%)
KK IV	554 (7.4%)
Bleeding (n= 7664)	
No bleeding	7348 (95.9%)
Minimal	191 (2.5%)
Minor	74 (1.0%)
Major	51 (0.7%)
Reinfarction	132 (1.7%)
PIA	160 (2.1%)
Cardiogenic shock *	728 (9.5%)
Intraaortic baloon pump	152 (2.0%)
Heart failure	1015 (13.2%)
Atrial fibrillation	341 (4.4%)
Electric cardioversion	365 (4.7%)
Pulmonary artery catheter	227 (3.0%)
Mechanical ventilation	646 (8.4%)
Ischemic stroke	67 (0.9%)

During the course of treatment (not applicable if on admission)
ECG: electrocardiogram; KK: Killip and Kimball; LAD: left anterior descending coronary artery; LBBB: left bundle branch block; LCx: left circumflex artery; LMCA: left main coronary artery; PIA: post-infarction angina; RCA: right coronary artery

through the REDCap platform. The contribution of researchers and participating institutions is vital to the project's sustainability. This registry model may be subject to reporting bias and does not have a sampling strategy.

Table 4. Causes of delays in reperfusion

Cause of delay	n = 7690
Patient presentation	2954 (38.4%)
Ambulance	1483 (19.3%)
Emergency room care	1037 (13.5%)
Medical error in the diagnosis of infarction	860 (11.2%)
Catheterization laboratory team	632 (8.2%)
Referral to another center for primary PCI	1577 (20.5%)
Cardiac arrest	184 (2.4%)
Administrative error	296 (3.8%)
First ECG inconclusive	264 (3.4%)

PCI: percutaneous coronary intervention; ECG: electrocardiogram

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Diagnosis and Management of Bicuspid Aortic Valve Disease in Argentina: an Analysis Revealing the Need for Improvement

Diagnóstico y manejo de la válvula aórtica bicúspide en Argentina: un análisis que revela la necesidad de mejoras

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ABSTRACT

Background: Bicuspid aortic valve (BAV), the most common congenital heart defect, presents a significant lifetime risk of cardiovascular complications. The extent to which healthcare professionals adhere to guidelines for managing BAV patients and the potential for significant heterogeneity in management between institutions in our setting remains unknown. The decision to recommend surgical treatment before complications arise increases the life expectancy of patients with BAV. Therefore, it is imperative to investigate these aspects in our setting. For this reason, a survey was designed to investigate the professional management of BAV in our country, including access to advanced diagnostic techniques, availability of multidisciplinary teams (Heart Teams), and adherence to clinical practice guidelines.
Objectives: The primary objective was to determine the characteristics of the diagnosis and current management of BAV at the national level. The secondary objective was to identify regional differences in the diagnosis and management of BAV, as well as access to more complex diagnostic and surgical techniques.
Methods: An anonymous, voluntary survey was designed and distributed online to cardiologists in Argentina between May 2024 and January 2025. The questionnaire explored demographic and professional aspects, diagnostic practices (including family screening and multimodality imaging), and management strategies (availability of a Heart Team, type of interventions performed, prophylaxis of infective endocarditis, and genetic counseling). The responses of 240 professionals were analyzed using descriptive and comparative statistics.
Results: Most professionals surveyed were men (65%); mean age was 48.1 ± 12.2 years; 37.4% (n = 86) practiced in the Buenos Aires Metropolitan Area (AMBA), 27.4% (n = 63) in the province of Buenos Aires, and 5.7% (n = 13) in the province of Córdoba. Ninety-five percent (n = 228) had access to Doppler echocardiography, and 60.3 percent (n = 144) to multimodality imaging at their centers, which were mostly tertiary care institutions ($p < 0.001$). According to 85.4% (n = 204) of respondents, patients are usually diagnosed in adulthood. Echocardiographic screening in first-degree relatives was requested by 60% of respondents, particularly by specialists in cardiovascular imaging ($p = 0.001$). Availability of Heart Teams for complex decision-making was limited (50%). This was more common in inland centers (61.7% vs. 43.3%; OR 2.1, 95% CI 1.2-3.6; $p = 0.007$) with no significant differences between public and private institutions. Access to a Heart Team was more frequent among professionals working in tertiary care centers (71.2% vs. 32.5%; OR 5.1, 95%: 2.9-8.9; $p < 0.001$). Indications for the Ross procedure and aortic valve replacement were uncommon, 40.7% reported having indicated transcatheter aortic valve implantation (TAVI) in some patients with BAV, despite limited evidence in this condition. Delayed surgical treatment of patients with BAV due to long waiting times was reported by 13% of survey respondents, especially in public institutions ($p < 0.001$). Adherence to current recommendations for prophylaxis of infective endocarditis was not uniform, and genetic counseling was rarely indicated (only in familial forms, in 47.1%).
Conclusion: The diagnosis and management of BAV in Argentina present significant challenges, including late detection, unequal access to advanced diagnostic and therapeutic resources, and variable adherence to clinical guidelines. Half of the professionals surveyed have no access to a Heart Team for complex decision-making, which is common in this scenario, as it involves the indication of valve replacements in young patients.
It is imperative to implement strategies at the national level to improve family screening, optimize access to multimodality imaging evaluation and multidisciplinary decision-making through Heart Teams. These strategies should also encourage adherence to evidence-based recommendations and create networks for treating complex patients.

Key words: Bicuspid aortic valve-Aortic stenosis-Professional management-Aortic regurgitation.

Rev Argent Cardiol 2026;94:12-19. https://doi.org/10.7775/rac.v94.i1.20974

Received: 10/26/2025 – *Accepted:* 12/19/2025

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RESUMEN

Introducción: La válvula aórtica bicúspide (VAB), la anomalía congénita cardíaca más común, presenta un riesgo significativo de complicaciones cardiovasculares a lo largo de la vida. Se desconoce la adherencia en nuestro medio a guías de manejo de pacientes con VAB, así como la posible heterogeneidad sustancial en el manejo entre instituciones. La toma de decisiones quirúrgicas adecuadas antes de la instalación de complicaciones permite aumentar la expectativa de vida de los pacientes con VAB, por lo que resulta relevante indagar sobre estos aspectos en nuestro medio. Para ello, se diseñó una encuesta de manejo profesional de la VAB en nuestro país, incluyendo el acceso a técnicas diagnósticas avanzadas, la disponibilidad de equipos multidisciplinarios (Heart Teams) y la adherencia a las guías de práctica clínica.
Objetivos: El objetivo principal fue determinar las características del diagnóstico y manejo actual de VAB a nivel nacional y como objetivo secundario se planteó identificar existencia de diferencias entre regiones en el diagnóstico y manejo de la VAB, así como el acceso a técnicas diagnósticas y quirúrgicas de mayor complejidad
Material y métodos: Se diseñó una encuesta anónima y voluntaria, distribuida de manera online a cardiólogos de Argentina entre mayo de 2024 y enero de 2025. El cuestionario exploró aspectos demográficos y profesionales, prácticas de diagnóstico (incluyendo screening familiar e imágenes multimodalidad) y estrategias de manejo (disponibilidad de Heart Team, tipo de intervenciones realizadas, profilaxis de endocarditis infecciosa y asesoramiento genético). Se analizaron las respuestas de 240 profesionales utilizando estadística descriptiva y comparativa.
Resultados: La mayoría de los profesionales encuestados (65 %) eran hombres, con una edad media de 48.1 ± 12,2 años. El 37,4 % (n=86) ejercía en el AMBA, el 27,4 % (n=63) en provincia de Buenos Aires y el 5,7 % (n=13) en Córdoba. Si bien el 95 % tenía acceso a ecocardiograma Doppler, solo el 60,3 % tenía disponibilidad de evaluación multiimágenes en su centro, significativamente más en instituciones de tercer nivel (p<0,001). En cuanto al diagnóstico de VAB, el 85,4 % (n=204) estaba de acuerdo con que el diagnóstico de los pacientes suele ser en la adultez. El 60 % de los profesionales refería solicitar screening ecocardiográfico en familiares de primer grado, con mayor frecuencia entre los especialistas en imágenes cardiovasculares (p=0,001). La disponibilidad de Heart Teams para la toma de decisiones complejas fue limitada (50 %). La falta de Heart Teams fue más frecuente en centros del interior (61,7 % vs. 43,3 %;OR 2,1, IC95 % 1,2-3,6; p=0,007), sin diferencias significativas según el tipo de financiación de la institución. Los profesionales que ejercían en instituciones de tercer nivel tuvieron acceso a Heart Team con mayor frecuencia (71,2 % vs. 32,5 %; OR 5,1, IC95 % 2,9-8,9; p< 0,001). Las indicaciones de cirugía de Ross y plástica valvular aórtica fueron muy infrecuentes, mientras que el 40,7 % refirió haber indicado implante percutáneo de válvula aórtica (TAVI) en algunos pacientes con VAB, a pesar de la escasa evidencia en esta patología. Un 13 % reportó tratamiento quirúrgico tardío de pacientes con VAB por tiempos de espera prolongados, especialmente en instituciones públicas (p<0,001). La profilaxis de endocarditis infecciosa no adhirió uniformemente a las guías actuales, y el asesoramiento genético fue indicado muy poco frecuentemente (solo ante formas familiares, en el 47,1 %).
Conclusiones: El diagnóstico y manejo de la VAB en Argentina presenta desafíos importantes, incluyendo la detección tardía, el acceso desigual a recursos diagnósticos y terapéuticos avanzados, y la adherencia variable a las guías clínicas. La mitad de los profesionales encuestados no tiene acceso a Heart Team para la toma de decisiones complejas, que en este escenario es frecuente ya que implica la indicación de sustitutos valvulares a pacientes jóvenes. Resulta fundamental la implementación de estrategias a nivel nacional para mejorar el screening familiar, optimizar el acceso a la evaluación multiimágenes y a la toma de decisiones multidisciplinaria a través de Heart Teams, así como promover la adherencia a las recomendaciones basadas en la evidencia y generar redes para el tratamiento de pacientes complejos.

Palabras clave: Válvula aórtica bicúspide - Estenosis aórtica - Manejo profesional - Insuficiencia aórtica

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart defect, affecting 0.5-2% of the population, with a higher incidence in males. (1,2) This congenital heart defect represents a valvuloaortopathy with family aggregation. (3) Because of its high prevalence, most cardiologists must deal with BAV patients during their medical practice. The lifetime risk of major cardiovascular complications is high, mainly severe aortic stenosis and regurgitation, infective endocarditis, and aortic aneurysm. (4–9) This condition can be diagnosed at any stage of life, from newborns to the elderly, and in the context of different clinical circumstances. (10–12)

In our setting, multimodality imaging is not readily accessible to the general population. There are no current national echocardiographic screening programs for the detection of BAV that allow for the evaluation of index cases and their first-degree relatives, and for periodic follow-up. In most cases, the diagnosis is incidental or is made when complications occur. The extent to which healthcare professionals request or have access to these methods while monitoring patients with BAV, (13) as well as the degree to which they adhere to guidelines for the management of these patients in our setting, remains unknown. Furthermore, we are unaware of the potential for significant heterogeneity in BAV management between institutions. The decision to recommend surgical treatment before complications arise increases the life expectancy of patients with BAV. Therefore, it is imperative to investigate these aspects and understand the diagnostic process, current management, and decision-making in our setting. So far, there is no information on the management of BAV in our country.

Decision-making for these patients has become a more complex process due to the development of new technologies and treatments. This often involves the participation of various disciplines to achieve patient-centered care. (14) The availability of a multidisciplinary Heart Team to make decisions in complex cases about the type of intervention and selection of valve replacement in young patients is an important aspect for managing the condition. In patients with BAV, the Heart Team should involve members of the Aortic Team, as both conditions often coexist. This team should include cardiovascular surgeons, cardiologists (interventional and non-interventional), specialists in

cardiovascular imaging, and cardiovascular anesthesiologists. Additionally, cardiologists or referral centers who have had the opportunity to get to know the patients for a longer period should be involved in the decision-making process during these regular team meetings. (15)

OBJECTIVES

The "Dr. Oscar Orías" Council on Doppler Echocardiography and Vascular Ultrasound, and the Research Area of the Argentine Society of Cardiology designed a voluntary and anonymous online survey for cardiologists in Argentina. The primary objective was to determine the characteristics of the diagnosis and current management of BAV at the national level. The secondary objective was to identify regional differences in the diagnosis and management of BAV, as well as access to more complex diagnostic and surgical techniques.

METHODS

A total of 240 cardiologists in Argentina who were treating patients with BAV anonymously and voluntarily completed the survey between May 2024 and January 2025.

The survey was distributed via a link in e-mails sent to the mailing list of the Argentine Society of Cardiology and through the social media accounts of the Argentine Society of Cardiology and the Council of Doppler Echocardiography and Vascular Ultrasound. Data were anonymously collected on the REDCap platform. The questions were divided into three sections: demographic characteristics and medical practice, diagnosis of BAV, and management and follow-up. A Likert scale was used to rate opinion and agreement/disagreement responses.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, or median and interquartile range (IQR), according to their distribution. Categorical variables are presented as absolute frequencies (n) and percentages. Continuous variables were compared using the two-tailed Student's t test in case of means or the Wilcoxon in case of medians. Categorical variables were compared using the chi-square test with Yates correction or the Fisher's exact test, as appropriate. Logistic regression analysis was performed to evaluate the association between categorical variables. The results were expressed as odds ratio (OR) and its corresponding 95% confidence interval (CI). All the statistical calculations were performed with R using SOFA Stats software package under Windows operating system. A p value < 0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the main characteristics of the 240 professionals surveyed and the institutions where they worked. Sixty-five percent (n = 156) of respondents were men; mean age was 48.1 ± 12.2 years, and 45.2% (n = 108) worked in tertiary care institutions. Most respondents (37.4%; n = 86) were from Buenos Aires Metropolitan Area (AMBA), 27.4% (n = 63) from the province of Buenos Aires, and 5.7% (n = 13) from Córdoba.

Ninety-five percent (n = 228) had access to Doppler echocardiography and 60.3 percent (n = 144) to multimodality imaging at their centers. This was more common among professionals working in tertiary care centers (84.1% vs. 40.9%; OR 7.6, 95% CI 4.1-14.2; $p < 0.001$), with no significant differences according to the geographical location of their medical practice.

Fifty percent (n =120) of respondents lacked a Heart Team for complex decision-making at their institution. This was more common in inland centers (61.7% vs. 43.3%; OR 2.1, 95% CI 1.2-3.6; p = 0.007) with no significant differences between public and private institutions (Figure 1). As expected, access to a Heart Team was more frequent among professionals working in tertiary care centers (71.2% vs. 32.5%; OR 5.1, 95% CI 2.9-8.9; $p < 0.001$).

According to 85.4% (n = 204) of respondents, patients are usually diagnosed in adulthood . When asked about echocardiographic screening in first-degree relatives, 60.4% (n = 145) of respondents indicated that they always request it, while 10% (n = 24) never do so (Figure 2). Among those who responded affirmatively, the proportion of specialists in cardiovascular imaging was higher (46.9% vs. 12.5%; OR 6.7, 95% CI 1.9-23.2; p = 0.001).

Computed tomography or magnetic resonance imaging was never requested at the time of diagnosis of BAV by 8.3% (n = 20) of respondents, 12.9% (n = 31) reported that these methods were not available, and 71.3% (n = 171) of professionals requested computed tomography (CT) or magnetic resonance imaging (MRI) scans in less than 40% of patients with BAV during follow-up

Figure 3 shows that only 30.8% of the professionals surveyed measure the distal ascending aorta, a common site of aortic dilatation in patients with BAV.

Regarding the type of intervention, 65.7% (n = 144) have never indicated the Ross procedure to any patient, 65.4% (n = 157) have not indicated aortic valve replacement to any patient. However, 40.7% (n=95) have recommended transcatheter aortic valve implantation (TAVI) to some patients with VAB.

Regarding the intervention of patients with indication for surgery, 12.9% (n = 31) reported that patients received delayed surgical treatment due to prolonged waiting times, with some deaths occurring while on the waiting list. This was more common among professionals working in public institutions (26.6% vs. 8.3%; OR 4, 95% CI 1.8-8.6; $p < 0.001$). In addition, 40.8% (n = 98) responded that they refer patients to centers with advanced expertise in the appropriate technique for each case (the Ross procedure, the Bentall-De Bono technique or aortic valve repair).

When asked about the number of patients they had managed with aortic dissection and BAV over the past 5 years,91.3% (n = 219) of the professionals responded that they had managed between 0 and 5 patients. Most respondents (57.1%, n = 137) reported

Table 1. Main characteristics of respondents and places of medical practice

Variable	n = 240
Male sex	156 (65%)
Age	48.1 ± 12.2
Clinical cardiology	114 (47.5%)
Cardiovascular imaging	109 (45.4%)
Years of practice	
1-10	75 (31.5%)
11-20	74 (31.1%)
> 20	89 (37.4%)
Institutional complexity	
Tertiary care	108 (45.2%)
Secondary care	55 (23.0 %)
Outpatient clinic	29 (12.1%)
Office	47 (19.7%)
Funding	
Public hospital	60 (25.4%)
Prepaid medical insurance	79 (33.5%)
Social security	90 (38.1%)
Any of the following available:	
Doppler echocardiography	228 (95%)
Multimodality imaging	144 (60.3%)
Heart Team	120 (50%)
How many patients with BAV do you follow-up and manage?	
< 10	134 (56.5%)
Between 10 and 99	97 (40.9%)
Between 100 and 299	3 (1.3%)
> 300	3 (1.3%)

BAV: bicuspid aortic valve

not restricting competitive sports activity due to the risk of aortic dissection.

Only 16.7% of respondents (n = 40) reported consulting the Heart Team for all complex patients with indications for intervention to discuss the best therapeutic decision. Meanwhile, 39.6% of respondents (n = 95) reported discussing only some of their patients with indications for intervention with the Heart Team.

Prophylaxis for infective endocarditis is prescribed to all patients with BAV by 41.4% (n = 99) of professionals, only in cases of high risk of endocarditis in 41.4% (n = 99) according to current guidelines, and 14.2% (n = 34) responded that they only indicated prophylaxis in patients with BAV and aortic valve dysfunction.

Regarding genetic counseling, 40.8% (n = 98) responded that they never request it in patients with BAV, and 47.1% (n = 113) responded that they only do so in cases of familial BAV.

DISCUSSION

This anonymous and voluntary survey, completed by 240 Argentine cardiologists, provides insight into the characteristics of the diagnosis and current management of BAV in our country. The findings reveal several important aspects that require detailed analysis in the context of international literature and clinical practice guidelines.

Detection and family screening

One of the main findings is the confirmation that, in Argentine clinical practice, the diagnosis of BAV is usually made in adulthood, a fact reported by 85.4% of the surveyed professionals. This finding highlights the lack of systematic population-based or family echocardiographic screening programs in our setting. This is different from the recommendation for early detection in first-degree relatives due to the family aggregation of BAV. (3) While a considerable proportion

Fig. 1. Availability of Heart Teams for complex decision-making according to the place of medical practice (AMBA vs. inland).

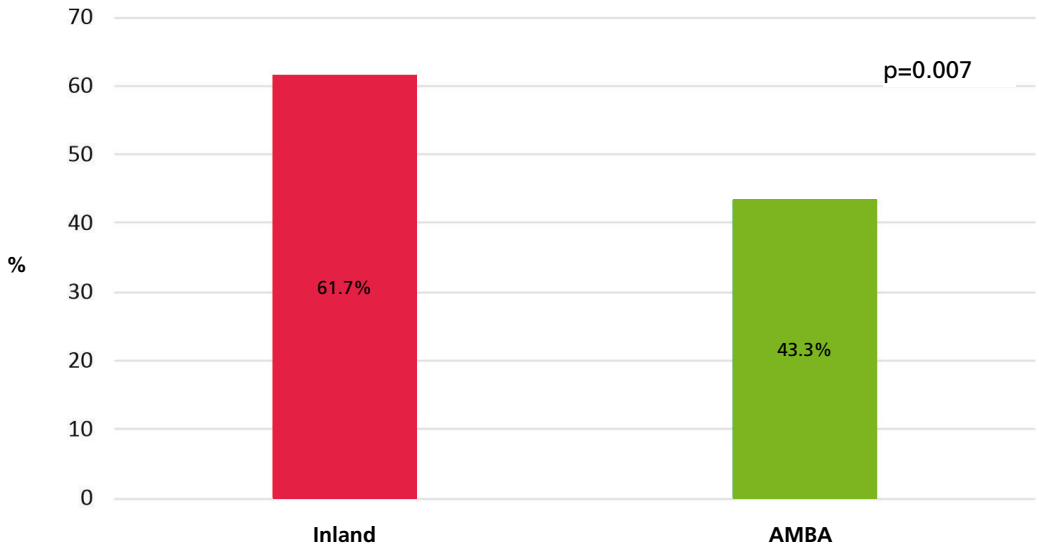


Fig. 2. Proportion of professionals who request echocardiographic screening and evaluation of the aorta at the time of the diagnosis of bicuspid aortic valve

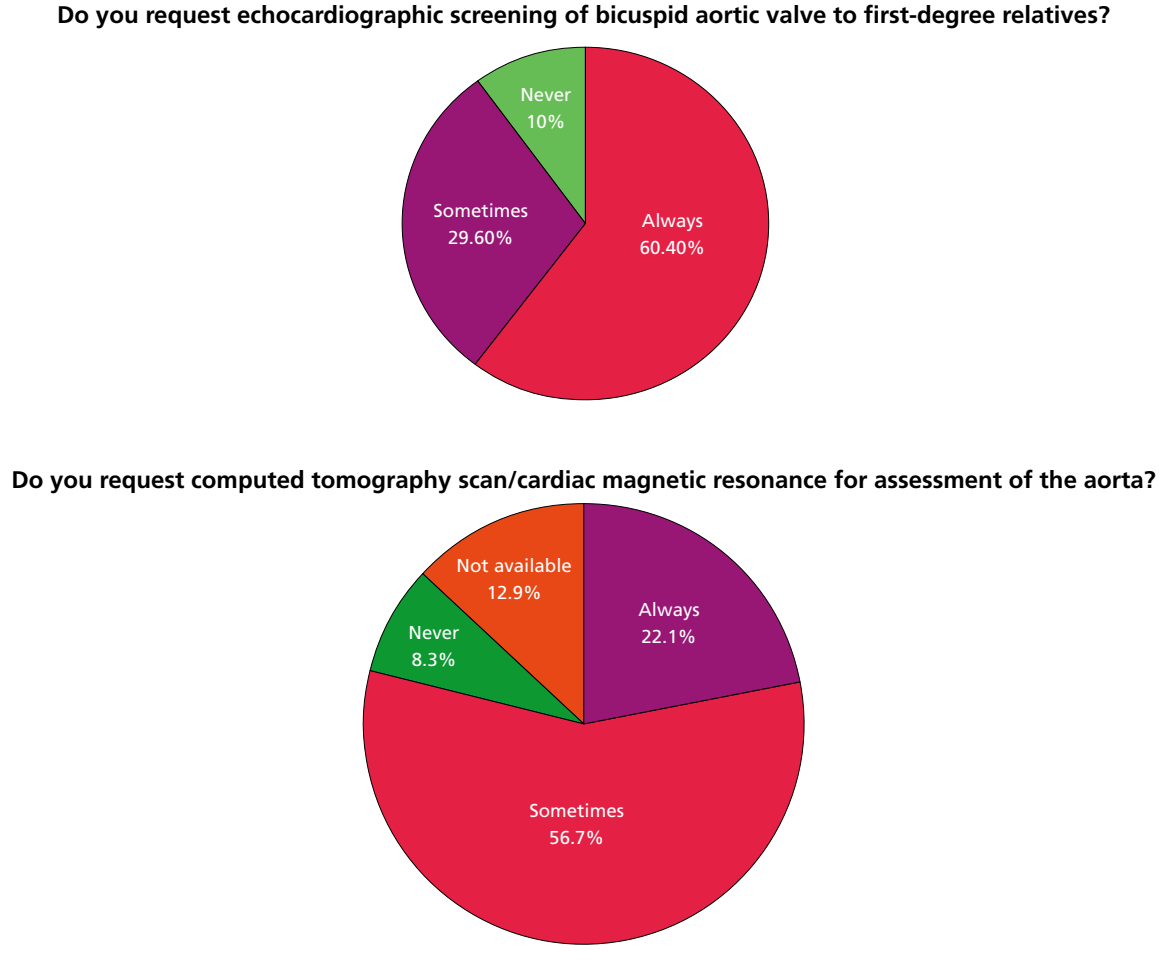
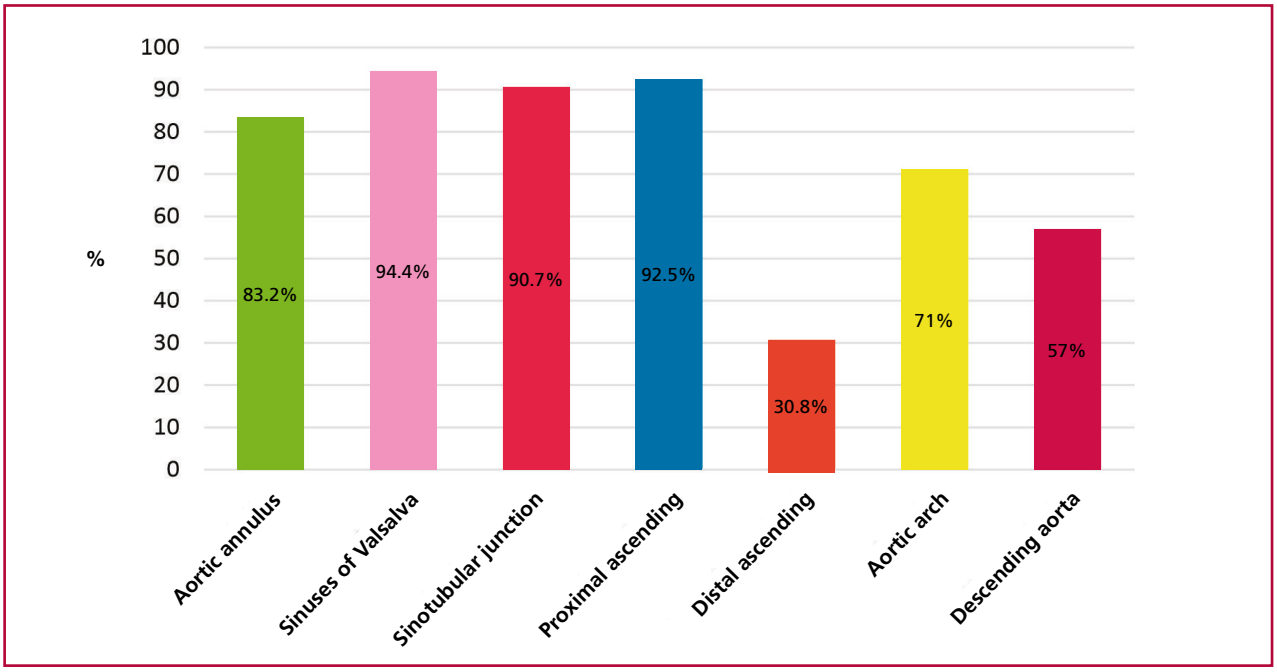


Fig. 3. More than 80% of the professionals surveyed reported that they measure the aortic annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta. Only 30.8% reported measuring the aorta in its distal tubular portion



of respondents (60%) reported requesting screening for family members, 10% never did so. The request was significantly higher among professionals specializing in cardiovascular imaging, which could suggest a bias due to the subspecialty practiced. This heterogeneity in medical practice underscores the necessity for enhanced dissemination of recommendations and the implementation of strategies to facilitate family screening.

Although international guidelines recommend echocardiographic screening of first-degree relatives of patients with BAV, adherence to this recommendation is unknown. A recent meta-analysis included 2297 patients (32 ± 21 years, 71% men) with BAV and 6054 screened relatives (29 ± 13 years, 50.6% men). The prevalence of BAV among first-degree relatives was 7.3% (95% CI 6.1%–8.6%, $p < 0.001$) and 9.4% for aortic dilatation. (15) Family members with BAV were about 6 times more likely to have aortic dilatation than family members with tricuspid aortic valves. The existence of aortic dilatation without BAV could be due to limitations of echocardiography to identify partial raphes. The indication for echocardiographic screening is based on a significantly higher prevalence of positive findings in relatives than in the general population. Given that echocardiography is a safe and relatively low-cost test in our country, implementing echocardiographic screening seems feasible and useful. However, the optimal age for recommendation remains unclear, whether it should be for pediatric or adult patients, and whether performing it at an early age is beneficial (given the anxiety surrounding the diagnosis and the potential complications in adulthood). Additionally, there is a need to determine whether a transthoracic echocardiogram is sufficient, considering the prevalence of false negative results.

Access to advanced diagnostic and therapeutic resources

Access to multimodality imaging assessment during follow-up of patients with BAV remains limited in our country. Although 60.3% of professionals work in centers with these techniques, they are significantly more available in tertiary care institutions. A considerable percentage of professionals (21.2%), including those working in centers lacking these techniques and those who never request them, do not have access to these tools at the time of diagnosis. The majority of these professionals request these tests for less than 40% of their patients under follow-up. This situation could lead to underdiagnosis of aortic dilation and affect adequate risk stratification and timely planning of interventions, considering the high prevalence of aortic complications in this population. (4–6)

Only half of the surveyed cardiologists reported Heart Teams available at their institutions. A lack of Heart Teams was more common among inland professionals. These results are consistent with those of a Canadian study that reported that 47.6% of the high-complexity centers surveyed lacked Heart Teams. (16) In that study, centers with Heart Teams highlighted that their main benefits were collaborative decision-making with shared responsibility and transparency, improvement in communication among professionals, improvements in patient care and outcomes, and inter-

professional learning for new approaches and technologies. The lower availability of Heart Teams in lower complexity centers could influence the homogeneity of management and access to optimal therapeutic strategies for complex cases. Although the guidelines for the management of patients with valvular heart disease recommend Heart Team assessment (Class I recommendation, level of evidence C), the assigned level of evidence demonstrates a lack of supporting data, as it is derived from expert consensus and/or small studies, retrospective series, or registries. (17,18)

Therapeutic and Intervention Strategies

When analyzing intervention strategies, the Ross procedure and aortic valve repair were indicated less frequently than conventional aortic valve replacement, and 34.3% and 34.6% of survey respondents did not indicate the Ross procedure and aortic valve repair, respectively, for any patient. Notably, a significant percentage of professionals (40.7%) indicated TAVI for some patients with BAV. This could reflect an increasing trend in the use of TAVI, despite limited evidence and unfavorable outcomes in this valve phenotype compared to degenerative aortic stenosis. This is a special concern given the still-undefined long-term role of TAVI in younger patients. (19,20)

A worrying finding was that 13% of respondents reported that patients with indication for surgery experience delayed treatment due to long waiting times, with cases of death while on the waiting list, particularly in public institutions. This situation highlights the barriers to timely treatment and underscores the need to optimize resources and waiting list management.

Low adherence to current guidelines on prophylaxis of infective endocarditis is also worth noting. Despite the recommendation to limit prophylaxis to high-risk patients, many professionals continue to prescribe it for all patients with BAV or in the presence of valve dysfunction. According to the current recommendations of the American Heart Association and the Argentine Society of Cardiology, BAV is no longer an indication for antibiotic prophylaxis, as it is a condition with a moderate risk of morbidity and mortality related to endocarditis. (19,20) However, adherence to these guidelines is low, and the incidence of endocarditis has been detected to increase since their publication. It is recommended that patients be informed that BAV is no longer an indication for antibiotic prophylaxis; yet, the decision to stop indicating it is complex.

Finally, genetic counseling for patients with BAV is not a systematic practice in our country. Most professionals only request genetic counseling for familial cases of BAV. There is still a lack of information on the usefulness of genetic testing in this scenario, although the identification of mutations associated with familial forms has been increasing in recent years. The limited availability of current panels for patients with BAV may contribute to the underutilization of genetic testing, which could hinder the early identification of other affected family members and the implementation of proactive follow-up strategies.

Study limitations

Our study has some limitations. As this was a voluntary online survey, there is a possibility of selection bias, as more cardiologists with a greater interest in the topic of BAV could have participated. Furthermore, the responses are based on the self-perception of the professionals, which may not fully reflect actual clinical practice. Although the sample size was significant, it may not fully represent the heterogeneity of cardiology practice nationwide.

Clinical implications and future lines of research

The findings of this study have significant implications for clinical practice in Argentina, underscoring the need to implement of echocardiographic familial screening strategies and improve access to multimodality imaging techniques. It is also necessary to encourage the creation and functioning of multidisciplinary Heart Teams, optimize waiting times for surgery, and promote greater adherence to updated clinical guidelines, especially with regard to the prophylaxis of infective endocarditis.

Future lines of research could focus on prospective studies evaluating the impact of different management strategies on the clinical outcomes of patients with BAV in Argentina. It would be worthwhile to investigate why aortic valve replacement and the Ross procedure are underused, and to examine the role and long-term outcomes of TAVI in this population. Similarly, developing strategies to improve access to genetic evaluations and family counseling could significantly impact the early detection and comprehensive management of BAV in our country.

CONCLUSION

This pioneer national study provides a valuable snapshot of the diagnosis and management of BAV in Argentina. The findings reveal an opportunity to improve medical practice, including implementation of early detection strategies, optimization of access to advanced imaging tests, multidisciplinary decision-making, and greater adherence to international clinical guidelines. It is imperative for the Argentine cardiology community to acknowledge these findings and collaborate to enhance the comprehensive management of BAV patients in our country.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None declared.

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

Acknowledgments

We are grateful to all the professionals who voluntarily agreed to participate in the survey.

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ORIGINAL ARTICLE

New Method for Estimating Left Atrial Volume Based on an Irregular Base Cylinder Model using Magnetic Resonance Imaging: Comparison with the Area-Length Method

Nuevo método para la estimación del volumen de la aurícula izquierda por resonancia magnética basado en un modelo cilíndrico de base irregular: comparación con el método de área-longitud

GUILLERMO JAIMOVICH[1], JULIAN CASTRO[2], LUCIANO DE STEFANO[2,3,4], PABLO G. STUTZBACH[2]

ABSTRACT

Background: Left atrial volume quantification is of great importance in various pathologies. For this purpose, models derived from echocardiography have been applied in magnetic resonance imaging, although they may not be completely accurate.
Objective: To validate a new method for estimating left atrial volume that is practical and more accurate than the method most commonly used at present.
Methods: Images of patients included in a cardiac magnetic resonance imaging database were used. Direct volumetric quantification and volumetric estimates using the area-length (AL) method and the irregular base cylinder (*cilindro de base irregular*, CBI) method were performed to measure correlation.
Results: Studies from 25 patients were analyzed. The mean age was 44 ± 15 years; 52% were male and 84% were studied on an outpatient basis. Pearson's correlation coefficient was higher for the CBI method (r=0.93; p <0.001) than for the AL method (r=0.83; p <0.001). The Bland-Altman analysis showed lower dispersion for the CBI method [-5.73 mL (18.6 to -30.11)] than for the AL method [-1.18 mL (43.82 to -46.17)]. Interobserver variability was lower for the CBI method [4.94 mL (44.76 to -34.88)] than for the LA method [19.7 mL (65.91 to -26.51)].
Conclusions: The CBI model showed better correlation than the AL model. We consider it a valid alternative that is equally simple and more accurate than the AL method for estimating left atrial volume by magnetic resonance imaging.

Key words: Cardiac magnetic resonance - Left atrium - Volume - Irregular base cylinder

RESUMEN

Introducción: La cuantificación volumétrica de la aurícula izquierda es de suma importancia en diversas patologías. Para ello se han aplicado en resonancia magnética modelos derivados de la ecocardiografía que pueden no ser completamente exactos.
Objetivo: Validar un nuevo método para estimación del volumen de la aurícula izquierda que sea práctico y más preciso que el más utilizado en la actualidad.
Material y métodos: Se utilizaron las imágenes de pacientes de una base de datos de resonancia magnética cardíaca (RMC). Se realizaron la cuantificación volumétrica directa, y las estimaciónes volumétricas por método de área-longitud (AL) y cilindro de base irregular (CBI) para medir correlación.
Resultados: Se analizaron los estudios de 25 pacientes. La edad media fue de 44±15 años; el 52% era de sexo masculino y el 84% pacientes estudiados en forma ambulatoria. El coeficiente de correlación de Pearson fue mayor para el método CBI (r = 0,93; p < 0,001) que para el de AL (r = 0,83; p < 0,001). El análisis de Bland-Altman mostró menor dispersión para el método CBI [- 5,73 mL (18,6 a -30,11)] que para el método AL [-1,18 mL (43,82 a -46,17)]. La variabilidad interobservador fue menor para el método CBI [4,94 mL (44,76 a -34,88)] que para el método AL {19,7 mL (65,91 a -26,51)].
Conclusión: El modelo CBI mostró mejor correlación que el de AL. Consideramos que representa una alternativa válida, igualmente simple y más precisa que el método de AL para la estimación del volumen de la aurícula izquierda por RMC.

Palabras clave: Resonancia magnética cardíaca - Aurícula izquierda - Volumen - Cilindro de base irregular

Rev Argent Cardiol 2026;94:20-24. https://doi.org/10.7775/rac.v94.i1.20979
SEE RELATED ARTICLE: Rev Argent Cardiol 2026:94:3-4. https://doi.org/10.7775/rac.v94.i1.20981

Received: 10/22/2025 – *Accepted:* 01/15/2026

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INTRODUCTION

The left atrium (LA) plays an important role in cardiac physiology, and its volume has been associated with various clinical conditions such as atrial fibrillation, heart failure, and increased cardiovascular risk. (1-3) Therefore, its volumetric measurement is an essential parameter in imaging studies in clinical practice.

The most commonly used echocardiographic methods for estimating LA volume are area-length (AL) and Simpson methods. (4,5) Cardiac magnetic resonance (CMR) imaging allows global and multiplanar assessment of the LA, and indirect estimates or direct quantification can be performed, the latter being the most accurate but also the most labor-intensive. The AL method has been the most widely used in CMR imaging from the beginning and remains the method of choice in our setting. (6-10) Despite its greater simplicity, it may not accurately reflect LA volume. Direct quantification of LA volume requires a greater number of slices for CMR imaging acquisition, resulting in a longer study and its subsequent analysis. (10-12)

Objectives

To propose and validate an alternative method for estimating LA volume using CMR. To compare accuracy and agreement of this new method with the AL method, using direct quantification by complete volumetric tracing of the LA in CMR imaging studies as the gold standard.

METHODS

Study population

Twenty-five patients aged over 18 years were randomly selected from a database of CMR imaging at our center. Patients were excluded if they had complex atrial anatomy, such as congenital heart disease with Fontan-Kreutzer circulation, poor image quality due to technical artifacts, or if, for any reason, they had not completed acquisition of the basic images required for analysis.

CMR imaging protocol

The images were acquired using a Siemmens Magneton Aera 1.5 T scanner. Image acquisition was performed in the supine position, with retrospective electrocardiography gating. The center basic CMR imaging acquisition protocol includes cine images obtained using steady-state free precession (SSFP) sequences in 2-chamber (2C), 3-chamber (3C), 4-chamber (4C), and complete short-axis (SA) views. During acquisition of the complete ventricular short-axis stack, the center protocol routinely includes the atria.

Image analysis

All images were analyzed using the free software Segment v4.0 (Medviso, Lund, Sweden). Two independent analyses were performed by two researchers experienced in the method. All measurements were performed at end-systole. The LA volume was directly quantified by manual tracing, excluding the left atrial appendage and pulmonary veins on all slices, and this was assumed to be the reference value. The estimation was performed using the usual biplane area-length (AL) method and the newly proposed irregular base cylinder (CBI) method.

When estimating the volume using the AL method, the area and height (length) of the LA were measured in the 2C and 4C cine views. The following formula was used: 8/3 Π (2C area x 4C area) / length.

When estimating the volume using the CBI method, the base of the cylinder was measured. The atrial area was traced in a perpendicular slice to its major axis, obtained from the complete short-axis acquisition between the orifice of the left atrial appendage and the orifices of the pulmonary veins; the atrial height was measured from the mitral annulus to the atrial roof in the 4C view. The volume was calculated using the area x height formula.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Categorical variables are presented as frequencies and percentages. Both estimates were compared with the gold standard (direct volumetry) using Pearson's correlation coefficient (r). A Bland-Altman analysis was performed to assess mean differences and dispersion between both methods and the gold standard.

RESULTS

Baseline characteristics

From our center imaging database, we analyzed previously acquired images from 25 patients with a mean age of 44 ± 15 years. Fifty-two percent were male, and 84% had been studied on an outpatient basis. The most frequent diagnoses included hypertrophic cardiomyopathy (20%), ventricular arrhythmia (16%), ischemic heart disease (16%), and dilated cardiomyopathy (12%). The mean left ventricular ejection fraction (LVEF) was 59 ± 8% and the mean left atrial volume was 97 ± 38 mL. The remaining baseline characteristics are presented in Table 1.

Quantification methods

Figure 1 shows images of direct LA volume measurement using the AL and CBI methods.

The correlation measured against direct volumetric quantification was very high for both methods (Figure 2). Pearson's correlation coefficient was higher for the CBI method ($r=0.93$; $p<0.001$) than for the AL method ($r=0.83$; $p<0.001$). The Bland-Altman analysis showed low bias for both methods, with less dispersion for the CBI method [-5.73 mL (18.6 to -30.11)] than for the AL method [-1.18 mL (43.82 to -46.17)]. Interobserver variability was lower for the CBI method [4.94 mL (44.76 to -34.88)] than for the AL method [19.7 mL (65.91 to -26.51)] (Figure 3).

DISCUSSION

Our results show an excellent correlation between both methods and direct volumetric quantification, with a higher correlation for the newly proposed method (CBI). In addition, dispersion with the new method is lower than with the AL method, and its interobserver reproducibility is higher.

It should be noted that acquiring the entire atrial volume is not necessary, since the base of the cylinder can be obtained with a slice beyond the mitral annulus plane. This makes the method practical and does not

Table 1. Population characteristics

Variables	Value
Age, years, mean (SD)	45 (15)
Male sex, n (%)	13 (52)
Weight, kg, mean (SD)	80 (19)
Height, cm - mean (SD)	169 (24)
Body surface area, m², mean (SD)	1.94 (0.29)
LV EDV, mL, median (IQR)	161 (134-187)
LV ESV, mL, median (IQR)	63 (42-85)
LVEF, %, mean (SD)	59 (8)
LV mass, g, mean (SD)	115 (43)
LA volume, mL, mean (SD)	97 (38)
Main pathology	
Hypertrophic cardiomyopathy, n (%)	5 (20)
Ventricular arrhythmia, n (%)	4 (16)
Ischemic heart disease, n (%)	4 (16)
Dilated cardiomyopathy, n (%)	3 (12)
Other, n (%)	9 (36)

EDV: end-diastolic volume; ESV: end-systolic volume; IQR: interquartile range; LA: left atrium; LV: left ventricle; LVEF: left ventricular ejection fraction; SD: standard deviation

require additional time for image acquisition.

The AL method is excellent, and its use in two-dimensional echocardiography has probably been the best option for approximating the actual volume, given the impossibility of direct quantification or the interposition of strictly orthogonal short-axis planes. For years, this method, derived from echocardiography, was adopted in CMR imaging because of its good correlation with direct quantification and the ease of image acquisition and processing.

From a clinical perspective, accurate estimation of LA volume is particularly important. In the context of remodeling, LA dilation is a marker of what is occurring in a patient's chronic hemodynamics. Volumetric measurement can provide a parameter for longitudinal assessment and is an independent predictor for major cardiovascular events, atrial fibrillation, heart failure, and embolic events. (13-20) In some cases, small differences in LA volumetric estimation may lead to a different diagnostic interpretation when values are close to the cutoff point defined by clinical guidelines or consensus statements. Therefore, greater precision in estimation would be expected to improve diagnostic accuracy and consequently benefit clinical practice.

Furthermore, according to our observations, the lower interobserver variability makes CBI a more

Fig. 1. Left atrial measurements performed in the complete short-axis, 4C, and 2C views with manual endocardial tracing at end-systole. Direct volumetry (A-B-C-D). AL method (E-F). CBI method (G-H)

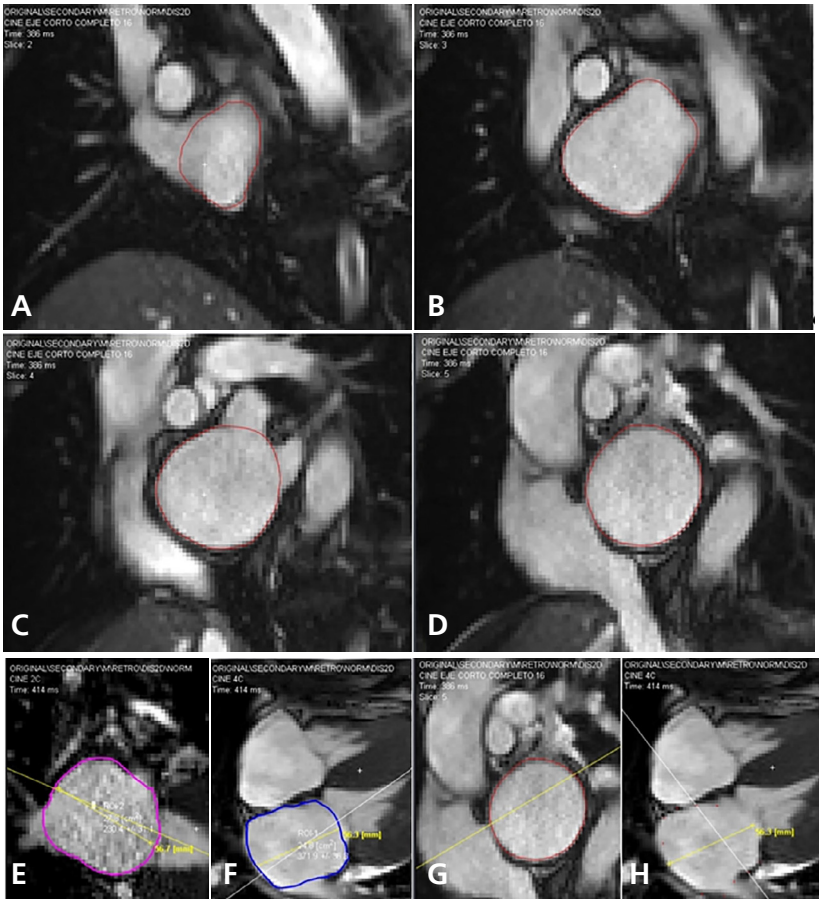


Fig. 2. Correlation between measurements by direct volumetry and area-length method (blue) and CBI method (red).

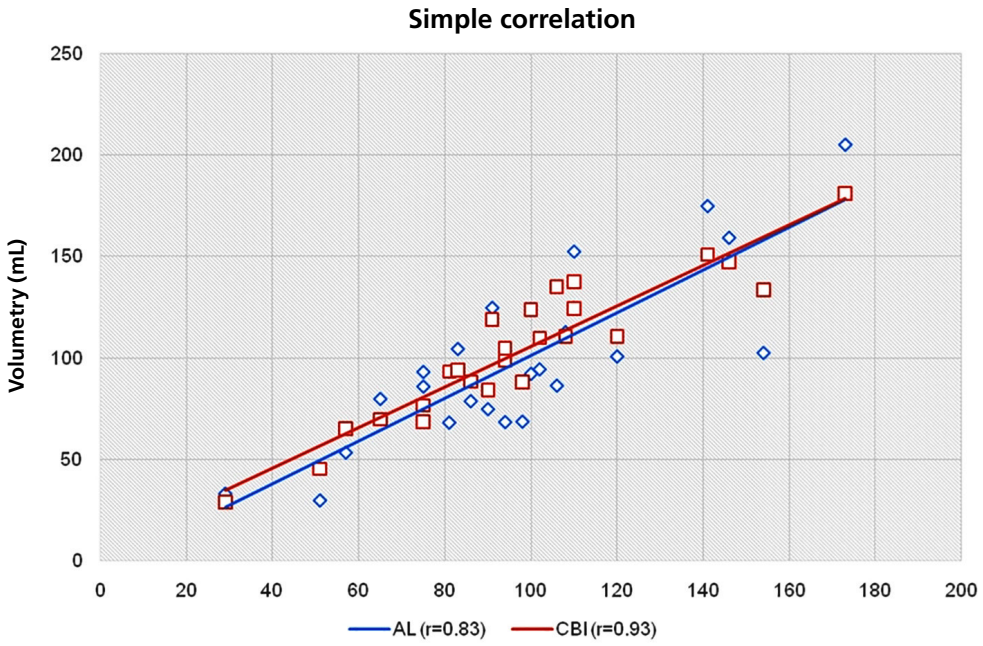
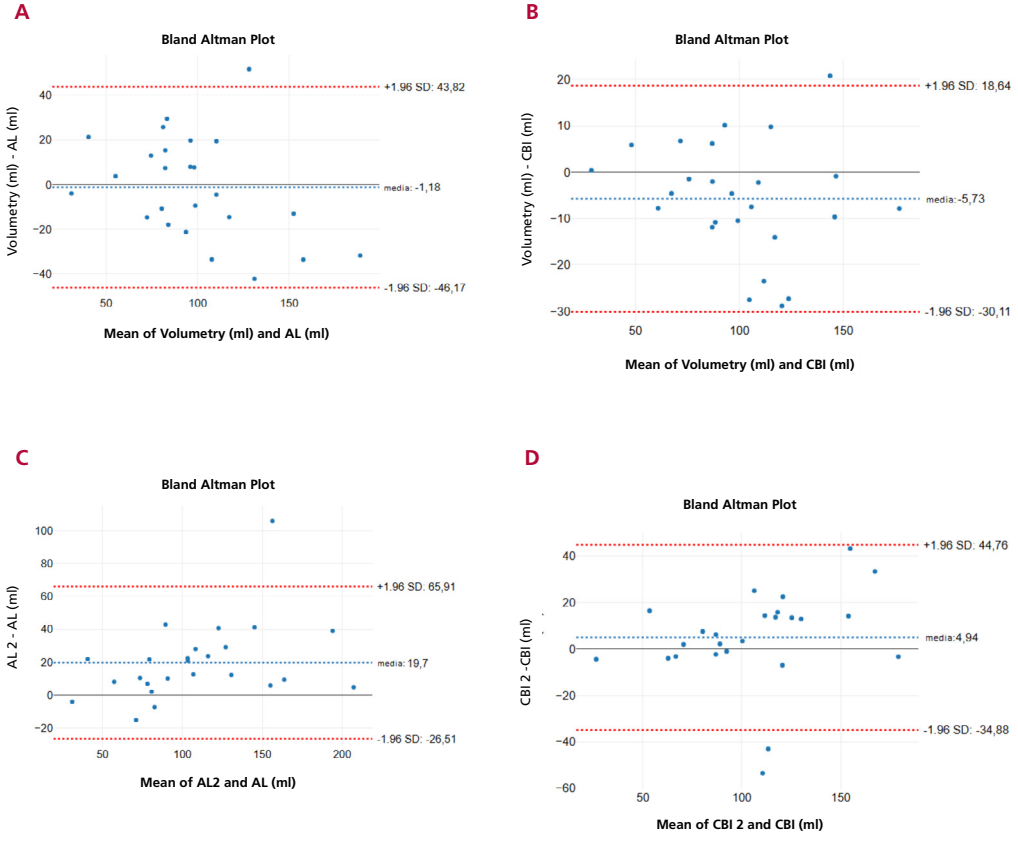


Fig. 3. Mean differences and dispersion in the measurement of left atrial volume: (**A**) Direct volumetry and area-length method. (**B**) Direct volumetry and irregular base cylinder method. Interobserver variability: (**C**) area-length method, (**D**) irregular base cylinder method.



AL: area-lenght; CBI: irregular base cylinder

robust method that may be particularly valuable in multicenter studies or serial evaluations, where methodological stability is essential to detect real changes in atrial remodeling.

In summary, CMR has the advantage over two-dimensional echocardiography of allowing image slices at any desired orientation and facilitates the use of geometric figures and shapes that better fit volumetric estimation. We believe that the CBI method, with its slightly more accurate approximation than the method commonly used, without compromising its practicality, may improve the interpretation of the study.

Limitations

A small number of cases were used assuming a coefficient r >0.8, and although the selection in the database was random, this geometric model and the AL method may not be extrapolated to all atrial morphologies.

CONCLUSIONS

The CBI method showed a better correlation with the direct measurement standard than that the AL method. It therefore represents a valid alternative that is equally simple and more accurate than the method commonly used to estimate LA volume by CMR.

Conflicts of interest

None declared.

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

Funding

This work received no financial support..

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ORIGINAL ARTICLE

Clinical and Imaging Factors Associated with Lower Peak Oxygen Consumption in Patients with Hypertrophic Cardiomyopathy: the Value of Ventricular Strain by Magnetic Resonance Imaging

Factores clínicos e imagenológicos asociados a un menor consumo máximo de oxígeno en pacientes con miocardiopatía hipertrófica: el valor del strain ventricular por resonancia magnética

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ABSTRACT

Background: Peak oxygen consumption (peak VO_2) is a key marker for assessing functional capacity and prognosis in patients with hypertrophic cardiomyopathy (HCM). Although multiple factors can influence this parameter, its relative impact and predictive value are not fully established.
Objective: The aim of this study was to analyze the association between clinical, echocardiographic, and cardiac magnetic resonance imaging (CMR) variables with peak VO_2 in patients diagnosed with HCM.
Methods: A retrospective, observational, single-center cohort study was conducted in patients diagnosed with sarcomeric HCM belonging to an institutional HCM registry between January 2017 and March 2025, who had echocardiography, CMR, and oxygen consumption tests performed within less than a year of each other. Clinical, imaging, and functional data were collected from electronic medical records. Cardiac magnetic resonance scans were done with a 1.5-T magnet (Avanto, Siemens Medical Solutions®, Erlangen, Germany). Late gadolinium enhancement (LGE) quantification and global longitudinal strain by CMR (GLS-CMR) were obtained using Circle Cardiovascular Imaging software (Tissue Tracking, cvi42). Univariate and multivariate linear regression models were used to evaluate associations with peak VO_2.
Results: Fifty-four patients with mean age of 53 ± 18 years (59% men) were included in the study. Mean peak VO_2 was 23.5±9.6 mL/kg/min. In the univariate analysis, male sex ($p=0.001$), indexed right ventricular end-diastolic volume ($p<0.001$), and GLS-CMR ($p=0.030$) were significantly associated with higher peak VO_2. Age was inversely associated with peak VO_2 ($p<0.001$). No significant associations were found with left ventricular ejection fraction, intraventricular obstructive gradient, left ventricular mass index, or LGE. In the multivariate analysis, the variables that showed an independent association with lower peak VO_2 were female sex ($p=0.007$), older age at diagnosis ($p<0.001$), and lower GLS-CMR value ($p=0.033$).
Conclusions: In patients with HCM, female sex, older age, and lower left ventricular global longitudinal strain by CMR were independently associated with lower peak VO_2. These findings highlight the usefulness of myocardial strain as a complementary functional marker that could contribute to improve prognostic stratification in this population.

Key words: Hypertrophic cardiomyopathy – Strain - Cardiac magnetic resonance imaging - Oxygen consumption

RESUMEN

Introducción: El consumo pico de oxígeno (VO_2 pico) es un marcador clave para evaluar la capacidad funcional y el pronóstico en pacientes con miocardiopatía hipertrófica (MCH). Aunque múltiples factores pueden influir en este parámetro, su impacto relativo y valor predictivo no están completamente establecidos.
Objetivo: Analizar la asociación entre variables clínicas, ecocardiográficas y de resonancia magnética cardíaca (RMC) con el VO_2 pico en pacientes diagnosticados con MCH.
Material y métodos: Estudio retrospectivo, observacional y unicéntrico que incluyó pacientes con diagnóstico de MCH sarcomérica pertenecientes a un registro institucional entre 2017 y 2025, que contaran con ecocardiograma, RMC y prueba de consumo de oxígeno realizados en un intervalo menor a un año de diferencia entre sí. Se recolectaron de la historia clínica electrónica datos clínicos, imagenológicos y funcionales. Las exploraciones de RMC se realizaron con un imán de 1.5-T (Avanto, Siemens Medical Solutions®,

Rev Argent Cardiol 2026;94:25-31. https://doi.org/10.7775/rac.v94.i1.20971

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Received: 12/09/2025 – *Accepted:* 01/21/2026

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Erlangen, Alemania). La cuantificación de realce tardío de gadolinio (RTG) y el *strain* longitudinal global por RMC (SLG-RMC) se efectuaron con el software Circle Cardiovascular Imaging (Tissue Tracking, cvi42). Se utilizaron modelos de regresión lineal univariados y multivariados para evaluar las asociaciones con el VO_2 pico.

Resultados: Se incluyeron 54 pacientes con una edad promedio de 53 ± 18 años, de los cuales el 59% eran hombres. El VO_2 pico promedio fue de 23,5 ± 9.6 mL/kg/min. En el análisis univariado, el sexo masculino (p=0,001), el volumen telediastólico del ventrículo derecho indexado (p<0,001) y el SLG-RMC (p=0,030) se asociaron significativamente con un mayor VO_2 pico. La edad presentó una asociación inversa con el VO_2 pico (p<0,001). No se hallaron asociaciones significativas con la fracción de eyección del ventrículo izquierdo, el gradiente obstructivo intraventricular, el índice de masa ventricular izquierda ni con el realce tardío de gadolinio. En el análisis multivariado, las variables que mostraron asociación independiente con un VO_2 pico más bajo fueron el sexo femenino (p=0,007), una mayor edad al diagnóstico (p<0,001) y un menor valor de SLG-RMC (p=0,033).

Conclusiones: En pacientes con MCH, el sexo femenino, una mayor edad y un menor *strain* longitudinal global del ventrículo izquierdo por RMC se asociaron de forma independiente con un menor VO_2 pico. Estos hallazgos resaltan la utilidad del *strain* miocárdico como marcador funcional complementario que podría contribuir a mejorar la estratificación pronóstica en esta población.

Palabras clave: Miocardiopatía hipertrófica - *Strain* - Resonancia magnética cardíaca - Consumo de oxígeno

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic clinical syndrome characterized by left ventricular (LV) hypertrophy in the absence of other cardiac, systemic, or metabolic disease (1). Its origin mainly lies in gene mutations of the sarcomere, and it is inherited in an autosomal dominant manner in most cases. (2) It presents a broad clinical spectrum, ranging from asymptomatic patients to those with advanced heart failure or sudden death. (3)

However, prognostic stratification in HCM remains challenging, given the heterogeneity in disease progression and the limited ability of conventional parameters to predict functional decline (3-5). Peak oxygen consumption (peak VO_2), obtained through cardiopulmonary exercise testing, is a robust marker of functional capacity and an independent predictor of morbidity and mortality in various heart diseases, including HCM (6). Thus, peak VO_2 was proposed as the primary endpoint in the main studies on this condition. (7-9) However, the clinical and imaging variables that determine lower peak VO_2 in this population are not clearly defined.

Cardiac magnetic resonance imaging (CMR) has become the gold standard for LV morphological and functional assessment, also allowing accurate quantification of fibrosis using late gadolinium enhancement (LGE) (1,2). Recently, the incorporation of global longitudinal strain analysis by cardiac magnetic resonance imaging (GLS-CMR) through feature tracking detects earlier stages of ventricular involvement, which are not evident with conventional techniques such as volumetric left ventricular ejection fraction (LVEF) measurement (10, 11). It should be noted that GLS was used in this study because it is the most reproducible parameter and the most widely used in clinical practice, with less variability than radial or circumferential strain (12, 13).

However, the prognostic value of this parameter in relation to functional capacity in HCM still requires further evidence. (14-17)

OBJECTIVES

We evaluated the association between GLS-CMR and other clinical, echocardiographic, and CMR variables with peak VO_2 measured in the cardiopulmonary exercise test in a contemporary cohort of patients with confirmed diagnosis of HCM, with the aim of identifying independent predictors of functional limitation that would optimize prognostic stratification in this group of patients.

METHODS

A retrospective, observational, single-center cohort study was conducted including patients belonging to an institutional HCM registry between January 2017 and March 2025. All patients gave informed consent prior to inclusion in the study. The data for the present analysis were obtained from a review of the institutional electronic medical records.

Hypertrophic cardiomyopathy was defined as the presence of increased thickness in any LV segment >15 mm, or >13 mm in first-degree relatives diagnosed with this disease, in the absence of any other justifiable cause. (1) Whenever possible, genetic studies were performed to confirm the sarcomeric etiology. Patients over 18 years of age with a confirmed diagnosis of sarcomeric HCM were included in the study, and phenocopies or other causes of ventricular hypertrophy were excluded.

For this study, only those patients who had echocardiogram, CMR, and cardiopulmonary exercise testing performed within an interval ≤ 12 months from each other were selected.

The following variables were collected: demographic (age, sex, height), clinical (NYHA functional class, treatment received), echocardiographic (LVEF, maximum intraventricular gradient, presence of obstructive HCM defined by a gradient ≥30 mmHg at rest and/or systolic anterior movement of the anterior mitral valve), and CMR-derived parameters (indexed ventricular volumes and mass, LVEF, and right ventricular ejection fraction, maximum wall thickness, presence and quantification of LGE, and LV GLS-CMR).

Cardiac magnetic resonance imaging was performed using a 1.5 T scanner (Avanto, Siemens Medical Solutions®, Erlangen, Germany) and LGE quantification (using a 5-threshold technique) and GLS-CMR were acquired using Circle Cardiovascular Imaging software (Tissue Tracking, cvi42, Figure 1). Peak VO_2 was obtained by cardiopulmonary testing on a cycle ergometer using an incremental protocol, expressed in mL/kg/min.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR),

depending on their distribution as assessed by the Shapiro-Wilk test, and were compared using Student's t-test or the Mann-Whitney test, depending on data distribution. Categorical variables were presented as absolute frequencies and percentages and were compared using the Chi² test or Fisher's exact test, as appropriate.

Linear regression models were applied to explore the associations between clinical, echocardiographic, and CMR variables with peak VO_2. In the univariate analysis, each predictor was evaluated individually to identify significant correlations with peak VO_2. Subsequently, those variables with statistical significance ($p < 0.05$) or clinical relevance were incorporated into a multivariate linear regression model to identify independent predictors of lower peak VO_2. All statistical analyses were performed using STATA software version 13.1 (StataCorp LP, College Station, TX, USA), and p values <0.05 were considered as statistically significant.

Ethical considerations

The study protocol follows the ethical guidelines of the Declaration of Helsinki, (18) and the design of the institutional hypertrophic cardiomyopathy registry from which the data were obtained was approved by the institutional ethics committee.

RESULTS

A total of 54 patients diagnosed with sarcomeric HCM were included in the study. Mean age was 53±18 years, and 59.2% (n=32) were men. The obstructive form of the disease was recorded in 26 patients (48.1%). Mean peak VO_2 in the population was 23.5±9.6 mL/kg/min.

Cardiac magnetic resonance parameters

Mean LVEF was 72±10% and mean maximum wall thickness 17±4 mm. Late gadolinium enhancement was present in 94.4% (n=51) of patients, with a median mass of 15 grams and a 95% confidence interval (CI) of 6.84-33.59 (no discrimination was made according to LGE percentage). Mean LV GLS-CMR was -13±3.3%. Figure 1 shows an example of GLS-CMR measurement in one cohort patient. The remaining clinical, echocardiographic, CMR, and cardiopulmonary exercise test variables are detailed in Table 1.

Univariate analysis

In the univariate linear regression model, significant associations were observed between peak VO_2 and age at diagnosis (β = -0.35; 95% CI: -0.46 to -0.24; $p < 0.001$), male sex (β= +8.26; 95% CI +3.37 to +13.14; $p = 0.001$), indexed right ventricular end-diastolic volume (β= +0.31; 95% CI +0.15 to +0.46; $p < 0.001$), and LV GLS-CMR (β= -0.85; 95% CI -1.62 to -0.08; $p = 0.034$). No significant associations were found with NYHA functional class, the presence of dynamic intraventricular obstruction, maximum intraventricular gradient, LVEF, LV volumes, LV mass, maximum wall thickness, or LGE. Table 2 details the variables

Fig. 1. Example of left ventricular global longitudinal strain analysis using Circle Cardiovascular Imaging (Tissue Tracking, cvi42).

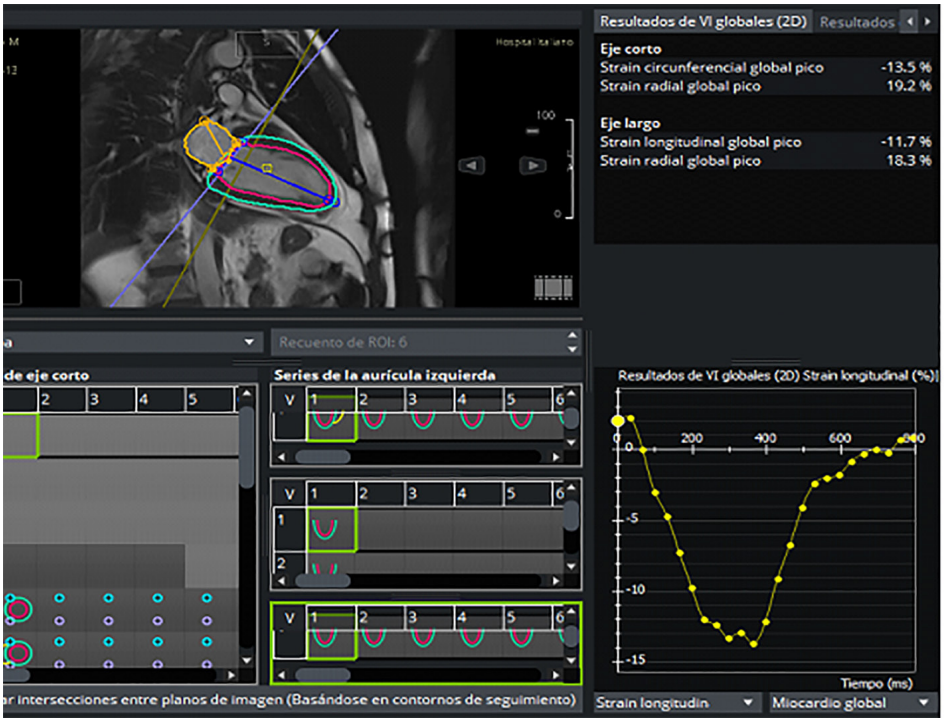

Table 1. General characteristics of the population

Clinical variables	
Age at diagnosis, years, mean ± SD	53 ±18
Male sex, n (%)	32 (59.3)
Height, centimeters, mean ± SD	161 ±33
NYHA functional class* ≥ 2, n (%)	16 (29.6)
BMI*, kg/m², mean ± SD	28.4 ± 5.1
Hypertension, n (%)	21 (38.9)
Diabetes mellitus, n (%)	6 (11.1)
Atrial fibrillation, n (%)	7 (13.0)
Dyspnea, n (%)	31 (57.4)
Angina, n (%)	12 (22.2)
Atrial fibrillation, n (%)	7 (13.0)
Beta-blockers, n (%)	38 (70.4)
Calcium channel blockers, n (%)	7 (13.0)
Myosin inhibitors, n (%)	3 (5.6)
ICD*, n (%)	6 (11.1)
Septal myectomy, n (%)	3 (5.6)
Septal alcoholization, n (%)	2 (3.7)
Ecocardiographic variables	
Wall thickness, mm, mean ± SD	17.4 ± 3.9
Left atrial anteroposterior diameter, mm, median (IQR)	42 [38-46]
Intraventricular gradient, mmHg, median (IQR)	30 [6-58]
SAM, n (%)	25 (46.3)
LVOTO, n (%)	32 (59.3)
Cardiac resonance variables	
LVEF, %, mean ± SD	72 ±10
Indexed LV end-diastolic volume, mL/m², mean ± SD	72 ±18
Indexed LV end-systolic volume, mL/m², median (IQR)	69 [60-78]
Maximum thickness, mm, mean ± SD	17 ±4
Presence of LGE, n (%)	51 (94.4)
LGE mass, grams, median (IQR)	15 [6.84-33.59]
Left ventricular GLS, %, mean ± SD	-13 ± 3.3
Right ventricular ejection fraction, %, mean ± SD	66 ±7
RV end-diastolic volume, mL, mean ± SD	71 ±15
RV end-systolic volume, mL, mean ± SD	27 ±24
LV mass, grams	86 ±24
Oxygen consumption variables	
Peak VO_2 (mL/kg/min), mean ± SD	23.5 ± 9.6
VO_2 (% of predicted), mean ± SD	83.3 ± 19.5
Heart rate at peak VO_2 (bpm), mean ± SD	133.7 ± 30.7
OUES, [(mL/min)/log10], mean ± SD	2156.8 ± 954.7

BMI: body mass index; ICD: implantable cardioverter defibrillator; IQR: interquartile range; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association; OUES: oxygen uptake efficiency slope; RV: right ventricular; SAM: systolic anterior mitral valve movement; SD: standard deviation.

included in the univariate analysis and their relationship with peak VO_2.

Multivariate analysis

In the multivariate linear regression model (Table 3), the independent predictors of lower peak VO_2 were: female sex (β = -6.1; 95% CI -10.56 to -1.75; p = 0.007), older age at diagnosis (β= -0.26; 95% CI: -0.37 to -0.15; p <0.001), and lower LV GLS-CMR (β= -0.59, 95% CI: -1.14 to - 0.04; p = 0.033).

DISCUSSION

In this contemporary cohort of patients with HCM, we observed that a lower LV-GLS-CMR value was independently associated with lower functional capacity, as measured by peak VO_2 in the cardiopulmonary exercise test. This finding could provide a relevant pathophysiological perspective, based on the hypothesis that functional limitation in HCM would depend not only on the degree of hypertrophy or the presence of dynamic obstruction, but also on both clinical and subclinical myocardial contractile failure, detectable by GLS-CMR, even in patients with preserved LVEF. Global longitudinal strain, by reflecting the longitudinal deformation capacity of the myocardium, is a sensitive marker of contractile efficiency and allows the detection of early mechanical dysfunction before global LVEF alterations or advanced symptoms become apparent (19, 20). It is noteworthy that all patients in our cohort had preserved LVEF.

Abnormal GLS probably represents the functional expression of the distinctive molecular mechanisms of HCM, characterized by a progressive loss of contractile efficiency, which translates into reduced myocardial shortening and, consequently, a limited ability to increase cardiac output during exercise. In other words,

Table 2. Univariate linear regression model

Variable	Univariate linear regression β coefficient (95% CI)	p value
Age at diagnosis	-0.35 (-0.46 to -0.24)	<0.001
Male	+8.26 (+3.37 to +13.14)	0.001
NYHA dyspnea	-2.59 (–5.35 to +0.17)	0.065
Maximum intraventricular gradient (mmHg)	-0.06 (–0.15 to +0.02)	0.110
Obstructive HCM	-1.14 (–6.44 to +4.17)	0.669
LVEF %	+0.11 (–0.16 to +0.38)	0.425
Indexed left ventricular end-diastolic volume, (mL/m²)	+0.08 (–0.06 to +0.23)	0.265
Indexed LV end-systolic volume, (mL/m²)	–0.05 (–0.15 to +0.05)	0.320
Left ventricular mass (g/m²)	–0.0007 (–0.11 to +0.11)	0.921
Maximum wall thickness (mm)	+0.09 (–0.60 to +0.79)	0.781
Quantitative LGE (%)	–0.004 (–0.10 to +0.09)	0.934
LGE (present)	+2.35 (-18 to 23.2)	0.821
RVEF (%)	+0.25 (–0.10 to +0.60)	0.162
Indexed RV end-diastolic volume (mL/m²)	+0.31 (+0.15 to +0.46)	<0.001
Indexed RV end-systolic volume (mL/m²)	–0.018 (–0.13 to +0.09)	0.743
CMR strain (%)	-0.85 (-1.6 to -0.08)	0.034

CMR: cardiac magnetic resonance; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RV: right ventricular; RVEF: right ventricular ejection fraction.

Table 3. Multivariate linear regression model

Variable	Multivariate linear regression β coefficient (95% CI)	p value
Age at diagnosis (years)	-0.26 (–0.37 to –0.15)	<0.001
Female sex	-6.10 (–10.56 to –1.75)	0.007
LV global longitudinal strain	-0.59 (–1.14 to –0.04)	0.033

LV: left ventricular

reduced GLS implies a lower contractile reserve and, therefore, a limitation in sustaining cardiac output, which translates into decreased peak VO_2. (14,19) This phenomenon could explain the association between greater GLS-CMR alteration and lower peak VO_2 observed in our study, in accordance with the findings of the STRAIN-HCM study, where GLS behaved as an independent predictor of adverse events. (14, 21)

On the other hand, we found no correlation between peak VO_2 and the amount of myocardial fibrosis measured by LGE, a finding that reinforces the idea that GLS identifies an earlier functional stage of myocardial damage. (22, 23) It should be noted that in our cohort, almost all patients had some degree of LGE, suggesting that the differential prognostic value of GLS does not depend exclusively on the presence or absence of fibrosis, but on the degree of underlying mechanical dysfunction.

The lower functional capacity observed in women in this study is consistent with reports from other series, where female sex is associated with more symptomatic phenotypes, smaller ventricular cavities, and greater predisposition to dynamic obstruction. (24) These anatomical features, combined with a frequently later diagnosis, could partly explain the functional gap observed. Similarly, older age was a negative determinant of peak VO_2, probably reflecting the cumulative impact of diffuse fibrosis, myocardial stiffness, and associated comorbidities. (25, 26)

From a clinical perspective, incorporating GLS-CMR into the evaluation of HCM may provide additional prognostic value and allow for a more accurate characterization of the functional phenotype. In patients with preserved LVEF, a significant reduction in GLS could anticipate clinical deterioration and guide early interventions. This integrated approach is in line with the current trend in the AHA/ACC international guidelines, (1) which promote personalized pathophysiological stratification, prevailing over a purely morphological approach.

In the future, it will likely be necessary to develop prognostic models that integrate clinical, imaging, and functional variables to refine risk prediction in this population.

Although this study has limitations inherent to its retrospective design and the single-center nature of the sample, the availability of high-quality complementary studies—echocardiogram, CMR, and cardiopulmonary testing— strengthens the robustness of the results. Furthermore, our population represents a clinical profile characteristic of HCM, with the presence of obstructive forms, which reinforces the representativeness of the sample and the applicability of the findings. Taken together, our data consolidate the notion that HCM is essentially a disease of myocardial mechanics rather than hypertrophy per se, and position GLS-CMR as a potentially important marker for understanding, quantifying, and monitoring contractile efficiency in clinical practice.

CONCLUSIONS

In this contemporary cohort of patients with HCM, female sex, older age, and reduced GLS-CMR were independently associated with lower peak VO_2.

These results highlight the usefulness of GLS-CMR as a complementary tool for prognostic stratification and functional assessment, beyond conventional parameters such as LVEF or LGE. Its systematic implementation could optimize the early identification of patients at higher risk of functional deterioration.

Limitations

The limitations of this study include its retrospective nature and the lack of stratification of peak VO_2 according to patient sex. It is also important to note that no comparison was made between strain measured by cardiac magnetic resonance imaging and strain assessed by echocardiography.

Conflicts of interest

None declared.

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

Acknowledgments

To the entire cardiology department of Hospital Italiano de Buenos Aires.

Sources of funding

None.

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ORIGINAL ARTICLE

Cardiac Glycosides in Heart Failure With Reduced Ejection Fraction in the Era of Contemporary Guideline-Directed Medical Therapy: A Systematic Review and Meta-Analysis

Glucósidos cardíacos en insuficiencia cardíaca con fracción de eyección reducida en la era del tratamiento médico dirigido por guías clínicas: revisión sistemática y metaanálisis

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ABSTRACT

Background: Heart failure with reduced left ventricular ejection fraction remains a major clinical challenge despite widespread implementation of contemporary guideline-directed medical therapy (GDMT). Cardiac glycosides, historically used for their inotropic and neurohormonal effects, declined in use following the DIG trial (1997), which demonstrated a reduction in HF hospitalizations (HFH) with no mortality benefit. However, that trial predated modern GDMT and device therapy. The recent DIGIT-HF trial (2025) has renewed interest in this drug class by suggesting a potential benefit of digitoxin in optimally treated patients.
Objective: We aimed to evaluate the impact of cardiac glycosides in patients with heart failure with reduced left ventricular ejection fraction, (≤ 40%, HFrEF) and mildly reduced ejection fraction (41%-49%, HFmrEF) receiving contemporary GDMT.
Methods: Four databases were systematically searched for randomized trials (RCTs) or propensity score-matched cohort studies recruiting adults with HFrEF and HFmrEF from the year 2000 onward, comparing cardiac glycosides with standard care or placebo and reporting at least one primary outcome (all-cause mortality or HFH). Data were pooled using an inverse-variance random-effects model.
Results: Six studies met inclusion criteria: one RCT (DIGIT-HF) and five propensity score-matched observational cohorts (2000-2023) studies, comprising around 4500 cardiac glycoside users and 5500 controls. DIGIT-HF evaluated digitoxin whereas the remaining studies assessed digoxin. Pooled analysis demonstrated no significant difference in all-cause mortality (HR 1.01 [95% CI 0.67-1.53]; $I^2 = 77\%$). Cardiac glycosides were associated with a significant reduction in HFH (HR 0.84 [95% CI 0.76-0.93]; $I^2 = 0\%$). No significant effect was observed for all-cause hospitalizations (HR 0.95 [95% CI 0.83-1.10]; $I^2 = 53\%$).
Conclusion: In the post-2000 era, cardiac glycosides may confer clinical benefit by reducing HFH in patients with LVEF < 50% receiving contemporary GDMT. However, interpretation of mortality outcomes is limited by substantial heterogeneity. This study underscores the crucial need for contemporary RCTs to clarify the role of cardiac glycosides as adjunctive therapy in contemporary management of these patients.

Key words: Systematic review - Meta-analysis - Heart failure - Reduced ejection fraction- Cardiac glycosides - Digitoxin - Digoxin

RESUMEN

Introducción: La insuficiencia cardíaca con fracción de eyección reducida continúa siendo un importante reto clínico a pesar del uso generalizado del tratamiento médico dirigido por guías clínicas (TMDG). El uso de glucósidos cardíacos, empleados históricamente por sus efectos inotrópicos y neurohormonales, disminuyó después del ensayo DIG (1997), en el que se demostró una reducción de las hospitalizaciones por IC (HIC), pero ningún beneficio respecto de la mortalidad. Sin embargo, ese ensayo fue anterior al TMDG y al tratamiento con dispositivos. El reciente ensayo DIGIT-HF (2025) ha renovado el interés por esta clase de fármacos al indicar un posible beneficio de la digitoxina en los pacientes tratados de forma óptima.
Objetivo: Nuestro objetivo fue evaluar el efecto de los glucósidos cardíacos en pacientes con insuficiencia cardíaca con fracción de eyección ventricular izquierda (FEVI) reducida (≤40 %, ICFEr) o levemente reducida (41 %-49 %, ICFElr) que reciben TMDG.

Rev Argent Cardiol 2026;94:32-45. https://doi.org/10.7775/rac.v94.i1.20972

Received: 11/14/2025 – *Accepted:* 01/20/2026

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Métodos: Se realizó una búsqueda sistemática en cuatro bases de datos para encontrar ensayos controlados aleatorizados o estudios de cohortes emparejados por índice de propensión en los que se reclutaran adultos con ICFEr o ICFElr a partir del año 2000, se compararan los glucósidos cardíacos con la atención habitual o el placebo, y se informara al menos un criterio de valoración principal (mortalidad por cualquier causa o HIC). Los datos se combinaron mediante el uso de un modelo de efectos aleatorios de varianza inversa.
Resultados: Seis estudios cumplieron los criterios de inclusión: un ensayo controlado aleatorizado (DIGIT-HF) y cinco estudios de cohortes observacionales emparejadas por índice de propensión (2000-2023). Estos estudios incluyeron alrededor de 4500 pacientes que recibían glucósidos cardíacos y 5500 controles. En el ensayo DIGIT-HF se evaluó la digitoxina, y en los demás estudios la digoxina. El análisis combinado no mostró diferencias significativas en cuanto a la mortalidad por cualquier causa (HR 1,01; IC 95% 0,67-1,53; I^2 = 77 %). Los glucósidos cardíacos se asociaron con una reducción significativa de la HIC (HR 0,84; IC 95% 0,76-0,93; I^2 = 0 %). No se observó ningún efecto significativo en cuanto a las hospitalizaciones por cualquier causa (HR 0,95; IC 95% 0,83-1,10; I^2 = 53 %).
Conclusión: En la era posterior al año 2000, los glucósidos cardíacos pueden aportar beneficios clínicos al reducir la HIC en pacientes con IC y FEVI < 50 % que reciben TMDG. Sin embargo, la interpretación de los resultados de mortalidad se ve limitada por la considerable heterogeneidad. En este estudio se destaca la necesidad crucial de realizar ensayos controlados aleatorizados modernos para dilucidar el papel que desempeñan los glucósidos cardíacos como terapia complementaria en estos pacientes..

Palabras clave: Infarto de miocardio - Intervención coronaria percutánea - Mortalidad - Registro

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a major global health burden despite remarkable advances in drug therapies and device-based therapies. (1, 2) According to the Heart Failure Association (HFA) Atlas, the median annual number of HF hospitalizations (HFH) in Europe is 2671 per million inhabitants, underscoring the magnitude of this condition. (2, 3) Given its clinical and economic impact, effective strategies to optimize HF management have become increasingly necessary.

The widespread implementation of contemporary guideline-directed medical therapy (GDMT), including angiotensin receptor-neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose linked transporter-2 inhibitors (SGLT2i), has significantly improved survival and reduced hospitalizations over the past two decades. (1) Nevertheless, a substantial proportion of patients continue to experience recurrent decompensations, frequent hospitalizations, and progressive functional decline, highlighting the need for further therapeutic optimization. (1, 2)

Cardiac glycosides have occupied a distinctive role in the management of HF for two centuries. (4) By inhibiting the Na^+/K^+-ATPase pump, these agents increase intracellular calcium availability, thereby enhancing myocardial contractility. Their vagotonic effects also provide rate control in patients with concomitant atrial fibrillation (AF). (5)

The landmark Digitalis Investigation Group (DIG) trial published in 1997 demonstrated that digoxin reduced HFH but did not confer a survival benefit. (6) However, subsequent observational studies and meta-analyses have yielded conflicting results, with some suggesting a potential association between digoxin use and increased mortality, particularly among patients with AF, leading to a progressive decline in its clinical use. (7-12) In contrast, the RATE-AF trial suggested that digoxin may remain a safe and effective option for rate control in selected patients with permanent AF, and demonstrated greater cost-effectiveness than beta-blockers and fewer adverse events and hospitalizations, without compromising quality of life. (13) Importantly, the DIG trial was conducted more than two decades ago, when background HF therapy was limited to ACEI and diuretics. Its findings may therefore not reflect outcomes in the era of contemporary GDMT and device-based therapies, including implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT). (1, 14, 15) Furthermore, the trial had relevant methodological limitations, including substantial crossover to digoxin in the placebo arm, which may have attenuated treatment differences. (6) Post hoc analyses suggested worse outcomes among patients with higher serum digoxin concentrations, raising concerns about dose–response effects and the narrow therapeutic range of the drug. (16, 17)

Growing evidence has renewed interest in this therapeutic class. In particular, the DIGIT-HF trial, which evaluated digitoxin versus placebo in patients with chronic HFrEF receiving optimal GDMT, demonstrated a significant reduction in the composite endpoint of all-cause mortality or HFH (hazard ratio [HR]: 0.82 [95% CI 0.69-0.98]; p=0.03) without an excess of major adverse events. (18) Notably, digitoxin, a glycoside structurally related to digoxin but with a longer half-life and more stable pharmacokinetics, may overcome some of the safety concerns historically associated with digoxin. (19-22)

Additionally, findings from a recent umbrella review of 12 meta-analyses suggest that previously reported mortality risks may have been confounded by indication bias, comorbidities, and outdated treatment contexts rather than reflecting a true causal relationship. (23)

Accordingly, the present meta-analysis aims to assess the effect of cardiac glycosides on clinical outcomes in patients with HFrEF and mildly reduced ejection fraction (HFmrEF) in the context of contemporary management by integrating data from modern

randomized controlled trials and propensity score-matched observational studies.

METHODS

Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24) (Supplementary Table 1) and was registered in PROSPERO (CRD420251185713).

A systematic search of four electronic databases (Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, EMBASE, and PubMed) was performed between October 10 and November 10, 2025. The search strategy included studies containing the terms "heart failure" and "cardiac glycosides" and was restricted to publications from 2000 onward to ensure inclusion of contemporary cohorts, consistent with the first modern ACC/AHA HF guideline issued in 2001. (25) That guideline incorporated evidence from pivotal trials of the 1990s (MERIT-HF, CIBIS-II, RALES, and Val-HeFT), which established beta-blockers, MRAs, and ARBs as disease-modifying therapies in addition to ACE inhibitors. The full search strategies are provided in Supplementary Table 2. No language restrictions were applied. Reference lists of included studies were manually screened to identify additional eligible records.

Inclusion and Exclusion Criteria

Eligible studies included randomized controlled trials (RCTs) or propensity score-matched cohort studies evaluating the effects of cardiac glycosides in patients with HF with reduced or mildly reduced left ventricular ejection fraction (LVEF <50%). Studies were required to report at least one of the predefined primary outcomes.

The primary outcomes were all-cause mortality and HFH. The secondary outcomes included all-cause hospitalizations and cardiovascular mortality.

Studies were excluded if they lacked a control group, did not provide sufficient data for outcome extraction, evaluated alternative therapeutic interventions, had a recruitment period beginning before 2000, or focused exclusively on a specific subgroup of patients with HF with reduced or mildly reduced LVEF.

Study selection process and data collection

Two reviewers independently screened titles and abstracts after removing duplicate records. Full-text articles of potentially eligible studies were then independently assessed by the same reviewers for inclusion according to the predefined criteria. Disagreements at the full-text stage were resolved based on consensus. No automation tools were used during the screening process. All references were managed using EndNote X9 (Clarivate Analytics).

Three reviewers independently extracted data from each included study using a standardized data extraction form. Extracted information included study design, population characteristics, baseline demographics and clinical features, interventions, and outcomes. For studies with multiple publications, care was taken to avoid duplication of data.

Data were analyzed according to the intention-to-treat principle whenever applicable; otherwise, an as-treated approach was used. For observational studies, only results derived from propensity score-matched analyses were included. All relevant data are presented in the main text and supplementary material.

Quality assessment

Two authors independently assessed the risk of bias of the DIGIT-HF trial using the Cochrane Risk of Bias tool, version 1 (RoB 1). For observational studies, risk of bias was independently evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. Publication bias was not formally assessed because fewer than ten studies were included, which limited the reliability of the funnel plot and Egger's regression test. According to established guidance, such tests lack statistical power when applied to a small number of studies and may yield misleading results.

Synthesis methods

A narrative synthesis was used to describe and interpret findings across studies, particularly when analysis was limited by heterogeneity in outcome reporting, study populations, or outcome definitions.

When appropriate, a meta-analysis was conducted using a random-effects model to account for anticipated between-study variability in treatment effects. Summary outcome measures were expressed as HR with the corresponding 95% confidence interval (95% CI), calculated using the inverse-variance method. HRs and incidence rate ratios were considered approximately equivalent estimates of relative risk under the assumption of proportional hazards and were therefore pooled together.

Statistical heterogeneity was assessed by visual inspection of forest plots and quantified using the I^2 statistic (<25% low, 25%-50% moderate, >50% high heterogeneity).

The meta-analysis was conducted using the software package Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration). All data were evaluated at a 5% significance level ($p<0.05$). Pooled HRs with 95% CI were recalculated for each scenario, and heterogeneity was reassessed using the I^2 statistic. A leave-one-out analysis was also performed for the primary outcomes to evaluate the robustness of the findings.

Ethical considerations

This study is a systematic review and meta-analysis that did not involve direct interaction with human participants or animals, therefore, no ethical approval or informed consent was required. However, the study was conducted in accordance with established standards for ethical scientific reporting outlined by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org/).

RESULTS

Search results

Figure 1 shows the study selection process. After removing duplicates, 3301 records were screened according to the predefined eligibility criteria. Six studies met the inclusion criteria: the recently published RCT DIGIT-HF, (18) and five propensity score-matched observational studies: one multicenter (26) and four single-center studies. (27-30) The recruitment periods ranged from 2000 to 2023 and included approximately 4500 patients in the cardiac glycoside group and 5500 in the control group. Except for the DIGIT-HF trial, which investigated digitoxin, all other studies evaluated digoxin. Table 1 summarizes the main characteristics of the included studies.

Population characteristics

Table 2 summarizes the characteristics of the study population. Mean age ranged from 52 to 76 years, with a predominance of male participants (47-80%). Hypertension and diabetes mellitus were common comorbidities, reported in approximately 47-67% and 30-70% of patients, respectively, while dyslipidemia affected 36-72%. Atrial fibrillation or flutter was observed in 12-60% of participants, and chronic kidney disease in 5-47%. When reported, ischemic etiology accounted for approximately half of the cases. Baseline LVEF was markedly reduced across studies, generally ranging from 18% to 29%. Most patients were receiving contemporary GDMT. Beta-blocker use ranged from 43% to 97%, ACE inhibitor or ARB use ranged from 70% to 80%, whereas MRA use varied widely from 10 to 76%. SGLT2i use was reported only in DIGIT-HF trial, reaching up to 20%. Device therapy (ICD and/or CRT) ranged from 1% to 29%, reflecting temporal differences in the study design and population characteristics.

Primary outcomes

Across five studies, (18, 26, 28-30) the pooled estimate for all-cause mortality showed no significant difference between the cardiac glycoside therapy group and the control group (HR 1.01, 95% CI 0.67-1.53; I^2 = 77%), indicating substantial heterogeneity (Figure 2A). Cardiac glycoside therapy was associated with a significant reduction in HFH (HR 0.84, 95% CI 0.76-0.93; I^2 = 0%), with no evidence of heterogeneity (Figure 2B).

The leave-one-out sensitivity analysis demonstrated that the statistical significance of the pooled results for all-cause mortality remained robust across all iterations. For HFH, exclusion of the Georgiopoulou study (27) did not change the direction or statistical significance of the pooled effect estimate; however, exclusion of any of the remaining studies led to loss of statistical significance.

Secondary outcomes

For all-cause hospitalizations, there was no significant difference between treatment and control groups (HR

Fig. 1. Literature search flow chart

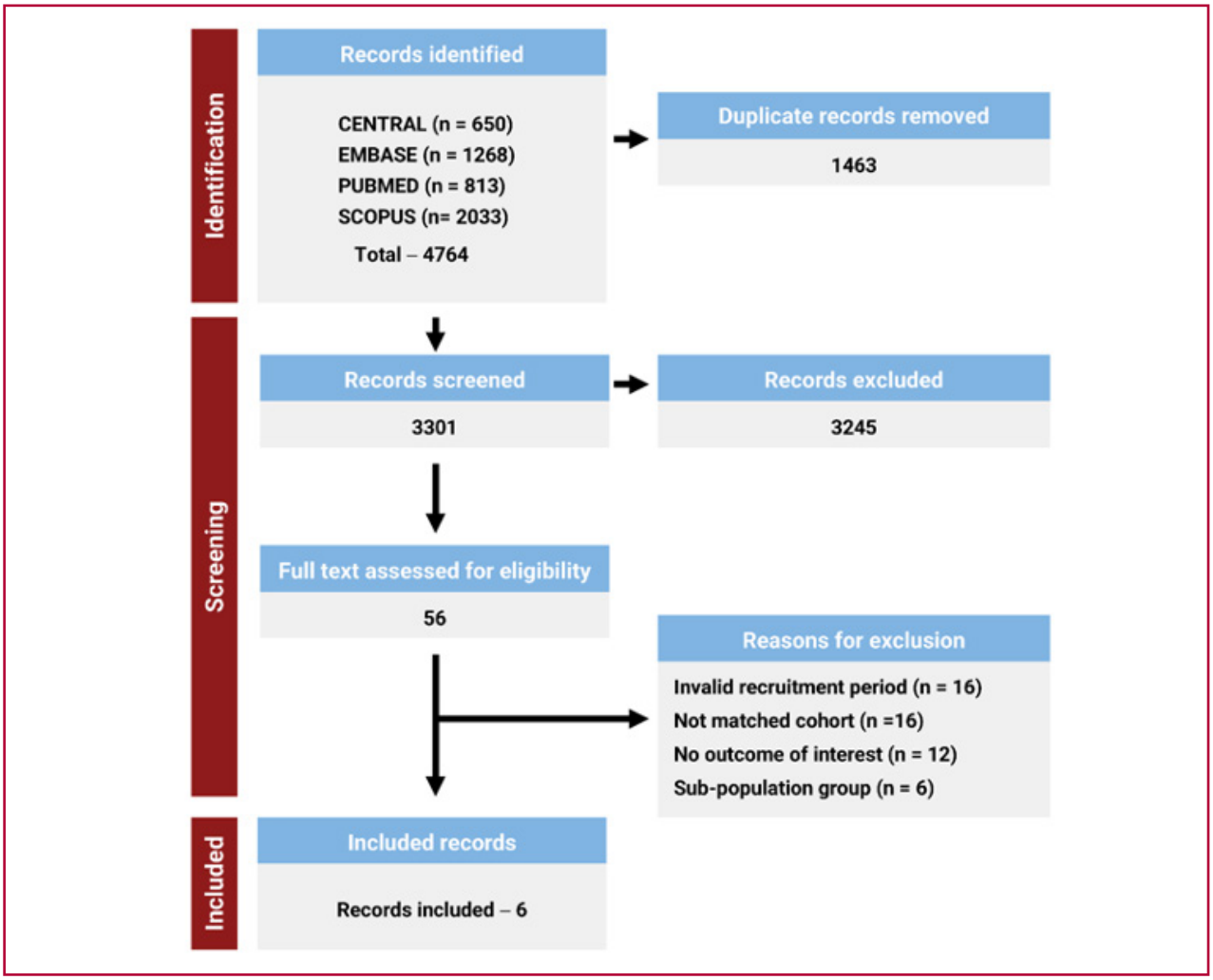


Table 1. Summary of included studies

Study	Inclusion and Exclusion Criteria	Patient Groups and Intervention	Primary outcome
DIGIT-HF (18) **2025** Austria, Germany, Serbia 65 Centers FU: 3 (0-110) years	**Inclusion Criteria:** - NYHA III-IV and a LVEF ≤40%; - NYHA II and a LVEF ≤30%; - GDMT for a duration of at least 6 months. **Exclusion Criteria:** - Recent MI/revascularization/device therapy, planned cardiac surgery, myocarditis or complex CHD; - advanced AV block or ventricular arrhythmia; - severe hepatic/renal disease, major electrolyte imbalance; - amiodarone use.	**Digitoxin** - 613 Control: - 599 **Recruitment period:** 2015-2023	- Composite of death or first HFH
Qamer, S. Z. et al. **2019 (26)** United States 259 Centers FU: 2.4 (0-6) years	**Inclusion Criteria:** - Medicare-linked OPTIMIZE-HF patients with LVEF ≤45%; - discharged alive. **Exclusion Criteria:** - Pre-admission digoxin use; - for sensitivity analysis: bradycardia (<60 bpm) or severe renal dysfunction (eGFR <15 mL/min/1.73m²).	**Digoxin** - 1531 Control: - 1531 **Recruitment period:** 2003-2004	- HF readmission at 30 days, 1 year, and 6 years.
Georgiopoulou et al. **2009 (27)** United States 1 Center FU: 2.3 (1.3-3.5) years	**Inclusion Criteria:** - Adults 18-70 years; - LVEF ≤30%; - NYHA II-IV, on maximally tolerated HF therapy; - referred for heart transplant evaluation. **Exclusion Criteria:** - CHD or planned cardiac surgery within 6 months.	**Digoxin** - 161 Control: - 161 **Recruitment period:** 2000-2006	- Death, urgent heart transplantation, or LVAD implantation.
Andrey, J. L. et al. **2011 (28)** Spain 1 Center FU: 3.8 (3.1-4.7) years	**Inclusion Criteria:** - ≥14 years;- newly diagnosed with HF according to Framingham criteria. **Exclusion Criteria:** - Patients non-permanent resident in the community of reference.	**Digoxin** - 1421 Control: - 1421 **Recruitment period:** 2001-2008	- All cause death
Freeman, J. V. et al. **2013 (29)** United States 1 Center FU: 2.5 (1.4-3.5) years	**Inclusion Criteria:** - Adults ≥21 years old with ≥1 inpatient admission with a primary discharge for HF or ≥3 outpatient encounters for HF; - LVEF ≤40%. **Exclusion Criteria:** - <12 months of continuous drug benefit before index date; - no follow-up after diagnosis; - prior cardiac/renal transplantation.		- All cause mortality
May Al-khateeb et al. **2017 (30)** Saudi Arabia 750+ Centers FU: 3.6 (1.6-6.3) years	**Inclusion Criteria:** - HF and LVEF < 45%. **Exclusion Criteria:** - If their vital status could not be verified.	**Digoxin** - 325 Control: - 750 **Recruitment period:** 2000-2015	- All-cause mortality

AV: atrio-ventricular; CHD: congenital heart disease; FU: follow-up; GDMT: guideline-directed medical therapy; HF: heart failure; HFH: heart failure hospitalization; LVEF: left ventricular ejection fraction; LVAD: left ventricular assist device; MI: myocardial infarction; NYHA: New York Heart Association.

0.95, 95% CI 0.83-1.10; $I^2 = 53\%$) (Figure 2C). Cardiovascular mortality was reported only in the DIGIT-HF trial (18) and showed no statistically significant difference between groups (HR 0.87, 95% CI 0.67-1.11).

Quality assessment

The DIGIT-HF trial was judged to have an unclear risk of bias (Supplementary Table 3). Among the five observational studies, three were judged to have a

Table 2. Summary of baseline characteristics of included patients

	DIGIT-HF (18)		Qamer et al (26)		Georgiopoulou et al. (27)		Andrey et al. (28)		Freeman et al. (29)		Al-khateeb et al. (30)	
	Digitoxin (n=613)	Control (n=599)	Digoxin (n=1531)	Control (n=1531)	Digoxin (n=161)	Control (n=161)	Digoxin (n=1421)	Control (n=1421)	Digoxin (n=529)	Control (n=2362)	Digoxin (n=325)	Control (n=750)
Age, years (mean ± SD)	66.0 ± 11.1	65.8 ± 11.4	75 ± 10	76 ± 10	51,9 ± 12,7	52,2 ± 11,9	70,7 ± 7,4	70,6 ± 7,3	68,2 ± 14,8	69,8 ± 14,4	54,7 ± 13,7	55,5 ± 13,4
Male: No./ total	491/613 (80.1%)	474/599 (79.1%)	856/1531 (55.9%)	855/1531 (55.8%)	112/161 (69.6%)	112/161 (69.6%)	663/1421 (46.7%)	665/1421 (46.8%)	354/529 (66.9%)	1583/2362 (67.0%)	231/325 (71%)	528/750 (70.4%)
HTN	-	-	987/1531 (64.5%)	949/1531 (62.0%)	-	-	668/1421 (47.0%)	665/1421 (46.8%)	316/529 (59.7%)	1577/2362 (66.8%)	194/325 (59.7%)	454/750 (60.5%)
T2DM	-	-	555/1531 (36.3%)	534/1531 (34.9%)	-	-	520/1421 (36.6%)	519/1421 (36.5%)	157/529 (29.7%)	806/2362 (34.1%)	226/325 (69.5%)	543/750 (72.4%)
DLP	377/613 (61.7%)	343/599 (57.6%)	-	-	-	-	511/1421 (36.0%)	513/1421 (36.1%)	329/529 (62.2%	1647/2362 (69.7%)	214/325 (65.8%)	536/750 (71.5%)
AF/AFL	169/613 (27.6%)	161/599 (26.9%)	552/1531 (36.1%)	554/1531 (36.2%)	60/161 (37.3%)	58/161 (36.0%)	849/1421 (59.7%)	850/1421 (59.8%)	209/529 (39.5%)	454/2362 (19.2%)	56/325 (17.2%)	91/750 (12.1%)
Tobacco use	-	-	248/1531 (16.2%)	267/1531 (17.4%)	-	-	435/1421 (30.6%)	435/1421 (30.6%)	-	-	102/325 (31.4%)	228/750 (30.4%)
Prior MI	-	-	-	-	-	-	-	-	42/529 (7.9%)	355/2362 (15.0%)	98/325 (30.2%)	266/750 (35.5%)
IHD	323/608 (53.1%)	310/592 (52.4%)	-	-	59/161 (36.6%)	65/161 (40.4%)	695/1421 (48.9%)	696/1421 (49.0%)	-	-	-	-
CKD	-	-	-	-	-	-	107/1421 (7.5%)	107/1421 (7.5%)	228/529 (43.1%)	1115/2362 (47.2%)	15/325 (4.6%)	41/750 (5.5%)
LVEF (%)	28.4 ± 6.9 (n=613)	28.9 ± 6.7 (n=599)	27 ± 10 (n=1531)	27 ± 10 (n=1531)	18.3 ± 8.7 (n=161)	18.7 ± 7.9 (n=161)	-	-	-	-	28.2 ± 6.4 (n=325)	25.9 ± 6.1 (n=750)
NYHA III/IV	432/613 (70.5%)	421/599 (70.3%)	-	-	-	-	-	-	-	-	23/325 (7.2%)	36/750 (4.8%)
ICD/CRT	-	-	98/1531 (6.4%)	101/1531 (6.6%)	43/161 (26.7%)	47/161 (29.2%)	-	-	4/529 (0.8%)	41/2362 (1.7%)	54/325 (16.6%)	108/750 (14.4%)
Guideline-directed Medical Therapy												
Beta-blocker	593/613 (96.7%)	567/599 (94.7%)	1120/1531 (73.2%)	1145/1531 (74.8%)	149/161 (92.5%)	147/161 (91.3%)	613/1421 (43.1%)	614/1421 (43.2%	209/529 (39.5%)	1205/2362 (51.0%)	313/325 (96.3%)	724/750 (96.5%)
ARNI	248/613 (40.5%)	231/599 (38.6%)	-	-	-	-	-	-	-	-	-	-
ACEi	222/613 (36.2%)	213/599 (35.6%)	-	-	117/161 (72.7%)	119/161 (73.9%)	-	-	196/529 (37.1%)	1112/2362 (47.1%)	262/325 (80.6%)	589/750 (78.5%)
ARB	113/613 (18.4%)	115/599 (19.2%)	-	-	34/161 (21.1%)	33/161 (20.5%)	-	-	40/529 (7.6%)	236/2362 (10.0%)	115/325 (35.4%)	282/750 (37.6%)
ACEi or ARB	-	-	1125/1531 (73.5%)	1095/1531 (71.5%	-	-	1119/1421 (78.7%)	1120/1421 (78.8%)	-	-	-	-
MRA	466/613 (76.0%)	458/599 (76.5%)	319/1531 (20.8%)	317/1531 (20.7%)	73/161 (45.3%)	74/161 (46.0%)	146/1421 (10.3%)	147/1421 (10.3%)	-	-	245/325 (75.5%)	553/750 (73.7%)
SGLT2 inhibitor	121/613 (19.7%)	113/599 (18.9%)	-	-	-	-	-	-	-	-	-	-

ACEi, angiotensin-converting enzyme inhibitor; AF/AFL, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DLP, dyslipidemia; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD: standard deviation; SGLT2, sodium-glucose linked cotransporter 2; T2DM, type 2 diabetes mellitus.

moderate risk of bias and two a high risk of bias (Supplementary Table 4).

DISCUSSION

Mortality and heart failure hospitalizations

This meta-analysis provides an updated assessment of cardiac glycosides in patients with HF, LVEF < 50% and contemporary GDMT. Consistent with the original DIG trial, our findings suggest that cardiac glycosides may reduce HFH without a consistent impact on all-cause mortality.

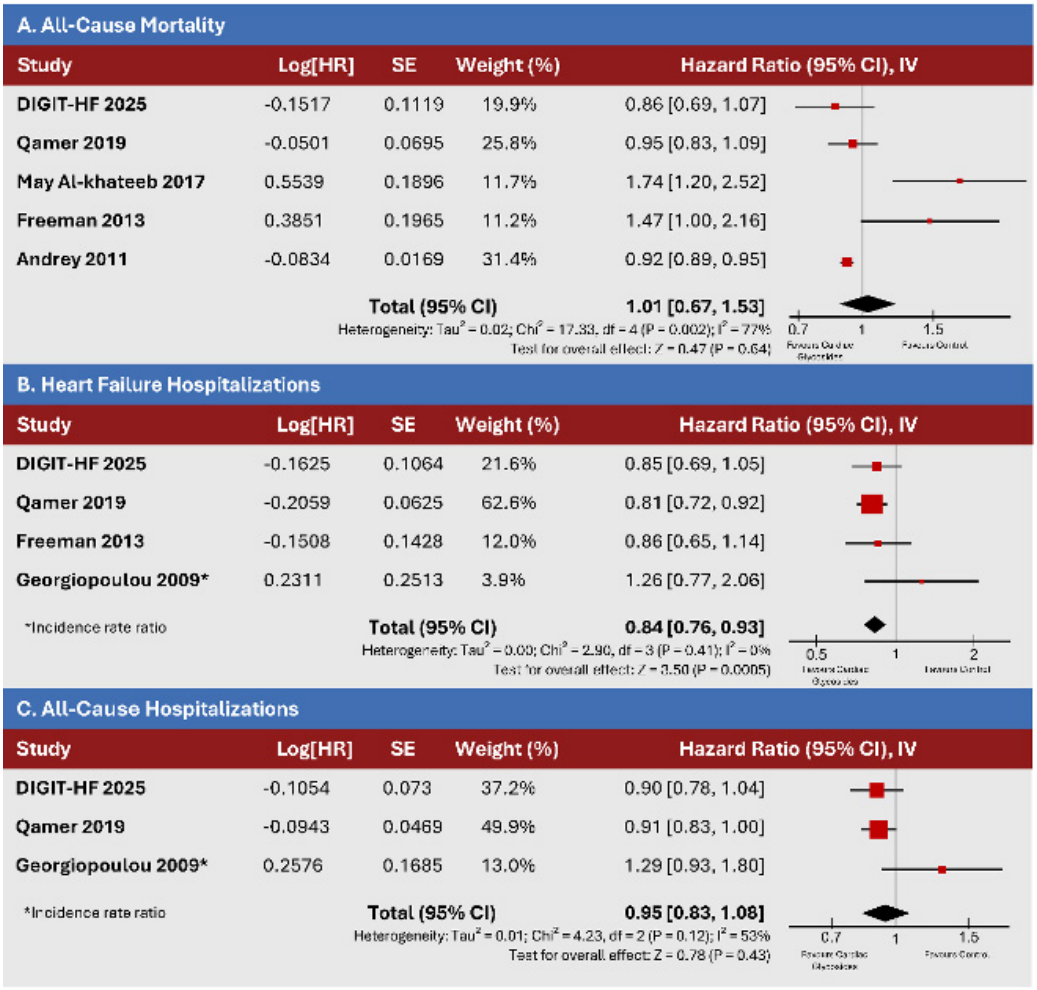
Despite pooled available data, definitive conclusions regarding the effect of cardiac glycosides on all-cause mortality cannot be drawn from the current evidence base. The meta-analytic estimates for mortality are undermined by substantial between-study heterogeneity and the limited number of contemporary high-quality trials. These limitations increase the risk of imprecise and potentially biased estimates, thereby reducing confidence in any pooled mortality effect.

Importantly, the reduction in HFH associated with cardiac glycosides was a consistent finding across heterogeneous study populations. This reproducible finding observed despite variability across studies suggests a robust signal for symptomatic improvement and event reduction that appears less sensitive to between-study differences than mortality outcomes. Nevertheless, the magnitude and clinical implications of HFH reduction should be cautiously interpreted.

Key sources of heterogeneity

Although the included studies generally reflect populations treated with contemporary pharmacotherapy,

Fig. 2. Meta-analysis of cardiac glycoside therapy in heart failure patients with reduced ejection fraction, including randomized controlled trials and propensity-matched cohort studies. Hazard ratios (HR) and incidence rate ratios (IRR) were considered approximately equivalent effect measures and were pooled using a random-effects model with inverse-variance weighting. Forest plots display pooled estimates and 95% confidence intervals (CIs) for (A) all-cause mortality, (B) heart failure hospitalizations, and (C) all-cause hospitalizations



IV: inverse variance; SE: standard error

including beta-blockers, renin–angiotensin–aldosterone system inhibitors, and SGLT2 inhibitors, patients included in this meta-analysis represent a broad and clinically heterogeneous spectrum.

Baseline characteristics , including age, comorbidities, renal function, and rhythm status varied substantially across studies and may influence both the efficacy and safety of cardiac glycosides. Recruitment periods spanned more than two decades, during which HF management evolved considerably, resulting in differences in absolute risk, event rates, and concomitant drug therapy.

Differences in study design, covariate adjustment strategies, and completeness of reporting further contributed to heterogeneity. In addition, the methodological quality of the included studies raises concerns that may undermine the robustness of our findings.
Finally, a key source of variability arises from the specific cardiac glycoside evaluated (digoxin versus digitoxin), which differs in pharmacokinetics, dosing requirements, and safety profiles.

Digoxin and digitoxin

The declining use of digoxin in contemporary HF practice reflects ongoing uncertainty regarding its safety profile. Observational studies and prior meta-analyses have suggested an association between digoxin therapy and increased mortality, particularly in patients with AF, (23, 31-33) an effect that appears more pronounced at higher serum levels.

Values exceeding the therapeutic range have been associated with pro-arrhythmogenic and pro-thrombotic mechanisms, including enhanced endothelial and platelet activation, which may contribute to increased cardiovascular risk. (34-36) These findings are consistent with post hoc analyses of the DIG trial, in which low serum digoxin levels (0.5-0.9 ng/mL) were associated with improved outcomes, whereas higher levels (>1.0 ng/mL) appeared to be harmful. (11, 16, 37) Although the safety and efficacy of cardiac glycosides likely depend on the appropriate serum drug level and dosing, this study was unable to evaluate dose-response relationships due to limited reporting of dosing strategies across studies.

In contrast, recent randomized evidence from the DIGIT-HF trial suggests that low-dose digitoxin may represent a potentially safe and effective therapeutic option. (18) Among patients with chronic HFrEF receiving GDMT, digitoxin significantly reduced the composite endpoint of all-cause mortality or hospitalization for worsening HF, with consistent benefits across prespecified subgroups.

Notably, the DIGIT-HF population exhibited a high symptomatic burden despite optimized GDMT, yet the absolute risk reduction and corresponding number needed to treat were comparable to those observed with other contemporary therapies, including ARNIs and SGLT2i. (18, 38-40) Importantly, these benefits were achieved with few major safety events, particularly in patients with renal dysfunction.

These findings may herald a therapeutic shift from digoxin to digitoxin, a more lipophilic cardiac glycoside with potentially improved safety characteristics.

Other important effect modifiers and interactions

Several clinical variables may meaningfully modify the effects of cardiac glycosides, although available data remain insufficient to elucidate these interactions.

The use of implantable cardiac devices, including ICD and CRT, present in up to 29% of participants in some cohorts, substantially alters the risk of sudden death and HF mortality, and may therefore modify the observed impact of glycoside therapy.

Similarly, the presence of AF and overall rhythm status influence both the clinical indication for glycoside use and dosing strategies, which in turn affect serum concentrations and pharmacodynamic responses. Variability in baseline renal function, together with the absence of standardized drug therapy monitoring further complicates interpretation, as glycoside clearance and toxicity are closely linked to renal function and serum levels.

Finally, concomitant medications that alter glycoside pharmacokinetics or affect renal function may introduce additional residual confounding, thereby influencing outcomes.

Limitations

This meta-analysis has several important limitations. First, the overall quality was suboptimal, as only one contemporary randomized controlled trial was included while the remaining studies were observational and therefore susceptible to selection bias and residual confounding despite the use of propensity score matching.

Second, the substantial between-study heterogeneity, likely attributable to differences in study design, patient characteristics, recruitment periods spanning more than two decades, and evolving background therapies, limits the interpretability of the results.

Third, safety endpoints were not systematically assessed, which is relevant given ongoing concerns regarding glycoside-related toxicity and potential mortality risk signals.

In addition, variability in covariate adjustment strategies across studies may have further contributed to heterogeneity. Finally, the limited number of included studies precluded a formal assessment of publication bias.

Clinical and research implications

Despite these limitations, our findings have relevant clinical and research implications. Cardiac glycosides may continue to provide therapeutic benefit in selected patients with HF and LVEF < 50% receiving contemporary GDMT, primarily through reduction of HFH. This observation suggests that indiscriminate

discontinuation of these agents may overlook a niche population: patients who remain symptomatic, have inadequate rate control in AF, or are intolerant to alternative treatments.

Moreover, digoxin remains an inexpensive and widely available medication that may be particularly valuable in healthcare systems with limited access to the full spectrum of disease-modifying therapies.

Nevertheless, the current evidence base is insufficient to support routine use. Well-designed, adequately powered RCTs are urgently needed to reassess the safety and efficacy of digoxin and/or digitoxin in the context of modern HF management. Future studies should ideally incorporate pharmacokinetic-guided dosing strategies, stratification according to rhythm status, and evaluation of potential interactions with device therapy.

CONCLUSIONS

In conclusion, in this contemporary meta-analysis, cardiac glycosides conferred clinical benefits in patients with HFrEF and HFmrEF, primarily by reducing HFH, an effect consistently observed across diverse populations and time periods. However, no consistent mortality benefit was demonstrated, and the certainty of the evidence is limited by substantial heterogeneity, incomplete dosing data, and the predominance of observational studies. These findings underscore the need for powered randomized controlled trials to more definitively define the role of cardiac glycosides as adjunctive therapy in HF management.

Author contributions

EM and MC contributed equally to this work and shared first authorship.

MC: conceptualization, study design, data curation, formal analysis, methodology, data interpretation, project administration, writing: original draft.

EM: conceptualization, study design, data curation, formal analysis, methodology, data interpretation, project administration, writing: original draft.

LP: data curation, formal analysis, data interpretation, writing: original draft.

BR: data curation, formal analysis, data interpretation, writing: original draft.

AMP: data curation, formal analysis, data interpretation, writing: original draft.

SR: supervision, formal analysis, methodological revision of the manuscript.

JP: supervision, formal analysis, methodological revision of the manuscript.

AL: supervision, writing: review and editing, final approval of the manuscript, guarantor of the study overall content.

All authors reviewed and approved the final manuscript. All authors accept responsibility for the accuracy, reliability and validity of the research data and analysis.

Conflicts of interest

None declared.

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

Funding

This research received no public or public financial support.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement checklist.

Section and Topic	Item #	Checklist item	Location where the item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study, and whether they worked independently, and, if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	
	13c	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13d	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	
	13e	Describe any methods used to explore possible causes of heterogeneity in study results (e.g., subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	

(continue)

(continuation)

Section and Topic	Item #	Checklist item	Location where the item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that may appear to meet the inclusion criteria but were excluded and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present the results of all statistical syntheses conducted. If a meta-analysis was done, present for each one the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present the results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present the results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b		
	24c	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
		Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Table 2. Search query

SEARCH TERMS	
Cochrane CENTRAL	("heart failure"):ti,ab,kw AND (digitoxin:ti,ab,kw OR "cardiac glycosides":ti,ab,kw OR digoxin:ti,ab,kw OR digoxine:ti,ab,kw)" with Cochrane Library publication date between Jan 2000 and Sep 2025
EMBASE	'heart failure'/exp AND ('digitoxin'/exp OR 'cardiac glycosides'/exp OR 'digoxin'/exp) AND [embase]/lim AND [01-01-2000]/sd NOT [18-09-2025]/sd AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ('article'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'clinical trial'/it) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
PUBMED	((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("digitoxin"[Supplementary Concept] OR "digitoxin"[All Fields] OR "digitoxin"[MeSH Terms] OR ("cardiac glycosides"[Supplementary Concept] OR "cardiac glycosides"[All Fields] OR "cardiac glycosides"[MeSH Terms] OR ("cardiac"[All Fields] AND "glycosides"[All Fields])) OR ("digoxin"[Supplementary Concept] OR "digoxin"[All Fields] OR "digoxin"[MeSH Terms] OR "digoxine"[All Fields] OR "digoxin s"[All Fields]))) AND ("analysis"[MeSH Subheading] OR "analysis"[All Fields] OR "an"[All Fields])) AND (2000:2025[pdat])
SCOPUS	(TITLE-ABS ("heart failure") AND (TITLE-ABS (digitoxin) OR TITLE-ABS ("cardiac glycosides") OR TITLE-ABS (digoxin) OR TITLE-ABS (digoxine))) AND (PUBYEAR > 2000 AND PUBYEAR < 2026)

Supplementary Table 3. Risk of bias assessment using risk of bias in non-randomized studies of interventions I (ROBINS-I).

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Qamer, S. Z. *et al.*, 2019	!	✓	✓	!	✓	✓	✓	!
May Al-khateeb *et al.*, 2017	✗	!	!	!	✓	✓	✓	✗
Freeman, J. V. *et al.*, 2013	!	✓	✓	!	✓	✓	✓	!
Andrey, J. L. *et al.*, 2011	!	!	!	!	✓	✓	✓	!
Georgiopoulou *et al.*, 2009	✗	!	✗	!	!	!	✓	✗

✓ **Low risk of bias**
! **Moderated risk of bias**
✗ **High risk of bias**
⊕ **Critical risk of bias**

Supplementary Table 4. Risk of bias assessment of included randomized controlled trials using Risk of Bias Assessment According to the Cochrane Collaboration's Tool

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk-of-bias judgement
DIGIT-HF 2025						

 **Low risk of bias**

 **Unclear risk of bias**

ORIGINAL ARTICLE

Prognostic Value of Right Ventricle–Pulmonary Artery Uncoupling in Transthyretin Amyloidosis

Valor pronóstico del desacoplamiento ventrículo derecho-arteria pulmonar en la amiloidosis por transtiretina

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ABSTRACT

Background: Right ventricular involvement is a common manifestation of transthyretin cardiac amyloidosis (ATTR-CA), especially in advanced stages, and may have significant prognostic implications. Echocardiographic assessment of the right ventricle (RV), however, remains challenging. In this context, the relationship between tricuspid annular plane systolic excursion (TAPSE) and systolic pulmonary artery pressure (SPAP), as well as the relationship between tissue Doppler S wave (S´TDI) and SPAP, have been proposed as markers of RV-pulmonary artery (RV-PA) uncoupling, which could more accurately reflect the functional load on the RV.
Objective: The aim of this study was to analyze the prognostic value of TAPSE/SPAP and S'TDI/SPAP ratios in patients with ATTR-CA, and to compare them with other traditional clinical and echocardiographic predictors regarding the risk of hospitalization for heart failure (HHF).
Methods: A retrospective analysis was performed of patients with confirmed diagnosis of ATTR-CA under outpatient follow-up at a cardiomyopathy clinic. Clinical, biochemical, and echocardiographic data were collected at the time of diagnosis, and events of HHF were documented during follow-up. The primary outcome was the first HHF. Univariate and multivariate Cox regression models were applied to identify independent predictors, and Kaplan-Meier analysis were used to evaluate event-free survival curves. The optimal cut-off points for continuous variables were defined by Youden's index.
Results: A total of 191 patients (mean age 80 ± 7.9 years, 88.5% men) were included, all with preserved or mildly reduced left ventricular ejection fraction, with a median value of 53% and interquartile range (IQR) 43-61, and echocardiographic evidence of RV dysfunction, with median TAPSE 18 mm (IQR 15–20) and S'TDI 9.5 (IQR 8–10). During a median follow-up of 391 days (IQR 84–704), 32% of patients had at least one HHF. In the univariate analysis, a higher TAPSE/SPAP ratio was associated with lower risk of hospitalization (HR 0.149; p = 0.039), as were higher TAPSE values alone (HR 0.959; p=0.040) and older age (HR 1.066; p=0.010), while SPAP alone was not significant (HR 1.014; p=0.100). In the multivariate analysis, a TAPSE/SPAP ratio ≤ 0.5 (optimal cutoff point with 78% sensitivity, 67% specificity, and area under the ROC curve 0.60) was independently associated with a higher risk of hospitalization (HR 2.05; 95% CI 1.10–4.33; p = 0.025). In contrast, the S'TDI/SPAP ratio showed no independent association (p = 0.843).
Conclusions: In patients with ATTR-CA, RV–PA uncoupling, estimated by a TAPSE/SPAP ratio ≤ 0.5, is associated with an increased risk of HHF, even with preserved ejection fraction. Conversely, the S'TDI/SPAP ratio did not provide prognostic value. Due to its simplicity and availability, the TAPSE/SPAP ratio could be incorporated as a complementary risk stratification tool in this population

Key words: Cardiac amyloidosis - Right ventricle - TAPSE - Pulmonary systolic pressure - Tissue Doppler – Hospitalization - Heart failure

RESUMEN

Introducción: La afectación del ventrículo derecho (VD) es una manifestación frecuente en la amiloidosis cardíaca por transtiretina (CA-TTR), especialmente en etapas avanzadas, y puede tener implicancias pronósticas relevantes. La evaluación ecocardiográfica del VD, sin embargo, continúa siendo desafiante. En este contexto, la relación entre el desplazamiento sistólico del anillo tricúspideo (TAPSE) y la presión sistólica de la arteria pulmonar (PSAP), así como la relación de la onda S por Doppler tisular (S'TDI) y la PSAP, han sido propuestas como marcadores del desacoplamiento VD-arteria pulmonar (VD-AP), lo que podría reflejar con mayor precisión la carga funcional del VD.
Objetivo: Analizar el valor pronóstico de las relaciones TAPSE/PSAP y S'TDI/PSAP en pacientes con CA-TTR, y compararlas con otros predictores clínicos y ecocardiográficos tradicionales, en relación con el riesgo de hospitalización por insuficiencia cardíaca (HIC).

Rev Argent Cardiol 2026;94:46-54. https://doi.org/10.7775/rac.v94.i1.20969

Received: 11/05/2025 – *Accepted:* 12/17/2025

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This article won the Dr. Oscar Orias Runner-up Prize at the 51st Argentine Congress of Cardiology.

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Material y métodos: Se realizó un análisis retrospectivo de pacientes con diagnóstico confirmado de CA-TTR bajo seguimiento ambulatorio en una clínica especializada en miocardiopatías. Se recolectaron datos clínicos, bioquímicos y ecocardiográficos al momento del diagnóstico, y se documentaron eventos de HIC durante el seguimiento. El desenlace primario fue la primera hospitalización por IC. Se emplearon modelos de regresión de Cox univariado y multivariado para identificar predictores independientes, y análisis de Kaplan Meier para evaluar curvas de supervivencia libre de eventos. Los puntos de corte óptimos de las variables continuas se definieron por el índice de Youden.
Resultados: Se incluyeron 191 pacientes (edad media 80 ± 7,9 años, 88,5 % hombres), todos con fracción de eyección del ventrículo izquierdo preservada o levemente reducida, con mediana 53% y rango intercuartílico (RIC) 43-61, y evidencia ecocardiográfica de disfunción del VD, con medianas de TAPSE 18 mm (RIC 15-20), y onda S´-TDI 9,5 (RIC 8-10). Durante un seguimiento mediano de 391 días (RIC 84–704), 32 % de los pacientes presentó al menos una hospitalización por IC. En el análisis univariado una mayor relación TAPSE/PSAP se asoció con menor riesgo de hospitalización (HR 0,149; p = 0,039), al igual que valores más altos de TAPSE de forma aislada (HR 0,959 p=0,040) y mayor edad (HR 1,066; p=0,010), mientras que la PSAP aislada no fue significativa (HR 1,014; p=0,100). En el análisis multivariado, una relación TAPSE/PSAP ≤ 0,5 (punto de corte óptimo con sensibilidad 78 %, especificidad 67 % y área bajo la curva ROC 0,60) se asoció de manera independiente con mayor riesgo de hospitalización (HR 2,05; IC95 % 1,10–4,33; p = 0,025). En contraste, la relación S'TDI/PSAP no mostró asociación independiente (p = 0,843).
Conclusiones: En pacientes con CA-TTR, el desacoplamiento VD–AP, estimado por una relación TAPSE/PSAP ≤ 0,5, se asocia con mayor riesgo de HIC, aun con fracción de eyección preservada. En contraste, la relación S'TDI/PSAP no aportó valor pronóstico. La relación TAPSE/PSAP, por su simplicidad y disponibilidad, podría incorporarse como herramienta complementaria de estratificación de riesgo en esta población.

Palabras clave: Amiloidosis cardíaca - Ventrículo derecho - TAPSE - Presión sistólica pulmonar - Doppler tisular - Hospitalización - Insuficiencia cardíaca.

INTRODUCTION

Transthyretin cardiac amyloidosis (ATTR-CA) is an infiltrative disease characterized by the extracellular deposition of this misfolded protein fibers in the myocardium. This process leads to increased wall thickness, ventricular stiffness, and, in the early stages, relative preservation of left ventricular (LV) systolic function. (1–4) With progression, elevated filling pressures, atrial remodeling, and secondary pulmonary hypertension are observed, with right ventricular (RV) overload. (5)

Right ventricular dysfunction in ATTR-CA has been associated with an increased risk of hospitalization and mortality, regardless of left ventricular function. (6,7) In this context, the RV ability to adapt to pulmonary circulation may be compromised by pressure overload and progressive myocardial stiffness, favoring the development of right ventricle–pulmonary artery (RV–PA) uncoupling. (8)

RV–PA coupling describes the interaction between ventricular contractility and pulmonary afterload. Its echocardiographic assessment using the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (SPAP) has proven to be a simple and noninvasive index, with good correlation with invasive measurements. (9,10) In heart failure and pulmonary hypertension, this parameter has been established as a clinical and prognostic marker. (11–15) However, in cardiac amyloidosis, the evidence remains limited and expanding. (16–19)

On the other hand, tricuspid annulus S′ wave velocity obtained by tissue Doppler imaging (S′TDI) is a sensitive parameter of RV longitudinal systolic function, with good correlation with ejection fraction measured by magnetic resonance imaging (20). However, its application in RV–PA coupling indices, such as the S′TDI/SPAP ratio, still lacks clinical validation in ATTR-CA.

In this context, the present study aimed to evaluate the prognostic value of RV–PA uncoupling in patients with ATTR-CA, estimated by the TAPSE/SPAP ratio, and to explore the usefulness of the S'TDI/SPAP ratio in predicting hospitalization for heart failure (HHF).

METHODS

Study design and population

A retrospective, single-center observational cohort study was conducted using data obtained prospectively from electronic medical records. Patients followed up on an outpatient basis at the institution's Cardiomyopathy Clinic between January 2011 and March 2025, with a diagnosis of ATTR-CA according to the diagnostic criteria in force during that period, were included. (21)

Demographic data (age, sex), clinical history, cardiovascular risk factors, and baseline echocardiographic parameters were recorded. Patients were followed up for clinical events, and their data were recorded in a database specific for the disease.

Confirmation of transthyretin cardiac amyloidosis

The diagnosis was established based on echocardiographic findings typical of infiltrative cardiomyopathy (LV wall thickness ≥ 12 mm) and grade 2 or 3 myocardial uptake on bone scintigraphy with technetium-99m hydroxymethylene diphosphonate (99mTc-HMDP, The Binding Site, Birmingham, UK), together with the exclusion of clonal dyscrasia by serum and urinary immunofixation and free light chain assay (Freelite, The Binding Site, Birmingham, UK). (4)

The scintigraphy was performed with 20 mCi of 99mTc-HMDP administered intravenously, acquiring flat images after 2 hours. Semiquantitative cardiac uptake relative to bone tissue was evaluated using the Perugini scale (0–3) and quantitative assessment was performed using the heart/lung ratio.

The final diagnosis of ATTR-CA was established by integrating the clinical evaluation with electrocardiographic, echocardiographic, and scintigraphy data, after excluding light chain (AL) disease (free light chains, serum and urinary immunofixation). (22,23) Gadolinium enhanced magnetic resonance imaging was indicated in selected cases, and

when diagnostic doubts persisted, a tissue biopsy was performed.

Echocardiography

Transthoracic echocardiograms (TTE) obtained in a stable clinical situation, corresponding to the time closest to the amyloidosis diagnosis, were retrieved and reanalyzed.

Images were acquired using Philips iE33 and HD15 ultrasound machines, and in subsequent years Philips EPIQ 7 and Affinity (Philips Medical Systems, Andover, MA, USA). Post-processing was performed independently by a trained cardiologist using QLAB and UniViewer workstations (Philips Medical Systems, Andover, MA, USA).

Measurements followed the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) for chamber quantification, ventricular function assessment, and pulmonary pressure estimation. (24,25)

The following measurements were obtained:

- TAPSE: tricuspid annular plane systolic excursion in M-mode (mm).
- S'TDI: longitudinal systolic velocity of the RV by pulsed tissue Doppler in the tricuspid annulus (cm/s).
- SPAP: calculated as 4 × (maximum tricuspid regurgitation velocity)² + right atrial pressure, estimated by inferior vena cava diameter and collapsibility (mmHg).
- LVEF: left ventricular ejection fraction, using Simpson's biplane method in 4- and 2-chamber apical projections (%).

Based on these variables, the RV-PA coupling indices were calculated: TAPSE/SPAP and S'TDI/SPAP.

Outcome and follow-up

The primary outcome was time to first HHF, defined as hospitalization ≥ 24 h for documented signs/symptoms of congestion with intensified treatment (IV diuretics and/or vasodilators/inotropic drugs)

Time 0 was defined as the date of baseline TTE (the study closest to diagnosis in a stable situation). Patients without an event were censored on the date of last documented contact or death without prior HHF. Follow-up duration was reported as median and interquartile range (IQR).

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and IQR according to their distribution (assessed with the Shapiro–Wilk test); homogeneity of variances was verified with the Levene test. For univariate comparisons, Student's t or Mann–Whitney U (for continuous variables) and χ^2 or Fisher (for categorical variables) tests were used, as appropriate.

The association between echocardiographic parameters and the primary outcome was evaluated using univariate and multivariate Cox proportional hazards models, reporting hazard ratios (HR) with their 95% confidence intervals (95% CI). The number of predictors in the multivariate model was limited by the approximate rule of ~10 events per predictor.

The discriminatory capacity of the RV–PA uncoupling indices (TAPSE/SPAP and S'TDI/SPAP) was analyzed using ROC curves with area under the curve (AUC) and 95% CI (DeLong method). The optimal cutoff point for TAPSE/SPAP was determined using the Youden index. Kaplan–Meier curves stratified by cutoff point were built and compared using the log-rank test. A p-value < 0.05 was considered significant.

The analyses were performed for complete cases using IBM SPSS Statistics version 29.0.

Ethical considerations

The protocol was approved by the institutional Ethics Committee. Informed consent was waived given the retrospective nature and the use of anonymized data. The study was conducted in accordance with the Declaration of Helsinki (26) and national regulations (Resolution 1480/2011 of the National Ministry of Health, Law 3301 of the City of Buenos Aires, and Resolution 6677/10 of ANMAT and its 4008 and 4009 amendments).

RESULTS

Study population (Table 1)

Between January 2011 and March 2025, 228 patients were evaluated and 37 were excluded (due to single TTE during hospitalization for decompensated HF, n = 16; no TTE or not performed at our institution, n = 7, TTE without sufficient data to assess SPAP, n = 14), leaving 191 for analysis (Figure 1).

Mean age was 80 ± 7.9 years, and 88.5% were men. Functional class at the time of baseline TTE was predominantly NYHA I in 62 patients (32.4%) and II in 100 (52.4%). The most frequent comorbidities were hypertension in 131 cases (68.8%) and dyslipidemia in 104 (54.5%). Among the "red flags" for ATTR-CA, carpal tunnel syndrome was observed in 55 patients (27.2%), neuropathy in 11 (5.4%), and spinal stenosis in 12 (5.9%). Atrial fibrillation was present in 93 cases (46.0%) and developed during follow-up in 26 (12.9%). The remaining baseline characteristics are shown in Table 1.

Echocardiographic parameters and RV-PA coupling (Table 2)

In baseline echocardiography, median LVEF was 53% (IQR 43–61) with verified increased LV wall thickness Median left atrial area was 28 cm² (25–33). Pseudonormal, restrictive, and monophasic wave mitral filling patterns predominated; median mitral E wave and tissue e' ratio (E/e') was 14 (IQR 10–18); TAPSE was 18 mm (15–20), and tricuspid annulus S'TDI was 9.5 cm/s (8–10). SPAP reached 38 mm Hg (31–48). The RV–PA coupling indices were 0.43 (0.32–0.62) for the TAPSE/SPAP ratio and 0.23 (0.18–0.32) for S1TDI/SPAP. Mild aortic stenosis was diagnosed in 3.9% of cases, moderate in 9.2%, and severe in 3.9%..

Predictors of hospitalization for HF (Tables 3 and 4)

During a median follow-up of 391 days (84–704), 32% of patients (n=61) had at least one episode of HHF. In the univariate analysis, a higher TAPSE/SPAP ratio was associated with lower risk of HHF (HR 0.149; 95% CI 0.023–0.962; p = 0.039).

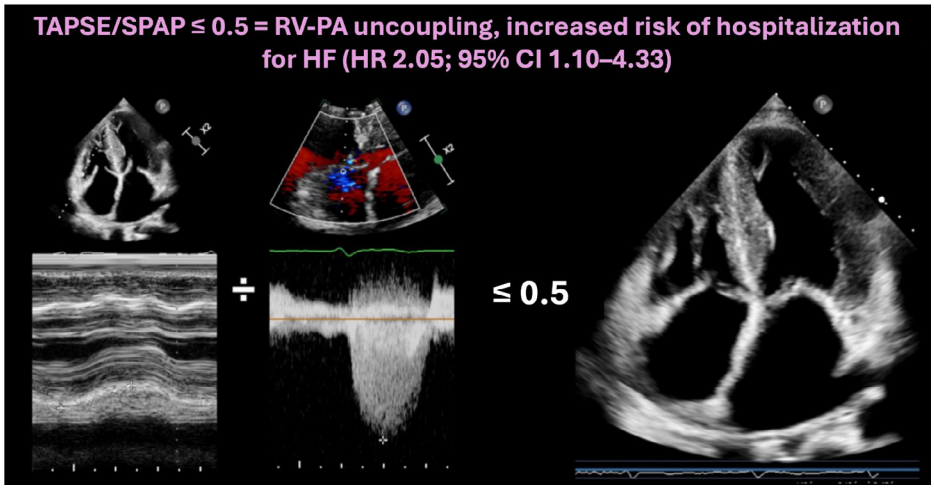
TAPSE (HR 0.959; 95% CI 0.921–0.998; p = 0.040) and age (for each year of increase: HR 1.066; 95% CI 1.015–1.120; p = 0.010) were also significant predictors, while SPAP did not reach statistical significance (HR 1.014; 95% CI 0.997–1.032; p = 0.100). The S'TDI/SPAP ratio showed no significant association in the univariate analysis (HR 0.096; 95% CI 0.00–24.33;

Table 1. Clinical population characteristics (n = 191)

Variable	Value*
Male sex, n (%)	169 (88.5%)
Age, years, mean ± SD	80 ± 7.9 years
NYHA functional class 1, n (%)	62 (32.4%)
NYHA functional class 2, n (%)	100 (52.4%)
NYHA functional class 3, n (%)	28 (14.6%)
NYHA functional class 4, n (%) †	1 (0.52%)
Hypertension	131 (68.8%)
Dyslipidemia	104 (54.5%)
Diabetes	28 (14.6%)
Smoking	67 (35%)
Acute coronary syndrome	25 (13.1%)
Coronary angioplasty	41 (20.3%)
Myocardial revascularization surgery	16 (7.9%)
Valve replacement surgery	14 (6.9%)
Carpal tunnel syndrome	55 (27.2%)
Neuropathy	11 (5.4%)
Spinal stenosis	12 (5.9%)
Previous atrial fibrillation	93 (46.0%)
Atrial fibrillation in follow-up/development	26 (12.9%)
Previous cardiomyopathies	46 (22.8%)
Implantable cardioverter defibrillator	1 (0.5%)
Cardiac resynchronization therapy	2 (1.0%)

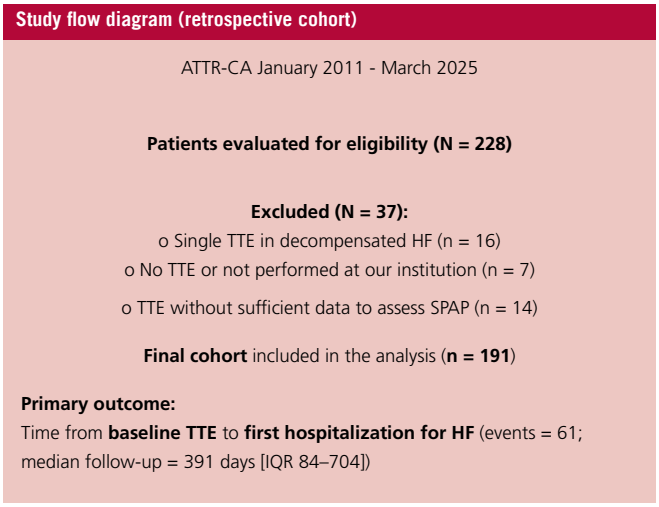
* Values are expressed as mean ± SD, median (IQR), or n (%), as appropriate. NYHA functional class is that present at baseline TTE.
† One patient in NYHA class IV evaluated during hospitalization for HF was excluded.
HF: heart failure; IQR: interquartile range; NYHA: New York Heart Association; SD: standard deviation; TTE: transthoracic echocardiogram

Central Figure. TAPSE/SPAP ≤ 0.5 and risk of hospitalization for heart failure in CA-TTR.



Schematic illustration of right ventricle–pulmonary artery (RV–PA) uncoupling in transthyretin cardiac amyloidosis (ATTR-CA). A TAPSE/SPAP value ≤ 0.5 identifies patients at higher risk of hospitalization for heart failure.
ATTR CA: transthyretin cardiac amyloidosis; HF: heart failure; RV-PA: right ventricle–pulmonary artery; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

Fig 1. Selection flow diagram for the ATTR-CA cohort



ATTR-CA: transthyretin cardiac amyloidosis; HF: heart failure; IQR: interquartile range; SPAP: systolic pulmonary artery pressure; TTE: transthoracic echocardiogram;.

p = 0.407), with an unstable estimate due to a low proportion of censored cases and lower availability of measurements. Also, the age-adjusted S'TDI/SPAP ratio showed no independent association (HR 0.968; 95% CI 0.721–1.300; p = 0.843). Isolated RV S'TDI was also not associated with the outcome (HR 0.929; 95% CI 0.702–1.230; p = 0.608).

The AUC of the TAPSE/SPAP ratio for HHF was 0.60 (95% CI 0.50–0.71). The optimal cutoff point according to Youden's index was 0.5, with a sensitivity of 78% and specificity of 67%.

In the multivariate analysis, a TAPSE/SPAP ratio ≤ 0.5 was independently associated with a higher risk of HHF (HR 2.053; 95% CI 1.10–4.33; p = 0.025). Kaplan–Meier curves stratified by TAPSE/SPAP ≤ 0.5 showed consistent risk separation (log-rank in line with Cox model results (Figure 2).

DISCUSSION

In this contemporary cohort of ATTR-CA, the RV–PA uncoupling index derived from the TAPSE/SPAP ratio showed independent prognostic value of hospitalization for HF. We would like to highlight three main messages: (i) a TAPSE/SPAP ratio ≤ 0.50 identified a high-risk subgroup, with an association that persisted after adjustment; (ii) among the separate components, lower TAPSE and older age—but not SPAP alone—were associated with the outcome; and (iii) neither S'TDI nor S'TDI/SPAP provided prognostic value in this cohort. This pattern suggests that, in ATTR-CA, the interaction between RV contractility and afterload is better reflected by the TAPSE/SPAP ratio than by its components considered in isolation.

Relationship with previous evidence

The use of noninvasive indices of RV–PA uncoupling for prognostic stratification was initially demonstrated in HF with preserved ejection fraction: in a large cohort, Guazzi et al. observed that TAPSE/SPAP < 0.35 was independently associated with the composite endpoint of HHF or death (27). Our findings are consistent in direction, although the optimal threshold was higher (0.50), a difference attributable to lower SPAP values.

In cardiac amyloidosis, studies in mixed AL and TTR cohorts showed that TAPSE/SPAP ratio predicts HHF and reported a mean TAPSE/SPAP value of ≈ 0.45 mm/mmHg as an independent predictor of death or HHF, (9) a finding subsequently confirmed in another smaller mixed cohort. (10)

Our work refines this evidence by focusing exclusively on ATTR-CA and evaluating multiple coupling indices. Even in a population mostly in early functional stages (85% NYHA ≤ II), RV–PA uncoupling retained independent prognostic value, suggesting that poor RV adaptation to afterload may be an early phenomenon in the natural history of the disease, possibly favored by preferential infiltration of the basal RV segments. (28,29)

Pathophysiological interpretation

ATTR-CA combines myocardial stiffness and secondary pulmonary hypertension in advanced stages, conditions that strain RV-PA coupling. The TAPSE/SPAP ratio integrates, in a single measure, the longitudinal contractile reserve of the RV (TAPSE) and afterload (SPAP), capturing the mismatch between the two. The fact that the S'TDI (tissue velocity) parameter was not significant may reflect (i) its greater susceptibility to noise and angle, (ii) the basal segmental involvement of the RV typical of amyloidosis, and (iii) that, in this disease, small isolated decreases in longitudinal func-

Table 2. Baseline echocardiography and RV–PA indices (n = 191)

Parameter	Value
LVDD, mm, median (IQR)	44 (40–49)
LVSD, mm, median (IQR)	30 (25–35)
IVST, mm, median (IQR)	16 (14–19)
PWT, mm, median (IQR)	13 (12–15)
LVEF, %, median (IQR)	53 (43–61)
LA area, cm², median (IQR)	28 (25–33)
Mitral filling pattern (0–4)†	0: 2.6%
	1: 13.9%
	2: 25.2%
	3: 23.2%
	4: 35.1%
E/e', median (IQR)	14 (10–18)
Lateral S' (mitral), cm/s, median (IQR)	5 (4.3–6.5)
Septal S' (mitral), cm/s, median (IQR)	4 (0–5)
TAPSE, mm, median (IQR)	18 (15–20)
RV S'TDI, cm/s, median (IQR)	9.5 (8–10)
SPAP, mm Hg, median (IQR)	38 (31–48)
TAPSE/SPAP ratio, median (IQR)	0.43 (0.32–0.62)
RV S'TDI/SPAP ratio, median (IQR)	0.23 (0.18–0.32)
AoS	No: 82.9%
	Mild: 3.9%
	Moderate: 9.2%
	Severe: 3.9%

† Mitral filling pattern: 0 = normal; 1 = prolonged; 2 = pseudonormal; 3 = restrictive; 4 = monophasic wave.
AoS: aortic stenosis; E/e': mitral E wave to tissue e' ratio; IQR: interquartile range; IVST: interventricular septal thickness; LA: left atrium; lateral S' (mitral): systolic velocity of the lateral mitral annulus by tissue Doppler; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; PA: pulmonary artery; PWT: posterior wall thickness; RV: right ventricle; RV S'TDI: systolic velocity of the tricuspid annulus by tissue Doppler imaging; septal S' (mitral): systolic velocity of the septal mitral annulus by tissue Doppler imaging; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion

Table 3. Univariate analysis of predictors for heart failure hospitalization

Variable	HR	95% CI	p
TAPSE/SPAP (continuous)	0.149	0.023–0.962	0.039
TAPSE (mm)	0.959	0.921–0.998	0.040
Age (years)	1.066	1.015–1.120	0.010
SPAP (mmHg)	1,014	0.997–1.032	0.100
S'TDI (cm/s)	0.929	0.702–1.230	0.608
S'TDI/SPAP (continuous)	0.096	0.003–24.33	0.407

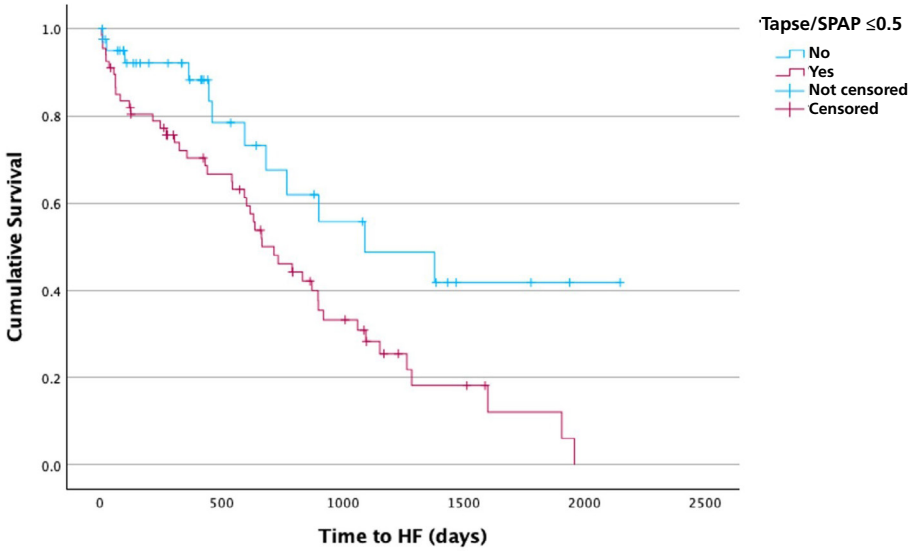
HR: hazard ratio; 95% CI: 95% confidence interval.
HF: heart failure; SPAP: systolic pulmonary artery pressure; S' TDI: S' wave by tissue Doppler imaging; TAPSE: tricuspid annular plane systolic excursion.

Table 4. Multivariate analysis of predictors for heart failure hospitalization.

Variable (model)	Adjusted HR	95% CI	p
TAPSE/SPAP ≤ 0.50	2.053	1.10–4.33	0.025
S'TDI (cm/s) + age + SPAP	0.968	0.721–1.300	0.828
S'TDI/SPAP + age	0.101	0.00–30.92	0.432

HR: hazard ratio; 95% CI: 95% confidence interval.
SPAP: pulmonary artery systolic pressure; S' TDI: S' wave by tissue Doppler imaging; TAPSE: tricuspid annular plane systolic excursion.

Fig. 2. Kaplan–Meier curves according to TAPSE/SPAP



Heart failure hospitalization-free survival curves stratified according to TAPSE/SPAP cutoff point ≤ 0.5. A significant separation of risks is observed (log-rank according to the Cox model).
HF: heart failure; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

tion might not translate into worse outcomes if they are not accompanied by elevated afterload. Taken together, this suggests that the contraction/afterload ratio provides more information than isolated "pieces" of RV mechanics.

Clinical implications

The TAPSE/SPAP index is simple, reproducible, and available in standard TTE. Its incorporation into baseline assessment could:

- Stratify risk and prioritize closer follow-up in patients with values ≤ 0.50.
- Inform therapeutic decisions, favoring early optimization of HF management and timely evaluation of disease-modifying therapies when appropriate.
- Monitor trajectory: variations in TAPSE/SPAP over time could signal progression ("dynamic" uncoupling).

This index should complement, not replace, multiparametric assessment with biomarkers, functional class, LV parameters, and, when available, RV free wall strain.

LIMITATIONS

The observational, retrospective, and single-center design implies a risk of selection bias. In addition, the estimation of SPAP by Doppler may introduce errors related to the tricuspid regurgitation signal and the estimation of right atrial pressure. Right ventricular strain indices and invasive hemodynamic measurements, which would have allowed the calculation of elastances, were not systematically incorporated. The primary outcome considered was the first HHF, excluding mortality and composite outcomes, which may limit comparison with other series. Finally, the cohort spanned several years, during which the management of ATTR-CA was modified, introducing a possible treatment-related confounding factor.

CONCLUSIONS

In this cohort of ATTR-CA with preserved LVEF, RV-PA uncoupling measured by TAPSE/SPAP was independently associated with an increased risk of first

hospitalization for HF, identifying a practical threshold (≤ 0.50) with potential clinical utility. In contrast, strain-based indices showed no independent association with the outcome.

Prospective, multicenter studies are warranted to: (i) externally validate the cutoff point ≤ 0.50; (ii) evaluate the incremental value of TAPSE/SPAP over clinical models and biomarkers; (iii) compare its performance with S'TDI and S'TDI/SPAP; (iv) analyze its longitudinal evolution and modulation by specific therapies; and (v) consider hard endpoints and phenotypic subgroups.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

Atrial Myopathy in Heart Failure with Preserved Ejection Fraction

Miopatía auricular en insuficiencia cardíaca con fracción de eyección preservada

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ABSTRACT

Background: Atrial myopathy is an underdiagnosed disorder whose pathophysiology is closely related to that of other conditions such as heart failure, atrial fibrillation, and stroke. Various methods such as electrocardiogram, echocardiogram, and magnetic resonance imaging allow us to approximate the diagnosis. However, definite confirmation is made through the pathological study of an atrial myocardium sample. Atrial myopathy is considered an early stage in the development of heart failure with preserved ejection fraction, so its detection through various diagnostic studies allows for the diagnosis of heart failure to be made earlier.

Key words: Heart failure with preserved ejection fraction; Atrial function; Atrial fibrillation; Stroke

RESUMEN

Introducción: La miopatía auricular es una entidad subdiagnosticada cuya fisiopatología se relaciona estrechamente con la de otros cuadros como la insuficiencia cardíaca, la fibrilación auricular y el accidente cerebrovascular. Diversos métodos como el electrocardiograma, el ecocardiograma y la resonancia magnética, nos permiten aproximarnos al diagnóstico; sin embargo, la confirmación definitiva se realiza por medio de un estudio anatomopatológico de una muestra de miocardio auricular. Se considera a la miopatía auricular como un estadio precoz en el desarrollo de la insuficiencia cardíaca con fracción de eyección preservada, por lo que su reconocimiento mediante distintos estudios diagnósticos permite adelantar el diagnóstico de esta última patología.

Palabras clave: Insuficiencia cardiaca con fracción de ejecución preservada; Función auricular; Fibrilación auricular; Accidente cerebrovascular

INTRODUCTION

The left atrium (LA) is a structure of fundamental importance for cardiac physiology and hemodynamics. However, for many years it was considered solely as a cavity with the passive function of conducting blood flow from the pulmonary veins to the left ventricle.

There are multiple diagnostic methods for detecting anatomical and functional alterations of the LA, but their usefulness in routine cardiological practice has not been widely disseminated, nor has their implication in the development, progression, and complications of multiple diseases, among which heart failure (HF), atrial fibrillation (AF), and stroke stand out.

To write this review, a thorough search and extensive literature review was conducted on the definition, pathophysiology, diagnosis, and current diagnostic implications of atrial myopathy in patients with heart failure with preserved ejection fraction.

The following sources of medical information were used: bibliographic databases (MEDLINE), evidence-based medicine databases (Cochrane Library, Uptodate), specialty journals, clinical practice guidelines (European Society of Cardiology, American College of Cardiology/American Heart Association), and the central library of the Italian Hospital of Buenos Aires.

The following words and terms were used for the search: "Atrial myopathy," "Atrial cardiomyopathy," "HFpEF," "Heart Failure with preserved ejection fraction," and their equivalents in Spanish.

Definition

The term atrial myopathy first appeared in 1972 following a study published by Nagle et al. (1) in which they described a familial syndrome that predominantly affected the atrium, associated with atrioventricular conduction disorders. An approximation of its

Rev Argent Cardiol 2026;94:55-60. https://doi.org/10.7775/rac.v94.i1.20966

Received: 11/10/2025 – *Accepted:* 01/04/2026

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definition emerged in 2018, when the European Heart Rhythm Association, together with the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society, and the Latin American Society of Cardiac Rhythm and Electrophysiology, developed a consensus defining atrial myopathy as "any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria that might produce clinically relevant manifestations." (2)

Pathophysiology

The LA performs five primary functions. First, it functions as a cavity that receives blood from the pulmonary veins. Second, it has a contractile function that helps fill the left ventricle at end diastole. Third, it acts as a conduit that admits passive filling of the left ventricle due to pressure differences. Fourth, it has the ability to detect changes in blood volume through baroreceptors, which allows it to regulate the release of natriuretic peptides and thus regulate diuresis. Finally, it has mechanoreceptors that increase the rate of discharges to the sinus node, facilitating tachycardia when venous return increases. (3,4)

Regarding the pathophysiology of atrial myopathy, multiple factors are taken into consideration that can lead to structural and functional deterioration of the LA. Shen et al. (5) propose a staging model of atrial myopathy progression that begins with a normal atrium, on which the effect of factors such as age, inflammation, atrial enlargement and oxidative stress, among others, lead to stage A, represented by a high risk of developing atrial myopathy. These risk factors progress, producing fibrosis, structural remodeling, and electrophysiological alterations (stage B), characterized by asymptomatic atrial myopathy that is detectable by imaging studies. Stage C presents clinical manifestations of reversible atrial myopathy and in stage D, irreversible atrial alterations take place.

Etiology

Multiple etiologies have been associated with the development of atrial dysfunction. The most frequent are: (6)

- Rhythm or conduction disturbances: they lead to structural and electrical alterations in the atrium. These can be arrhythmias such as AF, or conduction disorders that cause poor atrioventricular electrical coupling, such as complete left bundle branch block or advanced interatrial block.
- Atrial cardiomyopathy: This corresponds to a group of entities characterized by atrial fibrosis. Among the most frequent are idiopathic atrial fibrosis, atrial ischemia, and atrial involvement secondary to myocarditis.
- Atrial remodeling: These are conditions that cause structural, electrophysiological, and cellular alterations in the atrial myocardial tissue secondary to an increase in left atrial pressure or volume. Among the most common causes are AF and alterations of the left ventricle or the atrioventricular valves.

Diagnosis

There are currently no specific diagnostic criteria for atrial myopathy. Electrocardiogram (ECG), echocardiogram, and magnetic resonance imaging are among the studies that contribute to the diagnostic approach. It is considered that a histological study of the atrial myocardium is necessary to make an accurate diagnosis of atrial myopathy.(7)

In terms of electrocardiographic changes that point to the identification of atrial myopathy, interatrial block stands out, which can be partial, when the duration of the P wave is equal to or greater than 120 ms, or advanced, when P wave prolongation is accompanied by morphological changes in the inferior leads (biphasic P waves in DII, DIII, and aVF). There are also other changes that have prognostic implications in atrial myopathy, such as the terminal force of the P wave in V1 (>40 000 μV/ms) and the MVP (Morphology-Voltage-P) score. (8)

The MVP score can be obtained through an ECG and is based on three variables: the morphology of the P wave in inferior leads (the morphology of partial interatrial block is equivalent to 1 point and high-grade block to 2 points), the voltage in D1 (between 0.20 and 0.10 mV equals one point, and less than 0.10 mV to 2 points) and the duration of the P wave (between 120 and 140 ms equals one point and greater than 140 ms equals 2 points). The score was initially designed to identify patients at high risk of developing AF: 0 to 2 points represents low risk, 3 to 4 points intermediate risk, and 5 to 6 points high risk. However, the variables it analyzes, such as interatrial block and P wave voltage, are considered markers of atrial myopathy. (9)

Atrial fibrillation, as an entity, may be useful for the diagnostic approach to atrial myopathy. The appearance of f waves on the ECG may be an indicator of electrophysiological and structural changes in the atrial myocardium. There is still debate as to whether AF is a marker of atrial myopathy or whether arrhythmia per se as a pathological entity leads to the development of atrial fibrosis.(7)

The echocardiographic parameters commonly used to assess atrial structure include the anteroposterior length of the LA and the left atrial area and volume (total and indexed to body surface area).(10) Techniques such as Doppler and speckle tracking are used to assess left atrial function.(11)

Conventional echocardiography can be used to perform various calculations based on volumetric measurements to estimate left atrial function. The following calculations can be performed: (12–14)

- Total LA ejection fraction = [(Maximum LA volume - Minimum LA volume) / Maximum LA volume] × 100. This represents the reservoir function.

- LA expansion index = [(Maximum LA volume - Minimum LA volume)/Minimum LA volume] × 100. This also represents the reservoir function.
- Passive LA emptying fraction = [(Maximum LA volume – LA volume before the P wave in the ECG)/Maximum LA volume] × 100. It represents the conduction function.
- Active LA emptying fraction = [(LA volume before the P wave in the ECG – LA minimum volume)/LA volume before the P wave in the ECG] × 100. This represents the contraction function.

In addition to the anatomical parameters measured by conventional echocardiography, Doppler can be used to obtain indirect data on LA function, such as peak A wave and, using tissue Doppler, the A´ wave; however, these have the disadvantage of being dependent on loading conditions and age. (13,15)

In the review by F. Triposkiadis et al.,(16) four stages of LA dysfunction in patients with HF are proposed according to echocardiographic parameters.

- Stage 1: there is prolonged left ventricular relaxation, causing LA impaired passive emptying. On echocardiography, it manifests as preserved LA volumes and pressures with an increased Doppler A wave.
- Stage 2: there is an increase in LA pressure associated with a decrease in ventricular compliance. Doppler shows increased E wave relative to the A wave (pseudonormalization).
- Stage 3: there is marked LA dilation, and most ventricular filling occurs in early diastole. Doppler shows a more marked increase in the E wave relative to the A wave.
- Stage 4: it is mainly characterized by an increased risk of developing AF, with the consequent loss of LA pump function. Doppler shows E waves in the absence of A waves.

Three phases of the cardiac cycle can be measured using longitudinal LA strain: (17)

- Reservoir strain: it represents the isovolumetric contraction of the left ventricle, ejection, and isovolumetric relaxation. It is calculated by subtracting the peak value of the strain curve from the value at end-diastole, and is represented by a positive value.
- Conduction strain: it represents the time from mitral valve opening to the start of atrial contraction in patients in sinus rhythm (in patients with AF, it is considered until mitral valve closure). It is calculated by subtracting the strain value at the start of atrial contraction from the peak value of the strain curve, and is represented by a negative value.
- Contraction strain: it represents atrial contraction in patients with sinus rhythm and is calculated by subtracting the strain value at end diastole from the value at the onset of atrial contraction.

Pathan et al.(18) conducted a systematic review and meta-analysis to determine the normal values for LA strain, including 40 studies (2542 patients) with information on reservoir function; 14 studies (805 patients) with information on conduction function; and 18 studies (1005 patients) with information on contractile function. Analyses were carried out to rule out sources of heterogeneity and the following cut-off points were defined for normality: reservoir strain: 39.4% (95% CI 38.0%–40.8%), conduction strain: 23.0% (95% CI 20.7%–25.2%) and contraction strain 17.4% (95% CI 16.0%–19.0%).

An acceptable correlation has been described between atrial strain parameters measured by echocardiography and invasive measurements of intracavitary pressures. In a study by Lundberg et al.(19) in which 164 patients underwent right heart catheterization for suspected HF or dyspnea of unclear cause, it was concluded that measurement of LA global longitudinal strain is a useful and applicable tool for identifying elevated LA pressures and estimating left ventricular filling pressures. It has even been associated with the development of symptoms in patients in early stages of HF, as in the study published by Maffeis et al.(20) which included 185 patients in stages A and B of HF with preserved ejection fraction. The alterations in echocardiographic parameters such as indexed left ventricular (LV) volume, peak longitudinal strain, and contraction strain had a statistically significant association with the presence of symptoms in both stages.

Patients with HF with preserved ejection fraction often present varying degrees of secondary mitral regurgitation as a result of LA or LV dilation. In the study published by Tamargo et al. (21) including 280 patients undergoing invasive cardiac catheterization for exertional dyspnea evaluation, the prevalence of atrial dysfunction, defined as a reservoir strain below 24.5%, was twice higher in patients with mitral regurgitation compared with patients with competent mitral valves.

Magnetic resonance imaging is a tool of fundamental importance for studying atrial anatomy and function. The presence of late gadolinium enhancement at the LA level has been associated with an elevated risk of developing HF and stroke in this group of patients. In a study published by Zhou et al. (22) including 153 dialysis patients (96 with HF with preserved ejection fraction and 52 healthy controls) undergoing LA strain analysis using magnetic resonance imaging, the diagnostic accuracy for identifying patients with HF with preserved ejection fraction was increased over conventional parameters of atrial geometry and echocardiographic indices.

Figure 1 presents an overview of the different diagnostic methods for approaching atrial myopathy.

Prognosis

Structural alterations of the LA are associated with a poor prognosis in patients with HF, regardless of ejection fraction or the presence of arrhythmias. (23,24) In the general population, a 30% increase in left atrial volume is associated with 43% higher risk of develop-

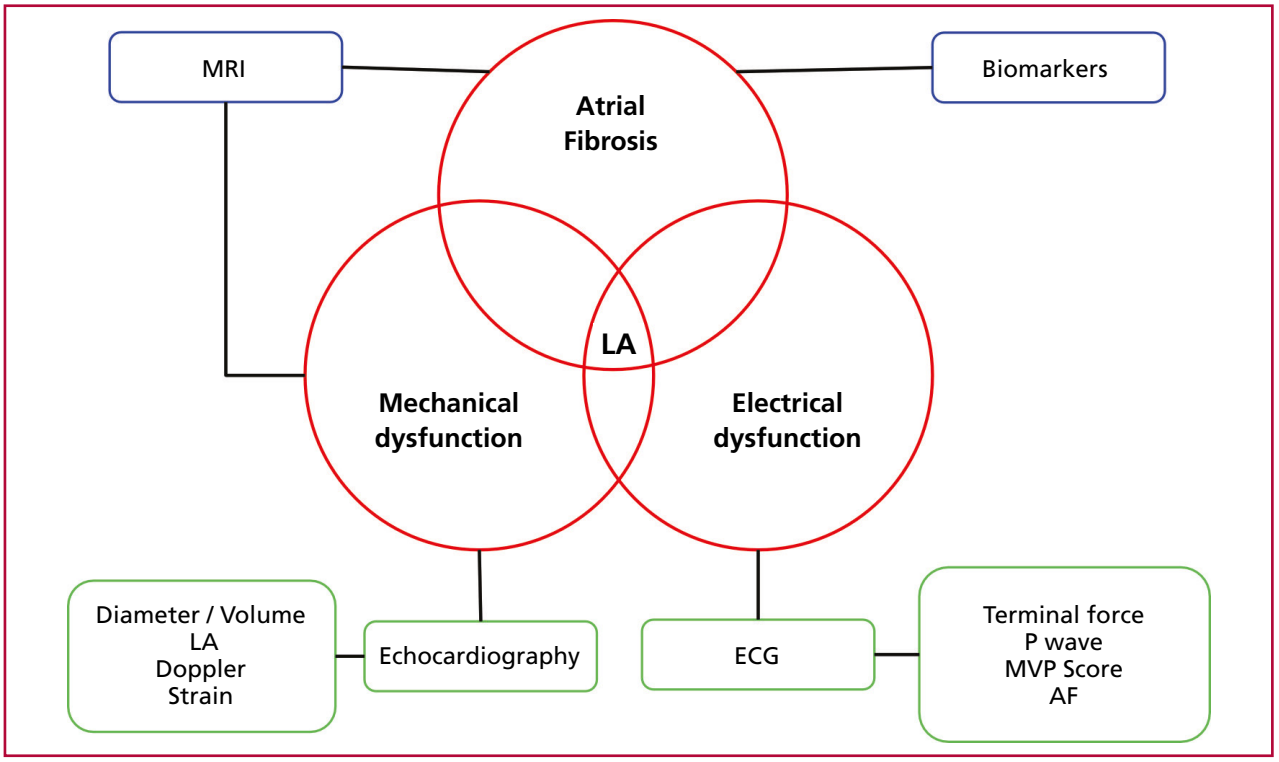
ing AF, and in patients over 65 years of age, it doubles the risk of developing HF.(4) In a systematic review and meta-analysis published by Khan et al. (25) that included 2 clinical trials and 20 observational studies with a total population of 1974 symptomatic patients with HF with preserved ejection fraction vs. 751 controls, alterations such as increased LA volume and reduced atrial strain were significantly more marked in patients with HF than in controls. However, this did not translate into greater prognostic capacity for the combined endpoint of all-cause mortality or hospitalizations for HF. On the other hand, in the Heart and Soul Study substudy which included 855 patients with stable coronary artery disease and left ventricular ejection fraction (LVEF) >50%; a decrease in the LA function index was associated with an increased risk of hospitalization for HF, regardless of variables such as age, classic cardiovascular risk factors, and other echocardiographic parameters such as indexed LA volume, LVEF and left ventricular mass index. (26)

Another substudy, published in 2016, considered patients enrolled in the TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) study. It included 357 patients with HF with preserved ejection fraction and echocardiography image quality sufficient to perform an AI analysis using speckle tracking. Among patients with normal atrial volume, 47% had abnormal atrial strain, compared with 71% of patients with atrial dilation. In an average follow-up of 31 months, lower values of peak atrial strain were associated with the primary composite endpoint of cardiovascular death, hospitalizations for HF, and resuscitated sudden cardiac death, in addition to hospitalizations for HF.(27)

In an analysis of the PARAMOUNT (LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction) study, which included symptomatic HF patients with preserved ejection fraction in functional class II – IV, 135 patients with sinus rhythm and echocardiographic images of sufficient quality to perform speckle tracking analysis were compared with 40 controls. Reservoir, conduction, and contraction strain values were significantly lower in patients with HF than in controls, even after adjusting for variables such as indexed LA volume, left ventricular end-diastolic volume, E´ value, and E/A and E/e´ ratios. In addition, lower values of systolic atrial strain were associated with a higher prevalence of hospitalizations for HF and a history of AF.(28)

Freed et al.(10) prospectively enrolled 308 patients who were hospitalized for HF with preserved ejection fraction and underwent echocardiography with speckle tracking analysis. All LA strain parameters

Fig. 1. Diagram of diagnostic methods for atrial myopathy



Using a pathophysiological approach to atrial myopathy based on three fundamental pillars—atrial fibrosis, mechanical dysfunction, and electrical dysfunction—an interpretive framework for diagnostic methods is developed.
AF: atrial fibrillation; ECG: electrocardiogram; LA: left atrium; MRI: magnetic resonance imaging; MVP: Morphology-Voltage-P

were predictors of hospitalization due to cardiovascular disease and death. Reservoir strain maintained prognostic utility regardless of AF history, LA volume, and left ventricular mass.

A systematic review and meta-analysis was recently published, including 25 cohort studies with a total of 252 504 patients, analyzing electrocardiographic, echocardiographic, and laboratory parameters associated with atrial myopathy and stroke. Results show that terminal P wave force in V1, LA diameter, reservoir strain, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were statistically associated with an increased risk of ischemic stroke. (29)

Therapeutic implications

There are currently no therapies with proven efficacy for the treatment of atrial myopathy. However, there are therapies for the treatment of closely related conditions such as HF and AF. In patients with symptomatic HF, both the European Society of Cardiology and the American Heart recommend the use of loop diuretics for symptomatic relief. (30,31) In patients with overt volume overload, LA pressure is typically elevated, so diuretic treatment is effective for symptomatic relief. However, the use of diuretics in euvolemic patients with the aim of lowering LA pressures can be harmful and may even lead to worsening renal function. (32)

In 2018, the REDUCE LAP-HF I (Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction) study was presented, including 94 patients with symptomatic HF with preserved ejection fraction and elevated end-expiratory wedge pressure during exercise testing. Patients were randomly assigned in 1:1 ratio to an interatrial shunt device (Corvia Medical) or control. At one month of follow-up, patients in the treatment arm had a greater reduction in wedge pressure compared with patients in the control group, though not reaching statistical significance, (change in wedge pressure of -3.5±6.4 mm Hg vs. -0.5 ±5.0 mm Hg, p=0.14). This did not translate into significant differences in terms of cardiovascular or cerebrovascular events.(33)

Later in 2022, the REDUCE LAP-HF II (Atrial Shunt Device for Heart Failure with Preserved and Mildly Reduced Ejection Fraction) study was published, in which 626 patients were randomly assigned in 1:1 ratio to placement of an atrial communication device or a placebo procedure. After a median follow-up of 2 years, no significant differences were observed in the composite primary endpoint of cardiovascular death, non-fatal ischemic stroke at 12 months post-randomization, HF events, or change in quality of life as measured by the Kansas City Questionnaire, nor in its individual components. The only point at which a benefit was demonstrated was in the change of functional class, but the patients who received the device experienced adverse cardiac events (cardiac death, myocardial infarction, cardiac tamponade, or emergency cardiac surgery) more frequently than the control group.(34)

CONCLUSIONS

Atrial myopathy is an underdiagnosed clinical entity that has important implications for the diagnosis and prognosis of patients with HF with preserved ejection fraction. However, its usefulness as a specific target for pharmacological and non-pharmacological treatment has not yet been demonstrated.

Funding

None.

Conflicts of interest

None declared.

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

Acknowledgments

We are deeply grateful to the Institute of Cardiovascular Medicine at Hospital Italiano de Buenos Aires.

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OPINION ARTICLE

Guided Decongestion Therapy in Acute Heart Failure: Towards a New Clinical Practice Based on Multiple Tools

Descongestión guiada en insuficiencia cardíaca aguda: hacia una nueva práctica clínica basada en múltiples herramientas

LUCRECIA MARÍA BURGOS[1, MTSAC], ROCIO CONSUELO BARO VILA[1], MIRTA DIEZ[1]

Acute heart failure (AHF) is one of the leading causes of hospitalization worldwide and is associated with high post-discharge morbidity and mortality. (1) Despite therapeutic advances, persistent signs of congestion at discharge are common and remain the most important and modifiable predictor of early rehospitalization, adverse events, and mortality. (2,3) This congestion, often subclinical, is frequently unnoticed on traditional physical examination, underscoring the need for more sensitive and reproducible assessment tools.

Traditional assessment methods used to determine discharge timing, such as changes in weight or physical examination findings, have proven insufficient to ensure adequate decongestion, as reflected by the high rates of rehospitalization within 30 days after discharge. (4) In clinical practice, the perception of "clinical stability" does not always equate to true decongestion, reinforcing the need to incorporate objective and reproducible measurements.

Historically, clinical assessment has been the cornerstone of therapeutic decision-making. However, multiple studies have demonstrated its limited sensitivity and prognostic accuracy. Subclinical congestion at hospital discharge may be present in up to 40% of patients, even among those considered clinically "compensated." (5) This dissociation between clinical findings and actual congestion led to the recognition of the concept of subclinical congestion and called into question the reliability of physical examination as the sole criterion for defining hospital discharge.

Achieving adequate decongestion is the central therapeutic goal during hospitalization for acute heart failure. Beyond symptomatic relief, achieving euvolemia provides the physiological basis necessary to tolerate and optimize prognostic-modifying therapies. However, defining and quantifying congestion remains challenging, as it may present as intravascular congestion, tissue congestion, or both, each with distinct diagnostic and therapeutic profile. (6)

In light of this limitation, complementary assessment tools have been developed. Biomarkers such as NT-proBNP (N-terminal pro-B-type natriuretic peptide), while useful for diagnosis and prognosis, have limitations as therapeutic guidelines during the acute phase. Clinical trials such as GUIDE-IT and PRIMA II demonstrated that a treatment strategy guided exclusively by NT-proBNP levels did not reduce mortality or rehospitalizations. (7,8) Other biomarkers—such as CA-125 (cancer antigen 125), sST2 (soluble suppression of tumorigenicity 2), and bio-ADM (biologically active adrenomedullin)—have been proposed as dynamic markers of volume overload, particularly in the outpatient setting; however, their clinical application remains limited. (9,10)

In recent years, the focus has shifted toward noninvasive tools. Lung ultrasound (LUS) enables the detection of B-lines indicative of pulmonary congestion with greater sensitivity than chest radiography. (11) Complementarily, inferior vena cava (IVC) ultrasound and Doppler assessment of hepatic, portal, and renal veins using the Venous Excess Ultrasound (VExUS) protocol allow objective evaluation of systemic intravascular congestion. (12–14) More recently, remote dielectric sensing (ReDS) has shown promising results for guiding decongestion management in hospitalized patients in a clinical trial. (15) These accessible and reproducible methods have demonstrated prognostic value across multiple cohorts.

In this context, our group conducted the CAVAL US-AHF (CAVA and Lung Ultrasound-guided Therapy in Acute Heart Failure) study, (16,17) a rand-

Rev Argent Cardiol 2026;94:61-64. https://doi.org/10.7775/rac.v94.i1.20977

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omized, single-center clinical trial conducted in Argentina that enrolled patients hospitalized for AHF. All patients underwent IVC and LUS assessments according to protocol at admission, during hospitalization, and at discharge. They were performed by trained physicians who were not involved in therapeutic decision-making. The images were analyzed and reported to the treating physicians by an external core lab blinded to the treatment assignment and patient identity. Congestion was classified into three categories (A, B, or C) according to ultrasound findings previously reported in the literature to be associated with an increased risk of hospitalization or mortality after discharge. Patients were randomly assigned and stratified by age and left ventricular ejection fraction into two groups: (a) a control group receiving standard care based on clinical, symptoms, and laboratory findings, and (b) an intervention group (CAVAL US) receiving standard care plus protocol-guided therapeutic adjustment based on IVC + LUS findings. The intervention algorithm included clinical assessment, the number of B-lines (assessed in 8 zones), and IVC parameters (diameter and collapsibility). Physicians in the intervention group had access to the ultrasound findings, whereas those in the control group remained blinded.

Prior to hospital discharge, a systematic checklist was implemented to ensure adherence to guideline-directed medical therapy, vaccination, patient education, and follow-up planning. All patients received structured counseling, including educational material and a written drug therapy plan. In both groups, outpatient follow-up visits were scheduled 7-10 days after discharge and at least monthly thereafter.

The primary endpoint of subclinical congestion at discharge (>5 B lines and/or dilated IVC) was observed in 13.3% of the CAVAL US group versus 66.6% in the control group ($p<0.001$), representing an 80% relative reduction. Similarly, the composite endpoint at 90 days (readmission, unplanned visit, or death) was significantly reduced (13.3% vs. 36.7%; $p=0.038$). This intervention was safe and not associated with a longer hospital stay.

Recently, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) proposed a multiparametric algorithm to assess decongestion at discharge, which includes three criteria: <5 B-lines on US, IVC diameter <21 mm with collapsibility >50%, and >30% reduction in NT-proBNP compared to admission. (3) These criteria were established based on recent prognostic studies and expert consensus. On this basis, we conducted a substudy recently published in the European Journal of Heart Failure. (18). According to the HFA-ESC criteria, patients were classified into two groups: optimal decongestion (IVC diameter <21 mm and collapsibility >50%, <5 B-lines on 8-zone LUS, and >30% reduction in NT-proBNP) and suboptimal decongestion (failure to meet any of the three criteria). The primary endpoint was a composite of HF rehospitalization, urgent visit due to worsening symptoms, or death at 90 days after discharge. Forty-five percent met all three optimal decongestion criteria. None experienced events during the 90-day follow-up, whereas 42.4% of patients with suboptimal decongestion reached the primary endpoint ($p<0.001$). No significant differences were observed between groups in furosemide dose at discharge, left ventricular ejection fraction, or use of guideline-directed medical therapy, suggesting that residual congestion may persist regardless of clinical assessment or treatment intensity. This analysis provides prospective evidence supporting the prognostic value of the HFA-ESC multiparametric algorithm and reinforces the applicability of an objective and guided decongestion strategy in routine clinical practice.

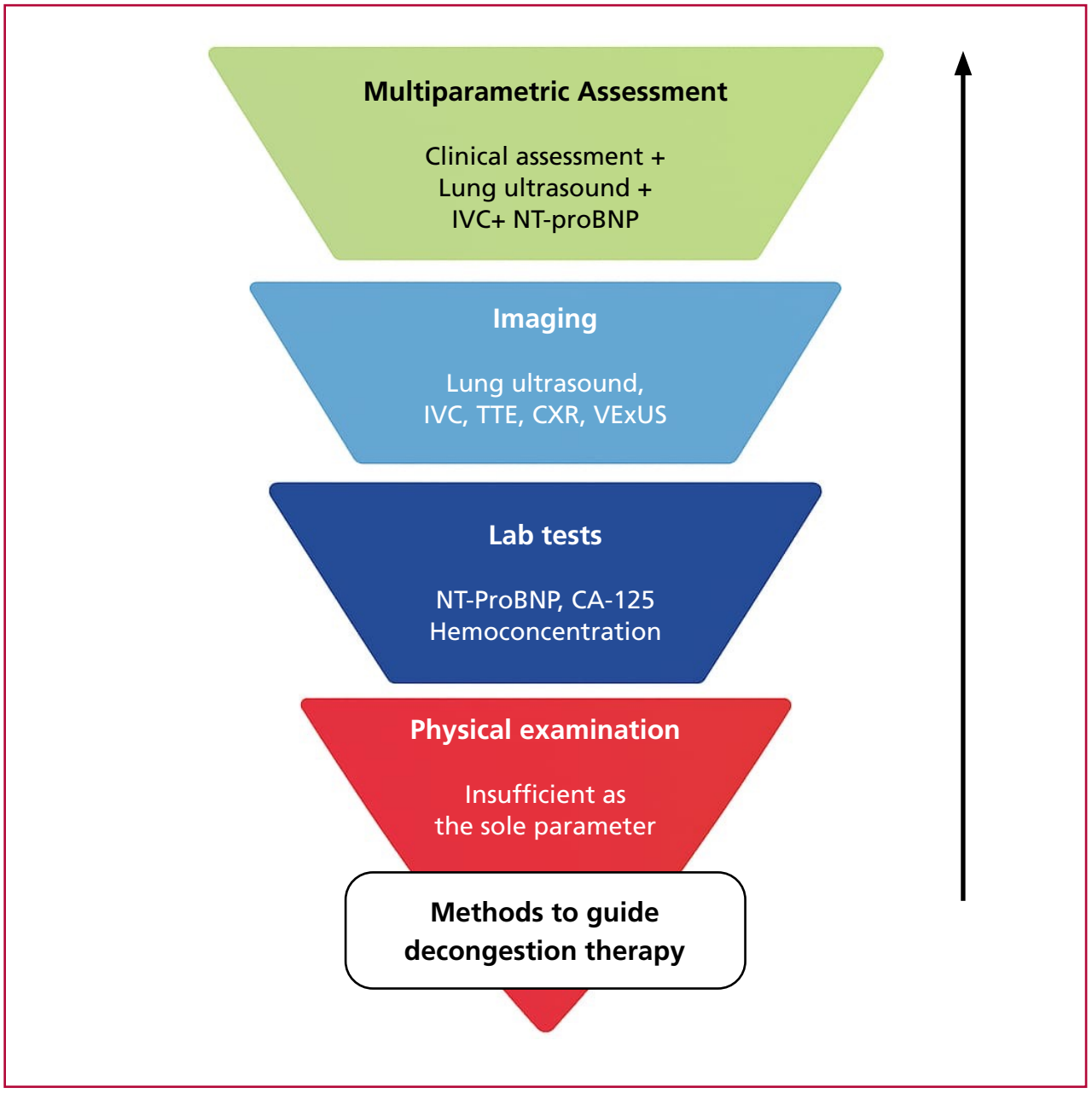
The incorporation of complementary tools does not represent unnecessary sophistication but rather an evolution toward more precise and reproducible medicine. Subclinical congestion is common, and its persistence after discharge remains one of the main determinants of adverse events. In this context, the integration of inferior vena cava and lung ultrasound with accessible biomarkers offers an objective, feasible, and high-impact clinical strategy, particularly in resource-limited health care systems.

Effective decongestion is not achieved with diuretics alone. Sodium retention reflects neurohormonal and inflammatory activation, which requires early and comprehensive initiation of guideline-directed prognosis-modifying therapy—angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose linked transporter 2 (SGLT2) inhibitors. (19) The STRONG-HF trial demonstrated that intensive up-titration of ARNIs, beta-blockers, and MRAs within the first weeks after discharge was not only safe but also significantly reduced mortality and rehospitalizations. (20) In a subanalysis of this trial, intensive titration of neurohormonal blockade was associated with more efficient and sustained decongestion at 90 days, together with a significant reduction in the risk of the primary endpoint. (21)

Guided decongestion therapy in acute heart failure must be precise, comprehensive, and reproducible. The integration of multiple objective tools combined with clinical criteria offers diagnostic synergy to achieve this goal. As illustrated in Figure 1, each of these pillars provides complementary information for a multiparametric assessment of congestion. Table 1 presents a clinical decalogue that summarizes the principles of this emerging practice integrating both evidence and clinical experience.

Achieving complete decongestion before hospital discharge is a decisive step toward reducing rehospitalizations and improving clinical outcomes. Residual congestion at discharge remains one of the strongest predictors of mortality and adverse events; therefore, its detection should be incorporated into the standard

Fig. 1. Assessment of Decongestion



CA-125: cancer antigen 125; CXR: chest X-ray; IVC: inferior vena cava;NT-proBNP:N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiography

Fig. 1. Decalogue of Congestion in Acute Heart Failure

1. Congestion is the key predictor of post-discharge events.
2. Subclinical congestion is common and associated with an increased risk of adverse events.
3. Physical examination alone is insufficient.
4. Congestion assessment should be multiparametric.
5. The HFA-ESC algorithm provides an objective framework.
6. Diuretics are necessary but not sufficient.
7. Guideline-directed medical therapy (GDMT) is an essential component of decongestion.
8. Decongestion is not equivalent to simply "removing water."
9. The vulnerable phase represents a critical window of opportunity.
10. Validating decongestion strategies in our setting is both feasible and necessary.

of care. However, the optimal assessment of decongestion and the appropriate strategies to guide treatment are not yet fully defined or standardized.

Recent literature indicates that no single parameter is sufficient. Therefore, a multiparametric assessment combining clinical, ultrasound, and laboratory tools—all of which are available, reproducible, and relatively low cost—is recommended. In health care systems such as those in Latin America, where pressure for early discharge is common and resources are often limited, the integration of lung ultrasound, inferior vena cava assessment, and biomarkers represents an objective, safe, and feasible strategy capable of improving decision-making and clinical outcomes.

In this context, the CAVAL US-AHF study and its substudy demonstrate that simple and effective evidence-based care models can be implemented to redefine how we assess congestion and determine the discharge timing. The true paradigm shift lies in incorporating this comprehensive approach into the standard of care. Moving from "treating decompensation" to "ensuring complete decongestion" before discharge represents a transition toward more precise, reproducible, and outcome-oriented medicine.

Conflicts of interest

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

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LETTER TO THE EDITOR

The Need to Include COPD as Cardiovascular Risk Modifying Factor in the Framingham Risk Score, ASCVD Risk Score and PREVENT Risk Calculator: A Call Based on the 2025 GOLD Guidelines

La necesidad de incluir la EPOC como factor modificador del riesgo cardiovascular en las escalas Framingham, ASCVD y PREVENT: un llamado desde las guías GOLD 2025

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Dear editor,

Chronic obstructive pulmonary disease (COPD) has traditionally been conceptualized as a pulmonary disease closely linked to smoking and characterized by chronic airflow limitation. However, over the past two decades, a growing body of evidence has revealed that COPD is much more than a lung disease. It is a systemic disorder with significant implications for cardiovascular health. (1) In this context, the recently updated GOLD 2025 guidelines (2) propose a paradigm shift, explicitly recognizing COPD as a relevant cardiovascular risk factor. This raises an urgent need to adapt our cardiovascular risk assessment tools, such as the Framingham and ASCVD risk score, and the PREVENT risk calculator. (3-5)

The link between COPD and cardiovascular disease is not unknown. Longitudinal studies have consistently shown that patients with COPD have an elevated risk of major cardiovascular events, including acute myocardial infarction, heart failure, and sudden cardiac death. (5) This risk is independent of traditional risk factors such as hypertension, dyslipidemia, or diabetes mellitus, and appears to be mediated by pathophysiologic mechanisms specific to COPD, such as chronic systemic inflammation, endothelial dysfunction, intermittent hypoxia, and oxidative stress. The concurrence of COPD and cardiovascular disease has been demonstrated to result in increased morbidity and mortality, as well as complications in the clinical management and quality of life of patients. (2,6-11)

Despite this clear association, the cardiovascular risk scores most commonly used in clinical practice do not consider COPD as a predictive variable. The Framingham Risk Score is a widely used tool that takes into account traditional variables such as age, sex, total cholesterol and HDL, systolic blood pressure, antihypertensive treatment, smoking habits, and diabetes. Although the ASCVD risk score developed by the ACC/AHA takes into account ethnic and treatment factors, it does not consider respiratory comorbidities such as COPD. (4) The most recent PREVENT risk score also fails to consider this issue. (6)

The new 2025 GOLD guidelines offer robust clinical and epidemiological monitoring to reconsider this omission. In their new classification of COPD phenotypes and redefinition of risk, the guidelines emphasize that COPD increases cardiovascular risk, even in the absence of traditional factors. The predominant emphysema phenotype, frequent exacerbations, and coexisting hypoxemia are particularly highlighted as indicators of elevated cardiovascular risk. (2, 10-12) The omission of COPD in risk scores has tangible clinical consequences. A significant number of patients are underestimated in terms of their actual risk, which can result in a lack of indication for preventive therapies. These include the use of statins, antiplatelet agents, or renin-angiotensin system inhibitors, all of which have been proven to be beneficial in patients with high cardiovascular risk. This underestimation also affects decisions about intensifying blood pressure control or strategies for smoking cessation. (13,14)

Certainly, the aim is not to abandon existing tools but rather to complement them. Just as type 2 diabetes or chronic kidney disease are recognized as equivalents of cardiovascular risk, we propose that

Rev Argent Cardiol 2026;94:65-66. http://dx.doi.org/10.7775/rac.v94.i1.20975

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COPD—particularly in moderate to severe stages—be considered a relevant risk modifier, at least until predictive models are recalibrated to include this variable.

One possible path for this integration is the external validation of existing scores in cohorts of COPD patients, analyzing their discrimination ability and calibration. Validation studies could establish adjusted cut-off points or specific risk coefficients for COPD patients, as has been done previously with other clinical conditions. Multicenter research should be promoted to incorporate respiratory variables into cardiovascular risk prediction and develop specific or modified risk scores. Modern medicine is moving toward precision and personalization. Ignoring the interaction between organs and systems perpetuates a reductionist view of health. Including COPD as a cardiovascular risk factor in our clinical tools is not only a matter of scientific justice, but also a concrete action to reduce preventable events in a vulnerable population. As a medical community, there is an obligation to update our practices in accordance with emerging evidence.

Given all that has been mentioned, we urge scientific societies, guideline developers, and clinical scale builders to promptly update cardiovascular prediction tools to include COPD as a risk-modifying variable, in accordance with the GOLD 2025 guidelines. This adjustment will better reflect the clinical complexity of our patients and allow for more timely and effective interventions to prevent cardiovascular morbidity and mortality in people with COPD.

Conflicts of interest

None declared.

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

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SCIENTIFIC LETTER

Isolated Left Ventricular Apical Hypoplasia in an Asymptomatic 45-Year-old Woman

Hipoplasia aislada del ápex del ventrículo izquierdo en una mujer de 45 años asintomática

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Isolated left ventricular apical hypoplasia (ILVAH) is a rare congenital heart disease that was first described in 2004. (1) Approximately 40–50 cases have been reported to date. It is characterized by a spheroidal left ventricle (LV) with apical truncation, abnormal papillary muscles, and an elongated right ventricle that partially surrounds the left apex. (2,3). The congenital heart defect is usually isolated but may be associated with other congenital heart diseases in approximately 16% of cases. The clinical manifestations are variable. Children may present with serious symptoms, while adult patients may be asymptomatic or present with heart failure, arrhythmias, or even cardiac sudden death. (4) We present the case of an asymptomatic adult female patient with ILVAH and an electrocardiographic pattern suggestive of structural heart disease, which prompted the diagnostic workup.

A 45-year-old female patient sought medical care for preoperative risk assessment before an endoscopic procedure. She had no history of cardiovascular risk factors, and the physical examination was normal.

The 12-lead electrocardiogram (Figure 1) showed deep S waves in the right precordial leads (V1–V3), low QRS voltage in the left precordial leads (V4–V6), and no signs of hypertrophy or ischemia. Due to these findings, additional imaging tests were required.

The chest X-ray showed a cardiothoracic index of 0.42, a rounded LV apex, slightly elevated above the left diaphragm, with normal lung fields.

A transthoracic Doppler echocardiogram revealed a spheroidal LV with apical truncation and an elongated right ventricle surrounding the apex. The LV ejection fraction was 52%. Both atria were normal, and there were no abnormalities in the heart valves (Figure 2).

Cardiac magnetic resonance imaging (CMRI) was performed using a 1.5 Tesla Philips device with the Compressed SENSE protocol. The acquisition protocol included survey sequences, SSFP short-axis cine images, 2-, 3-, and 4-chamber views, native T1 mapping, T2-weighted sequences with the STIR technique, and late gadolinium enhancement (LGE).Image analysis was performed using Segment software.

The LV had a spheroidal and truncated morphology with hypoplasia of the left ventricular apex that was partially occupied by the right ventricle. Wall thickness was preserved. The LV ejection fraction was 49% (Simpson-CMRI). Right chambers dimensions and function were preserved. There was abundant supepicardial fatty material in the apex and absence of significant late enhancement or myocardial edema. Conclusion: findings consistent with isolated apical hypoplasia of the left ventricle (Figures 3 and 4).

A 24-hour Holter monitoring showed sinus rhythm and no arrythmias.

The exercise stress test was submaximal and negative for ischemia, and without arrhythmias.

Isolated LVAH is a rare congenital heart defect in children and adults. Although the etiopathogenesis is unclear, abnormalities in the ventricular partitioning process and hypoplasia of the apical trabecular component have been proposed. Associated mutations in the LMNA gene (p.Arg644Cys) and NEXN gene have been described, linked to related myocardial phenotypes. (5)

The clinical presentation is highly variable. A systematic review conducted in 2022 identified 37 patients, mostly pediatric or young adults, with ventricular dysfunction and frequent arrhythmias. (4)

In our case, the 45-year-old patient represents an

Rev Argent Cardiol 2026;94:67-69. http://doi.org/10.7775/rac.v94.i1.20976

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Fig. 1. 12-lead electrocardiogram: sinus rhythm, normal QRS axis, poor R wave progression and low QRS voltage in V4-V6.

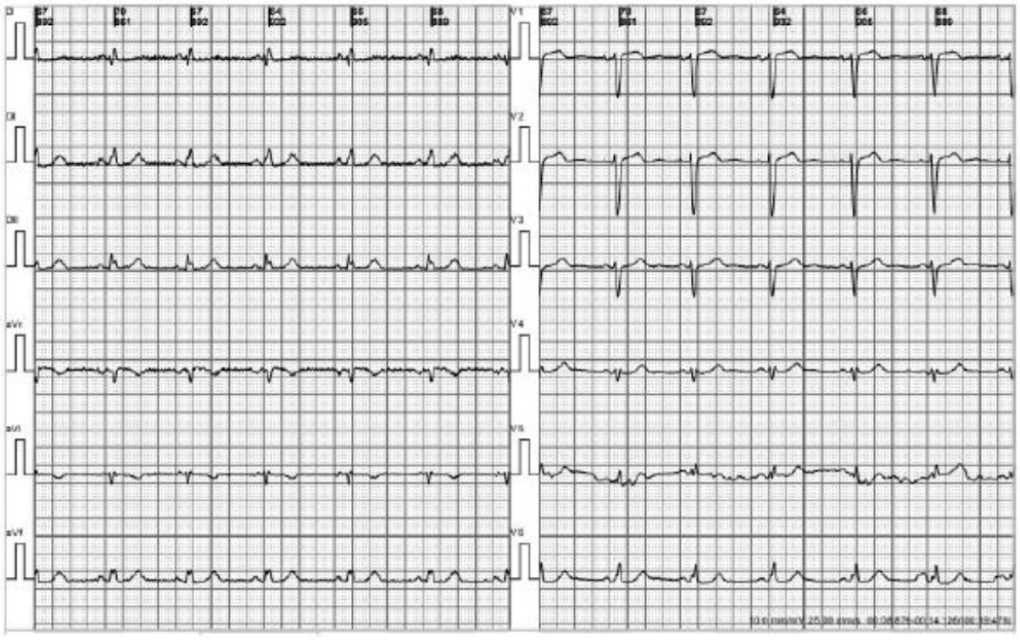


Fig. 2. Two-dimensional echocardiography, apical view

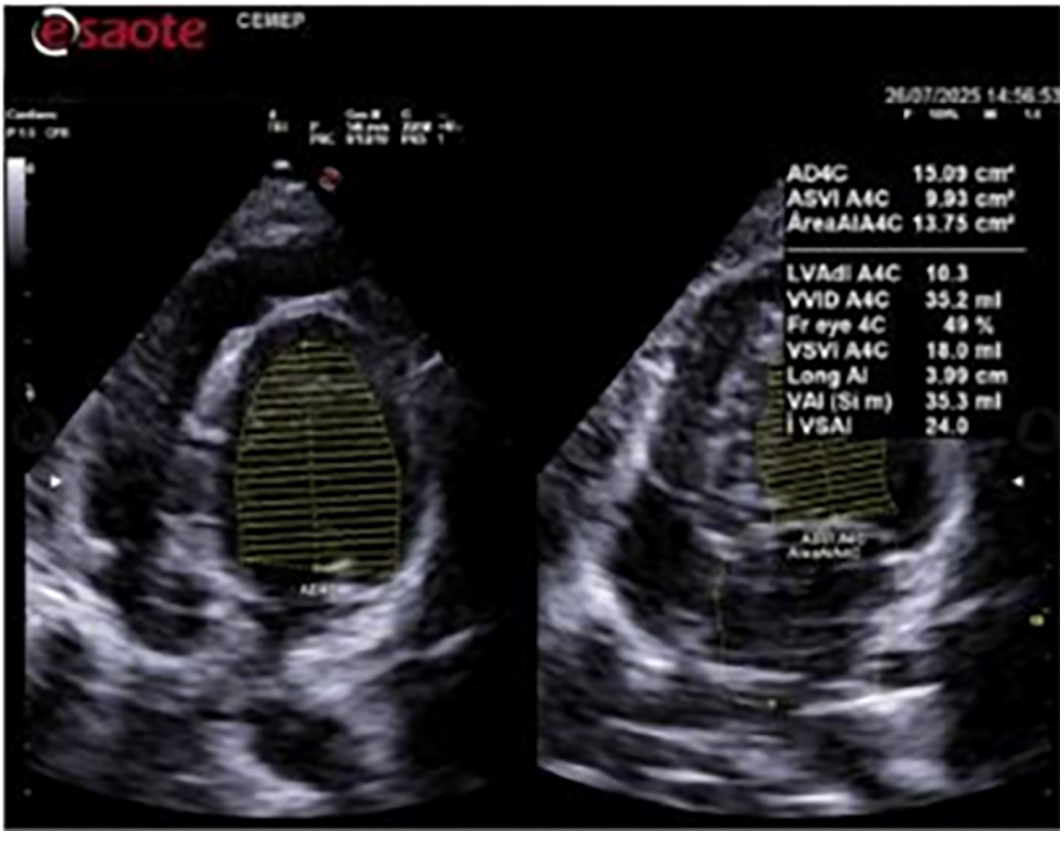


Fig. 3. Cardiac magnetic resonance imaging (4-chamber cine imaging): apical LV truncation with preserved contractility in basal and mid segments

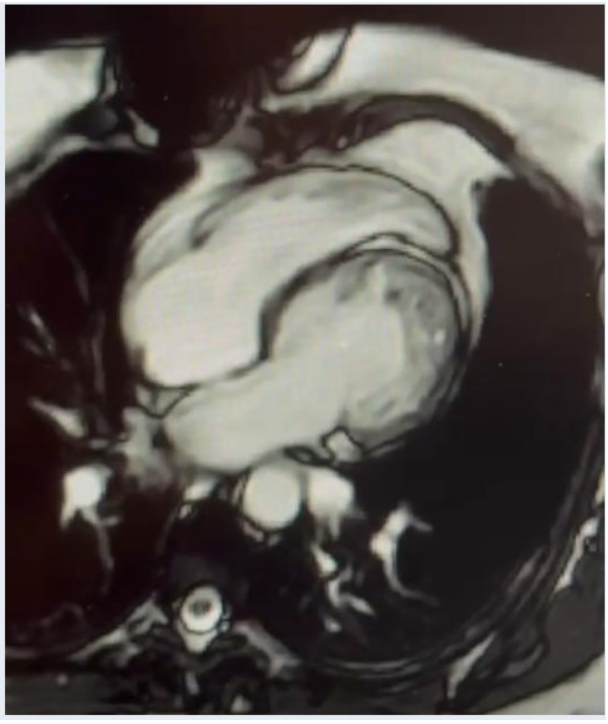
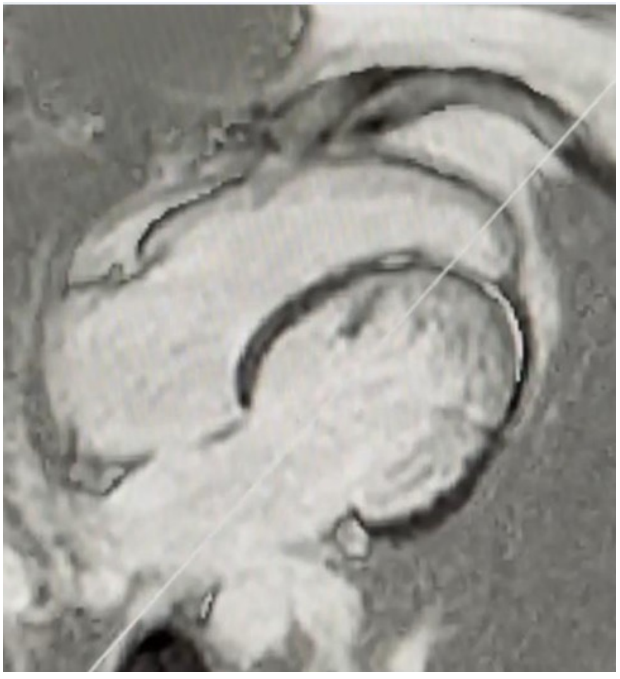


Fig. 4. Cardiac magnetic resonance imaging with absence of late gadolinium enhancement and myocardial fibrosis.



asymptomatic presentation in adults. Although there is no pathognomonic electrocardiographic pattern, the combination of deep S waves in the right precordial leads and low QRS voltage in the left precordial leads may prompt the search for structural abnormalities. Multimodality correlation between ECG, echocardiography, and cardiac magnetic resonance imaging is essential for establishing the diagnosis. This case report underscores the importance of integrating electrocardiographic findings with those of imaging tests for the identification of rare structural heart diseases.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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SCIENTIFIC LETTER

Septal Perforation as a Complication of Takotsubo Syndrome: Rare but Potentially Lethal

Perforación septal como complicación de síndrome de Takotsubo: rara, pero potencialmente letal

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Takotsubo syndrome was described as a transient ventricular systolic dysfunction by Sato et al. more than 30 years ago. (1) In most cases, it has a benign course with recovery of ventricular function within weeks or months.

However, complications are reported in up to 20% of patients, the most common being heart failure, mitral regurgitation, shock, and less frequently, atrioventricular (AV) block, free wall rupture, or septal rupture. (2) We present the case of a patient admitted in our institution for Takotsubo syndrome, who developed interventricular septal rupture during the course of the disease.

The patient was a 75-year-old woman with a history of hypertension and dyslipidemia, giant cell vasculitis, and a stroke in 2021 complicated by hemorrhagic transformation.

She consulted the emergency department for oppressive chest pain of 2 hours evolution. Her blood pressure was 100/60 mm Hg and the heart rate was 70 bpm. Physical examination showed no relevant findings. An ECG performed upon admission presented ST-segment elevation in the anterior and upper lateral walls, and blood tests revealed ultrasensitive troponin T level of 866 ng/dL and N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 1066 pg/mL. Given the suspicion of acute coronary syndrome, it was decided to refer her to the Hemodynamics Service on an emergency basis. Coronary angiography (CAG) exhibited coronary arteries with TIMI 3 flow and narrowing of the distal portion of the anterior descending artery, with no angiographically significant lesions. There were no signs of plaque rupture.

The patient's condition was stable, and she was transferred to the Coronary Care Unit, where a color Doppler echocardiogram was performed, revealing preserved left ventricular dimensions, akinesia of all apical segments, hypercontractility of the basal segments and mild to moderately reduced systolic function, with an estimated left ventricular ejection fraction (LVEF) of 45%. A mid-ventricular gradient of 45 mmHg was observed, and a pulmonary artery systolic pressure of 60 mmHg was estimated (Figure 1).

The patient remained stable until day 6, when she developed signs of decompensated heart failure. A new mesosystolic murmur at mitral focus was detected, which led to a new echocardiogram, revealing septal perforation in the apical septal segment with 12 mm diameter and 6 mm apical septum thickness (Figure 2).

After stabilization of the clinical condition with medical treatment, it was decided to proceed with surgery on the 16th day of hospitalization. The septal defect was closed with a cardiopulmonary bypass (CPB) time of 60 min and clamping time of 35 min. In the immediate postoperative period, the patient developed cardiopulmonary arrest that did not respond to resuscitation maneuvers.

Takotsubo syndrome, often associated with recent emotional or physical stress, (1) presents as transient left ventricular dysfunction, usually with hypokinesia, apical ballooning, and preservation of the basal segments.

This is usually the most common presentation, although there are atypical forms, such as the presence of left ventricular inferior or mid-ventricular hypokinesia, with increased contractility of the remaining segments.

This acute reversible cardiomyopathy mimics an acute coronary syndrome and imitates many of its characteristics, such as clinical presentation, electrocardiographic changes, and echocardiographic abnormalities.

It occurs in 90% of cases in postmenopausal wom-

Rev Argent Cardiol 2026;94:70-72. http://doi.org/10.7775/rac.v94.i1.20959

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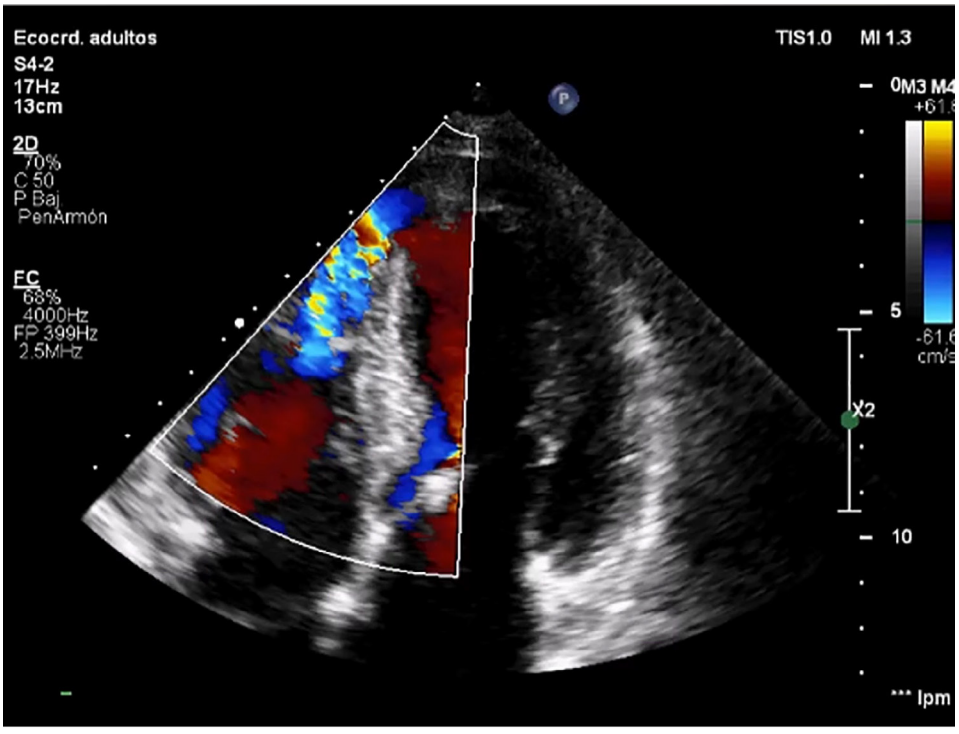
Fig. 1. Baseline echocardiogram

Fig. 2. Echocardiogram at the time of septal perforation



en between 58 and 75 years of age.

The Mayo Clinic diagnostic criteria, modified in 2008, (3) include:

1- Acute ECG changes with ST-segment elevation or T-wave inversion with modest troponin elevation

2. Transient alteration of left ventricular contractility, dyskinesia, hypokinesia, or akinesia, with or without apical involvement, extending beyond the territory of a specific coronary artery. It is occasionally, though not always, triggered by a stressful situation

3. Absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture

4. Absence of pheochromocytoma or myocarditis.

In the latest review of the 2018 diagnostic criteria, the presence of significant coronary artery disease is not considered a factor excluding Takotsubo syndrome, due to the high prevalence of coronary artery disease in this patient population. (4)

The pathophysiology of this syndrome is explained by a massive catecholaminergic discharge, which in women who have lost estrogen protection has a significant impact, generating calcium overload and free radicals at the cellular level, with loss of myocardial fiber contractility, inflammation, and left ventricular apical stunning. (5)

The symptoms that usually prompt a visit to the emergency department are chest pain and dyspnea, and on the ECG, ST-segment elevation, mainly in inferior and lateral leads, with only slightly elevated troponin values. (6) The diagnosis is confirmed by Doppler echocardiography showing predominantly apical ventricular dysfunction without coronary territory involvement and CAG without angiographically significant lesions that would justify such a wall motion disorder. (4)

The vast majority of patients recover from this episode and regain ventricular function within weeks or months. As mentioned above, some patients experience complications during the course of the disease, the most common being heart failure, shock, or mitral regurgitation. Cardiac rupture is very rare, but has a high mortality rate of over 85%. The factors that predict this complication are age, female sex, high blood pressure, persistent ST-segment elevation, elevated troponin levels, impaired ventricular function, and the presence of an intraventricular gradient. The review by Zalewska-Adamiec showed that the GRACE score and basal blood glucose levels (in non-diabetics) are also associated with cardiac rupture. (6) This serious complication usually occurs between days 2 and 8 of hospitalization and is usually diagnosed by the presence of a new mesosystolic murmur. (2) The course is torpid with a high mortality rate. There are no guidelines on the best type and timing of conservative vs. surgical treatment, so individualized evaluation is recommended. (5) There is also no consensus on the adequate time of surgery. Immediate surgical intervention is recommended in cases of hemodynamic decompensation, and in all other cases, by analogy with intraventricular communication after acute myocardial infarction, it is recommended to wait at least 14 days for tissue stabilization and a better postoperative prognosis. (5) As part of the treatment, the use of beta-blockers appears to have a protective effect and improve outcomes, but more specific studies are still needed in this regard. (2) The prognosis for septal rupture is more encouraging than that for free wall rupture, since if there is no hemodynamic instability, it can be managed with medical or corrective treatment with better survival.

To date, fewer than 20 cases of septal rupture due to Takotsubo have been published, (6) and given the increased incidence of the syndrome in our society, we recommend close and careful monitoring of patients at high risk for cardiac rupture. Early detection could improve the poor prognosis and high mortality of this complication.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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SCIENTIFIC LETTER

Myocardial Injury in Atrial Septal Defect Treatment. Is It Less Severe When Treating Patent Foramen Ovale?

Injuria miocárdica en el tratamiento de defectos del septum interauricular. ¿Es menor cuando tratamos foramen oval permeable?

ALEJANDRO CONTRERAS[1], FACUNDO LEDESMA[2], EDUARDO CUESTAS[2], ALEJANDRO PEIRONE[1]

The method of choice for treating atrial septal defects is catheterization. (1) To occlude both atrial septal defects (ASD) and patent foramen ovale (PFO), the most commonly used devices consist of a single nitinol wire that forms two discs with a center that joins both and occupies the defect itself. This wire mesh also contains polyester, a material that promotes endothelialization of the device. Catheter manipulation within the heart, as well as the pressure exerted by the implanted device on adjacent structures, causes myocardial injury characterized by increased troponin levels in the circulation. (2) Periprocedural myocardial injury has not been shown to be clinically relevant.

The treatment of ASD and PFO has similarities and some differences. The waist of the device used is different: it is 4-5 mm in PFO occluders, while in ASD closure devices it varies according to the size of the defect (between 8 and 38 mm), depending on the manufacturer. The ASD closure procedure may be slightly more complex in some cases, for example, the use of a balloon to measure the defect or the need to replace the device due to implant failure.

We conducted a retrospective and analytical study to compare troponin T concentration after PFO versus ASD closure procedures.

Patients undergoing percutaneous treatment of interatrial septal defects (PFO and ASD) between July 2020 and March 2025 were included in the study. Additionally, inclusion required an ultrasensitive troponin T measurement after percutaneous treatment to determine the presence of myocardial injury. Two groups were formed. The patent foramen ovale group (PFO-G) included patients treated for PFO with devices measuring 26 mm and 30 mm diameter discs and a small waist (Figure 1). In these patients, the disc size to weight ratio was 0.26 to 0.52.

The ASD group (ASD-G) consisted of all patients with ASD closure devices in which the disc size to weight ratio was within the same range as in patients treated for PFO.

Myocardial injury was defined as an increase in ultrasensitive troponin T above the 99th percentile without signs or symptoms of myocardial ischemia. Ultrasensitive troponin T was measured 6 hours after the completion of cardiac catheterization and its reference limit was 14 pg/mL.

The study was conducted in accordance with the standards for research involving human subjects established by the Ministry of Health of the Argentine Republic (Resolution 1480/2011) and the Declaration of Helsinki. Patients' identities and personal data were anonymized.

A total of 47 patients were included in the study, with median age of 41 years and interquartile range (IQR) 26-49, 25 of whom were women (53.2%). There were 22 patients in the PFO-G, with a median age of 46.5 years (IQR 41.2- 51.5), and 25 patients in the ASD-G, with a median age of 27 years (IQR 14-45). The table shows baseline characteristics of each group. Patients in the ASD-G were treated for right chamber dilation and/or symptoms, and patients in the PFO-G were treated for cryptogenic ischemic stroke or transient ischemic attack.

Patients in the PFO-G had a RoPE score of 7 points (IQR 6-7). Fluoroscopy time was 3.7 minutes (IQR 3.1-5.3) and the device disc size was 30 mm (IQR 26-30). The devices used were 26 and 30 mm, and all had a waist diameter of 5 mm. Nit Occlud PFO PFM Medical was always used. Patients in the ASD-G had a defect diameter of 13 mm (IQR 9-16); 6 patients (24%) had aortic edge deficiency and 11 (44%) had a flaccid posterior edge. In 6 cases (24%), a balloon was used to

Rev Argent Cardiol 2026;94:73-75. http://doi.org/10.7775/rac.v94.i1.20968

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Fig. 1. Box plot. Ultrasensitive troponin T 6 hours after completion of the percutaneous intervention. Patent foramen ovale (PFO). Atrial septal defect (ASD).

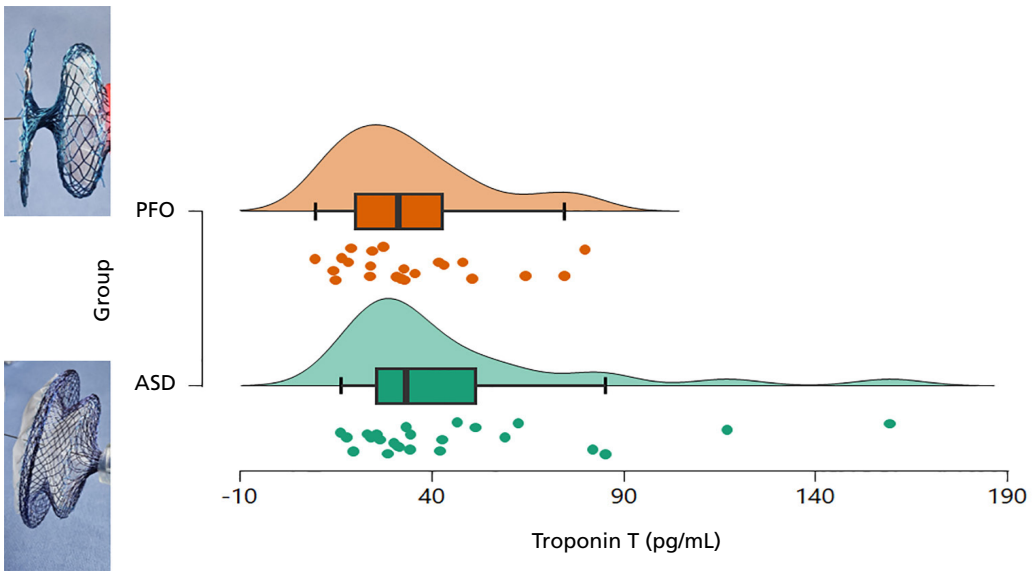

Table 1. Population characteristics

Variables	PFO group n= 22	ASD group n= 25	p value
Age (years), median (IQR)	46.5 (41.2-51.5)	27 (14-45)	< 0.001
Female gender, n (%)	12 (54.5)	13 (52)	0.861
Weight (kg), median (IQR)	72.5 (65-86)	75 (68-85)	0.822
MPAP (mmHg), median (IQR)	18 (15-21.5)	20 (18-22)	0.104
Aortic edge deficit, n (%)		6 (24)	
Flaccid posterior edge, n (%)		11 (44)	
Defect diameter (mm), median (IQR)		13 (9-16)	
Balloon measurement , n (%)		6 (24)	
Tunnel length (mm), median (IQR)	9 (7.2-11)		
Septum length (mm), median (IQR)	23 (21-26.7)		
Disc size (mm), median (IQR)	30 (26-30)	30 (24-33)	0.594
Disc/weight ratio, median (IQR)	0.40 (0.32-0.42)	0.40 (0.32-0.44)	0.833
ASA, n (%)	11 (50)		

ASA: atrial septal aneurysm; IQR: interquartile range; MPAP: mean pulmonary artery pressure.

measure the defect. Fluoroscopy time was 5.2 minutes (IQR 3.7-9) and the devices implanted in the ASD-G had a waist size of 18 mm (IQR 14-20) and discs of 30 mm (IQR 24-33). In all cases, the Nit Occlud ASD-R PFM Medical device was used.

Elevation of ultrasensitive troponin T was found in all patients 6 hours after the procedure. In the PFO-G, it was 31.3 pg/mL (IQR 20-1-42.7), and in the ASD-G, 33.3 pg/mL (IQR 25.7-51.3); p=0.234 (Figure). There were no clinical complications during patient follow-up.

In all percutaneous treatments of atrial septal defects, there is some degree of myocardial injury determined by an increase in the value of ultrasensitive troponin T. Two previous studies have included and compared troponin values after percutaneous treatment of ASD or PFO and have found no significant differences between the two groups, although in these

cases they were not matched for disc size or age. (2,3).

It cannot be determined which specific catheterization maneuvers could explain the presence of myocardial injury. Anatomopathological studies of patients who have suffered cardiac erosion reveal lacerations or perforations in areas of the left atrium that are not in contact with the device and are related to the manipulation of catheters within the cavity. Lacerations in the roof of the atrium or in the aorta in relation to the device discs have also been reported. (4,5) Although less frequently, cases of erosion with PFO closure devices have been found (6)

We can conclude that despite the lower technical complexity of PFO treatment, myocardial injury occurs to the same extent as in ASD treatment, although without clinical relevance.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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SCIENTIFIC LETTER

Preoperative Vascular Assessment in a Giant Left Atrial Myxoma: Significance of an Incidental Aberrant Right Subclavian Artery

Evaluación vascular preoperatoria en un mixoma auricular izquierdo gigante: relevancia de una arteria subclavia derecha aberrante incidental

EUGENIA P. CHONG VELÁSQUEZ[1], GABRIEL BIANCOTTI[2], LUIS BURGOS[3]

Myxomas are the most common primary benign tumors of the heart. They account for approximately 50% of primary cardiac neoplasms and occur in the left atrium in about 75% of cases. (1,2) Large myxomas (> 5 cm) can cause significant functional mitral valve obstruction, systemic embolization, and hemodynamic involvement, thus requiring rigorous and timely surgical planning.

An aberrant right subclavian artery (ARSA) is the most common congenital defect of the aortic arch, with an estimated prevalence of 0.5% to 2% in the general population. (3) In most cases, it has a retroesophageal course and is asymptomatic. However, certain anatomical configurations, especially those associated with Kommerell's diverticulum or a proximal origin, can interfere with surgical maneuvers on the ascending aorta or aortic arch. (3-5)

We present the case of a 44-year-old female patient with progressive dyspnea (class III of the NYHA), in whom transthoracic Doppler echocardiography revealed a pedunculated left atrial mass measuring 5.5 × 3.7 cm protruding into the mitral plane and a mean gradient across the mitral valve of 12 mmHg (Figure 1). These findings were consistent with significant functional obstruction.

A cardiothoracic computed tomography angiography (CTA) confirmed the diagnosis of left atrial myxoma and incidentally identified an ARSA with a retroesophageal course and no evidence of aneurysmal dilatation or compression (Figure 2).

The vascular anomaly did not require the surgical technique to be modified, and the tumor was resected via a median sternotomy with standard ascending aortic cannulation. Nevertheless, potentially complex anatomical configurations were ruled out during preoperative assessment to reduce intraoperative uncertainty.

At 12 months of follow-up, the patient remained asymptomatic, with no tumor recurrence on follow-up echocardiography and stable ARSA.

The coexistence of atrial myxoma and ARSA is extremely rare, with no established direct embryological link between these conditions. (4) However, this case illustrates a clinically relevant aspect: the systematic identification of aortic arch variants using CT angiography can provide strategic information even when the anomaly does not modify the surgical technique. In cases where anatomical structures are less favorable, failure to acknowledge these variants may result in unplanned intraoperative decisions or an elevated technical risk.

Beyond the rarity of the association, the key message lies in the integration of multimodal imaging as a structured tool for preoperative planning in structural cardiac surgery. (6) The combination of echocardiography and computed tomography optimizes anatomical and functional tumor characterization and allows for comprehensive vascular mapping, enhancing operative safety.

In this context, the presented experience raises a broader question: preoperative vascular assessment should be considered part of a systematic planning strategy in structural cardiac surgery, not just in cases with clinical suspicion of an anomaly. Detailed vascular mapping can transform incidental findings into a tool for clinical precision and operative safety.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Rev Argent Cardiol 2026;94:76-77. http://doi.org/10.7775/rac.v94.i1.20973

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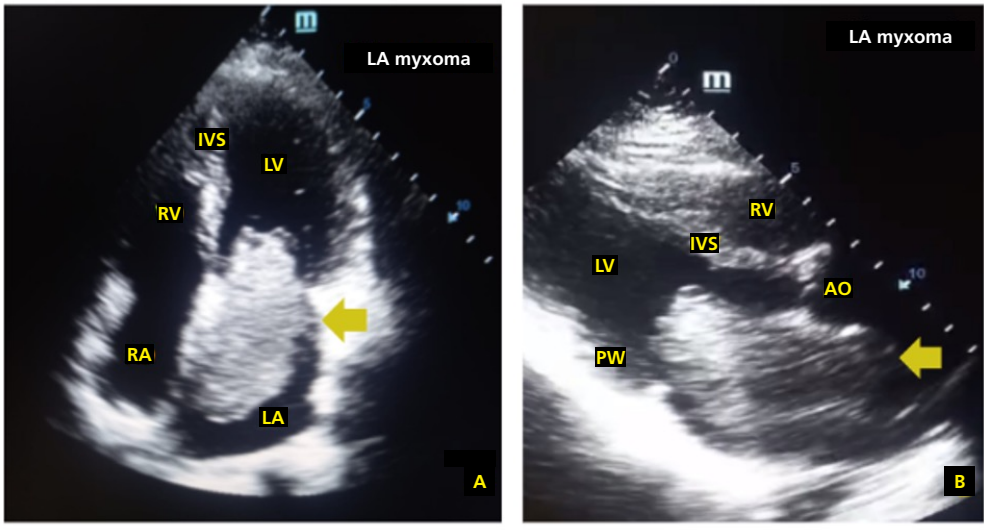
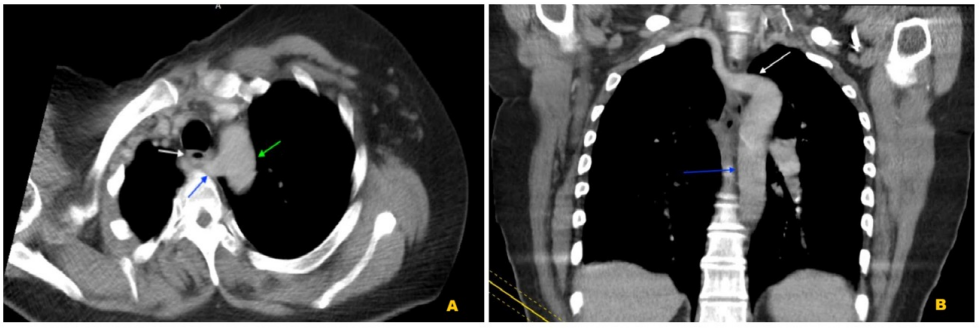
Fig. 1. 12-lead electrocardiogram: sinus rhythm, normal QRS axis, poor R wave progression and low QRS voltage in V4-V6.



RA: right atrium; LA: left atrium; Ao: aorta; PW: posterior wall; IVS: interventricular septum; RV: right ventricle; LV: left ventricle

Fig. 2. CT angiography: (A) Aberrant right subclavian artery with retroesophageal course. (B) Distal origin in the descending aorta



Ethical considerations

Not applicable

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National Data on Spontaneous Coronary Artery Dissection

Datos nacionales en disección coronaria espontánea

RAÚL ALBERTO LLANO[1]

Ischemic heart disease, particularly acute myocardial infarction, remains one of the leading causes of morbidity and mortality worldwide. Although atherosclerosis is the most common underlying etiology, other less prevalent conditions may also trigger acute coronary syndrome (ACS). Among these, spontaneous coronary artery dissection (SCAD) represents a significant cause, especially in certain patient populations. (1)

Although coronary angiography remains the gold standard diagnostic method, the development and increasing availability of intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have significantly improved diagnostic accuracy and enabled more appropriate treatment guidance. (2) However, given that these intracoronary imaging techniques are not always available or routinely used, SCAD remains a potentially underdiagnosed condition, with heterogeneous epidemiological registries. (3)

In our country, multicenter registries allowing adequate characterization of this condition have not been available to date, and the national literature mainly consists of isolated clinical case reports. (4) In this context, the registry published by Rodríguez Arias et al. represents a particularly relevant initiative, as it constitutes the first multicenter registry including both public and private centers. (5)

Consistent with international registries, this cohort shows a higher frequency of SCAD in young women, generally with few or no traditional cardiovascular risk factors. Likewise, the most common clinical presentation was non-ST-segment elevation acute coronary syndrome (NSTE-ACS), with the left anterior descending artery being the most frequently affected vessel.

Regarding treatment, the available evidence suggests that the therapeutic approach should be customized according to the patient's clinical presentation and coronary anatomy. A conservative approach is generally recommended, with revascularization reserved for specific situations such as persistent ischemia, hemodynamic instability, malignant ventricular arrhythmias, or involvement of the left main coronary artery (LMCA). In these scenarios, percutaneous coronary intervention is the primary revascularization approach, whereas coronary artery bypass grafting is reserved for specific cases such as LMCA dissection or extensive multivessel disease. Consistent with these recommendations, most cases derived from the registry were managed conservatively, with percutaneous coronary intervention involving stent implantation being performed in 46.1% of cases.

Although this registry includes a limited number of patients, its findings are consistent with international reports and represent a starting point for further advancing the understanding of this condition in our setting. Several clinical questions remain, particularly regarding the optimal duration of dual antiplatelet therapy, the potential role of anticoagulation, the indications for statin therapy and their therapeutic targets, as well as the strategies for clinical and imaging follow-up and the recommendations regarding physical activity.

In conclusion, this study is a valuable initiative for clinical and interventional cardiology in our country, as it not only allows our experience to be contextualized in relation to international registries but also represents an important step in further characterizing an uncommon but clinically relevant condition.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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Rev Argent Cardiol 2026;94:78-79. https://doi.org/10.7775/rac.v94.i1.20982

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AUTHORS' REPLY

Dear Dr. Llano

Thank you for your interest in the article by Rodriguez Arias et al. This work represents an initial effort by independent researchers to understand the characteristics of this condition in our country and the incidence of spontaneous coronary artery dissection (SCAD) in acute coronary syndromes. (1)

The pilot registry revealed a significant variation in the understanding of SCAD pathophysiology among cardiologists. This variation was reflected in the lack of consensus on SCAD diagnosis and management, as well as in the variability of antiplatelet therapy types and duration for these patients.

This pilot study enabled the development of the Argentine Registry of Spontaneous Coronary Dissection (DISCAR), which will begin in 2026 and will collect nationwide data on this condition. The DISCAR registry will use the support tools provided by the Research Area of the Argentine Society of Cardiology, and all public and private institutions in Argentina will be eligible to participate.

Likewise, we expect that the DISCAR registry will allow us to evaluate the use of intravascular imaging in uncertain cases to guide treatment. This will undoubtedly improve outcomes and provide a deeper understanding of the potential mechanisms responsible for SCAD.

Matías Rodriguez Granillo[MTSAC]
Principal Investigator
DISCAR Registry

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When the Brain Also Enters the Operating Room

Cuando el cerebro también entra en quirófano

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Postoperative delirium is one of the most frequent and complex complications and, paradoxically, one of the least integrated into routine clinical reasoning. Far from representing a transient or merely behavioral phenomenon, its occurrence is consistently associated with increased mortality, longer hospital stays, higher healthcare costs, persistent functional impairment, and long-term cognitive decline. (1) Despite this, it is still frequently interpreted as an epiphenomenon of surgical stress, more tolerated than anticipated and more treated than prevented.

In this context, the study by Crippa et al., based on data from the ARGEN-CCV national registry, provides robust local evidence on the incidence of postoperative delirium and its independent predictors in patients undergoing cardiovascular surgery. (2) The identification of variables such as prior coronary artery disease, postoperative sepsis, atrial fibrillation, and prolonged mechanical ventilation enables a shift from epidemiological description to clinically meaningful risk stratification, with direct implications for routine clinical practice.

Rev Argent Cardiol 2026;94:79-80. https://doi.org/10.7775/rac.v94.i1.20984

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Beyond its specific findings, the conceptual value of the study lies in reinforcing an integrative view of delirium as an expression of systemic vulnerability. The brain, like the heart or the kidney, responds to surgical trauma through biological mechanisms that include systemic inflammation, endothelial dysfunction, alterations in cerebral perfusion, neurohormonal activation, and loss of cognitive reserve. (3) In this sense, cardiovascular surgery may be understood as a true "biological stress test" capable of revealing previously compensated vulnerabilities.

The association among delirium, sepsis, and postoperative atrial fibrillation is not coincidental. These events share a common inflammatory and hemodynamic substrate, with direct effects on cerebral autoregulation. Similarly, the need for prolonged mechanical ventilation not only indicates greater clinical severity but also sustained exposure to sedatives, complex analgesia, and disruption of the sleep-wake cycle, factors which play a central role in the pathophysiology of delirium. (4)

From a clinical perspective, this study challenges the treating team to broaden the focus of perioperative care. Early identification of high-risk patients requires the implementation of multimodal preventive strategies, including hemodynamic optimization, rigorous infection control, protocolized mechanical ventilation management, systematic assessment of frailty, and structured cognitive monitoring. (4)

In short, the study by Crippa et al. reminds us of an uncomfortable but necessary truth. In contemporary cardiovascular surgery, technical success is no longer measured solely by the patency of a graft or the correction of a valve. The brain also enters the operating room. When delirium occurs, it does not represent an isolated accident but rather the intersection of biology, vulnerability, and the limits of the healthcare model. (2,5) Recognizing it early is not merely an academic exercise; it is a deeper way of caring for the patient.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

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AUTHORS' REPLY

We sincerely appreciate the comments by Drs. Escalada Lesme and Cabral on our article "Postoperative Delirium in Cardiovascular Surgery: Analysis of Predictive Factors Based on The ARGEN-CCV National Registry," as well as their careful reading and clinical reflections presented in their letter. We fully agree that postoperative delirium is a complication of major relevance in cardiovascular surgery, not only because of its frequency, but also because of its impact on clinical outcomes, functional recovery, length of hospital stay, and mid- and long-term prognosis.

As the authors of the letter point out, one of the key contributions of our study was the identification of factors associated with clear clinical utility, including prior coronary artery disease, postoperative sepsis, atrial fibrillation, and prolonged mechanical ventilation. We believe that these findings, derived from a national registry, contribute to improved risk stratification and reinforce the need for more systematic monitoring in the perioperative period. In this regard, we agree on the importance of promoting multimodal prevention and monitoring strategies, with particular attention to modifiable postoperative factors.

We also share the view that delirium should not be regarded as an isolated phenomenon but rather as an expression of increased biological vulnerability in patients undergoing cardiovascular surgery. In this regard, early recognition and the implementation of multimodal preventive strategies represent key elements of comprehensive patient care.

We once again would like to thank Drs. Escalada Lesme and Cabral for enriching the discussion of our work and for highlighting a clinical problem that deserves increasing attention in routine clinical practice.

The authors

Lessons from the ARGEN-IAM-ST Registry

Lecciones del registro ARGEN-IAM-ST

PABLO SANTILLI[1, 2], SOL GARCÍA TORO[1, 2]

The publication of the analysis by Castillo Costa et al. from the ARGEN-IAM-ST registry is a key tool for identifying opportunities for improvement and growth. (1) Documenting that 7.5% of patients with ST-segment elevation myocardial infarction (STEMI) are admitted after cardiac arrest (CA)—approximately one in thirteen cases—is essential for understanding the complexity of this condition.

However, to interpret this data correctly, we must consider selection bias. The registry captures information from centers affiliated with the Argentine Society of Cardiology (SAC) and the Argentine Federation of Cardiology (FAC), both institutions with an academic profile. In terms of volume, the registry included an average of 682 patients per year. When this data is compared with the estimated national incidence for a population of 46 million inhabitants—between 18 000 and 22 000 STEMI cases per year according to Western epidemiological standards—it becomes clear that only a fraction of the national reality is being captured. This is relevant data because, if mortality in the shock and cardiac arrest subgroup reaches 71% in the most complex centers, it is worth asking what happens in the remaining cases.

From the interventional cardiology perspective, the unfavorable course of these cases despite an adequate overall reperfusion rate (85% in the group with CA) suggests that simply opening the culprit artery is insufficient in the setting of hemodynamic collapse. In high-complexity centers in other countries, the use of advanced mechanical circulatory support (MCS) has begun to improve outcomes in this scenario. The DanGer Shock trial demonstrated that microaxial pump support (Impella) reduced mortality in cardiogenic shock to 45.8% versus 58.5% with standard therapy; a substantial difference compared with our setting, where intra-aortic balloon pump is often the only available resource, if any. (2) However, large-scale implementation of these measures is complex and entails considerable costs for the health system.

Therefore, an initial focus within our healthcare system should be to ensure that all patients receive a reperfusion rate comparable to those reported in this registry as early as possible. To achieve results similar to those reported in registries such as those of the European Society of Cardiology (ESC), (3) with reperfusion rates above 90%, or the SWEDEHEART registry, where primary percutaneous coronary intervention exceeds 90%, (4) it is imperative to further expand initiative such as Stent-Save a Life!. (5) This involves strengthening myocardial infarction reperfusion networks and the door-to-balloon programs but above all prioritizing the pharmaco-invasive strategy as an effective and equivalent alternative in our setting. In cases of ambulance transfers with prolonged delays or unpredictable logistics that threaten optimal reperfusion times, early thrombolysis should be considered a clinical priority, ensuring early arterial patency and reducing total ischemia time.

This registry and its analysis represent important tools to improve patient outcomes in our setting and constitute a step toward transforming fragmented care networks into a system that prioritizes reperfusion and early referral to high-complexity centers.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

We thank Drs. Santilli and García Toro for their valuable comments on our work. Although no national registries currently assess out-of-hospital mortality in acute myocardial infarction (AMI), community-based registries (1) suggest that it is approximately 40%, with severe arrhythmias (ventricular tachycardia [VT] / ventricular fibrillation [VF]) representing the leading cause.

We fully agree with Drs. Pablo Santilli and Sol Garcia Toro that the organization and sustainability of myocardial infarction reperfusion networks, tailored to the characteristics of each community, should be a public health priority in our country.

According to the ARGEN-IAM-ST registry, the largest and most continuously maintained registry in our country, the total ischemia time is prolonged, with a median of 310 minutes (interquartile range [IQR] 185-595) among patients undergoing percutaneous coronary intervention (PCI) and 165 minutes (IQR 90-287) among those treated with fibrinolytics. This likely explains the absence of differences in mortality between the strategies used. (2,3)

The opinion of the treating physicians participating in this registry was unequivocal: delays in initiating a reperfusion strategy occurred in approximately half of the cases (60% among patients undergoing PCI and 62% among those undergoing thrombolysis).

Population education is also essential to reduce delays in seeking care. In the ARGEN-IAM-ST registry, the median delay was 130 minutes (IQR 60-305), with the main causes being the patient's delay in seeking medical assistance (60% of cases) and delays in ambulance arrival (25%). (3)

In this context, public awareness of the basic symptoms of myocardial infarction, training in basic cardiopulmonary resuscitation, and greater availability of automated external defibrillators are of fundamental importance.

Any strategic plan aimed at achieving timely reperfusion in myocardial infarction should be carefully designed to reduce ischemia times and decrease both out-of-hospital and in-hospital mortality. This requires coordinated efforts among all stakeholders involved in the logistics of care, as well as the participation of scientific societies to provide a framework for a comprehensive care strategy.

Víctor Mauro[MTSAC]
on behalf of the authors

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Ventricular Arrhythmia Alerts in Remote Monitoring: Prognostic Markers or Triggers for Clinical Decision?

Alertas de arritmias ventriculares en la monitorización remota: ¿marcadores pronósticos o disparadores de decisiones clínicas

ENRIQUE MONJES[1], FEDERICO ZABALA[1], DANIEL CAMERINI[1]

Remote monitoring (RM) of cardiac implantable electronic devices has become established as a standard of care over the past decade. This system enables early detection of arrhythmic events and optimizes follow-

Rev Argent Cardiol 2026;94:82-83. https://doi.org/10.7775/rac.v94.i1.20970

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up of patients with implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D). However, debate persists regarding its impact on "hard" clinical outcomes, particularly mortality.

In this context, the study by Guzmán et al., published in the Argentine Journal of Cardiology (RAC), provides relevant real-world evidence by analyzing the prognostic value of ventricular arrhythmia alerts detected through RM in a cohort of patients with ICD and CRT-D. (1) The authors demonstrated that alerts for non-sustained ventricular tachycardia, ventricular tachycardia, or ventricular fibrillation were significantly associated with increased all-cause mortality, with an early and sustained separation of the survival curves. This finding reinforces the concept that remote monitoring provides clinically relevant information, beyond the mere detection of events, reflecting the progression of the underlying heart disease.

A notable aspect of the study is its observational nature and its conduct in a routine clinical practice setting, which allows it to reflect a heterogeneous and complex population, that differs from those typically included in randomized clinical trials. In this regard, the results are consistent with large observational registries, such as the ALTITUDE study, which identified ventricular arrhythmias and defibrillator therapies as adverse prognostic markers. (2) Similarly, previous studies have shown that the occurrence of appropriate shocks is associated with a significant increase in mortality, regardless of the underlying etiology of heart disease. (3)

However, the study also highlights a relevant clinical limitation: in most cases, the detection of ventricular alerts did not lead to substantial changes in therapeutic management. This finding raises a key question for daily practice: is early identification of high-risk patients sufficient if this information is not integrated into a structured intervention strategy?

The true value of RM may lie not only in the generation of alerts, but also in their interpretation within the patient's overall clinical context. Ventricular arrhythmias should act as a trigger for a comprehensive reassessment, including optimization of heart failure therapy, review of device programming, and consideration of advanced strategies such as catheter ablation or multidisciplinary management. (4)

In conclusion, the study by Guzmán et al. reinforces the role of ventricular alerts detected through RM as prognostic markers in patients with ICD and CRT-D. The future challenge is to translate this information into concrete clinical decisions that not only improve risk stratification but also modify the natural history of the disease, in line with current international consensus recommendations. (5)

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AUTHORS' REPLY

Dear Editor

We thank Drs. Monjes, Zabala, and Camerini for their comments. We agree with their interpretation that the true value of remote monitoring (RM) lies in the clinical response it generates.

Although the alerts were associated with higher mortality, in 60% of cases they did not lead to changes in therapy. This "clinical inertia" does not reflect lack of interest, but rather the absence of structured workflows. While dedicated units exist in many international centers, in our setting RM often relies on individual effort. The disconnection between those who receive the alert (usually the electrophysiologist and fellows in training) and those who manage the underlying disease may hinder timely intervention.

The challenge is to evolve from "technical surveillance" to "proactive clinical management." Alerts should not remain merely prognostic data points, but should instead act as triggers to bridge the gap between remote diagnosis and therapeutic action.

Sincerely,

Juan Pablo Guzmán MTSAC,
on behalf of the authors

Opening Speech of the 2026 Presidency of the Argentine Society of Cardiology

Discurso inaugural de la presidencia de la Sociedad Argentina de Cardiología 2026

Distinguished members of the Argentine Society of Cardiology, colleagues, friends, and families:

It is a great honor to address you as the future president of this institution, which has been a beacon in the scientific development of cardiovascular medicine since its founding. I consider it a great privilege to receive the recognition of my colleagues, which is not only a source of pride but also a wonderful challenge that I will undertake with responsibility, fairness, and respect for others.

To chart the path forward, we must look back to our profession's origins and the giants on whose shoulders it was built. Our history is inextricably linked to Professor Bernardo Houssay, a visionary leader whose influence extended beyond his specialty. In addition to promoting experimental science in Argentina and establishing CONICET (National Council for Scientific and Technical Research) he was a catalyst for excellence. He left us with an unshakeable creed: "Science is not expensive; ignorance is expensive." That scientific and rigorous spirit found its highest expression on April 9, 1937, with the establishment of this illustrious Society. The founders not only created an entity, but also established a pact of commitment to teaching, research, and the professionalization of cardiologists.

Our mission is to generate and disseminate scientific knowledge through research, continuing education, and specialized training. We promote medicine based on humanistic values and ethical principles to optimize health outcomes, manage resources efficiently, and ensure equitable access to cardiovascular care for patients.

In these new times, leading means navigating complexity. It's not just about hierarchy; it is also about influence, empathy, active listening, and vision. We are here to serve, not to be served. We need to continue building leadership anchored in the one thing that defines us: virtue.

I have heard the phrase "politically correct" for a long time. Personally, I would add another question: "Is it humanly correct?" On this point, I would argue that if something is humanly incorrect, it cannot be sustained just because it is politically correct; the end does not always justify the means. I emphasize the importance of searching for the truth, and being authentic and consistent. It is essential to align what I think, what I say, and what I do. In his book "The Oblivion That We Will Be", writer Héctor Abad Faciolince describes the importance of being authentic and not a hybrid between a horse and a cow, which neither trots nor gives milk. I believe cooperation is a more revolutionary strategy than competition in our Society setting. Self-improvement is useless if it is not used to help others.

The recently designed Strategic Plan is a general framework based on consensus that allows decisions to be made in a coherent and consistent manner to achieve the set objectives. To be sustainable, these guidelines must meet equity and accessibility criteria. As a leader, it is important to determine what and when, not how, as we have carefully selected the individuals responsible for this.

Ours is a time of fascinating and challenging crossroads. We are not facing a period of change; rather, we are experiencing a change of era. Cardiology has evolved exponentially. We now use technologies that would have been considered science fiction just a decade ago, ranging from artificial intelligence that analyzes risk patterns to the most sophisticated imaging techniques. However, amid this whirlwind of progress, we risk dehumanizing care by replacing attentive listening with perfect algorithms. The Humanics model, developed by Joseph E. Aoun, delves deeper into this aspect of the teaching-learning process. In today's technological world, technology will continue to be indispensable, data must be transformed into a language that can be decoded, the human dimension must be prepared to meet the challenge of serving as the balancing point where judgment, empathy, and ethics allow technology and data to be oriented toward the greater good. There will be no better organizations without better human beings.

To achieve greater coordination and integration between all its areas and district councils, the Society has redesigned its structure. To this end, it has established three pillars of action: Education, Research, and the SAC Membership Area.

Rev Argent Cardiol 2026;96:84-87. http://dx.doi.org/10.7775/rac.v94.i1.20978

Future education will be one that raises more questions rather than merely accumulating content. We must educate not only brilliant technicians, but also prudent and ethical doctors. The challenge is profoundly human. Following this path, the Teaching Area will continue to focus its efforts on creating the University Education Institute. Additionally, we will fulfill the longstanding desire of residents in districts offering the SAC Postgraduate Cardiology Course to obtain the specialty certificate from our society, with university endorsement. Similarly, it is time to update the Consensus on Cardiology Education. We will achieve this goal with the help of the advisory faculty, which has done significant work this year in defining the profile of the cardiologist and the teaching course for educators.

The Research Area will continue to develop a national network of researchers and proceed with two new registries related to cardiomyopathies and valvular heart disease within the framework of the European Society of Cardiology registries. Efforts will be made to increase the production of studies addressing the epidemiological reality in Argentina and the specific needs of our population. Additionally, the regulations governing research projects have been updated to ensure pluralism in data usage and publication participation, both of which are supervised by the society.

The quality of the new consensus statements to be developed in 2026 will be enhanced by integrating the GRADE methodology progressively and adapting the recommendations to the reality of medicine in Argentina. Additionally, new leaders will be promoted to develop the various guidelines, leveraging the experience of previous leaders as advisors.

Leadership should honor members' careers. The SAC's values must be reflected in every process, from admitting new members to electing authorities in different areas. The Area of Professional Career Development for Members, organized in 2025, will initiate its activities. The aim is to define the career training of our cardiologists by improving their managerial knowledge, leadership skills, research abilities, and teaching and advocacy skills.

We will expand implementation of the strategic plan to define work processes in the administrative, accounting, and IT areas. We will invest in staff training, task definition, workplace improvement and integration, and IT system updates and synchronization.

Another planned action is organizing a fundraising campaign to enhance the value of the Society's auditorium. We will complete the process of creating the SAC museum, which reflects our origins and history.

Our actions will focus on promoting the implementation of the "Networks that Save Lives" program, whose purpose is to guide and support cities, municipalities, and regions in Argentina in the design and implementation of local or regional acute myocardial infarction care networks, based on the recommendations of clinical practice guidelines and adapted to their local resources and capabilities.

The federalization of the Argentine Society of Cardiology is a growing reality that must integrate opportunities with meritocracy. In 2025, SAC Country professionals organized congresses, and by 2026, this objective will be consolidated by incorporating spaces for the participation of SAC districts in the hierarchical area of the scientific committee. The Congress on Cardiometabolism, the Digital Health Meetup, the Conference on Geriatric Cardiology, Cardiology Day, and the Argentine-Paraguayan Conference will be held in different districts within SAC Country.

The International Relations Area will continue to consolidate following the incorporation of former presidents and young leaders. The goal will be to strengthen the action plan, build on the contacts established in previous administrations, and maintain continuity. Along with our extensive list of international connections, including the ESC, AHA, ACC, South American Society, SIAC, and Latin American societies, our international activities will include the LATAM ESC 2026 Conference, an agreement with the IAS (International Atherosclerosis Society), and the initiation of collaborative efforts with the Asian Heart Society and the Chinese Cardiovascular Association.

The Argentine Society of Cardiology and the Argentine Cardiology Foundation should collaborate in a coordinated manner within their respective areas of expertise. We must abandon our past fears and embrace disruption in pursuit of higher goals. The Society will ensure that this new modality of integration is developed with respect and magnanimity. We will unify the identification logo with a new concept of the "brand manual." The Cardiovascular Congress for patients will be held within the framework of the Argentine Congress of Cardiology. Similarly, the book for patients is currently in the writing stage.

The districts are the SAC in every corner of the country. Their presidents are leaders who must make an impact in their areas of influence by organizing local and regional scientific activities, interacting with community members through health prevention and promotion initiatives, and advocating at the political and media levels.

Together with the SAC Women's Area, we will continue to work toward enacting the national law that declares October 9th "Women's Cardiovascular Disease Awareness Day." This date has already been established by law in several Argentine provinces. In 2026, we will promote the Liliana Grinfeld Award for the best work on cardiovascular disease in women.

The Argentine Society of Cardiology will work to serve as a consultative body in the enactment of the Nicolás Law, which aims to ensure the right to quality, safe healthcare focused on individuals and communities.

Measure to improve will be the project to bring our leaders together to define the quality metrics that

should be assessed in various areas of cardiology, establishing a benchmark for evaluation.

The editors have done an outstanding job of adapting the Argentine Journal of Cardiology to meet the new requirements for PubMed indexing. The formal presentation will be made next year, and we remain hopeful that we will achieve this goal.

I invite young people not to become discouraged, but to believe that a prosperous future is possible if they work hard for it. The SAC has done an excellent job of promoting its members in teaching, research, and districts. I am confident in saying that the future of Argentine cardiology is secure. We need stronger institutions to guarantee a development project focused not only on care, but also on professional growth. We sometimes ask ourselves what kind of healthcare system we will leave for our future residents. This question usually refers to a much broader and more complex framework of action and responsibility. Therefore, in the meantime, let us continue working on the quality of new cardiologists we will leave to the country.

The Sonqo activity, with the high-altitude indigenous communities, will continue with a new edition in 2026. For this new edition, we will incorporate scientific research in the field in collaboration with a prestigious international scientific society, and we will be presenting the project at the World Heart Federation in the Most Creative Campaign category.

As the aphorism goes, "The physician who knows only medicine, knows not even medicine." Beyond scientific knowledge, excellent physicians integrate empathy, communication skills, a holistic perspective, continuous learning, adaptability, ethics, and the humanities into their professional practice. In this sense, activities will be carried out with the aim of cultivating other aspects of knowledge, such as history, spirituality, the arts, leadership, and narrative medicine.

In recent years, new psychosocial risk factors have been identified, as well as others linked to the environment and pollution. Likewise, new disciplines such as genetics and artificial intelligence have emerged, offering contributions, promise, paradigm shifts, and new fears. The Argentine Society of Cardiology has recognized the changing times by establishing the Councils on Psychosocial Aspects, Digital Health, Genetic Cardiology, Cardioecology, and Healthy Habits in recent years. In this context of change, the SAC has contributed with vision, understanding, agility, and clarity of thought. Following this line of thinking, we will establish inter-council working groups to address specific conditions. We will begin with structural heart disease, an area in which clinical cardiology, imaging, cardiovascular surgery, and interventional cardiology can collaborate. We want interventional subspecialties to find a place in the SAC framework for developing their activities once again. This requires a shared vision of the future that transcends personal interests.

The success and significance of the SAC in the coming decades will depend not only on our technical skills, but also on our human excellence and the virtuous leadership we are capable of embodying. We must reaffirm our unwavering commitment to the patient, the true driving force and meaning of our profession. St. Paul writes to the Corinthians, "tempus breve est," referring to the brevity of our time on earth. These words resonate deeply in our hearts, serving as a reproach for our lack of generosity and as a constant invitation to demonstrate loyalty. Wisdom and compassion are inextricably linked. Jorge Luis Borges meditated on time, the raw material of our professional existence: "Time is the substance I am made of. Time is a river which sweeps me along, but I am the river; it is a tiger which destroys me, but I am the tiger; it is a fire which consumes me, but I am the fire." This Borgesian reflection, which places us as the active substance of time, is fundamental in medicine. We are, in fact, our patients' time. Our leadership and expertise define the quality of their future days. It is our duty to ensure that this time is dignified and supported by the best science.

In the 21st century, leadership in cardiology requires vision, heart, and character. We call on the SAC community to embrace this virtuous leadership and ensure that patients are not only the recipients of our work but also witnesses to our human and professional excellence.

I would like to express my gratitude by mentioning a few people, as I am afraid of omitting someone, and it would take too long to name everyone. Goals are achieved through personal effort and the generosity of many people and/or institutions, whether apparent or tacit. First, I would like to thank my parents, who taught me the value of honesty, simplicity, and doing a good job. I fondly remember the Lasallian community of San Martín and the Murialdine community of Villa Bosch. I am grateful to the University of Buenos Aires and the Hospital de Clínicas, where I had the unique opportunity to begin my training. I am also grateful to the teachers and fellow residents at Sanatorio Mitre, where I learned not only about cardiology, but also about taking a broad view of medicine, which included the importance of transformative leadership, high-quality training, and teamwork. Later, my time at CONAREC (Argentine Council of Cardiology Residents) broadened my perspective to include the entire country, allowing me to participate in the first national registry of coronary angioplasty. I also recall the SAC Research Area, where we learnt statistics, database development, and analysis. I am eternally grateful to the SAC for the opportunity to interact in multiple areas and grow alongside its great leaders since I started the UBA-SAC course in 1994.

The 2001 crisis was another uncertain time, and the idea of staying or emigrating became more pressing every day. At that time, my wife's timely advice

prompted me to reach out to Austral University Hospital. There, a new, transformative stage of my life began. When I arrived, there was much to be done. The department of cardiology welcomed me generously and affectionately, allowing me to integrate easily and encouraging initiatives that benefited the group. I am very proud and grateful to be part of such a generous team of excellent individuals who have helped me grow professionally, personally, and spiritually. I am deeply grateful to my patients, some of whom are here today, for giving me the chance to accompany them on their journeys.

At the institutional level, it was a pleasure working with Dr. Pablo Stutzbach to combine our strengths. I am grateful to you for allowing me to accompany you and share in your achievements in an atmosphere of camaraderie, respect, and generosity. I would also like to express my gratitude to Dr. Mirta Diez, Dr. Ricardo León de la Fuente, the Board of Directors, and the leaders of the Society.

Finally, I would like to thank my family: my wife, Laura, and my four children, Ignacio, Santiago, Pablo, and Sofía. They have experienced having a father divided between two loves, and they have given me understanding and support as I walked this path. I am grateful to my wife for her unconditional support, the breakfasts she made me every morning, and the advice she gave me that helped me improve my interpersonal relationships: "Language is neither innocent nor neutral." It has helped me learn to listen and to be more thoughtful in my choice of words. I do not think I have fully mastered this, but I have improved somewhat.

At the end of the day, we return to poetry, to the essence of what we do. If time is the substance of which we are made, as Borges said, then the time we devote to family, teaching, research, and patient care must be our masterpiece. "Dream, and you will fall short."

Sergio Baratta MTSAC,
President of the Argentine Society of Cardiology