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Hypertrophic Cardiomyopathy in Non-specialized Centers: an Opportunity to Standardize Clinical Practice

Miocardopatía hipertrófica en centros no especializados: una oportunidad para ordenar la práctica real

ADRIÁN FERNÁNDEZ^{1, 2}, MTSAC, FESC.

Hypertrophic cardiomyopathy (HCM) occupies a unique place among cardiovascular diseases. For decades, its definition was based on the presence of left ventricular hypertrophy not attributable to abnormal loading conditions. However, the current understanding of the disease is much broader: HCM constitutes a heterogeneous group of conditions with highly diverse genetic bases, pathophysiological mechanisms, clinical presentations and disease progression. This complexity explains why its management cannot be reduced to the mere echocardiographic detection of increased wall thickness, but rather requires a comprehensive clinical assessment, precise phenotypic characterization, risk stratification, family history investigation and, where appropriate, the integration of cardiovascular genetics. (1–8)

In this context, the Hypertrophic Cardiomyopathy Registry in non-specialized centers, presented by Cáceres et al. in this issue of the Argentine Journal of Cardiology represents a valuable contribution to understanding how this disease is diagnosed and managed in real-world settings. (9) The study included 160 adult patients from 8 provinces, with a mean age of 48 years and a predominance of male gender. Echocardiography was performed in 97.5% of cases, cardiac magnetic resonance imaging (CMRI) in 60%, and genetic testing in 40%. Among the patients evaluated via genetic testing, diagnostic yield was high, with a predominance of MYH7 and MYBPC3 variants; additionally, left ventricular outflow tract obstruction was observed in 34.3% of the cohort, and late gadolinium enhancement was common among those who underwent CMRI. (9)

The main strength of the study lies not only in its numbers, but in the scenario it describes. Most patients with HCM do not initially present at units

specialising in familial heart disease, but at general practices, outpatient centers or institutions without structured circuits for this condition. Therefore, understanding what happens in these settings is essential for identifying opportunities for improvement, guiding training strategies and building more effective care networks. In this regard, the registry has a unique special merit: it shifts the focus from the specialized center to the place where the patient's clinical history often begins.

The results show active cardiological practice, with high use of echocardiography and significant incorporation of CMRI and genetics. This point is worth highlighting, as it reflects that contemporary diagnostic tools are already part of the clinical practice of many cardiologists working outside specialized centers. In addition, the registry reveals that access to and the indication for these resources are not yet uniform. This observation should not be interpreted as a weakness of the study, but rather as one of its most important messages: the quality of diagnosis in HCM depends not only on individual medical knowledge, but also on the availability of tests, referral pathways and the organization of the healthcare system.

A particularly interesting aspect is the high proportion of delayed enhancement among patients assessed with CMRI and the high diagnostic yield of genetic testing in that subgroup. These findings likely reflect appropriate clinical selection of patients referred for more complex studies. They also open up an opportunity for future phases of the registry, in which it could prove highly valuable to characterize in greater detail the criteria of referral for CMRI and genetic testing, the differences between patients who underwent and those who did not undergo these tests, and the type of genetic panel used. This information would allow

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for a better understanding of how these tools are integrated into daily practice and would help to optimize their use in different clinical settings.

As with any real-world registry, the observational and retrospective design should be valued precisely for its ability to reflect standard care conditions. The inclusion of patients with a confirmed or highly probable diagnosis reflects a common situation in medical practice: not all patients have initial access to CMRI, cardiovascular genetics or assessment by specialized teams. In a condition with multiple differential diagnoses and possible phenocopies, this reality reinforces the need to continue moving towards shared diagnostic criteria, minimum assessment protocols and progressively more standardized referral circuits.

The Argentine Society of Cardiology's 2025 Argentine Consensus on the Diagnosis and Treatment of Hypertrophic Cardiomyopathy provides a particularly timely framework for interpreting the results of this registry. (7) The document proposes a comprehensive approach that includes clinical assessment, family history, electrocardiogram, echocardiography, CMRI, genetics and systematic risk stratification, always adapted to the patient's context and available resources. Furthermore, it emphasizes the need to consider differential diagnoses, phenocopies, family screening and longitudinal follow-up. (7) In this regard, the registry by Cáceres et al. shows that many of these recommendations are already in practice, albeit in a heterogeneous manner, and that the current challenge lies in transforming the available knowledge into reproducible care pathways.

Hypertrophic cardiomyopathy requires not only precision medicine but also organized medicine. It is not enough to have CMRI, genetics or advanced therapies if the patient is not identified, characterized and referred in a timely manner. Similarly, the absence of every resource in a center should not prevent an adequate initial assessment. Doppler echocardiography, family history, electrocardiography, 24-hour Holter monitoring, stress testing or exercise echocardiography, when available, remain invaluable tools for guiding diagnosis, quantifying obstruction, assessing symptoms, detecting arrhythmias and estimating risk. (5–7)

The registry also invites reflection on the very concept of a 'non-specialized center'. In Argentina, as in many other countries, specialization depends not only on patient volume, but also on the existence of multidisciplinary teams, access to advanced imaging, cardiovascular genetics, septal reduction surgery, septal ablation, electrophysiology, advanced heart failure care and family counselling. From this perspective, the solution should not be to draw a rigid line between specialized and non-specialized centers, but rather to create functional networks between the two. The clinical cardiologist occupies a central role in this network: he suspects the condition, initiates the investigation, supports the patient and decides when referral is necessary.

Recent therapeutic developments make this model of care even more important. In addition to conventional strategies, such as beta-blockers, calcium channel blockers, disopyramide, septal myectomy, septal ablation and implantable cardioverter-defibrillators, a new era marked by cardiac myosin inhibitors has emerged. Studies with mavacamten demonstrated a reduction in the obstructive gradient, symptomatic improvement and a reduced need for septal reduction therapy in selected patients with symptomatic obstructive HCM. (10–13) More recently, aficamten has expanded the field of research with significant results compared to conventional treatment. (14) This therapeutic evolution reinforces the need to accurately characterize the obstruction, systolic function, symptoms, and echocardiographic progression. The arrival of more specific therapies does not replace the need for rigorous clinical assessment; on the contrary, it makes it even more necessary.

For all these reasons, the work by Cáceres et al. should be read as more than just a descriptive registry. It is an invitation to organize care for HCM in Argentina. Its data show progress, heterogeneity and concrete opportunities for improvement. The registry provides national, multicenter, real-world information on a complex disease in a setting underrepresented in the literature, and its greatest value lies in transforming that information into a tool for action. Future stages may delve deeper into the characterization of patients studied using CMRI and genetics, into the criteria for indicating advanced investigations, into family screening and into referral pathways. Far from diminishing the value of the work, these questions point to its natural course of development.

Finally, this registry contributes to the field of hereditary genetic cardiomyopathies by transforming clinical perception into concrete information: HCM requires specialized knowledge, but also healthcare organization. Its findings, together with the 2025 Argentine Consensus, should stimulate more integrated, equitable and reproducible care for Argentine patients with HCM. Continuing medical education, the implementation of simple protocols, the prioritization of accessible tools, the early referral of complex cases and the establishment of regional networks are realistic steps towards reducing inequalities and improving the quality of care.

Conflicts of interest

None declared

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Coronary Artery Bypass Grafting Using Bilateral Internal Mammary Artery Without Cardiopulmonary Bypass

Cirugía coronaria con doble arteria mamaria y sin circulación extracorpórea

EDUARDO TURNER¹

The article by Navia et al., Off-Pump Coronary Artery Bypass Grafting Using Bilateral Internal Mammary Artery: Clinical Follow-up and 20-Year Postoperative Survival (1), is highly relevant for several reasons. First, a large number of patients with follow-up extending up to 20 years, and two aspects not necessarily related: on the one hand, the exclusive use of both internal mammary arteries to achieve complete myocardial revascularization, and on the other hand, the fact that the surgery was performed in all patients without cardiopulmonary bypass (CPB).

Although not explicitly stated in the article, this is the gold standard in coronary artery bypass grafting at the Instituto Cardiovascular de Buenos Aires (ICBA). It would have been useful to clarify in which patients or clinical situations the use of both internal mammary arteries is avoided or surgery is performed with CPB. However, the data shown in Table 1 are similar to those reported in previous reports on CABG.

Avoidance of the morbidity and costs associated with CPB led to the development of off-pump coronary artery bypass (OPCAB) surgery toward the end of the last century. This was followed by considerable enthusiasm, which gradually declined as surgical outcomes revealed a higher incidence of ischemic complications related to graft occlusion. Currently, this technique is used in no more than 20% of patients (2) and mainly at institutions with surgeons specifically dedicated to this technique to optimize outcomes. (3) It is self-evident that performing CABG without the advantages of a stopped and empty heart, as provided by CPB and cardioplegia, requires a significant learning curve that can only be overcome through specialized training and mentorship by experienced surgeons. This learning curve encompasses not only the construction of the anastomoses but also the exposure of the lateral

and inferior walls of the left ventricle, for which anesthesia is required for hemodynamic management—a process that can be extremely challenging.

The advantage of avoiding CPB-related morbidity seems to be overstated given the continuous advances in oxygenators and intraoperative management, as demonstrated by numerous studies on both CABG with CPB and comparisons between the two techniques. (4)

The use of both internal mammary arteries in CABG—which, notably, in the case of the article by Navia et al., is not only an OPCAB, but also involves revascularization of all three areas of the heart, resulting in exceptionally good results in terms of both extremely low morbidity and mortality, operative and in the long-term follow-up—is also controversial. (5)

The manner in which both mammary arteries are combined is novel and also involves a learning curve: the T-shaped anastomosis of both internal mammary arteries (6) should not be performed sporadically because, if not performed perfectly, the consequences could be catastrophic, unlike percutaneous coronary intervention, whose complications can usually be managed surgically.

Historically, the use of both internal mammary arteries has been recommended for patients under 60 years of age and in good general health, excluding those with diabetes or obesity. (7) Navia et al. do not appear to make such exceptions and report only a slightly higher incidence of mediastinitis in diabetic patients. The article does not report the measures taken to reduce this complication, such as optimizing perioperative glycemia control or postponing surgery in patients with elevated glycosylated hemoglobin levels.

This article also opens the discussion regarding

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the maximum age at which the use of both internal mammary arteries remains advisable compared to the standard approach (left internal mammary artery to the left anterior descending artery and saphenous vein grafts to the remaining coronary arteries). Figure 1 stratifies patients by age using a cut-off point of 65 years and includes a substantial number of patients with 15 years of follow-up. Figures 2 and 3 complement these findings by demonstrating the effect of ventricular dysfunction, obesity and diabetes on survival. Could these findings have been further explored by analyzing interactions between these variables?

In conclusion, the use of bilateral internal mammary artery in OPCAB to revascularize the three coronary affected territories is an excellent option—and probably the best one for most patients—but only when performed by experienced surgical and anesthesiology teams such as those at ICBA. For most cardiac surgeons who have not been trained in this technique, CABG with CPB and cardioplegia remains preferable.

Conflicts of interest

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Hypertrophic Cardiomyopathy Registry in Non-Specialized Centers: Final Results

Registro de miocardiopatía hipertrófica en centros no especializados: resultados finales

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, exhibiting a wide range of clinical presentations, from asymptomatic forms to advanced heart failure and sudden cardiac death. Although therapeutic strategies have improved outcomes, most patients are still managed in non-specialized centers with variable access to advanced diagnostic tests and a lack of a standardized approach.

Objectives: To describe clinical practice and access to diagnostic tests for patients with HCM in non-specialized centers in Argentina.

Methods: We conducted a nationwide, retrospective, multicenter and observational study. Patients > 18 years with a confirmed or highly probable diagnosis of HCM, followed up by cardiologists at outpatient clinics of non-specialized centers were included. Cases with secondary hypertrophy were excluded. Data were collected on the REDCap platform of the Argentine Society of Cardiology between June 1, 2023, and September 1, 2024.

Results: A total of 160 patients from 8 provinces were included (mean age 48 years; 60.6% men). The most common cardiovascular risk factors were hypertension (46.7%) and dyslipidemia (31.4%). The most common reason for consultation was a presumptive or confirmed diagnosis of HCM (43.4%), followed by symptoms such as dyspnea and angina. Echocardiography was performed in 97.5% of cases, cardiac magnetic resonance imaging (CMRI) in 60%, and genetic testing in 40%. Among patients who underwent genetic testing, the diagnostic yield was 82.8%, with a predominance of variants in sarcomere genes MYH7 and MYBPC3. Left ventricular outflow tract obstruction was present in 34.3% of patients, and late gadolinium enhancement was observed in 81.2% of those evaluated by CMRI. Most patients received beta-blockers, and a subgroup required interventions, including 26 implantable cardioverter-defibrillator implantations and 4 septal myectomy procedures.

Conclusions: This first Argentine registry of HCM in non-specialized centers reveals significant differences in the use of ancillary tests and implementation of therapeutic strategies. These findings evidence the presence of inequities in access to diagnostic resources and care pathways, underscoring the need to strengthen medical education, develop referral networks, and adapt international guidelines to the local context to optimize the diagnosis and management of this disease.

Key words: Hypertrophic cardiomyopathy – Registry - Real-world practice - Health inequity - Non-specialized centers

RESUMEN

Introducción: La miocardiopatía hipertrófica (MCH) es la enfermedad genética cardiovascular más frecuente, con una expresión clínica heterogénea que abarca desde formas asintomáticas hasta insuficiencia cardíaca avanzada y muerte súbita. Si bien las estrategias terapéuticas han mejorado el pronóstico, la mayoría de los pacientes continúa siendo atendida fuera de centros especializados, donde el acceso a estudios diagnósticos avanzados y a un abordaje estructurado puede ser variable.

Objetivo: Caracterizar la práctica clínica y evaluar el acceso a estudios diagnósticos de pacientes con MCH en centros no especializados de Argentina.

Material y métodos: Estudio observacional, retrospectivo y multicéntrico de alcance nacional. Se incluyeron pacientes mayores de 18 años con diagnóstico confirmado o altamente probable de MCH, en seguimiento ambulatorio por cardiólogos de centros no especializados. Se excluyeron casos con hipertrofia secundaria. La recolección de datos se realizó mediante la plataforma REDCap de la Sociedad Argentina de Cardiología entre junio de 2023 y septiembre de 2024.

Resultados: Se incluyeron 160 pacientes de 8 provincias (edad media 48 años; 60,6 % varones). Los factores de riesgo más prevalentes fueron hipertensión arterial (46,7 %) y dislipidemia (31,4 %). El motivo de consulta más frecuente fue el diagnóstico presuntivo o confirmado de MCH, seguido por síntomas, disnea y angina los más habituales. El ecocardiograma se realizó en el 97,5 % de los casos,

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la resonancia magnética cardíaca (RMC) en el 60 % y el test genético en el 40 %. Entre los pacientes sometidos a estudio genético, el rendimiento diagnóstico fue del 82,8 %, con predominio de variantes en MYH7 y MYBPC3.

El 34,3 % presentó obstrucción del tracto de salida del ventrículo izquierdo y en el 81,2 % de los pacientes evaluados con RMC se evidenció realce tardío. La mayoría recibió betabloqueantes y un subgrupo requirió intervenciones, incluyendo 26 cardiodesfibriladores implantables y 4 miectomías septales.

Conclusiones: Este primer registro argentino de MCH en centros no especializados muestra diferencias relevantes en la utilización de estudios diagnósticos y en la implementación de estrategias de manejo. Los hallazgos evidencian inequidades tanto en el acceso a recursos como en los circuitos asistenciales, y subrayan la necesidad de fortalecer la capacitación médica, desarrollar redes de derivación y adaptar las guías internacionales al contexto local para optimizar el diagnóstico y tratamiento de esta enfermedad.

Palabras clave: Miocardiopatía hipertrófica - Registro - Práctica clínica - Inequidad en salud - Centros no especializados

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with an estimated prevalence between 1 in 200 and 500 people. (1,2) Its etiology is related to mutations in genes encoding sarcomere proteins, resulting in left ventricular hypertrophy (LVH), myofibrillar disarray, and progressive myocardial fibrosis. (3,4)

The diagnosis remains a significant challenge, as increased wall thickness and chamber dilation are not exclusive to HCM but can also be observed in infiltrative cardiomyopathies that present as phenocopies. (5-7)

Current treatments include pharmacological strategies and invasive options, such as septal surgery and device implantation, which have been shown to improve survival and quality of life. (8-10) However, there are few centers specialized in this disease, so most patients are followed up at institutions not specifically dedicated to HCM.

This study presents the final results of the Hypertrophic Cardiomyopathy Registry in Non-specialized Centers, with the aim of providing data to assess the limitations in access to and use of advanced diagnostic methods outside of referral centers.

METHODS

We conducted a nationwide, observational, retrospective, and multicenter study in patients with confirmed or highly probable diagnosis of HCM.

The participants were clinical cardiologists practicing in outpatient clinics. For the purposes of this study, a non-specialized center was defined as one without a structured program dedicated to managing HCM or a systematic, multidisciplinary approach. These centers also had non-systematic access to advanced septal reduction therapies and high-complexity tests, such as cardiac magnetic resonance imaging or genetic testing.

Hypertrophic cardiomyopathy was defined as the presence of left ventricular hypertrophy with a maximum wall thickness >15 mm in a non-dilated left ventricle, documented by echocardiography and/or cardiac magnetic resonance imaging, in the absence of other conditions resulting in such hypertrophy. (2-6)

Cases that met the morphological and imaging criteria and had a positive genetic test result were categorized as confirmed HCM. (2,4,8-10) Patients who met all clinical and imaging criteria, but had not undergone genetic testing, were considered to be highly probable cases of MCH.

In all cases, the final diagnostic adjudication was left to the discretion of the treating cardiologist, without centralized review of images or validation of diagnoses by an independent reviewer.

Patients with conditions associated with secondary ventricular hypertrophy as the sole mechanism (such as infiltrative cardiomyopathies, hypertension, valvular heart disease, and high-performance athletes, among others) were excluded, as were those with HCM who were being followed up at specialized centers.

Data were collected on the REDCap platform of the Argentine Society of Cardiology between June 1, 2023, and September 1, 2024.

Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies. Continuous variables were described as mean and standard deviation (SD), or median and interquartile range (IQR 25-75), according to their distribution.

Because of the descriptive nature of the study, the analysis focused primarily on presenting descriptive statistics. Categorical variables were compared using the chi-square test or the Fisher's exact test, as appropriate. For continuous variables, the Student's t test or the Mann-Whitney test were used to compare independent groups, and the Wilcoxon signed-rank test was used to assess changes in paired data, as appropriate.

A p-value < 0.05 was considered statistically significant. All the statistical calculations were performed using R and Python software packages.

Ethical considerations

The study protocol was reviewed and approved by the institutional review board of *Hospital General de Agudos Donación F. Santojanni* of the City of Buenos Aires. The research was conducted in accordance with the ethical principles established in the Declaration of Helsinki (11) and its subsequent amendments, as well as with current local regulations regarding clinical research.

RESULTS

A total of 160 patients from 8 provinces in Argentina (Buenos Aires, Santa Fe, Formosa, Catamarca, Tucuman, Rio Negro, Mendoza, and Chubut) were included. Mean age was 48 years and 60.6% were men. The most common cardiovascular risk factors were hypertension (46.7%), dyslipidemia (31.4%), obesity (18.2%), diabetes (18.2%), and tobacco use (11.9%). The prevalence of comorbidities associated with cardiovascular disease was low: chronic obstructive pul-

monary disease (4.4%), prior myocardial infarction (3.8%), chronic kidney disease (2.2%), anemia (2.5%), and stroke (1.2%) (Table 1). Among patients with a family history of sudden cardiac death, 66.7% corresponded to events occurring in individuals <45 years of age.

The most common reason for consultation was a presumptive or confirmed diagnosis of HCM (43.4%), followed by symptoms (28.3%) and routine checkups (28.3%) (Figure 1). Among symptomatic patients, the most common symptoms were dyspnea (n=30) and angina (n=15), followed by palpitations (n=11), syncope (n=3), and one case of resuscitated sudden cardiac death. Among patients presenting with dyspnea, 22.7% were in New York Heart Association (NYHA) functional class (FC) I, 40.9% in FC II, and 36.4% in FC III–IV.

Median time from the diagnosis of HCM to inclusion in the registry was 3.9 years (IQR 2.0–10.0). An analysis of the frequency of follow-up visits revealed that 64.8% of patients had attended the outpatient clinic within the past 6 months, 23.9% between 6 and 12 months, and 11.4% more than 12 months ago.

Regarding ancillary tests, an electrocardiogram was performed in all patients; 88.5% were in sinus rhythm, and 87.5% showed signs of left ventricular hypertrophy. Sixty percent of the cohort underwent cardiac magnetic resonance imaging (CMRI) and 49.3% 24-hour Holter monitoring. In addition, genetic testing was performed in 40% of the patients, coronary angiography or coronary computed tomography angiography in 20%, and stress echocardiography in 10.6% (Figure 2).

Hypertrophy was predominantly septal (84.4% on echocardiography and 78.9% on CMRI) and apical (11.2% and 15%, respectively). There were no significant differences in left ventricular ejection fraction measured by echocardiography or CMRI [median 61% (IQR 52–70) vs. 66% (IQR 55–77); p = 0.114].

Among the 96 patients evaluated with CMRI, 81.2% had late gadolinium enhancement, predominantly with an intramyocardial pattern (92%). This pattern was most common in the interventricular septum (75%) with a patchy distribution in 55.4%; median fibrosis score was 5.1% (IQR 2.8–17).

Left ventricular outflow tract obstruction (>30 mmHg) was observed in 55 patients (34.3%). Median resting gradient was 43 mmHg (IQR 28–66) and increased to 62 mmHg (IQR 37–82) during the Valsalva maneuver.

In patients undergoing genetic testing, 82.8% tested positive for pathogenic variants or likely pathogenic variants (n=53/64). The most common variants were identified in the sarcomere genes MYH7 (n=21), MYBPC3 (n=13), and TNNT2 (n=6).

Patients who underwent genetic testing were compared with those without genetic testing (Table 2). Patients who underwent genetic testing were significantly younger [median age 37 years (IQR 25–48) vs. 58 years (QR 45–70); p < 0.001] and had a higher prevalence of a family history of sudden cardiac death (25% vs. 12.5%; p = 0.043). The sudden cardiac risk score was similar in both groups.

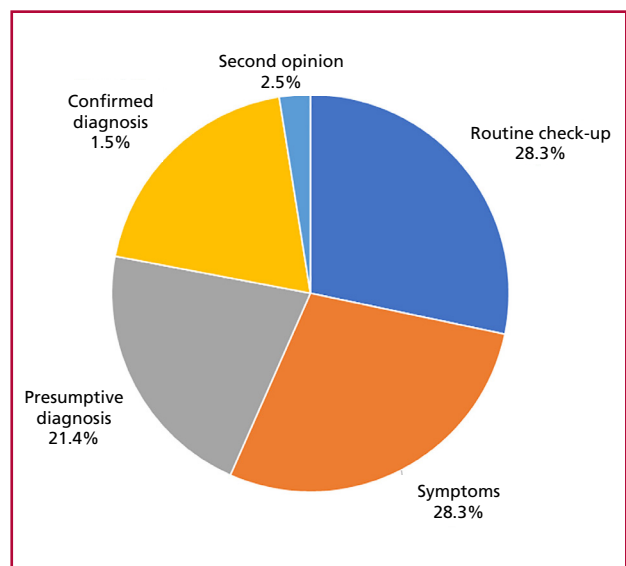
The main reasons for not performing genetic testing were lack of health insurance (n=29), local unavailability (n=16), and the treating physician’s decision (n=15). Other reasons were reported in a smaller group (n=21), while the cause could not be determined in the remaining patients.

Table 1. Baseline data

Characteristic (n=160)	
Age, years, mean ± SD	48±16
Gender (%)	
Male	60.6
Female	39.4
CVRF (%)	
HTN	46.7
DLP	31.4
TU	11.9
DBT	18.2
Obesity	18.2
History of sudden death (%)	
< 45 years	66.7
Comorbidities (%)	
Prior AMI	3.8
COPD	4.4
CKD	2.2
Anemia	2.5
Prior stroke	1.2

AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVRF: cardiovascular risk factors; DBT: diabetes; HTN: hypertension; SD: standard deviation; TU: tobacco use

Fig. 1. Reasons for consultation



Family screening was performed in 44.9% of the cohort (n=72), primarily through echocardiography (n=59), followed by genetic testing (n=35) and cardiac magnetic resonance imaging (n=22).

The most common medications prescribed were beta-blockers (42.5%), renin-angiotensin system inhibitors (16.9%), calcium channel blockers (15.6%), and furosemide (11.2%). Figure 3 shows the medications patients were receiving prior to their first visit and those subsequently prescribed based on clinical criteria.

Among the 20 patients with a prior diagnosis of HCM who were being followed up by their treating cardiologists, 11 had an implantable cardioverter-defibrillator (ICD) implanted, 4 had undergone myectomy, 3 had pacemakers, and 2 had undergone alcohol septal ablation. In the entire cohort analyzed, 35 patients had a history of therapeutic interventions following the diagnosis of HCM, including 26 ICD implants, 4 pacemaker implants, 4 septal myectomy procedures,

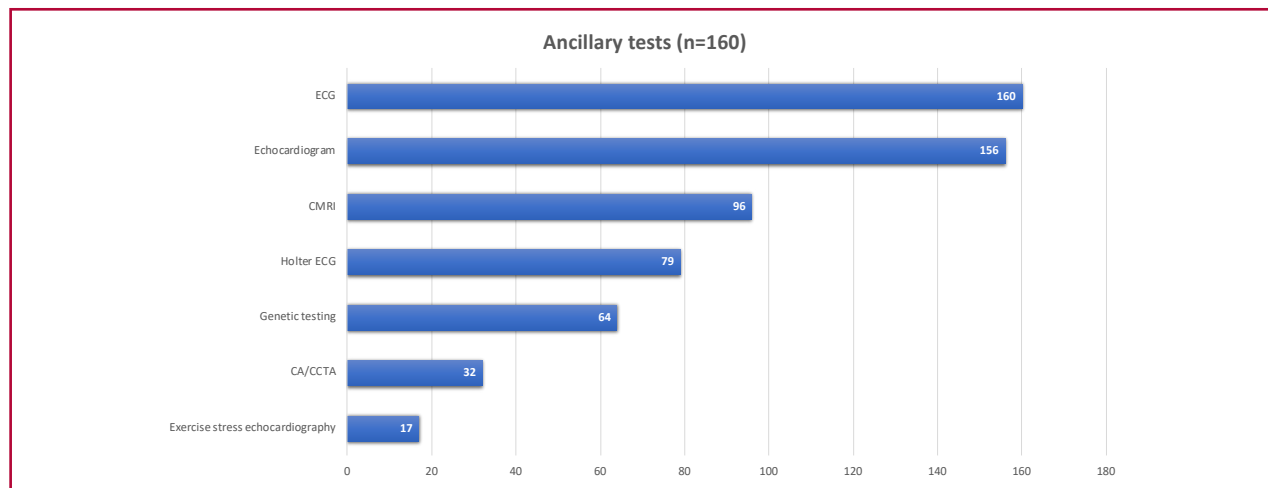
and 1 resynchronization device implant. Myectomy significantly reduced the LVOT gradient in two-thirds of the cases.

Of the 26 patients who received an ICD during follow-up, the European Society of Cardiology (ESC) score was available in 10 cases and the American Heart Association (AHA) score in 15. Median ESC score was 6.5% (IQR 5.1–8.2). According to the risk categories, 60% (6 patients) were in the high-risk category (score ≥ 6%), 2 patients were in the intermediate-risk category (4–6%), and 2 were in the low-risk category (<4%). Median AHA score was 6.3 (IQR 3.2–9.4). Three appropriate shocks (11.5% of patients with an ICD) were documented at the time of the registry.

DISCUSSION

This registry constitutes the first national study analyzing patients with HCM treated in non-specialized centers. Its relevance lies in the fact that most international literature comes from referral centers, where

Fig. 2. Ancillary tests during follow-up



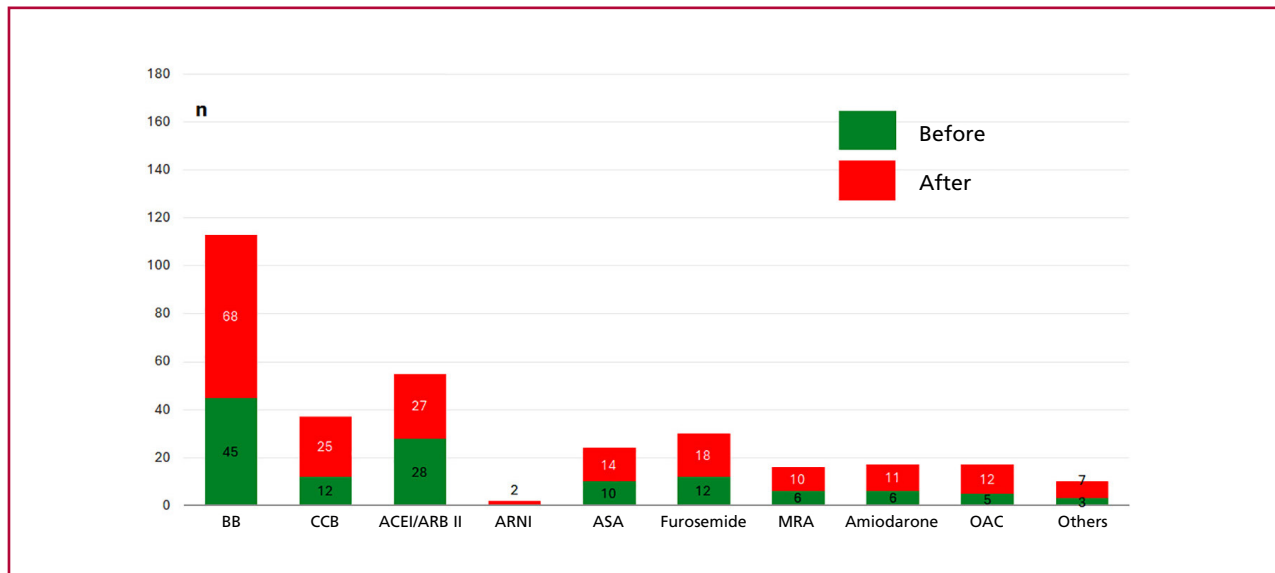
CA: coronary angiography; CCTA: coronary computed tomography angiography; CMRI: magnetic resonance imaging; ECG: electrocardiogram

Table 2. Comparison between patients with and without genetic testing

Variable	Genetic testing n=64	No genetic testing n=96	p
Age, years (median, IQR)	37 (25–48)	58 (45–70)	<0.001
Male, n (%)	38 (59.3)	58 (60.4)	0.401
Family history of SCD, n (%)	16 (25)	12 (12.5)	0.038
Dyspnea, n (%)	12 (18.7)	18 (18.7)	1
Angina, n (%)	7 (10.9)	8 (8.3)	0.592
LVOT obstruction, n (%)	15 (23.4)	21 (21.8)	0.818
CMRI, n (%)	33 (51.5)	63 (65.6)	0.564
Fibrosis on CMRI, n (%)	26/31 (83.8)	52/62 (83.8)	0.679
ESC SCD risk score, % (median, IQR)	5.8 (3.2–8.1)	6.5 (3.5–9.0)	0.417

CMRI: cardiac magnetic resonance imaging; ESC: European Society of Cardiology; IQR: interquartile range; LVOT: left ventricular outflow tract; SCD: sudden cardiac death.

Fig. 3. Medications before and after the first visit



ACEI: angiotensin-converting enzyme inhibitor; ARB II: angiotensin II receptor antagonist; ARNI: angiotensin receptor/neprilysin inhibitor; ASA: acetylsalicylic acid; BB: beta-blocker; CCB: calcium channel blocker; MRA: mineralocorticoid receptor antagonist; OAC: oral anticoagulant.

diagnosis and management are carried out following standardized protocols and with broad access to advanced imaging tests. (12-16) Conversely, our results reflect actual clinical practices in a country with significant differences in the availability of resources and access to specialized care.

While most of the cardiologists who monitored these patients practice in Buenos Aires and the City of Buenos Aires (CABA), centers from several inland provinces (Santa Fe, Formosa, Catamarca, Tucumán, Río Negro, Mendoza, and Chubut) were also included.

The diagnosis of HCM remains a challenge, even in settings with advanced resources, due to its heterogeneous clinical presentation and overlap with phenocopies. In our registry, the diagnosis was left to the discretion of the treating cardiologist and was not always supported by highly complex ancillary tests, reflecting the status of real-world clinical practice in non-specialized centers. This characteristic, which could be regarded as a limitation, also contributes to the study, as it facilitates the identification of diagnostic challenges in routine care settings outside of referral centers.

The mean age in our cohort (48 years) was similar to that reported in international registries, such as the Hypertrophic Cardiomyopathy Registry (HCMR, 49 years), (17) the EURObservational Registry (47 years), (18) the Portuguese Registry (53 years), (19) the Italian (44 years), (20) and the Sarcomeric Human Cardiomyopathy Registry (SHaRe, 45.8 years). (21) Likewise, we observed a male predominance (60.6%), comparable to that described in the HCMR (71%) and

SHaRe (63%). However, there is a growing consensus that the underrepresentation of women suggests underdiagnosis rather than a true difference in disease incidence.

A family history of sudden cardiac death was present in 17.5% of our patients, a proportion similar to that reported in the SHaRe registry. The systematic assessment of this variable is a key aspect of our registry, due to its impact on risk stratification in HCM.

Regarding the reasons for diagnosis, 28.3% of cases involved symptomatic patients, and 28.3% were detected during routine checkups. These proportions are similar to those reported in the EURObservational and Portuguese registries. However, in our cohort 36.4% of patients with dyspnea were in FC III–IV, whereas in most international registries this proportion was considerably lower (<10%), with a clear predominance of patients in FC I–II (≈80%). This difference may reflect a later diagnosis in our setting, likely associated with limitations in early access to specialists and advanced diagnostic methods. (9,10)

Hypertrophy was predominantly septal and, to a lesser extent, apical, consistent with findings described in the international literature. Similarly, the prevalence of fibrosis detected by CMRI was high (81.2% among the evaluated patients), consistent with previous registry reports. (7) However, this finding should be interpreted in the context of a selected population since CMRI was not systematically performed across the entire cohort, but rather in a subgroup of patients with clinical indications. This may have overestimated the prevalence of fibrosis.

In contrast, the proportion of patients undergoing stress echocardiography was markedly low (10.6%), despite this tool being accessible and essential for differentiating between baseline and induced obstruction through the Valsalva maneuver or during exercise. This finding likely reflects the absence of standardized protocols and the need for greater integration of stress echocardiography into routine diagnostic pathways at non-specialized centers.

Genetic testing was performed in 40% of patients, a proportion comparable to that of the Portuguese registry (51%) and somewhat lower than that of the SHaRe (60%).(19,21) The diagnostic performance was high (82.8%), with a predominance of classic sarcomere variants (MYH7, MYBPC3, and TNNT2). This finding should be interpreted in the context of selection bias. In the comparative analysis, patients undergoing genetic testing were significantly younger [median age 37 years (IQR 25–48) vs. 58 years (QR 45–70); $p < 0.001$] and had a higher prevalence of a family history of sudden cardiac death (25% vs. 12.5%; $p = 0.043$), with no differences observed in other clinical or morphological variables. These findings suggest that the test was primarily indicated in individuals with a higher suspicion of a genetic etiology rather than based on clinical severity or structural phenotype. When considered as a whole, this explains the higher diagnostic performance compared to that reported in unselected cohorts. Additionally, it suggests that the differences observed in the use of various diagnostic methods are more attributable to variations in their implementation in clinical practice than to their actual availability. Consequently, there is an opportunity to enhance the standardization of the diagnostic approach in non-specialized centers.

Likewise, the primary barrier to genetic testing was the lack of insurance coverage, which restricted not only individual access but also the implementation of family cascade screening strategies. In this context, only 44.9% of relatives were evaluated, predominantly through echocardiography, which contrasts with reports from European and American registries. (17-21)

Beta-blockers were the drugs most commonly used, consistent with reports from other registries. In the cohort analyzed, 26 patients had an implantable cardioverter-defibrillator (ICD) implanted due to disease progression.

The median ESC sudden cardiac death risk score was 6.5%, and most patients with an implanted ICD were in the high-risk category ($\geq 6\%$). These findings are consistent with the recommendations of the ESC guidelines for ICD implantation in primary prevention. (5)

However, ICDs had been also implanted in low or intermediate-risk patients, which likely reflects the consideration of additional clinical variables, such as syncope, non-sustained ventricular tachycardia, late gadolinium enhancement on CMRI, or family history in the decision-making process. The lack of stratifica-

tion scores in all cases made it impossible to perform a more comprehensive analysis. However, the overall trend suggests that most ICDs were implanted in high-risk patients.

These findings should be interpreted in the context of a cohort with a prolonged clinical course since diagnosis, a median of nearly 4 years, and a wide range of follow-up visits. This aspect could influence the frequency of the observed interventions, including ICD implantation, as it reflects different stages of disease progression rather than events occurring within a defined follow-up period.

The rate of myectomy procedures was low (4 cases on admission and 4 during follow-up), which is likely related to the lack of centers with expertise in interventional procedures in the country.

Our findings underscore two key challenges in the management of HCM in Argentina. First, inequity in access to diagnostic tests. Although stress echocardiography is widely available across most centers, its underutilization reflects the absence of standardized protocols and the need for greater integration into routine diagnostic pathways. In contrast, genetic testing was performed at a relatively high rate despite being less accessible, although this was limited by health system coverage.

Second, the limited dissemination and implementation of guidelines, recommendations, and diagnostic algorithms. The heterogeneous use of fundamental tools underscores the necessity to enhance training and integrate standardized diagnostic approaches in non-specialized centers. This could help reduce late diagnoses and the higher proportion of patients in FC III–IV observed in our registry.

In this context, the differences observed reflect not only the structural heterogeneity of the Argentine healthcare system but also the inequities in care pathways, including referral, timely diagnosis, and the implementation of risk stratification strategies.

Based on these findings, specific courses of action have been identified focused on improving care:

- Development of updated national guidelines adapted to the Argentine context considering the available resources and defining practical algorithms for diagnosis and treatment. In this regard, we can only welcome the recent publication of the Argentine Consensus on the Diagnosis and Treatment of Hypertrophic Cardiomyopathy, which provides a comprehensive review of the topic and recommendations aligned with scientific advances and local realities. (22)
- Implementation of continuing medical education programs aimed at professionals in non-specialized centers.
- Creation of referral and counter-referral networks to facilitate the timely referral of patients requiring advanced interventions.
- Promotion of equity strategies for the access to genetic testing and family screening.

When considered as a whole, our results, which are consistent with large international registries in terms of clinical characteristics, underscore the significant differences in the implementation of diagnostic and therapeutic processes. They also provide insight into the management of HCM in real-world clinical practice and set the groundwork for developing local strategies and policies that bridge the gap between the available evidence and its implementation in daily practice.

Study limitations

The study has several limitations that should be considered to interpret the results. First, the sample size and geographic distribution of the participating centers do not allow extrapolating the findings to the entire national population. Second, the retrospective nature of the registry and voluntary participation introduce potential selection and reporting biases, with possible over-representation of more complex patients or with tighter follow-up.

Likewise, the heterogeneous availability and use of ancillary tests across centers and provinces affect internal comparability and limit the standardization of the diagnostic approach. In this context, the final diagnosis of HCM was left to the discretion of the treating cardiologist which reflects actual clinical practice, although it may have introduced variability in case definition.

The lack of a systematic prospective follow-up limited the assessment of clinical events over time. Therefore, the findings are interpreted primarily in terms of the patients' history at the time of enrollment. Finally, the incomplete availability of key studies—such as stress echocardiography, CMRI, genetic testing, and risk stratification scores—restricted the comprehensive analysis of some subgroups and may have influenced the interpretation of certain results.

CONCLUSIONS

This first Argentine registry of patients with HCM treated in non-specialized centers allowed for a comprehensive characterization of the population and the diagnostic and therapeutic strategies used in real-world clinical practice. Although our findings are similar to those of large international registries in terms of clinical characteristics, we identified significant differences in the use of ancillary tests, timely diagnosis, and implementation of therapeutic strategies. These findings underscore the presence of inequities in the access to diagnostic resources and care pathways, including referral, risk stratification, and family-centered care. In this context, the results of the present study provide local evidence to guide the development of concrete strategies, including healthcare team training, the consolidation of referral networks, and the adaptation of international guidelines to the Argentine context, with the goal of optimizing the diagnosis and management of this disease nationwide.

Conflicts of interest

None declared.

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

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Appendix-supplementary material

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Off-Pump Coronary Artery Bypass Grafting Using Bilateral Internal Mammary Artery: Clinical Follow-up and 20-Year Postoperative Survival

Cirugía coronaria con doble arteria mamaria y sin circulación extracorpórea: seguimiento clínico y supervivencia a 20 años de postoperatorio

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ABSTRACT

Background: Off-pump coronary artery bypass (OPCAB) surgery using bilateral internal mammary arteries (BIMA) has demonstrated improved mid-term survival and reduced perioperative risk. However, evidence regarding its long-term effectiveness and safety remains limited, particularly in Latin American populations.

Objectives: To describe long-term survival (20 years) in a consecutive cohort of patients undergoing exclusively OPCAB surgery with BIMA and to assess the impact of age, ventricular function, diabetic status, and body mass index (BMI) on survival.

Methods: This retrospective open cohort study included patients who underwent exclusively OPCAB surgery with BIMA between January 2003 and December 2023. Emergency surgeries, combined procedures, and patients with prior heart surgery were excluded. Follow-up ranged from a minimum of 1 year to 20 years after surgery. Demographic characteristics were obtained from medical records, and survival status was assessed by telephone follow-up. For the primary endpoint, survival was estimated using tables and Kaplan-Meier curves. Cox proportional hazards regression models were used to evaluate associations between time to death and age, ventricular function, type of angina, diabetic status, and BMI. Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Results: During the study period, 4495 patients were included, with a median follow-up of 6.13 years (interquartile range, IQR, 2.62-10.36). The mean age was 64.1 ± 9.27 years, and 8.34% ($n = 375$) were women. A total of 28.2% ($n = 1269$) had diabetes. The median BMI was 28 (IQR 25.8–30.5). Overall survival was 70% (95% CI 68-72%) at 10 years and 31% (95% CI 28-34%) at 20 years. In patients aged ≤ 65 years, survival was 87.8% (95% CI 85.8-89.6) at 10 years and 60.8% (95% CI 55.6-65.7) at 20 years. Age > 65 years (adjusted HR 4.99; 95% CI 4.33-5.75; $p < 0.001$) and severe ventricular dysfunction (adjusted HR 2.20; 95% CI 1.73-2.80; $p < 0.001$) were independently associated with higher postoperative mortality. Diabetes was an independent predictor of mortality both without obesity (adjusted HR 1.30; 95% CI 1.13-1.50; $p < 0.001$) and with obesity (adjusted HR 1.28; 95% CI 1.05-1.56; $p = 0.015$), whereas obesity without diabetes was not (adjusted HR 1.05; 95% CI 0.88-1.24; $p = 0.603$).

Conclusion: In this 20-year retrospective cohort, off-pump CABG with BIMA demonstrated high long-term survival in younger patients. Severe ventricular dysfunction and diabetes, with or without obesity, were independently associated with increased mortality, whereas obesity and was not independent an independent predictor of mortality.

Key words: Coronary surgery - Bilateral internal thoracic artery - Cardiopulmonary bypass - Follow-up

RESUMEN

Introducción: La cirugía coronaria (CRM) con empleo de ambas arterias mamarias (DM) y sin circulación extracorpórea (sin CEC) ha demostrado una mayor supervivencia a mediano plazo con un menor riesgo perioperatorio. Sin embargo, no hay evidencia de la efectividad y seguridad a largo plazo, ni en población latinoamericana sobre este tipo de tratamiento quirúrgico.

Objetivos: Describir la supervivencia alejada (20 años) en un grupo consecutivo de pacientes en quienes se realizó, en forma exclusiva, CRM con DM y sin CEC, y analizar el impacto en la sobrevida de la edad, función ventricular, estado diabético e índice de masa corporal (IMC).

Material y métodos: Estudio retrospectivo de cohorte abierta en pacientes operados exclusivamente con CRM con DM sin CEC, entre enero de 2003 y diciembre de 2023. Se excluyeron cirugías de emergencia, combinadas, y pacientes con cirugías previas. El

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seguimiento se realizó con un mínimo de 1 año y hasta 20 años posteriores a la cirugía. Los datos demográficos se extrajeron de la historia clínica y la sobrevida se evaluó a través de contacto telefónico.

Para el objetivo primario se realizaron tablas de sobrevida y gráficos de Kaplan Meier. Para comparar el tiempo a la muerte con base en la edad, función ventricular, estado diabético e IMC, se realizaron modelos de regresión de Cox, reportando los Hazard Ratios crudos y ajustados por confundidores.

Resultados: Durante el periodo de estudio se incluyeron 4495 pacientes, con una mediana de seguimiento de 6,13 años (rango intercuartílico, RIC, 2,62-10,36). La edad media fue de 64,1 ± 9,27 años, y el 8,34 % (n = 375) eran mujeres. Eran diabéticos el 28,2% (n=1269). La mediana de IMC fue 28 (RIC 25,8-30,5).

La sobrevida global fue del 70% (IC 95% 68-72%) a los 10 años y del 31% (IC 95% 28-34%) a los 20 años. En pacientes de 65 años o menos, la sobrevida a los 10 años fue de 87,8 % (IC 95 % 85,8–89,6); y de 60,8 % (IC 95 % 55,6–65,7) a los 20 años. La edad > 65 años (HR ajustado 4,99; IC 95%: 4,33-5,75; p<0,001) y la disfunción ventricular grave (HR ajustado 2,20; IC 95% 1,73 -2,80, p<0,001) se asociaron a mayor mortalidad postquirúrgica de manera independiente. La diabetes fue predictor independiente de mortalidad, tanto sin obesidad (HR ajustado 1,30; IC 95 % 1,13–1,50; p<0,001), como con obesidad (HR ajustado 1,28; IC 95 % 1,05–1,56; p=0,015); no así la obesidad sin diabetes (HR ajustado 1,05; IC 95%:0,88-1,24; p=0,603).

Conclusión: En esta cohorte retrospectiva a 20 años, la CRM con DM y sin CEC mostró alta supervivencia en pacientes jóvenes. La disfunción ventricular grave y la diabetes, con o sin obesidad, se asociaron con mayor mortalidad. La obesidad no fue predictor independiente de mortalidad.

Palabras clave: Cirugía coronaria - Doble mamaria - Circulación extracorpórea - Seguimiento

INTRODUCTION

The use of the left internal thoracic artery (LITA), also known as left internal mammary artery (LIMA), as a graft to the left anterior descending artery (LAD) has become the gold standard in coronary artery bypass grafting (CABG), supported by robust evidence demonstrating excellent clinical outcomes and high long-term patency. (1) The demonstrated benefits of LIMA grafting have generated growing interest in the use of the right internal mammary artery (RIMA). (2) Several studies have shown that the use of one or both internal mammary arteries (bilateral internal mammary artery [BIMA]) does not significantly increase perioperative morbidity. (1–3) Furthermore, several retrospective studies and meta-analyses have suggested that the use of BIMA may be associated with improved long-term survival. (2,4-7) Despite these potential long-term survival benefits, the use of BIMA remains uncommon. Greater technical complexity and the additional perioperative risks may also have limited the widespread adoption of this technique. Furthermore, the Arterial Revascularization Trial (ART), the only randomized clinical trial comparing the use of a single mammary artery with the use of both mammary arteries, did not demonstrate a significant survival advantage during long-term follow-up. (8)

Concurrently, off-pump coronary artery bypass (OPCAB) surgery has emerged as an alternative to on-pump CABG (ONCAB) to reduce complications associated with the use of the extracorporeal circulation and to minimize manipulation of the ascending aorta. (9,10)

However, the debate over OPCAB surgery with BIMA has persisted for more than three decades. (11,12) The combination of OPCAB with BIMA offers theoretical advantages; however, its synergistic benefit remains poorly studied, with only case reports available to date. (13,14)

The primary endpoint of this study was to evaluate long-term survival in patients undergoing OPCAB

with BIMA. Secondly, the association between ventricular function, diabetic status, body mass index (BMI) and time to death was evaluated.

METHODS

Study Design and Setting

This was a single-center retrospective cohort study conducted at the Instituto Cardiovascular de Buenos Aires. The study included all adult patients (aged ≥18 years) who underwent OPCAB with BIMA between January 2003 and December 2023. This manuscript complied with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and was approved by the institution's Ethics Committee. The requirement for informed consent was waived due to the retrospective nature of the study.

Participants

From the initial patient population, we excluded those who underwent emergency CABG, combined valvular or aortic surgery, CABG using venous grafts or radial artery grafts, and patients with a history of prior coronary revascularization or who underwent ONCAB. Thus, the final cohort consisted of patients who exclusively underwent OPCAB with a BIMA T-graft configuration. To ensure complete arterial revascularization, only patients with two- or three-vessel coronary artery disease, defined as >70% stenosis in each affected territory, were included, and these patients received at least one mammary artery graft per diseased territory.

Surgical procedure

In 2002, with the availability of commercial cardiac stabilizing devices, off-pump CABG began to be used. From 2003 to the present, complete OPCAB using a BIMA T-graft configuration has been implemented. The mammary arteries were harvested using the skeletonization technique. The LIMA was anastomosed to the LAD, while the RIMA was connected as a T-shaped free graft to the LIMA, and then, sequentially, anastomoses were performed to the circumflex artery (Cx) and the distal right coronary artery (RCA). The RIMA anastomosis was located on the anterior surface of the LIMA, at the level of the left atrial appendage. All procedures were off-pump. Anastomosis quality was assessed by transit-time flow measurement (TTFM) and Doppler probes using the VeriQ system (Medistim, Oslo, Norway).

Data collection and variable definitions

Information on age, sex, BMI, diabetes, left ventricular ejection fraction (LVEF), and other baseline variables, as well as details of the surgical procedure, were obtained from the institutional electronic medical record (EMR).

For long-term follow-up, survival and the occurrence of major adverse cardiovascular events and other major post-operative complications were evaluated, including: 1) acute kidney injury, 2) stroke, 3) perioperative myocardial infarction, 4) mediastinitis, and 5) reoperations. Follow-up data were obtained from a review of electronic medical records, direct communication with the patient, their family members, and the treating physician, and telephone calls to confirm vital status at last known contact with the healthcare system.

Statistical analysis

Descriptive analysis of the study population was performed by calculating the mean and standard deviation for continuous variables or, in the case of non-normal distributions (assessed using the Shapiro-Wilk test), the median and interquartile range (IQR). Categorical variables were expressed as absolute numbers and percentages. To compare continuous variables between groups, the Student *t* test or the Mann-Whitney *U* test was used depending on the normality of the data; proportions were compared using the chi-square test or Fisher's exact test, depending on whether the assumptions of expected frequencies were met. Early postoperative complications were also reported, including in-hospital mortality, myocardial infarction, respiratory failure, acute kidney injury requiring dialysis, stroke, and mediastinitis, with the number of events and corresponding proportions and 95% confidence intervals calculated using Pearson's exact method.

For the primary endpoint, survival at 30 days (in-hospital mortality) and at 5, 10, 15, and 20 years was estimated using survival tables graphically represented by Kaplan-Meier curves, with patients aged <65 years and ≥65 years presented separately. Secondly, the association between age, BMI, LVEF, diabetes and time to death was analyzed using a Cox regression model. An unadjusted regression analysis was initially performed, followed by a regression model adjusted for potential confounders, including demographic variables (age, sex), comorbidities (chronic respiratory diseases, cerebrovascular diseases, dyslipidemia, smoking), and prior treatments (acetylsalicylic acid, calcium channel blockers, and statins). Furthermore, changes in mortality over time were assessed by comparing early mortality rates (30 days) across 5-year periods, from the beginning of follow-up in 2003 through 2023.

Finally, to assess the time elapsed until the performance of a subsequent coronary revascularization procedure, the cumulative incidence was estimated and graphically represented through curves illustrating the probability of reintervention throughout the follow-up.

Missing data were treated as completely random missing data (primarily comorbidities with a proportion of < 10% missingness). Therefore, multiple imputations were performed using the chained equation as a sensitivity analysis. Twenty imputed datasets were generated to reduce sampling error due to imputations. The proportion of missing data is presented in Table S1.

RESULTS

In the overall cohort of 4495 patients undergoing OPCAB with BIMA, the mean age was 64.1 ± 9.27 years,

and 8.34% ($n = 375$) were women. Patients were followed for a median of 6.13 years (IQR 2.62-10.36). Fifty six percent ($n = 2507$) were censored (lost to follow-up) at 10 years and 72% ($n = 3255$) at 20 years. Median preoperative LVEF was 58% (IQR 50-64); 84.2% ($n = 3345$) had normal or mildly reduced LVEF, while 15.8% ($n = 630$) had moderate or severe ventricular dysfunction. The procedure was performed on an emergency basis in 42.2% of cases ($n = 1884$). During surgery, the total number of arterial grafts showed a median of 3 (IQR 3-4), with an average of 1 graft derived from LIMA and 2 from RIMA. Demographic characteristics and comorbidities are presented in Table 1. In-hospital mortality was 0.6% ($n = 27$); other in-hospital complications are presented in Table 2. Early (30-day) mortality across the study periods was as follows: 1.0% ($n = 11/1153$) from 2003 to 2008; 1.1% (11/967) from 2009 to 2013; 0.2% (3/1154) from 2014 to 2019, and 0.2% (2/816) from 2020 to 2023. This downward trend was statistically significant ($p = 0.004$).

Overall survival was 70% (95% CI 68-72%) at 10 years and 31% (95% CI 28-34%) at 20 years.

In the age-stratified survival analysis, patients aged ≤65 years had a 5-year survival of 95.8% (95% CI 94.7-96.6), 10-year survival of 87.8% (95% CI 85.8-89.6), and 20-year survival of 60.8% (95% CI 55.6-65.7). In patients aged >65 years, 5-year survival was 86.2% (95% CI 84.5-87.7), 10-year survival was 54.1% (95% CI 51.2-56.9), and 20-year survival was 5.7% (95% CI 3.4-8.9). Age >65 years was an independent predictor of mortality (adjusted HR, 4.99; 95% CI 4.33-5.75; $p < 0.001$).

In unadjusted Cox analyses, moderate ventricular dysfunction was associated with an increased risk of death (HR 1.43; 95% CI 1.18-1.72; $p < 0.001$), as was severe dysfunction (HR 2.38; 95% CI 1.91-2.96; $p < 0.001$). After adjustment for covariates, the corresponding HRs were 1.22 (95% CI 1.00-1.49; $p = 0.049$) and 2.21 (95% CI 1.74-2.80; $p < 0.001$), respectively. For diabetes as the primary exposure, the unadjusted HR was 1.47 (95% CI 1.30-1.66; $p < 0.001$) and the adjusted HR was 1.30 (95% CI 1.15-1.47; $p < 0.001$). In the subgroup analysis of diabetes and obesity (reference: non-diabetic, non-obese individuals), obese non-diabetic patients had an unadjusted HR of 0.84 (95% CI 0.71-0.99; $p = 0.039$) and an adjusted HR of 1.05 (95% CI 0.88-1.24; $p = 0.605$); non-obese diabetic patients had an unadjusted HR of 1.58 (95% CI 1.37-1.82; $p < 0.001$) and an adjusted HR of 1.30 (95% CI 1.13-1.50; $p < 0.001$); and obese diabetic patients had an unadjusted HR of 1.13 (95% CI 0.93-1.38; $p = 0.214$) and an adjusted HR 1.28 (95% CI 1.05-1.56; $p = 0.015$) (Figures 2, 3, and 4).

DISCUSSION

This study represents one of the largest published cohorts of patients undergoing off-pump CABG using exclusively BIMA grafting, with long-term follow-up (20 years). Patients undergoing this surgical tech-

Table 1. Characteristics of study population according to diabetes status

Variable	All (n = 4495)	No diabetes (n = 3145)	Diabetes (n = 1350)	P	SMD
Female, n (%)	375 (8.34)	260 (8.27)	115 (8.52)	0.825	0.009
BMI, median (IQR)	28.0 (25.8; 30.5)	27.8 (25.6; 30.0)	28.7 (26.2; 31.6)	<0.001	0.205
Age, mean (SD)	64.1 (9.25)	63.4 (9.51)	65.8 (8.40)	<0.001	0.267
Emergency surgery, n (%)	1896 (42.2)	1265 (40.2)	631 (46.7)	<0.001	0.132
Ventricular function, n (%)				0.011	0.107
Normal	2352 (52.3)	1678 (53.4)	674 (49.9)		
Mild	1501 (33.4)	1052 (33.4)	449 (33.3)		
Moderate	416 (9.3)	265 (8.4)	151 (11.2)		
Severe	226 (5.0)	150 (4.8)	76 (5.6)		
Comorbidities, n (%)					
Prior AMI	1891 (42.1)	1247 (39.7)	644 (47.7)	<0.001	0.163
Prior PCI	1039 (23.1)	688 (21.9)	351 (26.0)	0.003	0.097
Supraventricular arrhythmia	65 (1.45)	44 (1.40)	21 (1.56)	0.792	0.013
Carotid artery stenosis	207 (4.61)	133 (4.23)	74 (5.48)	0.083	0.058
AAA	46 (1.02)	33 (1.05)	13 (0.96)	0.919	0.009
COPD	171 (3.80)	101 (3.21)	70 (5.19)	0.002	0.099
Prior stroke	131 (2.91)	81 (2.58)	50 (3.70)	0.049	0.065
Chronic kidney disease	283 (6.30)	149 (4.74)	134 (9.93)	<0.001	0.2
Blood hypertension	3549 (81.6)	2359 (78.4)	1190 (88.8)	<0.001	0.283
Dyslipidemia	3837 (85.4)	2638 (83.9)	1199 (88.8)	<0.001	0.144
Smoking	753 (16.8)	571 (18.2)	182 (13.5)	<0.001	0.128
Type 1 diabetes	184 (4.09)	0 (0.00)	184 (13.6)	<0.001	0.562
Type 2 diabetes	1085 (24.1)	0 (0.00)	1085 (80.4)	<0.001	2.862
Heart failure	1021 (23.5)	768 (25.5)	253 (18.9)	<0.001	0.161
Unstable angina	2200 (48.9)	1581 (50.3)	619 (45.9)	0.007	0.089
ASA, n (%)				0.695	0.028
≤7 days	3941 (87.7)	2758 (87.7)	1183 (87.6)		
>7 days	234 (5.21)	168 (5.34)	66 (4.89)		
No	320 (7.12)	219 (6.96)	101 (7.48)		
Statins, n (%)	3448 (76.7)	2379 (75.6)	1069 (79.2)	0.011	0.085
Total IMA grafts, n (%)				0.005	0.038
2	733 (16.3)	510 (16.2)	223 (16.5)		
3	2635 (58.6)	1859 (59.1)	776 (57.5)		
4	1048 (23.3)	735 (23.4)	313 (23.2)		
5	79 (1.76)	41 (1.30)	38 (2.81)		
Total LIMA grafts, n (%)				0.577	0.023
1	3923 (87.3)	2751 (87.5)	1172 (86.8)		
2	572 (12.7)	394 (12.5)	178 (13.2)		
Total RIMA grafts, n (%)				0.473	0.034
1	912 (20.3)	646 (20.5)	266 (19.7)		
2	2864 (63.7)	2009 (63.9)	855 (63.3)		
3	719 (16.0)	490 (15.6)	229 (17.0)		

AAA, abdominal aortic aneurysm; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IMA, internal mammary artery; IQR, interquartile range; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention; RIMA, right internal mammary artery; SD, standard deviation; SMD, standardized mean difference

nique demonstrated high long-term survival, with 60% of patients aged ≤65 years alive at 20 years. Severe ventricular dysfunction and diabetes were identified as predictors of increased mortality during follow-up; whereas obesity was not an independent predictor. Several observational studies and meta-analyses have suggested that the use of BIMA grafting offers greater survival compared to the use of a single internal mammary artery grafting. (15,16) The Arterial Revascularization Trial (ART) evaluated 10-year outcomes

and found no significant differences in survival. However, this result has been criticized for multiple reasons: high crossover, heterogeneous techniques across centers, and a high rate of use of other arterial grafts in both groups, which diluted the differences. (17,18) The low adoption rate observed in the use of BIMA, despite its benefits, could be attributed to the complexity and prolonged duration of surgery, as well as the increased risk of complications, such as sternal wound infections.

Table 2. Postoperative complications according to diabetes status

Variable	Total (n = 4495)	No diabetes (n = 3145)	Diabetes (n = 1350)	P
In-hospital mortality, n (%)	27 (0.60)	20 (0.64)	7 (0.52)	0.798
Heart failure, n (%)	41 (0.91)	23 (0.73)	18 (1.33)	0.076
Reoperation for bleeding, n (%)	69 (1.55)	57 (1.83)	12 (0.90)	0.031
Hemodynamic complications, n (%)	375 (8.34)	261 (8.30)	114 (8.44)	0.918
Acute myocardial infarction, n (%)	47 (1.05)	35 (1.12)	12 (0.90)	0.609
Atrial fibrillation, n (%)	552 (12.3)	360 (11.5)	192 (14.2)	0.011
Acute kidney injury requiring dialysis, n (%)	34 (0.76)	21 (0.67)	13 (0.96)	0.392
Neurological complications, n (%)	51 (1.13)	29 (0.92)	22 (1.63)	0.057
Stroke with sequelae, n (%)	12 (0.27)	8 (0.25)	4 (0.30)	0.763
Mediastinitis, n (%)	53 (1.18)	23 (0.73)	30 (2.22)	<0.001
Respiratory failure requiring MV, n (%)	65 (1.46)	51 (1.63)	14 (1.05)	0.173

MV: mechanical ventilation

Fig. 1. Overall survival according to patient age

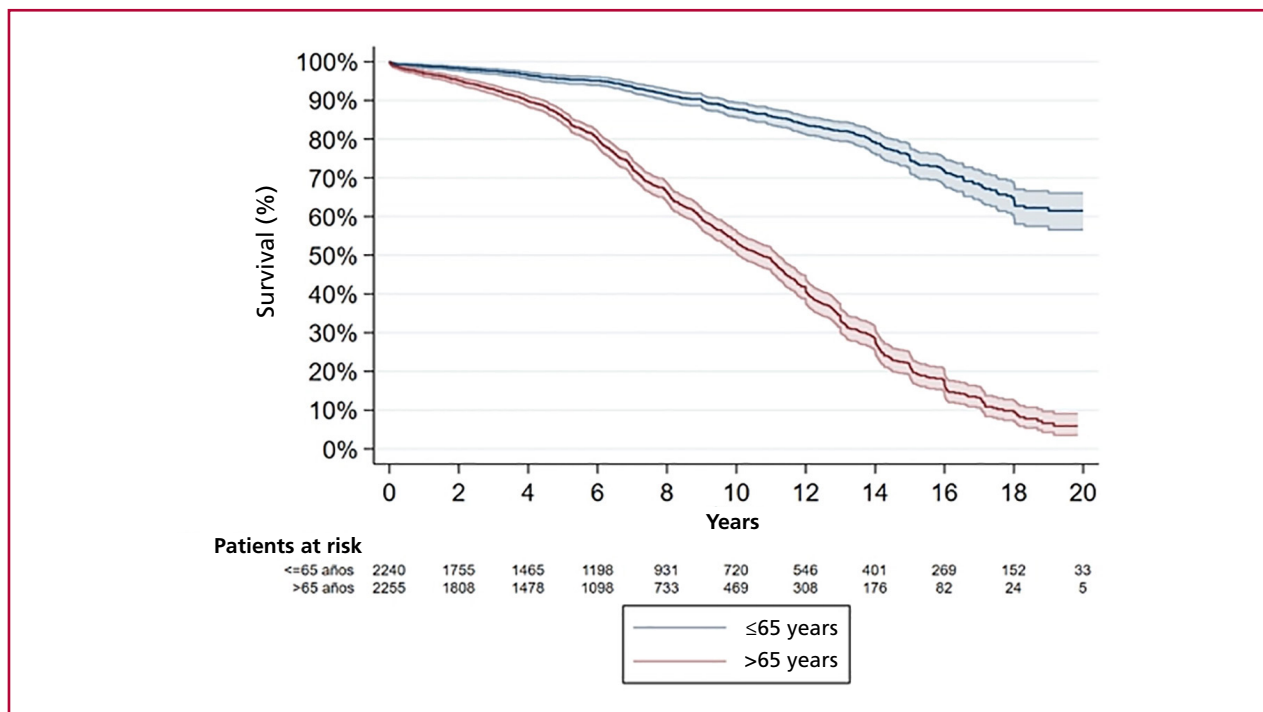


Fig. 2. Survival curve according to ventricular function

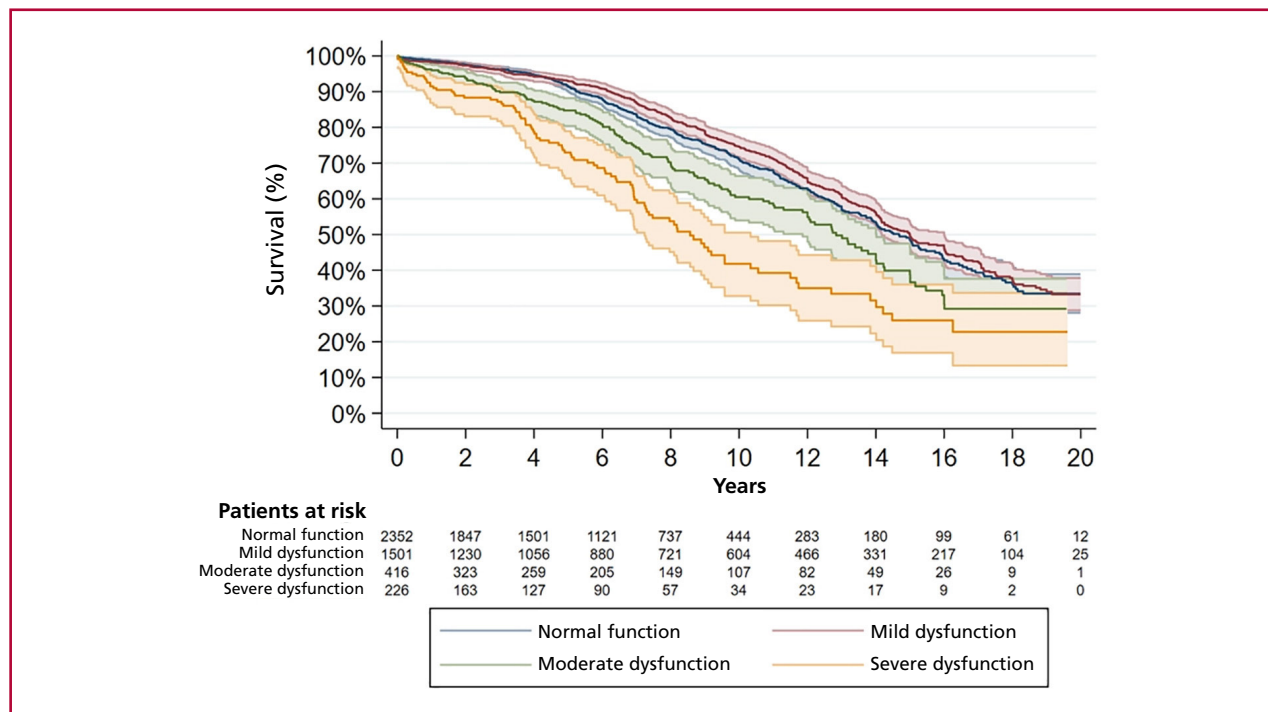
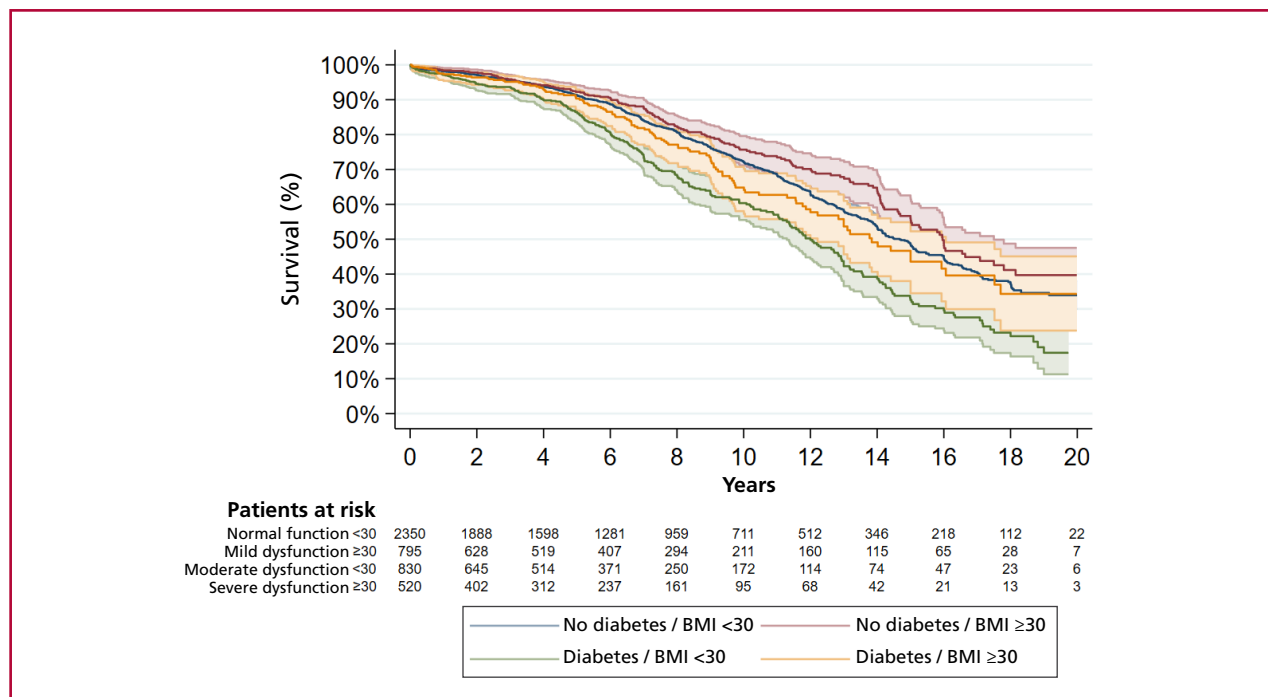


Fig. 3. Survival curve according to obesity and diabetes status.



BMI: body mass index

This study reflects our experience of over 20 years of exclusively performing off-pump CABG with BIMA in a T-graft configuration, as originally described by Tector et al. (19) The adoption of this technique resulted from a progressive evolution over time, aimed

at developing a low-morbidity procedure (off-pump and intraoperative extubation) using conduits with proven long-term patency (BIMA). In our initial series, we evaluated the technical feasibility, hospital outcomes, and the degree of early patency of the ar-

terial grafts according to this configuration. (20) In the second stage, we conducted comparative studies in the group of patients undergoing CABG using a single internal mammary artery plus venous grafts: patients with off-pump CABG with BIMA had higher long-term survival. (21) We also analyzed long-term survival with the use of these two CABG techniques in patients over 70 years of age, with better outcomes in the group of patients with OPCAB with BIMA. (22) The use of off-pump revascularization allowed us to avoid aortic manipulation, reducing the incidence of postoperative complications such as stroke. A recent meta-analysis demonstrated that the risk of postoperative stroke, mortality, renal failure, atrial fibrillation, bleeding, and length of stay in the recovery room was lower with off-pump CABG with BIMA, which avoids aortic manipulation and completely eliminates traction and clamping of the ascending aorta. (23) We believe that the low postoperative mortality and morbidity observed in our series are largely attributable to this technique.

The upper age limit for the benefit from using BIMA has been a subject of debate. Mohammadi et al. recently demonstrated that the survival benefit associated with BIMA or other arterial conduits is lost in patients older than 60 years. (24) In our study, patients older than 65 years had poorer long-term survival with the use of BIMA, with age as an independent predictor. Severe left ventricular systolic dysfunction in the context of significant coronary artery disease remains a powerful predictor of poor prognosis. The randomized STICH trial has consistently reported that CABG improves survival rates and reduces cardiovascular mortality in patients with severe ventricular dysfunction. (25) Ikeda et al. reported, in a series of patients undergoing OPCAB with BIMA and severe ventricular dysfunction (mean LVEF 24.8%) followed for 10 years, low in-hospital mortality (1.65%) and improved ventricular function in 75.2% of cases. In the long-term follow-up, they identified LVEF <30% and non-use of BIMA as independent predictors of death and cardiac events. (26) In our series, severe ventricular dysfunction was identified as an independent predictor of death during follow-up, whereas moderate ventricular dysfunction was not.

Diabetes doubles the risk of cardiovascular disease, and approximately 75% of deaths in diabetic patients are due to coronary artery disease. (27) Long-term survival in diabetic patients is lower; diabetes is an independent predictor of long-term mortality after CABG. (28) Type 2 diabetes presents with a diffuse anatomical pattern of coronary artery disease with rapid progression, lesions with smaller luminal diameters, and greater extracardiac comorbidity; in this scenario, OPCAB may represent a lower-morbidity option. (29) Renner et al. reported that off-pump CABG is associated with lower mortality and better postoperative outcomes in diabetic patients when comparing 355 diabetic patients who underwent off-pump CABG

and 502 who underwent on-pump CABG; the former was associated with a significantly lower 30-day mortality rate, fewer postoperative complications, and a significant reduction in mortality at 6 months and 1 year. (30) Srinivasan et al. reported in their propensity score-adjusted study that the incidence of stroke was six times higher, and the risk of renal failure was 2.3 times higher in the ONCAB group than in the OPCAB group. (31) The use of both internal mammary arteries—the arterial grafts of choice—is associated with a low need for reoperation, and when harvested using the skeletonization technique, it reduces the risk of potential deep sternal infections, particularly in diabetic patients. (32) Park et al., in a study exclusively involving OPCAB, demonstrated that diabetes was not a risk factor for either early or long-term outcomes. (33) In our study, diabetes was an independent predictor of lower long-term survival, and diabetic patients had a higher incidence of mediastinitis. To date, evidence regarding the relationship between obesity and outcomes following revascularization has yielded conflicting data. This is due, at least in part, to heterogeneous criteria for defining obesity and to variability in the assessed outcomes. Terada et al. evaluated the associations of BMI with short-, medium-, and long-term mortality after CABG in patients with varying grades of coronary anatomical risk and diabetes mellitus. There was lower medium- and long-term mortality in the group of overweight patients, but no differences in mortality in the obese groups after CABG. (34) Our study explored the interrelationship between diabetes and BMI, and their impact on long-term survival. Patients with diabetes had a higher risk of long-term mortality, regardless of BMI. In contrast, the group without diabetes but with a BMI ≥ 30 had a lower risk of mortality; this phenomenon has been defined by various surgical groups as the “obesity paradox.” (35)

Study strengths and limitations

One of the principal strengths of this study is that it represents one of the largest reported cohorts of patients undergoing off-pump CABG with BIMA, thereby providing evidence on the therapeutic impact of this surgical approach. A further strength is the 20-year follow-up, which enabled the evaluation of overall long-term survival and outcomes across patient groups with different baseline characteristics. Finally, the uniform surgical approach across the entire medical staff allowed the inclusion of all patients admitted with multivessel coronary artery disease, thereby reducing potential selection bias.

However, these findings should be interpreted in light of several limitations. First, this was a retrospective study without a control group. Although our previously published controlled study demonstrated improved long-term survival with this technique, the aim of this study was to report the therapeutic impact of off-pump CABG with BIMA over extended follow-

up to identify independent predictors. The observational design provides real-world data but can only provide evidence of association rather than causation. Second, as a single-center study, the generalizability of the findings is limited. Finally, although the analyses were adjusted for available confounders, residual confounding not accounted for in our analysis cannot be excluded.

CONCLUSIONS

This study represents one of the largest cohorts of patients undergoing off-pump CABG with BIMA with a long-term follow-up of 20 years. Patients aged ≤ 65 years undergoing BIMA grafting had a 20-year survival rate of 60%. Regarding predictors of mortality, we observed that while moderate ventricular dysfunction and obesity were not independent predictors, severe dysfunction and diabetes were.

Conflicts of interest

None declared.

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

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SUPPLEMENTARY MATERIAL**Table S1.** Proportion of missing data

Description	% Missing data
Female	0.00
Body mass index	9.52
Age	0.00
Emergency surgery	0.00
Intraoperative LVEF (continuous value)	11.20
Normal or mildly reduced LVEF	11.20
Moderately or severely reduced LVEF	11.20
History of acute myocardial infarction	3.97
History of percutaneous coronary intervention	3.97
History of supraventricular arrhythmia	5.09
History of carotid artery stenosis	3.99
History of abdominal aortic aneurysm	3.97
History of respiratory disease	7.34
Prior stroke	4.77
Chronic kidney disease	6.40
Blood hypertension	3.97
Dyslipidemia	3.97
Smoking	4.22
Diabetes	5.76
Family history of heart disease	3.97
Stable angina (clinical presentation)	6.78
Unstable angina (clinical presentation)	4.39
Anginal pain within 48 hours	4.37
AMI (clinical presentation)	4.37
Heart failure (clinical presentation)	4.37
Syncope (clinical presentation)	3.97
Prior intra-aortic balloon pump	3.97
Preoperative ASA use	8.48
Preoperative statin use	8.61
Total number of arterial grafts	0.00
Total left internal mammary artery grafts	0.00
Total right internal mammary artery grafts	0.00

ASA, acetylsalicylic acid; LVEF, left ventricular ejection fraction

RENACER-CV: National Registry of Cardiovascular Rehabilitation Centers in Argentina

RENACER-CV: Registro Nacional de Centros de Rehabilitación Cardiovascular en Argentina

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ABSTRACT

Background: Cardiovascular rehabilitation (CVR) is a fundamental intervention in cardiovascular secondary prevention, with a proven impact on reducing mortality and rehospitalizations, as well as improving functional capacity and quality of life. However, its implementation and availability show marked heterogeneity at global and regional levels.

Objective: The National Registry of Cardiovascular Rehabilitation Centers (RENACER-CV) aimed to describe the current status of CVR in Argentina, characterizing the geographic distribution, available resources, care modalities, and organizational aspects of the centers.

Methods: A descriptive cross-sectional study was conducted using a structured survey administered to institutional representatives of CVR centers nationwide between July and August 2025. The survey included institutional characteristics, regional distribution, human resources, rehabilitation phases offered, care delivery models (on site and remote), volume of patients treated, prevalent diseases, equipment, and functional assessment tools. The analysis was performed using descriptive statistics.

Results: Seventy-four CVR centers were identified, of which 59 responded to the survey. The Autonomous City of Buenos Aires and the Province of Buenos Aires concentrated 69.4% of centers. Permanent medical supervision was available in 84.7% of centers, and 59.3% had specialized kinesiologists. Most centers offered Phase II (79.6%) and Phase III (93.2%) programs. The mean annual number of patients enrolled was 278, with wide inter-center variability. At the time of the survey, 13.5% of centers reported implementing telerehabilitation programs.

Conclusions: RENACER-CV shows the availability of an active network of cardiac rehabilitation centers in Argentina, revealing an effective national network but also substantial geographic, organizational and access disparities. Expanding CVR programs in underserved regions and strengthening hybrid and telerehabilitation strategies should be considered key priorities to improve equity and quality of cardiovascular prevention.

Keywords: Cardiac rehabilitation - Health registries - Health care disparities

RESUMEN

Introducción: La rehabilitación cardíaca (RCV) es una intervención fundamental de la prevención secundaria cardiovascular, con impacto demostrado en la reducción de la mortalidad, las reinternaciones, la mejora de la capacidad funcional y la calidad de vida. Sin embargo, su implementación y disponibilidad presentan una marcada heterogeneidad a nivel global y regional.

Objetivos: El Registro Nacional de Centros de Rehabilitación Cardiovascular (RENACER-CV) tuvo como objetivo describir la situación actual de la RCV en Argentina, caracterizando la distribución geográfica, los recursos disponibles, las modalidades de atención y los aspectos organizacionales de los centros.

Material y métodos: Se realizó un estudio descriptivo de corte transversal mediante una encuesta estructurada dirigida a los referentes institucionales de centros de RCV de todo el país entre julio y agosto de 2025. El relevamiento incluyó características institucionales, distribución regional, recursos humanos, fases de rehabilitación ofrecidas, modalidades de atención (presencial y remota), volumen de pacientes atendidos, patologías prevalentes, equipamiento y herramientas de evaluación funcional. El análisis se efectuó mediante estadística descriptiva.

Resultados: Se identificaron 74 centros de RCV, de los cuales 59 respondieron la encuesta. El 69,4% se concentró en la Ciudad Autónoma

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noma de Buenos Aires y la provincia de Buenos Aires. El 84,7% de los centros contó con supervisión médica permanente y el 59,3% con kinesiólogos especializados. La mayoría desarrolló programas de fase II (79,6%) y fase III (93,2%). El número promedio anual de pacientes fue de 278, con amplia variabilidad entre centros. La telerehabilitación se implementó en el 13,5% de las instituciones al momento del relevamiento.

Conclusión: El RENACER-CV muestra que Argentina dispone de una red activa de centros de RCV, aunque con importantes desigualdades territoriales, organizacionales y de acceso. La expansión de programas en regiones con menor cobertura y el fortalecimiento de modalidades híbridas y de telerehabilitación representan prioridades estratégicas para mejorar la equidad y la calidad de la atención cardiovascular.

Palabras clave: Rehabilitación cardíaca - Registros de salud - Desigualdades en la atención de la salud

INTRODUCTION

Cardiovascular rehabilitation (CVR) is a proven intervention within the continuum of care for secondary cardiovascular prevention and risk factor management, with an impact on reducing mortality and rehospitalizations. Patients who adhere to these programs improve their functional capacity and quality of life, increase their ability to work and/or remain active, achieve greater autonomy, and, consequently, reduce the need for special care, disability, and loss of social productivity, as reflected in lower work absenteeism, lower social costs, and greater economic participation. (1–5) Despite these benefits, the implementation of CVR programs show marked heterogeneity in their global development and availability, influenced by economic, organizational, and healthcare access factors. (6–8)

In this context, the Exercise Cardiology Council of the Argentine Society of Cardiology (SAC), in conjunction with the Health Policy Division and methodological coordination and statistical analysis provided by the Research Division, undertook an updated survey of the country's CVR centers. This initiative, known as the National Registry of Cardiovascular Rehabilitation Centers (RENACER-CV), aimed to describe the organizational characteristics, geographic coverage, human resources, modalities of care, and equipment of CVR centers, as well as to identify opportunities for improvement and regional development.

METHODS

First, the existence of CVR centers in the country was surveyed, using the previous survey conducted by the 2019 SAC Exercise Cardiology Council as a starting point, supplemented by consultations with cardiologists in each province. For the purposes of this registry, a CVR center was defined as any public or private institution that reported offering structured CVR programs based on supervised physical exercise, involving at least one healthcare professional, and intended for patients with cardiovascular disease at any stage of its progression. In an initial stage of the survey, priority was given to identifying centers that had a lead physician or medical director responsible for the program. Subsequently, and with the aim of achieving a more comprehensive characterization of the actual availability of CVR nationwide, the inclusion criteria were expanded to incorporate centers coordinated by kinesiotherapists or professionals from other related disciplines, even if they exclusively offered Phase IV programs. Inclusion in the registry did not involve external verification of compliance with formal accreditation criteria

or international standards, and the collected information was based on self-reporting by the participating centers.

Subsequently, a descriptive cross-sectional study was conducted using a structured survey sent to institutional representatives of centers nationwide between July and August 2025. The questionnaire included questions aimed at exploring institutional characteristics, geographic coverage and regional distribution, available human resources (medical professionals, kinesiotherapists, physical education teachers, technicians, nursing staff, nutritionists, and mental health specialists, among others), the types of programs offered (Phase I or inpatient: early mobilization; Phase II: supervised rehabilitation; Phase III: transition or supervised maintenance; Phase IV: long-term maintenance, which begins once the supervised phases are completed), care modalities, the volume of patients treated, prevalent conditions, as well as equipment and functional assessment tools.

The data were analyzed by the SAC Research Area using descriptive statistics, including frequencies, percentages, and measures of central tendency.

Ethical considerations

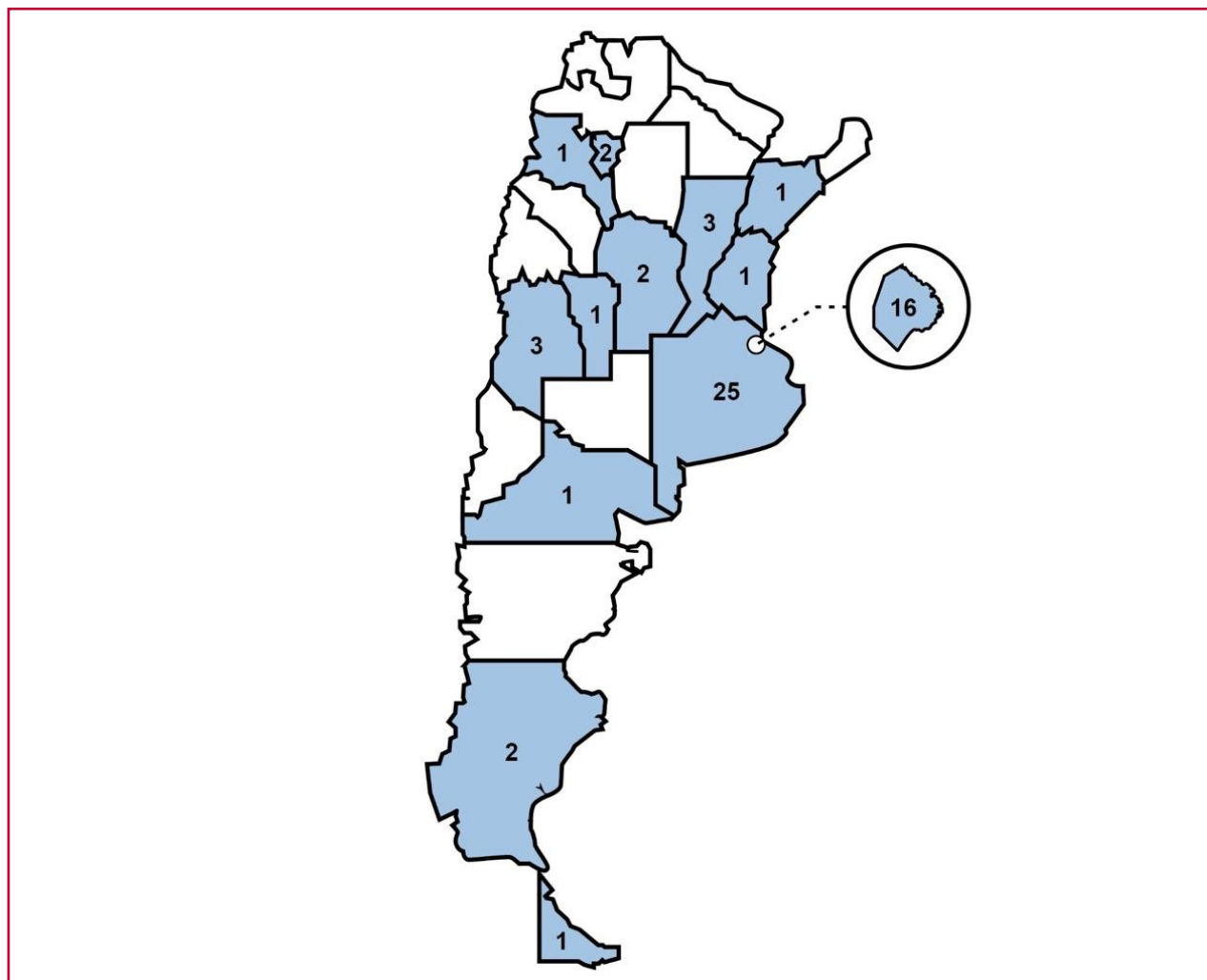
This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (29) and its subsequent amendments. It was an observational, descriptive, cross-sectional study based on an institutional survey, without the collection of individual clinical data or patient-identifying information. For this reason, individual informed consent was waived. Participation by the centers was voluntary, and the data were analyzed in aggregate form, ensuring the confidentiality of the information. The protocol was reviewed and approved by the Research Area of the Argentine Society of Cardiology.

RESULTS

A total of 74 centers were identified throughout Argentina. Fifty-nine complete responses were received from public and private centers, distributed as follows: the Autonomous City of Buenos Aires and the Province of Buenos Aires 69.4% (41 centers), the Central Region 10.1% (6 centers), the Cuyo Region 6.7% (4 centers), Patagonian Region 6.7% (4 centers), NOA Region (northwestern Argentina) 5% (3 centers), and NEA Region (northeastern Argentina) 1.7% (1 center). (Figure 1).

A total of 84.7% centers had permanent medical supervision during sessions, and 59.3% had kinesiotherapists specializing in CVR. Other professionals frequently included in the teams were physical education teachers (61%), nutritionists (55.9%), psychologists (37.2%), nursing staff (22%), and cardiac care technicians (22%).

Fig. 1. Distribution of the number of CVR centers by province. **Autonomous City of Buenos Aires:** Villa del Parque, Recoleta (3), Parque Chas, Caballito (3), Monserrat, Palermo (4), Balvanera, Belgrano (2) quarters; **Province of Buenos Aires:** Cañuelas, Ramos Mejía, El Palomar, Lomas de Zamora, Pergamino, Tigre, San Nicolás, Adrogué, Bahía Blanca (2), San Bernardo, Morón, Quilmes, La Matanza, Luján, Chivilcoy, Lanús, La Plata (2), Villa Bosch, Laprida, Ensenada, Berisso, Olavarría, San Justo; **Catamarca:** San Fernando del Valle; **Córdoba:** Villa María and Córdoba; **Corrientes:** Corrientes; **Entre Ríos:** Paraná; **Mendoza:** San Rafael; **Río Negro:** Bariloche; **San Luis:** Merlo; **Santa Cruz:** El Calafate; **Santa Fe:** Rafaela, Rosario (2); **Tierra del Fuego:** Ushuaia; **Tucumán:** San Miguel de Tucumán



Regarding rehabilitation phases, 79.6% of the centers (n=47) conducted Phase II programs, 93.2% (n=55) Phase III programs, and of the centers with inpatient facilities (n=30), 56% (n=17) conducted Phase I hospital-based programs.

During the COVID-19 lockdown period, 35.6% of the centers (n=21) implemented virtual CVR sessions. At the time of the survey, 13.5% (n=8) of the centers reported implementing telerehabilitation modalities.

The average annual number of patients admitted to CVR programs was 278, with marked variability among centers (range: 4–4500).

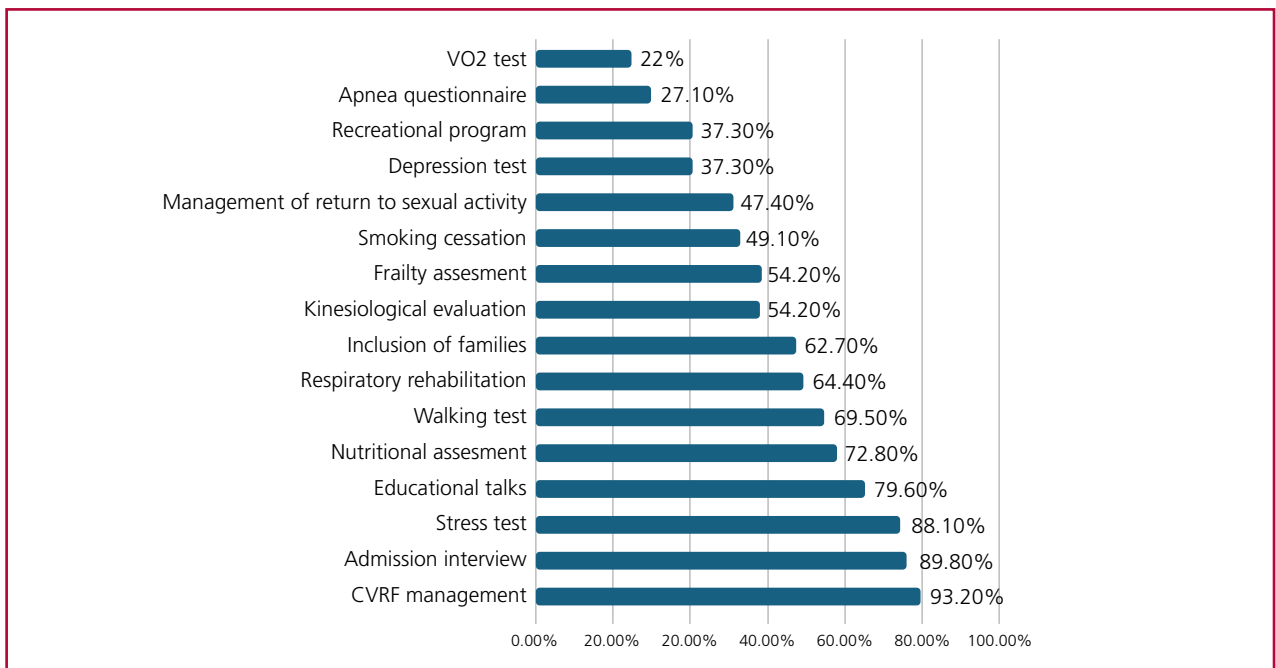
The most frequently treated conditions, expressed as a percentage of centers reporting inclusion in their programs, were coronary artery disease (96.6%), heart failure (94.9%), postoperative care following valve

surgery (89.8%), patients with implantable devices (72.8%), and peripheral vascular disease (69.4%).

Regarding CVR coverage, of the 59 centers surveyed, 54.2% have a mixed coverage system. Among this group, 44.1% are private centers, funded through social welfare programs, private health insurance, and private contributions, while 10.2% are public centers that, in addition to state funding, receive contributions from social welfare programs and private health insurance. Moreover, 18.6% of the centers rely exclusively on the public health system, another 18.6% receive only private contributions from patients, 5.1% are institutions belonging to union-affiliated health insurance plans, and 3.4% of the centers did not provide information on this matter.

Most centers reported conducting structured clini-

Fig. 2. Monitoring practices and strategies. Values are expressed as the percentage of centers reporting implementation of each practice. CVRF: cardiovascular risk factors; VO2: oxygen consumption.



cal evaluations, notably the management of cardiovascular risk factors (93.2%), the admission interview (89.8%), and the exercise stress test (88.1%). Functional and nutritional assessments were available in approximately two-thirds of the centers, while direct measurement of oxygen consumption was rare (22%). (Figure 2)

Complementary educational and recreational interventions were implemented to a lesser extent. Among these, the most frequently reported were sports and meditation (16.9%), followed by yoga (13.5%). In contrast, practices such as tai chi and healthy cooking showed considerably lower adoption rates (3.4% and 6.8%, respectively).

Fifty-six per cent of the centers ($n=33$) consider essential to have a stress test (with or without imaging) before beginning exercise sessions.

DISCUSSION

The results of the RENACER-CV registry reflect a reality consistent with that described in previous national and international surveys: CVR is established as an essential and cost-effective strategy within the continuum of cardiovascular care, although significant gaps persist in its implementation and accessibility. (9–11) Accumulated evidence robustly demonstrates that CVR programs reduce mortality, improve functional capacity, and optimize quality of life in patients with cardiovascular disease, (12–14) findings confirmed by contemporary meta-analyses even in the current era of advanced pharmacological and interventional therapies. (15) In agreement, international

cardiovascular prevention guidelines issue a Class I recommendation for participation in structured CVR programs. (16,17)

Unlike previous national surveys, RENACER-CV provides a comprehensive update on the state of CVR in Argentina in the post-pandemic era, incorporating for the first time systematic information on the implementation of telerehabilitation modalities and hybrid care models. In addition, the registry provides a detailed characterization of coverage and financing schemes, as well as the human resources and practices actually available at the centers— aspects of particular relevance for health planning. These elements enable not only for a description of the availability of CVR programs but also for the identification of organizational gaps and concrete opportunities for improvement in a dynamic and changing context.

As observed in other low- and middle-income countries, the registry shows a markedly unequal geographic distribution of CVR centers in Argentina, with a strong concentration in the province of Buenos Aires and the Autonomous City of Buenos Aires. The rest of the country has a significantly lower offer, with several jurisdictions lacking registered formal programs, highlighting a territorial inequity that limits effective access to this intervention, as noted in previous Latin American reports. (18,19) Characterization based on the population size of the area of influence reinforces this observation (Figure 3). The vast majority of centers (84.7%) are located in cities with more than 100 000 inhabitants, confirming that CVR remains a service strongly associated with urban settings, which

have better health infrastructure and availability of specialized human resources. In contrast, the presence of centers in small cities or rural settings is minimal, representing a significant structural barrier for large segments of the population. In fact, only 1.7% of centers are located in cities with fewer than 10 000 inhabitants, and the total percentage in areas with fewer than 50 000 inhabitants does not exceed 12%. Geographic distance, difficulty in travel, and limited availability of nearby services negatively impact treatment continuity, adherence, and, ultimately, clinical outcomes.

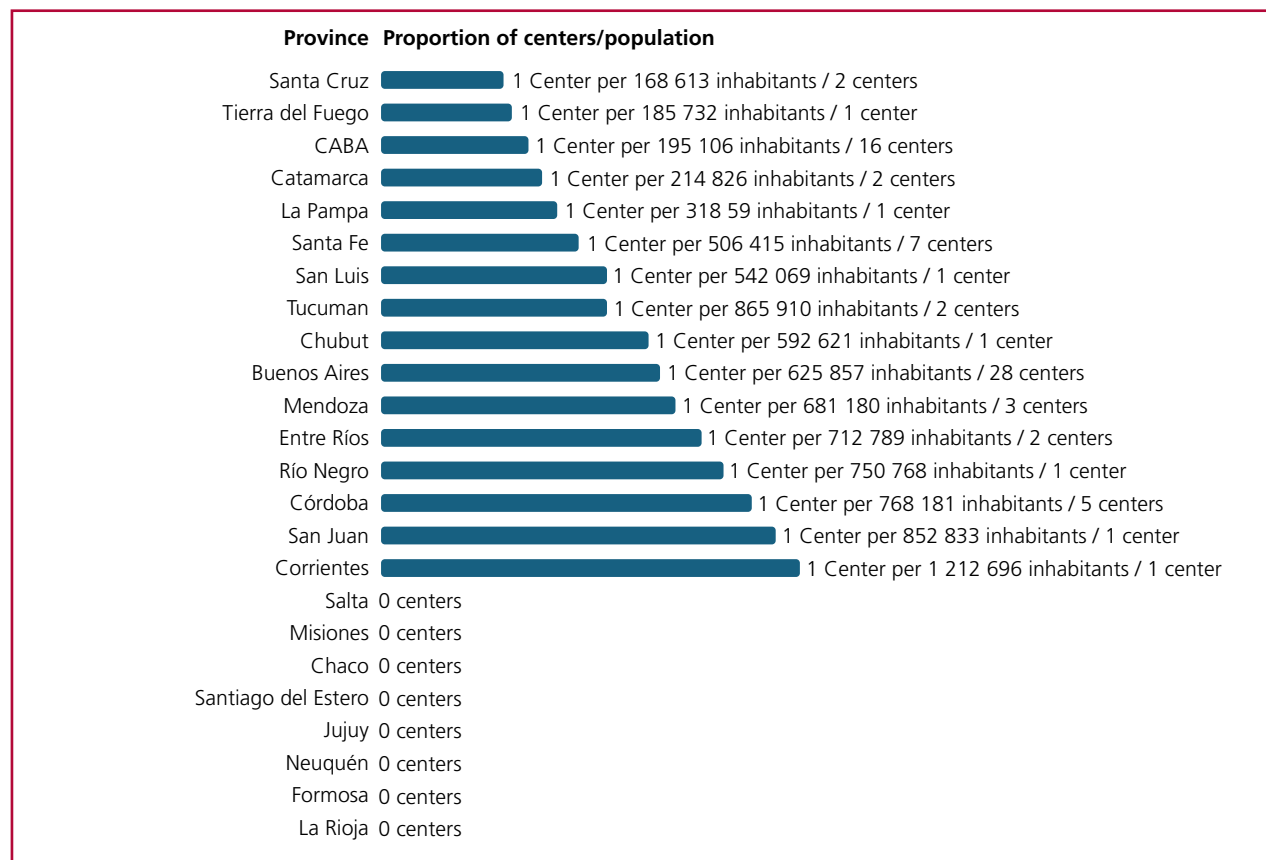
This scenario is not unique to Argentina. In Brazil, national studies have documented marked regional heterogeneity, with a concentration of centers in urban areas and a pronounced deficit in Northern and Northeastern regions. (20,21) In Colombia, a similar picture has been described, with a predominance of programs in large cities and persistent gaps in rural and intermediate areas. (22) In Chile, although progress has been observed in integrating CVR into the public system, organizational and territorial coverage challenges persist. (23) These trends have been highlighted in regional reviews that identify insufficient funding, territorial inequity, and a lack of process standardization as common obstacles. (18)

In addition to geographical barriers, economic and health coverage limitations emerge as an extra factor of inequity. Registry data indicate that the lack of health coverage is one of the main factors limiting participation in CVR programs. Patients with health insurance, private health plans, or the financial means to personally cover costs have greater access, while the offer of programs within the public system is insufficient to meet the demand of the population that depends exclusively on this subsystem. This situation reinforces the inequitable nature of access to CVR and underscores the need for health policies aimed at strengthening public provision and financing mechanisms.

Another relevant aspect identified by RENACER-CV is the heterogeneity in human resources, equipment, and working modalities across centers. While a considerable proportion meets basic international standards, there is less integration of psychosocial and nutritional components—fundamental aspects for a truly multidisciplinary and patient-centered CVR. This finding agrees with those described in other regional surveys and points to a specific area of improvement. (18)

In this context, the gradual adoption of hybrid and telerehabilitation modalities emerges as a strategic opportunity. Although their current implementation

Fig. 3. Proportion of CVR centers by population.



CABA: Autonomous City of Buenos Aires; CVR: cardiovascular rehabilitation

is still limited, experience during the pandemic and international evidence suggest that these models can help improve accessibility, adherence, and system efficiency, particularly in countries with vast territories and significant population heterogeneity. (24–27)

From a health planning perspective, the findings of RENACER-CV provide strategic information to guide public policy decisions and health system management. The geographic concentration of centers, heterogeneity in coverage, and limited availability of programs in regions with lower population density emphasize the need to prioritize the expansion of CVR within the public system and to promote financing mechanisms that ensure equitable access. Moreover, the characterization of available resources allows for the definition of minimum quality standards and accreditation processes. In this context, as previously discussed, strengthening hybrid and telerehabilitation models emerges as a possible strategy to reduce geographic barriers and optimize resource use. The development of a coordinated national CVR network, integrated into the various health subsystems, could substantially contribute to improving cardiovascular outcomes and system efficiency. (28)

Study Limitations

It should be noted that a small percentage of centers, identified through other scientific societies of cardiology, declined to participate in the survey, which constitutes a limitation to the full representativeness of the universe of institutions. In this regard, voluntary participation and the lower inclusion of institutions not affiliated with the SAC could have generated selection biases, which must be considered when interpreting the results.

CONCLUSION

The RENACER-CV registry provided an updated and representative overview of the availability of CVR in Argentina, identifying regional patterns, territorial inequities and organizational aspects relevant to health planning.

The gradual development of a national network of CVR centers, the expansion of programs in regions with lower coverage, and the consolidation of telerehabilitation strategies are priorities for the coming years. The Exercise Cardiology Council, together with the Health Policy Area, reinforce their commitment by promoting policies, standards, and professional training initiatives aimed at improving the quality and equity of CVR in our country, and fostering collaborative networks with other cardiology societies and participants of the healthcare system, as a key strategy to promote integrated, sustainable development aligned with international recommendations.

Conflicts of interest

None declared.

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

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Clinical, Imaging, and Disease Progression Sex-related Differences in Transthyretin Cardiac Amyloidosis

Amiloidosis cardíaca por transtiretina: diferencias clínicas, imagenológicas y evolutivas según el sexo

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ABSTRACT

Background: Transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly diagnosed disease. Sex-related differences in clinical presentation and disease progression have been described; however, we lack local data identifying these differences.

Objective: The aim of this study was to describe sex-related differences in clinical presentation, imaging characteristics at diagnosis, and disease progression in patients diagnosed with ATTR-CA.

Methods: A retrospective, multicenter (two centers) cohort study was conducted including patients diagnosed with ATTR-CA between 2010 and 2025. Clinical, electrocardiographic, and imaging variables at the time of diagnosis, as well as events during follow-up, were obtained from institutional electronic medical records. Baseline characteristics were compared between men and women using appropriate statistical tests. Kaplan-Meier curves were built to estimate the incidence of all-cause mortality, hospitalizations for heart failure, and a composite endpoint of both events.

Results: A total of 186 patients were included: 153 men (82.2%) and 33 women (17.8%). Women were diagnosed at an older age (83 vs. 80 years; $p=0.042$) and had thinner septal and posterior wall thicknesses (14.8 vs. 16.9 mm; $p=0.020$ and 12.7 vs. 14.3 mm; $p=0.005$, respectively) on baseline echocardiography compared with men. On cardiac magnetic resonance imaging ($n=108$), women had higher left and right ventricular ejection fractions (62% vs. 50%; $p=0.031$ and 56% vs. 47%; $p=0.011$, respectively) and lower maximum wall thickness (16.4 mm vs. 18.7 mm; $p=0.013$). During a median follow-up of 725.5 days (interquartile range, IQR, 342.5–1220), no statistically significant differences in mortality or hospitalizations for heart failure were observed between the two sexes.

Conclusions: In this national cohort of patients with ATTR-CA, women were diagnosed at an older age and had less structural and functional myocardial involvement at the time of diagnosis. However, these differences did not translate into a significant impact on clinical outcomes during follow-up.

Keywords: Amyloidosis - Transthyretin - Sex - Electrocardiogram - Echocardiogram - Magnetic resonance imaging

RESUMEN

Introducción: La cardiopatía amiloidótica por transtiretina (CA-TTR) es una entidad cuyo diagnóstico es cada vez más frecuente. Se han descrito diferencias en la presentación clínica y en la evolución según el sexo, sin embargo, no contamos con información local que describa estas diferencias.

Objetivo: Describir las diferencias en la presentación clínica, las características imagenológicas al diagnóstico y la evolución de pacientes con diagnóstico de CA-TTR según el sexo.

Materiales y métodos: Estudio de cohorte retrospectivo, multicéntrico (dos centros), que incluyó pacientes con diagnóstico de CA-TTR entre 2010 y 2025. Las variables clínicas, electrocardiográficas e imagenológicas al momento del diagnóstico, así como los eventos durante el seguimiento, se obtuvieron a partir de la historia clínica electrónica institucional. Se compararon las características basales entre hombres y mujeres mediante pruebas estadísticas apropiadas. Se realizaron curvas de Kaplan-Meier para estimar la incidencia de mortalidad por cualquier causa, internaciones por insuficiencia cardíaca y un punto final combinado de ambos eventos.

Resultados: Se incluyeron 186 pacientes, 153 hombres (82,2%) y 33 mujeres (17,8%). Las mujeres fueron diagnosticadas a mayor edad (83 vs. 80 años; $p = 0,042$). En el ecocardiograma basal, presentaron menor espesor septal y de la pared posterior (14,8 vs. 16,9 mm; $p = 0,020$ y 12,7 vs. 14,3 mm; $p = 0,005$, respectivamente) en comparación con los hombres. En la resonancia magnética cardíaca ($n = 108$), las mujeres mostraron mayor fracción de eyección del ventrículo izquierdo y derecho (62% vs. 50%; $p = 0,031$ y 56% vs. 47%; $p = 0,011$, respectivamente) y menor espesor parietal máximo (16,4 mm vs. 18,7 mm; $p = 0,013$). Durante una mediana de

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seguimiento de 725,5 días (rango intercuartílico, RIC, 342,5–1220), no se observaron diferencias estadísticamente significativas en la mortalidad ni en internaciones por insuficiencia cardíaca entre ambos sexos.

Conclusiones: En esta cohorte nacional de pacientes con CA-TTR, las mujeres fueron diagnosticadas a mayor edad y presentaron menor compromiso miocárdico estructural y funcional al momento del diagnóstico. Sin embargo, estas diferencias no se tradujeron en un impacto significativo en la evolución clínica durante el seguimiento.

Palabras clave: Amiloidosis - Transtiretina - Sexo - Electrocardiograma - Ecocardiograma - Resonancia magnética.

INTRODUCTION

Transthyretin cardiac amyloidosis (ATTR-CA) is a disease characterized by the deposition in the myocardium of misfolded fibrils derived from transthyretin, a protein produced primarily by the liver. (1,2) Transthyretin cardiac amyloidosis can be sporadic or hereditary. The non-hereditary wild-type form (ATTRwt-CA) is the most common; it presents in later stages of life and has a median survival of 3 to 5 years. The hereditary form (ATTRv-CA) is associated with mutations in the transthyretin gene and typically manifests at younger ages; it follows an autosomal dominant inheritance pattern with variable penetrance, while the course of the disease and survival vary among different families and among different genotypes. (3)

Historically, this condition was considered a rare disease; however, its diagnostic incidence has increased exponentially in recent years. (4) This increase is driven primarily by the availability of national and international diagnostic algorithms that enable the noninvasive diagnosis of the disease using imaging methods such as bone scintigraphy with bisphosphonates. (5,6) Moreover, the emergence of specific therapies that modify the natural course of the disease are likely to have contributed to the rise in diagnostic incidence. (7–9) Currently, the prevalence of ATTR-CA is high in very common cardiac conditions, such as heart failure with preserved ejection fraction and aortic stenosis, among others. (10–15)

It is well known that there is a clear male predominance in ATTR-CA. Various studies have reported that more than 85% of patients with ATTRwt-CA are men, (16) so the available information on the clinical characteristics of women with this condition is limited. On the other hand, although differences in clinical presentation and disease progression according to gender in ATTR-CA, have been reported, (17) the evidence in this regard is limited, and we lack local or regional data on these differences.

The objective of this study was to describe sex-related differences in clinical presentation, electrocardiographic and imaging characteristics at the time of diagnosis, and the course of the disease in patients diagnosed with ATTR-CA.

METHODS

Study Design and Population

A retrospective, multicenter (two centers) cohort study was conducted in patients diagnosed with ATTR-CA between January 2010 and June 2025, enrolled in our Institutional Amyloidosis Registry (IAR). The IAR is an active registry

that has been consecutively and retrospectively enrolling cases diagnosed with amyloidosis since 2010. It was approved by the Hospital Italiano de Buenos Aires Ethics Committee (CEPI 1675) and registered on ClinicalTrials.gov (NCT01347047).

The diagnosis of ATTR-CA was based on clinical suspicion by the patient's attending physicians and was established as follows:

- Positive bone scintigraphy with bisphosphonates (uptake grade ≥ 2 according to the Perugini visual scale) and confirmation of myocardial uptake via single-photon emission computed tomography (SPECT-CT), in the absence of hematological findings suggestive of light-chain amyloidosis.
- In cases diagnosed before 2017 (the year in which pyrophosphate bone scintigraphy was introduced at our institution), the diagnosis was accepted in the presence of a positive endomyocardial or extracardiac biopsy with Congo red staining, along with typical findings on cardiac magnetic resonance imaging and negative hematological studies.

Although not all patients underwent transthyretin gene sequencing, in most cases genetic testing was performed to rule out ATTRv-CA. Patients with other forms of amyloidosis or who were not followed up at our center were excluded from the analysis.

Variables

Demographic information (sex and age at diagnosis) and associated comorbidities (hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation and heart failure, among others) were collected. Laboratory data were also recorded, including serum creatinine, creatinine clearance calculated using the Cockcroft–Gault formula, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and ultrasensitive cardiac troponin T.

Pre-diagnosis electrocardiograms were also reviewed, assessing the baseline rhythm (sinus or atrial fibrillation/flutter), the presence of microvoltage—defined as a QRS complex amplitude of less than 5 mm in all limb leads and/or less than 10 mm in the precordial leads— the pseudo-infarction pattern—defined as the presence of pathological Q waves or loss of R-wave progression, without clinical or angiographic evidence of prior infarction—and the presence of right bundle branch block.

Imaging study variables were also analyzed, including classic echocardiographic and cardiac magnetic resonance imaging (MRI) parameters, using the studies closest to the diagnosis of ATTR-CA (within six months for echocardiography and within one year for MRI). Finally, hospitalizations for heart failure and all-cause mortality during follow-up were recorded.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation (SD) or as median and interquartile range (IQR), depending on their distribution. Categorical variables were

expressed as percentages. Baseline characteristics were compared between men and women using appropriate statistical tests, employing the chi-square test for categorical variables and Student's t-test or the Mann-Whitney test for continuous variables, according to their parametric or nonparametric distribution, respectively.

Finally, Kaplan-Meier curves were constructed to estimate the incidence of all-cause mortality, hospitalizations for heart failure, and the combined event of both outcomes during follow-up, stratified by sex. A two-sided p-value <0.05 was considered statistically significant. All analyses were performed using STATA software version 13.1 (Stata Corp LP, College Station, TX).

Ethical Considerations

The study protocol complied with the ethical principles of the Declaration of Helsinki. (18) The Institutional Amyloidosis Registry (IAR) was approved by the institutional ethics committee, and all participants provided informed consent prior to inclusion in the registry.

RESULTS

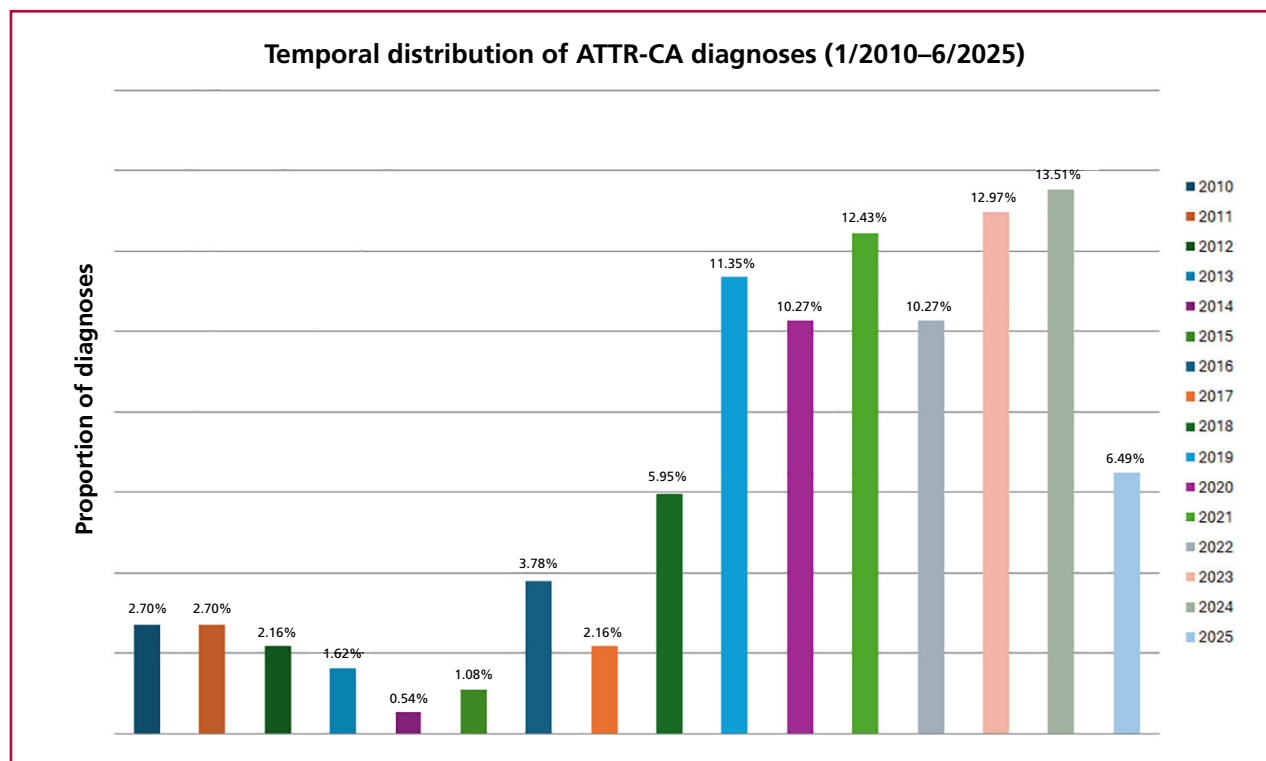
A total of 186 patients were included in the study, among whom 15 (8%) had a diagnosis of ATTRv-CA. Since the introduction of bone scintigraphy with bisphosphonates in 2017, 159 of the 186 patients (85.5%) included in the cohort were diagnosed, with a clear increase in disease incidence observed in recent years (Figure 1). Of the total number of patients diagnosed by scintigraphy (n=159), 92.4% (n=147) had a Perugini visual score of 3 points, 6.9% (n=11) had a score

of 2 points, and only 1 patient had a Perugini score of 1; the latter was diagnosed with ATTRv-CA due to Val50Met, with advanced cardiac and neurological involvement.

Population mean age was 80±8 years; 82.2% were men (n=153, 142 ATTRwt-CA and 11 ATTRv-CA), and 17.8% were female (n=33, 29 ATTRwt-CA and 4 ATTRv-CA). Clinical differences between men and women at the time of diagnosis evidenced that women were diagnosed at an older age (83 vs. 80 years; p=0.042), and more frequently presented with dyslipidemia (69.7% vs. 45.1%; p=0.012). They had poorer creatinine clearance (46 mL/min vs. 56 mL/min; p=0.024) compared with men, with no significant differences in NT-ProBNP and ultrasensitive cardiac troponin T levels. The differences in clinical and laboratory variables between men and women are presented in Table 1.

Regarding the baseline electrocardiogram at the time of diagnosis, 62% (33.3%) of patients presented with atrial fibrillation or flutter, with no significant differences observed between men and women (64.7% vs 51.5%, p=0.162). Among other electrocardiographic features, the most common finding was the pseudo-infarction pattern, observed in 67.2% of patients (67.9% in men vs. 60.6% in women, p=0.445), followed by microvoltage, present in 39.8% of cases, with a tendency to be more frequent in men (44.2% vs. 27.2%, p=0.063). Finally, right bundle branch

Fig. 1. Proportion of diagnoses of transthyretin cardiac amyloidotic from January 2010 to June 2025



block was present in 37.1% of patients, with no significant differences between men and women (39.1% vs. 24.2%, $p=0.161$).

On the baseline echocardiogram, women had a larger end-diastolic diameter normalized by body surface area (25 mm/m² vs. 23 mm/m²; $p=0.002$) and lower septal and posterior wall thickness (14.8 vs. 16.9 mm; $p=0.020$ and 12.7 vs. 14.3 mm; $p=0.005$, respectively) compared with men. On the other hand, a higher proportion of women had septal thickness <12 mm at the time of ATTR-CA diagnosis (12.1% vs. 1.9%; $p=0.005$) Moreover, women tended to have better myocardial fiber function with higher global longitudinal strain values (-14.1% vs. -11.1%; $p=0.072$), with no significant differences in left ventricular ejection fraction calculated using the Simpson method (Table 2).

A total of 108 patients (93 men and 15 women) underwent cardiac MRI within the year of diagnosis. In this study, women had higher left and right ventricular ejection fractions (62% vs. 50%; $p=0.031$ and 56% vs. 47%; $p=0.011$, respectively) and lower maximum wall thickness (16.4 mm vs. 18.7 mm; $p=0.013$) compared with men (Table 3). No differences were observed in T1 mapping and extracellular volume sequences between men and women. In the subgroup of patients with cardiac MRI, no differences were either observed in ejection fraction and global longitudinal strain by echocardiography.

During follow-up, only 34 patients received specific disease-modifying treatment (transthyretin stabiliz-

ers); among these, 29 were men and 5 were women ($p=0.462$) Finally, during a median follow-up of 725.5 days (IQR 342.5–1220), no statistically significant differences were observed in mortality or hospitalizations for heart failure between the two sexes (Figure 2 A, B, and C).

DISCUSSION

In this observational cohort, using local data, we describe the differences in clinical presentation, imaging characteristics at diagnosis, and clinical course of patients diagnosed with ATTR-CA according to sex. The first point to highlight is the marked male predominance (82%) observed in our cohort. This finding is consistent with previously reported epidemiological data for this condition. Studies conducted in European and North American populations have reported similar proportions (19–24), with some variability across series. The lowest prevalence among women was reported in 2022 in the international THAOS registry, where, out of a total of 1386 patients, only 6% were female. (20) On the other hand, the highest prevalence was recently reported in January 2026, using data from the ATTR-CA registry in Galicia, Spain, where, out of a total of 385 patients, 24.7% were women. (22)

In our population, women were diagnosed at a significantly older age than men, a finding that has also been consistently reported in previous international series. (19–21,24) There are hypotheses suggesting that the lower proportion of women and the

Table 1. Differences in clinical history and laboratory variables between men and women with ATTR-CA at the time of diagnosis.

	Men (n=153)	Women (n=33)	p
Age, years, mean \pm SD	80 \pm 7	83 \pm 9	0.042
Hypertension, n (%)	117 (76.5)	28 (84.8)	0.292
Dyslipidemia, n (%)	69 (45.1)	23 (69.7)	0.012
Diabetes Mellitus, n (%)	30 (19.6)	5 (15.2)	0.554
CKD (CrCl < 60 mL/min), n (%)	29 (19.0)	8 (24.2)	0.493
Coronary artery disease, n (%)	29 (19.0)	4 (12.1)	0.350
Stroke/TIA, n (%)	13 (8.5)	12 (36.4)	0.512
Heart failure, n (%)	94 (61.4)	20 (60.6)	0.921
NYHA Class III/IV, n (%)	53 (34.6)	12 (36.4)	0.633
History of atrial fibrillation/flutter, n (%)	80 (52.3)	14 (42.4)	0.302
Hypotension, n (%)	13 (8.5)	6 (18.2)	0.092
Carpal tunnel syndrome, n (%)	65 (42.5)	15 (45.5)	0.753
Lumbar spinal stenosis, n (%)	31 (20.3)	6 (18.2)	0.861
CrCl, mL/min, mean \pm SD	56 \pm 21	46 \pm 20	0.024
NT-proBNP, pg/mL, median (IQR)	2412 (988–5336)	3249 (2065–5464)	0.192
US-TT, pg/mL, median (IQR)	51 (35–77)	45 (29–58)	0.164

CKD: chronic kidney disease; CrCl: creatinine clearance; IQR: interquartile range; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA FC: New York Heart Association functional class; SD: standard deviation; TIA: transient ischemic attack; US-TT: ultra-sensitive cardiac troponin T.

Table 2. Differences in echocardiographic variables between men and women with ATTR-CA at the time of diagnosis.

	Men (n=153)	Women (n=33)	p
LVEDD, mm, mean ± SD	45 ±6	41 ±5	0.006
LVEDDi, mm/m ² , mean ± SD	23 ±3	25 ±3	0.002
LVESD, mm, mean ± SD	28 ±7	26 ±7	0.072
LVESDi, mm/m ² , mean ± SD	15 ±3	16 ±4	0.143
STh, mm, mean ± SD	16.9 ±3.5	14.8 ±3.5	0.020
SThi, mm/m ² , mean ± SD	9 ±2	9 ±2	0.562
PW, mm, mean ± SD	14.3 ±2.9	12.7 ±2.3	0.005
PWi, mm/m ² , mean ± SD	7.5 ±1.8	7.9 ±1.7	0.271
LVEF, %, mean ± SD	53 ±11	55 ±9	0.342
LA volume, ml/m ² , median (IQR)	56 (47–68)	56 (46–69)	0.932
Septal E/e ratio, mean ± SD	19 (16–24)	22 (14–26)	0.401
TAPSE, mm, mean ± SD	19 (±4)	20 (±4)	0.762
RV dysfunction, n (%)	43 (28.1)	8 (24.2)	0.613
PASP, mmHg, median (IQR)	39 (31–49)	39 (32–53)	0.333
Moderate or severe AS, n (%)	23 (15.0)	3 (9.1)	0.345
GLS, %, median (IQR) (n=82)	-11.1 (-9.1 – -14.1)	-14.1 (-10.1 – -18)	0.072

AS: aortic stenosis; GLS: global longitudinal strain; IQR: interquartile range; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEDDi: left ventricular end-diastolic diameter indexed to body surface area; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESDi: left ventricular end-systolic diameter indexed to body surface area; PASP: pulmonary artery systolic pressure; PW: posterior wall; PWi: posterior wall indexed to body surface area; RV: right ventricular; SD: standard deviation; ST: septal thickness; STi: septal thickness indexed to body surface area; TAPSE: tricuspid annular plane systolic excursion

Table 3. Differences in magnetic resonance imaging variables between men and women with ATTR-CA at the time of diagnosis.

Cardiac MRI (N = 108)	Men (n=93)	Women (n=15)	p
LVEF, %, median (IQR)	50 (42–61)	62 (48–71)	0.031
Maximum thickness, mm, mean ± SD	18.7 ±3.1	16.4 ±3.4	0.013
RVEF, %, mean ± SD	47 ±13	56 ±13	0.011
T1 mapping, ms, mean ± SD	1118 ±50	1108 ±72	0.582
ECV, %, median (IQR)	48 (41–53)	48 (33–58)	0.913

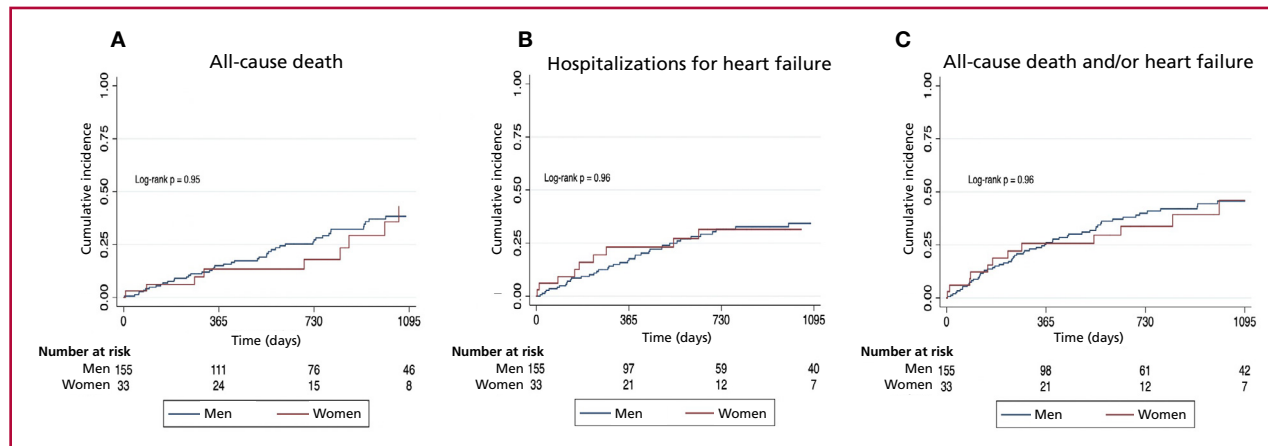
ECV: extracellular volume; IQR: interquartile range; LVEF: left ventricular ejection fraction; RVEF: right ventricular ejection fraction; MRI: magnetic resonance imaging; SD: standard deviation

later age at diagnosis could be explained by hormonal factors, particularly the protective role of estrogens on the myocardium and transthyretin metabolism. Experimental studies have suggested that estrogens may stabilize the transthyretin tetramer and reduce its propensity for dissociation and subsequent amyloid deposition, which would delay the onset of clinical manifestations in women. (25) In this context, it has been proposed that the decrease in estrogen levels following menopause could contribute to greater susceptibility to cardiac involvement and disease progression, which could explain, at least partially, the diagnosis at older ages in this group. (17)

In turn, both echocardiography and cardiac magnetic resonance imaging showed that women exhib-

ited a lower degree of wall thickening compared with men. These findings could also suggest that women present, at the time of diagnosis, with a “less infiltrative” phenotype, which could be interpreted as an earlier manifestation or a slower progression of the disease. However, several groups, including the National Amyloidosis Centre in London, have emphasized the importance of reviewing traditional diagnostic algorithms, where diagnostic suspicion is based on septal thicknesses greater than 12 mm on echocardiography. (26) In this regard, they highlight the importance of indexing septal thickness values to body surface area to avoid underdiagnosis in women. (21,27) Supporting this theory, in our cohort there were no differences in septal and posterior wall thickness values after in-

Fig. 2. Sex-related Kaplan–Meier curves for: A) all-cause mortality, B) hospitalizations for heart failure, and C) the composite event of all-cause mortality and/or hospitalization for heart failure.



dexing these values to the patients' body surface area. However, the indexing of septal thickness values is not yet included in the recommendations of the most widely recognized global echocardiographic clinical practice guidelines. (28) As an additional finding, in our cohort, 12% of women had a septal thickness <12 mm, which supports the theory that diagnostic algorithms and classic echocardiographic criteria may contribute to some underdiagnosis of the condition in women.

Regarding myocardial function at the time of diagnosis, in contrast to other studies in which women had a higher left ventricular ejection fraction on echocardiography, (20,27,29) in our cohort we did not observe statistically significant differences between sexes, probably due to the study's lack of statistical power. However, there was a trend towards better-preserved global longitudinal strain values in women, a tool recognized as more sensitive for the early detection of myocardial dysfunction, particularly in this condition. (30) On the other hand, cardiac MRI showed significantly higher left and right ventricular ejection fractions in women, which reinforces the hypothesis of less advanced functional impairment at the time of diagnosis. Cardiac MRI is the gold standard for assessing systolic ventricular function and may be more accurate for characterizing ventricular function in this population of patients with ATTR-CA. In the subgroup of patients who underwent cardiac MRI, no differences were observed in left ventricular ejection fraction and global longitudinal strain measured by echocardiography, ruling out the possibility that the observed findings were due to a particular patient selection. To date, available information regarding sex differences in cardiac MRI findings is scarce; therefore, our study provides useful insights in this regard.

In our cohort, only a small proportion of patients received specific disease-modifying treatment, with no significant differences observed between men and

women. This can be explained, first, by the fact that this is a historical cohort, in which the first patients were diagnosed starting in 2010, while specific therapies for ATTR-CA have only become available in our country in recent years. Second, this is an elderly population, in which the indication for high-cost treatments must be evaluated on an individual basis and, in many cases, is not cost-effective. Furthermore, the economic constraints inherent in our healthcare system constitute an additional factor limiting access to these types of therapies.

Despite differences in age at diagnosis and in the imaging characteristics described, no significant differences were observed in mortality or hospitalizations for heart failure during follow-up between men and women. This finding could be explained by the small number of women included in the cohort and the low proportion of patients who received specific disease-modifying treatment, which limits the statistical power to detect differences in clinical outcomes. The available evidence regarding the impact of sex on the prognosis of ATTR-CA remains contradictory, with some studies reporting worse outcomes in men and others, more recent ones, finding no significant differences between the two sexes, (17) consistent with our results.

Finally, our study has several limitations. First, it is an observational, retrospective study, with the limitations inherent to this type of design. Second, the number of women was low, which limits the interpretation of comparative analyses between sexes. Furthermore, not all patients had a complete genetic characterization, which could have affected the classification of the ATTR-CA subtype in some cases. Lastly, the proportion of patients receiving specific treatment was low, and, as previously mentioned, many patients were diagnosed in the era prior to specific treatments, which prevents an adequate assessment of the impact of sex on the therapeutic response.

CONCLUSIONS

In this national cohort of patients with ATTR-CA, women were diagnosed at an older age and had less structural and functional myocardial involvement at the time of diagnosis. However, these differences did not translate into a significant impact on the clinical course during follow-up.

Conflicts of interest

None declared.

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

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Predictive Value of Pre-Discharge Cardiac and Pulmonary Ultrasound in Older Adults Hospitalized for Acute Heart Failure

Valor pronóstico de la ecografía cardíaca y pulmonar previa al alta en adultos mayores hospitalizados por insuficiencia cardíaca aguda

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ABSTRACT

Background: Acute heart failure (AHF) remains a major clinical challenge due to its high morbidity and mortality. The use of cardiac and lung ultrasound has been increasingly recognized as valuable tools for the assessment of residual congestion.

Objective: The aim of this study was to assess the usefulness of cardiac and pulmonary congestion ultrasound parameters prior to discharge for identifying patients at risk of readmission and/or death within 180 days following the initial hospitalization.

Methods: This was a prospective study including consecutive patients over 65 years of age admitted with primary diagnosis of AHF. Patients with acute coronary syndromes, severe valvular disease requiring surgery, heart transplantation, and severe pulmonary disorders were excluded. Ultrasound characteristics at hospital discharge were assessed for their association with events during the 180-day follow-up period using univariate and multivariate Cox regression analyses. For B-lines, a ROC curve was generated, and the optimal cutoff point for predicting the primary endpoint was determined using the Youden index.

Results: A total of 200 patients were analyzed. Median age was 81 (interquartile range, IQR, 76–86) years, and 53% were men. During follow-up, 37.5% of patients experienced the composite endpoint of death or rehospitalization for AHF. The ultrasound variables significantly associated with the primary endpoint were the E/e' ratio (septal and lateral), the presence of dilated inferior vena cava (IVC), pulmonary artery systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE), and the number of B-lines present at hospital discharge ($p < 0.001$). In a multivariate model adjusted for age, sex and ultrasound variables, B-lines at discharge remained significantly associated with the primary outcome. Patients with ≥ 7 B-lines had a significantly higher incidence of rehospitalization and death within the 180-day follow-up period ($p < 0.001$).

Conclusions: A comprehensive ultrasound-based assessment—including parameters such as septal and lateral E/e' ratio, PASP, TAPSE, IVC assessment, and B-lines—provides valuable prognostic information at discharge in patients hospitalized for AHF.

Key words: Heart failure - Ultrasound - Elderly health

RESUMEN

Introducción: La insuficiencia cardíaca aguda (ICA) continúa siendo un desafío clínico mayor debido a su elevada morbimortalidad. El uso de la ecografía cardíaca y pulmonar se ha consolidado como una herramienta valiosa para la evaluación de la congestión residual.

Objetivo: El objetivo de este estudio fue determinar la utilidad de parámetros ecográficos cardíacos y pulmonares de congestión previos al alta para identificar pacientes en riesgo de muerte y/o reinternación por ICA a los 180 días de la hospitalización índice.

Materiales y métodos: Estudio prospectivo en el que se incluyeron en forma consecutiva pacientes mayores de 65 años internados con diagnóstico principal de ICA. Se excluyeron pacientes con síndrome coronario agudo, valvulopatías graves con indicación quirúrgica, trasplante cardíaco y trastornos pulmonares graves. Se analizaron las características ecográficas al egreso hospitalario y su asociación con eventos durante el seguimiento a 180 días en un análisis de Cox univariado y multivariado. En el caso de las líneas B, se elaboró una curva ROC y se calculó el punto de corte con mejor discriminación para el punto final utilizando el índice de Youden.

Resultados: Se incluyeron 200 pacientes. La mediana de edad fue de 81 años (rango intercuartílico, RIC, 76-86), y el 53% eran hombres. El 37,5% de los pacientes presentó el punto final primario combinado (muerte y/o rehospitalización por ICA durante el seguimiento). Las variables ecográficas que se asociaron significativamente con el punto final fueron la relación E/e' (septal y lateral), la presencia de vena cava inferior (VCI) dilatada, la presión sistólica pulmonar, la excursión sistólica del plano del anillo tricuspídeo (TAPSE) y la cantidad de líneas B al egreso hospitalario ($p < 0,001$). En un modelo multivariado ajustado por sexo, edad y variables ecográficas, las líneas B al egreso mantuvieron su asociación estadísticamente significativa con el punto final primario. Se observó

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que el grupo que presentó ≥ 7 líneas B tuvo mayor incidencia de reinternaciones y muerte durante los 180 días posteriores ($p < 0,001$). **Conclusiones:** Un abordaje ecográfico integral que incluya parámetros como la relación E/e' (septal y lateral), la presión sistólica pulmonar, el TAPSE, la evaluación de la VCI y líneas B aporta información útil previo al egreso de pacientes internados por ICA.

Palabras clave: Insuficiencia cardíaca - Ultrasonografía - Salud de la tercera edad

INTRODUCTION

Acute heart failure (AHF) is associated with high rates of morbidity and mortality and exerts a growing negative impact on public health systems worldwide. (1–3). In this context, AHF is the leading cause of unplanned hospitalizations in patients over 65 years of age, (4) with a threefold increase in hospitalization rates over the past decades due to various factors such as population aging, improved survival following acute myocardial infarction, and delays in the timely diagnosis and treatment of this condition. (5)

Furthermore, patients discharged from a health-care facility following an episode of AHF frequently have high rehospitalization rates, leading to poorer prognosis. (6) Therefore, the early identification of patients at high risk of readmission prior to hospital discharge is essential, especially in the elderly population with multiple comorbidities.

Volume overload and congestion are present in 95% of patients with acute AHF. (7) Despite treatment with diuretics, a significant proportion of these patients are discharged with residual congestion, which has been associated with an increased risk of mortality and readmission for heart failure. (8) However, the assessment of residual congestion in the pre-discharge phase remains a significant clinical challenge, as conventional methods, such as physical examination and chest X-ray, exhibit considerable interobserver variability and low sensitivity. (9)

In this regard, objective assessment of the patient's volume status is essential for optimizing both treatment and follow-up after hospital discharge. Several studies have demonstrated the value of echocardiography and pulmonary ultrasound in revealing anatomical and physiological abnormalities in patients with AHF, and when correctly applied, they can improve patient assessment, management, and outcomes during follow-up. (10–12) However, there is limited information regarding their application in the elderly population of our setting.

Therefore, the objective of this study was to evaluate the prognostic utility of these methods in a cohort of elderly patients with “pure” heart failure—without secondary causes—in order to identify those at higher risk of readmission and/or death following discharge for AHF.

METHODS

Study design and population

A prospective, consecutive cohort study was conducted including patients over 65 years of age hospitalized for AHF between December 2022 and December 2024, in a health-care organization comprising a university hospital and out-

patient centers. Patients with de novo AHF or decompensated chronic heart failure admitted to the Cardiac Intensive Care Unit were included in the study.

Patients with acute coronary syndrome, severe valvular heart disease requiring surgery, a history of heart transplantation, Takotsubo syndrome, acute myocarditis, and congenital heart disease were excluded. These exclusions were established due to differences in the pathophysiology and therapeutic management of the aforementioned conditions. Similarly, pulmonary diseases that could limit obtaining an adequate ultrasound window, such as pulmonary fibrosis, advanced chronic obstructive pulmonary disease (GOLD C/D), acute respiratory distress syndrome, or acute parenchymal infectious processes were excluded.

Follow-up was conducted for six months following hospital discharge. Data sources included the institutional electronic medical records and administrative databases.

Methods and image analysis

Transthoracic echocardiography and lung ultrasound (LUS) studies were performed at hospital admission (within the first 12 hours) and prior to discharge (within the preceding 24 hours).

For echocardiography, measurements were performed following standardized protocols recommended by international guidelines. (13,14) In the case of LUS, the simplified 4-zone protocol described by Platz et al. was used for B-line quantification. (12) All images were acquired, analyzed, and interpreted by trained ultrasound staff.

Endpoint

The endpoint was a composite of mortality or readmission for AHF within 180 days of the index hospitalization. Outcome assessment was performed by an investigator blinded to the results of the transthoracic echocardiogram and LUS.

Mortality: all-cause mortality within 180 days following the index hospitalization.

Hospitalization for AHF: first readmission due to AHF, characterized by a hospital stay of more than 6 hours in the Cardiac Intensive Care Unit or the Emergency Department, caused by a worsening of signs and/or symptoms of heart failure requiring intravenous diuretic therapy.

Statistical analysis

Consecutive sampling was used, including all eligible patients. Sample size calculation was performed to estimate the accuracy of the area under the ROC curve (AUC). Considering an expected AUC of 0.8 and a margin of error (difference between the true and estimated AUC) of 0.08 with a 95% confidence level, the estimated number of patients required was 200.

Continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution. Categorical variables were expressed as absolute and relative frequencies.

Bivariate associations were evaluated using Student's t-test or the Wilcoxon test for continuous variables, and the chi-square test or Fisher's exact test for categorical vari-

ables, as appropriate. Correlation was assessed using Spearman's correlation coefficient. A ROC curve analysis was performed to evaluate the ability of the B-line count to separate patients who presented with the composite endpoint. The optimal cutoff point to simultaneously maximize sensitivity and specificity was selected using the Youden index. Multivariate Cox proportional hazards models were used to estimate prognostic factors for the outcome. The hazard ratio (HR) and its 95% confidence interval were reported. The assumption of proportional hazards and the goodness of fit were evaluated.

Values of $p < 0.05$ were considered statistically significant, using two-tailed tests. Statistical analysis was performed using STATA software version 13.1 (StataCorp LP, College Station, TX).

Ethical considerations

The study was conducted in accordance with current regulations for research involving human subjects, following the Declaration of Helsinki (15) and the Personal Data Protection Act 25326. (16) The protocol was approved by an institutional ethics committee.

RESULTS

Baseline characteristics

The study included a total of 200 patients. Baseline characteristics are presented in Table 1. Median age was 81 years (IQR 76–86), and 53% were men. The most prevalent comorbidities were hypertension (85%), dyslipidemia (58%), history of heart failure (51%), chronic kidney disease (43%), and atrial fibrillation (44%). Additionally, 28% of patients had diabetes mellitus at the time of inclusion.

Characteristics of hospital stay

Pulmonary and/or systemic congestion was the most frequent clinical presentation, observed in 77% of cases, followed by acute pulmonary edema (21%) and low cardiac output syndrome (2%). On physical examination at admission, the predominant findings were pulmonary crackles (89%) and lower limb edema (72%). Median serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at admission was 6515 pg/mL (IQR 3077–14 202).

Among the echocardiographic variables measured at admission, several parameters are noteworthy. Mean left ventricular ejection fraction (LVEF) was $45\% \pm 14\%$ (Simpson method). Regarding diastolic dysfunction parameters, mean septal and lateral E/e' ratios were 19 ± 7 and 16 ± 6 , respectively; monophasic filling was observed in 48% of patients, and mean left atrial volume index was 58 ± 18 mL/m². A dilated inferior vena cava (IVC) (>20 mm) with inspiratory collapse <50% was observed in 67% of patients. In addition, mean TAPSE recorded was 19 ± 3.7 mm and mean pulmonary artery systolic pressure (PASP) was 47 ± 15 mmHg. In the case of significant valvular heart disease (moderate grade or greater), mitral regurgitation was the most common finding (39%), followed by tricuspid regurgitation (32%). At discharge, some echocardiographic variables showed no significant changes (LVEF, TAPSE, and left atrial index volume).

Table 1. Baseline characteristics

Characteristic	n=200
Age – years (median, IQR)	81 [76–86]
Male sex — n (%)	106 (53)
Hypertension — n (%)	170 (85)
Dyslipidemia — n (%)	116 (58)
Diabetes mellitus — n (%)	56 (28)
Coronary heart disease — n (%)	65 (32.5)
Prior functional class (NYHA) — n (%)	
I	102 (51)
II	89 (44.5)
III	6 (3)
IV	3 (1.5)
Chronic kidney disease — n (%)	86 (43)
History of heart failure — n (%)	103 (51.5)
Atrial fibrillation — n (%)	89 (44.5)
Medication — n (%)	
ACEI/ARB	88 (44)
Beta-blockers	138 (69)
MRA	30 (15)
Sacubitril/valsartan	6 (3)
SGLT2i	41 (20.5)
Furosemide	83 (41.5)
NT-proBNP — pg/mL (median, IQR)	6515 [3077–14202]
LVEF — % (mean \pm SD)	44 \pm 14

ARB 2: angiotensin II receptor blockers; ACEI: angiotensin-converting enzyme inhibitors; IQR: interquartile range; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

In contrast, septal and lateral E/e' ratios decreased to 14 ± 6 and 11 ± 5 , respectively, PASP decreased to 40 ± 14 mmHg, and the percentage of patients with dilated IVC without significant inspiratory collapse decreased to 8%. However, 29% of cases presented with a dilated IVC and significant inspiratory collapse at discharge.

On LUS, the median number of B-lines at admission was 13 (IQR 11–18), and it decreased to 4 (IQR 2–8) at discharge ($p < 0.001$), with a difference between admission and discharge of 9 (IQR 7–11).

Finally, median length of hospital stay was 5 days (IQR 3–7).

Post-discharge follow-up and variables associated with the incidence of the endpoint at 180 days

Median follow-up was 5.3 (IQR 2.9–5.9) months. The endpoint occurred in 75 patients (37.5%), comprising 25 deaths and 50 rehospitalizations for AHF.

A significant correlation ($p < 0.001$) was observed between the number of B-lines at discharge and established prognostic variables such as NTpro-BNP at

admission ($r = 0.22$) and at discharge ($r = 0.46$). Significant, albeit weaker, correlations were also found with LVEF ($r = 0.13$) and left atrial volume ($r = 0.19$). No significant associations were identified between the number of B-lines and sex, age, or chronic kidney disease.

In the univariate analysis, the echocardiographic variables obtained at hospital discharge that were associated with the endpoint were the septal (HR 1.04; 95% CI 1.03–1.11) and lateral (HR 1.12; 95% CI 1.07–1.17) E/e' ratio, IVC dilation (HR 6.1; 95% CI 3.6–10.35), PASP (HR 1.03; 95% CI 1.02–1.05), and TAPSE (HR 0.87; 95% CI 0.81–0.95).

In contrast, LVEF (HR 0.99; 95% CI 0.97–1.01) and left atrial index volume (HR 1.00; 95% CI 0.99–1.01) showed no association with the outcome.

The number of B-lines at discharge was significantly associated with the endpoint in the univariate analysis (HR 1.28; 95% CI 1.19–1.37). Association with the endpoint was also found for the absence of significant weight loss (HR 1.18; 95% CI 1.10–1.27), the presence of crackles (HR 2.46; 95% CI 1.55–3.94), and the persistence of lower limb edema (HR 3.65; 95% CI 2.31–5.76) at discharge.

In the multivariate analysis, the number of B-lines was the only variable included that showed a significant association with the endpoint (HR 1.42; 95% CI 1.23–1.64). Table 2 shows the model results, including the ultrasound variables measured at discharge, and the cumulative incidence of readmissions or death at 180 days.

Finally, ROC analysis revealed an AUC of 0.77 (95% CI 0.73–0.81) of B-lines at discharge for endpoint discrimination (Figure 1). The optimal cutoff point was ≥ 7 B-lines, with a sensitivity of 61% and specificity of 86%, a positive predictive value of 73%, and a negative predictive value of 79%. The cumulative incidence of events among the groups with the highest and lowest number of B-lines according to this cutoff point is presented in Figure 2 ($p < 0.001$, Log-rank test).

DISCUSSION

In light of current published data, this is the first study to evaluate the prognostic value of echocardiography combined with a simplified LUS method in an elderly population with “pure” AHF. We suggest naming it this way because we excluded secondary causes of HF—such as acute myocardial infarction or severe valvular heart disease requiring surgery—that could alter therapeutic management and prognosis. This characteristic constitutes the main difference compared with other cohorts in which this restriction was not applied in patient selection. (12, 17–19) It should be noted that our research group had previously conducted a validation study of LUS in a study with a smaller number of patients and the same selection criteria. (20)

One of the main findings of our study was that one-third of patients hospitalized for AHF experienced the composite endpoint of rehospitalization or death within 180 days of the index admission. This high incidence is consistent with reports by other authors, (21) confirming the poor prognosis of AHF and underscores the need to identify patients with residual congestion prior to hospital discharge.

Compared with other AHF registries, such as the ADHERE, (22) and OPTIMIZE-HF (23) studies and various Argentine registries, (24) our cohort had a 10-year older median age. Although age distribution was similar to that of an Italian cohort, our population showed a higher prevalence of female patients, kidney failure, and prior history of heart failure. (25)

As previously mentioned, although there is evidence that patients with residual pulmonary congestion prior to hospital discharge are at higher risk of adverse events related to heart failure, there is no universally accepted definition of residual congestion assessed by echocardiography and pulmonary ultrasound that has prognostic value in older adults.

In our study, echocardiographic variables—septal and lateral E/e' ratios, TAPSE, IVC assessment, and

Table 2. Echocardiographic variables measured at discharge associated with the cumulative incidence of readmissions or death at 180 days

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Male sex	0.82 (0.52–1.29)	0.945	1.59 (0.83–3.06)	0.166
Age	1 (0.98–1.02)	0.805	0.99 (0.97–1.01)	0.765
B-lines	1.28 (1.19–1.37)	<0.001	1.42 (1.23–1.64)	<0.001
Septal E/e' ratio	1.07 (1.03–1.11)	<0.001	1 (0.92–1.02)	0.264
Lateral E/e' ratio	1.12 (1.07–1.17)	<0.001	-	-
Dilated inferior vena cava	6.1 (3.6–10.3)	<0.001	2 (0.91–4.53)	0.080
TAPSE	0.88 (0.81–0.95)	0.002	-	-
LVEF	0.99 (0.97–1.01)	0.316	0.99 (0.96–1.01)	0.474
PASP	1.03 (1.02–1.05)	<0.001	1.01 (0.99–1.03)	0.254

LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

Fig. 1. ROC analysis revealed an area under the curve (AUC) of 0.77 (95% CI 0.73–0.81) for B-lines at discharge to discriminate the endpoint. The optimal cutoff point was ≥ 7 B-lines, with 61% sensitivity and 86% specificity.

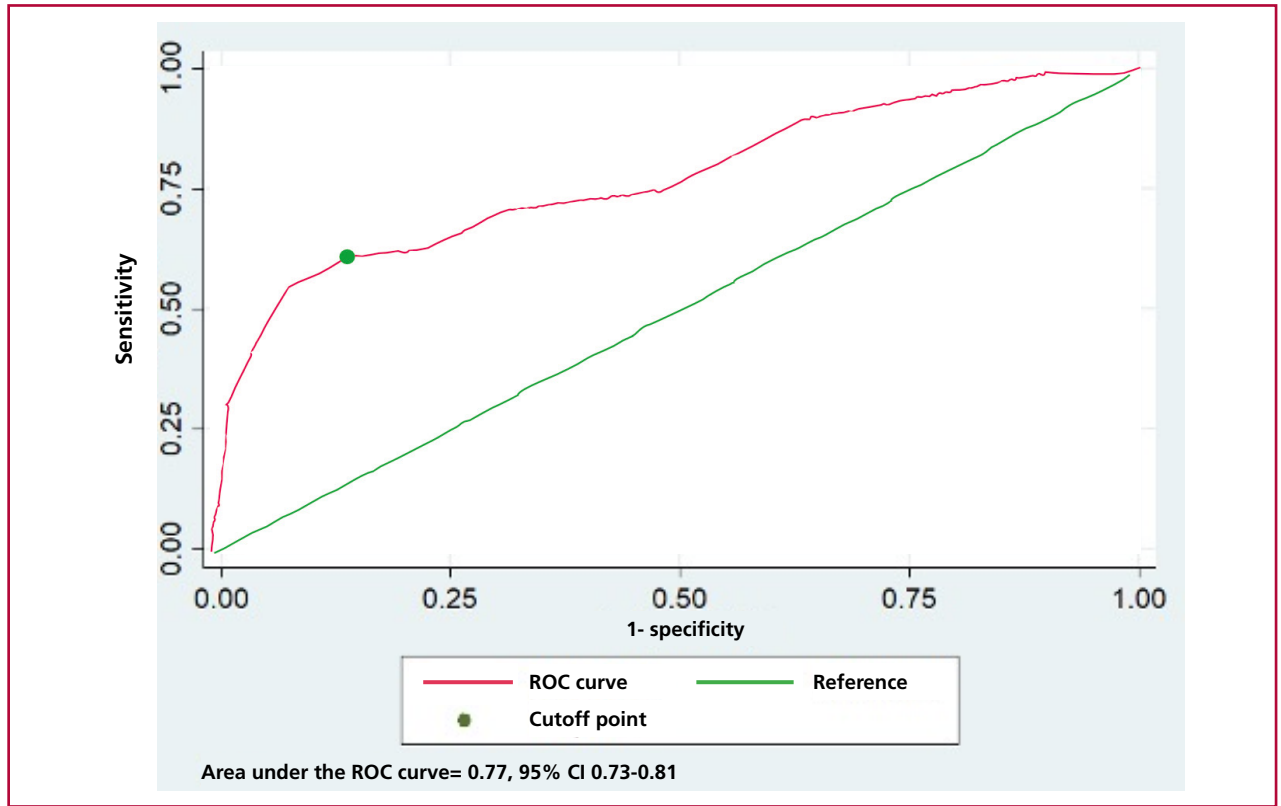
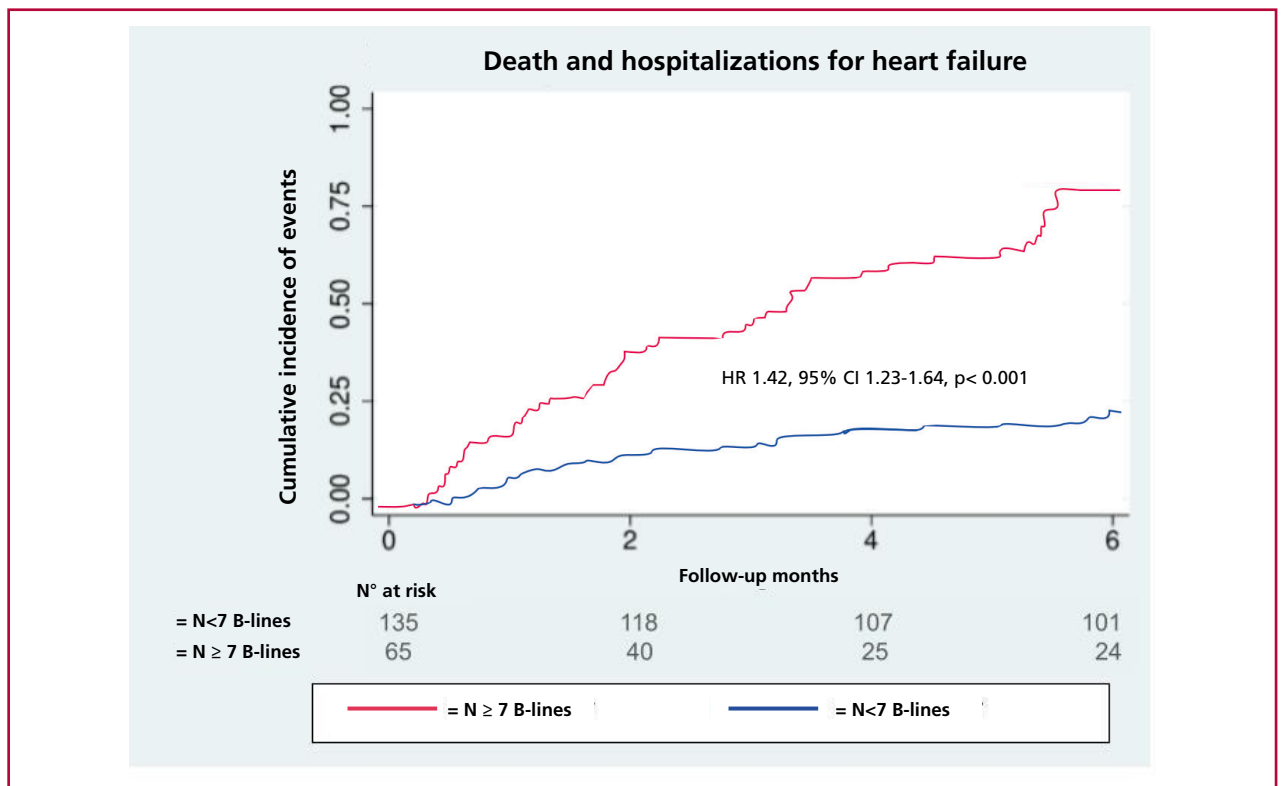


Fig. 2. Cumulative incidence of events among groups with the higher and lower number of B-lines according to the cutoff point of 7 B-lines



PASP—and the presence of B-lines on pulmonary ultrasound at hospital discharge were observed as predictors of the endpoint.

The E/e' ratio is a widely used parameter for assessing diastolic function. Its prognostic value has been extensively evaluated in other conditions such as acute myocardial infarction (26), hypertension (27), or atrial fibrillation. (28) In the field of heart failure, we can highlight studies that obtained conclusive results regarding the prognostic use of this variable, although they were conducted in a population with heart failure with reduced ejection fraction (HFrEF). (29) On the other hand, in patients with preserved ejection fraction (HFpEF), the study by Blanco et al., conducted at our institution in 2020, is worth noting. Following an analysis of diastolic dysfunction parameters in AHF, these authors concluded that an E/e' ratio greater than 14 measured at hospital discharge was significantly associated with the composite endpoint of all-cause mortality and readmissions for AHF (HR 4.63, 95% CI 2.71–18.2; $p < 0.001$). (30) Finally, Santas et al. conducted an analysis in a group of patients with AHF that included both HFrEF and HFpEF and demonstrated an independent association between elevated E/e' values and all-cause mortality. (19) Regarding the similarities between our study and the latter, we note that our population also included both HFrEF and HFpEF. The main difference lies in the patients' age: the mean age in the cited study was 72 years, whereas our median age exceeds it by 10 years, showing a substantially older population.

On the other hand, to compare our results from the IVC analysis, it is relevant to highlight the PRO-FUND-IC Registry. (31) This study evaluated the prognostic impact of LUS and IVC in a cohort of elderly patients with AHF, a population comparable to ours. The authors demonstrated that IVC collapsibility $< 50\%$ or a diameter > 2.25 cm was associated with increased short-term mortality, with greater predictive power than B-line quantification. A relevant methodological difference was the timing of the assessment: in the aforementioned registry, it was performed within the first 72 hours of hospitalization, whereas in our cohort, the measurements analyzed were taken at the time of hospital discharge.

The association between TAPSE, PASP, and the endpoint reflects the leading role of the right ventricle in this patient group. (32) It is known that right ventricular (RV) dysfunction is present in 4–50% of patients with heart failure and is a variable indicating poorer prognosis. (33–35) Several studies have reached similar conclusions when analyzing each of these parameters separately. (17, 36)

Regarding LUS, previous studies have identified several cutoff values for B-lines with prognostic significance, depending on the protocol used and the clinical context (12,31) Imanishi et al. investigated the correlation between the number of B-lines on LUS and pulmonary capillary pressure (PCP) and found that

a count of ≥ 6 B-lines was strongly correlated with elevated PCP values and associated with a higher risk of cardiac death and rehospitalization for AHF. (37) Similarly, we found that the identification of ≥ 7 B-lines at discharge was associated with an increased risk of death or rehospitalization during follow-up. Furthermore, the adoption of a simplified LUS protocol, such as the one used in this study, is beneficial in the hospital setting due to its shorter execution time and lower risk of data omission. This is particularly relevant in count-based quantification methods, in which the total number of B-lines in all evaluated areas is added. Additionally, although AHF can present with different clinical phenotypes, most patients exhibit some degree of pulmonary congestion, (38) which supports the usefulness of pulmonary ultrasound in assessing the state of decongestion. In this regard, all patients in our cohort presented with B-lines at admission. Finally, it is worth noting that we decided to prioritize the assessment at discharge in our analysis, rather than relying on measurements taken at admission and the admission-to-discharge variation. This choice was based on its greater feasibility in routine clinical practice, as it requires a single measurement.

Our findings highlight the prognostic value of echocardiography combined with pre-discharge LUS in patients hospitalized for AHF. Both methods represent a potential therapeutic target for decongestion, showing that different variables analyzed by both methods exhibit dynamic changes during hospitalization, with rapid positive changes in patients who respond to diuretic therapy and other interventions. Serial LUS, for its part, has proven to be an effective modality for guiding the titration of diuretic therapy, facilitating early resolution of congestion, and potentially contributing to a shorter length of hospital stay. (39) Further research is needed to evaluate the impact of both methods as therapeutic guides during hospitalization for AHF in order to achieve optimal decongestion, which could result in a lower incidence of adverse events during follow-up.

This study has several limitations that should be acknowledged. First, it was conducted at a single high-complexity center, which may limit the generalization of the findings to other healthcare settings or to populations with different clinical characteristics and access to care. Second, the multivariate model was developed to assess prognostic factors; therefore, we cannot establish causality. Third, although ultrasound is widely regarded as a highly useful noninvasive tool, it is operator-dependent, even when standardized protocols are used. Fourth, the exclusion of NT-pro-BNP in the multivariate model should be emphasized. This decision was based on two considerations: the limited number of events available to include additional variables in the model and, even more importantly, the priority of developing a clinical model that is feasible to apply in less complex centers at lower costs.

Future studies should validate these findings in

multicenter cohorts and explore interventions based on them to improve clinical outcomes during follow-up.

CONCLUSION

A comprehensive ultrasound approach that includes parameters such as the E/e' ratio (septal and lateral), PASP, TAPSE, IVC assessment and B-lines provides useful information prior to discharge of older adults hospitalized for AHF.

The main findings of our study were: a) one-third of patients hospitalized for AHF presented the composite endpoint of rehospitalization or death within 180 days of the index admission. b) several echocardiographic variables (septal and lateral E/e' ratios, TAPSE, IVC assessment, and PASP) and the presence of B-lines on the pulmonary ultrasound at hospital discharge were associated with the primary endpoint. c) The optimal cutoff point for B-lines at discharge to predict the endpoint was ≥ 7 .

Conflicts of interest

None declared.

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

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Acute Myocardial Infarction in Women in Argentina: Changes in Clinical Characteristics, Management and Outcome Over the Past 20 Years

Infarto agudo de miocardio en mujeres en Argentina: cambios clínicos, terapéuticos y pronósticos en los últimos 20 años

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death in women. There are differences in the clinical presentation, management, and outcome of acute myocardial infarction (AMI) based on sex, which have been historically associated with worse outcomes in the female population.

Objectives: The aim of this study was to describe the evolution of the clinical characteristics, risk factors, management strategies, and in-hospital outcome of women with ST-segment elevation acute myocardial infarction (STEMI) in Argentina over the past 20 years.

Methods: This retrospective, observational, and multicenter study in Argentina was based on data from the 2005, 2015 and 2024 national registries on AMI developed by the Argentine Society of Cardiology. A total of 2620 patients with STEMI were included. The clinical characteristics, coronary risk factors, times to presentation, reperfusion therapy modalities and in-hospital outcome were analyzed and compared according to sex and time period. Appropriate statistical tests were used depending on the type and distribution of the variables.

Results: The percentage of women remained stable over time (24.5%, 22.7%, and 20.7%, respectively; p trend = 0.182), while the median age at presentation decreased significantly (71.3 vs. 66.3 vs. 65.6 years; p = 0.049). The prevalence of hypertension and coronary artery disease in women decreased, while tobacco use and diabetes increased. Time to consultation exhibited a significant reduction. Reperfusion therapy increased markedly (44.4% vs. 80% vs. 94.9%; p trend < 0.001), as did primary percutaneous coronary intervention procedures. In-hospital mortality decreased significantly among women (15.3%, 10.9%, and 6.4%; p trend = 0.047), comparable to that of men in the most recent period.

Conclusions: Over the past 20 years, women with STEMI in Argentina have shown significant changes in their clinical profile and therapeutic approach. There has been a substantial improvement in access to reperfusion therapy, along with a reduction in in-hospital mortality. These findings reflect advances in AMI care for women, although there are still challenges for preventing and managing risk factors.

Key words: Acute myocardial infarction – Women – Cardiovascular disease – Reperfusion – In-hospital mortality.

RESUMEN

Introducción: Las enfermedades cardiovasculares continúan siendo la principal causa de mortalidad en mujeres. Existen diferencias en la presentación clínica, el tratamiento y el pronóstico del infarto agudo de miocardio (IAM) según el sexo, lo que históricamente se ha asociado a peores resultados en la población femenina.

Objetivos: Definir la evolución de las características clínicas, los factores de riesgo, las estrategias terapéuticas y el pronóstico intrahospitalario de las mujeres con infarto agudo de miocardio con elevación del segmento ST (IAMCEST) en Argentina a lo largo de los últimos 20 años.

Material y métodos: Estudio retrospectivo, observacional y multicéntrico realizado a partir de los registros nacionales de IAM de la Sociedad Argentina de Cardiología correspondientes a los años 2005, 2015 y 2024. Se incluyeron 2620 pacientes con IAMCEST. Se analizaron características clínicas, factores de riesgo coronario, tiempos de presentación, modalidades de reperusión y evolución intrahospitalaria, comparando los resultados según sexo y período. Se utilizaron pruebas estadísticas apropiadas según el tipo y distribución de las variables.

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Resultados: El porcentaje de mujeres se mantuvo estable a lo largo del tiempo (24,5%, 22,7% y 20,7%; p de tendencia=0,182), mientras que la edad mediana de presentación disminuyó significativamente (71,3 vs. 66,3 vs. 65,6 años; p=0,049). En mujeres se observó una disminución de la prevalencia de hipertensión arterial y enfermedad coronaria, con un aumento del tabaquismo y la diabetes. La demora a la consulta se redujo significativamente. La reperfusión aumentó de forma marcada (44,4% vs. 80% vs. 94,9% p de tendencia <0,001), así como la realización de angioplastia primaria. La mortalidad intrahospitalaria en mujeres descendió significativamente (15,3%, 10,9% y 6,4%; p tendencia=0,047), igualándose a la de los hombres en el período más reciente.

Conclusiones: En los últimos 20 años, las mujeres con IAMCEST en Argentina presentaron cambios significativos en el perfil clínico y en el abordaje terapéutico, con una mejora sustancial en el acceso a la reperfusión y una reducción de la mortalidad intrahospitalaria. Estos hallazgos reflejan avances en la atención del IAM en la mujer, aunque persisten desafíos en la prevención y el manejo de los factores de riesgo.

Palabras clave: Infarto agudo de miocardio - Mujeres - Enfermedad cardiovascular - Reperfusión - Mortalidad hospitalaria.

INTRODUCTION

Over the past few decades, significant advances have been made in the prevention, diagnosis, and treatment of cardiovascular diseases (CVDs). However, they remain the leading cause of death in both men and women. There are aspects of the pathophysiology, clinical presentation, and outcome of coronary artery disease (CAD) and peripheral vascular disease that are specifically linked to women and associated with pregnancy and hormone levels. Also, sociocultural factors influence gender concepts and their comprehensive impact on health. (1)

International and national registries show that the differences persist in the diagnosis, management, and outcome of women with acute myocardial infarction (AMI), which results in higher mortality in this group of patients.

Various studies evidence that women presenting with AMI are older, have a higher prevalence of risk factors such as hypertension (HTN), diabetes mellitus (DM), central obesity, and dyslipidemia (DLP). Women also experience atypical symptoms such as dyspnea, nausea, or epigastric pain, which can delay diagnosis and treatment initiation. (2) Furthermore, women are less likely to receive the recommended invasive and pharmacological therapies, thus contributing to higher in-hospital mortality and worse short- and long-term outcomes.

In recent years, there has been an increased focus on recognizing the significance of CVD in women and gender-related risk factors. This has led to a deeper understanding of these differences and greater visibility. Educational campaigns have been launched to raise awareness among the general population and the medical community, focused on promoting a more appropriate approach to these patients. It is imperative to properly understand the differences in the presentation of CVD in women to implement the most appropriate prevention, diagnosis, and treatment measures.

However, challenges persist. Women often delay seeking medical care during an AMI, partly due to a lack of awareness, downplaying of atypical symptoms, or sociocultural barriers.

The need to investigate this topic stems from the desire to reduce these disparities and improve patient

outcomes. One way to delve deeper into this issue is to highlight the progress made over time and acknowledge what remains to be achieved. The aim of this study was to compare the clinical characteristics, management and in-hospital outcome of women with STEMI in Argentina over the past 20 years.

METHODS

This retrospective, observational, and multicenter study in Argentina was based on data from the 2005 Argentine Society of Cardiology (SAC) AMI registry (3) and the ARGEN-IAM-ST registries conducted in 2015 and 2024. (4,5) A total of 2620 ST-segment elevation myocardial infarction (STEMI) patients were included: 505 patients in 2005, 1739 patients in 2015, and 376 patients in 2024. Informed consent was not required due to the retrospective design of the study.

The clinical characteristics of the included patients, coronary risk factors, presentation and time patterns, treatment modalities, and in-hospital outcome were analyzed and compared according to sex. Changes that have occurred over the past 20 years were also analyzed.

Qualitative variables are presented as frequencies and percentages. Quantitative variables are expressed as mean \pm standard deviation (SD), or median and interquartile range (IQR 25-75), according to their distribution.

Discrete variables were analyzed using contingency tables. For continuous variables, the t-test, the Kruskal-Wallis test for unmatched groups, or analysis of variance (ANOVA) were used, as appropriate. The chi-square test for trend was used to analyze changes across the three registries. A p-value < 0.05 was considered statistically significant. All the calculations were performed using Epi-Info 7.2.2.6 software package.

RESULTS

A total of 2620 patients were analyzed. The percentage of women in each group was 24.5%, 22.7%, and 20.7%, respectively (p = 0.182). The characteristics of the population by year are summarized in Table 1.

The median age of women decreased over the years: 71.3 vs. 66.3 vs. 65.6 years, respectively (p = 0.049).

Among women, HTN was the most prevalent coronary risk factor, with a reduction over the years (79.8% vs 69.9% vs 62.8%, respectively; p = 0.006).

The prevalence of DM exhibited a marked upward trend, with percentages of 21.8%, 36.7%, and 30.8%, respectively (p = 0.063).

The prevalence of tobacco use also increased significantly, from 29.8% to 48.7% ($p = 0.007$).

A history of CAD decreased from 27.4% to 10.4% and 8.9%, respectively ($p < 0.001$), likely related to changes in the age of AMI presentation.

Delays in consultation exhibited a marked improvement, with a reduction from 320 minutes to 180 minutes and 190 minutes, respectively ($p < 0.001$) (Table 2).

The prevalence of anterior wall infarctions increased significantly, rising from 37.7% to 51.9% and 57.7%, respectively ($p < 0.001$).

There was a significant increase in reperfusion therapy in women: 44.4% vs. 80% vs. 94.9%, respectively (p trend < 0.001). The rate of primary percutaneous coronary intervention was 24.2% vs 79.1% vs 81.1%, respectively ($p < 0.001$).

There was a non-significant decrease in the rate of Killip and Kimball (KK) class I (75.6%, 72.1%, and 65.4%, respectively) patients and a significant increase in KK class IV patients (5%, 3.5%, and 20.5%, respectively; $p < 0.001$).

In-hospital mortality decreased over the years, from 15.3% to 10.9%, and 6.4%, respectively ($p = 0.047$). Compared with men, the difference was not significant in 2005 (15.3% vs. 12.1%; $p = 0.342$), tended to be higher in 2015 (10.9% vs. 7.9%; $p = 0.061$), and there were no differences in 2024 ($p = 0.774$) (Figure 1).

DISCUSSION

In this study of 2620 patients, the percentage of women remained relatively stable, while the median age at presentation decreased significantly. There were

notable changes in the prevalence of risk factors. Hypertension decreased, while DM and tobacco use increased. The prevalence of prior CAD exhibited a marked reduction. Additionally, time to consultation improved, and reperfusion therapy and primary percutaneous coronary intervention rates increased significantly. In-hospital mortality in women showed a downward trend, becoming comparable to that of men in the most recent period.

These results are relevant because they reflect the epidemiological and clinical transition of AMI in the female population. The decrease in age at presentation and the rise in the prevalence of hypertension, in conjunction with the rise in DM and tobacco use, indicate a shift in the risk profile. This finding is consistent with international reports emphasizing the mounting significance of DM and tobacco use in young women. The higher rates in reperfusion therapy and primary percutaneous coronary intervention represent a significant advance, as historically women received fewer invasive interventions. (6) In this setting, the reduction in in-hospital mortality to levels comparable to those of men is a positive and rare finding in the literature, where female mortality is typically higher. (7,8)

There is a growing recognition that the pathophysiology and clinical manifestations of CAD differ between men and women. Women are more likely to present with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and non-obstructive ischemic heart disease, such as vasospasm or spontaneous coronary dissection, whereas obstructive CAD is more prevalent in men. (9,10)

Although typical angina remains the most common

Table 1. General characteristics of the study population

Year Total	2005 505				2015 1739				2024 376			
	Men		Women		Men		Women		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%
N	381	75.5	124	24.5	1344	77.3	395	22.7	298	79.3	78	20.7
Age (years)	60.5 ± 12.8		71.3 ± 13.4		59.8 ± 11.1		66.3 ± 13.3		60.0 ± 11.7		65.6 ± 13.2	
	$p < 0.001$				$p < 0.001$				$p < 0.001$			
HTN	243	63.8	99	79.8	727	54.1	276	69.9	163	54.7	49	62.8
	$p < 0.001$				$p < 0.001$				$p = 0.191$			
DM	73	19.2	27	21.8	633	47.1	148	36.7	84	28.2	24	30.8
	$p = 0.523$				$p < 0.001$				$p = 0.652$			
DLP	-	-	-	-	501	37.3	168	42.5	126	42.3	33	42.3
					$p = 0.059$				$p = 1$			
Tobacco	191	50.1	37	29.8	N/A	N/A	N/A	N/A	169	56.7	38	48.7
	$p < 0.001$				$p = 0.205$				$p = 0.652$			
Prior CAD	108	28.4	34	27.4	182	13.5	41	10.4	48	16.1	7	8.9
	$p = 0.847$				$p = 0.095$				$p = 0.113$			

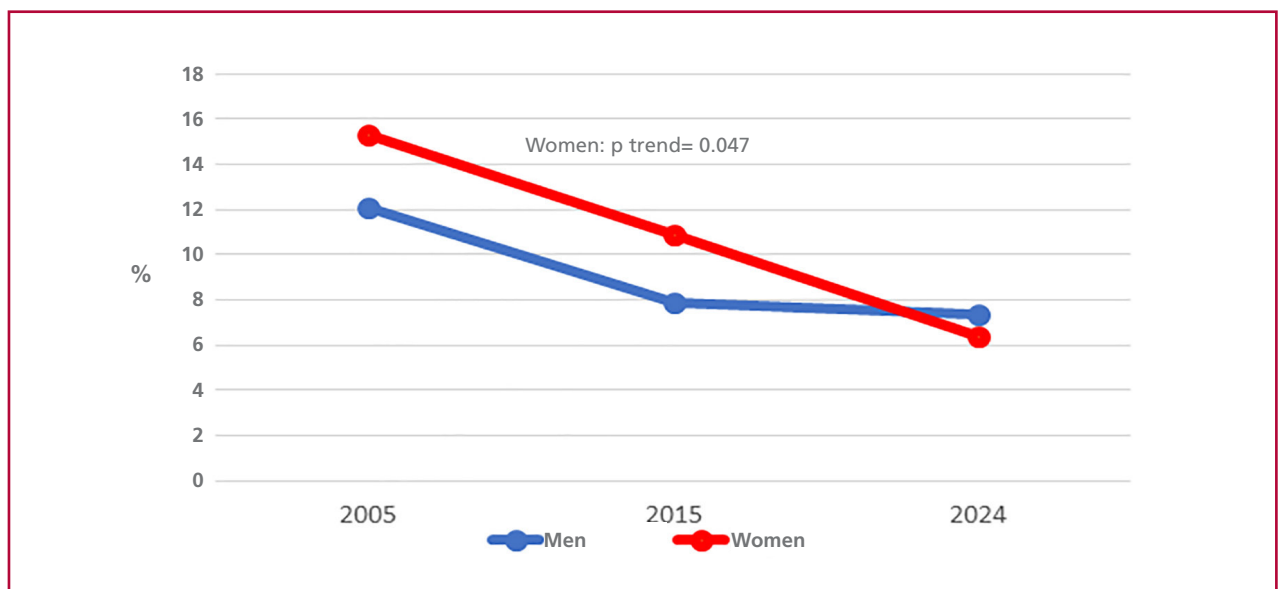
CAD: coronary artery disease; DLP: dyslipidemia; DM: diabetes mellitus; HTN: hypertension; N/A: not available

Table 2. Characteristics of AMI, treatment modality, and in-hospital outcome

Year	2005				2015				2024			
	Men		Women		Men		Women		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%
Delay (min)	240 (120–630)		320 (180 – 720)		168 (60 – 420)		180 (75 – 420)		225 (90 – 490)		190 (95 – 424)	
	p = 0.101				p = 0.402				p = 0.602			
Anterior wall AMI	157	44.2	43	37.7	654	52.2	197	52.0	148	49.6	45	57.7
	p = 0.221				p = 0.929				0.206			
Inferior wall AMI	100	28.2	34	29.8	595	47.5	180	47.5	137	46.0	30	38.5
	0.733				p = 0.992				p = 0.234			
Reperfusion YES	216	56.7	55	44.4	1145	85.5	316	80	287	96.3	74	94.9
	p = 0.017				p = 0.013				p = 0.568			
Primary PCI	135	35.4	30	24.2	851	74.3	250	79.1	230	80.1	60	81.1
	p = 0.023				p = 0.076				p = 0.857			
FBL	89	23.4	26	21.0	253	22.1	61	19.3	50	17.4	9	12.2
	p = 0.276				p = 0.055				p = 0.004			
KK I	295	78.5	90	75.6	1005	77.7	276	72.1	242	81.2	51	65.4
KK II	56	14.9	15	12.6	183	14.1	68	17.8	25	8.4	8	10.3
KK III	12	3.2	8	6.7	25	1.9	14	3.7	9	3.0	3	3.8
KK IV	13	3.5	6	5.0	81	6.3	25	3.5	22	7.4	16	20.5
	p = 0.276				p = 0.055				p = 0.004			
HF on admission	81	21.5	29	24.4	289	22.3	107	27.9	56	18.8	27	34.6
	p = 0.525				p = 0.023				p = 0.003			
IH mort.	46	12.1	19	15.3	106	7.9	43	10.9	22	7.4	5	6.4
	p = 0.342				p = 0.061				p = 0.774			

AMI: acute myocardial infarction; FBL: fibrinolysis; HF: heart failure; IH mort.: in-hospital mortality; KK: Killip and Kimball; PCI: percutaneous coronary intervention.

Fig. 1. In-hospital mortality due to STEMI over the past 20 years by sex



presentation of ACS in both sexes, up to one-third of patients do not present with typical symptoms, with atypical presentation being more common in women than in men (37% vs. 27%). Among women < 45 years, AMI most often presents without typical angina and is associated with a higher in-hospital mortality. (11,12)

Although other publications have reported that women with ACS are older, (13) in this study median age at presentation decreased significantly over the years, although the percentage of women who suffered an AMI remained relatively stable.

The prevalence of traditional coronary risk factors (CRFs) is higher in older women, while those < 65 years have higher prevalence of non-traditional CRFs, as family history, complications of pregnancy and childbirth, early menopause, emotional stress, depression, and chronic inflammatory diseases. (14-16)

Both men and women smokers have higher relative risk of presenting an AMI. Tobacco use was reported as the most significant risk factor in young women. It has even been suggested that women may be more susceptible than men to the effects of tobacco. (17,18)

Microvascular and macrovascular dysfunction, as well as atherosclerotic disease, are significant pathophysiological mechanisms in women; the etiology of myocardial infarction is more heterogeneous than in men and varies with age. Plaque rupture with thrombosis is the cause of fatal AMI in 76% of men and 55% of women. (19) In women < 65 years, up to 50% of ACS cases present with angiographically normal coronary arteries. In this population, plaque erosion is more prevalent, resulting in ischemia due to distal embolism and endothelial dysfunction. These mechanisms often remain undetectable by conventional angiography, leading to the erroneous conclusion that atherosclerotic disease is not present. (20) Women have a higher prevalence of MINOCA (myocardial infarction with non-obstructive coronary arteries). This condition, which involves multiple pathophysiological mechanisms, has a reported annual mortality rate of approximately 2%, and an increased risk of recurrent myocardial infarction, heart failure, stroke, and long-term cardiovascular events, as well as higher mortality and hospital readmission rates. (21-23).

The recommendations for the management of ACS are the same for both sexes; however, it has been reported that women tend to delay seeking medical care and, in general, receive fewer treatments recommended by the guidelines. (24) Women are more likely to present with nonspecific prodromal symptoms, such as anxiety, sleep disturbances, and unusual fatigue prior to the onset of ACS. Misinterpreting these symptoms could lead to a delay in patient evaluation. (25)

The comparative analysis of this study revealed that time to consultation improved, and reperfusion therapy and primary percutaneous coronary intervention rates significantly increased.

Like international registries, in-hospital mortality from STEMI is higher among women than men in

Argentina. (26) Nevertheless, some studies from European countries and the United States did not report the same results, with higher rates of mortality and major cardiovascular events in men, which is probably due to a higher prevalence of comorbidities. (27)

In young women, mortality is twice that of men. (28) The age of patients diagnosed with AMI has been decreasing in recent years, likely due to the higher prevalence of tobacco use, among other causes. (29)

This comparative analysis revealed that in-hospital mortality for women decreased over time, reaching a level comparable to that of men in the most recent period. This was observed despite a higher rate of KK class IV cases, probably due to the high reperfusion rates recorded in recent years.

It is important to note that these results reflect the situation of AMI in women in our country over the years. Although the number of patients recorded in 2024 is the lowest in the ARGEN-IAM-ST registry, the percentage of women remains stable, providing an accurate representation of the situation. The ARGEN-IAM-ST registry is the only independent tool open to the scientific community that facilitates a discussion of the reality of AMI in Argentina. (30)

CONCLUSION

The clinical characteristics of women admitted for AMI in Argentina over a 20-year period have changed. Women are gradually younger, less likely to have HTN, but more likely to be diabetics and to smoke, and with a lower incidence of a history of CAD.

There was a significant reduction in the time to presentation, along with an increase in the frequency of prior myocardial infarction. The rates of reperfusion therapy and primary percutaneous coronary intervention rose significantly, reaching levels similar to those in men. This translates into a significant decrease in in-hospital mortality among women with AMI, despite an increase in the prevalence of heart failure during hospitalization.

These findings underscore the need to continue promoting specific strategies for the prevention and care of AMI in women in Argentina.

Conflicts of interest

None declared.

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

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Prevalence of Hyperkalemia in a Cohort of Patients with Heart Failure with Reduced Ejection Fraction in a Specialized Unit

Prevalencia de hiperkalemia en una cohorte de pacientes con insuficiencia cardíaca con fracción de eyección reducida en una unidad especializada

RAÚL A ORTIZ¹, JOHAN G MENESES¹, GABRIELA M ORMAECHEA¹

ABSTRACT

Background: Hyperkalemia is a common condition in patients with heart failure (HF), impacting treatment and prognosis. However, its prevalence and risk factors in our region are not clearly defined.

Objective: The aim of the study was to determine the prevalence of hyperkalemia in a specialized HF unit and its association with clinical and pharmacological variables.

Methods: An observational, analytical, and retrospective study was conducted including 693 patients with heart failure with reduced ejection fraction (HFrEF) treated at the Multidisciplinary Heart Failure Unit (UMIC) of a university hospital between 2018 and 2022. Hyperkalemia was defined as serum potassium > 5.0 mEq/L and classified according to its level, as mild (>5.0–<5.5 mEq/L), moderate (5.5–6.0 mEq/L), or severe (>6.0 mEq/L). Chi-square and Mann-Whitney tests were used to assess associations.

Results: The prevalence of hyperkalemia was 27%, with a predominance of mild cases (85%). A significant association was found with chronic kidney disease (CKD), but not with diabetes. No significant relationship was either found with the use of disease-modifying drugs, including renin-angiotensin-aldosterone system inhibitors.

Conclusions: The prevalence of hyperkalemia in this cohort is high and is primarily associated with CKD. The absence of an association with disease-modifying treatments reinforces the importance of continuing these therapies, given their role in improving morbidity and mortality in HFrEF.

Key words: Hyperkalemia - Heart failure - Renin-angiotensin-aldosterone system - Chronic kidney disease

RESUMEN

Introducción: La hiperkalemia es una condición frecuente en pacientes con insuficiencia cardíaca (IC), con impacto en el tratamiento y pronóstico. Su prevalencia y factores de riesgo en nuestra región no están claramente definidos.

Objetivo: El objetivo del estudio fue determinar la prevalencia de hiperkalemia en una unidad especializada de IC y su asociación con variables clínicas y farmacológicas.

Material y métodos: Estudio observacional, analítico y retrospectivo en 693 pacientes con insuficiencia cardíaca con fracción de eyección reducida (ICFER) atendidos en la Unidad Multidisciplinaria de Insuficiencia Cardíaca (UMIC) de un hospital universitario entre 2018 y 2022. La hiperkalemia se definió como potasio sérico > 5,0 mEq/L y se clasificó según el nivel: leve (>5,0 - <5,5 mEq/L), moderada (5,5-6,0 mEq/L) o grave (>6,0 mEq/L). Se aplicaron pruebas Chi-cuadrado y Mann-Whitney para evaluar asociaciones.

Resultados: La prevalencia de hiperkalemia fue del 27%, con predominio de casos leves (85%). Se halló asociación significativa con la enfermedad renal crónica (ERC), no así con la diabetes. No se encontró relación significativa con el uso de fármacos modificadores de la enfermedad, incluyendo inhibidores del sistema renina-angiotensina-aldosterona.

Conclusiones: La prevalencia de hiperkalemia en esta cohorte es elevada y se vincula principalmente con la ERC. La ausencia de asociación con tratamientos modificadores de la enfermedad refuerza la importancia de mantenerlos, dado su papel en mejorar la morbimortalidad en la ICFER.

Palabras clave: Hiperkalemia - Insuficiencia cardíaca - Sistema renina-angiotensina-aldosterona - Enfermedad renal crónica

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INTRODUCTION

Heart failure (HF) is a disease with high prevalence and morbidity and mortality. One of its prognostic and therapeutic challenges is hyperkalemia, which is one of the most common electrolyte disturbances in this population, with a reported incidence of up to 25%. It is classified as mild (>5.0 – <5.5 mEq/L), moderate (5.6–6.0 mEq/L), or severe (>6.0 mEq/L). (1–3) Recent evidence demonstrates a U-shaped relationship between serum potassium levels and mortality in patients with HF, with increased risk at both low and high levels. (4,5)

The standard treatment for heart failure with reduced ejection fraction (HFrEF) includes drugs that act on the renin-angiotensin-aldosterone system. (6) Despite strong evidence supporting their use, a significant proportion of patients do not reach target doses, mainly due to the onset of hyperkalemia, symptomatic hypotension, or worsening renal function. (7–11)

This scenario presents a therapeutic dilemma between the long-term prognostic benefits of disease-modifying drugs and the immediate risks associated with hyperkalemia. (12,13) The coexistence of comorbidities such as chronic kidney disease (CKD) and diabetes mellitus further increases this risk. (14–16) In this context, the present study aimed to determine the prevalence of hyperkalemia and its associated risk factors in a cohort of patients with HFrEF treated at a specialized unit in Montevideo.

METHODS

An observational, analytical, descriptive, and retrospective study was conducted including outpatients over 18 years of age with HFrEF (left ventricular ejection fraction, LVEF, $\leq 40\%$) treated at the Multidisciplinary Heart Failure Unit (UMIC) of Hospital de Clínicas. The study period spanned from 2018 to 2022. Patients with acute kidney injury and stage D HF were excluded.

Definition of variables

Data were collected by reviewing the UMIC electronic databases. Hyperkalemia was defined as serum potassium ≥ 5.0 mEq/L, and severity ranges were based on those proposed by the European Society of Cardiology (ESC). (17)

Statistical analysis

Qualitative variables were expressed as frequencies and percentages, while continuous quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR). The chi-square test was used to assess the association between qualitative variables. Student's t-test was used for differences in normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed variables. The level of significance was set at $\alpha = 0.05$.

Ethical considerations

The study was conducted in accordance with the ethical considerations of the World Medical Association's Declaration of Helsinki. (18) and the project was approved by the Hospital de Clínicas ethics committee.

RESULTS

Among a total cohort of 1050 patients with heart failure, 693 meeting the inclusion criteria were included in the study, 69.8 % (478) of whom were women. The median population age was 73 years (IQR 64–81.5) and the prevalence of hyperkalemia was 27% (95% CI 23–30). Mean potassium level was 4.55 ± 0.61 mEq/L. The analysis of subgroups showed that patients with hyperkalemia had a mean potassium level of 5.28 mEq/L vs. 4.29 mEq/L in the rest of patients. Regarding disease severity, the most common presentation was mild (85.5%), compared with 12.9% moderate and only 1.6% severe (Figure 1).

The association between hyperkalemia and relevant clinical variables is presented in Table 1. The prevalence was 28.2% (135/478) for females and 23.7% (51/215) for males, with no significant difference ($p = 0.214$). Neither significant difference was observed between patients with and without hyperkalemia in terms of age ($p = 0.654$) or presence of diabetes ($p = 0.324$).

Notably, there was a statistically significant association between hyperkalemia and the presence of CKD (OR 1.469, 95% CI 1.046–2.062, $p = 0.026$) (Figure 2).

Regarding renal functional parameters, there was a clear association with reduced glomerular filtration rate and increased azotemia (Table 2).

Fig. 1. Degree of hyperkalemia. Most patients presented mild hyperkalemia, while only a very limited number of cases were severe

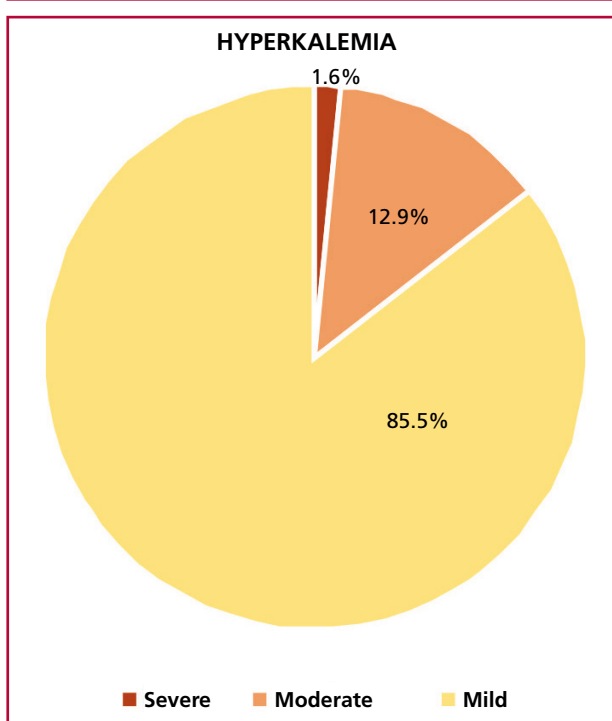
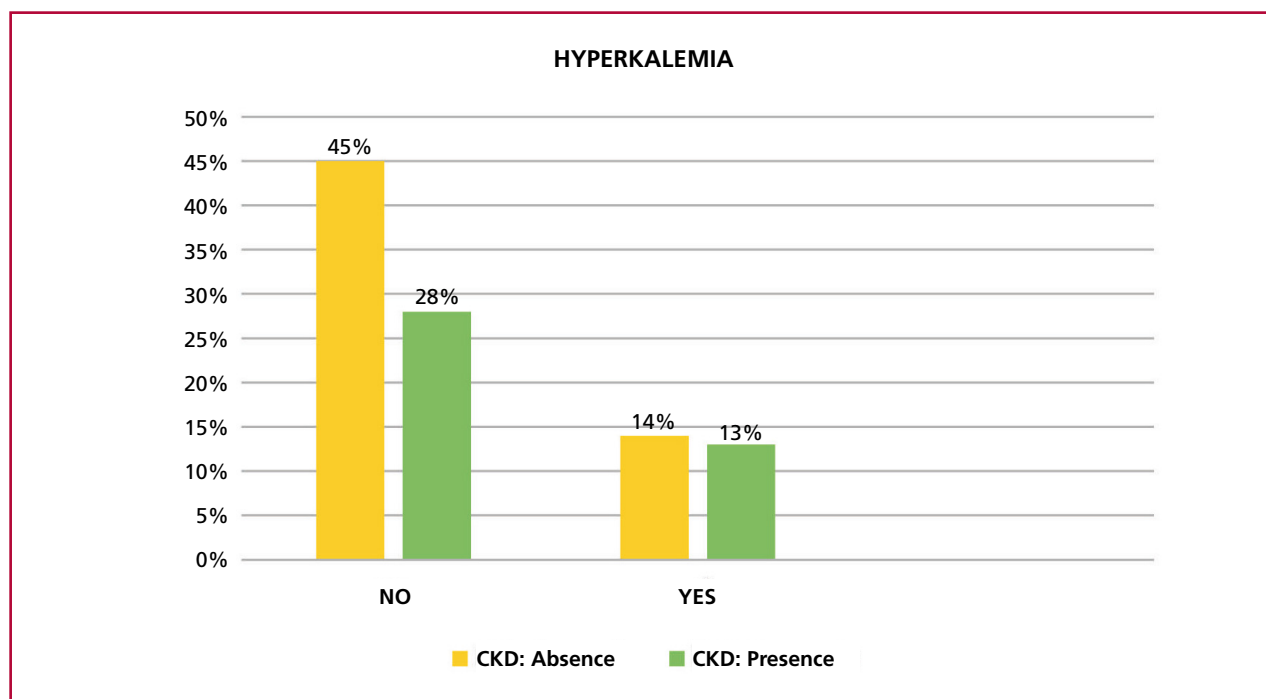


Table 1. Prevalence of hyperkalemia and clinical variables

Clinical variable	All (n=693)	Hyperkalemia YES (n=186)	Hyperkalemia NO (n=507)	p
Age, years, mean \pm SD	75 (\pm 13.02)	72.47 (\pm 12.54)	71.48 (\pm 13.20)	0.654
Diabetes Mellitus, n (%)	225 (32.5)	55 (29.6)	170 (33.5)	0.324
Hypertension, n (%)	596 (86.0)	161 (86.6)	435 (85.8)	0.798
CKD, n (%)	280 (40.4)	88 (47.3)	192 (37.9)	0.026
FC Dyspnea, n (%)				
0	3 (0.4)	----	3 (0.6)	----
1	217 (31.3)	60 (32.3)	157 (31.0)	0.816
2	314 (45.3)	87 (46.8)	227 (44.9)	0.702
3	147 (21.2)	38 (20.4)	109 (21.5)	0.841
4	11 (1.6)	1 (0.5)	10 (1.9)	0.319
Ischemic heart disease, n (%)	397 (57.3)	114 (61.3)	283 (55.9)	0.206

CKD: chronic kidney disease; FC: functional class; SD: standard deviation

Fig. 2. Hyperkalemia and CKD. The relative frequency of hyperkalemia is higher, though not exclusive, in patients with chronic kidney disease (CKD). The absence of hyperkalemia is associated more closely with absence of CKD.**Table 2.** Presence of hyperkalemia and other parameters studied

	All (n=693)	Hyperkalemia YES (n=186)	Hyperkalemia NO (n=507)	p
Creatinine (mg/dL)*	1.1 (0.9 – 1.4)	1.2 (0.9 – 1.5)	1.1 (0.9 – 1.4)	0.523
eGFR CKD/EPI**	67.0 \pm 1.4	62.7 \pm 1.7	68.6 \pm 1.2	0.007
Azotemia g/L*	45.5 (34.3 – 62.0)	50.0 (38.0 – 67.0)	44.0 (33.0 – 60.0)	0.003

*values expressed as median (IQR); **values expressed as mean \pm SD
eGFR CKD/EPI: glomerular filtration rate according to the CKD/EPI formula

Table 3 presents the relationship between hyperkalemia and stages of glomerular filtration rate. A strong association with stage 3B is notable.

The relationship between the presence of hyperkalemia and standard therapy for HF is detailed in Table 4. No statistically significant difference was observed in any of the cases.

DISCUSSION

Hyperkalemia in patients with HFrEF is common and is associated with increased morbidity and mortality. (19, 20) This first study in the UMIC cohort (Montevideo) found a prevalence of 27%, a figure higher than the 8–25% range reported internationally. (21, 22). Most cases were mild and were significantly associated with stage 3B CKD, a stage at which potassium excretion is significantly impaired. (23)

No significant association was found in stages 4–5 CKD. This could be explained by the small sample size in this subgroup, or by marked clinical caution and therapeutic inertia, characterized by low prescription of disease-modifying drugs (DMDs) due to the risk of severe hyperkalemia. (9, 16, 24) These findings underscore the clinical dilemma of balancing the benefits of DMDs against the risk of complications related to impaired potassium homeostasis in patients with ad-

vanced kidney disease, a group frequently excluded from clinical trials. (24)

Regarding treatment, the lack of an association between the use of ACEI/ARB II or mineralocorticoid antagonists and hyperkalemia differs from international reports describing a significantly higher incidence of hyperkalemia events in patients on triple therapy. (25) This finding may be attributed to the homogeneity of the sample due to the high local prescription rate, but it also suggests the success of optimized treatment regimens. The concomitant use of SGLT2i s likely exerts a compensatory diuretic effect that neutralizes the risk of elevated potassium. (26) Therefore, the risk associated with these drugs appears manageable under close monitoring in specialized units.

Among the study's strengths are the availability of a large, well-characterized cohort with standardized definitions according to international guidelines, allowing for precise risk stratification by CKD stage. As limitations, the retrospective observational design and the setting in a specialized unit may introduce selection and referral biases. These factors, along with therapeutic adjustment based on the risk of low baseline potassium levels, should be considered when generalizing the results.

Table 3. Presentation of the relationship between hyperkalemia and glomerular filtration rate stages

Stage	All (n=693)	Hyperkalemia YES (n=186)	Hyperkalemia NO (n=507)	p
1, n (%)	133 (19.3)	27 (14.8)	106 (21.0)	0.071
2, n (%)	262 (38.1)	64 (35,0)	198 (39.2)	0.287
3 A, n (%)	152 (22.1)	45 (24.6)	107 (21.2)	0.458
3 B, n (%)	94 (13.7)	37 (20.2)	57 (11.3)	0.005
4, n (%)	34 (4.9)	8 (4.4)	26 (5.1)	0.796
5, n (%)	13 (1.9)	2 (1.1)	11 (2.2)	0.528

Table 4. Occurrence of hyperkalemia and standard HF therapy

Stage	All (n=693)	Hyperkalemia YES (n=186)	Hyperkalemia NO (n=507)	p
ACEI – ARB II* , n (%)	585 (84.4)	156 (83,9)	429 (84,6)	0.966
Beta-blockers, n (%)	621 (89,6)	172 (92,5)	449 (88,6)	0.135
Loop diuretics, n (%)	429 (61,9)	109 (58,6)	320 (63,1)	0.278
Thiazides, n (%)	26 (3,8)	4 (2,2)	22 (4,3)	0.183
Spironolactone, n (%)	184 (26,6)	52 (28,0)	132 (26,0)	0.612
ARNI, n (%)	19 (2,7)	5 (2,7)	14 (2,8)	0.958
Statins, n (%)	408 (58,9)	115 (61,8)	293 (57,8)	0.339
Antiplatelet agents, n (%)	292 (42,1)	86 (46,2)	206 (40,6)	0.185
SGLT2i n (%)	26 (3,8)	9 (4,8)	17 (3,4)	0.362

ACEI: angiotensin-converting enzyme inhibitors ARB II: angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitors; SGLT2i: sodium-glucose cotransporter 2 inhibitors

* 577 ACEI patients, 8 ARA II patients.

CONCLUSIONS

The prevalence of hyperkalemia in patients with HFrEF in our cohort is high, with the majority of cases being mild. Hyperkalemia is primarily associated with the presence of CKD, especially in 3B stage. The absence of a significant association between hyperkalemia and the use of DMDs highlights the importance of maintaining disease-modifying therapy, aimed at reducing morbidity and mortality in this patient group.

Conflicts of interest

None declared.

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

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Probable Arrhythmic Syncope: A Conversation With Artificial Intelligence

Síncope probablemente arrítmico: dialogando con la inteligencia artificial

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ABSTRACT

The integration of artificial intelligence (AI) into clinical practice has led to the development of new tools for literature searches, knowledge organization, and decision-making support. However, its true potential emerges when it is integrated into a dynamic reasoning process, similar to a clinical discussion between colleagues.

Based on a case of probable arrhythmic syncope in a young patient with a structurally normal heart, we developed a structured conversation with AI that focuses on differential diagnosis, genetic testing, and risk stratification. The analysis applies Bayesian models to estimate the predictive value of genetic tests and their impact on therapeutic decisions, such as the need for an implantable cardiac defibrillator.

The conversation highlights the strengths and limitations of AI, as it facilitates access to information and the structuring of reasoning, while also revealing the reliance on assumptions and the uncertainty of certain parameters. In high-pressure scenarios, the prioritization of evidence and the contextual interpretation of data prove decisive.

In conclusion, integrating AI into a clinical conversation is a valuable strategy for exploring and validating medical reasoning. However, the ultimate decision remains contingent on clinical judgment, which serves as a unifying force amid complexity and ambiguity.

Key words: Artificial intelligence - Clinical reasoning - Arrhythmic syncope - Bayesian analysis - Cardiovascular genetics - Decision-making.

RESUMEN

La incorporación de la inteligencia artificial (IA) en la práctica clínica ha generado nuevas herramientas para la búsqueda bibliográfica, la organización del conocimiento y el apoyo en la toma de decisiones. Sin embargo, su verdadero potencial emerge cuando se integra en un proceso de razonamiento dinámico, similar al diálogo clínico entre colegas.

A partir de un caso de síncope probablemente arrítmico en un paciente joven con corazón estructuralmente normal, se desarrolla un intercambio estructurado con IA orientado al diagnóstico diferencial, el rol del estudio genético y la estratificación del riesgo. El análisis incluye la aplicación de modelos bayesianos para estimar el valor predictivo de los tests genéticos y su impacto en decisiones terapéuticas como la indicación de cardiodesfibrilador implantable.

El diálogo pone de manifiesto fortalezas y limitaciones de la IA: facilita el acceso a información y la estructuración del razonamiento, pero también evidencia la dependencia de supuestos y la incertidumbre de algunos parámetros. En escenarios de tensión, la jerarquización de la evidencia y la interpretación contextual de los datos resultan determinantes.

En conclusión, la IA, integrada en un diálogo clínico, constituye una herramienta valiosa para la exploración y validación del razonamiento médico. No obstante, la decisión final continúa sustentándose en el juicio clínico, que actúa como elemento integrador frente a la complejidad y la incertidumbre.

Palabras clave: Inteligencia artificial - Razonamiento clínico - Síncope arrítmico - Análisis bayesiano - Genética cardiovascular - Toma de decisiones

INTRODUCTION

The integration of artificial intelligence (AI) into clinical practice enables different approaches. In its most basic form, AI is a useful tool for conducting targeted literature searches and answering specific clinical

questions. Its value has been demonstrated in research and in the writing of medical texts.

Nevertheless, the most significant potential of AI does not lie in its capacity to provide information in isolation; rather, its true value lies in its integration

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within an interactive reasoning process. When AI is interrogated by simulating a conversation among colleagues, it enables users to explore hypotheses, refine interpretations, and prioritize evidence within a specific clinical context.

In this sense, it ceases to function as a mere reference tool and evolves into a dynamic aid to clinical reasoning, with the capacity to support, though not to replace, the decision-making process.

The aim of this presentation is to analyze, using a fictional clinical case, the role of artificial intelligence integrated into medical conversation. This analysis will highlight the contributions, limitations, and interactions of artificial intelligence with clinical judgment.

CLINICAL CASE

A 32-year-old patient experienced an episode of syncope without prodromal symptoms, accompanied by loss of consciousness, while walking on the street during a heated argument. He recovered quickly and fully after receiving initial care and was transferred to a high-complexity center. The patient was admitted for continuous electrocardiographic monitoring.

The episode was clinically defined as "probable arrhythmic syncope."

A comprehensive cardiovascular assessment was performed.

His medical history revealed no use of medication, vitamin supplements, hormonal treatments, or other substances. There was no family history of cardiovascular disease or sudden cardiac death.

The physical examination and ECG were normal. Laboratory tests, including thyroid function tests, were within normal ranges.

Doppler echocardiography and magnetic resonance imaging ruled out structural cardiovascular disease. The coronary arteries did not present obstructive lesions on coronary computed tomography angiography. The stress test results were normal, with the patient reaching an exercise load appropriate for his age and weight. There were no abnormalities on the ECG during exercise or recovery. A pharmacological test with flecainide also showed no abnormalities.

DIFFERENTIAL DIAGNOSIS

Question

In a young patient with probable arrhythmic syncope and a structurally normal heart, is it appropriate to consider the presence of a channelopathy as a differential diagnosis? What is the likely order of probable etiologies in terms of probability?

Answer

Yes, in this clinical context, the differential diagnosis is primarily directed towards channelopathies. Among the diagnostic possibilities, ranked in order of probability, the following should be considered: (1)

- Idiopathic ventricular tachycardia
- Long QT Syndrome (LQTS)

- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Brugada syndrome
- Early repolarization syndrome
- Short QT syndrome

The relative probability depends on the clinical context, the ECG and the results of the ancillary tests.

Question

Are there any particular considerations regarding early repolarization syndrome and short QT syndrome?

Answer

Early repolarization may represent a benign condition when the ECG shows J-point elevation with an upward-sloping ST-segment in inferior or lateral leads. However, even in the presence of probable arrhythmic syncope, the finding should be interpreted with caution. In these circumstances, the morphology of the ST-segment and the clinical context become particularly important, as an isolated ECG finding is insufficient to establish the clinical significance of the pattern. (2)

As for short QT syndrome, its incidence in the general population is extremely low.

Question

Can the ECG be normal in LQTS and short QT syndrome?

Answer

A normal baseline ECG may not rule out LQTS and short QT syndrome, in which ventricular arrhythmia may be the first clinical manifestation. (3,4)

ROLE OF GENETIC TESTING

Question

When investigating a channelopathy, would it be appropriate to request genetic testing?

Answer

In a patient with probable arrhythmic syncope and negative initial test results, an implantable loop recorder is a reasonable strategy for documenting the responsible arrhythmia.

At the same time, genetic testing may be considered if the differential diagnosis includes inherited channelopathies such as:

- Long QT Syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Brugada syndrome

Genetic panels typically include genes such as:

- o YR2 (associated with CPVT) (5)
- o KCNQ1 and KCNH2 (LQTS) (6)
- o SCN5A (Brugada syndrome) (7)

Question

What is the prevalence of these three channelopathies in the general population?

Answer

In the general population, the prevalence of a positive genotype, with or without an associated phenotype, varies for each condition: as a rough estimate, LQTS 2.5%, Brugada syndrome 0.2%, and CPVT 0.07%. Penetrance—the percentage associated with the positive phenotype—averages 15–20% and is much higher in LQTS than in the other two. These prevalences rise substantially when we consider the relatives of an index case.

In the detailed clinical context, the probability of identifying a pathogenic variant is relatively low (approximately 10–20%), and variants of uncertain significance are often identified. Therefore, genetic testing is not a substitute for documentation of arrhythmias and does not determine the indication for an implantable cardioverter-defibrillator (ICD) by itself. The primary usefulness of genetic testing is for diagnosis and within the context of family screening. (8)

PROBABILITY AND BAYESIAN ANALYSIS**Question**

Is it possible to apply Bayesian analysis to assess the impact of genetic testing on clinical management?

Answer

Conceptually, Bayesian analysis can be used to estimate how a test result modifies the probability of a clinical event occurring.

In this scenario, the following definitions could be used:

- Event to be predicted: future malignant ventricular arrhythmia (resuscitated cardiac arrest or sudden cardiac death).
- Pretest probability: in this case, the pretest probability is the baseline risk of experiencing the clinical event (malignant ventricular arrhythmia) in a patient diagnosed with 'probable arrhythmic syncope and a structurally normal heart' (negative phenotype)

- Positive test: identification of a pathogenic genetic variant associated with channelopathies as a predictor of the clinical event.

In a theoretical model, the following values can be applied: (9,10)

- Pretest probability: 10% / 10 years
- Sensitivity (S): 60%
- Specificity (Sp): 80%

The result of the calculation is:

- Positive predictive value (PPV): 25%
- Negative predictive value (NPV): 95%

In other words, according to the calculation, if the test is positive, the probability of experiencing a resuscitated cardiac arrest or an episode of sudden cardiac death is 25% over 10 years; if the test is negative, that probability falls to 5%.

Question

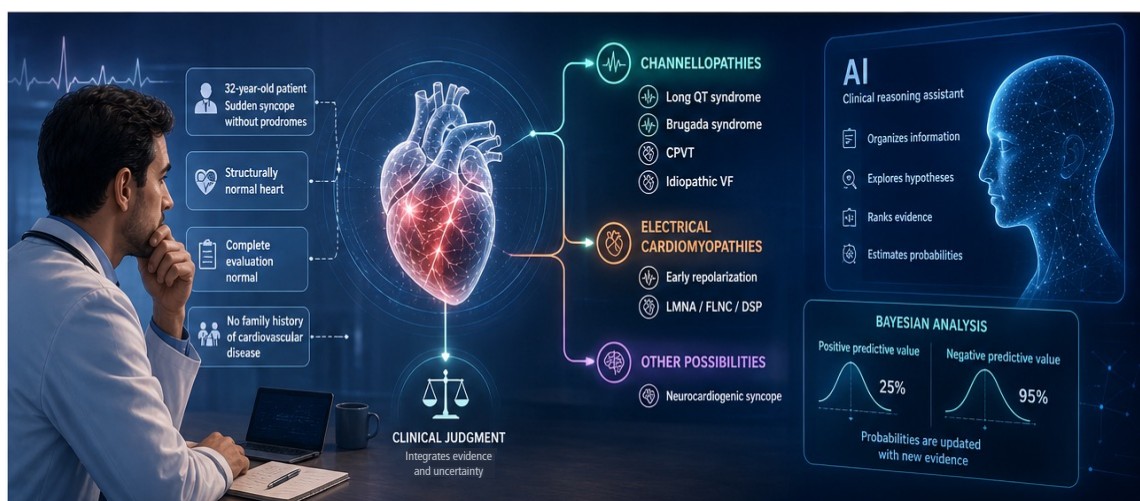
Do the calculated values apply to the three channelopathies selected for evaluation—Brugada, LQTS and CPVT?

Answer

The calculation can be interpreted as an overall estimate for a channelopathy in a patient with arrhythmic syncope and a structurally normal heart. However, genetic sensitivity varies greatly depending on the syndrome, and the test described above applies only to the clinical presentation outlined. (10)

In this case, the PPV and NPV are reasonably reliable for Brugada syndrome and CPVT, but only approximate for LQTS due to its greater heterogeneity and lower phenotypic expression in certain scenarios. However, the overall PPV is comparable across the primary channelopathies when the clinical pretest is similar.

In conclusion, in LQTS the PPV may be lower in cases with a borderline phenotype and a lower pretest probability, but it is not inherently lower.



Central illustration. Interaction with artificial intelligence. See text for abbreviations

FAMILY SCREENING FOR CHANNELOPATHIES

Question

Assuming that the same genetic variant as in the patient or index case is confirmed in a relative with no cardiovascular disease or personal history, do the PPV and NPV vary in the index case?

Answer

In this case, the pretest probability of the index case is likely to be higher, at 15%, so that, with the same S and Sp, the PPV rises to 35% and the NPV remains unchanged at 92%. (10,11)

Question

And in the case of the family member, with a positive genotype and negative phenotype (G+ / P-), what are the PPV and NPV?

Answer

The pretest probability, or risk of experiencing a future episode of resuscitated cardiac arrest or sudden cardiac death, is low, perhaps close to 3% at 10 years, meaning that the PPV falls to 9% at 10 years and the NPV rises to 99% over the same period. (10,11). It should be noted that this pretest probability in the general population is much lower than that of relatives of the index case with G+/P-.

Question

Is it possible to create a comparative table of the Bayesian analysis for the three scenarios considered?

Answer

Yes, of course. (Table 1). In these scenarios —index case by relative, with positive or negative genotype, and relatives with positive genotype but negative phenotype— the Bayesian analysis is based on uncertain assumptions; therefore, the numerical estimates are limited. The usefulness of Bayesian analysis lies in its conceptual framework for probabilistic interpretation, which frequently underpins clinical decision-making.

GENETIC TESTING: CONSISTENCY IN RISK ESTIMATION

Question

How reliable are the PPV and NPV calculations resulting from Bayesian analysis?

Answer

In inherited channelopathies as LQTS, Brugada syndrome or CPVT, the sensitivity of genetic testing, derived from series of specialized centers with phenotypically clear patients, is considered relatively reliable. Conversely, the pretest probability and specificity estimated from low-prevalence population-based studies are much more uncertain. This uncertainty mainly affects the estimation of the PPV and NPV, which can vary significantly depending on the population and phenotypic definition. (11,12)

Question

So, even if the calculated PPV for the index case was about 25%, could the indication for ICD still be unjustified?

Answer

Although a calculated PPV may indicate a high risk ($\approx 25\%$) in modeled scenarios, for the reasons already discussed it should be interpreted as a relative guide and not as an absolute risk. The clinical decision, such as the indication for ICD, must combine phenotypic evidence with the uncertainty of genetic and clinical parameters, recognizing that, while genetic sensitivity remains more robust, the other statistical factors are less reliable. (13)

Question

So, the conclusion would be...

Answer

Genetics informs and underscores the diagnostic suspicions, but the absolute risk of sudden cardiac death or arrhythmic shock, clinically suspected, remains the primary criterion for indicating an ICD. This is precisely what justifies the observation: "While a Bayesian calculation may show a high PPV, therapeutic decisions require direct phenotypic evidence, as genetics alone does not define absolute risk."

The patient experienced an episode of syncope without prodromal symptoms during emotional stress while walking. Recovery was spontaneous; subsequent electrocardiographic and structural workups were unremarkable, and there was no family history of sud-

Table 1. Bayesian analysis of the 10-year probability of serious arrhythmic events in the index case with a positive genotype and positive phenotype (G+/P+), according to the genetic status of the family member [negative genotype (G-) or positive genotype (P+)], and in the family member with a positive genotype and negative phenotype (G+/P-)

The pretest probability differs between scenarios, whilst sensitivity and specificity are considered constant. Consequently, the positive predictive value (PPV) and negative predictive value (NPV) vary depending on baseline risk.

Variable	Preliminary test (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Family member G+/P-	3	60	80	9	99
Index case G+/P+ (family member G-)	10	60	80	25	95
Index case G+/P+ (family member G+)	15	60	80	35	92

den cardiac death. Upon initial review, this presentation could be classified as "improbable sudden cardiac death", as no instances of ventricular fibrillation or resuscitated cardiac arrest were documented. According to the established guidelines, the indication for an ICD is not rational. Genetic testing may help confirm the diagnosis and guide family surveillance; however, therapeutic decisions should be based primarily on the clinical phenotype (clinical presentation) and documentation of the arrhythmia. Continuous electrocardiographic monitoring and close follow-up are recommended until a high-risk episode is documented. (10-12)

Question

How should the family member be managed?

Answer

In a first-degree relative with a negative cardiovascular assessment who is a carrier of the variant (G+/P-), the recommended approach is: (10)

- regular clinical monitoring
- education on warning signs
- early management of fever
- avoid proarrhythmic drugs (especially in Brugada syndrome and LQTS)

CARDIOMYOPATHIES WITH EARLY ELECTRICAL PHASE

Question

Is it possible for a structural cardiomyopathy with minimal changes undetectable by standard methods to initially manifest with severe arrhythmias?

Answer

Yes, some cardiomyopathies may initially present an early electrical phase, in which electrical instability precedes evident structural changes.

This can be observed in: (13)

- arrhythmogenic cardiomyopathy
- dilated cardiomyopathy associated with LMNA, FLNC or DSP variants.

In these cases, cellular changes or microscopic fibrosis may generate arrhythmias before imaging techniques detect structural changes.

From channelopathies to cardiomyopathies

Question

Leaving aside the possibility that this is a channelopathy, can a structural cardiomyopathy with minimal, undetectable changes initially debut with an arrhythmic episode, as in the case that prompted this discussion?

Answer

Once again, there are structural cardiomyopathies that can present with arrhythmias even before structural abnormalities are evident on conventional echocardiography.

Some cardiomyopathies present an early electrical

phase in which cellular changes (microscopic fibrosis, myocyte disorganization, or desmosomal alterations) generate electrical instability before imaging tests reveal clear structural disease. (13)

Question

Even with normal cardiac magnetic resonance imaging?

Answer

Yes, microscopic fibrosis may be undetectable by gadolinium enhancement or minor cellular alterations (desmosomes, cytoskeleton) may be present.

Question

How often do severe arrhythmias occur at this stage?

Answer

They can occur, but are rare.

Question

To be clear, in the clinical case presented, is it advisable to investigate genetic variants associated with the cardiomyopathies mentioned?

Answer

The guidelines recommend that genetic testing should focus on the suspected clinical phenotype. The use of broad panels without a highly-specific phenotype—for example, including cardiomyopathy genes in a patient without structural abnormalities—increases the detection of variants of uncertain significance without improving diagnostic performance. (14)

CARDIOMYOPATHIES, GENETIC TESTING AND CLINICAL DECISION-MAKING

Question

Setting aside "cardiomyopathies in the early electrical phase," is the limited value of genetic testing applicable to cardiomyopathies in general, as was concluded when discussing channelopathies?

Answer

The clinical value of genetics in channelopathies cannot be extrapolated to structural myocardial diseases. In cardiomyopathies, the genotype can have an impact on prognosis and on the individual treatment strategy. The performance of genetic testing, particularly for diagnosis, is 30–60% and is even lower in channelopathies. (15)

Question

Can you give a specific example of an indication for ICD implantation supported by genetic testing?

Answer

A specific example might be the case of a dilated cardiomyopathy associated with pathogenic mutations such as LMNA. For instance, a patient with left ventricu-

lar ejection fraction (LVEF) of 40–45% may not meet the traditional criteria for an ICD based on ventricular function. However, if a pathogenic variant, such as LMNA, is identified, particularly if non-sustained ventricular tachycardia or conduction disorders are present, the arrhythmic risk is significantly higher. In these cases, guidelines recommend implanting an ICD as a primary prevention measure, even with LVEF greater than 35%. In this case, the genetic result directly influences the therapeutic decision. (16)

Question

Does family screening for cardiomyopathies influence the medical decision?

Answer

In family screening, the impact is even greater. For hypertrophic, dilated, or arrhythmogenic cardiomyopathy, identifying a pathogenic variant obviates the need to monitor non-carriers, allowing clinical efforts to focus on carriers. This, in turn, optimizes risk management, follow-up, and resource allocation.

It should be noted that, although a family history of sudden cardiac death increases the baseline risk, it does not replace the phenotype when stratifying individual risk. (15)

The problem of hypertrophic cardiomyopathy

Question

Why has the indication for ICD implantation, supported in part by genetic testing in dilated cardiomyopathies with certain variants, not been successful in hypertrophic cardiomyopathy?

Answer

In hypertrophic cardiomyopathy, the use of genotype as an indication for ICD implantation has not been successful due to significant genetic heterogeneity, variable penetrance, and the absence of a gene consistently associated with high arrhythmic risk. The risk of sudden cardiac death correlates better with the structural phenotype (syncope, wall thickness, fibrosis, gadolinium enhancement) than with the genetic variant itself; therefore, genotyping does not provide sufficient incremental predictive value to guide ICD implantation. (13)

Question

Given the lack of usefulness of genetic testing for prognostic stratification in hypertrophic cardiomyopathy, could the same situation occur in the future with dilated cardiomyopathy caused by the LMNA genetic variant or other variants? Is the evidence strong enough to rule out that possibility?

Answer

As was the case with hypertrophic cardiomyopathy, where genetic testing proved ineffective for prognostic stratification, a similar scenario could occur with

dilated cardiomyopathy associated with LMNA. While there is a consistent association with increased arrhythmic risk, the evidence primarily comes from observational cohorts in specialized centers. Therefore, it is possible that the actual predictive value may be lower in larger, less selected populations. (16)

Question

In conclusion, in both the index case and family screening, is the value of genetic testing greater in cardiomyopathies compared with channelopathies?

Answer

Yes, the clinical value is clearly greater in cardiomyopathies. (15)

GENETIC VARIANT, PENETRANCE AND EXPRESSIVITY

Question

During the discussion, it became evident that, for any genetic test, the sensitivity of the test—assessed in case series from genetic centers—is a more reliable indicator than specificity, which is evaluated only partially in population-based studies.

However, in a given phenotype, the detection of a genetic variant implies the presence of other determinants—both genetic and epigenetic—that influence penetrance and expressivity. Is this statement correct?

Answer

The conclusion that sensitivity, as estimated in case series from specialized centers, is a more reliable measure than specificity, which is only partially assessed due to the scarcity of well-designed, large-scale population studies, must be adjusted. Indeed, sensitivity itself must be interpreted with caution due to the inherent selection biases in these series.

On the other hand, it is right to state that, for a given phenotype, the detection of a genetic variant implies the coexistence of other genetic and epigenetic determinants that influence the penetrance and expressivity of the clinical trait. These factors, which contribute to the expression of the phenotype and partly explain the sensitivity observed in clinical series, are not assessed by the genetic test itself, which is limited to identifying only the presence of a specific variant. Consequently, the diagnostic performance observed in selected populations may not be directly extrapolated to other clinical or population-based contexts. (17)

Based on the current state of knowledge, it can be concluded that channelopathies, such as long QT syndrome, CPVT and Brugada syndrome, are genetic disorders with Mendelian inheritance for which mutations in specific genes have been identified. However, their clinical presentation does not follow a strict Mendelian pattern due to incomplete penetrance and the influence of multiple modifier factors, which limits the predictive value of these variants individually.

Question

In comparative terms, are there differences in penetrance between channelopathies and cardiomyopathies?

Answer

Penetrance is lower and more variable in channelopathies and intermediate in arrhythmogenic cardiomyopathy. In contrast, penetrance is high and more constant in LMNA. This difference in penetrance translates into different predictive values for variants and clearly different clinical impact.

In short, genetics has high diagnostic value but limited value for arrhythmic stratification when the phenotype is absent. A particular case is that of the G+ / P- index case in a family with a history of sudden cardiac death where the risk is high.

FINAL INTERPRETATION OF THE CLINICAL CASE**Medical team decision**

Returning to the case that prompted this discussion, the genetic panel analysis revealed a variant of uncertain significance.

For decision-making, the issue focuses on how to interpret the episode of loss of consciousness as a determining factor in the strategy to be followed. (18-20)

In this regard, two possible scenarios can be considered:

- 1) Classifying the episode as a major arrhythmic event, possibly idiopathic ventricular fibrillation. With this interpretation, the guidelines support ICD implantation.
- 2) Considering the syncopal episode as likely, but not definitively, arrhythmic in origin. This places the patient within the context of primary prevention of sudden cardiac death. In this case, the recommended course of action would include regular clinical follow-up, beta-blocker therapy, and the implantation of a loop recorder.

The medical team considers this second possibility to be more likely.

Both interpretations are possible. However, if the treating team considers the episode to be of uncertain arrhythmic origin, the approach is reasonable.

CONCLUSIONS ON THE CONVERSATION

The dynamics of the dialogue underscores several key aspects of assisted clinical reasoning:

- **Precise definition of the problem**

The initial formulation of the question is a critical step, as it defines the scope of analysis and guides all subsequent developments. A well-constructed question allows the discussion to be focused and prevents digressions into irrelevant clinical scenarios.

- **The value of cross-questioning as a cognitive tool.**

Cross-questioning not only serves a clarifying function but also acts as an active mechanism for vali-

dation and correction. Throughout the exchange, this iterative inquiry enables the detection of ambiguities, the adjustment of implicit assumptions, and the redefinition of the interpretive framework where necessary.

- **Internal coherence of reasoning**

The storyline remains consistent throughout the dialogue, with no significant conceptual contradictions. This reflects the logical progression of knowledge development, where each answer builds on previous ones.

- **Bibliographic support**

The concepts developed are supported by the cited literature, which provides strength to the discussion. The evidence is not presented in isolation, but rather integrated into the clinical reasoning process.

- **Hierarchization of evidence in situations of uncertainty**

A point of tension is identified when the Bayesian analysis suggests a high probability of serious clinical events that could justify major interventions, such as ICD implantation. In this scenario, the deliberative process is not limited to the quantitative result. Rather, it prioritizes the quality of the underlying evidence, giving precedence to clinical practice guidelines overestimates based on parameters with greater uncertainty (pretest probability, specificity).

- **Integrating data, context and pathophysiology**

The dialog illustrates that clinical, genetic, and statistical data are not interpreted in isolation but rather integrated into a broader clinical context. The meaning of the data depends on the context in which it is interpreted and the underlying assumptions; even if they are technically correct, they may result in partial conclusions if not subjected to critical integration.

- **Centrality of clinical judgment**

Finally, the process emphasizes that medical decision-making is ultimately based on clinical judgment, even when advanced analytical tools and literature-based evidence are available. The judgment of the treating team acts as an integrating and organizing element in the face of uncertainty. The dialogue collectively presents a model of clinical reasoning. This model illustrates how the interaction between clinical questions, evidence, quantitative analysis, and medical judgment enables the formulation of prudent decisions. These decisions help avoid both the overinterpretation of data and its underutilization.

Conflicts of interest

None declared.

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

Note

During the preparation of this manuscript, an artificial intelligence model (ChatGPT, OpenAI) was used to support the organization and editorial review of the text. The authors critically reviewed the scientific content, clinical interpretation, and conclusions and assume final responsibility for the work.

The central illustration was created by ChatGPT.

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Dipyron-induced Type 2 Kounis Syndrome: A Diagnostic Challenge

Síndrome de Kounis Tipo II inducido por dipirona: un reto diagnóstico

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Kounis syndrome (KS) is defined as the occurrence of an acute coronary syndrome in the setting of a hypersensitivity reaction. This represents a diagnostic challenge that extends beyond the traditional understanding of coronary artery disease. It was previously described as “allergic angina” due to its pathophysiology based on the activation of mast cells located in the arterial tunica adventitia and atherosclerotic plaques. (1) Over time, the understanding of this condition has shifted from a purely vasospastic phenomenon to one involving plaque erosion and rupture mediated by inflammatory processes.

Three clinical variants are recognized: type 1 is characterized by vasospasm in angiographically normal coronary arteries; type 2 involves erosion or rupture of a preexisting plaque, and type 3 presents as stent thrombosis. Recognition of type 2 is crucial because it involves the coexistence of stable chronic coronary artery disease and a concomitant immunologic trigger for instability, requiring prompt clinical management. (2,3) This manuscript presents a case of type 2 KS.

We report a case of a 68-year-old female patient, with appropriate informed consent. She had a history of hypertension, non-insulin-dependent type 2 diabetes mellitus, stage 3a chronic kidney disease, moderate to severe aortic insufficiency, two-vessel coronary artery disease treated with percutaneous coronary intervention (PCI) with stent placement in the circumflex and posterior descending arteries, with no further revascularization options as of 2018, and right knee osteoarthritis. She was admitted to a tertiary care center on an outpatient basis on September 6, 2025 for elective right knee replacement surgery. The procedure was performed without complications.

On September 7, 2025, during the immediate postoperative period (approximately 5:30 a.m.), following the administration of dipyron (metamizole) for pain control, the patient developed a 5-minute episode of sudden, oppressive chest pain without radiation, as-

sociated with dyspnea, requiring oxygen support therapy via nasal cannula at 1 L/min. On room air (FiO₂ 0.21), arterial oxygen saturation was 88%. The electrocardiogram showed sinus rhythm at 85 bpm, regular R-R intervals, and Q waves in the inferobasal wall, without ST-segment elevation. Laboratory tests were performed, and cardiac biomarkers showed elevated troponin T on the second measurement (Table 1). A chest CT angiography using a pulmonary thromboembolism protocol was performed, and the result was negative. Transthoracic echocardiography showed a non-dilated left ventricle with concentric hypertrophy, preserved left ventricular systolic function, no segmental wall motion abnormalities, and an ejection fraction of 61%, as well as severe aortic regurgitation due to retraction and partial prolapse of the right coronary cusp, with no evidence of pulmonary hypertension. Transesophageal echocardiography confirmed these findings.

Based on these findings, a non-ST-segment elevation acute myocardial infarction was diagnosed, with a GRACE score of 128 points and suspected type 2 KS. Coronary angiography performed on September 19, 2025 revealed a severe lesion in the distal segment of the right coronary artery, with a previously implanted stent in a circumflex artery that was patent, without restenosis and with adequate flow; stent implantation was performed in the right coronary artery (Figure 1).

Following coronary angiography, the patient was transferred to the intensive care unit, with a favorable clinical course. Dual antiplatelet therapy and high-intensity statins with ezetimibe were initiated. No evidence of impaired wound healing, infection, or discharge was observed; therefore, the orthopedic team opted for outpatient management.

This case highlights that a single dose of metamizole may destabilize a previously stable coronary plaque. In type 2 KS, the hypersensitivity reaction triggers massive mast cell degranulation. (4) This leads to the release of preformed mediators such as

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Table 1. Basal laboratory test results and following the onset of chest pain.

Parameter	September 6, 2025	September 7, 2025
White blood cells	17.66 x 10 ³ /μL	16.45 x 10 ³ /μL
Neutrophils	16.54 x 10 ³ /μL	14.71 x 10 ³ /μL
Lymphocytes	0.65 x 10 ³ /μL	0.69 x 10 ³ /μL
Monocytes	0.34 x 10 ³ /μL	0.95 x 10 ³ /μL
Eosinophils	0 x 10 ³ /μL	0 x 10 ³ /μL
Basophils	0.02 x 10 ³ /μL	0 x 10 ³ /μL
MCV	88.2 fL	88.1 fL
Platelets	275 x 10 ³ /μL	255 x 10 ³ /μL
Hematocrit	44.6%	36.5%
Hemoglobin	14.6 g/dL	12 g/dL
Triglycerides		98.6 mg/dL
VLDL		19.7 mg/dL
HDL		29.9 mg/dL
LDL		28.8 mg/dL
Total cholesterol		71.9 mg/dL
HbA1C		6.2%
Troponin T*	14.3 ng/mL	77.7 ng/mL
Blood urea nitrogen		31.6 mg/dL
Creatinine		1.76 mg/dL

*Troponin delta values showed a significant increase, supporting the diagnosis of ongoing NSTEMI. MCV: mean corpuscular volume

Fig. 1. Coronary angiography findings.

leukotrienes and histamine, which induce vasospasm, as well as proteases such as tryptase and chymase. These, in turn, activate matrix metalloproteinases that degrade collagen in the fibrous cap of the atherosclerotic plaque, facilitating erosion or acute rupture. In this patient, the presence of a severe distal lesion in the right coronary artery suggests inflammatory stress secondary to drug exposure, which acted as a trigger in a previously vulnerable coronary anatomy.

Metamizole (dipyrone) is a widely used analgesic, but its immunological safety profile requires close monitoring. (4) Agranulocytosis is the most widely recognized risk. However, this syndrome and immediate hypersensitivity reactions may frequently occur without evident cutaneous manifestations, as in this case. (5) A history of nonsteroidal anti-inflammatory drug (NSAID) intolerance is noteworthy, as it may indicate a pre-existing susceptibility to shift metabolism toward the leukotriene pathway.

From a therapeutic standpoint, KS remains a dilemma. Beta-blockers are contraindicated in the acute phase due to the risk of exacerbating coronary vasospasm. Adrenaline should be used with caution and reserved for anaphylactic shock, as it increases oxygen demand and may worsen ischemia. Therefore, a multidisciplinary approach involving cardiology is essential to guide revascularization along with corticosteroids and antihistamines. (6) This case underscores that, in the setting of an allergic reaction, the heart is also a critical target organ.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

The authors declare that all procedures complied with institutional ethical standards and that patient confidentiality was ensured.

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Wenckebach-Type Second-Degree Block in the Intraventricular Conduction System. An Underdiagnosed Phenomenon that May Mimic Intermittent Bundle Branch Block

Bloqueo de segundo grado tipo Wenckebach en el sistema de conducción intraventricular. Un fenómeno subdiagnosticado que puede simular un bloqueo de rama intermitente

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Mobitz type I second-degree atrioventricular (AV) block, also known as the Wenckebach phenomenon, is defined as an intermittent failure of AV conduction preceded by a progressive prolongation of AV conduction time. It typically occurs in tissues composed of slow-response cells, such as those of the sinoatrial and AV nodes. Conversely, the possibility of its occurrence in the His-Purkinje system has been overlooked and even denied, as evidenced by the limited literature available. In 1969, Rosenbaum et al. (1) described the electrocardiographic characteristics of the different forms of the phenomenon in the bundle branch system, whereas Kretz and Da Ruos experimentally demonstrated it in the divisions of the left bundle branch. (2)

We present the case of a patient whose electrocardiogram (ECG) showed a second-degree right bundle branch block interpreted as incompletely concealed Wenckebach phenomenon. (1)

This is the case of a 64-year-old female patient with chronic Chagas cardiomyopathy, admitted for evaluation of aortic stenosis. Serial ECGs showed intermittent right bundle branch block (RBBB). Figure 1A shows regular sinus rhythm at 72 bpm and a constant PR interval of 160 ms. Beats 1, 2 and 3 display a complete RBBB pattern with a QRS duration of 160 ms. Beat 4 shows normal intraventricular conduction (QRS duration 80 ms) without preceding changes in sinus cycle length or PR interval. This sequence corresponds to a 4:3 second-degree right bundle branch block. Figure 1B, recorded with the same sinus cycle length and PR interval, shows 2:1 complete RBBB. Figure 1C, recorded later, shows persistent complete RBBB.

The Wenckebach phenomenon is a type of conduction disorder in which impulse propagation progres-

sively slows until conduction block occurs. This phenomenon is usually observed in structures composed of slow-response cells, such as the AV node, and in pathological conditions affecting the sinoatrial node. The His-Purkinje system, composed of fast-response cells, exhibits the Wenckebach phenomenon only under pathological conditions, when fast-response fibers acquire slow-response properties, thereby creating the substrate required for this phenomenon. (3) Rosenbaum et al. (1) described and classified the Wenckebach phenomenon in the bundle branches according to its mode of presentation into three types: 1) Direct Wenckebach phenomenon: Beginning with a beat exhibiting a narrow QRS complex and a constant sinus rate, a progressive increase in QRS duration is observed in the affected bundle branch until complete bundle branch block occurs. This is followed by a beat with a narrow QRS complex that initiates a new cycle (see Figures 2 and 6 in Reference 1). 2) Incompletely concealed Wenckebach phenomenon: This type exhibits a complete bundle branch block pattern in the beat that initiates the cycle, which remains unchanged until normalization of QRS complex occurs. The first beat of each cycle shows a complete block pattern whenever impulse delay in the affected branch exceeds 40–60 ms, corresponding to trans-septal conduction time. Impulse delay increases with each beat while maintaining the same pattern until complete block of the impulse occurs, followed by a beat with normal conduction, as illustrated in Fig. 1A. Similar examples are shown in Figures 3, 4 and 7 of Reference 1. In our case, the incompletely concealed Wenckebach phenomenon was not preceded by a direct Wenckebach, unlike the cases published by Rosenbaum et al. and illustrated in Figures 2 and 6.

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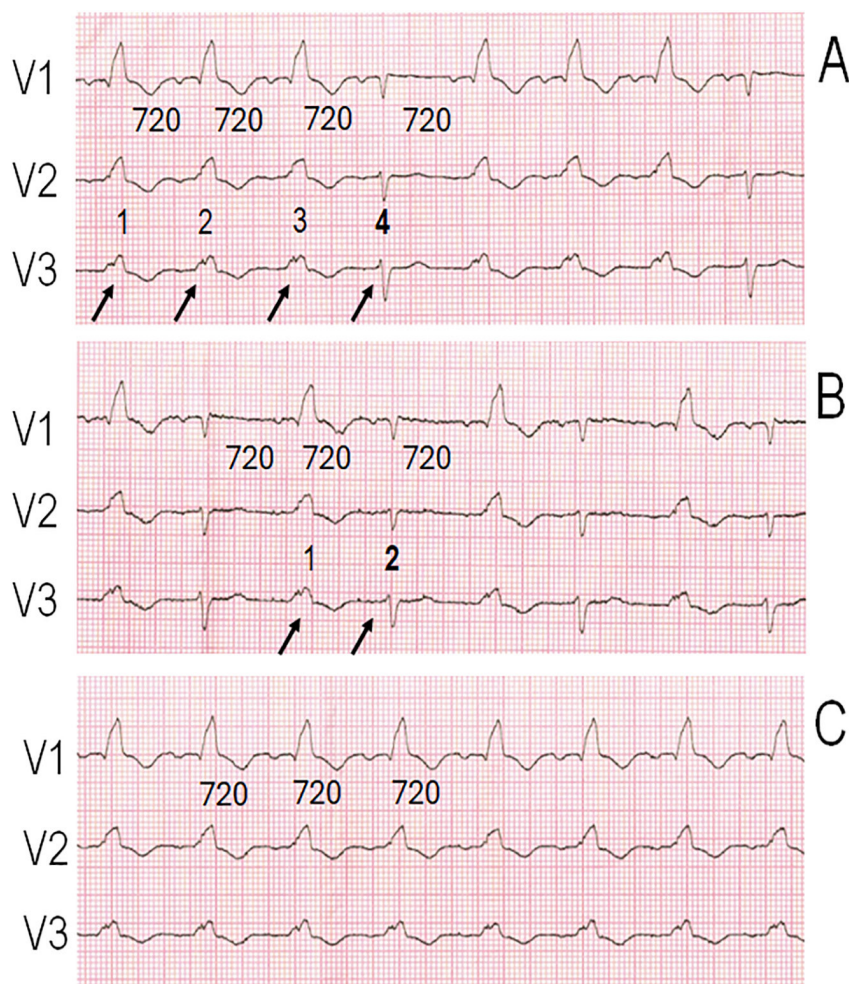
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Fig. 1. A. Continuous electrocardiographic recording (V1-V3) showing sinus rhythm with a cycle length of 720 ms and a PR interval of 200 ms. At the beginning of the tracing, beats 1, 2 and 3 exhibit a complete right bundle branch block (RBBB) pattern, whereas beat 4 shows normal intraventricular conduction, constituting a 4:3 second-degree incompletely concealed Wenckebach-type block. **B.** With the same cycle length, 2:1 RBBB is observed. This sequence could be explained by rightward displacement of refractoriness due to contralateral retrograde activation of the right bundle branch during the beat with normal conduction. **C.** Persistent complete RBBB with the same heart rate and PR interval may correspond to a completely concealed Wenckebach-type block or to permanent complete block of the right bundle branch. See text for further explanation of the figures.



An essential condition for this sequence to occur is the absence of retrograde activation of the affected bundle branch or fascicle originating from the contralateral ventricle. 3) Completely concealed Wenckebach phenomenon: This occurs when conduction delay of the first beat in the cycle exceeds 40 to 60 ms, such that the QRS complex exhibits a complete block pattern, as do the subsequent beats with longer delays in impulse propagation until complete block occurs. The new cycle will consistently show complete block of the affected bundle, and the phenomenon therefore will remain concealed. Figure 1C may correspond to this type of block. This possibility is inferential and can only be suspected when preceded by either a direct Wenckebach pattern or an incompletely concealed Wenckebach pattern (Fig. 1A). In all three types of

block, the PR interval remains unchanged, and a stable sinus rate facilitates interpretation. Differential diagnoses include supernormal conduction, (4) the linking phenomenon, (5) intermittent bundle branch block, (6) and Mobitz II second-degree AV block. (6)

Demonstrating the different types of bundle branch or fascicle block by means of an electrophysiological study is extremely difficult because it requires recording electrograms both proximal and distal to the site of block. Furthermore, as this practice provides no benefits for patient management, it is not recommended.

We believe that an important contribution of this case report is to highlight that the Wenckebach phenomenon is not exclusive to AV conduction, and that its occurrence within the intraventricular conduction

system should be suspected on the basis of the features described in this article.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable.

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Infective Endocarditis Caused by *N. Gonorrhoeae*. A Rare Etiology

Endocarditis infecciosa a N. Gonorrhoeae, una rara etiología

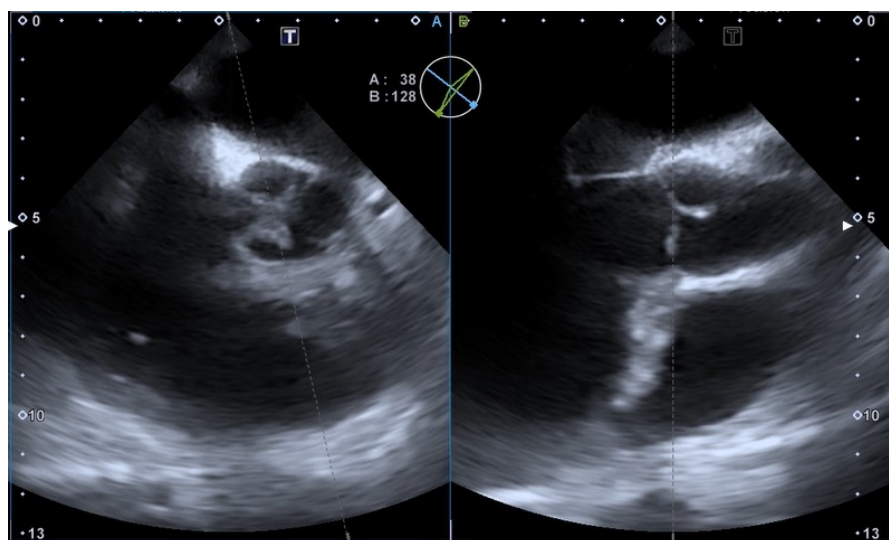
MARÍA FLORENCIA HERMAN CAVARRA¹, ANA BELÉN VALDES², MARÍA JIMENA GAMBARTE², CLAUDIO C. HIGA²

Infective endocarditis is still a diagnostic challenge due to its variable clinical presentation. The most common associated microorganisms are *Staphylococcus aureus* and streptococci of the oral cavity, and, to a lesser extent, *Enterococcus faecalis*. We report the case of a young patient with infective endocarditis caused by *Neisseria gonorrhoeae*, a relatively uncommon etiology. (1-3)

A 28-year-old otherwise healthy male, with a history of tobacco use and overweight, presented to a local hospital with a three-week history of fever, abdominal pain, and diarrhea. Internal Medicine reviewed the case and diagnosed the patient with uncomplicated diverticulitis. Of the two blood cultures taken, one resulted positive for *N. gonorrhoeae*. Antibiotic treatment was therefore initiated with metronidazole, ceftriaxone and

doxycycline to cover both sites of infection. The patient denied engaging in risky sexual behaviors and tested negative for sexually transmitted infections. Physical examination revealed a previously unknown grade 3/6 diastolic murmur at the aortic area. Consequently, the patient underwent transthoracic and transesophageal Doppler echocardiography. Both imaging modalities revealed a 9 mm x 4 mm vegetation on the non-coronary cusp of the aortic valve, associated with severe regurgitation (Figures 1 and 2). Additionally, the left ventricle was mildly dilated (measuring 6.2 cm in diastole on transesophageal echo), and a 6.3 mm mobile, pedunculated vegetation was observed on the atrial aspect of the P1-P2 segments of the mitral valve; this mass prolapsed into the ventricle during diastole without causing valvular dysfunction.

Fig. 1. Short-axis view and long-axis view showing vegetation on the noncoronary cusp of the aortic valve.



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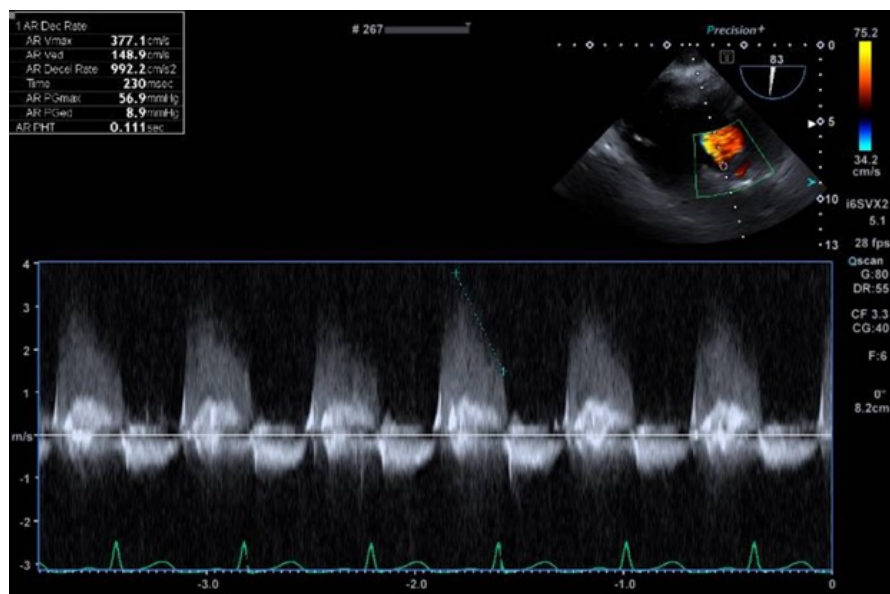
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Fig. 2. A severe regurgitant jet was observed in the transgastric view, with a PHT of 0.11 s and a deceleration rate of 992 cm/s at the aortic valve level.



The clinical picture was interpreted as definitive native valve infective endocarditis, caused by *Neisseria gonorrhoeae*, involving both the aortic valve and mitral valve. There were no signs of septic embolism. The patient was admitted to a general ward and remained haemodynamically stable, with no evidence of arrhythmias on telemetry or abnormalities on the baseline electrocardiogram.

Due to severe acute aortic regurgitation associated with infective endocarditis, surgery was decided once antibiotic therapy for diverticulitis with metronidazole and ceftriaxone had been completed. Aortic valve replacement was performed using a 21 mm mechanical prosthesis, with debridement of an abscess in the mitral-aortic intervalvular fibrosa and placement of an autologous pericardial patch. An atrial septal defect closure was also performed. Intraoperative transoesophageal echocardiogram confirmed adequate prosthetic valve function without associated regurgitation or mismatch. The excised native valve tested positive for *N. gonorrhoeae* via polymerase chain reaction (PCR). Antibiotic treatment with ceftriaxone was continued, and anticoagulation was indicated due to the mechanical valve.

The patient had a favorable postoperative course and was discharged to complete antibiotic treatment at home for a total of 6 weeks following aortic valve replacement.

N. gonorrhoeae endocarditis is a rare and infrequently reported entity. Clinical suspicion based on compatible physical findings and early echocardiography are essential for diagnosis. (4,5)

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable.

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Inferior Myocardial Infarction in a Pediatric Patient with Coronary Aneurysms Secondary to Kawasaki Disease

Infarto inferior en paciente pediátrico con aneurismas coronarios por enfermedad de Kawasaki

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Acute myocardial infarction in children is rare and may be associated with various etiologies, including congenital coronary anomalies, prothrombotic states, and sequelae of Kawasaki disease, the leading cause of acquired heart disease in children.

We present the case of a four-year-old male patient with a history of Kawasaki disease two years prior, without documented structured follow-up. He was admitted with symptoms that had been present for four hours, characterized by vomiting, mucocutaneous pallor, perioral cyanosis, and transient loss of consciousness. On admission, he was hemodynamically stable, with a blood pressure of 90/59 mmHg and a heart rate of 70 bpm.

The 12-lead electrocardiogram showed ST-segment elevation in leads II, III, and aVF, with ST-depression in the anterior leads, consistent with acute inferior myocardial infarction (Figure 1). Laboratory results showed C-reactive protein level of 0.14 mg/dL, white blood cell count of 16 770/ μ L with neutrophilia, hemoglobin 12.1 g/dL, platelets 570 000/ μ L, creatinine 0.43 mg/dL, and electrolytes within normal ranges. Total creatine kinase was 228 U/L and high-sensitivity troponin I was 0.94 ng/mL, with markedly elevated quantitative troponin level (28 336.7 pg/mL), confirming significant myocardial necrosis.

The initial echocardiogram showed preserved biventricular function and mild dilation of the proximal segment of the left coronary artery. Given the suspicion of coronary artery involvement and the limitations of the echocardiographic study in characterizing the distal anatomy, cardiac catheterization was performed at a tertiary care center.

The hemodynamic study revealed a giant aneurysm of the left coronary artery located distal to the trunk and involving the origin of the left anterior descending and circumflex coronary arteries, as well as

a proximal aneurysm of the right coronary artery with total occlusion and distal perfusion through collateral circulation (Figure 2). Ventriculography showed inferior wall hypokinesis with preserved global function.

Given the anatomical complexity, multivessel involvement, and location of the lesions, it was determined that the risk of percutaneous intervention outweighed the potential benefit; (1,2) therefore, medical management with dual antiplatelet therapy and close follow-up by pediatric cardiology was decided upon. The patient progressed without recurrence of ischemic symptoms.

The clinical presentation of myocardial infarction in children is often atypical, making timely recognition difficult. Unlike in adults, children rarely present with typical chest pain; instead, nonspecific manifestations such as vomiting, pallor, irritability, or altered consciousness predominate. In this context, the integration of electrocardiographic findings consistent with ST-segment elevation and a significant elevation of biomarkers of myocardial necrosis, such as troponin, is essential for establishing the diagnosis. (3,4)

Cardiac catheterization is essential in the evaluation of these patients, as it allows for a precise anatomical characterization of the coronary anatomy, including the identification of aneurysms, occlusions, bifurcation involvement, and the development of collateral circulation. (5) In the case presented, this information was decisive for therapeutic decision-making, as it revealed a complex anatomy with multivessel involvement that limited intervention options.

The management of coronary aneurysms associated with Kawasaki disease depends on their size, location, and the presence of thrombotic or ischemic complications. In patients with giant aneurysms and diffuse involvement, percutaneous intervention

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Fig. 1. Twelve-lead electrocardiogram showing ST-segment elevation in leads II, III, and aVF, with reciprocal changes in the anterior precordial leads, consistent with acute inferior myocardial infarction.

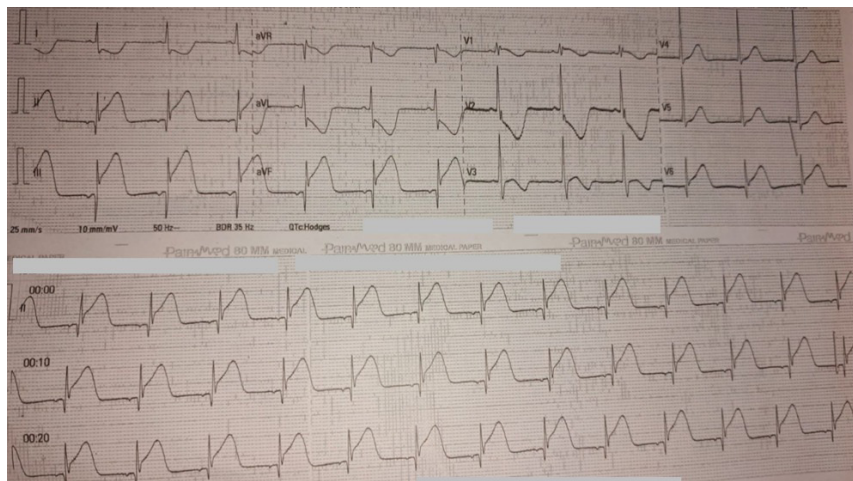
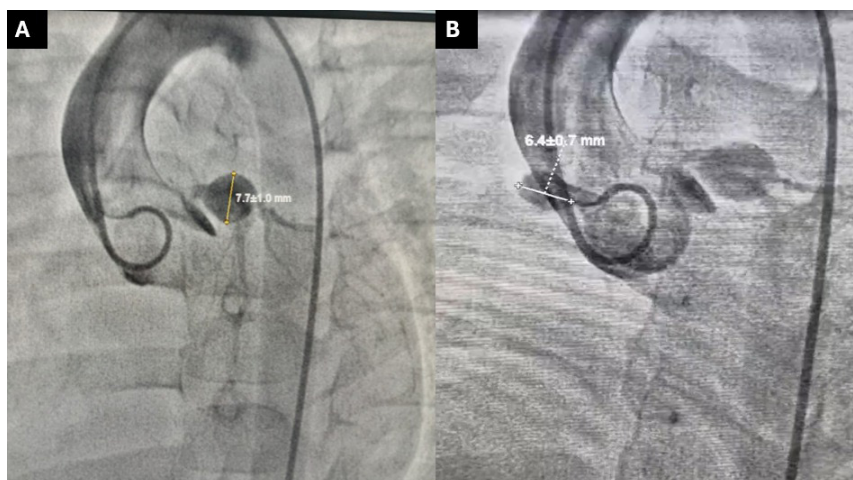


Fig. 2. Coronary angiography (A) Left coronary artery, with a giant aneurysm located distal to the trunk, involving the origin of the anterior descending and circumflex arteries. (B) Right coronary artery, with a proximal aneurysm with total occlusion and distal perfusion via collateral circulation.



can be technically challenging and associated with a higher risk of complications, such as distal embolization, reocclusion, or difficulty in properly implanting devices. Similarly, surgical revascularization is not always feasible, especially in small patients or those with complex anatomy. (6)

In this context, medical treatment with antiplatelet therapy, as initiated in this case, represents a reasonable strategy aimed at reducing the risk of thrombotic events and stabilizing the disease. This approach requires close long-term follow-up, given the persistent risk of cardiovascular complications.

Finally, this case emphasizes the importance of structured follow-up in patients with a history of Ka-

wasaki disease, especially in those with coronary involvement. Regular evaluation allows for the timely detection of vascular abnormalities and appropriate long-term risk stratification. (6) It also highlights the need to consider acute coronary syndrome within the differential diagnosis in pediatric patients with non-specific symptoms and relevant history, as well as the value of cardiac catheterization in comprehensive evaluation and individualized therapeutic decision-making.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable.

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Scientific Research in Argentina: The Value of Integrating Clinical Care, Teaching, and Research

La investigación científica en Argentina: el valor de integrar asistencia, docencia e investigación

MARTÍN DONATO¹

Dear Editor,

Basic and clinical research with a translational focus has historically been one of the strengths of Argentine medicine, particularly in the cardiovascular field. Since the seminal work of Dr. Bernardo Houssay and his disciples, Drs. Eduardo Braun Menéndez and Juan Carlos Fasciolo, on the mechanisms of nephrogenic hypertension, Argentina has consolidated a model in which basic research and clinical practice mutually reinforce one another.

This tradition found a privileged setting for its development in public hospitals. At *Hospital Argerich*, the group led by Dr. Carlos Bertolasi made significant contributions to clinical and pathophysiological research on coronary artery disease, while at *Hospital Ramos Mejía*, the work of Drs. Mauricio Rosenbaum and Marcelo Elizari led to landmark contributions in electrophysiology, which achieved international recognition. Likewise, this integration between basic and clinical research has continued through figures such as Dr. Liliana Grinfeld, who, together with the group led by Dr. Ricardo Gelpi, reaffirmed the value of the translational approach to scientific research.

However, this historical trajectory contrasts with the current situation. The progressive decline in funding for science and technology, together with the lack of sustained policies to promote biomedical research, directly affects the ability of hospitals and universities to generate knowledge, train human resources, and sustain competitive research groups.

In this context, the growing notion that the State should not play a central role in funding science and technology is a cause for concern. International experience demonstrates exactly the opposite. Institutions such as the National Institutes of Health (NIH) in the United States and the research structures of the National Health Service (NHS) in the United Kingdom demonstrate that public funding and coordination among hospitals, universities, and scientific institu-

tions constitute fundamental pillars of biomedical development. Developed countries have not reduced State involvement in science; rather, they have strengthened it as part of their health and development strategies.

The importance of maintaining hospitals with academic and scientific activity is not merely conceptual. A study published in *JAMA* in 2017 that analyzed more than 21 million hospitalizations in the United States demonstrated lower adjusted 30-day mortality rates in university and teaching hospitals compared to non-teaching institutions. These findings suggest that the integration of care, teaching, and research not only promotes knowledge generation but also directly improves the quality of care and patient outcomes. (*Burke LG et al. Association Between Teaching Status and Mortality in US Hospitals. JAMA. 2017*).

Given this scenario, scientific societies, universities, hospitals, and academic and research institutions must take an active role in promoting and disseminating the strategic value of biomedical science and translational research. Preserving Argentina's scientific tradition and the international prestige achieved by generations of researchers and physicians requires not only adequate funding but also a sustained institutional commitment to uphold and convey the importance of integrating care, teaching, and research as inseparable pillars of a modern health system.

Revitalizing and projecting Argentina's scientific tradition is a strategic necessity. Strengthening research in public and university hospitals, ensuring adequate funding, and promoting coordination with the scientific system do not represent ancillary expenses, but rather an indispensable investment to sustain high-quality medicine and the country's capacity to generate original knowledge with global impact. Weakening the scientific system not only compromises knowledge production but also the future capacity to deliver excellence in cardiovascular medicine.

Sincerely,

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Our Data on Mortality from ST-segment Elevation Myocardial Infarction

Nuestros datos acerca de la mortalidad del infarto agudo de miocardio con elevación del segmento ST

CONSTANZA BELÉN ZACARIAS^{1,2}

Acute myocardial infarction is one of the leading causes of mortality in Argentina. In ST-segment elevation acute myocardial infarction, the total duration of ischemia is crucial in determining the prognosis, as 'time is myocardium'. Technological advances have reduced ischemic times worldwide, which has been associated with a decrease in mortality. In Argentina, the ARGEN-IAM-ST registry is the only national registry of ST-segment elevation myocardial infarction with 10 years of follow-up. (1) The best way to monitor this condition is through such registries, which reflect real-world care, thereby enabling the planning of health policies and the evaluation of their outcomes.

The national effectiveness in terms of reperfusion therapy is noteworthy, with door-to-reperfusion times similar to those in international registries and reperfusion rates exceeding 90% in 8 of the 10 years of the study.

However, our main weakness, as evidenced by the registry, lies in the prolonged time from the onset of symptoms to presentation, which could explain the lack of decline in mortality over these 10 years compared with registries from other countries. (2,3) The average symptom-presentation time is 120 minutes, significantly longer than that reported in registries such as the Spanish registry, which is approximately 60 minutes. (4)

It is essential to improve public education on recognizing symptoms consistent with myocardial infarction and to implement national strategies to optimize patient referral to achieve early reperfusion.

It is worth noting the decline in patient enrolment over the years. A limitation of these registries is their representativeness. Given that participation is voluntary, they tend to reflect the practice of institutions with greater academic motivation—generally those with higher patient volumes, which are the ones that sustain the registry over time. (5) It is essential to re-

inforce the importance of maintaining and expanding these registries within the medical community to promote more equitable and effective health policies.

The lack of reduction in the mortality rate over these 10 years, despite the therapeutic advances, is discouraging; yet there is still hope that the healthcare system will improve, ensuring universal access and reducing delays. This will help to achieve a mortality rate from acute myocardial infarction similar to that seen in international registries.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

As Dr Zacarías emphasizes, the data reveal a reality that leaves us with a bittersweet taste. On the one hand, we see high rates of reperfusion and, on the other, high mortality rates. When we take a closer look and realize how long it takes to seek medical care, we feel responsible for the lack of health promotion regarding acute myocardial infarction, as cardiovascular causes are the leading cause of death in Argentina, as evidenced by the vital statistics reports from the Ministry of Health. (1) Moreover, this is largely preventable if risk factors are managed appropriately, and when it does occur, mortality should be lower compared to other countries. (2) National publication records indicate that since 2008, mortality has not fallen below 8%. (3) But then, what does the high reperfusion rate tell us? It does not appear that the healthcare system has a problem with resources (we are, of course, speaking in general terms, as there are situations where resources are scarce), nor with the concept, since patients do undergo reperfusion. So why is mortality so high? The answer could lie in the failure to meet operational targets that have an impact on the total duration of ischemia. And how can we address the situation? The hospital door is a useful point at which to divide the problem into two parts. From the door outward, we must promote the early recognition of chest pain and warning signs. Inside the hospital, we must optimize our organization to receive patients and perform proper triage. Every institution should also be part of a myocardial infarction care network to effectively manage resources. Low-complexity centers should be aware of their support centers, which, in turn, should be aware of their role within the network to avoid delays, particularly within a fragmented healthcare system such as the one in Argentina. As we have previously mentioned, the ARGEN-IAM-ST is not the only registry showing these data, as they are available in previous studies and vital statistics from the Ministry of Health: from different angles, with the same results. One activ-

ity that could prove constructive at conferences is to discuss, in addition to mortality in myocardial infarction, potential solutions to the consultation and care process, such as the feasibility of implementing artificial intelligence to enhance triage in the emergency department, the use of data to improve the logistics of patient transfers, and coordination with cardiac catheterization laboratories, etc. (4)

Finally, it is important to mention the long-term costs for heart attack survivors. The total duration of ischemia accounts for not only mortality, but also in- and out-of-hospital complications. Although the ARGEN IAM-ST registry does not report on the latter, these complications are well known and generate a significant burden of healthcare costs due to left ventricular dysfunction, which, depending on its severity, leads to specific treatments for heart failure, the implantation of expensive devices and, in the longer term, the need for a heart transplant in some cases — all of which are preventable and avoidable. (5)

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Prognostic Value of the TAPSE/SPAP Ratio

Valor pronóstico de la relación TAPSE/SPAP

LUCRECIA SECCO¹, MTSAC,

The study by Freyre Hernando J et al., published in the latest issue of the Argentine Journal of Cardiology, (1) investigates the prognostic value of right ventricle (RV)-pulmonary artery (PA) uncoupling in patients with transthyretin cardiac amyloidosis (TTR-CA).

In this study, which analyzed 191 patients, the authors concluded that the tricuspid annulus plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (SPAP) ratio is an effective predictor of future hospital admissions for heart failure. A TAPSE/SPAP ratio ≤ 0.5 is an independent predictor of risk, even in the presence of preserved ejection fraction (EF). This cut-off point of 0.5 was determined to be optimal due to its clinical balance, with a sensitivity of 78% and a specificity of 67% for predicting heart failure events. (1,2)

In contrast, other indicators, such as the S-wave on tissue Doppler imaging, did not provide relevant information for predicting disease progression. This is because the S'-wave on tissue Doppler may be more susceptible to noise artifacts, measurement angles and the involvement of the basal segments characteristic of amyloidosis, which limits its prognostic value in this disease. (3)

The TAPSE/SPAP ratio reflects the ability of the RV to adapt to pulmonary circulation, a phenomenon known as RV-PA coupling; it integrates the relationship between RV contractility and afterload into a single measurement. In TTR-CA, progressive stiffness compromises this adaptation, promoting 'uncoupling'. (1,4)

One of the primary strengths of this study is its specificity in the TTR-CA population, unlike prior studies that used mixed populations with AL amyloidosis. Furthermore, this parameter stands out for its simplicity and clinical applicability. The TAPSE/SPAP ratio is a non-invasive, reproducible index that can be obtained using standard echocardiography equipment, which makes it easy to use. (1,5)

There are areas of opportunity that this study has not explored, which would be fundamental to consoli-

dating this parameter. The incorporation of RV free wall strain could be valuable for obtaining a more precise measurement of deformation that is not dependent on the geometric limitations of TAPSE. (4)

In conclusion, the data provided by this article regarding the TAPSE/SPAP ratio identifies a practical threshold (≤ 0.5), which allows clinicians to identify high-risk patient subgroups at an early stage—something that other traditional markers do not achieve with the same precision in this specific population. (1,2).

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 would like to extend our special thanks to Dr Secco for her detailed analysis and for underscoring the clinical relevance of the TAPSE/SPAP ratio as a marker of right ventricular–pulmonary artery uncoupling in transthyretin cardiac amyloidosis.

We agree that this ratio represents a simple, non-invasive, widely available tool to integrate right ventricular contractility and its afterload into a single measurement, providing prognostic value even in patients with preserved ejection fraction.

Furthermore, we consider the observation regarding the possible inclusion of additional parameters,

such as right ventricular free wall strain, to be highly pertinent, as these could complement the assessment and provide greater precision in future studies.

The aim of our work is to provide evidence in a specific population, such as that with TTR-CA, where the early identification of high-risk patients remains a significant clinical challenge.

We would like to thank you once again for your comments and for the opportunity to enrich the discussion on this topic.

Kind regards,

Jaqueline Freyre Hernando
On behalf of the authors

The Gap in the Management of Bicuspid Aortic Valve Disease in Argentina

La brecha en el manejo de la válvula aórtica bicúspide en Argentina

VANESA DEL V. AUDIL¹

Bicuspid aortic valve (BAV) is the most common congenital heart disease in adults and is associated not only with valvular dysfunction but also with progressive involvement of the ascending aorta, constituting a true valvuloaortopathy. Its management requires a comprehensive assessment and a multidisciplinary approach aimed at optimizing long-term outcomes.

In the paper entitled "*Diagnosis and Management of Bicuspid Aortic Valve Disease in Argentina*", Carrero et al. (1) describe the current status of this condition in our setting, highlighting a significant gap between international guideline recommendations and daily practice. One of the most significant findings is that 50% of centers lack a Heart Team for complex decision-making, a figure that rises to 61.7% in inland centers, which is particularly worrying given the complexity of this condition.

From a surgical perspective, BAV disease should not be approached as an isolated condition. Surgery on the valve without an adequate assessment of the aorta and/or ascending, or vice versa, can lead to incomplete treatment strategies, with a negative impact on mid- and long-term outcomes. In this regard, it is essential to move towards the concept of an 'Aortic

Team', integrating specialists with experience in aortic diseases into the multidisciplinary team. (2)

Another relevant aspect is the high proportion of indications for transcatheter aortic valve implantation (TAVI), which reaches 40.7%, despite the limited evidence available in patients with BAV. (1) Although recent trials have explored its use in low-risk populations, (3) durability and long-term outcomes in young patients remain uncertain. In this group, conventional surgery, valve repair and the Ross procedure offer advantages in terms of hemodynamics and reoperation-free survival.

Furthermore, the study highlights the low frequency of strategies such as valve repair or the Ross procedure in our setting, (1) which may reflect limitations in both surgical expertise and timely referral to specialized centers.

Furthermore, current evidence highlights the importance of family screening. Various studies demonstrate a significant prevalence of BAV and aortic dilatation in first-degree relatives, reinforcing the recommendation for systematic evaluation in this group. (4) However, adherence to this practice remains sub-optimal in our context.

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Finally, it is noteworthy that only 30.8% of specialists systematically assess the distal ascending aorta, (1) a region frequently involved in acute events such as dissection, which highlights a diagnostic gap with potential clinical impact.

Taken together, these findings underscore the need to improve the organization of the healthcare system, promote multidisciplinary work and adopt a comprehensive approach to managing BAV. Heart Teams represent a paradigm shift in decision-making, enabling more individualized and evidence-based medicine. (5) Bridging the gap between knowledge and practice is, in this context, a priority challenge.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

We thank Dr Vanesa del V. Audil for her interest in our work and her valuable comments regarding the reality of bicuspid aortic valve (BAV) disease management in our country. We fully agree with her perspective on the inherent complexity of this condition. As Dr Audil points out, BAV should be understood not as an isolated valvular heart disease, but as a true valvuloaortopathy. We share her concern regarding the low number of centers with Heart Team, which is useful for making complex decisions, as well as her suggestion to move towards the concept of Aortic Team. In such groups, multidisciplinary integration—including specialists in aortic diseases—is essential for designing long-term therapeutic strategies that go beyond a purely valvular approach.

Furthermore, the concern raised about the indication for TAVI in patients with BAV is highly pertinent. Our study reveals a trend towards the increasing use of this technique, likely driven by technological avail-

ability, but this must be analyzed with caution, as there is limited literature supporting this indication, and indeed, with adverse outcomes in patients with BAV.

Regarding the current scientific evidence on the therapeutic options, the results of the NOTION-2 study reinforce our stance of caution. (1) This randomized clinical trial, which is one of the few to have included a significant proportion of low-risk BAV patients who are excluded from most TAVI studies, demonstrated a higher incidence of moderate or severe paravalvular leaks (17.4% vs. 0% in the surgery group) and a higher incidence of the combined primary endpoint of death, stroke or rehospitalization in patients with BAV who underwent TAVI compared with those who underwent surgery, although the difference was not statistically significant (14.3% vs. 3.9%, $p=0.08$). These findings suggest that, even in experienced hands, the complex anatomy of the BAV remains a technical challenge that may compromise long-term clinical outcomes.

Furthermore, data from real-world registries and comparative follow-up studies indicate that, in young patients, TAVI in BAV is associated with a higher rate of immediate hemodynamic complications and a prosthetic durability that has yet to be established, compared with surgical aortic valve replacement. The presence of asymmetric calcification and frequent aortic root dilatation increases the risk of incomplete device expansion or annular damage. And prosthetic durability is a key factor in these very young patients, in contrast with those with degenerative aortic valve stenosis. Therefore, the lack of evidence about durability and long-term outcomes in younger patients with this valvular phenotype reinforces the need for rigorous Heart Team discussion before making decisions that compromise the clinical future of these patients.

Finally, Dr Audil's call to encourage timely referral to high-complexity centers for surgical techniques such as valve repair or the Ross procedure highlights a priority challenge for our healthcare system. We hope that this exchange will help highlight these gaps and encourage improvements in the organization of the healthcare system while increasing adherence to evidence-based recommendations.

Yours sincerely,

María Celeste Carrero

On behalf of the research group of "Dr. Oscar Orías" Council on Doppler Echocardiography and Vascular Ultrasound

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Measuring to Heal: A Contribution to the Improvement of Patient-Centered Quality of Care

Medir para curar. Un aporte a la mejoría de la calidad asistencial centrada en el paciente

“What is not defined cannot be measured. What is not measured cannot be improved. What is not improved always deteriorates.”

Lord Kelvin

“What is not measured cannot be managed.”

Peter Drucker

Three cardiologists from an imaginary world—whom I shall call Sergio Nonrich, Mirza Ten and Mario Halcón—discuss the future of cardiovascular health in Argentina. They wonder why issues related to the healthcare system, with the exception of those linked to doctors' financial circumstances, do not generate the same level of interest as many aspects strictly related to the individualized treatment of various clinical syndromes. In this regard, they consider how to highlight opportunities to improve patient-focused medical processes using an appropriate methodology that is amenable to external evaluation. This would be not only a management tool but also a patient's right to receive safe care in accordance with quality standards that reflect technical and human expectations.

From the healthcare system perspective, having access to quality indicators is essential for assessing the current status of various prevalent cardiovascular conditions. In this regard, for example, the “National Survey on Acute Myocardial Infarction” provided information on reperfusion status in cases of ST-segment elevation myocardial infarction. The results highlight treatment delays and the different areas requiring improvement, and suggest “that the implementation of medical education programs and supportive healthcare policies that consider regional characteristics and the cost-benefit ratio of reperfusion strategies in practice may help reduce the time to reperfusion, for both thrombolytic therapy and for primary percutaneous coronary intervention.” (1)

In this regard, the Argentine Society of Cardiology will embark on a process aimed at defining quality indicators to evaluate and improve medical care, with a particular focus on cardiovascular diseases and, mainly, a patient-centered approach. “Measuring to

heal” is likely an ambitious title given the national healthcare reality and the system's tendency to resort to bureaucratic constraints. Furthermore, we wonder where the patient's decision-making lies when required to accept treatment in healthcare centers with high morbidity and mortality rates. This aspect is not merely a technical assessment on the quantification of processes and their outcomes. It reflects a compassionate, patient-centered approach to care and a refusal to be complicit in the system's shortcomings. We are dealing with a human and social issue, not merely medical and technical aspects. While we await decisions from the relevant health authorities, we could begin to design a system to measure outcomes in cardiology services. This would highlight the strengths and weaknesses of cardiovascular healthcare, following the model of international societies. (2–5)

The European Society of Cardiology proposes a structured four-step method that involves defining target populations and validating data to ensure that the metrics are both scientifically sound and feasible. (6) The texts emphasize the importance of using these data to improve clinical performance and transparency, thereby enabling the comparison of outcomes across different healthcare centers. The success of these systems depends on multidisciplinary collaboration involving medical professionals, managers, and patient representatives.

Quantifying quality in healthcare provision has become an indispensable tool for identifying gaps in care and promoting continuous improvement. There is a growing recognition that optimizing clinical outcomes requires tools that allow the performance of healthcare providers to be assessed and compared. Measuring quality is not an end in itself, but it is a means of bridging the “gap between evidence and practice” that ensures that science-based treatments are effectively translated into daily clinical practice. (7)

In this regard, it is important to assess outcomes at center level rather than just by region or country. For instance, in the meta-analysis of outcomes of transcatheter aortic valve implantation in South America, Boissonnet et al. reported significant vari-



ability in terms of procedural success, the need for a permanent pacemaker, and the presence of significant residual aortic regurgitation. These findings provide a basis for evaluating the performance of the technique and serve as a catalyst for future clinical optimization initiatives. (8)

THE IMPORTANCE OF MEASURING QUALITY FOR IMPROVEMENT

The measurement and public reporting of healthcare processes and outcomes are key catalysts for quality improvement initiatives. Performance measurement serves to: (9)

1. Foster evidence-based medicine: quality indicators act as mechanisms to support care delivery aligned with clinical practice guidelines.
2. Facilitate benchmarking: comparisons across providers motivate learning and the adoption of best practices.
3. Identify disparities and variations: substantial variation in care delivery has been documented, reflected in unequal outcomes across regions and centers. Systematic measurement brings these disparities to light for targeted intervention.
4. Ensure accountability and transparency: the use of indicators engages multiple stakeholders, including health authorities, payers and the public, facilitating pay-for-performance programs and greater transparency.
5. Improve patient outcomes: the implementation of structural and process measures has been consistently associated with reduced mortality and improved outcomes in critical conditions, such as acute myocardial infarction.

However, measurement alone does not improve quality; it should be regarded as a tool within a broader quality improvement strategy that incorporates cycles of learning and adaptation.

For indicators to be useful, they must be developed following a structured process that ensures their scientific validity and practical applicability: (10, 11)

1. Identification of key domains of care. The first step is to construct a conceptual framework that defines the dimensions of measurement. The Donabedian model is recommended, which classifies indicators into three types: (12)
 - Structural: These describe organizational aspects such as facilities, human resources and available protocols.
 - Process: These capture actions taken by providers or patients, such as adherence to recommended therapies.
 - Outcome: These relate to the effects of care on patients' health and well-being, including mortality and patient-reported outcome measures (PROMs).
2. Development of candidate indicators. This is carried out through a systematic review of the literature and existing clinical practice guidelines to

identify gaps in care where improvement is possible. (13)

3. Selection of the final set of indicators. To ensure acceptance and reliability, consensus should be achieved among experts and stakeholders (clinicians, researchers, managers and patient representatives). (14, 15)
4. Feasibility assessment. An indicator is only valuable if it can be implemented with reasonable effort and cost. (16)

QUALITY CRITERIA FOR THE SELECTED INDICATORS

For an indicator to be considered robust, it must meet the following criteria: (15)

- Importance: it must address a clinical area with a high burden of disease or disparities in care.
- Validity: it must accurately measure what it is intended to measure and distinguish between high- and low-quality care.
- Reliability: it must be reproducible and yield consistent results when measured by different people.
- Actionability: results must be interpretable by healthcare providers and professionals to enable corrective action.
- "Less is more": prioritizing a limited number of robust indicators avoids measurement fatigue and ensures a clear focus on improvement priorities.

CONCLUSION

Systematic quality measurement represents the essential first step towards a high-performing healthcare system. By employing rigorous and transparent methodologies to construct indicators that are both scientifically valid and feasible in practice, healthcare organizations can identify critical gaps, reduce unwarranted variability and ultimately improve patient survival and quality of life. The Argentine Society of Cardiology will move into the lead in defining a minimum set of indicators that can make a real contribution. The key lies in selecting "few but high-quality" indicators, thus ensuring that each measure serves as a genuine driver of positive change rather than merely an administrative burden".

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