40 AÑOS

Revista Colombiana de Cardiología

Volume 33 Number 1 January / February 2026

ISSN: 2938-1525

Indexada en / *Indexed in*: Scopus, DOAJ, EBSCO, EMBASE, MIAR, SciELO

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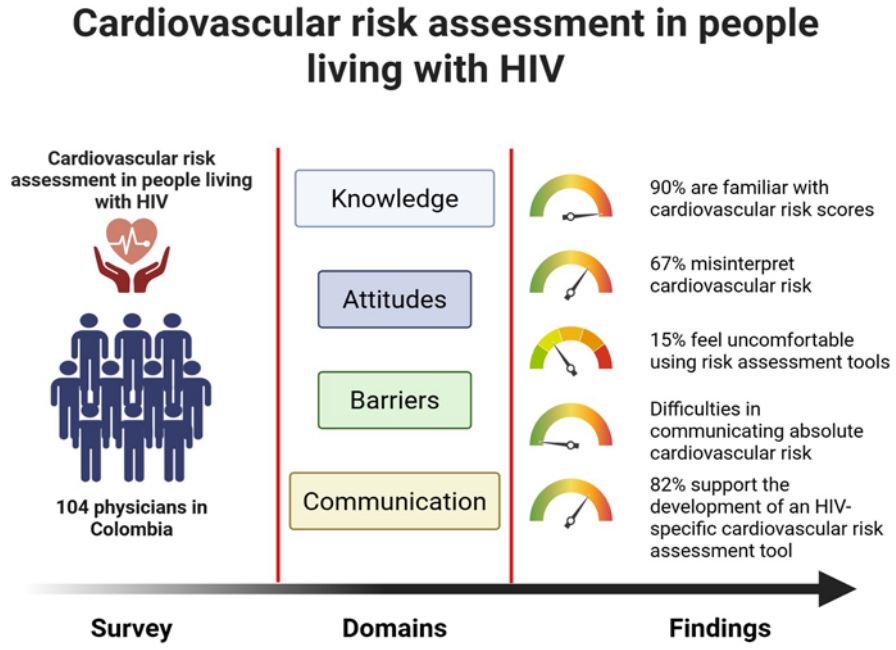

Cardiovascular risk assessment in people living with hiv. Overall results. Á.A. García-Peña et al. Physicians' attitudes, barriers, and subjective knowledge in evaluating cardiovascular risk in people living with HIV.

- **Redefining the strict use of intracoronary imaging**
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EDITORIAL

Redefining the strict use of intracoronary imaging The best tool-still locked away!

Redefiniendo el uso estricto de la imagen intracoronaria ¡La mejor herramienta, aún guardada bajo llave!

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Over the last three decades, intracoronary imaging (ICI), also known as intravascular imaging (IVI), has evolved from a complementary experimental tool to a solid technology, backed by evidence, and able to redefine the diagnosis and treatment of coronary artery disease. However, despite this progress, its use in daily clinical practice continues to be surprisingly limited. Global adoption is still low, with Japan being a notable exception, and its use even varies among operators within the same institution[1]. This paradox – abundant evidence and scant implementation – poses relevant questions not only for interventional cardiologists but also for clinical cardiologists and internists involved in the comprehensive care of patients with coronary artery disease (CAD).

Intracoronary imaging, which includes intravascular ultrasound (IVUS) and optical coherence tomography (OCT), offers information that clearly surpasses the luminographic limitations of conventional angiography. These modalities allow a detailed evaluation of the severity of the lesion and clarify the type of disease present (atherosclerosis, spontaneous coronary dissection, and vasculitis, among others), the composition of the atherosclerotic plaque, and the actual vessel dimensions, as well as play a central role in optimizing percutaneous coronary intervention (PCI). Furthermore, they help identify complications of the procedure, like stent edge dissection, malapposition, tissue protrusion and stent failure mechanisms, including intrastent restenosis and stent thrombosis[2].

From a modern clinical perspective, ICI should not be considered an optional or restricted technology. On the contrary, it should be understood to be an essential tool in the catheterization laboratory, with a direct impact on both the success of the procedure as well as the patient's clinical outcomes. In addition, ICI has significantly contributed to an understanding of the disease, atherosclerotic plaque progression and regression, and vascular response to the intervention, closing the gap between pathophysiology and clinical decision making[3].

This paradigm shift is reflected in today's clinical guidelines. The 2024 European Society of Cardiology guidelines for managing chronic coronary syndrome recommend using ICI to optimize PCI, with a Class 1, Level A recommendation[4]. Likewise, the 2025 American guidelines for managing acute coronary syndrome recommend using ICI in left main trunk interventions and complex coronary procedures, also with a Class 1, Level A recommendation[5]. These recommendations are based on evidence showing that ICI-guided PCI is associated with better security and effectiveness compared to PCI guided only by angiography and the "operator's intuition and experience," significantly reducing mortality, myocardial infarction, repeat revascularization, and

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Date of reception: 20-01-2026
Date of acceptance: 05-02-2026
DOI: 10.24875/RCCARE.M26000207
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):1-3
www.rccardiologia.com

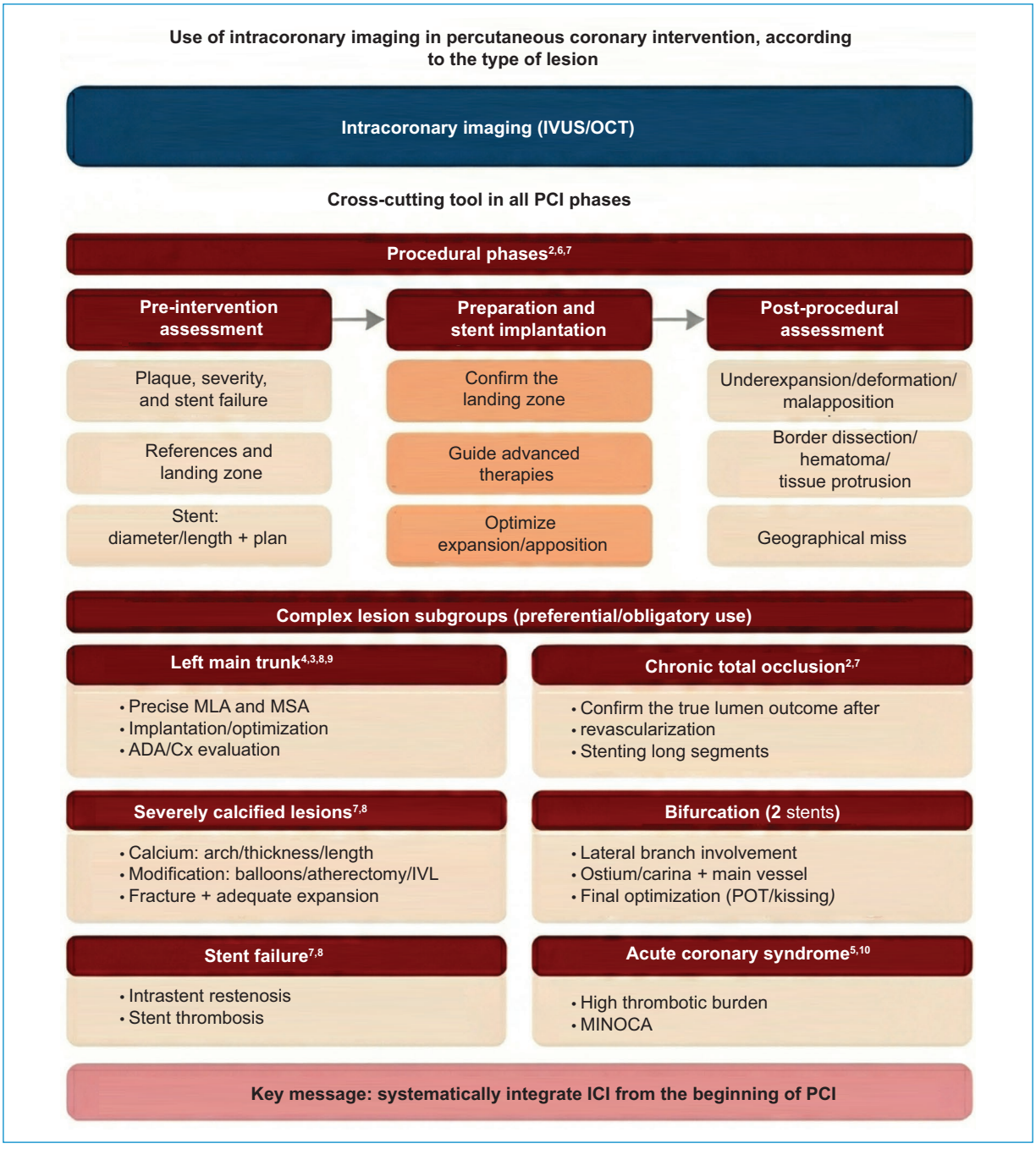

Figure 1. A phased approach to the use of intracoronary imaging (IVUS/OCT) during percutaneous coronary intervention (PCI), according to the type of lesion. In the pre-intervention phase, IVUS/OCT helps characterize the plaque and severity, define reference segments and landing zones, select the size/length of the stent, and plan the preparation of the lesion. During preparation and implantation, it guides advanced therapies and optimizes stent expansion and apposition. In the post-procedural assessment, it identifies underexpansion and malapposition, complications (border dissection/hematomas) and rules out geographical miss. Its use is preferential or mandatory in complex PCI, in which it improves decision making and optimizes outcomes. IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; MLA: minimal lumen area; MSA: minimal stent area; ADA: anterior descending artery; Cx: circumflex artery; POT: proximal optimization technique; IVL: intravascular lithotripsy; ICI: intracoronary imaging; MINOCA: myocardial infarction with non-obstructive coronary arteries.

stent thrombosis, as shown in a recently published meta-analysis[6].

Intracoronary imaging provides detailed anatomical information throughout all PCI phases. In the pre-intervention stage, it helps accurately determine the size of the vessel, length of the lesion, and morphology of the plaque. This enables proper selection of the size and length of the stent and defines the landing zones or the need to prepare a calcified lesion using advanced techniques like rotational or orbital atherectomy or specialized balloons, depending on the identified characteristics. In the post-intervention phase, ICI helps confirm optimal stent expansion and apposition, as well as detect complications like edge dissection, plaque dislodgement, or geographical miss, which, if not detected and corrected, may affect long-term results[7]. These procedural benefits translate into sustained clinical improvement, as proven by studies with extended follow-up of patients undergoing IVUS-guided PCI.

The value of ICI is evident in complex clinical scenarios like left main trunk disease, chronic total occlusions, acutely calcified lesions, diffuse and extensive disease, intrastent restenosis, stent thrombosis, and procedures that require minimal use of contrast[8]. In the context of complex PCI – a concept that lacks a universal definition but generally includes multivessel treatment, multiple stent implantation, bifurcations with two-stent techniques, and chronic total occlusions – ICI provides an essential guide to improve the precision and safety of the procedure[9].

Beyond its interventional role, ICI has relevant diagnostic usefulness, especially in patients with acute myocardial infarction (AMI) in whom the responsible vessel cannot be identified with conventional angiography. In the context of myocardial infarction with non-obstructive coronary arteries, OCT helps establish an etiological diagnosis in approximately 50% of cases, with direct implications for subsequent clinical management[10].

Despite mounting evidence, barriers to generalized adoption of ICI remain, including cost, the length of the procedure, and the need for specialized training. However, recent cost-effectiveness studies have questioned these perceptions, showing that routine use of IC can improve the efficiency of the procedure and the overall value of care when integrated within the standard workflow of the catheterization laboratory. Team training, education on the technologies, and a systematic approach are key elements for successful implementation[1,7,8].

Based on the available evidence, ICI should be used more systematically and proactively, and be compulsory in specific subgroups of lesions, including left main trunk disease, chronic total occlusions, complex PCI, severely calcified lesions, stent failure (restenosis or thrombosis) and complications during PCI. The optimal time to employ ICI must also be determined, prioritizing its use from the beginning of the procedure and not limiting it to late confirmation of a good angiographic result. Finally, the creation of national or regional registries will help identify gaps in use, determine the subgroups of patients who benefit the most, and evaluate its actual cost-effectiveness in our healthcare systems.

In an age marked by precision medicine and value-based care, ICI represents a mature technology with the potential to significantly improve outcomes in patients with coronary disease. The current challenge lies not in the lack of evidence, but rather in the collective decision of the cardiovascular community to free a tool that has been locked away, metaphorically speaking, for too long (Fig. 1).

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ORIGINAL ARTICLE

Determination of cardiovascular risk according to nutritional status (BMI) in minor league baseball players aged 11 to 18 years

Determinación del riesgo cardiovascular según el estado nutricional (IMC) en beisbolistas de ligas menores de entre 11 a 18 años

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Abstract

Introduction: *Worldwide, cardiovascular disease (CVD) persists as a leading cause of morbidity and mortality. High-intensity physical activity has been shown to require a series of lifestyle changes that may have short- and long-term consequences.* **Objective:** *To determine cardiovascular risk according to nutritional status in minor league baseball players aged 11 to 18 years.* **Methods:** *This was a descriptive, observational, cross-sectional and prospective study, in which the anthropometric measurements of 40 baseball players from a sports complex in Santo Domingo, Dominican Republic, were evaluated.* **Results:** *The population had a mean age of 15 ± 1.05, weight of 69.25 kg ± 11.93, and height of 1.85 ± 0.07 m. The majority had a low cardiovascular risk, and a significant relationship was found between body fat percentage and systolic blood pressure.* **Conclusions:** *It was evident that athletes with a high percentage of body fat have a higher risk of developing CVD.*

Keywords: *Heart disease risk factors. Nutritional status. Body mass index. Athletes. Waist-hip ratio.*

Resumen

Introducción: *Las enfermedades cardiovasculares persisten como causa principal de morbimortalidad en el mundo. Se ha visto que la actividad física de alta intensidad requiere una serie de cambios en el estilo de vida, que pueden tener consecuencias a corto y largo plazo.* **Objetivo:** *Determinar el riesgo cardiovascular según el estado nutricional en beisbolistas de ligas menores entre 11 a 18 años.* **Métodos:** *Estudio descriptivo, observacional, de corte transversal y prospectivo, en el cual se evaluaron las medidas antropométricas de 40 beisbolistas de un complejo deportivo en Santo Domingo, República Dominicana.* **Resultados:** *La población presentó una media de edad de 15 ± 1.05, peso 69.25 kg ± 11.93 y estatura de 1.85 ± 0.07 m. La mayoría tuvo un riesgo cardiovascular bajo, con un 97.5%, y se encontró una relación significativa entre el porcentaje de grasa corporal y la presión arterial sistólica.* **Conclusiones:** *Se evidenció que los atletas que presentan alto porcentaje de grasa corporal tienen mayor riesgo de desarrollar enfermedades cardiovasculares (ECV).*

Palabras clave: *Factores de riesgo de enfermedad cardíaca. Estado nutricional. Índice de masa corporal. Atletas. Relación cintura-cadera.*

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Date of reception: 22-11-2024
Date of acceptance: 14-11-2025
DOI: 10.24875/RCCARE.M25000206

Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):4-10
www.rccardiologia.com

Introduction

Cardiovascular disease (CVD) continues to be the main cause of morbidity and mortality worldwide[1]. In the Dominican Republic, it is responsible for 53% of premature deaths. Data from 2014 indicate that an estimated 200,000 people live with CVD[2].

It has been established that most of the pathophysiological changes begin during childhood, and therefore, interventions like physical activity are needed to treat the risk factors associated with the onset of CVD[3]. However, high-intensity physical activity has proven to have short- and long-term consequences[4]. Previous studies have shown these changes, evidencing increased blood pressure and anthropometric measurements in young athletes[5]. This is important in young people, since these alterations occur early, along with persistent exposure to risk factors that ultimately trigger the onset of CVD in adulthood[6].

This is why these athletes' nutritional intake is crucial for their professional performance[7] and, therefore, certain factors have been identified that are appropriate for establishing a correlation with individual cardiovascular risk. Body mass index has been used in pediatric and adult populations to evaluate how overweight and obesity affect different CVD risk factors[8]. Anthropometric techniques measure body weight, height, length, diameters, circumferences, and skinfolds[9], while the waist-hip ratio (WHR) is considered a relevant tool for evaluating cardiovascular risk due to its ability to provide a direct indication of body fat distribution.

Currently in the Dominican Republic, there is insufficient evidence related to athletes' cardiovascular risk. Thus, there is a need to study this topic, especially among young people, so that the scientific community's findings can enable timely intervention to contribute to the long-term overall health of this population. This study seeks to determine cardiovascular risk based on the nutritional status (BMI) of minor league baseball players between the ages of 11 and 18 in the Dominican Republic.

Methods

A descriptive, observational, cross-sectional, and prospective study was performed, including all minor league baseball players between the ages of 11 and 18 at the selected baseball training center. Players with any type of heart disease were excluded, as this could have interfered with a proper determination of cardiovascular risk. The players' parents or legal guardians were contacted directly to determine preexistent heart disease in the players. Thus, the study population ultimately consisted of 40 athletes. Non-probability convenience sampling was used, taking players who were present at the center on the assessment days.

The study was performed after obtaining ethical approval from the research committee at Hospital Pediátrico Dr. Hugo Mendoza and the respective authorization from the selected baseball training center, consisting of the team owners and trainers. At the time of data collection, the study participants were given detailed information regarding the procedures to be followed. The informed consent document drafted by the investigators was also explained and provided to the participants. A private room within the sports complex was requested for data collection, where the participants were seen individually, with their parents, to obtain the data while maintaining each participant's privacy.

Body composition was evaluated using anthropometric measurements like weight, height, skinfolds, and body circumferences. In addition, the participants' blood pressure (BP) was used to obtain data to help corroborate their potential cardiovascular risk.

Blood pressure was measured with a Greater Goods sphygmomanometer, which is an aneroid device with a standard cuff adjusting to sizes between 8¾ and 16½ inches, with a range of arterial pressure measurements from 0 to 300 mmHg and a precision of ± 3 mmHg. This measurement was taken in the left arm, while sitting. An initial measurement was taken; if the figure was more than 120 mmHg, a second measurement was taken five minutes later. If the difference between these measurements was more than 5 mmHg, a third measurement was taken. The percentile of each participant's systolic and diastolic BP was obtained using the professional version of the MSD Manual calculator, called "Blood Pressure Percentiles for Boys (2-17 years)"[10], with which the percentiles of both BP levels were obtained for each person. Variables like age (in years), height (in cm) and systolic and diastolic BP levels were evaluated for each person, to calculate the percentiles. Based on the classification of blood pressure in children and adolescents by the Sociedad Española de Pediatría [Spanish Society of Pediatrics], a normal BP was defined as a value < the 90th percentile, prehypertension covered percentiles ≥ 90 and < 95, and hypertension was defined as figures ≥ the 95th percentile[11].

A Bveiugn electronic scale (with a weight limit of 400 lb/180 kg, 6 mm tempered glass, and an 11.8 x 10.2-inch surface) was used for weighing and evaluating weight. Individuals were weighed without

shoes or socks; however, they were allowed to use pants that did not affect their weight on the scale. Height was measured in centimeters, using a flexible and retractable measuring tape approximately 6.8 feet long. Participants were required to stand with their feet, heels and knees together and facing forward.

Body mass index (BMI) was assessed using the following formula:

$$\frac{weight\ (kg)}{height\ (meters^2)}$$

These values were interpreted using the Stanford Medicine Children's Health BMI scale[12], which establishes low weight as less than 18.5, normal weight between 18.5 and 24.9, overweight as BMIs between 25.0 and 29.9, and obesity as BMIs over 30.0.

As far as anthropometric measurements, the protocol followed the standards established by the International Society for the Advancement of Kinanthropometry (ISAK). The athletes were requested to present to the evaluation room wearing shorts and no shirt, to simplify measurement and avoid interference from clothing.

Four skinfolds were measured using a Sequoia brand Lange caliper, with 1 mm precision, while body circumferences were measured using a flexible steel anthropometric tape with a 10 mm scale (1 mm error).

The triceps (TR) skinfold was measured, taking as a reference the midpoint between the lower edge of the acromion and the olecranon, on the posterior surface of the arm.

The subscapular (SS) skinfold was measured 1 cm from the diagonal fold formed by the inferior angle of the scapula. This measurement was done going from lower to higher and from the inside out, at a 45° angle to the horizontal plane.

The suprailiac (SI) skinfold was measured at the mid-axillary line, just above the anterior superior iliac crest.

Finally, the abdominal (AB) skinfold was measured in the upright position, parallel to the longitudinal axis of the body at the level of the umbilicus. This measurement was taken approximately five centimeters from the umbilicus on the right side of the rectus abdominis muscle.

Once the data from the four skinfold measurements was obtained, percent body fat (PBF) was calculated using Faulkner's formula:

$$\%F = [(TR + SS + SI + AB) \times 0.153 + 5.783]$$

The PBF classification criteria were: low adiposity (≤ 10 mm), normal adiposity (11-25 mm), and high adiposity (≥ 26 mm)[13].

Arm circumference was measured at the midpoint between the acromion and the olecranon, with the arm resting next to the body.

Waist circumference was measured at the end of a normal exhalation, at the midpoint between the lowest rib and the iliac crest, at the narrowest part of the abdomen. Measurements ≤ 90 cm were considered normal. Hip circumference was taken at the uppermost point of the gluteal muscles, with the person standing with his feet together and the gluteal muscles completely relaxed. For the WHR, those with results equal to or less than 0.94 were considered to have no risk[14].

The data were organized in a Microsoft Excel spreadsheet, where the information was also tabulated. The mean was used as the measure of central tendency, and standard deviation as the measure of dispersion (Fig. 1).

The athletes presented informed consent signed by their parents or legal guardians, and assent given by the children and adolescents. The sports facility approved the study with its athletes, and study variable measurements were always witnessed by the participants' parents and baseball coaches. The right to privacy was protected, in line with the Declaration of Helsinki in Fortaleza and Resolution 8430 of 1993.

The database was only accessed by the principal investigator. Likewise, only participants who provided informed consent and assent were included. The study was approved by the ethics committee at Hospital Pediátrico Dr. Hugo Mendoza.

Results

Overall, the study population (n = 40) had a mean age of 15 years (± 1.05), weight of 69.25 kg (± 11.93) and height of 1.85 m (± 0.07) (Table 1). The mean PBF, based on skinfolds, was 10 mm (2.31), BMI was 19.90 kg/m^2 (± 3.13) and WHR was 0.80 (± 0.08). The mean systolic arterial pressure (SAP) was 120 mmHg (± 11.48), with 7.5% (n = 3) considered to have a prehypertensive SAP (90-95th percentile) and 7.5% a hypertensive SAP (> 95th percentile), while the mean diastolic arterial pressure (DAP) was 80 mmHg (± 7.76), with 2.5% (n = 1) found to have a prehypertensive DAP, and 5% (n = 2) a hypertensive DAP (Table 1).

After confirming a normal distribution of the BMI and SAP variables (norm BMI = 0.81; norm SAP = 0.056), the Pearson correlation test was run, obtaining a significant relationship between these variables (sig. = 0.438; sig. < 0.05) (Table 1 and Fig. 2).

The relationship is weak and directly proportional (r = 0.126). Altogether, 1.6% (r^2 = 0.126^2 = 0.0158) of the change in SAP can be attributed to the change in BMI (Table 2).

Nutritional status was determined based on each participant's body mass index percentile. A total of 77.5% of the athletes had a normal weight (≥ 5th percentile and ≤ 85th percentile), 15% were overweight (≥ 85 and ≤ 95), 5% were underweight (≤ 5) and, finally, 2.5% were obese (≥ 95) (Table 2).

Table 1. Demographic and anthropometric characteristics of minor league athletes.

Variables	Mean ± SD	Statistical significance
Age (years)	15 ± 1.05	
Weight (kg)	69.25 ± 11.93	
Height (m)	1.85 ± 0.07	
BMI	19.90 ± 3.13	r = 0.126
Systolic BP (mmHg)	120 ± 11.48	sig. = 0.438; sig. < 0.05
Diastolic BP (mmHg)	80 ± 7.76	
SAP percentile (mmHg)	47 ± 32.09	
DAP percentile (mmHg)	83 ± 2.27	
WHR	0.80 ± 0.08	
Cardiovascular risk according to WHR Low Moderate High	 97.5% 0 2.5%	
Triceps skinfold (mm)	8 ± 3.11	
Abdominal skinfold (mm)	9.5 ± 6.11	
Subscapular skinfold (mm)	6 ± 3.09	
Suprailiac skinfold (mm)	6 ± 4.2	
PBF (mm)	10.07 ± 2.31	
Arm circumference (mm)	32 ± 3.66	
Waist circumference (mm)	80.5 ± 9.18	
Hip circumference (mm)	98.5 ± 9.5	

This table shows the participants' anthropometric measurements. The results are shown as means ± standard deviation.
SAP: systolic arterial pressure; DAP: diastolic arterial pressure; PBF: percent body fat; BMI: body mass index; WHR: waist-hip ratio; r: Pearson correlation coefficient

Discussion

Obesity is a variable that has increased cardiovascular risk (CVR) in both children and adults[3]. Each player's WHR, as a potential CVR indicator, was used to determine this factor.

The study population had a low CVR, which could be due to the fact that regular exercise, especially aerobic exercise, is associated with a reduction in different parameters, including waist and hip circumference[15]. This was shown by establishing that overweight/obesity was minimal among the athletes (7.5%), compared to 62.5% who had a normal weight.

Physical exercise is associated with lower blood pressure levels in both adults and children[16,17]; therefore, physical training is assumed to be a cardioprotective factor against the onset of HTN and other related cardiovascular diseases. When the relationship between BMI and SAP was established, it proved to be statistically significant, backed by other studies linking HTN to overweight and obesity[18,19]. In this group of baseball players, we maintain that a higher BMI is related to a higher PBF and not lean mass. On the other hand, there are studies showing the premise that HTN is associated with underweight[20].

It is true that prehypertension and HTN continue to be present; this can be shown in this study, as 15% of all the athletes evaluated were classified as having an abnormal SAP, a finding that concurs with other studies showing that HTN is one of the most prevalent diseases among athletes[18,21].

Other factors that affect the energy balance to maintain people's weight and, therefore, prevent obesity, are the characteristics of their diet[22]. Athletes must follow a diet that allows good performance and recovery. However, it has been found that dietary regimens do not meet their nutritional needs for their level of physical activity, which can lead to weight loss[23]. However, most of the study participants had a normal weight. This could be attributed to demographic differences between athletes in the Dominican Republic and those who have participated in studies in other countries or regions. Thus, it would be useful to describe the diet followed by national athletes.

This study found a statistically significant relationship between BMI and other parameters, like systolic arterial pressure, percent body fat, and waist-hip ratio, with the latter being an indicator of cardiovascular risk. Based on this result, body mass index is found to be an effective parameter for predicting cardiovascular risk in this population, which coincides with studies which have found a correlation between BMI and other measurements, like blood pressure[24,25].

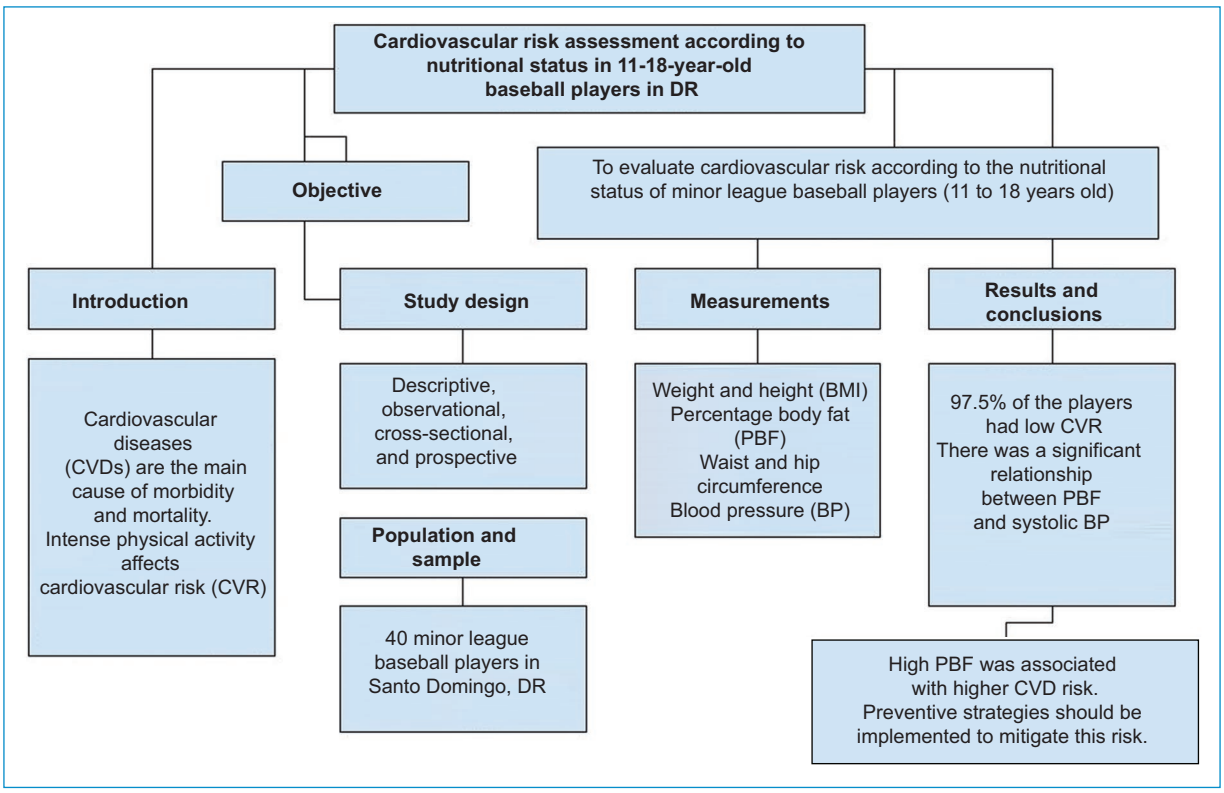

Figure 1. Main Figure. Main summary of the study on determining cardiovascular risk according to the nutritional status of minor league baseball players in Santo Domingo, Dominican Republic, highlighting the objectives, methods, main findings and conclusions.

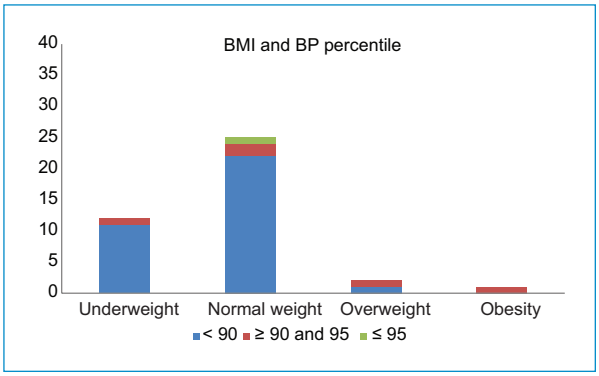

Figure 2. Relationship between body mass index and blood pressure.

Table 2. Nutritional status of baseball players according to body mass index percentile.

Nutritional status (BMI)	n	%
Underweight	2	5%
Normal weight	31	77.5%
Overweight	6	15%
Obesity	1	2.5%

The table presents nutritional status according to body mass index percentile, divided into underweight, normal weight, overweight, and obesity.

Biases

There was selection bias, since the sample was limited to the baseball players of a sports complex in Santo Domingo, Dominican Republic, which could affect the representative aspect of the study population. Measurement bias was also evaluated, which could have occurred if the elements used in the study to measure anthropometric variables had a manufacturing or calibration defect.

Conclusions

This study established that, in minor league baseball players between the ages of 11 and 18, cardiovascular

risk is linked to nutritional status, due to the statistically significant relationship between body mass index and systolic arterial pressure, which indicates that BMI affects cardiovascular risk in this population. It also concluded that most participants have low cardiovascular risk.

We recommend having a larger group of subjects, to be able to extrapolate the results. Furthermore, to more accurately evaluate cardiovascular risk, we suggest performing laboratory tests like lipid profiles and blood sugar levels, among others, that are directly related to the risk of cardiovascular disease.

These discoveries underscore the relevance of regularly assessing the nutritional status and cardiovascular parameters of young athletes, even those with seemingly healthy profiles. We also recommend implementing preventive and early intervention strategies aimed at improving their nutritional status and mitigating factors that affect their cardiometabolic condition.

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

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

Declaration on the use of artificial intelligence (AI). The authors declare that they did not use any type of generative artificial intelligence to write this article.

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Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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ORIGINAL ARTICLE

Predictive value of right ventricular function and ventriculo-arterial coupling in patients with heart failure with preserved or slightly reduced ejection fraction

Valor pronóstico de los índices de función ventricular derecha y el acoplamiento ventrículo-arterial en pacientes con insuficiencia cardíaca con fracción de eyección preservada o ligeramente reducida

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Abstract

Introduction: *The right ventricle (RV) and pulmonary circulation play a fundamental role in the pathophysiology of heart failure (HF). In this context, it may be of particular interest to evaluate not only right ventricular function but also the coupling between the RV and pulmonary circulation. Several studies have proposed the tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio as a relatively simple measure that provides information on right ventricular-arterial coupling with a potential prognostic role in patients with HF.* **Objective:** *To evaluate the prognostic value of the TAPSE/PASP and right ventricular strain (RVFWS)/PASP ratios in patients with heart failure and preserved or mildly reduced ejection fraction.* **Methods:** *A prospective cohort design was used, including patients with confirmed HF who had been admitted to the hospital due to decompensation. The TAPSE/PASP and RVFWS/PASP indices were quantified, and their relationship with cardiovascular mortality was studied. Results: The RVFWS/PASP ratio was statistically significantly associated with cardiovascular mortality at six months (p = 0.021). In contrast, the TAPSE/PASP ratio showed no association with cardiovascular mortality (p = 0.24).* **Conclusions:** *Longitudinal strain of the right ventricular free wall and its ratio to PASP (RVFWS/PASP), as a right ventricular-arterial coupling parameter, are indicative of unfavorable outcomes in patients with HF, proving to be powerful predictors of cardiovascular mortality.*

Keywords: *Heart failure. Strain. Right ventricle.*

Resumen

Introducción: *El ventrículo derecho y la circulación pulmonar desempeñan un papel fundamental en la fisiopatología de la insuficiencia cardíaca (IC). En este contexto tiene especial interés evaluar no solo la función ventricular derecha, sino también el acoplamiento entre el VD y la circulación pulmonar. En diversos trabajos se ha propuesto la relación TAPSE/PAPs (cociente entre el desplazamiento sistólico del plano del anillo tricúspide/TAPSE) y la presión arterial pulmonar sistólica (PAPs) como una medida relativamente sencilla que aporta información del acoplamiento ventrículo-arterial derecho con potencial*

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Date of reception: 12-06-2025
Date of acceptance: 04-11-2025
DOI: 10.24875/RCCARE.M25000204

Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):11-16
www.rccardiologia.com

papel pronóstico en pacientes con IC. **Objetivo:** *Evaluar el valor pronóstico del cociente TAPSE/PAPs y SLpVD/PAPs (strain de ventrículo derecho) en pacientes con insuficiencia cardíaca con fracción de eyección preservada o ligeramente reducida.* **Métodos:** *Se realizó un diseño de cohortes prospectivo que incluyó pacientes con IC confirmada que habían presentado un ingreso hospitalario por descompensación de la misma. Se cuantificaron los índices TAPSE/PAPs y SLpVD/PAPs. Se estudió su relación con la mortalidad cardiovascular.* **Resultados***: La relación SLpVD/PAPs se relacionó con la mortalidad cardiovascular a seis meses de manera estadísticamente significativa (p = 0.021). En cambio, la relación TAPSE/PAPs no mostró relación con la mortalidad cardiovascular (p = 0.24).* **Conclusiones:** *El strain longitudinal de la pared libre del ventrículo derecho y la relación del mismo con la PAPs (strain de VD/PAPs) como parámetro de acoplamiento ventrículo-arterial derecho son indicativas de evolución desfavorable en pacientes con IC con fracción de eyección preservada o ligeramente reducida, mostrándose como potentes predictores de mortalidad cardiovascular.*

Palabras clave: *Insuficiencia cardíaca. Strain. Ventrículo derecho.*

Introduction

The right ventricle (RV) plays an essential role in the pathophysiology of heart failure (HF)[1]. While left ventricular function parameters have been widely studied in this context, there is less information on the usefulness of right ventricular function indices[2].

In HF, it may be particularly interesting to evaluate not only right ventricular function but also the coupling between the RV and pulmonary circulation. This relationship may be altered by either increased pulmonary vascular resistance or intrinsic RV dysfunction. This relationship is especially interesting in the context of failure with preserved ejection fraction[3].

Some papers have proposed the tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio. It may have significant prognostic implications for patients with HF and for pulmonary hypertension (PH)[4,5].

This relatively simple measurement can be obtained noninvasively through echocardiography. It provides information regarding right ventriculo-arterial coupling: between the RV and pulmonary circulation. A TAPSE/PASP of less than 0.55 mm/mmHg is considered pathological.

The objective of this study was to evaluate the medium-term prognostic value of the TAPSE/PASP ratio in patients with HF admitted for decompensation.

A known limitation of TAPSE in RV function studies is that it is a regional parameter that studies the most basal segment. Thus, more novel parameters like right ventricular free wall strain (RVFWS) may yield more reliable information by representing the function of more myocardial segments and, therefore, could relate better to overall myocardial function.

This also led to the conjecture of whether RVFWS and the RVFWS/PASP ratio (as a novel parameter for right ventriculo-arterial coupling) provided relevant prognostic information.

Methods

We used a prospective cohort design that included patients with HF admitted for decompensation.

Patients with preserved or mildly reduced ejection fraction were included. The exclusion criteria were as follows:

- Significant valve disease. Having prosthetic valves or valve repair material.
- Hypertrophic cardiomyopathy (an imaging test compatible with hypertrophic cardiomyopathy or a genetic diagnosis).

The echocardiogram was performed once acute decompensation was stabilized following depletion therapy. Patients were considered stable when congestive symptoms improved, a minimum of 24 hours after admission. This was thought to be appropriate because the acquisition of some of the study's target variables could be affected by abnormal hemodynamic parameters (volume overload, tachycardia, etc.) in the initial phase of decompensated HF.

We used the Philips® aCMQ tool with semi-automated strain calculation for myocardial deformation analysis. A four-chamber view with focus on the right chambers was obtained to determine right ventricular free wall strain (RVFWS), optimizing the image by visualizing the entire RV wall.

The basal, medial and apical segments were analyzed, taking the mean of the three as the RVFWS. The equipment's software automatically detected the endocardial border. If any segment had suboptimal follow-up, this was corrected. None of the three segments could be eliminated from the analysis.

The TAPSE was determined through M-mode acquisition over the RV base in an apical four-chamber view, measuring systolic excursion of the tricuspid annulus.

Pulmonary artery systolic pressure (PASP) was calculated by measuring the maximum tricuspid regurgitation velocity using continuous Doppler and adding it to the estimated right atrial pressure.

The patients were followed for six months, and adverse events were recorded. Cardiovascular mortality was defined as death from heart failure, myocardial infarction or sudden cardiac death.

Results

A total of 71 patients were included, 39 males and 32 females. The median age of the sample was 80.6 years.

The comorbidities of the patients included in the sample are shown in figure 1. In summary, 93% were hypertensive, 54% had a history of atrial fibrillation, 50% had dyslipidemia, 43% had type 2 DM, 38% had a recorded history of CKD, and 20% had a history of COPD.

The percentage of patients with a mildly reduced ejection fraction (mrLVEF 40-50%) was 35%. The epidemiological data and most relevant medical history according to LVEF group are shown in table 1. There were no statistically significant differences between the groups.

The main echocardiographic variables of left-sided chamber size and function are described in table 2.

The LA was significantly dilated (volume indexed for body surface area: 50 and 48 ml/per square meter). The mean left ventricular ejection fraction for the total patient sample was 55%.

The main right chamber echocardiographic variables are presented in table 3. The mean right ventricular free wall strain was –17.29%.

As far as adverse events, at six months of follow-up, 34% of the patients had been readmitted for HF and 14% had died from a cardiovascular cause. The main cause of cardiovascular mortality was HF, and only one case was due to sudden death related to acute myocardial infarction. The mean time elapsed to the first admission for HF was 56.19 days, and 114.35 days to death.

As far as right ventricular function parameters, neither TAPSE nor FAC nor the S wave were associated with a higher likelihood of cardiovascular death six months after enrollment (Table 4).

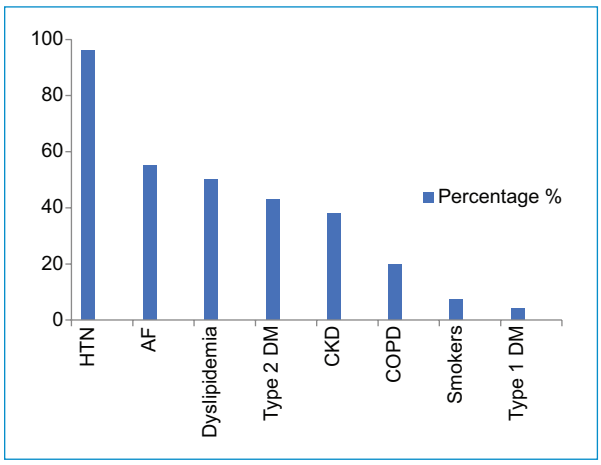

Figure 1. Comorbidities. Medical history. Type 1 DM: type 1 diabetes mellitus; Type 2 DM: type 2 diabetes mellitus; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; AF: atrial fibrillation; HTN: hypertension.

Table 1. Epidemiological data and prior medical conditions by LVEF group

Clinical variable	Intermediate	Preserved	p
Age (years)	74.1	79.5	0.064
Female sex	47%	53%	0.103
Male sex	68%	32%	0.103
AF	39%	56%	0.17
HTN	93%	92%	0.82
CKD	24%	46%	0.07
COPD	16%	22%	0.56
Type 2 DM	40%	43%	0.777
Ischemic heart disease	38%	11%	0.711

AF: atrial fibrillation; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HTN: hypertension; Type 2DM: type 2 diabetes mellitus.

Right ventriculo-arterial coupling parameter results

The TAPSE/PASP ratio showed no correlation with cardiovascular mortality at six months (non-significant p; p = 0.24), as shown in table 5.

The right ventricular free wall strain/PASP ratio was statistically significantly related to cardiovascular mortality at six months (p = 0.021) (Table 6).

An ROC curve was constructed to look for the optimal RVFWS/PASP ratio cut-off (Fig. 2).

Table 2. Echocardiographic parameters of the left chambers

Parameter	Echocardiographic value (SD)
LA diameter	45.72 (7.38)
LAVi	50.38 (18.08)
LVEDD	50.83 (6.59)
LVESD	33.77 (7.91)
MI	99.75 (27.64)
MI in women	88.56
MI in men	108
RWT	0.42 (0.08)
LVEDVi	52.88 (17)
LVEDVi in women	44 (11.83)
LVEDVi in men	60.16 (17)
LVEF	55.1 (8.64)
LVGLS	14.27 (3.39)
mr-LVEF/pLVEF (N/%)	25/46 (35/65)

LA diameter: left atrial diameter, in mm; LAVi: left atrial volume index, in ml/m^2; LVEDD: left ventricular end-diastolic diameter, in mm; LVEDVi: left ventricular end-diastolic volume index, in ml/m^2; LVEF: left ventricular ejection fraction, as a percentage; LVESD: left ventricular end-systolic diameter, in mm; LVESVi: left ventricular end-systolic volume index, in ml/m^2; LVGLS: left ventricular longitudinal strain, as a percentage (percentage); MI: left ventricular mass index in g/m^2; N: number of patients; RWT: relative wall thickness; SD: standard deviation.

Table 3. Echocardiographic parameters of the right chambers

Parameter	Echocardiographic value (SD)
Proximal RVOT diameter	29.24 (5.47)
Distal RVOT diameter	23.34 (4.24)
Apical 4 C RV basal diameter	39.66 (5.51)
Apical 4 C RV mean diameter	30.12 (6.27)
RA area	21.89 (6.10)
TAPSE	19.03 (3.36)
S	11.025 (0.30)
FAC	52.6%
Tei index	0.51 (0.13)
RVFWS	-17.29% (4.41)
PAT	87.09 (19.56)
VTI of pulmonary flow	15.20 (4.39)
PASP mmHg	48.20 (16.48)

4 C: four-chamber; FAC: fractional area change, as a percentage; PASP: pulmonary artery systolic pressure; PAT: pulmonary acceleration time, in ms; RA: right atrium, in cm^2; RV: right ventricle; RVFWS: right ventricular free wall longitudinal strain as a percentage and absolute value; RVOT: right ventricular outflow tract, in mm; S: lateral tricuspid annulus systolic wave velocity, in cm/s; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; VTI: velocity-time integral, in cm.

For an RVFWS/PASP cut-off of 0.3, the area under the curve was 0.77, showing a good relationship between Se and 1- Specificity.

We explored the discriminatory role of the value found. Then we explored whether this was related to a worse prognosis. We found that, indeed, an RVFWS/PASP ratio of less than 0.3 was related to a higher likelihood of cardiovascular death at six months (p = 0.008), as shown in table 7.

However, an abnormal TAPSE/PASP (defined as a value less than the 0.55 described in previous studies[4,5]) was not related to a higher likelihood of cardiovascular death (p = 0.56), as seen in the data in table 8.

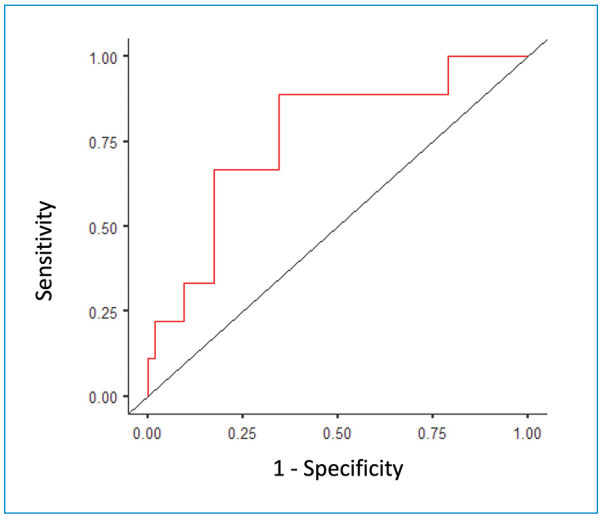

Figure 2. ROC curve. ROC: receiver operating characteristic; AUC: area under the curve: 0.765, for a cut-off value of 0.3.

Discussion

Although it has been shown to play a relevant role in HF pathophysiology, there is limited information in the literature on RV[1] function in this condition. One of the pathophysiological phenomena that occurs is adverse right ventricular remodeling, affecting its longitudinal function, as reflected in an abnormal RVFWS.

Table 4. Cardiovascular mortality at six months and right ventricular function indices

Parameter	(Total) (n = 71)	No (n = 61)	Yes (n = 10)	OR	p
RVFWS	18.7 [13.73; 20.73]	18.9 [14; 20.9]	13.96 [10.83; 18.82]	0.86 [0.74; 0.99]	0.04
TAPSE	18.05 [17.07; 21]	18.05 [17.23; 21]	18.25 [16.90; 22]	1 [0.81; 1.22]	0.97
S	11 [10; 12]	11 [10; 12]	10 [9; 11]	0.84 [0.58; 1.2]	0.33
FAC	0.52 [0.46; 0.62]	0.52 [0.45; 0.61]	0.67 [0.51; 0.73]	1.00 [0.97; 1.04]	0.87

FAC: fractional area change, as a percentage; RVFWS: right ventricular free wall strain on the first echocardiogram, as a percentage and absolute value; S: tricuspid DTI S wave; TAPSE: tricuspid annular plane systolic excursion, mm.

Table 5. Cardiovascular death at six months

Predictor	Estimate	SE	Z	p
TAPSE/PASP	-3.488	2.94	-1.187	0.24

TAPSE/PASP: ratio of TAPSE to pulmonary artery systolic pressure.

Table 6. Cardiovascular death at six months

Predictor	Estimate	SE	Z	p
RVFWS/PASP	-7.217	3.13	-2.303	0.021

RFVWS/PASP: ratio of RV strain to pulmonary artery pressure.

Table 7. Cardiovascular death at six months

Parameter	6M CV death		Total
Abnormal RVFWS/PASP ratio	No	Yes	
No	40	3	43
Yes	12	6	18
Total	52	9	61

χ^2 Test			
	Value	Df	p
χ^2	7.01	1	0.008
N	61		

Our study found that RVFWS was a sensitive indicator of an adverse prognosis. Right ventricular deterioration in patients with HFpEF and HFmrEF, manifested in longitudinal strain, leads to a worse clinical course. On the other hand, other classic right function parameters, like TAPSE or fractional area change (FAC), were not related to the likelihood of readmission or cardiovascular mortality.

A normal TAPSE in patients with HF is not always synonymous with normal RV systolic function. Tricuspid annular plane systolic excursion is a regional indicator, as it describes circumscribed longitudinal function in the lateral basal region of the RV; it may also be affected by load conditions. Despite its wide use and validated prognostic value, it is less sensitive to ventricular dysfunction than RVFWS. Likewise, a reliable FAC measurement depends on the quality of the image and proper plane acquisition. The endocardial border (which is more trabeculated than that of the LV) must be meticulously traced, making it very time-consuming.

As far as ventriculo-arterial coupling, an abnormal TAPSE/PASP ratio was not indicative of a worse prognosis, but the RVFWS/PASP ratio was, indicating that it is a more robust parameter for right ventricular impairment[6]. In this context, strain has higher sensitivity for detecting early dysfunction[7] while TAPSE is still normal.

Another strength is that it is less dependent on right ventricular geometry compared to a linear measurement like TAPSE, which is subject to inconsistencies due to heart movements[8] throughout the cardiac cycle.

With today's technological development, calculating RV strain takes less and less time, increasing its applicability for daily practice. Altered myocardial deformation is shown to be a sensitive indicator of an adverse prognosis and could be related to the fibrosis and right ventricular remodeling produced in HF.

Conclusions

In patients admitted for HF decompensation with preserved and mildly reduced ejection fraction, right ventricular free wall longitudinal strain, as a ventricular function index, and its ratio to PASP (RVFWS/PASP), as a right ventriculo-arterial coupling parameter, are

Table 8. Cardiovascular death at six months

Parameter	6M CV death		Total
Abnormal TAPSE/PASP	No	Yes	
No	29	12	41
Yes	12	7	19
Total	41	19	60

	Value	Df	p
χ^2	0.344	1	0.557
N	60		

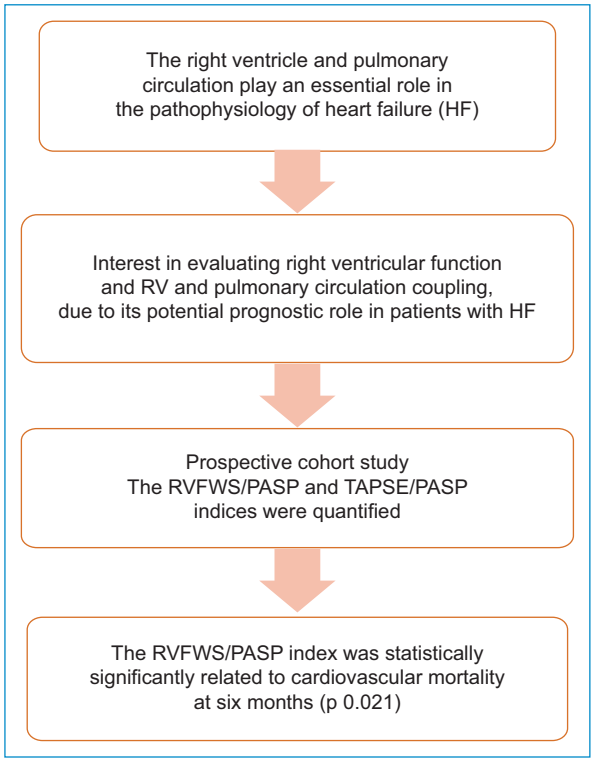

Figure 3. Main Figure. The study of right ventricular function using RV strain, and the evaluation of ventriculo-arterial coupling using the ratio of RV strain to PASP have great prognostic utility in patients with HF (strong predictors of cardiovascular mortality).

indicative of a negative course: a higher likelihood of death (Fig. 3. Main Figure). On the other hand, TAPSE and the TAPSE/PASP ratio are not associated with a worse prognosis. Myocardial deformation parameters, like strain and its relationship to pulmonary pressure, provide relevant prognostic information which reflects the pathophysiological abnormality of the pulmonary circuit in HF.

Acknowledgements

We would like to thank the cardiology service and, especially, the heart failure unit at Hospital de Barbastro.

Funding

The authors declare they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent and ethical approval. The authors followed their health facility/institution's protocols for accessing medical chart information. Informed consent was obtained from the patients, along with ethics committee approval. The SAGER guidelines were followed.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used for writing or creating content for this manuscript.

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ORIGINAL ARTICLE

Acute coronary syndrome comorbidities in Colombia: a real-world data analysis

Comorbilidades del síndrome coronario agudo en Colombia: un análisis de datos poblacionales

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Abstract

Introduction: *Acute coronary syndrome (ACS) is a leading cause of morbidity and mortality worldwide; however, data on ACS in Colombia is limited and outdated.* **Objective:** *To determine the prevalence of acute coronary syndrome (ACS) in Colombia, using a nationally representative database, as well as its association with its main comorbidities: hypertension, dyslipidemia, obesity, diabetes, sleep apnea, peripheral artery disease (PAD), and atrial fibrillation (AF), by age group and sex.* **Methods:** *This descriptive, cross-sectional study used data from the Ministry of Health for 2019-2023, including all individuals aged 20-100 who had had any contact with the healthcare system. The five-year prevalence of ACS and each of the conditions of interest was estimated and analyzed by sex and 10-year age groups. Subsequently, the prevalence ratio (PR) for ACS was calculated for each comorbidity.* **Results:** *During the five-year period, 247,818 individuals (58% males), from a total population of 34,985,391, were diagnosed with ACS; the mean age was 64.2 in males and 66.5 in females. The overall five-year prevalence was 7.1 cases per 1,000 individuals over the age of 20 (males: 8.9; females: 5.6). Hypertension, diabetes, dyslipidemia, and obesity were more prevalent in females. Atrial fibrillation had the highest PR (13.5), followed by PAD (10.1), hypertension (9.8), diabetes (4.8), sleep apnea (3.2), obesity (1.5), and dyslipidemia (1.5). Prevalence ratios were higher in younger people and in males.* **Conclusions:** *This large nationwide database shows the magnitude of the association of ACS with a set of chronic conditions.*

Keywords: *Acute coronary syndrome. Atrial fibrillation. Epidemiology. Hypertension. Peripheral artery disease. Sleep apnea syndromes.*

Resumen

Introducción: *El síndrome coronario aguda (SCA) es una de las principales causas de morbi-mortalidad a nivel mundial, sin embargo, la información para este síndrome en Colombia es limitada y desactualizada.* **Objetivo***: Utilizando una base de datos de cobertura nacional, se determinará la prevalencia del síndrome coronario agudo (SCA) en Colombia, así como su asociación con una serie de comorbilidades seleccionadas: hipertensión, dislipidemia, obesidad, diabetes, apnea de sueño, enfermedad arterial periférica (EAP) y fibrilación auricular (FA) por grupo etario y sexo.* **Métodos:** *Estudio descriptivo, transversal, con datos poblacionales del Ministerio de Salud para el período 2019-2023. Se incluyeron todos los individuos entre 20 y 100 años que tuvieron contacto con el sistema de salud. Se estimó la prevalencia a cinco años del SCA y cada una de las comorbilidades*

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Date of reception: 07-02-2025
Date of acceptance: 04-11-2025
DOI: 10.24875/RCCARE.M25000202
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):17-22
www.rccardiologia.com

de interés, por sexo y decenios de edad. Posteriormente, se calcularon las razones de prevalencia (RP) para el SCA y cada comorbilidad. **Resultados:** *Durante el período de estudio, se diagnosticaron 247.818 individuos (58% hombres) de SCA de una población total de 34.985.391 personas. La edad promedio fue 64,2 años en hombres y 66,5 años en mujeres. La prevalencia global a cinco años fue 7,1 casos por 1000 individuos de 20 años o más (hombres 8,9; mujeres 5,6). La prevalencia de todas las comorbilidades, excepto EAP, fue mayor en mujeres que en hombres. Las RP más altas fueron para FA (13,5), seguida por EAP (10,1), hipertensión (9,8), diabetes (4,8), apnea de sueño (3,2), obesidad (1,5) y dislipidemia (1,5). Las RP de mayor magnitud se evidenciaron en hombres y en la población más joven.* **Conclusiones:** *Esta base de datos nacional muestra la magnitud de la asociación de un conjunto de condiciones crónicas con el SCA utilizando datos poblacionales.*

Palabras clave: *Arteriopatía periférica. Epidemiología. Fibrilación atrial. Síndrome coronario agudo. Hipertensión. Síndromes de apnea del sueño.*

Introduction

Cardiovascular disease (CVD) stands as the leading global cause of death, accounting for an estimated 17.9 million fatalities each year[1]. Over the last century, numerous modifiable and non-modifiable risk factors (RFs) have been identified either through cohort studies like the Framingham Study[2,3] or case control studies like INTERHEART[4]. Administrative or "claims" databases and disease-specific registries have provided yet another option to study cardiovascular RFs or comorbidities in the so-called "real world," usually with much larger sample sizes[5,6].

Since 1993, the Colombian healthcare system has attained universal coverage for its over 50 million inhabitants[7,8]. To receive reimbursement, health providers at each patient contact fill out a data registry which is summarized in the Integrated Social Protection Information System (SISPRO, in Spanish) database, available for research purposes through a username and password[9]. This database has been extensively used to calculate disease prevalences, for burden of disease studies, and to estimate prevalence ratios (PRs) between a disease and its comorbidities[10-13]. The latter is a method that, to our knowledge, has not been used to study acute coronary syndrome (ACS) and its associated comorbidities, which is what gave rise to the idea for this paper. We will be using the SISPRO database to estimate the prevalence of ACS in Colombia by age and sex. Additionally, we will calculate the PR for ACS and the following conditions: hypertension, diabetes, obesity, dyslipidemia, sleep apnea, peripheral artery disease (PAD), and atrial fibrillation (AF).

Methods

With a username and password provided to our senior author (DR), we accessed the SISPRO database using an Excel dynamic table tool. We adjusted the parameters to include any person in Colombia over the age of 20 who had had contact with the system during the five-year period from January 2019 to December 2023. We stratified the population by sex and 10-year age groups. Acute coronary syndrome was defined as having been diagnosed with any of the following ICD-10 codes: acute myocardial infarction (I210-I229), other forms of acute ischemic heart disease (I248), and unspecified acute ischemic heart disease (I249). The codes used for the selected RFs were hypertension (I10X), diabetes (E10-E14), obesity (E660 to E662, E668), dyslipidemia (E780, E781, E782, E783, E784, E785), sleep apnea (G473), PAD (I700, I701, I702, I708, I709), and AF (I48X).

With this data, we estimated the five-year prevalence of ACS and each of our selected comorbidities in this population, using as the denominator the total number of subjects who accessed the healthcare system during the period, by sex and age group. As this database has nationwide coverage, a contact with the health system includes all medical practice settings: inpatient, emergency room, outpatient, and even home care. If the same person had two contacts with the healthcare system during the established period, he/she was only counted once.

To calculate the PRs, we used the database to obtain the number of people with ACS and one of the comorbidities studied ("ACS ∩ comorbidity"). This included people diagnosed with only ACS, only the comorbidity, and those with both diagnoses. We then added the number of people with only ACS to the number of people with only the comorbidity and subtracted that value from "ACS ∩ comorbidity," which gave us the number of people with both diagnoses ("ACS ∪ comorbidity"). Using these values, we calculated the prevalence of ACS in the population of people with a comorbidity as well as the prevalence of ACS in the population of people without that same comorbidity. We calculated the ratio of these two results to obtain the PR. This process

was repeated with ACS and each comorbidity, by age group and sex.

It is worth noting that this database is not suitable for calculating incidence or relative risks (RRs) as it is impossible to determine the number of new cases per period, or whether a comorbidity or risk factor appeared prior to the studied outcome. We did not analyze other associated conditions such as alcohol intake, physical activity, genetic predisposition, or smoking, as they are either not an ICD-10 diagnosis or are frequently misclassified or underdiagnosed, leading to unreliable results[14].

Observational studies like ours are classified as "risk-free" according to the classification outlined in Resolution 8430 of the Ministry of Health of Colombia, as they use non-sensitive information from anonymized, publicly available databases. The study adhered to the Strobe guidelines for observational studies as well as current national and international recommendations, particularly the Declaration of Helsinki.

Results

During the five-year period from 2019 to 2023, a total of 34,985,391 individuals over age 20 (females = 54.2%) contacted the Colombian healthcare system. Table 1 shows the absolute number of people with ACS and each of the comorbidities. Altogether, 247,818 of these individuals (females = 105,101; 42%) were registered with the diagnosis of ACS, for an overall prevalence of 7.1 cases per 1,000 people (males = 8.9, females = 5.5) (Table 2). The male to female ratio was 1.61 to 1, highest in the 60 to 69 age group, reaching 2.23 (as compared to 1.10 at ages 20 to 29, or 1.27 at ages over 80). Figure 1 shows the prevalence of ACS by sex and age.

Females had higher prevalences than males in most comorbidities, particularly in obesity, but also in diabetes, hypertension and dyslipidemia (Table 3); this was true in all age groups. In sleep apnea, PAD and AF there was a slight male predominance.

Hypertension stood out as the most prevalent of the conditions of interest, with its prevalence progressively rising from 2.4% of the population in the 20 to 29 age group, to 60.2% of those age 80 or over (63.5% of females; 55.5% of males). The next most common diagnosis was dyslipidemia, but here the highest prevalence was in the 50 to 59 age group (11.6%; 13.3% in females and 9.6% of males). A similar pattern was seen in obesity, with the highest prevalence occurring in the 50 to 59 age group (46.3 per thousand females; 21.4 in males). In diabetes and sleep apnea, prevalence

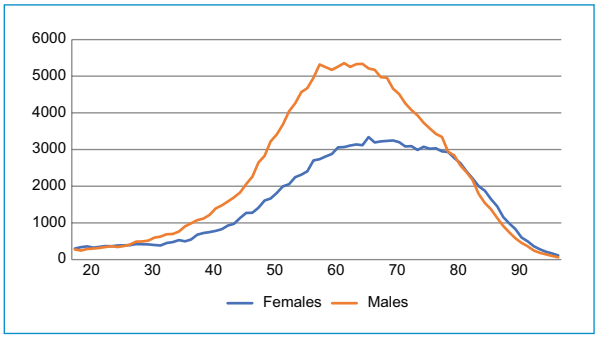

Figure 1. Main Figure. This figure illustrates the distribution of ACS cases in Colombia by age and sex. Distribution of all ACS cases (n = 247,818) that were registered from 2019-2023 in Colombia, by age and sex.

peaked in the 70 to 79 age group; 18.7% of females and 15.5% of males had a diabetes diagnosis, while 19.4 per thousand females and 17.9 per thousand males had sleep apnea.

Concerning the PRs, all values had a positive association (i.e., a PR of more than 1.0), both in males and females, and in every age group. Atrial fibrillation had the highest total PR at 13.5, while obesity and dyslipidemia had the lowest, at 1.5. When analyzed by age groups, there was a trend for all risk factors to exhibit decreasing PRs with advancing age (Table 4).

Discussion

In this study, we have quantified the statistical association between ACS and some of its most important comorbidities using real-world data. Prevalence ratios were used to determine whether, during the five-year study period, ACS was diagnosed more often in patients with each of the conditions of interest or in a control group consisting of subjects of the same sex and age group but without the given condition.

Our first finding relates to the prevalence of all the diagnostic conditions grouped under ACS. Our results align with what has been amply described in the literature: ACS prevalence increases with age, and males have higher figures than females in all age groups. The Global Burden of Disease Study[15] estimated a total of 313 million cases of ischemic heart disease worldwide in 2022, with males constituting 58% of these cases. The most recent data on the prevalence of ACS in Colombia and Latin America come from a study conducted between 2011 and 2019[16] which identified 383,566 cases of myocardial infarction within the

Table 1: Total population and absolute number of people with ACS and each of the comorbidities, by age group

Age groups	Total population	ACS	Hypertension	Dyslipidemia	Obesity	Diabetes	Sleep apnea	PAD	FA
20-29	11,186,228	7,139	265,068	182,315	196,243	68,637	24,315	937	818
30-39	10,053,815	11,050	532,547	403,244	271,673	151,270	58,705	1,143	1,549
40-49	8,445,752	22,083	1,075,581	641,203	274,951	334,164	86,067	2,274	2,782
50-59	7,598,317	46,765	1,913,405	884,386	268,654	653,492	115,887	7,098	7,037
60-69	5,739,957	66,394	2,265,334	650,241	180,620	791,390	107,934	17,288	15,929
70-79	3,295,734	58,934	1,756,438	277,079	73,577	567,920	61,694	20,630	23,849
80+	1,705,717	43,777	1,026,072	89,682	22,877	285,858	24,198	17,092	26,494
Total	34,985,391	247,818	6,864,618	2,938,162	1,225,582	2,259,508	428,115	63,806	74,345

Table 2: Five-year prevalence of ACS per 1,000 people in Colombia, by age group

Age (years)	Females	Males	Total
20-29	0.61	0.67	0.64
30-39	0.84	1.42	1.10
40-49	1.85	3.60	2.61
50-59	4.00	8.92	6.15
60-69	7.89	16.14	11.57
70-79	13.97	22.74	17.88
80+	23.08	29.30	25.66
Total	5.55	8.90	7.08

Source: integrated social protection information system (SISPRO) database.

Table 3. Five-year prevalence per 1,000 people aged 20 or above and female to male (F/M) ratio of each of the seven comorbidities of interest in Colombia.

Risk factors	Females	Males	F/M
Hypertension	219.8	168.3	1.31
Dyslipidemia	93.2	73.1	1.27
Obesity	47.1	20.7	2.28
Diabetes	71.6	56.3	1.27
Sleep apnea	12.1	12.4	0.97
PAD	1.7	2.0	0.84
AF	2.0	2.3	0.85

PAD: peripheral artery disease; AF: atrial fibrillation.
Source: integrated social protection information system (SISPRO) database.

Colombian population. Of these, 52.2% were reported in individuals aged 65 and older, and males accounted for 60.0%. We also found a higher overall prevalence in males, but beyond age 82, females surpassed males (Fig. 1). An explanation for this, besides women's greater longevity, could be that males who reach ages 80 and older are more likely to have a lower burden of cardiovascular risk factors and disease[17].

As with ACS, most of its comorbidities tended to be diagnosed more in older age groups, except for obesity, where the highest prevalence was found in the 50 to 59 age group, both in females (accounting for almost two thirds of patients) and in males. These findings are similar to those described in previous studies[13]. A reduction in prevalence beyond the 60 to 69 age group was also found in sleep apnea, which correlates with what has been reported in the literature[18].

Atrial fibrillation showed the greatest prevalence increase with age[19], as well as the highest PR. This could be explained by the different pathophysiologic mechanisms of AF in both age groups[20,21]. Unfortunately, there is limited literature studying the impact of AF on individuals younger than 45, given the low overall prevalence. The much higher magnitude of our PR for AF, as compared with previous case-control or cohort studies could be the result of an active search for AF in Colombian patients with ACS. The significance of AF as a comorbidity for ACS is that it has proven to be an indicator of a worse prognosis[22].

The PRs for each of the conditions considered in this study showed a progressive reduction in magnitude as age increased, both in males and females. This is consistent with the fact that age is an independent risk factor for ACS, but is also associated with a broader list of chronic comorbidities. Each of the conditions

Table 4: Prevalence ratios for ACS and its comorbidities stratified by 10-year age groups

Age groups	Hypertension	Dyslipidemia	Obesity	Diabetes	Sleep apnea	PAD	FA
20-29	5.86	2.29	2.15	5.27	4.55	33.54	85.38
30-39	6.27	1.93	2.29	3.90	3.36	16.75	38.57
40-49	5.87	1.52	2.10	3.34	3.34	15.03	25.43
50-59	4.82	1.14	1.77	2.79	2.69	9.51	14.14
60-69	3.84	1.01	1.50	2.33	2.14	5.64	8.03
70-79	3.00	1.06	1.47	1.90	1.91	3.82	4.76
80+	2.35	1.11	1.37	1.57	1.56	2.27	3.17
Total	9.75	1.45	1.49	4.79	3.24	10.11	13.53

PAD: peripheral artery disease; AF: atrial fibrillation.
Source: integrated social protection information system (SISPRO) database.

analyzed here would be, in itself, a more powerful predictor of ACS in younger adults than in the more compromised elderly subjects. Additionally, younger individuals are more likely to have more aggressive presentations of these conditions. Some examples of this are familial hypercholesterolemia and early onset hypertension[23-27]. Another explanation for this trend, however, could be diagnostic suspicion bias. As ACS is less common in younger individuals, they are more likely to be more rigorously studied for the presence of comorbidities, and these comorbidities are more likely to be reported in their clinical records[28].

A surprising finding in our study was that obesity and dyslipidemia had the lowest PRs. These comorbidities are regarded as two of the main risk factors for CVD and ACS, as they exhibited some of the highest population attributable risks in the INTERHEART study[4]. A systematic review and meta-analysis found that the prevalence of dyslipidemia in patients with ischemic heart disease was 49.6%[29], and the EUROASPIRE II study found that approximately 31% of patients with coronary heart disease are classified as obese[30]. The percentage of patients with dyslipidemia in the ACS population was 18.1%, while 5.9% were obese. We consider this to be due to the database's limitations, as it has been proposed that, with nationwide databases, the quality of information improves when the main diagnosis is severe rather than mild, and when the patients receive inpatient rather than outpatient care[9,14].

While large-scale studies conducted using population-wide databases such as this one have the advantage of reducing selection and participation bias[14], they have serious limitations. The main and most important one is the uncertainty regarding the quality of the data, as homogeneity in the diagnostic criteria used in each individual case cannot be assured[9]. Additionally, a study conducted in South Korea assessing the use of a population-wide database for research purposes concluded that several factors affect the quality of the data, mainly through misclassification or underreporting of the diagnoses[14]. As previously discussed, the severity of the disease and the medical care setting (inpatient vs. outpatient) are two such factors, but the level of specialization of the medical center and the specialist who provided the care are also mentioned in the study. Additionally, as the database is limited to main diagnoses based on ICD-10 codes, other relevant comorbidities or risk factors had to be excluded from the study.

Conclusions

We calculated an ACS prevalence in Colombia of 7.1 cases per 1,000 people. The prevalence of ACS and each of the comorbidities studied, except for PAD, sleep apnea, and AF, was found to be greater in females than males, but the PR for all the comorbidities was higher in men. We also found that PRs rose as age decreased. The results of our study could potentially inform future prevention strategies and clinical decision making.

Data availability

Data can be accessed using a username and password provided by the Colombian Ministry of Health and Social Protection. Specific data used in this analysis is available upon request.

Ethics approval statement

This study is classified as "risk-free" according to the classification outlined in Resolution 8430 of the Ministry of Health of Colombia, as it uses non-sensitive information from anonymized databases. The study adhered to national and international recommendations, particularly the Declaration of Helsinki.

Acknowledgments

The authors would like to thank Dr. Edward Cáceres for his help in the early stages of this project.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI) The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Physicians' attitudes, barriers, and subjective knowledge in the evaluation of cardiovascular risk in people living with HIV

Actitudes, barreras y conocimientos subjetivos de los médicos en la evaluación del riesgo cardiovascular en personas que viven con el VIH

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Abstract

Introduction: *Cardiovascular risk assessment is essential in caring for people living with HIV, as it requires accurate interpretation of risk prediction tools and effective communication with patients. Despite the availability of multiple cardiovascular risk models, uncertainty remains regarding whether physicians have the necessary knowledge and skills to use these tools appropriately, which may negatively affect the quality of clinical care and therapeutic decision-making.* **Objective:** *To evaluate attitudes, barriers, and both subjective and objective knowledge regarding cardiovascular risk assessment tools among Colombian physicians caring for people living with HIV, and to explore potential differences according to level of training and clinical experience.* **Methods:** *A cross-sectional study was conducted using an online survey administered to 104 physicians from different specialties, including internal medicine, cardiology, infectious disease, and related fields, all with experience in caring for people living with HIV. The questionnaire covered four domains: general information, experience and knowledge of cardiovascular risk assessment methods, attitudes and barriers to their use, and interpretation and communication of risk results. Responses were collected using 5- to 7-point Likert scales and multiple-choice questions.* **Results:** *Although 90% of participants reported being familiar with cardiovascular risk scores and more than 90% recognized their clinical importance, 15% felt uncomfortable using them, and 13% reported difficulties understanding the results. One-third of respondents misinterpreted cardiovascular risk scores, particularly regarding absolute risk and the communication of event probabilities. Additionally, 82% supported the development of an HIV-specific cardiovascular risk assessment tool. No significant differences were observed according to specialty or clinical experience.* **Conclusions:** *Despite recognizing the importance of cardiovascular risk assessment, physicians caring for people living with HIV exhibit relevant gaps in knowledge, interpretation, and risk communication. Addressing these deficiencies is essential to improve clinical decision-making and comprehensive care.*

Keywords: *HIV. Cardiovascular risk. Barriers. Knowledge.*

Resumen

Introducción: *La evaluación del riesgo cardiovascular es esencial en la atención de las personas que viven con el VIH, ya que exige una interpretación precisa de las herramientas de predicción del riesgo y una comunicación eficaz con los pacientes. A pesar de la disponibilidad de múltiples modelos de predicción, persiste la incertidumbre sobre si los médicos cuentan*

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Date of reception: 31-03-2025
Date of acceptance: 04-11-2025
DOI: 10.24875/RCCARE.M25000209
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):23-31
www.rccardiologia.com

con los conocimientos y habilidades necesarios para utilizarlos de manera adecuada, lo que puede afectar la calidad de la atención clínica y la toma de decisiones terapéuticas. **Objetivo:** *Evaluar las actitudes, las barreras y los conocimientos, tanto subjetivos como objetivos, sobre las herramientas de evaluación del riesgo cardiovascular entre médicos colombianos que atienden a personas que viven con el VIH, y explorar posibles diferencias según el nivel de formación y la experiencia clínica.* **Métodos:** *Se realizó un estudio transversal mediante una encuesta en línea aplicada a 104 médicos de distintas especialidades, incluyendo medicina interna, cardiología, infectología y otras áreas relacionadas, con experiencia en la atención de personas que viven con el VIH. El cuestionario incluyó cuatro dominios: información general, experiencia y conocimientos sobre métodos de evaluación del riesgo cardiovascular, actitudes y barreras para su uso, e interpretación y comunicación de los resultados. Las respuestas se recolectaron mediante escalas tipo Likert de 5 a 7 puntos y preguntas de opción múltiple.* **Resultados:** *Aunque el 90 % de los participantes reportó familiaridad con las escalas de riesgo cardiovascular y más del 90 % reconoció su importancia clínica, el 15 % se sintió incómodo al utilizarlas y el 13 % manifestó dificultades para comprender sus resultados. Un tercio de los encuestados interpretó erróneamente las puntuaciones de riesgo, especialmente en relación con el riesgo absoluto y la comunicación de probabilidades de eventos. El 82 % apoyó el desarrollo de una herramienta específica para personas que viven con el VIH. No se observaron diferencias significativas según especialidad o experiencia clínica.* **Conclusiones:** *A pesar de reconocer la importancia de la evaluación del riesgo cardiovascular, existen brechas relevantes en el conocimiento, la interpretación y la comunicación del riesgo, que deben abordarse para mejorar la atención integral.*

Palabras clave: *VIH. Riesgo cardiovascular. Barreras. Conocimiento.*

Introduction

Cardiovascular risk assessment is an important component of clinical care, particularly for high-risk populations such as people living with human immunodeficiency virus (HIV)[1-14]. Clinical practice guidelines consistently recommend its use to identify individuals at increased risk of cardiovascular events (acute myocardial infarction, stroke, angina, myocardial revascularization, and death) over a 5- or 10-year period. This assessment relies on risk prediction models, which are basically equations that incorporate variables such as age, sex, blood pressure, and cholesterol levels to accurately estimate risk[15].

The accurate estimation of cardiovascular risk allows the physician to recommend changes in the patient's lifestyle, determine if the patient could benefit from pharmacological therapies (i.e. statins) and define particular objectives in patient follow-up. However, these possible and desirable benefits require complex interactions between specific medical knowledge, the correct use and interpretation of cardiovascular risk model results, and effective communication of the results and implications to the patient.

People living with HIV are at heightened risk for cardiovascular events due to a combination of modifiable risk factors including hypertension, dyslipidemia, obesity, and smoking, as well as unique factors such as impaired lipid metabolism, chronic inflammation, and side effects of antiretroviral therapy (ART). As such, cardiovascular risk assessments should be performed routinely, at least once a year, to monitor and mitigate these risks[16-20].

Despite the recognized importance of these assessments, the level of knowledge and skill among physicians who routinely conduct cardiovascular risk evaluations in people living with HIV remains unclear. In this study, we explore the attitudes, barriers and subjective and objective knowledge of cardiovascular risk assessment models among physicians who perform cardiovascular risk estimation in people living with HIV, with a focus on understanding potential gaps in their ability to apply these tools effectively in clinical practice.

Methods

A descriptive cross-sectional study was used. The questionnaire was developed based on a review of prior literature and existing instruments related to cardiovascular risk assessment and HIV care. To ensure content validity, the preliminary version was reviewed by a panel of five experts in cardiology, internal medicine, and infectious disease with experience in HIV care. Their feedback led to minor modifications in terminology and the clarity of certain items. An electronic survey-type instrument was created in REDCap®, with 54 questions that included 4 domains: i) general variables (age, sex, professional profile and years of clinical experience); ii) experience and knowledge of cardiovascular risk assessment and clinical research methodology; iii) attitudes and barriers towards using

existing tools; and iv) knowledge of the tools and results communication, evaluated in two hypothetical clinical cases. Responses were given using Likert-type scales (5-7 points) and multiple-choice options (a questionnaire available as supplementary material). Eligibility criteria: Participants were eligible if they were physicians currently engaged in clinical practice in Colombia and had provided care to at least one person living with HIV (PLWH) in the previous 12 months. Both specialists (e.g., cardiologists, internists, infectious disease physicians) and general practitioners were included. Physicians not in active practice or who had not cared for PLWHs within the past year were excluded.

A pilot evaluation of this questionnaire was carried out among five cardiologists who are experts in cardiovascular risk assessment and two experts in methodology (epidemiologists), to assess the proper understanding of the questions and the response time. The self-administered survey was applied anonymously (by accepting an electronic invitation) during the Colombian Internal Medicine and Cardiology Congresses in 2019, to doctors who had evaluated at least one HIV patient in the last year. The questionnaire was designed and data were collected using REDCap®, with data processed in Microsoft Excel 2016® and Stata® (2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

We employed a convenience sampling approach, selecting physicians based on their availability and willingness to participate during the recruitment period. This decision was primarily due to the absence of a comprehensive sampling frame for the target population and the logistical limitations in accessing a randomized physician registry across the diverse clinical settings involved. Although this non-probabilistic approach may reduce the representativeness of the sample, it was consistent with the exploratory nature of the study and enabled the inclusion of participants across multiple institutions with varying levels of involvement in the care of PLWHs. The study specifically targeted physicians with recent clinical experience in managing PLWHs, aiming to capture attitudes and knowledge relevant to real-world cardiovascular risk assessment in this population. Given the exploratory and descriptive nature of the study, a formal sample size was not calculated.

Descriptive analysis of the information was carried out using frequencies and percentages for categorical variables and measures of central tendency for quantitative variables. Data completeness was assessed prior to analysis. Listwise deletion was applied for cases with missing responses on key outcome variables. Participants with incomplete data for any of the core knowledge or attitude questions were excluded from the corresponding domain-specific analyses. The overall proportion of missing data was low (< 5%), and no imputation techniques were applied.

The questionnaire was administered electronically using a secure online platform. Invitations were distributed during two national academic congresses and through professional networks, targeting physicians practicing in Colombia. To minimize the risk of ineligible or duplicate responses, the invitations clearly stated the inclusion criteria (active clinical practice and recent care of at least one PLWH), and access was limited to one response per device/IP address. No personally identifiable information was collected, and participation was voluntary and anonymous.

The research protocol was approved by the ethics and research committee (FM-CIE-0619-18). Due to the anonymous nature of the survey and the minimal risk involved, a waiver of written informed consent was requested and approved by the institutional ethics committee. Participants were provided with study information at the beginning of the survey and consent was implied by voluntary completion.

Results

We included all 104 responses that were obtained in the analysis; 37% of the participants were women and the average age of all participants was 40.1 years (standard deviation [SD] 9.8). Most participants worked in outpatient services (71%) (Table 1), and approximately 18.2% were general practitioners or residents. The physicians had an average of 9 years (range 1-36) of clinical experience since their last degree. During the past year of professional practice, each physician had evaluated an average of 57 patients (range 1-1,500) and performed 32 cardiovascular risk assessments in PLWHs in the last month (Table 1). Among the clinical specialists' group (95% of the sample), 33% were internists, 33% cardiologists, 28% infectious disease specialists, and 12% had other specialties.

Two thirds of the participants indicated that they had attended courses on methodology or research during some point of their training, 48% had attended specific courses in cardiovascular risk assessment and 91% would be interested in receiving courses in cardiovascular risk assessment in PLWHs (Table 2).

The opinions regarding the ideal frequency (monthly, biannual, and annual) for performing cardiovascular

Table 1. Characteristics of the 104 physicians who participated in the study

Variable	Female	Male	Total
Total sample, n (%)	38 (36.5)	66 (63.5)	104
Mean age (SD)	37.3 (7.7)	41.7 (10.5)	40.1 (9.8)
Work in HIV outpatient services	27 (36.4%)	47 (66.1%)	74 (71.1%)
Work in HIV inpatient services	17(29.8%)	40 (70.1%)	57 (54.8%)
Work in emergency departments	8 (22.8%)	27 (77.1%)	35 (33.6%)
Mean years of clinical experience (SD)	7.4 (5.6)	10.2 (9.2)	9 (8.1)
Professional profile: General practitioners, n (%) Residents, n (%) Specialists, n (%)	 2 (1.9) 8 (7.6) 28 (26.9)	 4 (3.8) 5 (4.8) 57 (54.8)	 6 (5.7) 13 (12.5) 85 (81.7)

risk assessment in PLWHs varied widely: most opting for the bi-annual (41%) and annual (44%).

About a quarter (24%) of the respondents considered that performing cardiovascular risk assessment would take up too much time during office visits. Almost all respondents (90%) indicated knowledge of some cardiovascular risk assessment scale; however, 15% felt uncomfortable using it and 13% did not understand its results (Table 3).

Of all respondents, 12% did not feel capable of clearly communicating the cardiovascular risk scores' interpretation and consequences to their patients. Most indicated that they understood the concepts of relative risk (RR, 84 %) and odds ratio (OR, 86%), and 86% indicated that they understood the concept of hazard ratio (HR) (Table 4).

Although > 90% indicated that they would consider it useful, profitable, and relevant to acquire knowledge regarding cardiovascular risk assessment tools for PLWHs, 51% would consider this "boring." The participants identified the following barriers hindering their learning process or clinical application of cardiovascular risk assessment tools in PLWHs: 1.) The perceived complexity of the task; 2.) The fear of erroneous interpretation of the cardiovascular risk score; and 3.) Lack of knowledge of the implications that the results might have for patients. Participants obtained a very low score (less than 10%) on items related to the experience or exposure to care of PLWHs or lack of training on cardiovascular risk assessment in medical schools.

Regarding knowledge and results communication skills, 21% of the participants were unaware of the existence of a specific cardiovascular risk assessment score for PLWHs (D: A: D - Data Collection on Adverse Effects of Anti-HIV Drugs Cohort)[20]; 76% of the participants considered the Framingham Score adjusted for Colombia to be the best scale[21]; 10% elected the Framingham Score[22]; 9% chose D: A: D[20], and 5% considered the Atherosclerotic Cardiovascular Disease Risk Algorithm (ASCVD) to be the best scale[23]. When asked about the interpretation of the cardiovascular risk scores, around a third selected the correct answers (32.5%) and likewise in the process of communicating the results to the patients (Tables 4 and 5). The most common errors were erroneous interpretations of the cardiovascular risk scores and the probability of events at 1 and 10 years, respectively, and the way of communicating the results to the patients. The majority of false responses were along the line of interpreting the risk score of X for 10 years to mean "X% more risk of cardiovascular events in this patient in the next 10 years compared to a person of his/her age and gender without an HIV diagnosis" rather than the absolute risk of a CV event in the coming 10 years. Many respondents (82%) considered that the development of a specific cardiovascular risk monitoring and evaluation tool for the population of PLWHs and for individual use would be "useful" to "very useful." No differences were found in the results based on specialty or years of clinical experience. Figure 1 provides a graphical summary of the study design, the domains assessed, and the main findings.

Discussion

The findings of this study underscore several critical challenges faced by physicians in effectively using cardiovascular risk assessment tools for PLWHs. While

Table 2. Reported levels of received and desired training in clinical research and cardiovascular risk assessment of the participating physicians

Question	Primary Care Physicians (n, %)		Residents (n, %)		Specialists (n, %)		p*
	Yes	No	Yes	No	Yes	No	
Have you ever received or taken specific courses in research, research methodology, or epidemiology?	4, 3.8%	2, 1.9%	6, 5.7%	7, 6.7%	59, 56.7%	26, 25%	0.25
Have you ever received or taken specific courses in cardiovascular risk assessment?	3, 2.8%	3, 2.8%	3, 2.8%	10, 9.6%	44, 42.3%	41, 39.4%	0.15
Would you be interested in receiving a specific course in cardiovascular risk assessment?	5, 4.8%	1, < 1%	13, 12.5%	0	77, 74.3%	8, 7.6%	0.41

*Pearson's chi².

Table 3. Colombian physicians' self-reported levels of acquaintance with and comfort in using cardiovascular risk assessment tools

I am acquainted with any of the models for cardiovascular risk assessment						
Profile	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Totally agree**	**p***
General physicians, n (%)	1 (< 1%)	0	0	3 (2.8%)	2 (1.9%)	0.66
Residents, n (%)	1 (< 1%)	0	0	6 (5.7%)	6 (5.7%)	
Specialists, n (%)	2 (1.9%)	4 (3.8%)	1 (< 1%)	31(29.8%)	47 (45.1%)	
I am comfortable using any of the models for cardiovascular risk assessment						
General physicians, n (%)	0	1 (< 1%)	0	2 (1.9%)	3 (2.8%)	0.54
Residents, n (%)	1 (< 1%)	1 (< 1%)	0	7 (6.7%)	4 (3.8%)	
Specialists, n (%)	1 (<1%)	4 (3.8%)	9 (8.6%)	38 (36.5%)	33 (31.7%)	
I clearly understand the result of the model						
General physicians, n (%)	0	1 (<1%)	1 (<1%)	2 (1.9%)	2 (1.9%)	0.54
Residents, n (%)	1 (< 1%)	0	0	9 (8.6%)	3 (2.8%)	
Specialists, n (%)	1 (< 1%)	4 (3.8%)	6 (5.7%)	45 (43.2%)	29(27.8%)	

*Pearson's chi².

most respondents acknowledged the importance of these tools and expressed interest in acquiring further knowledge, significant barriers persist that may hinder their practical application. Most of our respondents (90%) were familiar with cardiovascular risk scales, only 15% felt uncomfortable using them, and 13% reported difficulty in understanding the results. However, substantially more than this 13% (up to 67%) wrongly interpreted the scores, with common errors related to understanding event probabilities and communicating results to patients.

The perception that cardiovascular risk assessment is a complex and time-consuming task, combined with concerns over misinterpreting risk scores, suggests a need for more targeted training and education[21,24,25]. This need for proper training in the use, meaning and communication of these risk tools coincides with respondents' answers, with less than 10% of them reporting experience with or exposure to cardiovascular risk assessment training in medical school. Current and future physicians should be equipped with the knowledge and skills to understand and correctly use these

Table 4. Self-reported level of understanding of the concepts of hazard ratio, relative risk and odds ratio

Profile	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Totally agree	p*
I understand the concept and meaning of hazard ratio						
General physicians, n (%)	0	1 (< 1%)	1 (< 1%)	2 (1.9%)	2 (1.9%)	0.41
Residents, n (%)	1 (< 1%)	0	0	9 (8.6%)	3 (2.8%)	
Specialists, n (%)	1 (< 1%)	4 (3.8%)	6 (5.7%)	45 (43.2%)	29 (27.8%)	
I understand the concept and meaning of relative risk						
General physicians, n (%)	0	1 (< 1%)	1 (< 1%)	2 (1.9%)	2 (1.9%)	0.92
Residents, n (%)	0	1 (< 1%)	1 (< 1%)	7 (6.7%)	4 (3.8%)	
Specialists, n (%)	2 (1.9%)	6 (5.7%)	4 (3.8%)	40 (38.4%)	33 (31.7%)	
I understand the concept and meaning of odds ratio						
General physicians, n (%)	0	1 (< 1%)	1 (< 1%)	2 (1.9%)	2 (1.9%)	0.69
Residents, n (%)	0	2 (1.9%)	1 (< 1%)	7 (6.7%)	3 (2.8%)	
Specialists, n (%)	1 (< 1%)	5 (4.8%)	3 (2.8%)	44 (42.3%)	32 (30.7%)	

*Pearson's chi^2.

kinds of tools, and the response by many that this kind of training is "boring" indicates that educational approaches should be restructured to engage healthcare professionals more effectively, probably with more real-life and interactive teaching methods[26-29].

Such training should also include efforts to enhance communication skills, as difficulties in communicating risk scores were common, and a lack of effective communication is detrimental for informed decision-making and patient adherence to treatment plans. The patient-doctor interaction required to adequately transmit information regarding certain risks and achieve changes in patient behavior, specifically in self-care and cardiovascular health protection, is complex. This scenario has prompted the creation of innovative methodologies that aim to respond more effectively to the complexity of the issue. These approaches seek to integrate not only specialized knowledge on the subject but also communication strategies that include both verbal and nonverbal dimensions, along with emotional intelligence components. Although these elements have shown great promise in improving outcomes and engagement, their real-world application remains limited and inconsistent. As such, there is a growing need to move from theoretical frameworks to practical implementation in diverse settings[27].

To date, our findings are not unique to Colombia or HIV-related care: previous studies related to cardiovascular risk assessment in general have reported that primary care physicians are uncertain of how to communicate results and make pharmacological decisions based on the results of the tools[24], with severe limitations in understanding and barriers derived from the computer tools for calculating risk[25]. To our knowledge, ours is the first such study to be performed specifically in the HIV population.

Physicians responsible for patients at high risk of cardiovascular and peripheral artery disease[26] have knowledge gaps related to cardiovascular risk assessment. The implementation of both pharmacological and non-pharmacological therapies remains very limited, despite their proven benefits in reducing cardiovascular events and long-term complications. This is largely due to the lack of routine assessment of cardiovascular risk factors, inaccurate risk estimation, insufficient knowledge of emerging therapies, and poor adherence to clinical practice guidelines. Additionally, the limited use of effective educational and communication strategies further contributes to this gap in care[26,29].

The main limitations of our study include its application within a specific physician population and the lack of information regarding non-responders. However, achieving participation from 104 physicians involved in the care of PLWHs, with 99 of them being medical specialists or residents, represents a valuable and relevant sample. These are professionals who, by

Table 5. Interpretation of the cardiovascular risk scores (10-year risk of heart attack, stroke, or death from cardiovascular disease)

You use an electronic risk calculator that you found quickly during your consultation and the result is 11%. What does this mean?					
Variable	**11% probability of cardiovascular events in the following year**	**11% more risk of cardiovascular events than a person of his/her age and gender in the following year**	**11% probability of cardiovascular events at 10 years****	**11% more risk of cardiovascular events than a person of their age and gender in the next 10 years**	**p***
General physicians, n (%)	0	3(2.8%)	1 (< 1%)	1 (< 1%)	0.52
Residents, n (%)	3 (2.8%)	2 (1.9%)	1 (< 1%)	7 (6.7%)	
Specialists, n (%)	1 (< 1%)	9 (8.6%)	32 (30.7%)	44 (42.3%)	
TOTAL	4 (3.8%)	14 (13.5%)	34 (32.7%)	52 (50.0%)	
Physicians who indicated that they understood the concepts of HR, RR and OR (all) but had an incorrect answer (n = 88)	4 (4.5%) Incorrect answer	15 (17%) Incorrect answer	29 (32.9%) Correct answer	40 (45.4%) Incorrect answer	
When the patient asks about the meaning of 11 (% or probability), what would your answer be?					
	11/100 patients like you will have a cardiovascular event in the following year.	**You have an 11% higher risk of having a cardiovascular event than a person of your age and gender in the following year**	**11/100 patients like you will have a cardiovascular event in the next 10 years****	**You have an 11% higher risk of having a cardiovascular event than a person of your age and gender in the following 10 years**	**p***
General physicians, n (%)	3(2.8%)	0	3 (2.8%)	0	0.71
Residents, n (%)	3 (2.8%)	1 (< 1%)	2 (1.9%)	7 (6.7%)	
Specialists, n (%)	0	9 (8.6%)	50 (48.1%)	26 (25%)	
TOTAL	6 (5.7%)	10 (9.6%)	55 (52.9%)	33 (31.7%)	
Physicians who stated that they understood the concepts of HR, RR and OR (all) and provided correct answers in the clinical cases (n = 88)	2 (2.2%) Incorrect answer	12 (11.5%) Incorrect answer	27 (30.6%) Correct answer	47 (53.4%) Incorrect answer	

*Pearson's chi^2.
**Correct answer.

training and clinical exposure, are expected to be familiar with cardiovascular risk assessment tools and their application in practice. Furthermore, the diversity of medical profiles and range of clinical experience among respondents enhances the richness of the findings. While the instrument underwent expert review and pilot testing with good internal consistency, no formal construct validation was conducted. Future studies could expand psychometric testing using exploratory and confirmatory factor analysis in larger samples.

A key methodological limitation of this study is the use of convenience sampling, which may introduce selection bias. Participants who chose to respond might differ systematically from those who did not, potentially affecting the external validity of our findings. We acknowledge that the lack of randomization limits the generalizability of the results beyond the specific sample studied. However, this limitation was partially mitigated by the inclusion of physicians from both specialized HIV clinics and general cardiology settings, which allowed for a broader representation of clinical perspectives. Although the study was not powered for hypothesis testing, the achieved sample size allowed for exploratory analyses and descriptive comparisons. Nonetheless, future research with larger, probabilistically selected samples may improve precision and external validity.

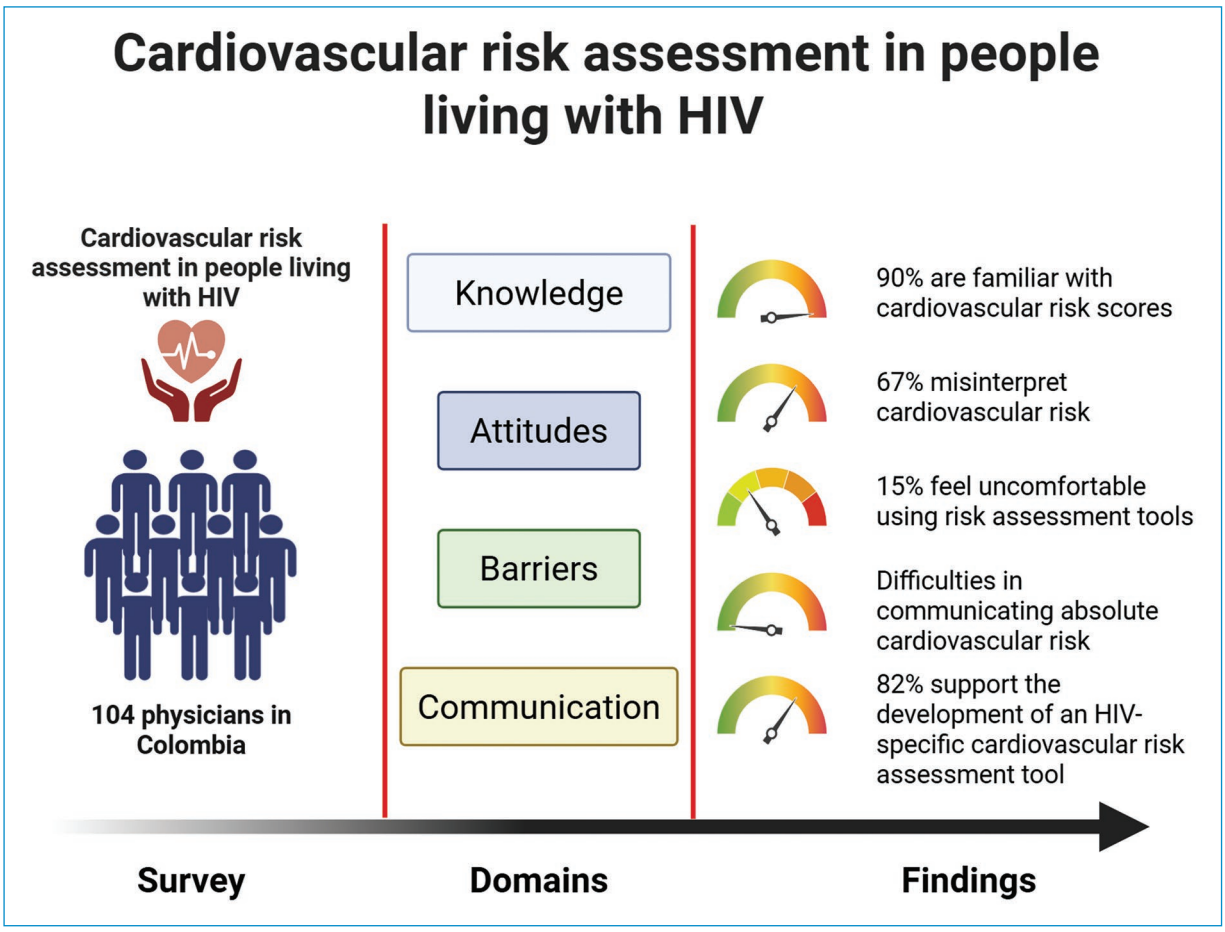

Figure 1. Main Figure. Cardiovascular risk assessment in people living with HIV. Overall results.

Another potential limitation of our study is the presence of volunteer bias. Participation was voluntary and relied on self-selection through electronic invitations distributed during academic congresses and professional networks. This recruitment strategy may have favored the inclusion of physicians with a greater interest in or awareness of cardiovascular health in PLWHs. Consequently, the findings may reflect a more engaged or informed subset of the physician population, potentially overestimating levels of knowledge or favorable attitudes toward cardiovascular risk assessment in this group.

Understanding physicians' perceptions regarding the use of cardiovascular risk assessment tools, their attitudes towards their integration into clinical practice, and the barriers they report (including limited knowledge, uncertainty in interpreting results, and low confidence in their clinical applicability), is crucial. This information is not only relevant for healthcare providers and patients, but also for those involved in the design and implementation of these tools.

It is important to highlight that multiple factors contribute to the underutilization of cardiovascular risk assessment tools, including time constraints, lack of local or HIV-adapted risk scores, perceived complexity, absence of systematic training, and limited institutional reinforcement. Addressing these limitations is essential to promote more effective and standardized use of cardiovascular risk tools, particularly in high-risk populations, such as PLWHs.

Conclusions

Physicians responsible for managing PLWHs recognize the importance of cardiovascular risk assessment; however, there are big gaps in knowledge regarding the use of cardiovascular risk scores, correct interpretation of results, and effective transmission of information to patients. Education in methodological and communication aspects is a fundamental aspect that must be improved to achieve

success in the evaluation of cardiovascular risk, treatment changes and the acquisition of healthy habits and self-care behaviors.

Acknowledgements

The authors would like to thank Pontificia Universidad Javeriana and Hospital Universitario San Ignacio for their support.

Funding

This research was funded by Pontificia Universidad Javeriana and Hospital Universitario San Ignacio.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the ethics committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed The research protocol was approved by the ethics and research committee of the School of Medicine at Pontificia Universidad Javeriana (FM-CIE-0619-18; 2018-189). Informed consent was not required.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in writing this manuscript.

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Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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REVIEW ARTICLE

Anticoagulation in patients with atrial fibrillation undergoing major surgery

Anticoagulación en pacientes con fibrilación auricular sometidos a cirugía mayor

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Abstract

Oral anticoagulation, particularly with vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), is essential for preventing thromboemboli. However, in patients with atrial fibrillation (AF) requiring major surgery, interrupting anticoagulation presents a clinical dilemma, as it increases thrombotic risk while reducing the risk of perioperative bleeding. This article evaluates perioperative anticoagulation management strategies in patients with AF undergoing major surgery. For this, a systematic review of randomized controlled trials (RCTs) was conducted in adult patients with AF who were on chronic anticoagulation and underwent major surgery. The search was performed in databases such as MEDLINE, EMBASE, and Cochrane. Risk of bias was assessed using the Cochrane RoB 2.0 tool. Eight RCTs were included, comprising a total of 13,793 patients. The BRIDGE study (n = 1,884) showed that omitting heparin bridging therapy did not increase the risk of thromboembolism (0.4 vs. 0.3%; p = NS) but significantly reduced major bleeding (3.2 vs. 1.3%; p < 0.01). Furthermore, PERIOP2 (n = 1,471), showed no benefit from bridging therapy in high-risk patients (thromboembolism 1.0 vs. 1.2%; p = NS). In BRUISE CONTROL I (n = 681), continuing warfarin in cardiac device surgeries significantly reduced surgical hematomas (3.5 vs. 16.0%; p < 0.001). The evidence suggests that omitting bridging therapy in most AF patients on VKAs is safe and reduces hemorrhagic complications. Direct oral anticoagulants allow for shorter interruption and earlier resumption without increasing thromboembolic events.

Keywords: *Atrial fibrillation. Oral anticoagulants. Perioperative management. Bridging therapy. Major surgery.*

Resumen

La anticoagulación oral, especialmente con antagonistas de la vitamina K (AVK) y anticoagulantes orales directos (ACOD), es fundamental para la prevención de la tromboembolia. Sin embargo, en pacientes con fibrilación auricular, que requieren cirugía mayor, la suspensión de la anticoagulación supone un dilema clínico, ya que aumenta el riesgo trombótico mientras reduce el riesgo de hemorragia perioperatoria. En este artículo se evaluaron las estrategias de manejo perioperatorio de la anticoagulación en pacientes con fibrilación auricular sometidos a cirugía mayor. Para ello se hizo una revisión sistemática de ensayos clínicos aleatorizados (ECA) en pacientes adultos con fibrilación auricular que recibían anticoagulación crónica

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Date of reception: 17-03-2025
Date of acceptance: 04-11-2025
DOI: 10.24875/RCCARE.M25000204
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):32-40
www.rccardiologia.com

y fueron sometidos a cirugía mayor. La búsqueda se llevó a cabo en bases de datos como MEDLINE, EMBASE y Cochrane. Se evaluó el riesgo de sesgo con la herramienta Cochrane RoB 2.0. Se incluyeron 8 ECA, con un total de 13 793 pacientes. El estudio BRIDGE (n = 1884) mostró que omitir la terapia puente con heparina no aumentó el riesgo de tromboembolia (0.4 vs. 0.3%; p = NS), pero sí redujo el sangrado mayor (3.2 vs. 1.3%; p < 0.01). En PERIOP2 (n = 1471), la terapia puente tampoco mostró beneficios en pacientes de alto riesgo (tromboembolia 1.0 vs. 1.2%; p = NS). En BRUISE CONTROL I (n = 681), continuar warfarina en cirugías de dispositivos cardíacos redujo de manera significativa los hematomas quirúrgicos (3.5 vs. 16.0%; p < 0.001). La evidencia sugiere que omitir la terapia puente en la mayoría de los pacientes con FA en AVK es seguro y reduce las complicaciones hemorrágicas. Los ACOD permiten una suspensión más corta y la reanudación temprana, sin aumentar los eventos tromboembólicos.

Palabras clave: *Fibrilación auricular. Anticoagulantes orales. Manejo perioperatorio. Terapia puente. Cirugía mayor.*

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, with a prevalence that increases with age and the presence of cardiovascular comorbidities[1]. An estimated 2 to 3% of the world's population has AF, and its incidence is even higher in people over the age of 65. This arrhythmia is characterized by disorganized and chaotic atrial activity that leads to ineffective atrial contractions and blood stasis, fostering intracardiac thrombi mainly in the left atrium and appendage. Consequently, patients with AF have an up to five times greater risk of thromboembolic events, with ischemic stroke being one of the most serious and disabling complications[2].

To mitigate this risk, oral anticoagulation has become the cornerstone of treatment in patients with nonvalvular AF and additional thromboembolic risk factors, as determined by scales like CHA_2DS_2-VASc[3]. Vitamin K antagonists (like warfarin) have traditionally been the standard treatment for preventing thromboemboli in these patients. However, over the last decade, direct oral anticoagulants (DOACs) like dabigatran, rivaroxaban, apixaban, and edoxaban have gained importance due to their safety profile and efficacy, lower need for monitoring, and lower risk of drug interactions compared to warfarin.

Nevertheless, managing anticoagulation in patients with AF who need major surgery poses a significant clinical challenge. In these cases, anticoagulation should be suspended to minimize the risk of perioperative bleeding, which, in turn, increases the risk of thrombosis. Anticoagulation interruption and reintroduction should be personalized and will depend on multiple factors, including the patient's thrombotic risk, the type of surgery to be performed, and the pharmacokinetics of the anticoagulant being used. This balance between reducing the risk of surgical bleeding and preventing postoperative thromboembolic events presents a clinical dilemma in perioperative decision making[4].

Although clinical practice guidelines with recommendations for perioperative management of anticoagulation in patients with AF are available, significant areas of uncertainty and variability remain in their implementation. There are disagreements in the optimal length of anticoagulation suspension prior to surgery and when it should be reintroduced after the procedure. The available evidence varies depending on the type of anticoagulant used, as DOACs have a shorter half-life than warfarin, which affects treatment interruption and reinstatement strategies[5].

Another aspect under discussion is the use of bridging therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin in patients with high thromboembolic risk. Although bridging therapy has been used over the years to cover the period during which patients are off oral anticoagulation, some studies have questioned its benefit in certain subgroups of patients, suggesting that this therapy may increase the risk of bleeding without significantly reducing thromboembolic risk[6].

Furthermore, the diversity of the available studies makes it difficult to establish standardized recommendations. Many studies have been observational, with small study populations and varied methodology, which prevents extrapolation of the results to general clinical practice. Likewise, the lack of large randomized clinical trials on this topic has contributed to uncertainty in clinical decision making[7].

Therefore, a systematic review of the current literature is needed to analyze and synthesize the available evidence on the different perioperative anticoagulation strategies for patients with AF undergoing major surgery. This review will help identify the best evidence-based practices and guide clinical recommendations for optimizing these patients' outcomes.

Methods

We conducted a systematic review of the literature to evaluate perioperative anticoagulation strategies for patients with AF undergoing major surgery. We included randomized clinical trials (RCTs) that analyzed different strategies within this context. Observational studies, pilot studies without definitive results, and previous narrative or systematic reviews were excluded.

The participants were adult patients diagnosed with AF who were on chronic anticoagulation and underwent major surgery or invasive procedures. Studies of populations with any type of AF (paroxysmal, persistent or permanent) and different levels of thromboembolic risk, according to $CHADS_2$ or CHA_2DS_2-VASc, were included.

The included studies compared different perioperative management strategies, such as suspending vitamin K antagonists (warfarin) with or without bridging therapy with LMWH or unfractionated heparin (UFH), continuous DOACs vs. perioperative interruption, and the comparison between different anticoagulants in this context.

The primary outcomes were the incidence of perioperative thromboembolic events (arterial thrombosis, stroke, systemic embolism) and the rate of major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria or those established in each study. The secondary outcomes included the incidence of minor or clinically relevant bleeding, overall mortality in the perioperative period, the presence of postoperative hematomas (for example, pocket hematomas in cardiac device implantations) and the timing of anticoagulant suspension and reinstatement.

To identify the studies, a systematic search was done in MEDLINE (using PubMed), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The MeSH terms and keywords related to *"atrial fibrillation"*, *"anticoagulation"*, "*perioperative management"*, "*bridging therapy,"* and "*surgical procedures"* were used. No language or publication date restrictions were applied. The reference lists of relevant articles and previous reviews were also reviewed, and the authors of recent studies were contacted to obtain information on unpublished data or additional analyses.

Two independent reviewers selected the studies by screening the titles and abstracts. A full-text review was conducted on eligible articles, and any disagreements were resolved by consensus or through the intervention of a third reviewer. Data extraction was done using a standardized form on which the study characteristics (author, year, design, sample size), population characteristics (type of AF, $CHADS_2$/CHA_2DS_2-VASc, type of surgery), procedures, comparisons and outcomes of interest were recorded. The data were handled using specific systematic review software (*RevMan* and *Excel*).

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias (RoB 2.0) tool, considering aspects like random sequence generation, assignment blinding, participant and outcome assessor blinding, missing outcome data, and the risk of selective reporting bias.

Results

A search of the different databases yielded 883 references, of which, after title and abstract review, 64 remained for full-text review. Ultimately, eight relevant RCTs (Fig. 1) that met the inclusion criteria were included. Table 1 summarizes the main characteristics of these studies. Of note were two large double-blind RCTs that evaluated the need for "bridging therapy" with heparin when warfarin was interrupted (the BRIDGE and PRIOP2 studies); two elective cardiac procedure trials (BRUISE CONTROL I and II) that studied continuing vs. suspending perioperative anticoagulation; and DOAC vs. warfarin trial subgroup analyses that provide information on the perioperative management of the new anticoagulants. These are described in detail below.

For patients with AF who are anticoagulated with warfarin and undergo major surgery, the randomized trials show that omitting bridging therapy with heparin does not increase thromboembolic risk and reduces bleeding. In BRIDGE[8], conducted mainly in moderate-risk AF (average $CHADS_2 \approx 2$) and surgeries that are not highly thrombogenic, the non-bridging strategy was not inferior for thromboembolic events at 30 days (0.4 vs. 0.3%; a nonsignificant difference), and there was more bleeding with bridging: major bleeding 3.2 vs. 1.3% ($p = 0.005$) and minor bleeding 20.9 vs. 12.0% ($p < 0.001$), with no differences in perioperative mortality (≈ 0.5% in both groups). PERIOP2[9], which enrolled higher risk patients (including those with mechanical valves) and evaluated postoperative bridging, showed no benefit with this therapy; thromboembolic events at more than 90 days: 1.0% with bridging vs. 1.2% without bridging ($p = 0.64$), and major bleeding: 1.3 vs. 2.0% ($p = 0.32$).

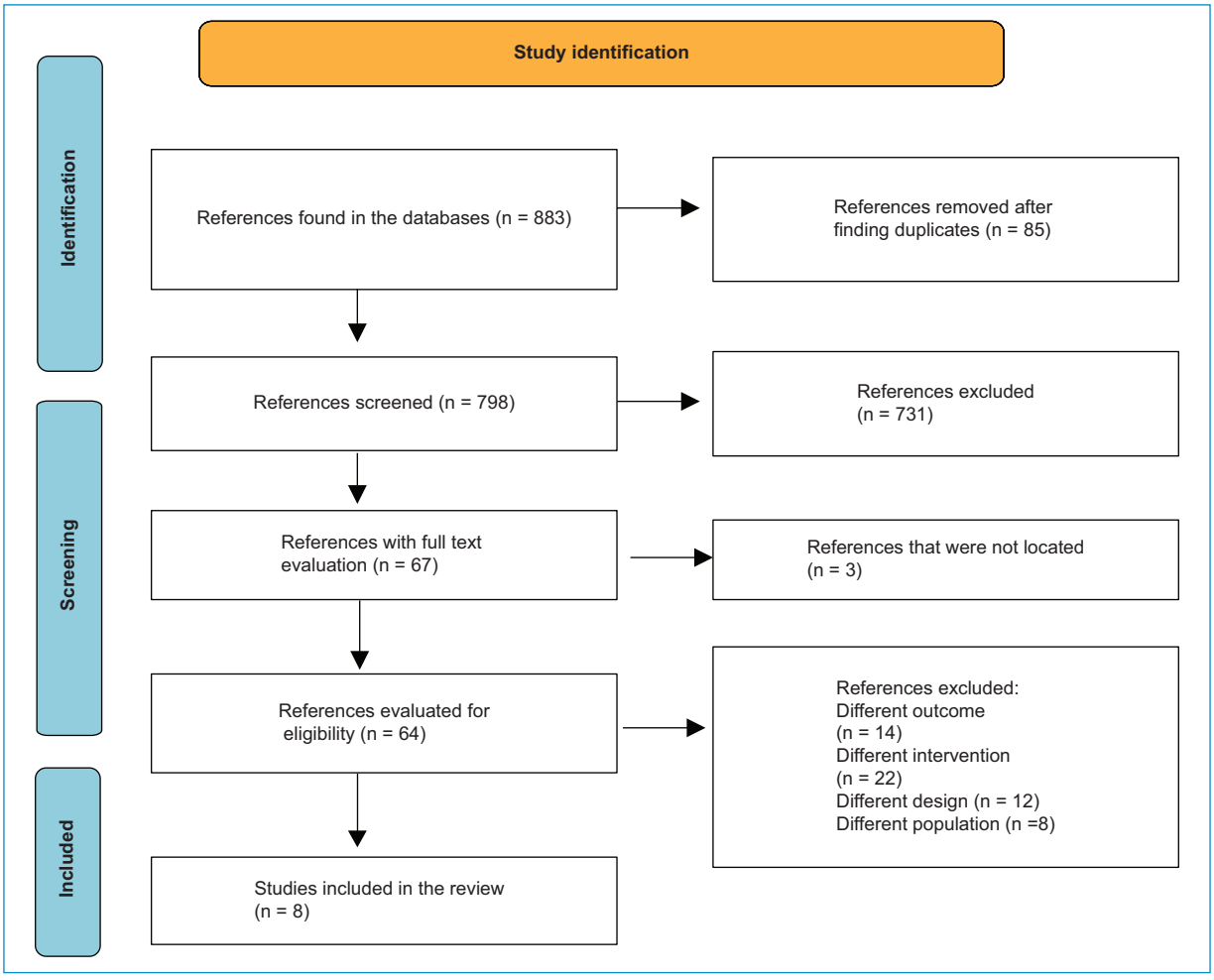

Figure 1. PRISMA flowchart.

The meta-analysis of both major bleeding trials (DerSimonian-Laird random-effects model) yielded a global effect of a 1.28 RR (95% CI: 0.37-4.39), with high heterogeneity (I^2 = 82.2%); on the fixed-effect sensitivity analysis, the RR was 1.41 (95% CI: 0.85-2.35). Figure 2 shows the forest plot with estimates by study and the overall effect rhombus.

Regarding the DOACs, perioperative data from RE-LY and other reports indicate similar major bleeding rates for dabigatran and warfarin when standardized suspension guidelines are followed (≈ 4-5% within 30 days), as well as shorter interruption times with DOACs (median ~ 49 h vs. ~ 114 h with warfarin), with no differences in thromboembolism (< 0.5%)[10,11]. In the cohort study administered by the PAUSE protocol, the "non-bridging" strategy with DOACs was associated with thromboembolism in 0.5% and major bleeding in 1.5%[10,11]. In cardiac device procedures, BRUISE CONTROL II found no differences in pocket hematomas between continuing or briefly suspending DOACs (2.1 vs. 2.1%), with no differences in strokes or other thromboembolic events (0.3 vs. 0.3%)[10,11]. Furthermore, in a non-randomized sub-analysis of the warfarin arm of RE-LY, the patients who received bridging had more events than those who did not (thromboembolism 1.8 vs. 0.3% and bleeding 6.8 vs. 1.6%)[10].

In special contexts, PERIOP2 included heart surgery and mechanical valve cases, with no significant differences between strategies[9]. In device procedures with warfarin, BRUISE CONTROL I showed fewer clinically relevant hematomas when warfarin was not interrupted compared to suspension with bridging[12]. Altogether, the RCT and protocol cohort results support low rates of thromboembolism during brief anticoagulation interruptions and indicate that adding bridging increases the

Table 1. Randomized clinical trials on perioperative anticoagulation management in AF

Study Author	Population (n)	Intervention vs. control	Main outcomes
BRIDGE Douketis, et al.[8]	AF on warfarin, $CHADS_2$ ≥ 1, non-high risk elective surgeries (n = 1,884). Excluded cardiac, neurological, etc., surgeries.	Warfarin suspension with dalteparin (LMWH) bridging therapy vs. warfarin suspension without bridging (placebo).	Arterial thromboembolism at 30 days: 0.4 vs. 0.3% (no difference). Major bleeding: 3.2 vs. 1.3% (increased with bridging, p < 0.01). Minor bleeding: 20.9 vs. 12.0% (increased with bridging, p < 0.01). No differences in mortality (≈ 0.5% in both groups).
PERIOP2 Kovacs Anderson et al.[9]	AF (including valvular AF) or mechanical valve on warfarin, high risk (high CHADS2 or valves) (n = 1,471). Included various major surgeries.	Postoperative dalteparin bridging vs. placebo (both arms suspended warfarin perioperatively).	Thromboembolism at 90 days: 1.0 vs. 1.2% (no difference). Major bleeding: 1.3 vs. 2.0% (no difference). No benefit of bridging in AF subgroups or valves.
BRUISE CONTROL I Birnie et al.[12]	AF or another indication for warfarin with an annual risk of TE ≥ 5%, undergoing pacemaker/ defibrillator implantation (n = 681). Minor but relevant procedure.	Continue warfarin (therapeutic INR during the procedure) vs. suspend warfarin and bridge with heparin (LMWH/IV) perioperatively.	Device pocket hematomas: 3.5 vs. 16.0% (much higher with bridging; p < 0.001). Thromboembolic events: 0 vs. 0.3% (two events in the warfarin group, both with subtherapeutic INRs; no significant difference).
BRUISE CONTROL II Birnie et al.[13]	AF being treated with DOACs (dabigatran, rivaroxaban or apixaban) undergoing cardiac device implantation (n = 662).	Continue DOACs (usual dose up to the day of the procedure) vs. Interrupt DOACs two days before (without heparin bridging; restart later).	Clinically significant hematomas: 2.1 vs. 2.1% (no difference). Thromboembolic events (e.g., stroke): 0.3 vs. 0.3% (no difference).
RE-LY perioperative analysis Healey et al.[10]	Sub-analysis of patients with AF in the RE-LY trial (dabigatran vs. warfarin) who underwent surgery (n ≈ 4,500 procedures). Not a specific RCT, but relevant evidence from large RCTs.	Indirect comparison: standard management with dabigatran (suspended 24-48 h before, depending on risk) vs. management with warfarin (suspended 5 days before, some with bridging) within an original RCT. Also, analysis of patients with and without bridging.	Perioperative bleeding: dabigatran 110 mg 3.8%, dabigatran 150 mg 5.1 vs. warfarina 4.6% (no significant differences). Shorter interruption with DOACs: dabigatran was able to be suspended 49 hours before vs. warfarin 114 hours before surgery without increasing bleeding. Bridging (warfarin): in RE-LY, patients who received heparin bridging had more thromboembolic events (1.8 vs. 0.3%) and more major bleeds (6.8 vs 0.1.6%) than those without bridging.
Ghavami et al.[14]	POAF after CABG (n = 66).	Rivaroxaban (n = 34) vs. warfarin (n = 32, with heparin bridging).	Thromboembolism: 0% in both groups. Major bleeding: 0% in both groups. Minor bleeding: 4 events (3 for rivaroxaban, 1 for warfarin; p = 0.614). Left atrial diameter: greater in patients with persistent AF (40.5 vs. 37.8 mm; p = 0.01).
ARISTOTL Guimarães et al.[16]	AF with bioprosthetic valve (BPV) replacement or prior valve repair (n = 156).	Apixaban (n = 87) vs. warfarin (n = 69).	Thromboembolism (stroke/systemic embolism) 2.77 vs. 1.64% (HR = 1.714; p = 0.53). Total mortality: 4.61 vs. 4.79% (p = 0.98). Major bleeding: 5.87 vs. 6.44% (p = 0.82).
ENGAGE AF-TIMI 48 Douketis et al.[15]	AF on anticoagulation, undergoing surgery or an invasive procedure (n = 7,193).	Warfarin (n = 2,368) vs. high-dose edoxaban (HDER, n = 2,379) vs. low-dose edoxaban (LDER, n = 2,446).	Thromboembolism: no significant differences between the groups, with rates of 0.6-1.1% depending on the anticoagulant interruption (p > 0.5). Major bleeding: 1.0-3.6% depending on the group and strategy (p > 0.1). Mortality: similar between the groups (1.2-1.5%; p = 0.85).

LMWH: low molecular weight heparin; TE: thromboembolism; INR: international normalized ratio.

risk of bleeding without leading to a demonstrable reduction in ischemic events[8-13].

For thromboembolic events at 30 days (0.4 vs. 0.3%; a nonsignificant difference), bridging was more associated with bleeding: major bleeding 3.2 vs. 1.3% (p = 0.005) and minor bleeding (20.9 vs. 12.0%; p < 0.001), with no differences in perioperative mortality (≈ 0.5% in both groups). PERIOP2[9], which included higher risk patients (including those with mechanical valves) and only evaluated postoperative bridging, showed no benefit with bridging: major thromboembolic events at 90 days: 1.0% with bridging vs. 1.2% without (p = 0.64) and major bleeding: 1.3 vs. 2.0% (p = 0.32).

The meta-analysis of both major bleeding trials (DerSimonian-Laird random-effects model) yielded a global effect of a 1.28 RR (95% CI: 0.37-4.39), with high heterogeneity (I^2 = 82.2%); in the fixed-effects sensitivity analysis, the RR was 1.41 (95% CI: 0.85-2.35). Figure 2 shows the forest plot with the estimates by study and the overall effect rhombus.

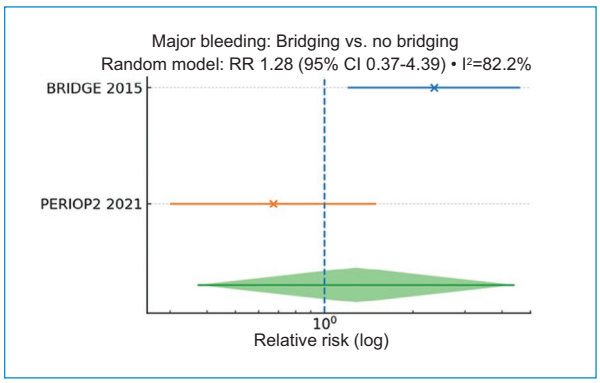

Figure 2. Meta-analysis of major bleeding (bridging vs. no bridging).

Meta-analysis

Two randomized clinical trials were included that compared heparin bridging with no bridging around major surgery (BRIDGE 2015 and PERIOP2 2021), with a total of 1,738 patients in the bridging arm and 1,545 without bridging. For the primary outcome of major bleeding, the meta-analysis with a random-effects model (DerSimonian-Laird) showed a global effect of a 1.28 RR (95% CI: 0.37-4.39), with high heterogeneity (I^2 = 82.2%). In the fixed-effects sensitivity analysis, the result was an RR of 1.41 (95% CI: 0.85-2.35). Figure 2 shows the forest plot with the specific effects per study and the rhombus representing the global effect.

Risk of bias assessment for the included studies

The risk of bias assessment using the ROB-2 tool reveals important nuances in the methodological quality of the studies. As far as randomization, most of the trials (like ARISTOTLE, ENGAGE AF-TIMI 48, PERIOP2, and BRUISE CONTROL I and II) had low risk scores, suggesting that intervention assignment was done properly. However, some concerns were detected in the study by Ghavami et al.[14] and the BRIDGE[8] trial, and the perioperative RE-LY analysis, especially, showed high risk in this domain, which could reflect deficiencies in the generation or concealment of the random sequence.

Regarding deviations from the planned interventions, the evidence is largely favorable, as several studies, such as the one by Ghavami et al.[14], ENGAGE AF-TIMI 48[15], and BRIDGE[8], were classified as low risk. Even so, some trials (ARISTOTLE[16], PERIOP2[9], BRUISE CONTROL II[13] and RE-LY´s perioperative analysis) present certain concerns, which indicates that, while most of the participants adhered to the assigned protocol, there were possible deviations that may have affected the effect estimation.

The handling of missing outcome data was robust, with most of the studies assessed to be low risk, except for ARISTOTLE, in which there were some concerns. This reinforces confidence in the integrity of the data reported in the majority of the studies. Furthermore, outcome measurement was satisfactorily evaluated in almost all studies, with the only exception being the one by Ghavami et al.[14], that showed some concerns in this aspect. This suggests that, in general, consistent and appropriate methods were used to define and measure the outcomes.

Regarding the selection of reported results, most of the included studies were classified as having a low risk of bias. This suggests that the presented findings correspond closely to the previously established protocols, minimizing the possibility of selective data reporting. However, there were some concerns with both Ghavami et al.[14] and ARISTOTLE, which could reflect certain biases in presenting the findings.

Combining all these domains shows that, while studies like ENGAGE AF-TIMI 48 and BRUISE CONTROL I have a low overall risk, other trials – including Ghavami et al.[14], ARISTOTLE, BRIDGE, PERIOP2 and BRUISE CONTROL II – show some concerns that advise a certain degree of caution in interpreting their

findings. RE-LY's perioperative analysis is noteworthy, as it is classified as having high overall risk, meaning that its results should be integrated into the synthesis of the evidence with special consideration of its methodological limitations (Table 2).

Discussion

The findings of this systematic review contribute robust evidence for guiding anticoagulation management in patients with AF undergoing major surgery. In general, the results support a paradigm shift regarding traditional practices: previously, bridging therapy was liberally used due to fear of thromboembolic events, but the clinical trials show that this practice is unnecessary in most cases and may even be harmful. Today, a risk-based individualized strategy is advocated in which most patients (low to moderate risk of stroke) will not receive bridging, and the few extremely high-risk cases could be considered candidates (although even in those cases, the evidence does not show a clear benefit)[17].

The synthesis of the available evidence shows no benefit of bridging in terms of major bleeding and is compatible with a potentially increased risk, although the confidence intervals are wide. The high heterogeneity justifies the use of the random-effects model and appears to be explained by clinical and intervention differences between studies: BRIDGE applied bridging pre and post-operatively in AF, while PERIOP2 only used postoperative bridging and included higher-risk patients (e.g., those with mechanical valves), along with differences in the length of follow-up. The low rate of events limits the accuracy of the estimates and suggests caution in extrapolating to subpopulations with extreme thromboembolic risk, in which the decision should be personalized. Our findings (Fig. 2) support avoiding routine bridging during warfarin interruption for elective surgery and highlight the need for additional trials aimed at very high-risk patients, as well as joint evaluation of thromboembolic and bleeding outcomes for more precise risk-benefit estimates.

The consistency of the results across different scenarios is notable: there was no increase in thrombosis when bridging was omitted for either minor procedures (device implantation)[18], general surgery[13] or high-risk patients[19], but there was increased bleeding when it was used. This gives great confidence in the generalizability of the recommendation to avoid routine bridging. It also confirms that DOACs have simplified perioperative management without sacrificing safety, in line with their proven efficacy in preventing strokes in AF. In fact, an additional benefit of DOACs is convenience for the patients and healthcare system: since INR monitoring or heparin injections are not required, the perioperative burden of care is reduced. Patients can suspend their DOACs shortly before surgery and restart them shortly after, with no need for lengthy hospitalizations for intravenous bridging, except in very select cases.

The methodological quality of the evidence was high in the basic studies. BRIDGE and PERIOP2 are randomized placebo-controlled trials, eliminating performance and detection bias (the patients and evaluators did not know if they were receiving heparin or placebo). Both achieved complete follow-up and intention-to-treat analysis. BRIDGE met its non-inferiority objective and was well designed, although its main limitation is the exclusion of certain very high-risk patients, which has already been discussed. PERIOP2 supplemented this gap, although its nine-year recruitment suggests that clinical practice evolved during the study (for example, after BRIDGE was published in 2015, many clinicians stopped bridging, which made it difficult to enroll patients in a trial where they might receive placebo). Nevertheless, PERIOP2 achieved a robust sample, and its results concur with the rest of the studies.

Although they were more specific (invasive cardiology procedures), the BRUISE CONTROL I and II trials were randomized and contribute valuable practical information. Despite being open, BRUISE CONTROL I had an objective outcome (significant hematomas) evaluated by blinded staff, and the effect size was so large that it is unlikely that any bias would alter the conclusion: in this context, continuing warfarin is clearly superior to suspending it[20]. Its level of evidence is considered high (Level 1b), and, in fact, it rapidly influenced clinical guidelines. BRUISE CONTROL II was stopped early; its statistical power was limited, which is a weakness, but at the same time, it showed that even assuming a possible beta error, any clinically relevant difference was minute. In summary, the overall quality of the evidence is good, with multiple mutually consistent RCTs. This translates into strong recommendations in the current guidelines: for example, in their 2017 clinical pathway, the American College of Cardiology and American Heart Association supported not bridging most patients with nonvalvular AF, based on BRIDGE[8], and recent European guidelines also emphasize the importance of avoiding unnecessary systemic heparins.

Table 2. Risk of bias assessment of the included studies (RoB2)

Domain	Ghavami et al.[14]	ARISTOTLE-Guimarães et al.[16]	ENGAGE AF-TIMI 48 / Douketis et al.[15]	BRIDGE-Douketis et al.[8]	PERIOP2-Kovacs/Anderson et al.[9]	BRUISE CONTROL I-Birnie et al.[12]	BRUISE CONTROL II-Birnie et al.[13]	RE-LY perioperative analysis -Healey/Douketis et al.[10]
Domain 1: Risk of bias arising from the randomization process	Some concerns	Low	Low	Some concerns	Low	Low	Low	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Low	Some concerns	Low	Low	Some concerns	Low	Some concerns	Some concerns
Domain 3: Missing outcome data	Low	Some concerns	Low	Low	Low	Low	Low	Low
Domain 4: Risk of bias in outcome measurement	Some concerns	Low	Low	Low	Low	Low	Low	Low
Domain 5: Risk of bias in selection of the reported result	Some concerns	Some concerns	Low	Low	Low	Low	Low	Low
Overall risk of bias	Some concerns	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns	High

Red: high risk of bias. Yellow: some concerns. Green: low risk of bias.

Considering all major surgeries, this review suggests that the optimal anticoagulant management strategy in AF is one that minimizes exposure to anticoagulation during surgery (to reduce bleeding) but resumes chronic anticoagulation as soon as it is safe (to limit the thrombotic risk window), all without routinely inserting full-dose heparin. In practical terms, suspend warfarin five days before (without heparin bridging in most patients), or suspend DOACs one or two days before (without bridging); perform the surgery, ensure hemostasis, and restart the oral anticoagulant 24 to 72 hours later, depending on the type of surgery and risk of residual bleeding. Use mechanical measures and/or heparin at prophylactic doses for VTE while the anticoagulant is suspended, as this does not entail a high risk of bleeding and does prevent venous complications. In exceptional cases (for example, postponed surgeries in which the wait without anticoagulation would be very long, or in patients with multiple prior thrombotic events), personalize the decision to bridge, but keep in mind that the evidence has shown no net benefit.

In conclusion, optimal perioperative anticoagulation management in patients with AF requires individualized risk-based planning, but with a clear trend toward not routinely using heparin bridging therapy. The priority is to avoid perioperative bleeding (which may be devastating) while reinstating anticoagulation protection as soon as it is safe to do so. Applying these premises, supported by robust evidence, the surgical period can be traversed with minimal risk of both thromboembolism and bleeding, optimizing patient safety. The comparative tables and studies analyzed in this systematic review firmly support these current recommendations at the crossroads of cardiology (AF management) and perioperative medicine.

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that the procedures followed were in line with the ethical norms of the responsible human experimentation

committee and in accord with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the institution's ethics committee.

Confidentiality, informed consent and ethical approval. The study did not involve personal patient information or require ethical approval. The SAGER guidelines did not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that they used artificial intelligence in writing this manuscript (Chat GPT for translating the Spanish abstract to English).

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REVIEW ARTICLE

The role of piRNAs and PIWI-like proteins in the cardiovascular system: a systematic review

El papel de los piARN y las proteínas similares a PIWI en el sistema cardiovascular: una revisión sistemáticac

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Abstract

The role of PIWI-interacting RNAs (piRNAs) and PIWI-like proteins in cardiovascular biology is an area of growing interest. Initially identified for their role in maintaining genome stability in germline cells, piRNAs have now been detected in somatic tissues, including the cardiovascular system. This systematic review synthesizes current knowledge on how piRNAs and their associated PIWI-like proteins influence cardiovascular function and disease. We focus on their involvement in key processes such as gene regulation, epigenetic modifications, and cellular stress responses, which are crucial in conditions like atherosclerosis, myocardial infarction, and heart failure, among others. Evidence from experimental and clinical studies suggests that piRNAs could serve as novel biomarkers or therapeutic targets in cardiovascular medicine. However, the field is still in its early stages and much remains unknown about the specific mechanisms through which piRNAs and PIWI-like proteins contribute to cardiovascular pathology. Future research should prioritize understanding these mechanisms and exploring the translational potential of targeting piRNAs in cardiovascular disease. This review underscores the promise of piRNAs in advancing our understanding and treatment of cardiovascular conditions.

Keywords: *piRNA. PIWI-like proteins. Cardiovascular diseases. Gene regulation. Epigenetics.*

Resumen

El papel de los ARN que interactúan con PIWI (piRNA) y las proteínas similares a PIWI en la biología cardiovascular es un área de creciente interés. Inicialmente identificados por su papel en el mantenimiento de la estabilidad del genoma en las células de la línea germinal, actualmente se han detectado piRNA en tejidos somáticos, incluido el sistema cardiovascular. Esta revisión sistemática resume el conocimiento actual sobre cómo los piRNA y sus proteínas similares a PIWI asociadas influyen en la función y la enfermedad cardiovascular. Nos centramos en su implicación en procesos clave como la regulación genética, las modificaciones epigenéticas y las respuestas al estrés celular, que son cruciales en enfermedades como la aterosclerosis, el infarto de miocardio, la insuficiencia cardíaca, entre otras. La evidencia de estudios experimentales y clínicos sugiere que los piRNA podrían servir como nuevos biomarcadores u objetivos terapéuticos en la medicina cardiovascular. Sin embargo, el campo aún se encuentra en sus primeras etapas y aún se desconoce mucho sobre los mecanismos específicos a través de los cuales los piRNA y las proteínas similares a PIWI contribuyen a la patología cardiovascular. Las

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Date of reception: 07-09-2024
Date of acceptance: 15-12-2025
DOI: 10.24875/RCCARE.M25000201
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):41-54
www.rccardiologia.com

investigaciones futuras deberían priorizar la comprensión de estos mecanismos y la exploración del potencial traslacional de atacar los piARN en las enfermedades cardiovasculares. Esta revisión subraya la promesa de los piRNA para mejorar nuestra comprensión y tratamiento de las enfermedades cardiovasculares.

Palabras clave: *piRNA. Proteínas similares a PIWI. Enfermedades cardiovasculares. Regulación génica. Epigenética.*

Introduction

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, driven by complex pathophysiological processes that involve intricate molecular interactions and cellular responses. Among these processes, the regulation of gene expression by small non-coding RNAs has emerged as a critical area of investigation. PIWI-interacting RNAs (piRNAs), a class of small non-coding RNAs traditionally associated with gene silencing and transposon control, have recently been implicated in various aspects of cardiac pathology[1-6].

This review aims to consolidate current understanding of the role of piRNAs in cardiac diseases, with a focus on their contributions to myocardial ischemia-reperfusion injury, diabetic cardiomyopathy (DCM), and *Trypanosoma cruzi* (TC) infection. By examining recent findings and identifying gaps in knowledge, we aim to provide a comprehensive overview of how piRNAs influence cardiac disease and their potential as biomarkers and therapeutic targets[7-10].

Methods

This systematic review was registered with PROSPERO (registration number: CRD42024581269). The reporting of this review followed the guidelines set by the 2020 PRISMA Statement[11,12] (Fig. 1).

Literature search strategy

To systematically evaluate the role of piRNA and PIWI-like proteins in the cardiovascular system, a comprehensive literature search was conducted using the PubMed database.

Search terms, inclusion and exclusion criteria

The search terms included: ((piRNA[Title/Abstract]) OR ("PIWI-like protein"[Title/Abstract]) OR ("PIWI protein"[Title/Abstract])) AND ((Heart) OR (Heart disease) OR (Cardiac disease) OR (Cardiovascular) OR (Cardiovascular system)). Studies were selected based on the following inclusion criteria:

- Study type: original research articles, clinical trials, and systematic reviews.
- Population: studies involving human subjects or relevant animal models related to the cardiovascular system.
- Intervention/focus: research on piRNAs, PIWI-like proteins, or their related pathways in the cardiovascular system.
- Language: articles published in English.
- Outcome: studies that explored the role, function, or mechanism of piRNAs and PIWI-like proteins in the cardiovascular system.

Exclusion criteria

- Study type: case reports, editorials, letters to the editor, and non-peer-reviewed articles.
- Population: studies focusing exclusively on non-cardiovascular systems.
- Focus: research not addressing the role or function of piRNAs or PIWI-like proteins in the cardiovascular system.
- Language: articles not available in English.
- Outcome: studies that did not provide specific insights into the role of piRNAs or PIWI-like proteins in the cardiovascular system.

Data extraction and management

Data extracted from the selected studies included:

- Study characteristics: authors, publication year, study design, sample size, and patient demographics.
- piRNA/PIWI-like protein

Data extraction was performed by two independent reviewers to ensure accuracy and minimize bias. Discrepancies were resolved through discussion or consultation with a third reviewer.

Quality assessment

The methodological quality of the included studies was evaluated using appropriate tools based on study design. Non-randomized studies were assessed using the Newcastle-Ottawa Scale (Table 1)[13]. Quality

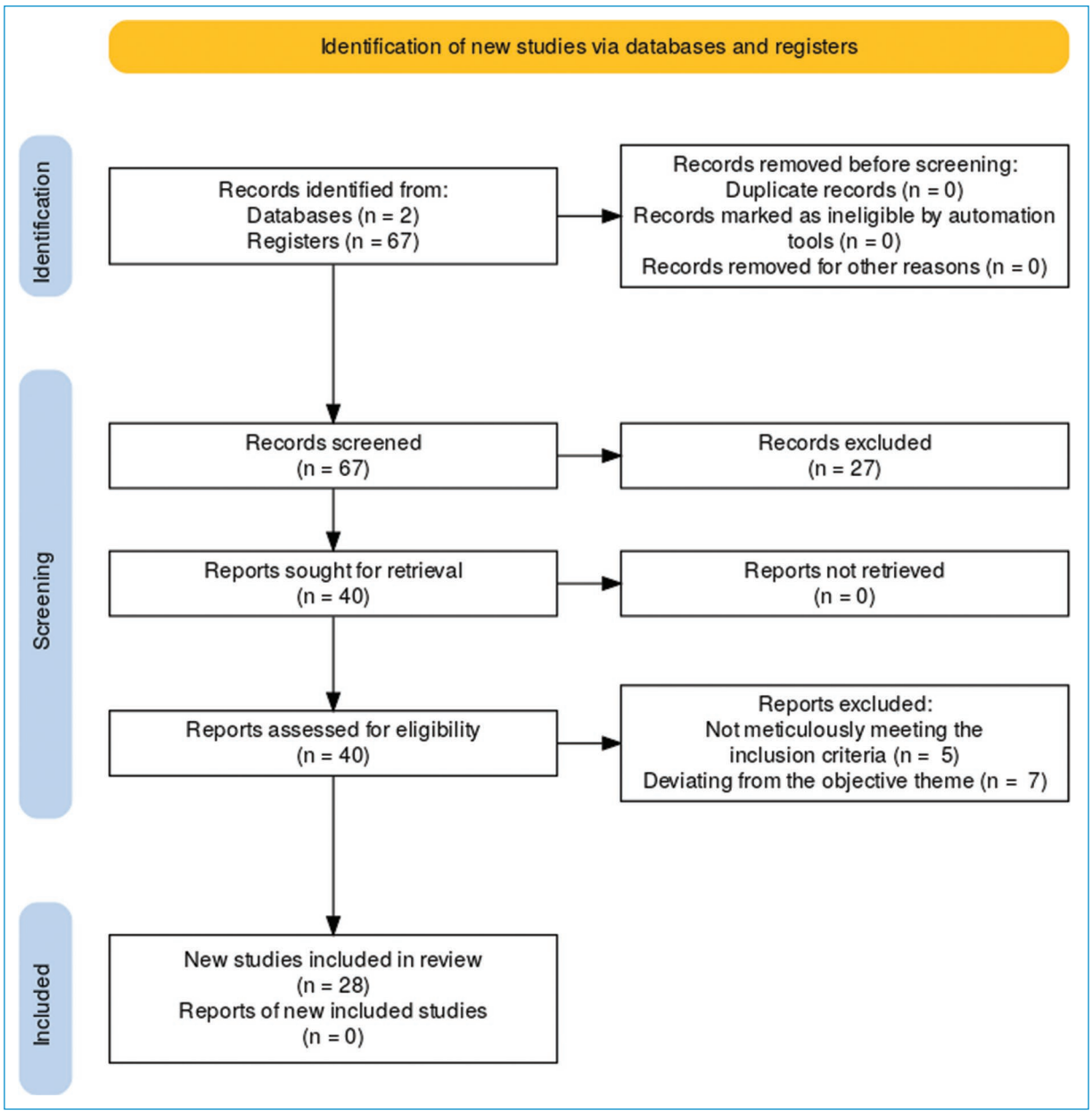

Figure 1. PRISMA flow chart.

assessment aimed to evaluate the risk of bias, study validity, and overall reliability of the findings.

Data synthesis

A narrative synthesis was conducted to summarize the findings of the reviewed studies.

Results

A total of 67 studies were initially identified through a PubMed and ScienceDirect search. After applying the inclusion and exclusion criteria, 40 studies were selected for full-text review. Out of these, 28 studies met the criteria for inclusion in the final analysis (Table 2).

piRNA expression during cardiac differentiation

La Greca et al.[14] investigated the expression of piRNAs in H9 pluripotent stem cells, as well as the expression of piRNAs in cardiac progenitor cells and cardiomyocytes.

Table 1. Newcastle-Ottawa Scale of the reviewed studies

Author	Year	Selection			Comparability			Exposure			Total quality score
		The case definition is adequate with independent validation	Consecutive or obviously representative series of cases	Community controls	Controls with no history of disease (end point)	Cases and controls with comparable ages	Cases and controls with comparability on any other factors	Ascertainment of exposure using secure records (e.g. surgical records) or structured interviews with blinding to case/control statuses	Ascertainment of exposure using the same method for cases and controls	Ascertainment of exposure with non-response rate for both groups	
Rajan KS et al.	2014	*	*	*		*	*	*	*	*	8
Vella S et al.	2016	*	*	*	*		*	*	*	*	8
Rajan KS et al.	2016	*	*	*	*	*	*	*	*		8
Yang J et al.	2018	*	*	*	*	*	*	*	*	*	9
La Greca A et al.	2020	*	*	*	*		*	*		*	7
Gao XQ et al.	2020	*	*	*	*	*	*	*	*		8
Rayford KJ et al.	2020	*	*	*		*	*	*		*	7
Li M et al.	2021	*	*	*	*	*	*	*	*	*	9
Bai XF et al.	2021	*	*	*	*	*	*	*	*	*	9
Chen W et al.	2021	*	*	*	*	*	*	*	*		8
Zhou Y et al.	2021	*		*	*	*	*	*		*	7
Cheang I et al.	2021	*	*	*	*	*	*	*	*	*	9
Wang K et al.	2022	*	*	*	*	*	*	*	*	*	9
Zhong N et al.	2022	*	*		*	*	*	*	*	*	8
Cooley A et al.	2022	*	*	*	*	*	*		*	*	8
Wang Y et al.	2023	*	*	*	*		*	*	*	*	8
Rayford KJ et al.	2023	*	*	*	*	*	*	*	*		8
Zhang K et al.	2023	*	*	*		*	*	*	*	*	8

(*Continues*)

Table 1. Newcastle-Ottawa Scale of the reviewed studies *(continued)*

Author	Year	Selection			Comparability			Exposure			Total quality score
		The case definition is adequate with independent validation	Consecutive or obviously representative series of cases	Community controls	Controls with no history of disease (end point)	Cases and controls with comparable ages	Cases and controls with comparability on any other factors	Ascertainment of exposure using secure records (e.g. surgical records) or structured interviews with blinding to case/control statuses	Ascertainment of exposure using the same method for cases and controls	Ascertainment of exposure with non-response rate for both groups	
Li M et al.	2023	*	*	*	*	*		*	*	*	8
Aharon-Yariv A et al.	2023	*	*	*		*	*	*	*	*	8
Wang K et al.	2023	*	*	*	*	*	*	*	*		8
Chi H et al.	2024	*	*			*		*	*	*	6
Chen B et al.	2024	*	*		*	*	*	*	*	*	8
Han D et al.	2024	*		*	*	*	*	*	*	*	8
Liu Z et al.	2024	*	*	*	*	*	*	*	*	*	9
Liu Y et al.	2024	*	*	*	*		*			*	6
Jiao A et al.	2024	*	*	*	*	*	*	*	*		8
Lv L et al.	2024	*	*	*	*	*	*	*	*	*	9

Table 2. Characteristics of the reviewed studies

Author	Year	Condition (s)	piRNA/PIWI-L protein	Pathway
Rajan KS et al.	2014	NCP, HY, CS	piRNA	AKT
Vella S et al.	2016	CPC	piRNA	AKT
Rajan KS et al.	2016	HY	piRNA	NA
Yang J et al.	2018	HF	has-piR-020009/has-piR-006426	NA
La Greca A et al.	2020	CPC	piRNA	NA
Gao XQ et al.	2020	HY	PIWIL4	METTL3-mediated N (6)-methyladenosine (m (6) A) methylation
Rayford KJ et al.	2020	TC	piRNA	NFATC2, FOS, TGF-β1
Li M et al.	2021	CVD	piRNA	NA
Bai XF et al.	2021	IRI	piRNA	NA
Chen W et al.	2021	AS	piR-hsa-32167/piR-hsa-116589	NA
Zhou Y et al.	2021	CPC	piRNA	NA
Cheang I et al.	2021	CVS	piRNA	NA
Wang K et al.	2022	IRI	HAAPIR	HAAPIR-NAT10-TFEC-BIK
Zhong N et al.	2022	HF	piRNA-6426	DNMT3B-mediated SOAT1 methylation
Cooley A et al.	2022	TC	piR_004506/piR_001356/piR_017716	IL-6
Wang Y et al.	2023	AS	PiRNA DQ614630	LDL
Rayford KJ et al.	2023	TC	piRNA	SMAD2, EGR1, ICAM1, CX3CL1, and CXCR2
Zhang K et al.	2023	CVD	piRNA	NA
Li M et al.	2023	AD	piRNA-823	H3K9ac/H3K27ac
Aharon-Yariv A et al.	2023	NCP	piRNA	NA
Wang K et al.	2023	IRI	piRNA	HNEAP-DNMT1-ATF7-CHMP2A
Chi H et al.	2024	IRI	piR-000699	SLC39A14
Chen B et al.	2024	HF	piRNA-000691	Pi3k-AKT-mTOR
Han D et al.	2024	AVD	piRNA	N (6)-methyladenosine reader IGF2BP1
Liu Z et al.	2024	CVD	piRNA	NA
Liu Y et al.	2024	AD	HAAPIR	MMP9 and Mef2D
Jiao A et al.	2024	DCM	piR112710	Txnip/NLRP3
Lv L et al.	2024	CF	piRNA	TGF-β1/SMAD3

NA: not available; piRNA: PIWI interacting RNA; NCP: neonatal cellular proliferation; HY: hypertrophy; CS: cellular survival; CPC: cardiac progenitor cells; HF: heart failure; TC: *Trypanosoma cruzi;* CVD: cardiovascular disease; IRI: ischemia-reperfusion injury; AS: atherosclerosis; HAAPIR: heart-apoptosis-associated piRNA; AD: aortic dissection; AVD: aortic valve disease; HAAPIR: antagomir targeting heart-apoptosis-associated piRNA; DCM: diabetic cardiomyopathy; CF: cardiac fibrosis.

piRNA SIGNATURES IN CARDIAC PROGENITOR CELLS

Vella et al.[15] generated the expression categorization of 15311 piRNAs in cardiospheres, cardiosphere-derived cells and cardiac fibroblasts. One of the main findings of the study was a significant difference in piRNA expression depending on the tissue studied. A total of 641 piRNAs were upregulated and 1,301 were downregulated in cardiospheres, compared to cardiosphere-derived cells. In cardiospheres, 255

piRNAs were upregulated and 708 were downregulated. In cardiosphere-derived cells, 181 piRNAs were overexpressed and 129 were underexpressed. Bioinformatics analysis underscored that the deregulated piRNAs were mostly found on a few chromosomes, pointing to a genomic clustering pattern. Furthermore, most of the piRNAs upregulated targeted transposons (particularly LINE-1 elements), as confirmed by qRT-PCR. These processes were associated with the activation of the AKT signaling pathway, which supports cardiac regeneration. They were differentiated into mesodermal progenitor cells and cardiomyocytes, identifying 447 piRNA transcripts. Of those identified, 241 were found in pluripotent cells, 218 in mesodermal cells, and 171 in cardiac cells. Most of these piRNAs originated from the sense strand of protein-coding genes and long non-coding RNAs at all stages of differentiation, although no evidence of ping-pong amplification was observed. The genes hosting piARNs in our cardiac samples were associated with critical cardiac functions, such as contraction and muscle development. These findings suggest that piARNs play an important role in fine-tuning gene expression involved in the different stages of stem cell differentiation into cardiomyocytes[14].

Role of the piRNA pathway in cardiovascular function

Zhou et al.[16] reviewed the role of piRNAs in cardiovascular system (CVS). Previously known for their role in silencing transposable elements in germ cells, piRNAs have also been implicated in somatic functions. New evidence suggests and highlights piRNA pathways and their crucial role in the development and maintenance of normal CVS functions.

piRNA expression in cardiac hypertrophy and heart failure (Fig. 2)

piRNA expression in cardiac hypertrophy

Rajan et al.[17] performed a study of piRNA expression and its relationship to cardiac hypertrophy using *in vivo* and *in vitro* models which showed altered expression. This study was validated by qPCR and RNA immunoprecipitation. Notably, these piRNAs were predicted to target various retrotransposons and mRNAs within the rat genome. The study also identified specific piRNAs in the serum of myocardial infarction patients, indicating their potential as diagnostic biomarkers for cardiac conditions.

Exosomal piRNA profiling in heart failure

Yang et al.[18] explored the exosomal expression profiles of piRNAs to assess the difference in expression between heart failure patients and healthy subjects. Exosomes were isolated from serum samples, and RNA sequencing revealed that 585 piRNAs were upregulated and 4,623 downregulated in heart failure patients. It is noteworthy that has-piR-020009 and has-piR-006426 were among the most downregulated. This study suggests that serum exosome-derived piRNAs could serve as valuable biomarkers for heart failure and highlights the potential of exosome-based piRNA sequencing for clinical diagnostics.

CHAPIR and cardiac hypertrophy

Gao et al.[19] identified a cardiac hypertrophy-associated piRNA (CHAPIR). This regulates the pathological hypertrophy of cardiomyocytes by modulating METTL3-dependent N(6)-methyladenosine methylation of Parp10 mRNA. Deletion of CHAPIR mitigated cardiac hypertrophy and restored cardiac function in pressure-overloaded mice, while CHAPIR mimic administration exacerbated hypertrophy. CHAPIR-PIWIL4 complexes interact with METTL3 to inhibit m(6)A methylation of Parp10 mRNA, leading to increased PARP10 expression and subsequent cardiac remodeling.

piRNA-6426 and heart failure

Zhong et al.[20] investigated the role of piRNA-6426 in heart failure, focusing on the impact of DNMT3B-mediated methylation of SOAT1. The authors found reduced levels of piRNA-6426 in patients with heart failure. Functional studies using lentiviral vectors demonstrated that overexpression of piRNA-6426 increased DNMT3B binding to the SOAT1 promoter, inhibiting SOAT1 expression and ameliorating hypoxia-induced cardiomyocyte dysfunction. Conversely, downregulation of piRNA-6426 exacerbated heart failure symptoms.

Targeting CFRPi for cardiac fibrosis

Chen et al.[21] identified a cardiac-specific piRNA, CFRPi, that is highly expressed in cardiac fibroblasts and upregulated in heart failure models. CFRPi promotes cardiac fibrosis, and its knockdown alleviated fibrosis and improved cardiac function in pressure-overloaded mice.

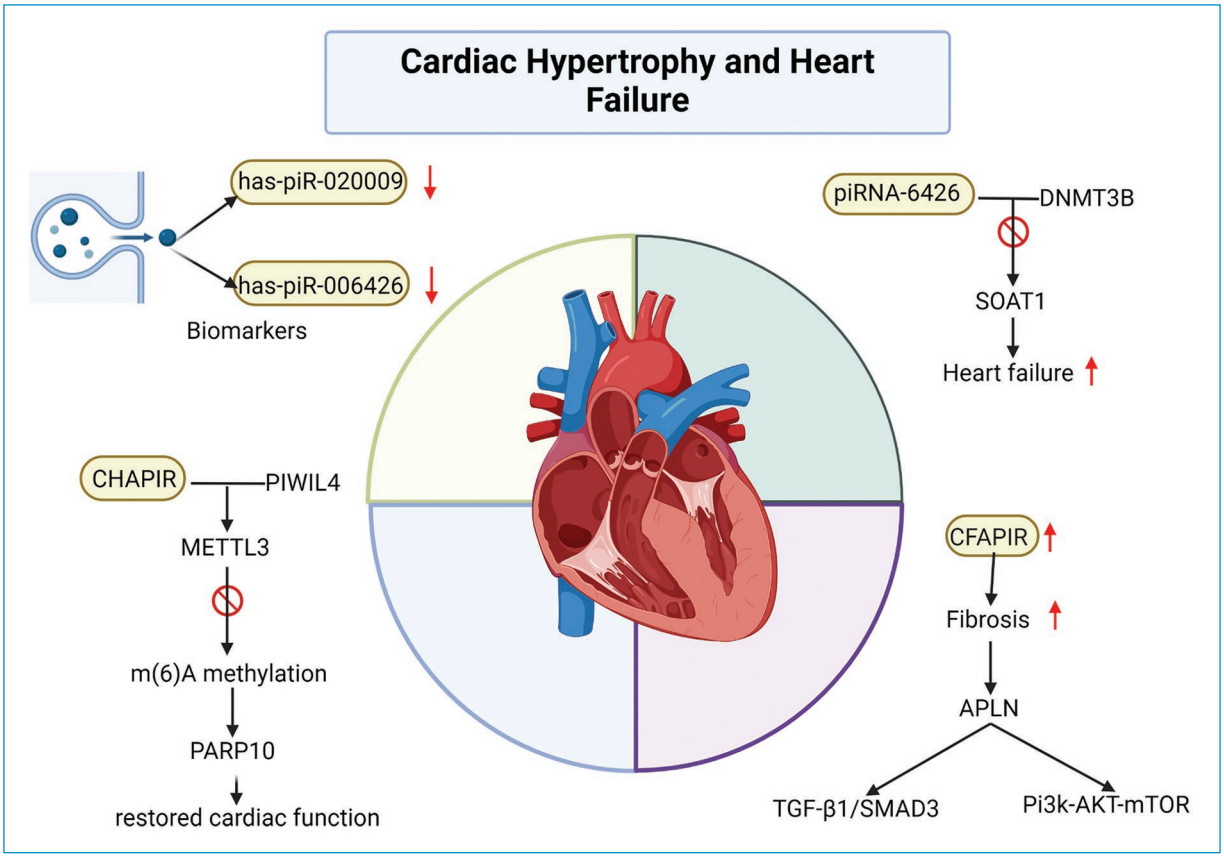

Figure 2. Mechanisms that increase or decrease hypertrophy and heart failure.

Mechanistically, CFRPi was shown to inhibit the protective peptide APLN and affect the Pi3k-AKT-mTOR signaling pathway. Targeting CFRPi thus holds promise for therapeutic strategies aimed at reducing cardiac fibrosis and improving heart failure outcomes.

CFAPIR and cardiac fibrosis

Lv et al.[22] identified CFAPIR, a piRNA associated with cardiac fibrosis. Overexpression of CFAPIR was found to reverse fibrosis in both *in vivo* and *in vitro* models. CFAPIR was shown to interact with muscleblind-like protein 2 (MBNL2) and the cyclin-dependent kinase inhibitor P21, modulating the TGF-β1/SMAD3 signaling pathway. This study suggests that CFAPIR could serve as a novel target for therapeutic intervention in cardiac fibrosis, potentially improving outcomes in heart failure patients.

piRNA expression in myocardial ischemia-reperfusion injury

piRNA roles in myocardial ischemia-reperfusion injury

Bai et al.[23] reviewed the involvement of noncoding RNAs (ncRNAs) including long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), piRNAs, and microRNAs (miRNAs) in myocardial ischemia-reperfusion injury (MIRI). The review elaborated on the critical roles of these ncRNAs in the pathophysiology of MIRI and summarized studies focusing on lncRNA-miRNA-mRNA, lncRNA-transcription factor-mRNA, and circRNA-miRNA-mRNA interactions. The research provides a comprehensive perspective on ncRNAs and their associated networks in MIRI, offering a theoretical premise for ncRNA-based gene therapies for treating MIRI.

piRNA regulation of cardiomyocyte apoptosis

Wang et al.[24] identified a heart-apoptosis-associated piRNA (HAAPIR) that regulates cardiomyocyte apoptosis by enhancing N-acetyltransferase 10 (NAT10)-mediated N4-acetylcytidine (ac4C) acetylation of transcription factor EC (Tfec) mRNA. Deletion of HAAPIR improved cardiac function and reduced myocardial infarction severity in mice. The study demonstrated that piRNA-mediated acetylation is involved in cardiomyocyte apoptosis regulation, suggesting that the HAAPIR-NAT10-TFEC-BIK signaling axis could be a potential target for reducing myocardial injury in ischemic heart disease.

piRNA regulation of necroptosis in cardiomyocytes

Wang et al.[25] discovered a piRNA associated with necroptosis in the heart, termed HNEAP, which regulates cardiomyocyte necroptosis by targeting DNA methyltransferase 1 (DNMT1)-mediated 5-methylcytosine (m5C) methylation of activating transcription factor 7 (Atf7) mRNA. Elevated HNEAP levels were found in cardiomyocytes subjected to hypoxia/reoxygenation and in ischemia-reperfusion-injured mouse hearts. Loss of HNEAP mitigated cardiomyocyte necroptosis and improved cardiac function. The findings highlight the role of piRNA-mediated m5C methylation in necroptosis regulation and propose the HNEAP-DNMT1-ATF7-CHMP2A axis as a potential therapeutic target for ischemic heart disease.

piRNA regulation of ferroptosis in aging myocardial ischemia-reperfusion injury

Chi et al.[26] investigated how the piRNA piR-000699 regulates ferroptosis in myocardial ischemia-reperfusion injury with aging. Using aging rat models and cardiomyocyte lines, the study found that piR-000699 is upregulated following hypoxia/reoxygenation. Bioinformatics analysis identified SLC39A14 as a target gene of piR-000699. The results underscore the role of ferroptosis in myocardial injury and suggest that piR-000699 regulates SLC39A14 in aging cardiomyocytes under hypoxic conditions, offering insights into potential therapeutic approaches for age-related heart disease.

piRNA expression in atherosclerosis and aortic dissection

Extracellular vesicle YRNA in atherosclerosis

Chen et al.[27] investigated the roles of extracellular vesicle (EV)-enclosed YRNAs and their fragments, YsRNAs, in atherosclerosis. Their study highlights that YsRNA-5p transcripts contribute to foam cell apoptosis and inflammatory responses by binding to Ro60. YRNAs can interact with several proteins, such as nucleolin and Ro60, and are detectable in blood plasma. Notably, Y4sRNA-3p and Y5sRNA-3p (piR-hsa-32167 and piR-hsa-116589) are implicated in atherosclerosis. The review emphasizes the potential of YsRNAs as biomarkers for atherosclerosis and suggests that gut microbiota may influence atherosclerosis progression through these YRNAs and YsRNAs (Fig. 3).

Ox-LDL

Wang et al.[24] analyzed the impact of oxidized low-density lipoprotein (Ox-LDL) on small non-coding RNAs (sncRNAs) in rat endothelial cells. Small RNA sequencing revealed 42 upregulated and 38 downregulated piRNAs, with piRNA DQ614630 promoting endothelial cell apoptosis. Additionally, the authors noted alterations in snoRNAs, snRNAs, miRNAs, and repeat-associated RNAs. This study provides new insights into the role of sncRNAs in endothelial cell injury and atherosclerosis, suggesting potential diagnostic and therapeutic markers.

piRNA-823 is a therapeutic target in aortic dissection (AD)

Li et al.[28] identified piRNA-823 (piR-823) as a key regulator in AD. Elevated levels of piR-823 were found in AD patients. Functional assays demonstrated that piR-823 promotes vascular smooth muscle cell proliferation, migration, and phenotypic transformation, partly by suppressing histone deacetylase 1 (HDAC1) and regulating histone acetylation. In murine models, piR-823 antagomir reduced AD pathogenesis through vascular remodeling, positioning piR-823 as a potential therapeutic target for AD.

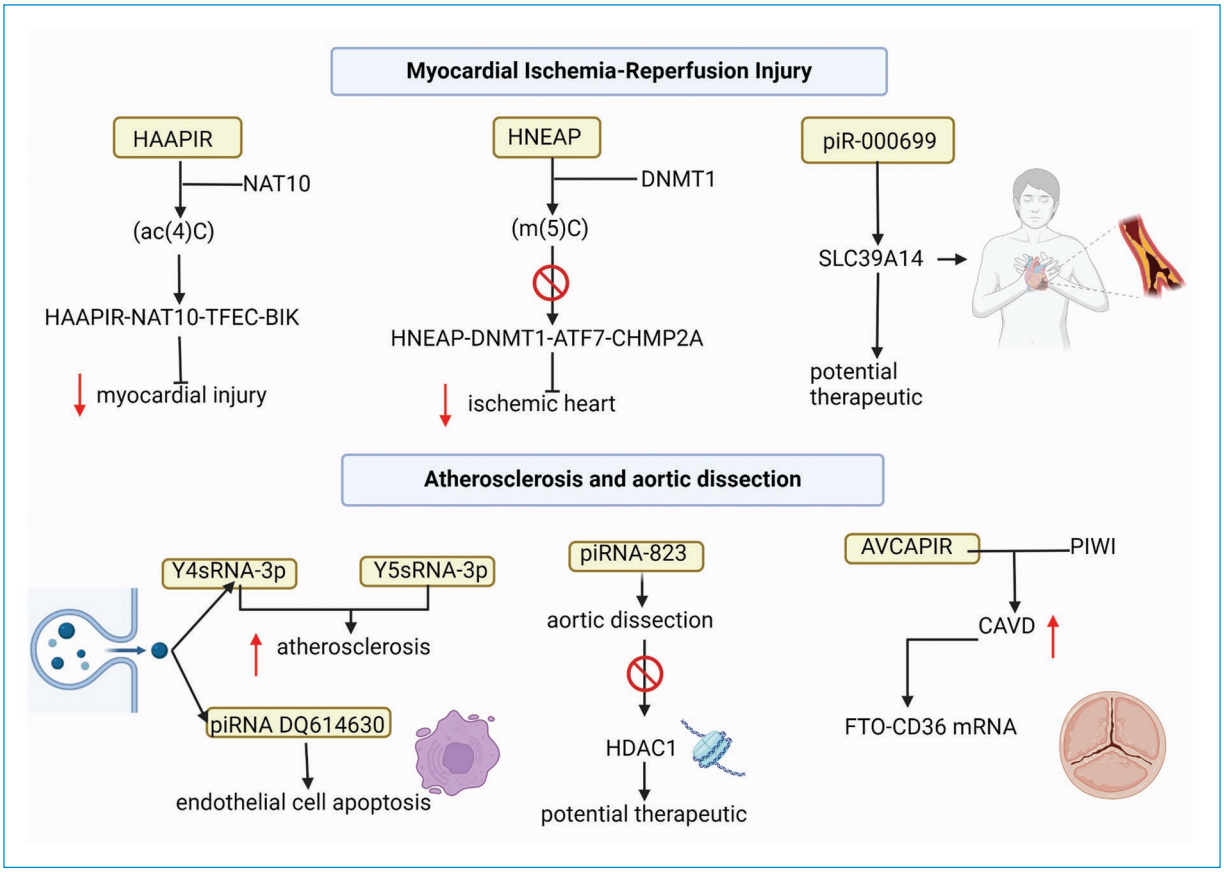

Figure 3. Potential ncRNAs and pathways as therapeutic targets to reduce cardiac ischemia and piRNAs that have been found to increase atherosclerosis.

AVCAPIR

Han et al.[29] discovered AVCAPIR, a PIWI-interacting RNA associated with calcific aortic valve disease (CAVD). AVCAPIR was found to enhance valvular calcification and accelerate CAVD progression by interacting with FTO and stabilizing CD36 mRNA. AVCAPIR deletion improved valve function and reduced calcification in murine models. The study suggests that AVCAPIR could serve as a diagnostic marker and therapeutic target for CAVD through its RNA epigenetic mechanisms.

Oral PIWI-interacting RNA delivery mediated by green tea-derived exosome-like nanovesicles (PELNs) for AD treatment

Liu et al.[30] explored the use of green tea-derived PELNs for delivering an antagomir targeting HAAPIR in AD. The study demonstrated that the HAAPIR antagomir encapsulated in PELNs effectively regulated vascular remodeling, reducing AD incidence and improving survival in mice. This approach shows promise for persistent AD prevention and treatment, highlighting the potential of nanovesicle-encapsulated nucleic acids in cardiovascular disease management.

piRNA dysregulation in TC infection

piRNA modulation by TC in cardiac myocytes

Rayford et al.[31] investigated the impact of TC on piRNA expression in primary human cardiac myocytes. Their study utilized RNA sequencing to uncover significant changes in piRNA profiles during the early phase of infection. A total of 217 unique piRNAs were identified as differentially expressed, with potential regulatory effects on genes like NFATC2, FOS, and TGF-β1. These findings provide novel insights into how piRNAs contribute to the pathogenesis of TC infection and highlight their potential as biomarkers and therapeutic targets.

piRNA dysregulation targeting IL-6 signaling in cardiac fibroblasts

Cooley et al.[32] focused on the dysregulation of piRNAs in primary human cardiac fibroblasts during early TC infection. The study used computational predictions to identify piRNAs targeting IL6 and SOCS3 genes. Validation of these piRNAs showed an inverse relationship with their target gene expression, suggesting a role for piRNAs in modulating IL-6 signaling pathways. This research underscores the potential of piRNAs as therapeutic targets for mitigating TC -induced cardiomyopathies.

Early piRNA expression changes in cardiac fibroblasts during TC infection

Rayford et al.[33] explored piRNA expression alterations in primary human cardiac fibroblasts during the early phase of TC infection. RNA sequencing revealed 441 unique piRNAs with significant differential expression. An *in silico* analysis indicated that these piRNAs might regulate key genes involved in infection and cardiomyopathy, including SMAD2, EGR1, and CXCR2. This study provides a deeper understanding of piRNA-mediated gene regulation in the context of infectious diseases and their potential as biomarkers and therapeutic targets.

piR112710 attenuates DCM

Jiao et al.[34] explored the role of piRNAs in DCM, focusing on piR112710, a piRNA associated with pyroptosis. Their study investigated how piR112710 impacts cardiac remodeling by targeting the Txnip/NLRP3 signaling axis, which is involved in inflammasome activation and mitochondrial dysfunction. Using db/db mice and neonatal cardiomyocyte models exposed to high glucose and palmitate, they found that piR112710 significantly improved cardiac function, reduced fibrosis, and decreased levels of inflammatory and pyroptosis-associated proteins. Additionally, piR112710 supplementation reversed adverse effects induced by high glucose and palmitate. The cardioprotective effects of piR112710 were linked to its ability to eliminate reactive oxygen species and inhibit the Txnip/NLRP3 signaling pathway, suggesting its potential as a therapeutic target for reducing myocardial injury in DCM (Fig. 4).

Discussion

Recent research has increasingly highlighted piRNAs as crucial players in several cardiac diseases, revealing their important roles in MIRI, CT infection, and DCM. These studies highlight the potential of piRNAs as biomarkers and therapeutic targets.

For MIRI, Bai et al.[35] provide a comprehensive review of non-coding RNAs, including piRNAs, and their involvement in this condition; piRNAs, along with long non-coding RNAs, circular RNAs, and microRNAs, are integral to the pathophysiology of MIRI. The review underscores how these RNAs interact through complex networks involving lncRNA-miRNA-mRNA, lncRNA-transcription factor-mRNA, and circRNA-miRNA-mRNA. This intrinsic interaction suggests that piRNAs could be crucial in modulating gene expression and cellular responses during cardiac injury, opening new avenues for therapeutic intervention[35-37].

Studies focusing on TC, the causative agent of Chagas disease, reveal intriguing insights into piRNA dynamics in response to infection. Rayford et al.[38] and Cooley et al.[39] have documented how TC infection leads to significant alterations in piRNA expression in primary human cardiac myocytes and fibroblasts. Their findings suggest that these alterations are not simply byproducts of infection but actively contribute to the disease process by modulating inflammatory responses and gene expression. The discovery of 217 unique piRNAs significantly differentially expressed in response to TC infection, some of which target genes crucial to the infection process, points to their potential utility in understanding and monitoring Chagas disease progression[38,39].

In DCM, Jiao et al.[40] have explored the role of piR112710, identifying it as a key modulator of cardiac remodeling. Their study demonstrates that piR112710 alleviates cardiac dysfunction in diabetic mice by targeting the Txnip/NLRP3 signaling axis, which is pivotal in regulating pyroptosis and mitochondrial dysfunction. The cardioprotective effects observed with piR112710 supplementation, including improved cardiac function and reduced inflammation, suggest that this piRNA could be a valuable therapeutic agent for DCM[40,41].

The accumulated insights from these studies underscore the importance of piRNAs in cardiac diseases and their potential as biomarkers and therapeutic targets. The significant dysregulation of piRNAs observed in response to infectious and degenerative cardiac conditions points to their role in modulating disease pathways and cellular responses. The exact mechanisms through which piRNAs exert their effects are still not fully understood, and further research is needed to unravel these molecular interactions. Furthermore, the translation of these findings into clinical practice requires validation through rigorous studies to establish the efficacy and safety of piRNA-based therapies[39,40].

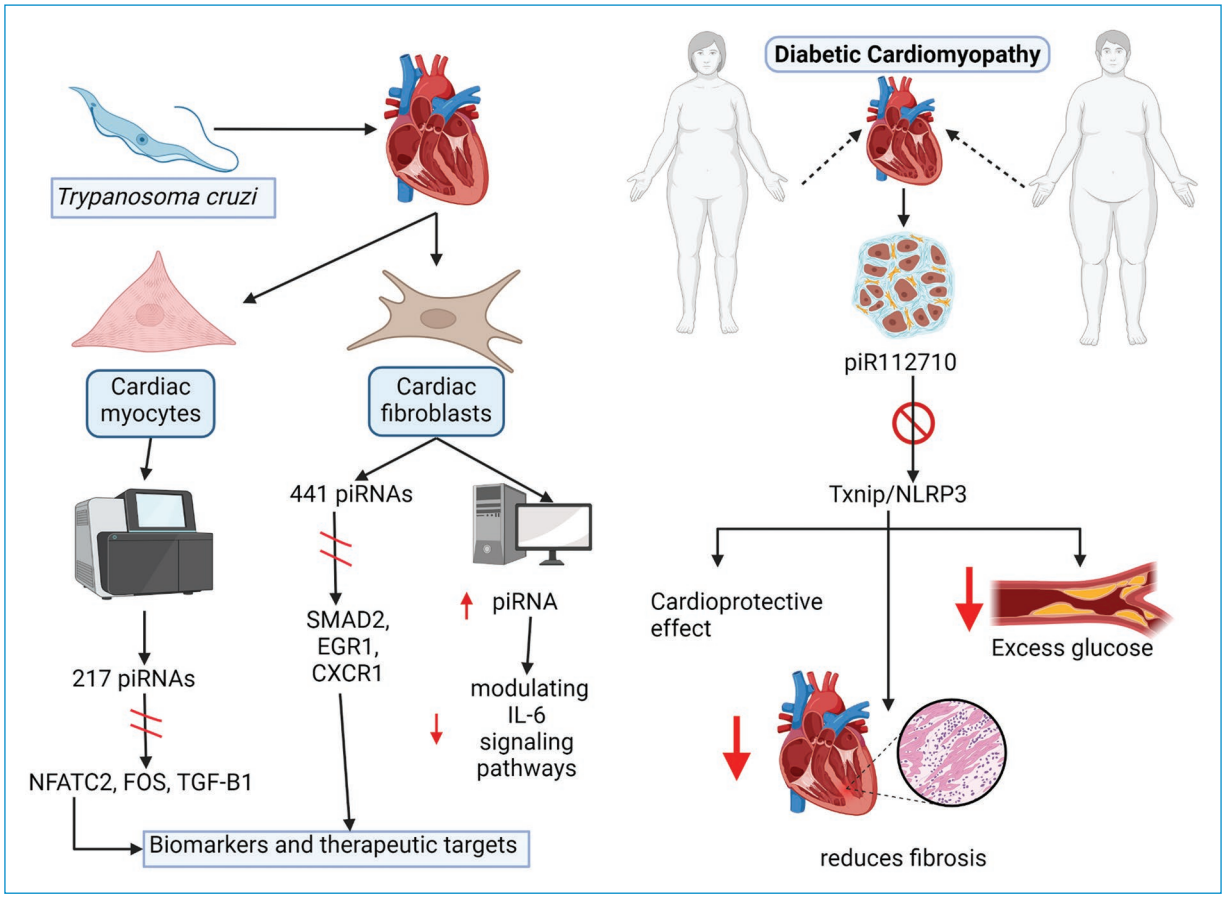

Figure 4. Early detection of *Trypanosoma cruzi* infection in heart disease and possible treatments to reduce diabetic cardiomyopathy.

Conclusions

The exploration of piRNAs in cardiac diseases has revealed their crucial role in modulating diverse physiological and pathological processes. This body of research highlights that piRNAs are critical for the regulation of gene expression and cellular responses in conditions such as myocardial ischemia-reperfusion injury, CT infection, and DCM.

Recent studies have provided deep insights into how piRNAs, such as piR112710, influence cardiac diseases; piR112710 has been shown to alleviate cardiac remodeling in DCM by targeting the Txnip/NLRP3 signaling pathway, thereby mitigating inflammation and pyroptosis. Similarly, the interaction between CT and host cells has been linked to significant changes in piRNA expression profiles, which in turn affect inflammatory responses and infection outcomes. Furthermore, differential piRNA expression presents a promising avenue for diagnostic and therapeutic innovation. Their ability to modulate critical signaling pathways positions piRNAs as potential biomarkers for early disease detection and as targets for novel therapeutic interventions. This potential is particularly relevant given the complexities associated with traditional approaches to diagnosing and treating heart disease[40,41].

Despite these advances, there is clearly still much to learn about the precise mechanisms through which piRNAs exert their effects. Further research is needed to elucidate these mechanisms and validate piRNAs as reliable biomarkers and effective therapeutic targets. Rigorous clinical investigations will be crucial for translating these scientific discoveries into practical applications that could benefit patient care[42-44].

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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

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CASE PRESENTATION

Neurological presentation of infective endocarditis: a case of bulbar syndrome

Presentación neurológica de endocarditis infecciosa: un caso de síndrome bulbar

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Abstract

Infective endocarditis (IE) is a severe condition that may initially present with neurological complications. Early recognition and timely management are essential to improve clinical outcomes. We report the case of a patient with native-valve IE complicated by an ischemic cerebrovascular event, integrating diagnostic imaging and standardized clinical criteria. A 58-year-old man with a history of prostate adenocarcinoma presented with acute neurological deficits. Magnetic resonance imaging showed a right medullary infarction, and echocardiography demonstrated severe aortic regurgitation with valvular vegetations meeting modified Duke criteria. Targeted beta-lactam therapy was initiated with multidisciplinary monitoring. Due to the ischemic neurological event, surgical intervention was deferred to reduce the risk of intracranial hemorrhage. Aortic valve replacement was performed during the fifth week, with favorable postoperative recovery. Infective endocarditis complicated by ischemic stroke represents a therapeutic challenge, particularly regarding the timing of surgery. Coordinated management involving cardiology, neurology, infectious diseases, and cardiovascular surgery is essential to optimize outcomes in patients requiring delayed surgical intervention.

Keywords: *Aortic insufficiency. Infective endocarditis. Stroke. Streptococcus anginosus. Valve vegetations. Valve surgery.*

Resumen

La endocarditis infecciosa (EI) es una enfermedad de alta morbilidad que puede debutar con complicaciones neurológicas. Su reconocimiento temprano mejora el pronóstico. Se describe el caso de un paciente con EI nativa complicada con evento cerebrovascular isquémico, confirmado mediante estudios de imagen y criterios diagnósticos estandarizados. Paciente masculino de 58 años con antecedente de adenocarcinoma de próstata, quien presentó déficit neurológico súbito. La resonancia magnética evidenció infarto medular derecho y el ecocardiograma mostró insuficiencia aórtica grave, con vegetaciones compatibles con EI, cumpliendo criterios de Duke modificados. Se instauró antibioticoterapia dirigida y seguimiento multidisciplinario. Debido al antecedente neurológico isquémico, la intervención quirúrgica se realizó después del periodo recomendado para disminuir el riesgo de hemorragia intracraneal. El reemplazo valvular aórtico se efectuó en la quinta semana, con evolución favorable. La EI con compromiso neurológico plantea desafíos diagnósticos y terapéuticos. El manejo coordinado entre cardiología, neurología, infectología y cirugía cardiovascular es determinante para optimizar los resultados clínicos, especialmente en pacientes con indicación quirúrgica diferida tras un evento isquémico.

Palabras clave: *Accidente cerebrovascular. Cirugía valvular. Endocarditis infecciosa. Insuficiencia aórtica. Streptococcus anginosus. Vegetaciones valvulares.*

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Date of reception: 03-07-2025
Date of acceptance: 30-01-2026
DOI: 10.24875/RCCARE.M26000208
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):55-60
www.rccardiologia.com

Introduction

Infective endocarditis (IE) is a potentially fatal disease characterized by endocardial inflammation and heart valve damage. Its annual incidence in developed countries ranges from 4 to 7 cases per 100,000 inhabitants[1,2], which has been growing as the population ages and chronic conditions (like diabetes mellitus, the need for hemodialysis, invasive device implantation,[2] and intravenous opioid abuse[3]) increase. One of the most serious complications of IE is stroke secondary to septic emboli, which may affect 16 to 25% of these patients, significantly increasing morbidity and mortality rates[4,5]. Both symptomatic and silent ischemic strokes may occur in this context. The diagnosis can be made using neuroimaging like computed tomography (CT) and magnetic resonance imaging (MRI), which have a greater ability to characterize the lesions[6].

Both ischemic and hemorrhagic cerebrovascular events are associated with a higher risk of mortality compared to cases of IE without these events[7,8]. Functional outcomes are also worse in patients with IE-associated strokes than in those with another cause[9], which is why early diagnosis is important. Predictive factors have been identified, such as location on the mitral valve[10], isolation of *S. aureus*[11], vegetations larger than 10 millimeters[7], and a history of hypertension, atrial fibrillation, and dyslipidemia[12]. Recently, predictive frameworks based on Bayesian networks have corroborated a higher risk of stroke in patients with vegetations larger than 10 mm and *S. aureus* isolation[13].

The standard treatment for patients in the first 4.5 hours after ischemic stroke is intravenous thrombolysis. However, the risk of intracranial hemorrhage is considerably higher in patients with IE compared to other causes of ischemic stroke[14], especially when intravenous thrombolysis is used, rather than mechanical thrombectomy[15] (which, in IE, is associated with an equal success rate[16] and fewer hemorrhagic complications[17]).

In certain cases, surgical treatment is essential to control the infection and prevent further complications. However, it is challenging to make decisions in these scenarios, given the balance between the need for surgery and the associated neurological risks. Selecting the proper timing for the intervention is critical, considering the risk of recurrent embolization and possible neurological damage, although the evidence today leans toward early surgical treatment in these patients[18]. Below, we present the case of a patient with an ischemic stroke secondary to IE, with established surgical criteria, and the multidisciplinary approach used at a tertiary care center.

Clinical case

A 58-year-old male patient with a history of Gleason 3+4 prostatic adenocarcinoma presented to the emergency room with loss of consciousness of uncertain duration. On physical exam, he had a swallowing disorder, ataxia, and decreased muscle strength in his lower limbs. A simple head CT was reported to be within normal limits, and a transthoracic echocardiogram showed dilated cardiomyopathy and moderate aortic regurgitation. He was referred to a tertiary care facility where a new simple head CT reported a probable right medullary infarct (Fig. 1), and a brain MRI confirmed this suspicion (Fig. 2).

Within the search for the cause of the ischemic event, TOAST (Trial of ORG 10172 in Acute Stroke Treatment) investigative tests were conducted. A transthoracic echocardiogram showed severe aortic regurgitation and an image compatible with a mobile vegetation measuring more than 9 x 8 mm, with multiple filiform images on its surface (Fig. 3). Serial blood cultures were taken, and antibiotic treatment was started with ampicillin/sulbactam. A transesophageal echocardiogram confirmed severe organic aortic regurgitation, and masses compatible with vegetations, as well as leaflet perforation with sclerosis and thickening, and three masses on the ventricular side (Fig. 4).

The blood cultures reported growth of *Streptococcus anginosus*, so the antibiotic treatment was scaled back to ampicillin, and a thoracoabdominal CT was ordered, which ruled out intracavitary abscesses.

The patient was seen by cardiovascular surgery, who determined that valve replacement surgery was needed, along with resection of the vegetations, due to their size. However, in light of the cerebral event, the team waited five weeks to perform aortic valve replacement with a #23 Avalus™ bioprosthesis, with a favorable perioperative course. He was discharged a few days later with orders for comprehensive cardiopulmonary, physical, and swallowing rehabilitation.

Discussion

We present the case of a patient who debuted with symptoms compatible with a stroke, who was diagnosed with infective endocarditis through an echocardiogram performed as an ancillary test for the embolic brain event. The literature has reported worse clinical

Figure 1. Simple computed axial tomography of the head showing loss of grey matter differentiation in the bulbar area.

Table 1. Duke criteria modified by ESC in 2023

Major criteria
Positive blood cultures: A) Two separate blood cultures isolating typical infective endocarditis microorganisms (*S. aureus,* oral streptococci, *Streptococcus gallolyticus* (*bovis*), HACEK group, *Enterococcus faecalis*) B) Persistently positive blood cultures: Two or more positive blood cultures from samples taken more than 12 hours apart Three positive blood cultures, or the majority of four or more blood cultures with an hour or more between the first and last sample A single blood culture positive for *C. burnetii,* or > 1:800 IgG titers against *C. burnetii*
Endocardial evidence with anatomical changes (vegetation, abscess, or new dehiscence of a prosthetic valve), a new heart murmur or a change in a pre-existent murmur: Echocardiogram (transthoracic or transesophageal) Cardiac CT F-FDG PET/CT SPECT/CT with labeled white blood cells
Minor criteria
Predisposing factors: use of intravenous drugs or a predisposing heart condition
Fever equal to or greater than 38
Vascular phenomena: major arterial embolism, pulmonary septic infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions
Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
Microbiological evidence: positive blood cultures that do not meet the major criteria or serological evidence of active infection with an organism compatible with infective endocarditis

outcomes in patients who present with endocarditis and neurological emboli[7,8]; unfortunately, a significant percentage of cases debut like this[8]. The annual incidence of IE in developed countries ranges from 4 to 7 cases per 100,000 inhabitants[1,2], with an inpatient mortality of 15-25%, establishing it as a disease with significant clinical repercussions[19]. Its epidemiological behavior in Colombia is similar to that found in other parts of the world[20,21].

The most common etiological agents in infective endocarditis are *Staphylococcus aureus*, followed by oral streptococci[22], similar to the findings of epidemiological studies in our setting[21]. Streptococci are more prevalent in patients with periodontal disease or who have undergone medical procedures[1,2,22]. The modified Duke criteria, updated by the European Society of Cardiology (ESC) in 2023 (Table 1)[23], are used for diagnosis. According to this classification, two major criteria, one major criterion and three or more minor criteria, or five minor criteria must be met to confirm the diagnosis of endocarditis. In this case, the patient's infection was caused by *Streptococcus anginosus*, an infrequent etiological agent, with echocardiographic evidence of a vegetation on the aortic valve.

Up to 55% of patients with infective endocarditis may develop neurological complications[19], ischemic stroke being the most common. It occurs in as many as 14 to 35% of cases and is associated with worse adverse outcomes[19,24], with a mortality of up to 39% in patients who require cardiovascular surgery, especially when it is not performed promptly[18]. Septic metastases are more common in the greater circulation, and therefore our case is atypical, although similar to the brain stem infarcts reported by Marquardt et al.[15], a location in which MRI has a greater diagnostic capacity[6].

Treatment of patients with infective endocarditis and neurological involvement is especially complex due to the interaction of infectious, hemodynamic and surgical factors. From an infectious point of view, proper antibiotic treatment is the cornerstone, as it reduces the risk of ischemic stroke by 0.3 to 0.5% per day[23].

Procedures like thrombolysis and mechanical thrombectomy raise questions in IE-associated ischemic

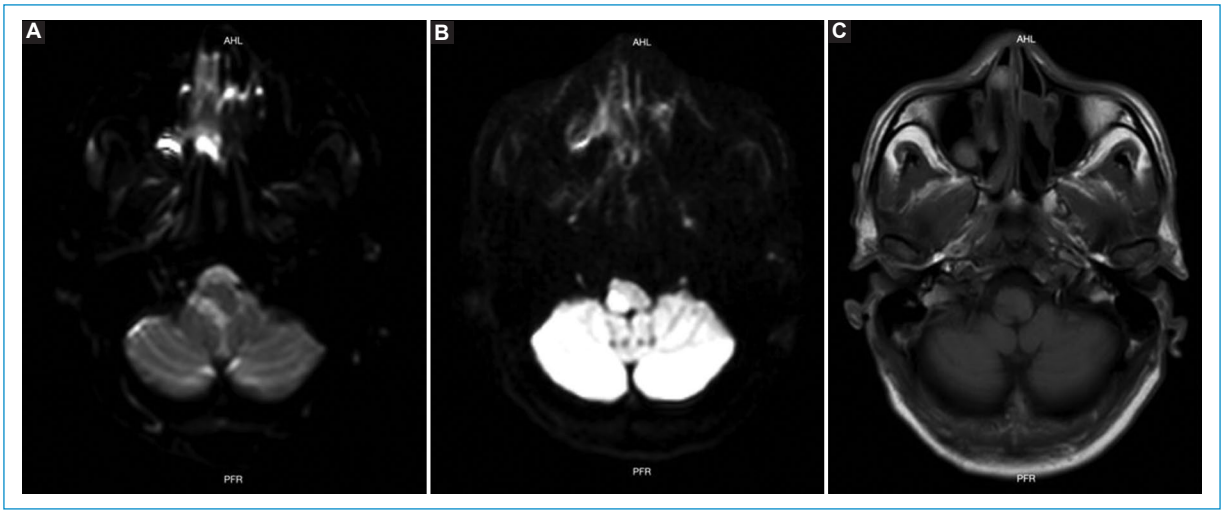

Figure 2. Brain magnetic resonance imaging. **A:** DWI sequence with right bulbar hyperintensity. **B:** diffusion sequence with hyperintensity in the right bulbar area. **C:** FLAIR sequence with hypointensity in the right bulbar area.

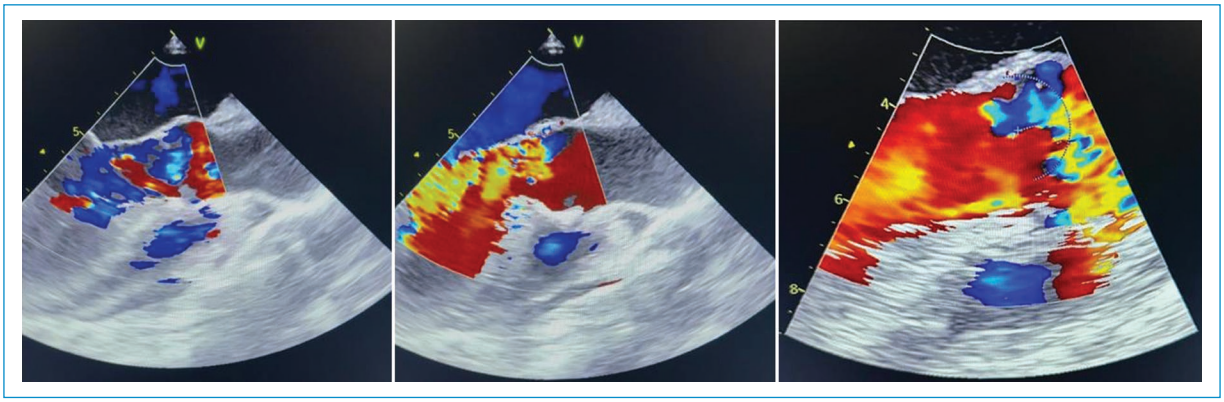

Figure 3. Echocardiogram showing perforation of the non-coronary and right coronary leaflets, with a regurgitation jet on color Doppler occupying more than 60% of the LVOT, classified as severe, with an organic etiology (EROA: 0.5 cm^2, vena contracta: 8 mm, regurgitant volume: 94 ml, PISA radius: 10 mm).

stroke, due to the higher risk of hemorrhagic complications[14]. This risk has been documented more often with intravenous thrombolysis than with mechanical thrombectomy[15], which, in the context of IE, is associated with an equal or better rate of success[16,17]. Our patient already had an established ischemic stroke, which limited the possibility of treatment using thrombolysis or mechanical thrombectomy.

On the other hand, up to 50% of patients with infective endocarditis will require valve surgery (Table 2), either due to severe regurgitation or the need to prevent emboli from the vegetations on the affected valves[19]. In our patient, acute valvular regurgitation justified surgical intervention. In clinical practice, the risks of anesthesia and extracorporeal circulation lead to deferring surgery, in most cases, until the patient is neurologically stable for a minimum of two weeks to reduce the risk of intracranial hemorrhage[23]. However, the evidence increasingly leans toward early surgical treatment, always individualizing each case and evaluating the risk-benefit ratio[18,25]. This waiting period is based on studies showing that surgery in the very early phases can increase the risk of significant brain hemorrhage and thus affect neurological recovery and increase postoperative mortality. In the case we have presented, surgery was delayed up to five weeks, in line with the recommendations in the guidelines[23,26], obtaining a favorable outcome with the patient's functional recovery.

Figure 4. Transesophageal echocardiogram showing masses compatible with vegetations associated with leaflet perforations: trileaflet; leaflet sclerosis and thickening. Three masses are seen on the ventricular side, one on the right coronary leaflet, measuring 7×7 mm, and another, larger one (7×8 mm) on the non-coronary leaflet. Multiple, mobile filiform images are seen on the surface of this mass. A third, smaller mass is seen on the left coronary leaflet.

Table 2. Indications for surgery in infective endocarditis

Surgical indications	Description
Heart failure	Heart failure due to acute aortic or mitral regurgitation which cannot be controlled with medical treatment.
Perivalvular extension	Abscesses, fistulas or heart block caused by perivalvular invasion.
Persistent infection	Persistent bacteremia after 5 to 7 days of appropriate antibiotic treatment.
Difficult-to-treat microorganisms	Resistant fungal or bacterial infections, such as some *Staphylococcus aureus* strains.
Large vegetations	Mobile vegetations measuring > 10 mm associated with embolization despite antimicrobial treatment.
Prosthetic endocarditis	Prosthetic valve dysfunction or abscess indicating mechanical deterioration or infectious progression.

Acknowledgements

We would like to thank Clínica Neurodinamia for providing access to the clinical information and images included in this report.

We also thank Universidad del Sinú for providing bibliographic support during this manuscript's writing.

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors have completed the ICMJE form for disclosure of conflicts of interest and report no relevant relationships for the content of this manuscript.

Ethical considerations

Human and animal protection. The authors declare that the procedures followed were in line with the ethical norms of the responsible human (or animal, as applicable) experimentation committee, according to the World Health Organization and the Declaration of Helsinki. The procedures were authorized by the institution's ethics committee.

Confidentiality, informed consent, and ethical approval. The authors followed their health center's protocols for accessing data from the medical charts. Informed consent was obtained from the patients, and approval was granted by the ethics committee. The SAGER guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that they used the ChatGPT artificial intelligence tool exclusively for support in language editing and manuscript formatting and structuring. None of the scientific content, results analysis, clinical interpretation, or discussion was generated by artificial intelligence tools.

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CASE PRESENTATION

Libman-Sacks endocarditis of the tricuspid valve in a young patient with systemic lupus erythematosus and secondary antiphospholipid syndrome

Endocarditis de Libman-Sacks de válvula tricúspide en una paciente joven con lupus eritematoso sistémico y síndrome antifosfolípido secundario

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Abstract

Aseptic vegetations in Libman-Sacks endocarditis rarely involve right heart valves. Libman-Sacks is typically associated with autoimmune diseases with circulating antiphospholipid antibodies. This diagnosis is often incidental, due to its asymptomatic nature. We report the case of a 19-year-old female patient with Libman-Sacks endocarditis of the tricuspid valve and systemic lupus with secondary antiphospholipid syndrome.

Keywords: *Endocarditis. Tricuspid valve. Systemic lupus erythematosus. Antiphospholipid syndrome. Antiphospholipid antibodies.*

Resumen

La endocarditis de Libman-Sacks hace referencia a la presencia de vegetaciones asépticas en las válvulas cardíacas izquierdas con compromiso excepcional e infrecuente de las válvulas derechas, generalmente asociado a enfermedades autoinmunes con anticuerpos antifosfolípidos circulantes. En cuanto a la clínica, suele ser asintomática, por lo que su diagnóstico llega a ser incidental. Se presenta el caso de una paciente femenina de 19 años con Libman-Sacks de válvula tricúspide y lupus eritematoso sistémico con síndrome antifosfolípido secundario, cuya única manifestación fueron lesiones cutáneas.

Palabras clave: *Endocarditis. Válvula tricúspide. Lupus eritematoso sistémico. Síndrome antifosfolípido. Anticuerpos antifosfolípido.*

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Date of reception: 19-12-2023
Date of acceptance: 17-12-2025
DOI: 10.24875/RCCARE.M25000205
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):61-66
www.rccardiologia.com

Introduction

Libman-Sacks endocarditis (LSE) refers to heart valve abnormalities caused by noninfectious or sterile vegetations. It is mostly associated with hypercoagulable states secondary to malignancies, systemic lupus erythematosus (SLE), or antiphospholipid syndrome (APS)[1].

Tricuspid and pulmonary involvement is rare. The mitral valve is primarily affected, followed by the aortic valve, with mild or moderate functional repercussions (generally regurgitation); therefore, vegetations or valvular thickening may be asymptomatic or incidental findings[1]. Below, we present the case of a young woman with Libman-Sacks endocarditis of the tricuspid valve and severe regurgitation associated with a history of SLE, who was diagnosed with triple-positive APS during her hospital stay.

Clinical case

This was a 19-year-old female patient with a five-year history of SLE, which she chose not to have treated. She consulted for skin lesions that had appeared four days prior, initially described as pinpoint (Fig. 1), which later coalesced to form erythematous plaques on her arms, legs, chest, and back (Fig. 2) associated with malar erythema and photosensitivity.

She did not report any symptoms on the review of systems, and no additional abnormalities were found on physical exam. Due to suspected disease activation, a point-of-care ultrasound (POCUS) was done in the emergency room to check for serositis, with an incidental finding of a tricuspid valve regurgitation jet.

Dermatology considered that the patient had acute generalized cutaneous lupus and subacute annular cutaneous lupus and, therefore, added a topical steroid to the systemic treatment with prednisolone and hydroxychloroquine.

Further, given the POCUS findings, a transthoracic echocardiogram (TTE) was performed, which suggested noninfective endocarditis and mild tricuspid regurgitation. Therefore, a transesophageal echocardiogram (TEE) was done to describe the findings (Table 1). This showed thickening of the distal third of the valve leaflets, with the same echogenicity as the myocardium, and nodular images on the atrial side around the anterior and posterior leaflets and subvalvular apparatus associated with severe tricuspid regurgitation, which was considered to probably be related to Libman-Sacks endocarditis of the tricuspid valve (Figs. 3 and 4) (Supplementary Material 1-4).

Figure 1. The pinpoint lesions described on the right arm.

Ancillary laboratory tests included two blood culture sets, which were negative. Due to the echocardiographic findings, an antiphospholipid syndrome panel was ordered, which was triple positive (Tables 2 and 3), establishing an indication for warfarin anticoagulation, with which she was discharged from the hospital. Her discharge orders also included continuing hydroxychloroquine, prednisolone, and azathioprine as an outpatient, as well as following up with cardiovascular surgery, since she refused to continue the pre-surgical studies.

Discussion

Libman-Sacks endocarditis is an uncommon complication of SLE, facilitated by concomitant APL positivity[2]. It is more frequently found in the mitral and aortic valves, making tricuspid valve involvement unusual. In this clinical case, we present a patient with SLE and cutaneous lupus, whose LSE was found incidentally with POCUS and was subsequently confirmed with echocardiography.

The pathophysiology of LSE involves the formation of fibrin and platelet thrombi on a previously altered and vulnerable valve surface due to underlying endothelial damage. These thrombi are arranged in vegetations, which are prone to deposits of circulating immunoglobulins, mainly anticardiolipins and complements. This process leads to valve fibrosis, thickening and scarring, resulting in valve dysfunction[3].

Libman-Sacks endocarditis occurs in approximately 10% of patients with SLE[4]. In a cohort of patients with SLE followed for four years, only one case of LSE with tricuspid involvement was documented among 342 patients evaluated[5].

Figure 2. The coalescent lesions described on the right and left arms.

Table 1. Echocardiographic findings documented by the cardiology service at Hospital Universitario de La Samaritana

TTE 21/04/2023	TEE 22/04/2023
Conclusions Massive tricuspid regurgitation with evidence of thickened tricuspid valve leaflets with a hyperechoic lesion toward the tip that could correspond to Libman-Sacks vs. infective endocarditis. Normal shape and size of the left ventricle, with preserved systolic function. LVEF: 55%. Normal diastolic function. Normal size and function of the right ventricle. Mild tricuspid regurgitation with a PASP of 42 mmHg.	Conclusions Severe tricuspid valve regurgitation. Findings suggestive of noninfective endocarditis (correlate with clinical picture) Normal shape and size of the left ventricle with preserved systolic function. LVEF: 66%. Normal diastolic function. Normal size and function of the right ventricle. Normal mitral and aortic valve planes.
Description Tricuspid valve: massive regurgitation jet with V_{max}: 2.9 m/s|G_{max}: 34 mmHg, for an estimated PASP of 42 mmHg.	Description Tricuspid valve: thickening of the distal third of the leaflets with nodular images at this level having the same echogenicity as the myocardium (the masses are on the atrial side; they measure 0.8 x 0.8 cm on the anterior leaflet and 0.6 x 0.5 cm on the posterior leaflet), with an abnormal coaptation surface, leaving a severe regurgitation jet with V_{max}: 3.1 m/s|G_{max}: 38 mmHg, for an estimated PASP of 43 mmHg. (VC: 0.75 mm EROA: 1.1 cm^2); in addition, another 0.6 x 0.8 cm hyperechoic nodular image is seen in the subvalvular apparatus.

TTE: transthoracic echocardiogram; TEE: transesophageal echocardiogram.

Table 2. Laboratory tests to evaluate systemic inflammation

Blood chemistries	Blood cultures	APRs	Serology
Leukocytes 5,120 U/l Neutrophils 3,700 U/l Lymphocytes 1,560 U/l Monocytes 350 U/l Eosinophils 20 U/l RBCs 4,610,000 U/l Hemoglobin 13.2 g/dL Platelets 80,000 U/l	Aerobic #1 and #2: negative after five days of incubation Anaerobic: negative after seven days of incubation	CRP 4.02 mg/L	Nontreponemal test: negative Treponemal test: non-reactive Hepatitis B surface antigen: 0.32 Anti-hepatitits C antibodies: negative

RBCs: red blood cells: APRs: acute phase reactants; CRP: C-reactive protein.

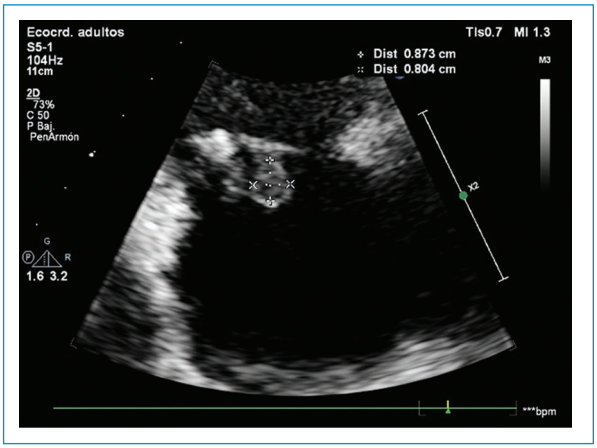

Figure 3. A four-chamber view of the tricuspid valve showing intermediate echogenicity (0.8 x 0.8 cm) on the atrial side of the anterior leaflet.

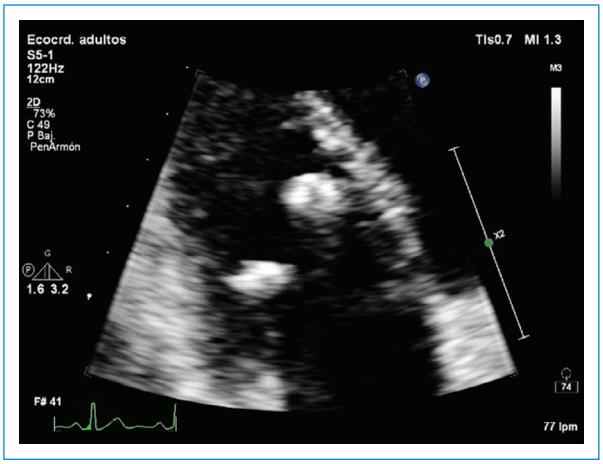

Figure 4. A four-chamber view of the tricuspid valve showing two hyperechoic images in the subvalvular apparatus, corresponding to the septal and anterior leaflets, respectively.

Table 3. Laboratory tests to evaluate autoimmunity

ANAs 1:160; Anti-dsDNA: negative; complement C3: 71 mg/dL; complement C4: 1.76 mg/dL; LA ratio 2.6; aCL-IgM: 18.8 MPL; aCL-IgG: 143 GPL; anti-B2GP1-IgG: 123; anti-B2GP1-IgM: 18.2

ANAs: antinuclear antibodies; Anti-dsDNA: anti-double-stranded DNA; LA: lupus anticoagulant; aCL: anticardiolipin; anti-B2GP1: anti-beta-2 glycoprotein antibody.

The clinical presentation of LSE may vary and can include murmurs, pulmonary or central nervous system emboli, respiratory symptoms and immunological signs and symptoms. In this case, the patient did not have typical LSE symptoms; her chief complaint was a skin problem. Point-of-care ultrasound allowed the incidental finding of valve involvement, which highlights the importance of cardiovascular assessment in patients with SLE, even without cardiac symptoms.

An approximately 30 to 40% correlation has been found between antiphospholipid antibodies and LSE in patients with SLE who are positive for APL[5], as occurred in the case we have reported, reinforcing the relationship between antiphospholipid antibodies and the formation of noninfectious vegetations in LSE.

The LSE diagnosis is based on histological confirmation, generally obtained postmortem or through surgery. However, when tissue cannot be obtained for study, imaging documentation of valve characteristics suggestive of LSE, along with the absence of clinical and laboratory signs of active infection, may be useful for diagnosis[1]. In this case, POCUS was used as the initial approach, followed by transthoracic and transesophageal echocardiography, to confirm the diagnosis of severe LSE of the tricuspid valve, associated with negative blood cultures.

Normally, LSE treatment consists of treating the underlying SLE, as there are no specific guidelines for treating isolated LSE. Immunosuppressive therapy with glucocorticoids and antimalarials may be effective in controlling disease activity and cardiac signs and symptoms after reducing the size of the vegetations and improving valve function. Serious cases with significant valve dysfunction or which are refractory to pharmacological treatment may require surgery, in which case valve repair is preferable to replacement[6].

In summary, there is scant literature on tricuspid involvement, and it is based on case reports, due to the rarity of LSE at this location. Therefore, we reviewed published clinical cases of LSE of the tricuspid valve (Table 4), which shared the following characteristics: 100% involved female patients in their 20s to 40s, and the most frequently reported signs and symptoms were dyspnea, a new murmur, and chest discomfort. In addition, all the women had been previously diagnosed with autoimmunity or were diagnosed during their hospital stay, and all but one were positive for APLs, mainly lupus anticoagulant and anticardiolipin.

Thus, we can say that the clinical case in this article is comparable to the previously mentioned population with regard to sex, age group, history of SLE and APL positivity. However, it is noteworthy that the symptoms were strictly limited to the skin. Therefore, we looked

Table 4. Case reports in the literature of Libman-Sacks endocarditis with isolated tricuspid involvement

Article	Sex (age in years)	Signs and symptoms	History	Echocardiogram	APL	Treatment	Death
Unic, et al., 2017[3]	Female (47)	Dyspnea, peripheral edema, chest discomfort, heart murmur	SLE and secondary APS 15 months prior	Severe tricuspid regurgitation Tricuspid valve vegetations Significant right atrial and ventricular enlargement	LA aCL	Surgery	No
Bai, et al., 2015[6]	Female (20)	Fatigue, nocturnal dyspnea and orthopnea, heart murmur and joint pain	SLE for three years without treatment for the last two years	Severe tricuspid regurgitation Vegetations on the atrial surface of the anterior leaflet of the tricuspid valve	No	Medical, then surgery	No
Wang, et al. 2015[4]	Female (40)	Dyspnea, fever, symmetric arthritis, heart murmur	SLE diagnosed five years ago	Moderate tricuspid regurgitation Tricuspid valve thickening with vegetations on the three cusps and the atrial side of the leaflets. Size: 8 x 8 mm.	aCL	Medical, then surgery	No
Moaref, et al., 2010[9]	Female (42)	Dyspnea, chest discomfort, heart murmur, and joint symptoms	Diagnosed with SLE during her hospitalization	Tricuspid thickening with mild stenosis, regurgitation and nodular images on the three cusps.	aCL	Medical	No
Mahajan, et al., 2017[7]	Female (30)	TIA, *livedo reticularis* on the palms of the hands and soles of the feet, heart murmur	APS three months after hospitalization	Mild tricuspid thickening with regurgitation and a 6 x 8 mm vegetation	LA aCL	Medical	No
Zurich III, et al., 2007[8]	Female (38)	CVA and splenic infarct (paradoxical embolism)	SLE for 12 years with secondary APS	Severe tricuspid regurgitation and thickening with two vegetations on the ventricular side of the anterior and septal leaflets	LA aCL	Medical	No
Unnikrishnan, et al., 2018[10]	Female (47)	Pneumonia, pleuritic pain, hemoptysis, dyspnea, heart murmur	History of Raynaud's, APS during hospitalization and limited cutaneous systemic sclerosis	Severe tricuspid regurgitation, a 1.3 x 2.1 cm mass on the tricuspid valve	LA aCL Anti-B2GP1	Medical	No

APL: antiphospholipid antibodies; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; LA: lupus anticoagulant; anti B2GP1: anti-beta-2 glycoprotein antibody; aCL: anticardiolipin; TIA: transient ischemic attack; CVA: cerebrovascular accident.

for reports of skin involvement and LSE and only found a description of *livedo reticularis* in the context of APS, and malar erythema with photosensitivity in patients with SLE. This lends importance to the present case, in which the involvement was evidenced by coalescent plaques on the upper and lower limbs and the thorax, without the symptoms most mentioned in the published cases.

In another vein, LSE is reported to have a relatively low risk of embolization, regardless of the affected valve, and it is therefore interesting that two patients in the reviewed cases had central nervous system emboli[7,8]. The patient in our clinical case did not have this manifestation; however, it is worth noting because it could help trigger a suspicion of these events when the right-sided valves are involved, or vice versa.

Conclusions

We present a rare case of LSE with tricuspid valve involvement in a patient with SLE and cutaneous lupus. The incidental detection of the valve abnormality through POCUS underscores the importance of cardiovascular assessment in patients with SLE, even without cardiac symptoms. The positive correlation between antiphospholipid antibodies and LSE reinforces the relationship between these conditions. Libman-Sacks endocarditis treatment is based on treating the underlying SLE, and valve surgery may be required in serious cases.

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

Supplementary material

The supplementary material is available at DOI: 10.24875/RCCAR.23000112. This material is provided by the corresponding author and published online for the readers' benefit. The authors are solely responsible for the content of the supplementary material.

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LETTER TO THE EDITOR

Metastatic hematolymphoid tumors of the heart and the diagnostic and therapeutic dilemma: additional methodological approaches

Los tumores hematolinfoides metastásicos al corazón y el dilema diagnóstico y terapéutico: enfoques metodológicos adicionales

Andrés Arboleda-Jaramillo[1], *Juan M. Correa-Ramírez*[1], *and Jorge A. Castrillón-Lozano*[2]*

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Dear Editor:

We read with interest the article by Carmona et al.[1] titled "Metastatic hematolymphoid tumors of the heart and the diagnostic and therapeutic dilemma: A case series," whose objective was to escribe the sociodemographic, clinical and therapeutical findings in patients with metastatic hematolymphoid tumors of the heart. Therefore, we would like to make the following comments.

The study was published as an original article, but we did not find a methods section describing the type of sampling, statistical software used or inclusion and exclusion criteria. An analysis of the association between the patients' clinical presentation and surgical outcomes would have been helpful for the extrapolability of the results and epidemiological findings. We did not find proper adherence to the STROBE and CARE guidelines (Enhancing the Quality and Transparency of Health Research), which are specific to these text types *and* ensure the reliability and validity of the studies[2]. Not omitting this information is good research practice; we consider that studies' method sections should state all this information verbatim.

In line with the above, Carmona et al.[1] discussion does not provide an adequate comparative analysis of other case series and studies with similar characteristics to allow clinical, statistical and sociodemographic comparisons. If they were unable to find other similar case series or studies, this should be clarified to further highlight the pertinence of their study. This should be consistent with a new branch of research which has been described for more than 10 years, known as "meta-research," whose goal is to analyze and improve the way in which the studies themselves are performed, communicated and verified[3].

In conclusion, we must highlight the authors' study, which will provide useful descriptive data to generate studies that can yield management guidelines and evidence-based recommendations for better outcomes in patients with these medical-surgical conditions. We also emphasize the need for greater methodological rigor, as this will lead to better positioning for Colombian and Latin American scientific production.

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Date of reception: 14-03-2025
Date of acceptance: 14-11-2025
DOI: 10.24875/RCCARE.M25000203
Available online: 06-05-2026
Rev Colomb Cardiol. 2026;33(1):67-68
www.rccardiologia.com

Funding

The authors declare that they received no funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. Does not apply (the study did not involve experimentation).

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

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

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