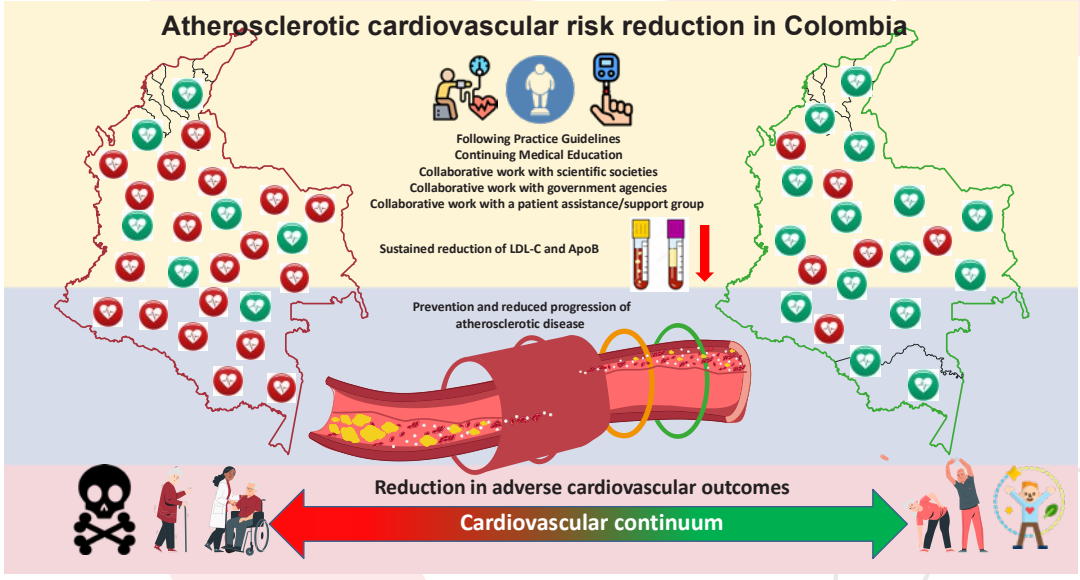
Revista Colombiana de
Cardiología

Volume 32 Number 1 January / February 2025

ISSN: 2938-1525

www.rccardiologia.com
www.revcolcard.org

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



Cardiovascular risk in Colombia. L.C. Zárate-Correa et al. Cardiovascular disease: the need for urgent measures.

- **"To the rescue of medical judgment"**
- **Critical pulmonary valve stenosis**
- **Cardiovascular disease**
- **Atrial appendage closure in atrial fibrillation and dialysis**
- **Experience in aortic valve replacement**
- **Risk scores and acute coronary syndrome**
- **Characterization of tetralogy of Fallot**

Órgano oficial de la Asociación

SOCIEDAD COLOMBIANA
DE CARDIOLOGÍA & CIRUGÍA CARDIOVASCULAR

PERMANYER
www.permanyer.com

11002ACOL251

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

Check for updates

EDITORIAL

A tribute and thanks to our reviewers

Homenaje y agradecimiento a nuestros revisores

Darío Echeverri

Department of Cardiology, La Cardio/Fundación Cardioinfantil, Bogotá, Colombia

"The strongest arguments prove nothing so long as the conclusions are not verified by experience. Experimental science is the queen of sciences and the goal of all speculation". (R. Bacon)

Linkov F, Lovalekar M, LaPorte R. Journal of the Royal Society of Medicine. 2006;99:596-8.

Introduction

Scientific journals continue to be the main source for updating and renewing global knowledge. They have been essential for scientific advances over the last three centuries and have allowed the scientific world to express its results and opinions in the search for truth, helping us to make the best decisions for our patients, based on the best evidence.

The *Revista Colombiana de Cardiología* has been advancing in an improvement process. However, it is facing great challenges and threats, such as greater availability of information on the internet, social networks and the proliferation of predatory journals. These global conditions help explain the radical change that medical literature and learning have undergone in the last decade.

Today, more than ever, we must strengthen our Journal with articles that have higher scientific quality, the latest news and critical analysis of the available literature.

The word "review" seems simple but is loaded with great complexity. Reviewers have the enormous responsibility of facing these radical changes and improving our periodical. The "art" of functioning as an arbitrator requires knowledge, ethics, impartiality, sensitivity and a great deal of generosity to guide the authors toward a better manuscript which showcases their main results. The availability of an appropriate and rigorous peer review aligned with the scientific method is a fundamental principle of scientific journals. The reviewers' goal of maintaining objectivity, preserving scientific soundness, stating conflicts of interest and preventing fraud are essential characteristics of their function. Peer reviewers ensure the quality and suitability of the journal. Their good work enables the Journal to maintain credibility and the readers' "faith" in the Journal's publishing process.

In this issue, we would like to pay tribute to our reviewers; distinguished and highly selected professionals who practice their profession in Colombia and other countries, and in whom we have placed all our trust throughout more than three decades of existence. Thank you for your selfless, quiet and valuable work, which is the essential basis of the Journal's editorial process. We hope that you will be strengthened in your work and will continue with much passion, discipline and responsibility as reviewers, for the good of science.

Our sincere thanks to the following reviewers:

Pedro Abad, Claudia V. Anchique, Manuel Álvarez, Carlos Arias, Dagnóvar Aristizábal, Julián M. Aristizábal, Álvaro Avezum, José R. Azpiri, Ana M. Barón, César Barrera, Daniel Berrocal, Juan C. Briceño, John

Correspondence:
Darío Echeverri
E-mail: decheverri@lacardio.org

Date of reception: 15-01-2025
Date of acceptance: 23-01-2025
DOI: 10.24875/RCCARE.M25000141
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):1-2
www.rccardiologia.com

Bustamante, Jaime Cabrales, Lina Caicedo, Jaime Camacho, Paul Camacho, Ivonne J. Cárdenas, Jonathan Cardona, Marisol Carreño, Carlos Carvajal, Gabriel Cassalett, Mauricio Cassinelli, Roque A. Córdoba, John A. Conta, Tomás Chalela, Gabriel Díaz, José F. Díaz, Pedro Forcada, Hernán Fernández, Argemiro Fragozo, Ángel A. García, Alejandra Gallego, Juan E. Gómez, Mabel Gómez, Efraín Gómez, César Hernández, Édgar Hernández, Heinz Hiller, Andrés Iñiguez, Nicolás Jaramillo, Alejandro Jiménez, Carlos A. Luengas, Fernando Manzur, Sandra Matiz, Erika M. Martínez, Sara E. Mendoza, Enrique Melgarejo, Iván Melgarejo, Óscar Mendiz, Fernán Mendoza, Néstor Mercado, Carlos Mestres, Jorge D. Mor, Guillermo Mora, Carlos Morillo, Ana Múnera, Jaime Murillo, Federico Núñez, Luz A. Ocampo, Ricardo Peña, Iván D. Rendón, Jairo A. Rendón, Fanny Rincón, Mónica Rincón, Nubia L. Roa, Diego Rodríguez, Nohora I. Rodríguez, Fernando Rosas, Álvaro Ruiz, José F. Saaibi, Carlos Sánchez, Juan M. Sarmiento, Jaime A. Serna, Alberto Suárez, Miguel Urina, Édgar Varela, Óscar Velásquez, Sebastián Vélez, Boris E. Vesga, and Ricardo Zalaquett.

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

Check for updates

EDITORIAL

"To the rescue of medical judgment"

"Al rescate del criterio médico"

Dora I. Molina-Salazar

Faculty of Health Sciences, Medical Program, Universidad de Caldas; Research Center, IPS Médicos Internistas de Caldas, S.A.S. Manizales, Colombia

The word "criterion" comes from the Latin *criterĭum*, which comes from the Greek *kritḗrion,* derived from *krínein*, "to judge." In the medical field, it refers to healthcare professionals' ability to interpret the information provided by patients and their families; therefore, acting on it involves the patients, as well as their families, the physician, and the healthcare facility, among others[1].

Traditionally, medical criteria have been the core of clinical decision making. This professional judgement is based on three fundamental pillars: theoretical knowledge and clinical experience, curiosity, the ability to reflect on errors, and an understanding of each patient's individual context. As proposed in the article "What do clinicians mean by good clinical judgment: A qualitative study"[2] good clinical judgement requires solid training in medical knowledge as well as the ability to analyze and adapt to complex situations. The curiosity to review diagnoses and the wisdom obtained from reflection on previous mistakes are also essential. Furthermore, physicians must be able to evaluate and prioritize the relevant factors in each case, considering the patients' life context[1,2].

However, in today's changing medical continuum, technological advances, the growing use of algorithms and patients' easy access to information have transformed medical practice. While technology has facilitated diagnosis and treatment, it has also created the risk of dehumanizing health care by favoring automated decisions that do not always consider each person's particular characteristics[3].

With the Hippocratic Oath, physicians assume the responsibility of saving lives. But, what does this phrase refer to? I think it sometimes goes beyond preserving life; therefore, in many cases, medical judgement must be used rather than incurring in what we call "therapeutic obstinacy." Providing quality of life is just as or more important than merely preserving life. This is where medical judgement comes into play, based on science, knowledge of the factors involved in the prognosis, and how much a disease can affect the person, his/her independence, interpersonal relationships and mental health, to make decisions from this holistic perspective[4].

According to the World Health Organization (WHO), health is complete physical, mental and social wellbeing, not merely the absence of disease. This comprehensive perspective should guide medical practice, considering how the illness affects the patient's independence, interpersonal relationships, mental health and ability to have a functional, quality life. Thus, medical criteria should be integrated with a careful assessment of the prognosis and quality of life the treatment will provide[5].

In the age of evidence-based medicine (EBM), rigorous research and clinical trials have allowed treatments to be standardized. However, medical judgement

Correspondence:
Dora I. Molina-Salazar
E-mail: doraines56@gmail.com

Date of reception: 30-11-2024
Date of acceptance: 06-12-2024
DOI: 10.24875/RCCARE.M24000142
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):3-5
www.rccardiologia.com

should not be displaced by this trend toward protocols. We must remember that clinical guidelines are useful tools, but do not replace the need to personalize treatment according to each patient's particularities[6], as medical judgement allows protocols to be adapted to individual needs, considering aspects like age, comorbidities, personal preferences, and the socioeconomic context. The phrase, "we treat patients, not diseases," reflects this reality; each patient is unique, and physicians must make decisions that benefit that specific person, regardless of what general studies dictate. This means that, although a given treatment may be considered the gold standard for a disease, the physician should evaluate if this treatment is appropriate for his/her particular patient, or if it should be modified[1,7].

Furthermore, the incursion of artificial intelligence (AI) and advanced technologies in the field of medicine has been very helpful in many ways, as they improve diagnostic precision and treatment efficiency. Despite this, they also posed new challenges for medical judgement. In some cases, trust in machines and algorithms has displaced clinical judgement, causing a dangerous disengagement between physicians and patients. More and more patients access information online and, without appropriate professional interpretation, fall into the trap of self-diagnosis and self-medication, putting their health at risk. In addition, content creators without academic and scientific training publish incorrect information and, with their high degree of social influence, produce treatment changes that are inappropriate for people's health[3].

Medical judgement should function as a counterweight to this trend. Physicians should continue to be the main guides for interpreting information and designing personalized treatment. While technology is a powerful tool, it can never replace the experience, in-depth knowledge and empathy that characterize good clinical judgement.

Medical judgement is based not only on science and clinical knowledge, but also on the relationship a physician establishes with his/her patients. Empathy and compassion are essential for creating an environment of trust in which the patients can share their fears, concerns and wishes. Through this relationship, physicians can better understand the patients' individual needs and adapt the treatment to be not only effective from a clinical standpoint, but also satisfactory for the patients[7].

Personalized care, based on an in-depth knowledge of the patient, is what makes medical judgement an indispensable tool for health care. Although technology and AI can improve many aspects of diagnosis and treatment, the human component of medical judgement is essential for achieving quality care that respects patients' dignity[3,7].

It is worth noting that respect for patient autonomy is one of the most important principles in modern health care. Each person has the right to make informed decisions about his/her health, even when these are contrary to medical recommendations. Statutory Law 1751 of 2015, together with the guarantee in the 1991 Colombian Constitution, protect the patients' freedom to choose, recognizing that their dignity and autonomy must be respected, even when these decisions may entail risks[8,9].

This approach poses an ethical dilemma for healthcare professionals, since, although medical judgement is designed to preserve the patients' life and wellbeing, physicians must respect the patients' decisions, even when they do not coincide with their own clinical judgement. This reinforces the need for clear communication and informed consent, in which physicians provide all the necessary information regarding the risks, benefits and available alternatives, but the patients always have the final word on their health. This emphasizes the need for medical judgement to be flexible and adapt to each patient's individual circumstances[10].

In conclusion, this is a call to action to rescue medical judgement, which is not simply a matter of professional preference, but rather an ethical and practical imperative to improve health care. Recognizing and valuing the uniqueness of clinical judgement not only improves the quality of care but also strengthens the doctor-patient relationship and restores confidence in a healthcare system that prioritizes the comprehensive wellbeing of each individual.

As medicine moves forward, we should ensure that medical judgement continues to be not only relevant but essential for clinical excellence and humanized health care. It is in the science and art of medicine where we find the true promise of comprehensive health care that honors the individuality and complexity of each human being.

Medical judgment must be rescued in modern clinical practice. Technology and AI can be valuable tools, but they should never replace clinical judgement based on knowledge, experience, ethics, empathy and compassion. Physicians should continue to develop their skills and knowledge, adapting to the individual needs of each patient and empowering the patients, their families and caregivers, always maintaining a holistic view of health.

References

1. Álvarez Montero S. El cuidado del criterio profesional autónomo. RIB. 2016;(2):1-14. https://revistas.comillas.edu/index.php/bioetica-revista-iberoamericana/article/view/7332.
2. Tsang M, Martin L, Blissett S, Gauthier S, Ahmed Z, Muhammed D, et al. What do clinicians mean by "good clinical judgment": a qualitative study. Int Med Educ. 2023;2:1-10. Doi: 10.3390/ime2010001.
3. Lanzagorta-Ortega D, Carrillo-Pérez DL., Carrillo-Esper R. Inteligencia artificial en medicina: presente y futuro. Gac Méd Méx. 2022; 158(Suppl 1): 17-21. http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0016-38132022001100017&lng=es.
4. Lanzagorta-Ortega D, Carrillo-Pérez DL, Carrillo-Esper R. Inteligencia artificial en medicina: presente y futuro. Gac Med Mex [Internet]. 2023;158(91). Disponible en: http://dx.doi.org/10.24875/gmm.m22000688
5. Sanchez-Salvatierra JM, Taype-Rondan A. Evolución del juramento hipocrático: ¿qué ha cambiado y por qué? Rev Méd Chile. 2018;146(12):1498-500. http://dx.doi.org/10.4067/s0034-9887201800120149 8.
6. Alcántara Moreno G. La definición de salud de la Organización Mundial de la Salud y la interdisciplinariedad. Sapiens. Revista Universitaria de Investigación. 2008;9(1):93-107.https://www.redalyc.org/articulo.oa?id=41011135004.
7. Karthikeyan G, Pais P. Clinical judgement and evidence-based medicine: time for reconciliation. Indian J Med Res. 2010;132(5):623-6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3028959
8. Castro LR, Gubert IC, Duro EA, Cudeiro P, Sotomayor MA, Estupiñan EMB, et al. Humanizar la medicina: un desafío conceptual y actitudinal [Humanization: A Conceptual and Attitudinal Problem]. Rev Iberoam Bioet. 2018;(8):10.14422/rib.i08.y2018.002. Spanish. doi: 10.14422/rib.i08.y2018.002.
9. La libertad de decisión del paciente versus el criterio médico en Colombia. 2024. https://repository.unilibre.edu.co/handle/10901/29919.
10. República de Colombia. Congreso de la República. Ley Estatutaria 1751 de 2015. Bogotá: Diario Oficial; 2015. https://www.cancilleria.gov.co/sites/default/files/Normograma/docs/pdf/ley_1751_2015.pdf.

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

Check for updates

ORIGINAL ARTICLE

Interventional treatment of neonatal critical pulmonary valvular stenosis

Tratamiento intervencionista de la estenosis valvular pulmonar crítica neonatal

Isabel C. Sánchez-Escobar[1], Rafael Lince-Varela[2], Luis H. Díaz-Medina[2], and Diana Restrepo[3]*

[1]Department of Pediatric Cardiology, Clínica Cardio-VID; [2]Hemodynamics Area, Hemodynamics, Clínica Cardio-VID; [3]Area of Epidemiology, Universidad CES. Medellín, Colombia

Abstract

Introduction: *balloon valvuloplasty is currently the first-line therapy in neonates with critical pulmonary valve stenosis, considered to be less invasive, with a lower risk of complications and death, compared to surgery.* **Objective:** *to determine the clinical and hemodynamic characteristics of patients with this condition who underwent balloon valvuloplasty, along with the immediate and short-term outcomes of this procedure.* **Method:** *this was a retrospective cohort study at a cardiovascular referral center.* **Results:** *there was a high success rate for valvuloplasties, with a significant reduction in the transvalvular gradient and right ventricular systolic pressure, with few complications (these being rhythm disturbances and infundibular rupture, with no major clinical repercussions). In general, there were few severe infundibular reactions and mortality related to the interventional procedure was nil.* **Conclusion:** *balloon valvuloplasty is an effective and safe procedure for the treatment of neonates with critical pulmonary valve stenosis, with good immediate and short-term results.*

Keywords: *Balloon valvuloplasty. Pulmonary valve stenosis. Newborn. Cardiac catheterization. Complications.*

Resumen

Introducción: *en la actualidad, la valvuloplastia con balón es la terapia de primera línea en neonatos con estenosis valvular pulmonar crítica, pues es considerada como un procedimiento menos invasivo y que acarrea menor riesgo de complicaciones y muerte en comparación con la cirugía.* **Objetivo:** *definir las características clínicas y hemodinámicas de los pacientes con estenosis valvular pulmonar crítica, llevados a valvuloplastia con balón y sus desenlaces inmediatos a corto plazo.* **Método:** *estudio de seguimiento retrospectivo de una cohorte, en un centro de referencia cardiovascular.* **Resultados:** *se evidenció un alto porcentaje de valvuloplastias exitosas, con disminución significativa del gradiente transvalvular y de presión sistólica del ventrículo derecho (VD), con pocas complicaciones, dadas por alteraciones del ritmo y ruptura infundibular, sin mayores repercusiones clínicas. En general, las reacciones infundibulares graves se dieron en baja frecuencia y la mortalidad relacionada con el procedimiento intervencionista fue nula.* **Conclusión:** *la valvuloplastia pulmonar con balón es un procedimiento efectivo y seguro para el tratamiento de neonatos con estenosis valvular pulmonar crítica, que arroja buenos resultados inmediatos y a corto plazo.*

Palabras clave: *Valvuloplastia con balón. Estenosis valvular pulmonar. Neonatos. Complicaciones. Cateterización cardíaca.*

***Correspondence:**
Isabel C. Sánchez Escobar
E-mail: isasanchez36@gmail.com

Date of reception: 28-02-2024
Date of acceptance: 08-11-2024
DOI: 10.24875/RCCARE.M24000144
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):6-12
www.rccardiologia.com

Introduction

Pulmonary valve stenosis is a type of right ventricular (RV) outflow tract obstruction characterized by fused or absent commissures with thickened pulmonary valve leaflets. Critical stenosis is the most serious case and leads to insufficient anterograde pulmonary blood flow. As a result, the survival of affected patients depends on maintaining a patent ductus arteriosus to ensure pulmonary blood flow[1].

This condition is the third most common congenital heart malformation, with an overall incidence of 6.6 per 1,000 live births, accounting for 5.8% of congenital heart diseases. Furthermore, pulmonary stenosis is a component of half of all congenital heart defects[1].

It sometimes occurs in a familial form, especially with dysplastic valves, with a 2.9% possibility of recurrence in siblings[1].

It presents with intense cyanosis and is a neonatal emergency due to its high mortality, which in some studies reaches 50% within the first two weeks and 85% in the first six months of life. Currently, balloon pulmonary valvuloplasty is the first-line treatment[2-4].

The Colombian literature does not provide its current prevalence, but hemodynamics studies show that up to 22.5% of patients undergoing balloon valvuloplasty had a diagnosis of critical pulmonary stenosis[5].

The procedure has high short and medium-term success rates, at 93.8%, defined as a single valvuloplasty event[6].

After the good initial results reported with pulmonary valvuloplasty, few articles have been published exploring outcomes in patient subgroups like newborns, in whom clinical complexity, interventional risk and other unanalyzed variables could lead to other outcomes. Therefore, we posed the need to determine the clinical and hemodynamic characteristics of patients with neonatal critical pulmonary valve stenosis who underwent balloon valvuloplasty at a pediatric cardiology center in Medellín, Colombia.

Method

This was a retrospective cohort study in which all patients underwent balloon pulmonary valvuloplasty to treat critical pulmonary valve stenosis. These patients were followed for 30 days.

Newborn patients (under 30 days old) of both sexes with critical pulmonary valve stenosis diagnosed by echocardiography and confirmed through a hemodynamics study at Clínica Cardio VID in Medellín, Colombia (a congenital heart disease referral center) were included. These patients underwent percutaneous balloon valvuloplasty between January 1, 2010, and May 30, 2021. All completed the follow-up period.

The participants were found in a database created by the pediatric interventional cardiologists which was constructed prospectively immediately after each catheterization, and was recently reviewed by one of the investigators (ICS) looking for missing data.

The study's dependent variable was 30-day outcomes after valvuloplasty. Other independent variables included: a) clinical data: age, weight, height, total body surface area, prematurity, birth weight, mechanical ventilation, intraprocedural bleeding, the need for transfusions, and the use of prostaglandins and vasopressor support; b) hemodynamic data: pulmonary annulus diameter, pulmonary annulus Z-score, balloon/annulus ratio, right ventricular systolic pressure (RVSP) before and after the procedure, right ventricular end-diastolic pressure (RV EDP) before and after the procedure, pulmonary artery (PA) pressure before and after the procedure, transvalvular gradient before and after the procedure, infundibular gradient, type of right ventricle, other heart anomalies, and patent ductus arteriosus: diameter of the pulmonary and aortic ends; c) angioplasty information: access site, fluoroscopy time, catheterization time, balloon diameter, and other procedures; d) outcomes: reintervention, complications, length of hospital stay and mortality related to the interventional procedure.

Success and the primary outcome were defined as valvular opening and a reduced transvalvular gradient.

For this study, critical pulmonary valve stenosis was defined as the need for prostaglandin infusion, baseline desaturation, signs and symptoms of low cardiac output and ductal -dependent pulmonary blood flow[7].

The pulmonary valve was considered dysplastic when it was significantly thickened, with restricted leaflet mobility[8].

Reintervention was described as a surgical or other transcatheter intervention during follow-up, which was required after successful balloon valvuloplasty[8].

Right heart pressures were measured with an intracardiac catheter, and systemic arterial pressure was measured noninvasively or invasively if the patient had an arterial line.

The following procedures were performed:

– Hemodynamics: balloon valvuloplasty was performed under general anesthesia. There were no significant differences in techniques or equipment throughout

the study, and the same pediatric interventional cardiologists performed follow-up. Heparin (50-100 IU per kilogram of weight) was administered intravenously as soon as the femoral vein was cannulated.

Right chamber pressures were measured and right antero-posterior (AP) ventriculography was performed with cranial angulation and lateral projection using a Phillips® biplane system (Allura Xper). Then, the guidewire was advanced through the pulmonary valve and placed distally in the left pulmonary artery or in the descending aorta, passing through the ductus arteriosus. The valve annulus was measured, and the measurements were compared to those of the previous echocardiogram to select the balloon diameter, maintaining a 1.2 to 1.4 balloon/annulus ratio. After this, the balloon was advanced over the guidewire, and valvuloplasty was performed, inflating the balloon to 2 to 4 atmospheres of pressure until the balloon waist disappeared. Subsequently, the balloon was withdrawn, and the pulmonary artery and right ventricular pressures were measured again. If the pulmonary transvalvular pressure gradient remained higher than 30 mmHg, a 1-mm larger balloon was inserted, the balloon was inflated again, and the pulmonary and ventricular pressures were measured once more. Finally, follow-up ventriculography was done to evaluate the final outcome and rule out complications. The patient was then taken to the pediatric cardiovascular intensive care unit for post-intervention monitoring and follow-up echocardiography.

– Echocardiography: the patients were initially diagnosed with transthoracic echocardiography performed using two machines (Philips® Epic and Vivid 7). The findings associated with critical pulmonary valve stenosis were a transvalvular gradient greater than 40 mmHg without right ventricular dysfunction or tricuspid valve regurgitation with a transvalvular gradient reflecting a right ventricular systolic pressure greater than 75% of the systemic arterial pressure, as well as bidirectional or right-to-left shunting through the foramen ovale and a patent ductus arteriosus.

Selection bias was controlled by consecutively including all patients who underwent balloon valvuloplasty for critical pulmonary stenosis during the study period. Information bias was minimized by the high quality of the data, as it was derived directly from the person who performed the procedure (RLV/LHD). Furthermore, each medical chart was retrospectively reviewed to verify the information. When in doubt, the principal investigator verified any inconsistencies with the person who extracted the information. Follow-up bias was minimized as all patients were followed for a minimum of 30 days. Finally, the database was cleansed by two of the investigators (AC, DR), one of whom had experience in database management, looking for duplicate or inconsistent records.

All cases who were sequentially admitted to the institution with a diagnosis of critical valve stenosis and underwent balloon valvuloplasty during the study period were included in the study.

The quantitative variables in the analysis were treated as detailed below, according to the clinical judgement of the interventional cardiologist (RLV/LHD). Age was taken as a continuous variable; the figure recorded during angioplasty (in millimeters of mercury [mmHg]) was used for the pre- and post-valvuloplasty transvalvular gradient. Then, 30 mmHg was taken as the reference value and, based on this, the case was reclassified as successful or having residual stenosis.

Finally, a descriptive analysis of the sociodemographic and clinical variables was done. The raw complication rate 30 days after pulmonary valvuloplasty was used as an epidemiological indicator. Qualitative variables were presented using absolute and relative frequencies; summary measures like medians and interquartile range were used for quantitative variables, because the Shapiro-Wilks test indicated that the quantitative variables were not normally distributed. Possible associations between 30-day complications and the patients' age and weight were explored using the Wilcoxon signed-rank and Mann-Whitney U non-parametric tests. A p value < 0.05 was considered significant. The SPSS® version 21.0 software (SPSS® Inc.; Chicago, Illinois, USA) was used for data analysis, under a covered license.

The study was approved by the Institutional Review Board.

Results

Twenty-five newborns with a diagnosis of critical pulmonary valve stenosis who underwent balloon valvuloplasty were included in the study. Only one of the patients had undergone previous surgery with BT fistula implantation and subsequently developed stenosis of the distal end, which was found during the interventional procedure.

The analyzed variables were not normally distributed, and therefore the median was used as the measure of central tendency, with interquartile range for the measure of dispersion.

The gender distribution was predominantly male. Demographic and clinical characteristics are listed in table 1.

Five patients had other associated heart defects, each with a 4% incidence: atrial septal defect, ventricular septal defect, aortic valve stenosis, pulmonary annular hypoplasia and RV hypoplasia. All patients had a tripartite RV, and for those with PDA, the median measurement of the aortic end was 4.5 mm (IQR: 2.8) and the median of the pulmonary end was 3.0 mm (IQR: 1.0).

During the interventional procedure, the patients received ventilatory support with orotracheal intubation or a laryngeal mask (n = 23, 92% and n = 2, 8%, respectively), 18 patients (72%) required prostaglandin infusion, and no patients warranted vasopressor support (n = 25, 100%). The approach was mostly through the right femoral vein (n = 18, 72%), followed by the right femoral vein and artery (n = 3, 12%), left femoral vein (n = 3, 12%) and, finally, the left femoral artery (n = 1, 4%). As far as fluoroscopy time and total catheterization time, the median was 12 minutes (IQR 1.13) and 40 minutes (IQR: 19), respectively. One of the patients received simultaneous stent implantation in a PDA that was wide and tortuous, with critical stenosis at the pulmonary end. This patient had a very small jet through the stenotic pulmonary valve during systole.

As far as immediate outcomes, 100% (n = 25) of the valvuloplasties were successful, with a statistically significant reduction in the transvalvular gradient and RV systolic pressure. There were no statistically significant differences in RV EDP or PA pressure, as shown in table 2.

The patients with associated congenital heart anomalies had statistically significant differences on the Wilcoxon test (Z –3.517, p < 0.001) in the change intravalvular gradient, compared with those who had pure stenosis (Z –1.826, p = 0.068).

Two patients had complications (8%); one had an abnormal heart rhythm (n = 1, 4%), due to increased atrial automatism with an atrio-ventricular conduction disorder; and the other patient (n = 1, 4%) suffered infundibular perforation during attempted passage through the pulmonary annulus, without hemodynamic instability and with satisfactory progress during follow-up. Three patients had a severe infundibular reaction. The reinterventions were not associated with the pulmonary annulus Z-score (Mann-Whitney U 44.000, p = 0.921).

Complications were not associated with a weight under 2.5 kg (p = 0.70), prematurity (p = 0.77), having other associated cardiac anomalies (p = 0.63) or having a dysplastic valve (p = 0.45). None of the patients bled during the procedure or required a transfusion.

Three patients had reinterventions (12%), one of whom underwent another balloon valvuloplasty and stent implantation in the ductus arteriosus, and two of whom required surgical treatment, both for BT fistulas.

Neither of the two deaths during follow-up were due to conditions related to the procedure; both patients developed septic shock, one secondary to gastrointestinal sepsis and the other secondary to multilobar pneumonia.

Regarding the patients' clinical characteristics, one was premature; the ages at valvuloplasty were 11 and 18 days; one had a dysplastic valve and the other had associated heart defects (atrial septal defect). Both patients had successful valvuloplasties, with no associated complications and no immediate procedures required. Both required invasive mechanical ventilation. During follow-up, one underwent another surgical procedure, and his hospital stays were two and six days, respectively.

There was no relationship between mortality and weight under 2.5 kg (p = 0.30), prematurity (p = 0.23) or other procedures (p = 0.92).

Table 1. Sociodemographic, clinical and echocardiographic characteristics of the study population

Characteristics	n (%)
Sex Female Male	 9 (36) 16 (64)
Birth weight (kg)	2.92 (0.64)*
Prematurity	3 (12)*
Age (days)	7.3 (5.25)*
Weight (kg)	3.0 (0.6)*
Length (cm)	49.0 (3.0)*
BSA (m^2)	0.20 (0.01)*
Pulmonary annulus diameter	6.30 (1.32)*
Pulmonary annulus Z-score	0.4240
Balloon/annulus ratio	1.32 (0.10)*
Dysplastic valve	17 (68.0)
PDA	23 (92.0)
Other cardiac anomalies	5 (20.0)

*Median (IQR); PDA: patent ductus arteriosus.

Table 2. Hemodynamic variables before and after valvuloplasty

Variable	Balloon valvuloplasty		Pulmonary annulus Z score	p
	Before	After		
RVSP	82.88	47.84	–4.319	< 0.0001
RV EDP	10.40	10.40	–1.117	0.264
PA pressure	31.60	32.04	–1.688	0.91
Transvalvular gradient	48.88	7.7	–4.287	< 0.0001

RVSP: right ventricular systolic pressure; RV EDP: right ventricular end-diastolic pressure; PA pressure: pulmonary artery pressure.

Some possible associations between successful valvuloplasty and other study variables were explored. No association was found between age and successful valvuloplasty (Mann-Whitney U 5.50, p = 0.18), nor was there an association with birth weight, the timing of the procedure, sex or body surface area (p > 0.05). A significant association was found between the pulmonary annulus Z-score and successful angioplasty (p = 0.04). (Table 3).

Discussion

Balloon valvuloplasty has been a widely accepted technique ever since it was performed by Kan et al. In 1982[9] to treat patients with pulmonary valve stenosis, with its safety and success supported by several studies[2,6,7,9,10-12].

This study's follow-up time and sample size were comparable to those of other studies[7,13-15]. The study by Alsawah et al. included a larger sample of 72 newborns, but with a longer follow-up time (10 years), and the average age at the time of the procedure was 13.8 days (SD: 7.8), which was similar to ours. Likewise, in Yucel et al.'s study which included 56 newborns with critical pulmonary stenosis, the average age and weight at the time of the procedure were 7 days (1-28 days) and 3,100 g (1,600-4,500 g), respectively, which are similar to what we found in our study[8].

As far as valve characteristics, the mean pulmonary valve annulus diameter in the previously mentioned study by Yucel et al. was 6 + 0.9 mm and the pulmonary annulus Z-score was –1.74 + 1 (–4.34 to 0.05), comparable to our study, which found a median pulmonary valve diameter of 6.25 (IQR: 2.45) and a pulmonary annulus Z-score of –0.1600. Regarding the right ventricular morphology, 100% of our patients had a tripartite RV, differing from Yucel et al., who found that 12.5% of the patients with critical pulmonary stenosis had a bipartite RV. As far as the balloon/annulus ratio, these same authors reported an average of 1.29 + 0.12 (1.06-1.55), similar to our results[8].

On another note, in Loureiro et al.'s study, 33.3% had a dysplastic pulmonary valve on echocardiography[7], which differs from our findings, in which seven out of ten valves were classified as dysplastic on angiography. This difference could be partially explained by the different techniques used for diagnosis.

Males predominated in the enrolled patients, similar to what has been reported previously[12]. As far as prematurity, the study by Vall Camell et al. included four preterm patients (17.4%)[11], which is slightly higher than what we found (n = 3, 12%). There was a high incidence of PDA in this group of patients, similar to what our group found. In Loureiro et al.'s study, all of the patients had PDA[7]. Regarding associated heart defects, these have been reported in 27.8%[5], and in our study, one out of five patients had them.

During the interventional procedure, six out of seven patients required prostaglandin infusion to keep the PDA open, which was higher than in other studies, in which 92% of the patients required these infusions[7], as well as Alsawah et al.'s study, in which 80% required them. The difference could be explained by the earlier use of balloon valvuloplasty at our center. All of the reported patients received general anesthesia, similar to what other authors have described[2].

As far as the puncture site, in seven out of ten of our patients, access was gained through the left femoral vein, followed by the right femoral vein, which is similar to other studies[13]. Regarding the transjugular approach described by Hoetama et al. in a series of eight patients, the total procedure, pulmonary cross-clamp and fluoroscopy times were significantly lower compared with the femoral approach[14]. Other access routes have

Table 3. Bivariate analysis: angioplasty success and other variables included in the study

Transvalvular gradient < 20 mmHg					p
Variables	Yes		No		
	n	%	n	%	
Prematurity					
Yes	3	12	0	0	0.786
No	22	88	2	100	
Dysplastic valve					
Yes	18	72	1	50	0.513
No	7	28	1	50	
Other cardiac anomalies					
Yes	6	24	0	0	0.598
No	19	76	2	100	
Ventilation					
Yes	23	92	2	100	0.855
No	2	8	0	0	
Other procedures					
Yes	1	4	0	0	0.926
No	24	96	2	100	
Use of prostaglandins					
Yes	17	68	1	50	0.564
No	8	32	1	50	
Support					
Yes	1	4	0	0	0.926
No	24	96	2	100	
Mortality					
Yes	0	16	0	0	NC*
No	23	84	2	100	
Complications					
Yes	2	8	0	0	0.855
No	23	92	2	100	

*Not calculable.

been described, like arterial and umbilical catheters[2]. However, our institutional procotol does not include these approaches.

In regard to the immediate outcomes, the effectiveness of this procedure is defined by the reduction in the transvalvular gradient. Juárez et al, as well as other groups, found an association between procedure failure and age, a dysplastic valve morphology, the pre-angioplasty pulmonary valve gradient and elevated RV systolic pressure prior to the procedure[15,16]. We did not find these associations in our study. Overall, high effectiveness rates have been reported for this procedure. Alsawah et al. reported an effectiveness of 94.4%, and Manica et al. reported 100%, similar to our study[12].

As far as PDA stenting, Alsawah et al.'s study reported difficulties in crossing the pulmonary valve in two premature infants (2.7%), due to severe tricuspid regurgitation and severe RV hypertrophy; therefore, they decided to place a stent in the PDA[2]. One patient in our study required PDA stenting.

Balloon valvuloplasty is more complex and prolonged in newborns compared to other pediatric age groups, especially for critical pulmonary valve stenosis, due to the right ventricular morphology and hypoplasia and the size of the tricuspid annulus, with high complication rates during the procedure that range from 14 to 31%. Our rate of complications fell within this range. Mortality has been reported in 4.2% of cases[10,15,17,18]; there were no deaths associated with the procedure in our study.

The main complications reported in these patients are related to rhythm disorders. In Hoeatama et al.'s study, six out of 15 patients had atrio-ventricular block and right bundle branch block with transient sinus bradycardia[7].

In our study, one patient experienced infundibular rupture (4%); other authors, like Ronai et al., have reported this complication in seven out of 127 procedures (5.5%). Like theirs, our case was managed medically[19].

Reinterventions have been reported in 10-34%[10,13,15] of cases, and the incidence of reintervention in our patients fell within this range. In some studies, the pulmonary annulus Z-score was significantly lower in those who required reintervention: - 2.4 (IQR: –2.9 to –0.95) vs. –0.59 (IQR: –1.3 to –0.15, p = 0.02)[10]. A Z-score less than – 1.69 predicted the need for increased pulmonary flow, with a sensitivity of 74%[8]. In our study, the average pulmonary annulus Z-score was lower in the reintervention group (–0.800 vs. –0.6169), but the difference was not significant (p = 0.891).

Previous studies have reported that a final pulmonary transvalvular gradient > 25 mmHg is associated with a higher likelihood of reintervention[6]. Furthermore, in some studies, a bipartite RV was a significant predictor of the need for reintervention (OR 9.6), which does not apply to our case, because 100% of the cases were tripartite.

Limitations

Due to its nature as a retrospective cohort study, the associations found are exploratory and should in no way be interpreted as causal. Moreover, this study did not have a control group, which also limits the scope of the results. Likewise, the small sample size limits the incidence of low-prevalence complications, and, finally,

follow-up was only for 30 days, and therefore some later-onset complications and outcomes were not found.

Conclusions

Our study confirms that balloon pulmonary valvuloplasty is a safe and successful procedure for newborns with critical pulmonary valve stenosis. The complications found in this case series were similar to those reported by other investigators.

Acknowledgements

The authors would like to thank Clínica CardioVID, the institution that allowed us to perform the study.

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 involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from 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. The authors declare that no generative artificial intelligence was used in writing this manuscript.

References

1. Dayton JD, Holzer RJ, Anderson RH. Pulmonary stenosis. En: Anderson´s (ed.). Pediatric Cardiology. 4th. ed.; 2019.
2. Alsawah GA, Hafez MM, Matter M, Abo-Haded HM, Rakha S, Almarsafawy H. Balloon valvuloplasty for critical pulmonary valve stenosis in newborn: A single center ten-year experience. Prog Pediatr Cardiol [Internet]. 2016;43:127-31. https://linkinghub.elsevier.com/retrieve/pii/S1058981316300388.
3. Faella HJ, Sciegata A, Marantz P, Micheli D, Alonso J, Capelli H. Valvuloplastia con cateter balon en la estenosis valvular pulmonar critica. Rev Arg Cardiol. 1993(61)5:457-61.
4. Savío Benavides A, García Guevara C, Ramiro Novoa JC, García Morejón C. Estenosis pulmonar valvular crítica, angioplastia posnatal o intervencionismo fetal? Rev Cuba Pediatría [Internet]. 2012;84(3):301-6. http://scielo.sld.cu/scielo.php?script=sci_abstract&pid=S0034-75312012000300011&lng=es&nrm=iso&tlng=es.
5. Cadavid AM, Díaz LH, Lince R, Donado JR, Ruz M. Valvuloplastia pulmonar percutánea con balón. Resultados y seguimiento a corto y mediano plazo. Rev Col Cardiol. 2006;12:483-91. http://www.scielo.org.co/pdf/rcca/v12n7/v12n7a6.pdf.
6. Ramírez-González M, León-Guerra OJ, Lince-Varela R, Díaz LH. Valvuloplastia pulmonar en menores de 21 años. Rev Colomb Cardiol [Internet]. 2017;24(1):71-7. https://linkinghub.elsevier.com/retrieve/pii/S0120563316301371.
7. Loureiro P, Cardoso B, Gomes IB, Martins JF, Pinto FF. Long-term results of percutaneous balloon valvuloplasty in neonatal critical pulmonary valve stenosis: a 20-year, single-centre experience. Cardiol Young [Internet]. 2017;27(7):1314-22. https://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=28619122&lang=es&site=ehost-live.
8. Yucel IK, Bulut MO, Kucuk M, Balli S, Celebi A. Intervention in patients with critical pulmonary stenosis in the ductal stenting era. Pediatr Cardiol [Internet]. 2016;37(6):1037-45. https://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=27033245&lang=es&site=ehost-live.
9. Kan JS, White RI, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary-valve stenosis. N Engl J Med [Internet]. 1982;307(9):540-2. http://www.nejm.org/doi/abs/10.1056/NEJM198208263070907.
10. Aggarwal V, Mulukutla V, Maskatia S, Justino H, Mullins CE, Qureshi AM. Outcomes after balloon pulmonary valvuloplasty for critical pulmonary stenosis and incidence of coronary artery fistulas. Am J Cardiol [Internet]. 2018;121(12):1617-23. https://linkinghub.elsevier.com/retrieve/pii/S0002914918302856.
11. Vall Camell M, Rodríguez-Fanjul J, Bautista Rodríguez C, Pradda FH, Caffarena-Calvar JM, Iriondo Sanz M, et al. Percutaneous management of pulmonary atresia with intact ventricular septum and critical pulmonary stenosis. Ann Pediatría Engl [Internet]. 2019;91(5):336-43. https://linkinghub.elsevier.com/retrieve/pii/S2341287919300298.
12. Manica JL, Bodini A, Borges MS, Machado PRM, Rossi Filho RI. Cateterismo intervencionista na estenose valvar pulmonar crítica do recém-nascido e na atresia pulmonar com septo interventricular íntegro: 13 anos de experiência de um serviço terciário. Rev Bras Cardiol Invasiva [Internet]. 2011;19(4):423-9. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S2179-83972011000400014&lng=pt&nrm=iso&tlng=en.
13. Binh HA, Minh Chau NN, Xuan NT, Tuan TV, Son NH. Balloon valvuloplasty for critical pulmonary valve stenosis in a newborn. J Pediatr Surg Case Rep [Internet]. 2020;101591. https://linkinghub.elsevier.com/retrieve/pii/S2213576620302256.
14. Hoetama E, Prakoso R, Roebiono P, Sakidjan I, Kurniawati Y, Siagian S, et al. Balloon pulmonary valvuloplasty in neonates with critical pulmonary stenosis: Jugular or femoral. Ann Pediatr Cardiol [Internet]. 2020;13(1):11-5. https://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=141194254&lang=es&site=ehost-live.
15. Juarez M, Alva C, Ledesma M, Lázala G, Jiménez S, Sánchez A, et al. Valvuloplastia pulmonar con balón, experiencia de 15 años en el Centro Médico Nacional Siglo XXI IMSS. Archivos de Cardiología de Mexico. 2003(73): 190-6. http://www.scielo.org.mx/pdf/acm/v73n3/v73n3a4.pdf.
16. Latson LA. Critical pulmonary stenosis. J Intervent Cardiol [Internet]. 2001;14(3):345-50. http://doi.wiley.com/10.1111/j.1540-8183.2001.tb00343.x.
17. Chubb H, Simpson J. The use of Z-scores in paediatric cardiology. Ann Pediatr Cardiol [Internet]. 2012;5(2):179. http://www.annalspc.com/text.asp?2012/5/2/179/99622.
18. Holzer RJ, Gauvreau K, Kreutzer J, Trucco SM, Torres A, Shahanavaz S, et al. Safety and efficacy of balloon pulmonary valvuloplasty: a multicenter experience. Catheter Cardiovasc Interv [Internet]. 2012;80(4):663-72. http://doi.wiley.com/10.1002/ccd.23473.
19. Ronai C, Rathod R, Marshall A, Gauvreau K, Colan S, Brown D. Left ventricular dysfunction following neonatal pulmonary valve balloon dilation for pulmonary atresia or critical pulmonary stenosis. J Am Coll Cardiol [Internet]. 2014;63(12):A517.https://linkinghub.elsevier.com/retrieve/pii/S0735109714605179.

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

Check for updates

ORIGINAL ARTICLE

Cardiovascular disease: the need for urgent action

Enfermedad cardiovascular: la necesidad de medidas urgentes

Luz C. Zárate-Correa[1], Ángel A. García-Peña[2], Pablo Corral[3], and Kausik Ray[4]*

[1]Cardiology Division, Universidad del Valle, Cardiodec and Clínica Cardio Neurovascular DIME, Cali, Colombia; [2]Cardiology Unit, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia; [3]Departament of Pharmacology and Research, Universidad Fasta, Mar del Plata, Argentina; [4]School of Public Health, Imperial College London, London, United Kingdom.

Abstract

Introduction: *atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide, associated with subendothelial deposits of ApoB-rich particles such as LDL cholesterol (LDL-C). Multiple clinical studies highlight the importance of reducing LDL-C and ApoB levels to prevent and manage atherosclerosis. This requires addressing modifiable risk factors and utilizing pharmacological therapies such as statins, ezetimibe, PCSK9 monoclonal antibodies, inclisiran, and bempedoic acid.* **Objective:** *to review the available evidence on pharmacological therapies and their impact on LDL-C reduction, and cardiovascular event prevention, with a focus on adherence and long-term implementation.* **Method:** *a review of the scientific literature was conducted, focusing on the effects of lipid-lowering therapies and evaluating their potential impact on cardiovascular event prevention and public health relevance.* **Results:** *the evaluated therapies reduce the risk of cardiovascular events, with long-term adherence being a key factor. Inclisiran, a small interfering RNA therapy, sustainably lowers LDL-C, and simulation studies demonstrate a significant impact in preventing thousands of cardiovascular events over 10 years, with improved adherence.* **Conclusion:** *pharmacological therapies, such as inclisiran, represent a significant advance in the management of ASCVD. Their large-scale implementation, combined with lifestyle modifications, can substantially mitigate the burden of cardiovascular disease.*

Keywords: *Atherosclerotic cardiovascular disease. LDL cholesterol. Atherosclerosis. Cardiovascular mortality. Statins. Ezetimibe. Monoclonal antibodies against PCSK9. Inclisiran.*

Resumen

Introducción: *la enfermedad cardiovascular aterosclerótica (ECA) es la principal causa de morbimortalidad mundial, y está relacionada con el depósito subendotelial de partículas ricas en ApoB, como el colesterol LDL (C-LDL). Diversos estudios clínicos destacan la importancia de reducir el C-LDL y la Apo B para prevenir y tratar la aterosclerosis. Esto requiere abordar los factores de riesgo modificables y terapias farmacológicas, como estatinas, ezetimibe, anticuerpos monoclonales contra PCSK9, inclisirán y ácido bempedoico.* **Objetivo:** *revisar la evidencia disponible sobre las terapias farmacológicas y su impacto en la reducción del C-LDL y la prevención de eventos cardiovasculares, con enfoque en la adherencia e implementación a largo plazo.* **Método:** *se realizó una revisión de la literatura científica centrada en los efectos de las terapias hipolipemiantes, y se evaluó el potencial impacto de estas estrategias en la prevención de eventos cardiovasculares y su relevancia en salud pública.* **Resultados:** *las terapias evaluadas reducen el riesgo de eventos cardiovasculares, con la adherencia a largo plazo como elemento clave. Inclisirán, una terapia de ARN pequeño de interferencia, reduce, en forma*

***Correspondence:**
Luz C. Zárate-Correa
E-mail: clemenciazarate@gmail.com

Date of reception: 23-05-2024
Date of acceptance: 22-10-2024
DOI: 10.24875/RCCARE.M24000143
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):13-17
www.rccardiologia.com

sostenida, el C-LDL, y los estudios de simulación muestran un impacto significativo en la prevención de miles de eventos cardiovasculares a diez años y con mayor adherencia. **Conclusión:** *las terapias farmacológicas, como inclisirán, representan un avance importante en el manejo de la ECA. Su implementación a gran escala, junto con el control de estilos de vida, puede mitigar de manera significativa la carga de la enfermedad cardiovascular.*

Palabras clave: *Enfermedad cardiovascular aterosclerótica. Colesterol LDL. Aterosclerosis. Mortalidad cardiovascular. Estatinas. Ezetimibe. Anticuerpos monoclonales contra PCSK9. Inclisirán.*

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the main cause of morbidity and mortality, worldwide[1]. Atherosclerosis, in turn, results from subendothelial deposits of ApoB-rich particles, particularly low-density lipoprotein cholesterol (LDL-C), remnant particles and lipoprotein a [Lp(a)][2]. Ample evidence, derived from observational, genetic and pharmacological intervention studies, underscores the goal of lowering LDL-C and ApoB levels not only to prevent atherosclerosis, but also to provide treatment for established vascular lesions and atherosclerosis[3].

According to the Departamento Administrativo Nacional de Estadística [National Administrative Department of Statistics] (DANE, in Spanish) 2023 report, the main cause of morbidity and mortality in Colombia over the last 10 years has been cardio-cerebrovascular disease, similar to what has been reported in all countries in our continent and the world. Approximately one out of three Colombians die from this cause, with a constant increase that is greater in men than women. This group of diseases generates substantial costs for the healthcare system and a significant number of disability-adjusted life years (DALYs), without considering the associated social, familial and work impact. Therefore, early detection and comprehensive treatment of modifiable cardiovascular risk factors is one of the most cost-effective strategies to reduce the consequences of this disease in the population[4,5].

It should be noted that most cardiovascular events will occur in people without extremely high cholesterol, which reflects an inherited genetic vulnerability to accumulating, retaining and responding to cholesterol accumulation in the vessel wall. Atherosclerosis prevention requires a global approach and management of all risk factors, including the adoption of healthy lifestyles. This specifically includes lowering LDL-C levels with both non-pharmacological methods (like diet) and pharmacological strategies based on LDL-C-lowering drugs like statins, ezetimibe, PCSK9 monoclonal antibodies, inclisiran and bempedoic acid, either as single-drug or combination therapy. The choice is made based on the patient's risk profile and treatment goals, such as the desired blood lipoprotein levels or values. These drugs, supported by different levels of evidence, have proven to lower the risk of future cardio-cerebrovascular events, and the magnitude of this effect depends on the initial LDL-C level, the risk profile, the LDL-C level achieved and the duration of pharmacological therapy. These drugs are generally well tolerated and are cost-effective in local settings. However, since these drugs are usually taken chronically, the main challenge lies in achieving adherence to and persistence in these therapies[6-9].

Treatment effectiveness has been shown to reduce up to 80% when taken intermittently or discontinued for several weeks. For patients in secondary prevention, this increases the risk of having another myocardial infarction by 12% when doses are intermittent and by 26% when treatment is suspended for more than one month in the 24 months after the first event. In addition, the risk of experiencing new cardiovascular events increases by 22% in the following five years and may reach 50% in the following 10 years[7,9].

Despite the availability and proven efficacy of statins, ezetimibe and PCSK9 monoclonal antibodies, 83.5% of adults with established ASCVD have LDL-C levels $\geq$ 70 mg/dl, due to a lack of implementation of clinical practice guidelines. Furthermore, long-term, the actual or perceived tolerance to first-line treatments (statins) and low adherence to medication may result in deficient long-term persistence in lipid-lowering regimens that require daily doses or patient self-administration[10].

Prescription and long-term follow-up patterns must be changed to ensure that treatment changes follow the risk profiles and can change over time. In general, prescriptions change very little over time (therapeutic inertia). According to the 2023 DANE report in Colombia, less than half of patients with high and very high risk are achieving their treatment goals, and medium and long-term adherence to this strategy is less than 30%. This is compounded by the difficulties related to obtaining new prescriptions, medication dispensing and disease follow-up over time[8-12]. Initiatives are needed

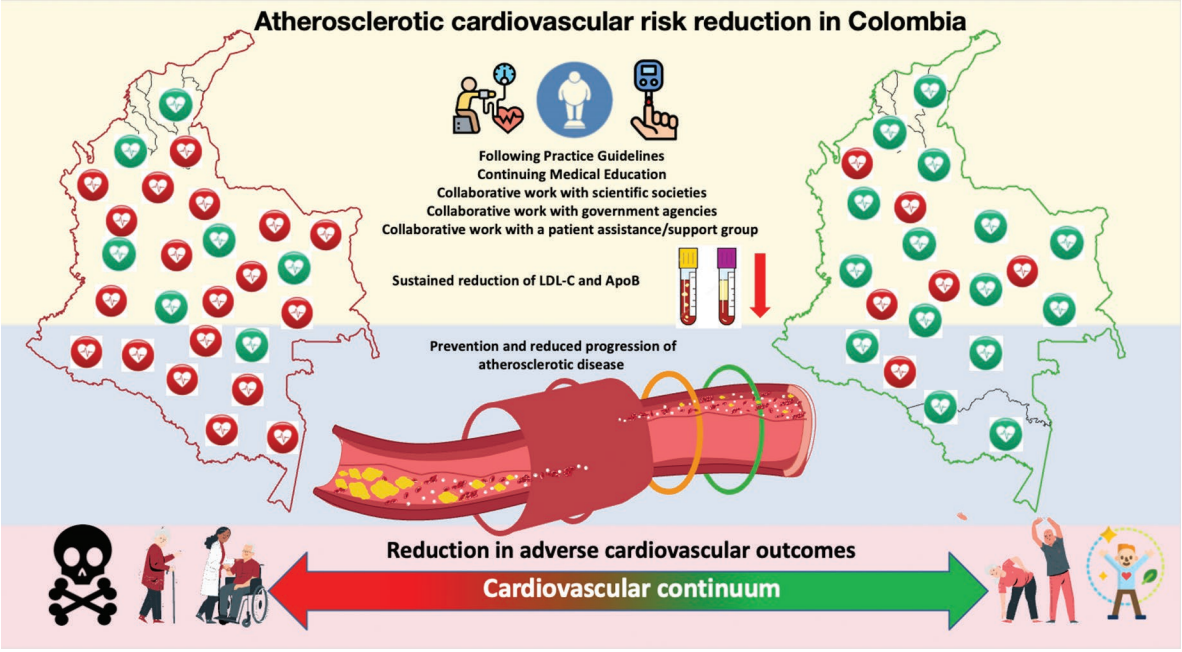


Figure 1. Cardiovascular risk in Colombia.

to improve the prescription of and access to treatments with proven effectiveness, like statins and ezetimibe, as well as the development of strategies to implement the new therapies and drugs, like RNA, peptide and monoclonal antibody based therapies, which are powerful additions to the oral agents and greatly improve the capacity to achieve lower LDL-C and Apo B levels with a highly favorable specificity and safety profile.

Global multidisciplinary collaborative work groups are needed to optimize equitable access to treatments with sufficient evidence and the implementation of new therapies, involving the industry, regulatory agencies, the government and the community. In this context, a call to action for new global approaches to pharmacological solutions for cardiovascular diseases published by the American Heart Association (AHA) in 2021 highlights the need to phenotype patients, moving away from syndromic approaches and delving into patient stratification based on biological mechanisms and identifying those who progress faster, especially in the context of ASCVD and heart failure, and working on all the measures that will allow the population to participate more in dyslipidemia control[11-14].

If we are to fulfill the commitment to reduce the number of premature deaths related to noncommunicable diseases by 25% by 2025, according to the World Health Organization's Global Action Plan 2013-2030[15], as well as the Colombian Decennial Public Health Plan 2022-2031 to reduce the burden of preventable disease and disability in individuals, families and communities according to the regional realities, easily scalable strategies must be created and implemented to reduce the population's risk, along with intersectoral and trans-sectoral policies focused on the biological, social, economic and political determinants, to improve health and wellbeing[16]. Healthcare professionals and public health and policy institutions should measure and highlight the impact of cardiovascular risk factor changes maintained over time in many people, on cardiovascular outcomes in the population (Fig. 1).

To accomplish this, Monte Carlo is a mathematical multiple probability simulation tool used to estimate the possible outcomes of uncertain events. It helps evaluate the impact of risk in real situations and analyzes the sensitivity to evaluate the impact of individual entries on a given outcome, calculate the correlation between entries to understand the relationships between the variables, and create a model of possible outcomes using a probability distribution. The Monte Carlo simulation method allows data from short-term clinical trials to be extrapolated to long-term health outcomes in the population, estimating how the implementation of interventions against ASCVD in the

population could alleviate a large part of the future burden on patients and healthcare systems[17].

Inclisiran is a small interfering RNA (siRNA) therapy designed to produce sustained PCSK9 inhibition and, therefore, lower LDL-C. Inclisiran has been shown to effectively lower LDL-C levels with each six-month dose. Since LDL-C reduction through different strategies has been shown to reduce cardiovascular events in proportion to its absolute reduction, the LDL-C reduction found in the ORION 10 and 11 trials, if maintained for another nine years with 18 additional inclisiran injections, could reduce the 10-year cardiovascular risk[15-18]. The potential cardiovascular health benefits of inclisiran, combined with statins, have been evaluated using Monte Carlo simulation with 500,000 individuals similar to the ORION 10 and ORION 11 trial populations. To do this, the baseline 10-year cardiovascular risk was calculated for the ORION 10 and 11 populations, using the Second Manifestations of ARTerial diseases (SMART) equation in patients with prior cardiovascular disease[19]. The SMART equation has external validation in cohorts from Western Europe, Southern Europe, United States, Canada, Mexico, South Africa, Australia and New Zealand[20].

A simulation study of a healthcare system intervention to estimate the cardiovascular health benefits of an siRNA approach, shows significant potential cardiovascular benefits of using inclisiran in individuals with a high risk of cardiovascular events (25% predicted 10-year risk and an LDL-C of 104 mg/dl). The simulation predicts that 31,522 potential cardiovascular events could be prevented in the first 10 years by using inclisiran plus statins, compared with a projected increase of 1,426 first cardiovascular events in the group with placebo injections and statins alone in this simulated population. In individuals with a ≥ 20% risk of cardiovascular events, inclisiran treatment could prevent up to 23,552 cardiovascular events (first events) over 10 years, highlighting the potential benefit in high-risk populations[19].

These findings suggest that significant gains could be made in the population's health over 10 years by implementing large-scale strategies with the capacity to provide substantial and sustained LDL-C reductions, beyond the gains that can be achieved with statins. This highlights inclisiran's potential to have an impact on public health by reducing the incidence of cardiovascular events. This article concludes that the cardiovascular outcomes with inclisiran are awaited to confirm its long-term benefits and cardiovascular safety, along with studies in real-world settings, providing a more complete understanding of its potential benefits and limitations[19-22].

Conclusions

These promising population-level results are a reference point for Colombia and reflect the potential benefits of large-scale strategies. Using data from the ORION 10 and 11 studies, enrolling a very high cardiovascular risk population on maximum statin doses, baseline LDL-C levels were lowered by 52.3% (United States population, ORION 10) and 49.9% (European and African population, ORION 11). This indicates a 50% global reduction in LDL-C, equivalent to 52 mg/dl, which remains stable over time with just two doses per year and minimal side effects. Although there is insufficient data in Colombia to replicate the simulations described or extensive secondary prevention follow-up cohorts, there is reliable evidence that the impact on humans of a 38 mg/dl reduction in LDL-C results in an approximately 10% reduction in cardiovascular mortality and 22% reduction in cardiovascular events, if maintained for five years, without considering the initial risk profiles. Adjusting for the risk profile, there would be an absolute rate difference (ARD) for all-cause mortality of –1.33 (–1.76; –0.76), which, undoubtedly, would have a very positive impact on the national vital statistics. It is also important to point out that inclisiran has significant advantages in its twice-yearly dosing schedule (due to its mechanism of action). This ensures sustained LDL-C reductions and promotes high long-term patient adherence and persistence, overcoming the current barriers, facilitating large-scale implementation, and ensuring a sustained positive impact on cardiovascular risk reduction in the population.

Funding

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

Conflicts of interest

The authors declare that they have received fees from companies related to dyslipidemia management drugs for research support, consulting and honoraria.

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 study does not involve patient personal

data nor does it require ethical approval. The SAGER guidelines do not apply.

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

References

1. Tsao CW, Aday AW, Almarzooq ZI, Anderson AM, Arora P, Avery C, et al. Heart disease and stroke statistics-2023 update: A report from the American Heart Association. Circulation. 2023;147:e93-e621.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459-72.
3. Ference BA, Graham I, Tokgozoglu L, Catapano AL. Impact of lipids on cardiovascular health: JACC health promotion series. J Am Coll Cardiol. 2018;72:2980-95.
4. García-Peña ÁA, Zárate-Correa LC, Campo RL, Rodríguez-Plazas JA, Aristizábal D, Arango J, et al. Ruta colombiana del colesterol. Mesa redonda nacional sobre el colesterol en Colombia. Llamado a la acción. Revista Colombiana de Cardiología. 2024 Jan 9;30(6).
5. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases, 2013-2020.
6. Muñoz OM, García ÁA, Fernández-Ávila D, Higuera A, Ruiz ÁJ, Aschner P, et al. Guía de práctica clínica para la prevención, detección temprana, diagnóstico, tratamiento y seguimiento de las dislipidemias: evaluación del riesgo cardiovascular. Revista Colombiana de Cardiología. 2015 Nov;22(6):263–9.
7. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. J Am Coll Cardiol. 2020 Dec;76(25):2982–3021.
8. Murphy A, Faria-Neto JR, Al-Rasadi K, Blom D, Catapano A, Cuevas A, et al. World Heart Federation Cholesterol Roadmap. Glob Heart. 2017;12(3):179-197.e5.
9. Lash DB, Mack A, Jolliff J, Plunkett J, Joson JL. Meds-to-Beds: The impact of a bedside medication delivery program on 30-day readmissions. JACCP 2019;2(6):674-80.
10. Soffer D, Stoekenbroek R, Plakogiannis R. Small interfering ribonucleic acid for cholesterol lowering – Inclisiran: Inclisiran for cholesterol lowering. J Clin Lipidol. 2022;16:574-82.
11. Taddei C, Zhou B, Bixby H, Carrillo-Larco RM, Danaei G, Jackson RT, et al. Repositioning of the global epicentre of non-optimal cholesterol NCD Risk Factor Collaboration (NCD-RisC)*.
12. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics—2016 Update. Circulation. 2016 Jan 26;133(4).
13. Hwang TJ, Lauffenburger JC, Franklin JM, Kesselheim AS. Temporal Trends and Factors Associated With Cardiovascular Drug Development, 1990 to 2012. JACC Basic Transl Sci. 2016 Aug;1(5):301–8.
14. Figtree GA, Broadfoot K, Casadei B, Califf R, Crea F, Drummond GR, et al. A Call to action for new global approaches to cardiovascular disease drug solutions. Circulation. 2021;144(2):159-69.
15. NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. The Lancet. 2020;396:918-34.
16. Ruíz F, Escobar GM, Milena Cuellar Segura C, Teresa Buitrago Grupo ME, María Henríquez Grupo GM, Stella Ríos Grupo LM, et al. PLAN DECENAL DE SALUD PÚBLICA PDSP 2022 - 2031. Bogota; 2022
17. Nguyen THT, Mouksassi M, Holford N, Al□Huniti N, Freedman I, Hooker AC, et al. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol. 2017 Feb 10;6(2):87–109.
18. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-19.
19. Ray KK, Gunn LH, Conde LG, Raal FJ, Wright RS, Gosselin NH, et al. Estimating potential cardiovascular health benefits of improved population level control of LDL cholesterol through a twice-yearly siRNA-based approach: A simulation study of a health-system level intervention. Atherosclerosis. 2024;117472.
20. Dorresteijn JA, Visseren FL, Wassin, AM, Gondrie MJ, Steyerberg EW, Ridker PM, et al; SMART Study Group. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;99(12):866-72.
21. Borén J, John Chapman M, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41:2313-30.
22. Ennezat PV, Guerbaai RA, Maréchaux S, Le Jemtel TH, François P. Extent of low-density lipoprotein cholesterol reduction and all-cause and cardiovascular mortality benefit: a systematic review and meta-analysis. J Cardiovasc Pharmacol. 2023;81(1):35-44.

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

Check for updates

ORIGINAL ARTICLE

Atrial appendage occlusion in patients with atrial fibrillation on renal replacement therapy

Cierre de orejuela en pacientes con fibrilación auricular en terapia de reemplazo renal

*Jorge M. Palmezano-Díaz[1], Julián M. Aristizábal[1,2,4], Juan C. Díaz[1,2,4], Jorge E. Marín[1,2,4], César D. Niño[1,3], Oriana Bastidas[1,2,4], Juanita Velásquez[5], and Mauricio Duque[1,2]**

[1]Electrophysiology Postgraduate Course, Universidad CES; [2]Electrophysiology Department, Hospital San Vicente; [3]Electrophysiology Department, Hospital Pablo Tobón Uribe; [4]Electrophysiology Department, Clínica Las Américas; [5]Cardiology Department, Clínica CES. Medellín, Colombia

Abstract

Introduction: *left atrial appendage occlusion (LAAO) is a therapeutic alternative in patients with nonvalvular atrial fibrillation (NVAF) when anticoagulation is contraindicated. In patients with NVAF on renal replacement therapy, the embolic risk is accompanied by a very high risk of bleeding. Anticoagulant therapy has not shown an adequate risk-benefit relationship.* **Objective:** *to describe the population of patients with atrial fibrillation on renal replacement therapy who undergo percutaneous atrial appendage occlusion, and the immediate results of the intervention.* **Method:** *this was a retrospective, multicenter, descriptive study of patients with NVAF and chronic kidney disease on renal replacement therapy who underwent LAAO from 2017 to 2022.* **Results:** *this series of 25 patients had the following characteristics: average age: 68.8 years; 68% were men, 100% had hypertension, 52% had type 2 diabetes mellitus, and 36% had coronary disease. The average CHA2DS2-VASc score for measuring embolic risk was 4 points. The average systolic function measured by left ventricular ejection fraction (LVEF) was 55%. A total of 48% were on anticoagulation. As far as the devices used, 76% were WATCHMAN and 24% were Amulet devices. The procedure was successful in 96%. There were four non-serious complications. There were no intervention-related ischemic cerebrovascular events or deaths.* **Conclusion:** *LAAO in patients on renal replacement therapy has proven to be an effective and safe alternative, with a low rate of complications and a favorable initial follow-up.*

Keywords: *Atrial fibrillation. Renal replacement therapy. Atrial appendage. Anticoagulants. Vascular closure devices.*

Resumen

Introducción: *el cierre de la auriculilla izquierda es una alternativa terapéutica en pacientes con fibrilación auricular no valvular (FANV) con contraindicación para anticoagulación. Los pacientes con terapia reemplazo renal y FANV tienen alto riesgo embólico, acompañado de un elevadísimo riesgo de sangrado. La anticoagulación no ha demostrado una relación adecuada de riesgo-beneficio.* **Objetivo:** *describir la población de pacientes con fibrilación auricular en terapia de reemplazo renal que son llevados a cierre percutáneo de orejuela y los resultados inmediatos de la intervención.* **Método:** *estudio descriptivo retrospectivo, multicéntrico, de pacientes con FANV y enfermedad renal crónica en terapia de reemplazo renal llevados a LAAO desde 2017 a 2022.* **Resultados:** *serie de 25 pacientes cuya edad promedio fue 68.8 años; 68% fueron hombres,*

***Correspondence:**
Mauricio Duque
E-mail: mduquer@ces.edu.co

Date of reception: 30-07-2023
Date of acceptance: 22-10-2024
DOI: 10.24875/RCCARE.M24000145

Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):18-23
www.rccardiologia.com

100% hipertensos, 52% diabéticos y 36% con enfermedad coronaria. El riesgo embólico por CHA2DS2-VASc promedio fue 4 puntos. La función sistólica medida por FEVI fue, en promedio, 55%. El 48% recibía anticoagulante previamente. Respecto al tipo de dispositivo, 76% tenía WATCHMAN y 24% Amulet. El procedimiento fue exitoso en el 96%. Hubo cuatro complicaciones no graves. No se presentaron eventos cerebrovasculares isquémicos ni muertes relacionadas con la intervención. **Conclusión:** *el cierre de la auriculilla izquierda en pacientes con terapia de reemplazo renal ha mostrado ser una alternativa efectiva y segura, con una baja tasa de complicaciones y un seguimiento inicial favorable para los pacientes.*

Palabras clave: *Fibrilación atrial. Terapia de reemplazo renal. Apéndice atrial. Anticoagulación. Dispositivos de cierre vascular.*

Introduction

In patients on renal replacement therapy with nonvalvular atrial fibrillation (NVAF), the risk of embolism is accompanied by a very high risk of bleeding; therefore, anticoagulant therapy has not categorically shown an appropriate risk-benefit ratio, and the best treatment for this population has not yet been determined[1]. The left atrial appendage is a lethal source of emboli in patients with atrial fibrillation; therefore, left atrial appendage occlusion (LAAO), with its lower embolic risk and long-term bleeding reduction (by avoiding anticoagulation), is an alternative with a solid pathophysiological basis and encouraging results in initial studies of patients around the world[1]. Atrial appendage occlusion can also reduce the risk of stroke in patients for whom oral anticoagulation is contraindicated. Oral anticoagulant (OAC) therapy has proven to be feasible in mild to moderate chronic kidney disease (CKD). On the other hand, the optimal antithrombotic treatment for patients with atrial fibrillation and end-stage renal disease is not known and has is insufficient evidence to support it[2,3].

Chronic kidney disease is associated with the onset of cardiovascular disease and can also increase the risk of atrial fibrillation; therefore, these conditions have a reciprocal relationship. Regardless of its severity, CKD is associated with a higher prevalence of atrial fibrillation and a greater risk of stroke or systemic thromboembolism and bleeding[4-6]. The risk of major bleeding in patients on hemodialysis increases significantly with anticoagulant and antiplatelet therapy[7].

Oral anticoagulants are not associated with a lower risk of thromboembolism in patients with atrial fibrillation on long-term dialysis. Warfarin, dabigatran and rivaroxaban are associated with a significantly higher risk of bleeding compared with apixaban and no anticoagulant. The risk-benefit ratio of OACs in patients with atrial fibrillation on dialysis is not well established and, therefore, percutaneous occlusion of the atrial appendage in this group of patients is an encouraging alternative for reducing embolic risk[8]. Anticoagulation is an effective measure for reducing this risk; however, there are groups of patients for whom evidence is lacking or anticoagulation is contraindicated. Despite having the option of percutaneous occlusion of the atrial appendage, the short and long-term outcomes in patients on renal replacement therapy are unknown[2,8].

Thus, percutaneous occlusion could become a therapeutic option for reducing embolic risk in patients with atrial fibrillation on renal replacement therapy for whom evidence is lacking or anticoagulation is contraindicated. The objective is to describe the population of patients with atrial fibrillation on renal replacement therapy who undergo percutaneous atrial appendage occlusion, as well as the immediate outcomes of the intervention.

Method

This was a retrospective multicenter study of patients with NVAF and CKD on renal replacement therapy who underwent LAAO between January 2017 and December 2022. The study sample was collected using non-probability convenience sampling. All patients who met the inclusion criteria during the study period (patients over the age of 18 with NVAF and CKD on renal replacement therapy who underwent atrial appendage occlusion, with a high embolic risk measured by CHADS-VASc and an indication for anticoagulation) were included. Patients with total functional dependency, CKD without renal replacement therapy, mechanical heart valves and anticoagulant therapy prescribed for a reason other than atrial fibrillation were excluded.

A chart review was done of the patients available at the various healthcare facilities. An exhaustive search was done for all cases that met the inclusion criteria. The charts were reviewed and analyzed, selecting the patients who underwent LAAO and had CKD. After the exhaustive search, the data was extracted from the charts. A digital data collection form was filled out for

each patient, and the data was stored in a previously designed Excel form. A Google spreadsheet was designed by the investigators and stored in the cloud on Google Drive, which allowed the data to be accessed and edited at any time from mobile devices or computers. Editing access to the database was restricted and only available for the study investigators. Considering the potential information bias due to the data collection tool (which was controlled through proper database handling and appropriate patient selection based on the inclusion and exclusion criteria), unified criteria between the investigators was essential to ensure proper data collection. Data processing for statistical analysis was done using SPSS Statistics 24.0. The data was managed on Windows 8, and Microsoft Excel 2010 was used to generate the database. For the analysis plan, qualitative variables were analyzed using frequencies and percentages, and quantitative variables with averages and standard deviation. For asymmetric variables (with noncentral distribution), medians and percentiles were calculated. The bivariate analysis was done using Chi^2 and the comparison of means or medians (T test, U test, ANOVA). A p less than 0.05 was considered statistically significant. Approval was received from the ethics committees of the participating institutions, respecting the principles of beneficence, nonmaleficence and justice. According to Article 11 of Resolution 008430 of 1993, our research project was considered to be "no-risk."

Results

Twenty-five patients were analyzed, with an average age of 68.8 years; 68% were male and 100% had hypertension, 52% had type 2 diabetes mellitus, 36% had coronary disease, 36% had dyslipidemia, 28% had prior cerebrovascular disease, 24% had hypothyroidism, 20% had heart failure and 8% had chronic obstructive pulmonary disease (Table 1).

Of the 100% of patients with atrial fibrillation and CKD on renal replacement therapy, 92% were on hemodialysis and 8% on peritoneal dialysis. The average CHA2DS2-VASc score for embolic risk was 4 points, classified as high risk (a minimum of 1 point and a maximum of 6 points). The main indication for percutaneous atrial appendage occlusion was renal replacement therapy in 100%, along with a history of gastrointestinal bleeding in 20%, another type of bleeding in 20% and a brain bleed in 8%.

The average systolic function measured by left ventricular ejection fraction (LVEF) was 55% (minimum of 33% and maximum of 70%). A total of 48% were on prior anticoagulant therapy (28% on warfarin and 20% on apixaban). As far as the device, 76% had a WATCHMAN device and 24% an Amulet device, with an average size of 26 mm. The mean fluoroscopy time during the procedure was 16 minutes, and the mean total procedure time was 78 minutes (Table 2); intracardiac echocardiography was used in 52% of the patients. The procedure was successful in 96% of the patients.

There were four complications related to the procedure, corresponding to 16% of the patients: one hematoma at the access site that did not require intervention, one AV fistula that required surgery, one cardiac tamponade that required pericardial drainage, and one intracavitary thrombus in which percutaneous atrial appendage occlusion could not be performed. There were no deaths related to the intervention.

After the procedure, pharmacological management involved direct oral anticoagulants in 48%, dual antiplatelet therapy in 28%, single antiplatelet therapy in 24%, low-molecular-weight heparin in 4% and no therapy in 4%. None of the patients had clinically documented ischemic cerebrovascular disease (one patient had a mild cerebral hemorrhage that did not require surgical drainage while on single antiplatelet therapy). The overall mortality in this population was 28%, and none of these deaths were related to the procedure or intervention; 20% died from kidney disease complications, 4% due to diabetes complications, and 4% due to advanced cancer (Table 3).

Table 1. Sociodemographic and clinical characteristics of the patients

Characteristic	n (%)
Sex Female Male	 8 (32) 17 (68)
Age, average ± SD	68.80 ± 7.30
Hypertension	25 (100)
Type 2 diabetes mellitus	13 (52)
Hypothyroidism	6 (24)
Dyslipidemia	9 (36)
Cerebrovascular disease	7 (28)
Chronic obstructive pulmonary disease	2 (8)
Heart failure	5 (20)
Coronary disease	9 (36)

Table 2. Procedural characteristics and left ventricular ejection fraction (LVEF) characteristics

	n	Minimum	Maximum	Mean	Standard dev.
LVEF (%)	25	33.0%	70.0%	54.9%	8.7%
Size of the device (mm)	25	18.0	35.0	26.40	5.3
Fluoroscopy time (min)	16	6.0	35.0	15.9	8.0
Procedure time (min)	15	40.0	150.0	78.5	31.5

Discussion

The incidence, prevalence and outcomes of atrial fibrillation reported in patients with end-stage renal disease vary, as do the outcomes in patients on renal replacement therapy[9]. Fink et al.[2] described a population of 604 patients with CKD, and only 49 were on renal replacement therapy. In this study, we reported 25 cases in fewer study centers, which could be considered a significant sample. The population in Fink's study also had similar characteristics, despite having a higher mean age (76 vs. 68 years)[2]: shared percentages of comorbidities like hypertension, diabetes and vascular disease; the same embolic risk with a CHA2DS2-VASc score of 4 vs. 4; and a contraindication for anticoagulation. Considering the paucity of evidence for using OACs in patients on renal replacement therapy, as well as the high risk of bleeding, studies report wide differences in the use of anticoagulant and antiplatelet therapy in these patients. For instance, Sood et al.'s study reported a range of 0.3-18%, while our study found a high percentage (48%) of pharmacological treatment, even in patients on renal replacement therapy[10].

On the whole, despite the high burden of comorbidities in patients with CKD and atrial fibrillation, they generally have preserved systolic function[2]; our study found preserved left ventricular systolic function, with an average of 50%. In some studies, percutaneous atrial appendage occlusion has been done exclusively using the Amulet device[11], while in others, only the WATCHMAN device has been used[12]. In our study, different available techniques and devices were employed for atrial appendage occlusion, 76% using WATCHMAN devices and 24% Amulet devices, which allows a comparative analysis of outcomes with the different techniques.

One Italian multi-center registry analyzed 142 patients on hemodialysis who underwent percutaneous atrial appendage occlusion and compared their clinical and procedural outcomes with those of patients on hemodialysis who received OACs or no antithrombotic therapy. They found few periprocedural complications, as well as significantly lower overall mortality during the 21-month follow-up in patients who underwent percutaneous occlusion[13]. The rate of periprocedural complications was 16%, and these were very mild and did not require complex interventions; in addition, there was a lower rate of hemorrhagic complications, which coincides with information from Luani's studies[14]. A prospective registry found that, despite patients with CKD having a higher cardiovascular risk profile, device implantation was safe, and percutaneous atrial appendage occlusion was associated with effective stroke prevention in all CKD stages[15]. Our study found a 0% rate of ischemic embolic complications (only one case had mild hemorrhagic cerebrovascular disease that did not require complex interventions and could be related to residual antiplatelet therapy). Of those who underwent atrial appendage occlusion with a device, patients with

Table 3. Outcomes of the intervention

Characteristic	n (%)
Success of the procedure	24 (96)
Amulet device	6 (24)
WATCHMAN device	19 (76)
Exclusive use of intracardiac echocardiography	13 (52)
Single antiplatelet therapy after the intervention	6 (24)
Dual antiplatelet therapy after the intervention	7 (28)
Oral anticoagulant therapy after the intervention	12 (48)
Low-molecular-weight heparin after the intervention	1 (4)
No pharmacological therapy after the intervention	1 (4)
Ischemic cerebrovascular event	0 (0)
Hemorrhagic cerebrovascular event	1 (4)
Procedure-related complications	4 (16)

CKD and those with normal kidney function had similar procedural safety[16], which favors the indication for occlusion in patients on renal replacement therapy.

A retrospective cohort found that apixaban was associated with a lower risk of bleeding[17]. In our study's postoperative treatment, the most frequently used anticoagulant was apixaban, which could confer a protective effect against the elevated risk of bleeding after the intervention.

Mortality varies, and despite being patients with a high burden of comorbidities, most deaths after device implantation are related to the kidney disease itself as well as the patients' own diseases. Our study found a mortality rate of 28%, and none of the deaths were related to the procedure or the intervention; 20% were secondary to kidney disease complications. The mortality rate in other studies has been lower, from 10-18%[2].

Patients on dialysis have been under-represented in cardiovascular trials that have shown a net benefit from commonly used preventive treatments (e.g., antihypertensive treatment, low-dose aspirin, carotid revascularization and thromboprophylaxis for atrial fibrillation), and there is still uncertainty regarding the safety and efficacy of many of these treatments in this high-risk population[18-20].

Limitations

Having a chart review as the only source of data could be a source of bias, and therefore the charts were exhaustively reviewed and patients with more than 90% of the data recorded were included. In view of the lack of evidence for anticoagulation in patients with kidney disease, patients were selected according to the criteria of at least two specialists, to ensure they were good candidates for the procedure.

Conclusion

The experience with LAAO in patients on renal replacement therapy has proven to be an effective and safe alternative, which also has a low rate of complications. These are patients with multiple comorbidities but preserved systolic function, in whom anticoagulation is contraindicated due to a lack of evidence to support its use and who benefit from this treatment option, with a low rate of periprocedural complications. Despite having high mortality, this mortality is not due to either the intervention or embolic events. New studies are needed in larger populations to validate these results in other patient groups.

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 involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from 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. The authors declare that no generative artificial intelligence was used in writing this manuscript.

References

1. Johnson WD, Ganjoo AK, Stone CD, Srivyas RC, Howard M. The left atrial appendage: our most lethal human attachment! Surgical implications. Eur J Cardiothorac Surg. 2000;17:718-722.
2. Fink T, Paitazoglou C, Bergmann MW, Sano M, Keelani A, Sciacca V, et al. Left atrial appendage closure in end-stage renal disease and hemodialysis: Data from a German multicenter registry. Catheter Cardiovasc Interv. 2023.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373-498.
4. Alonso A, Lopez FL, Matsushita K, Chen LY, Agarwal SK, Soliman EZ, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123(25):2946-53.
5. Baber U, Howard VJ, Halperin JL, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhyth Electrophysiol. 2011;4:26–32.
6. Olesen JB, Lip GYH, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012; 367:625–35.
7. Holden RM, Harman GJ, Wang M, Holland D, Day AG. Major bleeding in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3:105–10.
8. Kuno T, Takagi H, Ando T, et al. Oral anticoagulation for patients with atrial fibrillation on long‐term dialysis. JACC. 2020;75:273–85.
9. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta‐analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant. 2012t;27:3816–22.
10. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013;84:600–8.
11. Hildick‐Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer™ amulet™ device: full results of the prospective global observational study. Eur Heart J. 2020;41:2894–901.
12. Boersma LV, Ince H, Kische S, et al. Evaluating real‐world clinical outcomes in atrial fibrillation patients receiving the Watchman left atrial appendage closure technology: final 2‐year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. Circ Arrhythm Electrophysiol. 2019;12:e006841.

13. Genovesi S, Porcu L, Slaviero G, et al. Outcomes on safety and efficacy of left atrial appendage occlusion in end stage renal disease patients undergoing dialysis. J Nephrol. 2021;34:63–73.
14. Luani B, Genz C, Herold J, et al. Cerebrovascular events, bleeding complications and device related thrombi in atrial fibrillation patients with chronic kidney disease and left atrial appendage closure with the WATCHMAN™ device. BMC Cardiovasc Disord. 2019;19:112.
15. Fastner C, Brachmann J, Lewalter T, et al. Left atrial appendage closure in patients with chronic kidney disease: results from the German multicentre LAARGE registry. Clin Res Cardiol. 2021;110:12–20.
16. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end–stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138:1519–29. Erratum in: Circulation, 2018;138:e425.
17. Kefer J, Tzikas A, Freixa X, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. Int J Cardiol. 2016;207:335–40.
18. Herrington W, Haynes R, Staplin N, Emberson J, Baigent C, Landray M. Evidence for the prevention and treatment of stroke in dialysis patients. Sem Dialysis. 2015;28:35–47.
19. Almutairi AR, Zhou L, Gellad WF, et al. Effectiveness and safety of non–vitamin K antagonist oral anticoagulants for atrial fibrillation and venous thromboembolism: a systematic review and meta– analyses. Clin Ther. 2017;39:1456–78.e36.
20. Badhwar V, Rankin JS, Damiano RJ, Gillinov AM, Bakaeen FG, Edgerton JR, et al. The Society of thoracic surgeons 2017 clinical practice guidelines for the surgical treatment of atrial fibrillation. Ann Thorac Surg. 2017;103:329-41.

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

Check for updates

ORIGINAL ARTICLE

Experience in aortic valve replacement using different surgical accesses between 2018 and 2021: a cross-sectional study

Experiencia en el recambio valvular aórtico mediante diferentes accesos quirúrgicos entre 2018 y 2021: estudio de corte transversal

Rafael Figueroa-Casanova[1], Juan D. Saavedra-Henao[1], Carlos J. Pérez-Rivera[2], Juan S. Figueroa-Legarda[3], Diego A. Beltrán-Rincón[1], Raúl G. Aguiar-Barreo[4], and Valentina Arboleda-Cárdenas[4]*

[1]Department of Cardiovascular Surgery, Clínica Avidanti, Ibagué; [2]Department of General Surgery, Universidad El Bosque, Bogotá; [3]Faculty of Medicine, Universidad El Bosque, Bogotá; [4]Faculty of Medicine, Universidad del Tolima, Ibagué. Colombia

Abstract

Introduction: *aortic valve replacement is one of the most common cardiac surgeries today, traditionally performed through open-heart surgery (median sternotomy). However, alternative surgical approaches, such as minimally invasive surgery through a mini-median sternotomy and transcatheter aortic valve implantation (TAVI), have been developed.* **Objective:** *to describe the experience of a cardiovascular center in Tolima with aortic valve replacement using different surgical approaches between 2018 and 2021.* **Method:** *a descriptive, cross-sectional study was conducted. A descriptive and bivariate analysis was performed of the surgical approach used.* **Results:** *the population consisted of 131 patients. Degenerative aortic valve disease was found in 71.7% (n = 94) of cases, followed by congenital conditions in 28.2% (n = 37). Regarding the surgical approach, 64.9% (n = 85) underwent open-heart surgery, followed by 24.4% (n = 32) who had minimally invasive surgery, and in third place, 10.7% (n = 14) with transcatheter replacement. Bivariate analysis revealed that the minimally invasive approach showed better results.* **Conclusions:** *the open surgical approach is the most commonly implemented; however, the minimally invasive approach should be considered as an option due to its excellent results and a similar cost. This approach offers benefits such as reduced postoperative pain and a smaller surgical scar. Transcatheter access is preferred for patients at high surgical risk.*

Keywords: *Aortic valve. Aortic valve stenosis. Aortic valve insufficiency. Transcatheter aortic valve replacement.*

Resumen

Introducción: *en la actualidad, el reemplazo valvular aórtico es una de las cirugías cardiacas que más se realiza. Durante décadas, se hizo por vía abierta (esternotomía media); sin embargo, se han desarrollado otros accesos quirúrgicos, como la miniesternotomía media (mínima invasión) y el reemplazo vía transcatéter (TAVI).* **Objetivo:** *describir la experiencia de un centro cardiovascular en el reemplazo de válvula aórtica por los diferentes accesos quirúrgicos entre 2018 y 2021.* **Método:** *se llevó a cabo un estudio descriptivo, de corte transversal, que incluyó un análisis descriptivo y bivariado respecto al acceso quirúrgico utilizado.* **Resultados:** *la población estuvo conformada por 131 pacientes. Se registró valvulopatía aórtica de origen degenerativo en el 71.7% (n = 94), seguida de la origen congénito en el 28.2% (n = 37). Respecto al abordaje quirúrgico,*

***Correspondence:**
Juan D. Saavedra-Henao
E-mail: juansaavedra1427@gmail.com

Date of reception: 24-11-2023
Date of acceptance: 06-12-2024
DOI: 10.24875/RCCARE.M24000147
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):24-30
www.rccardiologia.com

fue abierto en el 64.9% (n = 85), mínimamente invasivo en el 24.4% (n = 32) y transcatéter en el 10.7% (n = 14). El análisis bivariado mostró que el abordaje mínimamente invasivo tenía mejores resultados. **Conclusiones:** *el acceso abierto es el más implementado; no obstante, el mínimamente invasivo se debe plantear como una opción que ofrece excelentes resultados y un costo económico similar, además de beneficios como la disminución del dolor posoperatorio y una cicatriz quirúrgica menor. Se prefiere implementar el acceso transcatéter en pacientes con alto riesgo quirúrgico.*

Palabras clave: *Válvula aórtica. Estenosis de la válvula aórtica. Insuficiencia de la válvula aórtica. Reemplazo de la válvula aórtica transcatéter.*

Introduction

Heart valve disease is a public health problem around the world, due to its heightened incidence. Thus, an estimated one out of eight people over the age of 75 have this condition[1]. Aortic valve disease is the most prevalent, which is secondary to heart valve stenosis in 40 to 50% of those affected [2]. Its prevalence ranges from 2.8% in people 60 to 74 years of age to 13.1% in those over the age of 75[2,3]. In high-income countries, aortic valve disease is mainly degenerative; on the other hand, in middle and low-income countries, the main cause is rheumatic[3].

Currently, valve replacement is the second most common heart surgery procedure[4], with the main valvular surgery being aortic valve replacement[5], which for decades was done with open surgery using median sternotomy. However, over the years, different surgical approaches have been developed for valve replacement, such as mini-median sternotomy (minimally invasive) and transcatheter aortic valve implantation (TAVI), whose goal is to reduce surgical trauma and hospitalization time, and leave smaller surgical scars[2,4,6]. However, their use will depend on the patients' characteristics and the surgeons' expertise. Therefore, the objective of this paper is to describe the aortic valve replacement experience of a tertiary care cardiovascular center in Tolima, using different surgical approaches, between 2018 and 2021.

Method

This was a descriptive, cross-sectional study at a tertiary care institution in a city in Tolima, between September 2018 and September 2021.

Patients over the age of 18 who underwent aortic valve replacement surgery with no other heart procedure between September 2018 and September 2021 were included. Patients under the age of 18 or those with incomplete medical records were excluded.

A total of 131 patients who met the inclusion criteria were found in the medical chart system in the cardiovascular surgery department. A data collection tool was structured that included sociodemographic, laboratory and imaging variables, the characteristics of the surgical procedure, immediate postoperative complications and total cost for each type of surgical approach employed.

A descriptive analysis was done in which qualitative variables were expressed as absolute values and percentages, while quantitative variables were described as measures of central tendency and dispersion, according to their normality. In addition, the average total cost of the procedures in Colombian pesos was recorded, from the preoperative to the postoperative stage, which included the cost of the hospital stay, and was converted to dollars using the international exchange rate. A bivariate analysis was done for the type of surgical approach used in the valve replacement procedure (open-minimally invasive-transcatheter). Student's t and Mann-Whitney U tests were used for quantitative variables, and Chi square and Fisher's test were used for dichotomous variables, as required, considering a p value less than 0.05 to be statistically significant. The statistical analysis was done using R-Studio Desktop version 1.3.1073. The study was reviewed and approved by the institutional ethics and research committee with code CICAI-02-2023.

Results

The population consisted of 131 patients, 60.3% (n = 79) of whom were male, with a median age of 66 years (interquartile range [IQR]: 56.5-73.5). The procedures were scheduled in 98.5% (n = 129) of the study population, and only 1.5% (n = 2) were emergency procedures. Hypertension was the most frequent pre-existing condition, with 77.1% (n = 101); heart failure with Framingham criteria and proBNP levels with a cutoff point of 750 mg/dl was in second place, with 60.3% (n = 79); and dyslipidemia and smoking were in third and fourth place, with 39.7% (n = 52) and 38.2%

(n = 50), respectively. The rest of the sociodemographic variables studied are shown in table 1.

Table 1 also mentions the presurgical scales used to measure morbidity and mortality: EUROscore II, which reported a median of 2.2% (IQR: 1.3-5.1) and the STS morbidity and mortality score, that reported a median of 11.8% (IQR: 7.9-18.7), with a mortality value of 4.02% (1.78-5.8). As far as diagnostic imaging, the presurgical echocardiogram reported a left ventricular ejection fraction (LVEF) of 52% (IQR: 39-62), with peak and mean gradients of 75 mmHg (IQR: 38.6-100.3) and 44 mmHg (IQR: 31-56), respectively.

Degenerative valve disease was present in 71.7% (n = 94), followed by congenital disease in 28.2% (n = 37), 49.6% (n = 65) of whom had signs of mixed structural damage (regurgitation and stenosis), with the remaining 50.4% (n = 69) having stenosis (28.3%) or regurgitation (23.7%). Regarding the surgical approach, 64.9% (n = 85) were open procedures, that is, using a median sternotomy with central cannulation for extracorporeal circulation (arterial access through the ascending aorta and venous access directly in the right atrium). These were followed by 24.4% (n = 32) using the minimally invasive approach with a minithoracotomy through the fifth intercostal space with peripheral cannulation, which was done using both arterial and venous femoral access. In third place, 10.7% (n = 14) were transcatheter procedures which were all done using femoral access, where it is important to mention that the patients with a history of atrial septal defects received pericardial patching in an open procedure (n = 2) and minimally invasive surgery (n = 2). The open and minimally invasive procedures were performed with extracorporeal circulation, in which extracorporeal circulation and aortic clamp times of 82 (IQR 73-97.3) and 64 minutes (IQR 57.7-73) were reported, respectively. The type of valve most frequently implanted was a biological valve, with 90.8% (n = 119) and the most frequently used prosthetic valve size was 23 cm^2, in 29.8% (n = 39), followed by 21 cm^2 in 25.2% (n = 25.2); these sizes were determined during the surgical procedure, when the respective valve annulus was measured with a set of scientifically supported valve measurers (Table 2).

The most frequent postoperative outcome was postoperative atrial fibrillation, with 24.4% (n = 32), followed by prolonged mechanical ventilation (more than 24 hours after surgery) and dialysis, which occurred in 6.1% (n = 8) of the population. Reinterventions for any reason were performed in 2.3% (n = 3), and the postoperative mortality rate was 3.0% (n = 4), with 2.4%

Table 1. Description of patients undergoing aortic valve replacement surgery

Characteristics	n = 131
Sociodemographic characteristics	
Sex, n (%) Male Female	 79 (60.3) 52 (39.7)
Age (IQR)	66 (56.5-73.5)
Emergency surgery, n (%) Yes No	 2 (1.5) 129 (98.5)
History	
Hypertension, n (%)	101 (77.1)
Diabetes mellitus, n (%)	25 (19.9)
Stroke, n (%)	6 (4.6)
Dyslipidemia, n (%)	52 (39.7)
Chronic obstructive pulmonary disease, n (%)	30 (22.9)
Asthma, n (%)	2 (1.5)
Cancer, n (%)	4 (3.1)
Peripheral artery disease, n (%)	2 (1.5)
Coronary disease, n (%)	18 (13.7)
Atrial fibrillation, n (%)	8 (6.1)
Atrial septal defect, n (%)	4 (3.1)
Obesity, n (%)	14 (10.7)
Smoking, n (%)	50 (38.2)
Chronic kidney disease, n (%)	35 (26.7)
Endocarditis, n (%)	3 (2.3)
Heart failure, n (%)	79 (60.3)
Preoperative risk scales	
ASA classification, n (%) III IV	 18 (13.7) 113 (86.3)
Euroscore II (IQR)	2.18 (1.3-5.1)
STS morbidity and mortality score (IQR)	11.84 (7.92-18.36)
STS mortality score (IQR)	4.02 (1.78-5.8)
Preoperative echocardiogram	
Preoperative LVEF% (IQR)	52.5 (39-62)
Peak gradient (IQR)	75 (38.6-100.3)
Mean gradient (IQR)	44 (31-56)
AVA by CE (IQR)	0.7 (0.6-0.9)
V_{mean} (IQR)	0.8 (0.7-0.9)
V_{max} (IQR)	4.3 (3.4-4.9)
V_{mean}/V_{max} (IQR)	0.15 (0-0.2)

IQR: interquartile range.

(n = 2) for open repair, and 14.3% (n = 2) for transcatheter repair. The postoperative intensive care unit stay was five days (IQR 4-5). The remaining postoperative outcomes are found in table 3.

The costs related to the type of surgical approach are those billed by the institution and are summarized in table 4. The open approach was the least expensive, followed by the minimally invasive approach, and the transcatheter approach was the most expensive (Table 4).

On the bivariate analysis of the type of surgical approach for aortic valve replacement, the patients who underwent transcatheter and sternotomy interventions had a higher average age (67 years vs. 59 years) than those undergoing minimally invasive procedures. Furthermore, there was a higher percentage of preoperative medical conditions like diabetes mellitus and prior coronary disease in those who underwent transcatheter or open interventions, which is related to higher percentages on the EUROSCORE II scale and STS score. As far as postoperative outcomes, a large percentage of patients with transcatheter replacement were found to require dialysis and mechanical ventilation (Table 5).

Table 2. Clinical and aortic valve replacement procedure characteristics

Characteristics	n = 131
Clinical characteristics of aortic valve disease	
Cause of aortic valve disease, n (%)	
Congenital	37 (28.2)
Rheumatic	0 (0)
Degenerative	94 (71.8)
Type of valve lesion, n (%)	
Regurgitation	35 (26.8)
Stenosis	31 (23.7)
Regurgitation + stenosis	65 (49.6)
Surgical procedure	
Type of prosthesis, n (%)	
Biological	119 (90.9)
Mechanical	12 (9.2)
Valve number, n (%)	
19 mm	12 (9.2)
21 mm	33 (25.2)
23 mm	39 (29.8)
25 mm	16 (12.2)
26 mm	4 (3.1)
27 mm	13 (9.9)
28 mm	1 (0.8)
29 mm	11 (8.4)
34 mm	2 (1.5)
Surgical approach, n (%)	
Open	85 (64.9)
Ministernotomy	32 (24.4)
Transcatheter	14 (10.7)
Pump time (IQR)	82 (73-97.3)
Clamp time (IQR)	64 (57.7-73)

IQR: interquartile range.

Discussion

Aortic valve disease is the most common valve disease and causes high morbidity and mortality rates around the world. In Tolima, aortic valve disease has had a significant impact, and it is ranked as the seventh Colombian department with the most total valve replacements; aortic valve replacement is the most frequent, with a significant figure (75% of the total)[7]. This situation reflects the impact of the disease not only on the individuals' quality of life, but also on the healthcare system's finances, due to the costs of valve disease treatment. Technical advances have allowed the use of different approaches for aortic valve replacement in selected patients, including open, minimally invasive and transcatheter procedures.

In our study, the median age of patients undergoing surgery was 66 years, similar to the data published by Revista Colombiana de Cardiología regarding valve surgery in Colombia, in which the highest number of valve replacements occurred in the 60-to-79-year age range[7]. In contrast, the median age of the study population in a registry of 25 centers in the United States, Canada and Germany was higher, at 85 years for the open group and 84 years for the transcatheter group[8]. This age difference could be attributed to increased life expectancy in developed countries, possibly due to health-related improvements and progress which results in progressive population aging.

On the other hand, the previously mentioned analysis showed that more than half of the patients who underwent transcatheter or open surgery interventions were male (57.8 vs. 56.7%), which does not differ from our study or Revista Colombiana de Cardiología's study which have already been discussed, in which males were found to be most affected in both types of procedures. There was a similar trend in a randomized clinical trial in the United Kingdom and an article published by the Massachusetts Medical Society[9,10]. This could be explained by the fact that males have the highest proportion of cardiovascular risk factors like smoking and dyslipidemia, which makes them more prone to developing the disease.

We should also highlight that, in our study, hypertension was the most important pre-existing condition, with

Table 3. Postoperative outcomes of the aortic valve replacement surgical procedure

Postoperative discharges	n = 131
Stroke, n (%)	1 (0.8)
Atrial fibrillation, n (%)	24 (32.4)
Postoperative dialysis, n (%)	8 (6.1)
Pulmonary thromboembolism, n (%)	1 (0.8)
Infarction, n (%)	1 (0.8)
Reintervention, n (%)	3 (2.3)
Mechanical ventilation for more than 24 hours, n (%)	8 (6.1)
Length of stay in the intensive care unit (days) (IQR)	5 (4-5)
Mortality, n (%)	4 (3.0)
Echocardiogram 30 days after surgery	
Postoperative LVEF % (SD)	52.1 (13.9)

IQR: interquartile range; SD: standard deviation.

Table 4. Total cost in Colombian pesos of aortic valve replacement according to type of surgical approach

Type of surgical approach	Open	Minimally invasive	Transcatheter
Average cost in Colombian pesos	44,400,000	48,100,000	119,400,000
Average cost in dollars	10,249.30	11,103.40	27,562.30

77.1%, followed by heart failure, with 60.3%, while dyslipidemia and smoking were third and fourth, with 39.7 and 38.2% respectively. These findings concur with the results reported in a registry in California[11]. This study showed that hypertension was the most relevant prior condition, followed by heart failure and smoking. Very similar data were reported in an article by the European Society of Cardiology[12]. In contrast, significant differences were found in a registry by the Mayo Foundation[13], which showed that the most frequent prior medical condition in the population was heart failure, followed by coronary artery disease, hypertension and kidney failure.

Another relevant aspect is that the study performed in 25 centers that we discussed initially[7] found no significant differences between the transcatheter and open approach groups as far as the median STS score for morbidity and mortality (11.8 vs. 11.7%), which does not resemble our records, as the STS score was much higher for the transcatheter intervention compared to open and minimally invasive valve replacement. This is related to the fact that, in Colombia, the transcatheter approach is selected for patients with a higher surgical risk, which does not occur in other countries that prefer to use this approach for patients with lower risk and opt for the open approach in patients with other characteristics. The postoperative mortality rate in our patients was 3% (4 patients), which is in a similar range to the scores used to predict mortality at international level, such as the EUROSCORE II and the STS score.[8-10].

As far as the etiology of valve disease, our data showed degenerative aortic valve disease in 71.7%, followed by congenital disease in 28.2%, which coincides with our patients' advanced median age, due mainly to valve hardening and calcification. Thus, we can see that valve disease was dominated by degenerative processes, which reflects the pattern shown in the Euro Heart[14] survey and registries like the one compiled at a tertiary care center in Portugal[15]. Regarding the types of intervention, our data showed, in descending order, that the most frequent was the open approach (64.9%), followed by minimally invasive (24.4%) and transcatheter approaches (10.7%). These findings coincide with what has been reported by university hospitals in Finland, where the percentage of open surgeries surpassed the transcatheter interventions[16].

With regard to postoperative complications, the most frequent ones in our population were postoperative dialysis and mechanical ventilation for more than 24 hours, unlike a study published in Chile, in which the most frequent were new-onset atrial fibrillation and acute kidney failure (for which only one patient required dialysis). Moreover, the mortality (3%), stroke (0.8%) and reintervention (2.3%) rates recorded in our data are lower than those reported by the Chilean article (14.7, 4.0 and 5.3%, respectively) despite having a smaller study population, which could be due to the patients in the Chilean study having a higher mean age and, therefore, a higher likelihood of complications[17]. Thus, our results are comparable to those reported earlier using open or minimally invasive surgical approaches in low or medium-risk patients and the transcatheter approach in high-risk patients.

In terms of cost effectiveness, it is important to mention that in more economically developed countries like Japan and Singapore[18,19], the cost of a TAVI is close to $284,267,506 and $344, 860,740 COP, respectively, compared to that of our study, which was $27,562.30 USD. The cost of an open valve replacement in more

Table 5. Bivariate analysis of the type of surgical approach employed for aortic valve replacement

Variables	Open approach (n = 85)	Minimally invasive approach (n = 32)	Transcatheter approach (n = 14)	p
Age (IQR)	67 (58-74)	59 (52-68.5)	67 (62.5-72)	0.042[b]
Diabetes mellitus, n (%)	16 (18.8)	2 (6.3)	7 (50)	0.0023[a]
Prior coronary disease, n (%)	10 (11.76)	2 (6.3)	6 (42.9)	0.0027[a]
Euroscore II (IQR)	2.3 (1.5-5)	1.38 (1.0-2.7)	9.45 (5.1-16.2)	7.09×10^{-6}
STS score (IQR)	10.42 (7.87-14.32)	10.05 (6.50-15.68)	24.01 (23.80-30.60)	5.45×10^{-5}
Preoperative LVEF, n % (IQR)	55 (25-75)	55.5 (49.25-60.0)	37 (33.0-42.5)	0.0014
Pump time (IQR)	78 (70-83.3)	102 (94.5-112.5)	33 (33-33)	3.04×10^{-11}
Clamp time (IQR)	62 (56-65)	74 (73-83)	NA	1.33×10^{-11}
Postoperative dialysis, n (%)	4 (4.7)	1 (3.1)	3 (21.4)	0.038[a]
Mechanical ventilation > 24 h after surgery, n (%)	4 (4.7)	1 (3.1)	3 (21.4)	0.038[a]

a. Chi-square.
b. Kruskal test.

economically developed countries is approximately $226,987,689 and $191,931,120 COP, while in our study it was $10,249.30 USD. Likewise, in low-income countries like Thailand[20], the transcatheter approach was more expensive than the open approach ($215,305,241 COP versus $64,146,897 COP, respectively). This difference in costs is related to the added cost of the valve for TAVI.

Since this was a cross-sectional study, potential biases were evaluated. To address selection bias, all aortic valve replacement patients who met the inclusion criteria were included. For information bias, which evaluates the process of measuring the different variables, the variables were described, and the principal investigators' data collection processes were periodically reviewed. As far as the confounding bias, the type of surgical approach could not be randomized, as it depended on the surgical team's judgement.

Conclusion

Thus, we present the first outcomes in Tolima regarding the different types of approaches for aortic valve replacement, with the open approach being the most frequently employed. However, the minimally invasive approach should be proposed as an option offering excellent outcomes, just like the open approach, with a similar cost, less postoperative pain and a smaller sternal scar. In addition, the transcatheter approach, which reduces surgical trauma, is preferred for patients with high risk using the open or minimally invasive approach.

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 declare that the procedures followed were in line with the ethical norms of the responsible human research committee and the World Medical Association and Declaration of Helsinki. The procedures were authorized by the institutional ethics committee.

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

References

1. Iglesias S. Una de cada ocho personas de 75 o más años padece alguna valvulopatía moderada - Sociedad Española de Cardiología [Internet]. Secardiologia.es. 2022 [Cited 5 Sep 2023]. https://secardiologia. e s /co m u n i c a c i o n / n o t a s - d e - p r e n s a / n o t a s - d e - p r e n s a -sec/ 13588-una-de-cada-ocho-personas-de-75-o-mas-anos-padecealguna-valvulopatia-moderada.
2. Si S, Hillis GS, Sanfilippo FM, Smith J, Tran L, Reid CM, et al. Surgical aortic valve replacement in Australia, 2002–2015: temporal changes in clinical practice, patient profiles and outcomes. ANZ J Surg. 2019 [Internet]; 89(9):1061-7.
3. J Larry J, Fauci A, Kasper D, Hauser S, Longo D, Loscalzo J. Trastornos del aparato cardiovascular. Enfermedad vascular coronaria y periférica. En: Harrison. Principios de Medicina Interna. 20th. ed. McGraw Hill Education; 2018. p. 1872-85.
4. Mendiz OA, Gamboa JP. Reemplazo valvular aórtico por cateterismo. Estado actual [Internet]. Org.ar. [Cited 5 Sep 2023]. http://www.scielo.org.ar/pdf/medba/v80n5/1669-9106-medba-80-05-516.pdf.
5. Venegas G. JC. Estenosis aórtica severa: nueva aproximación diagnóstica. Rev Médica Clín Las Condes. 2015 [Internet]; 26(2):217-22. [Cited 5 Sep 2023];https://www.elsevier.es/es-revista-revista-medica-clinica-las-condes-202-articulo-estenosis-aortica-severa-nueva-aproximacion-S0716864015000425.
6. Kugelman N, Jaffe R, Aronson D, Sharoni E, Adawi S, Khader N, et al. Outcome of patients with low-gradient aortic stenosis undergoing transcatheter or surgical aortic valve replacement. Cardiovasc Revasc Med. 2020 [Internet]; 21(3):257-62. https://www.sciencedirect.com/science/article/pii/S1553838919303008.
7. Maldonado-Torres N, Goez L, Rosselli D. Reemplazo valvular cardíaco en Colombia: un análisis de los registros oficiales. Rev Colomb Cardiol. 2024 [Internet]. [Cited 12 Oct 2024]; 31(2):92-8. http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-56332024000200092&lng=en.
8. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
9. The UK TAVI Trial Investigators. Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. JAMA. 2022;327(19): 1875-87.
10. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med. 2020.
11. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. N Engl J Med. 2017;377(19):1847-57.
12. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. Eur Heart J. 2015;37(34):2658-67.
13. Alharbi AA, Khan MZ, Osman M, Khan MU, Munir MB, Syed M, et al. Transcatheter aortic valve replacement vs surgical replacement in patients with pure aortic insufficiency. Mayo Clin Proc. 2020;95(12):2655-64.
14. Goldbarg SH, Elmariah S, Miller MA, Fuster V. Insights Into degenerative aortic valve disease. J Am Coll Cardiol. 2007:50(13):1205-13. (https://www.sciencedirect.com/science/article/pii/S0735109707021353).
15. Esteves AF, Brito D, Rigueira J, Ricardo I, Pires R, Pedro MM, et al. Profiles of hospitalized patients with valvular heart disease: Experience of a tertiary center. Revista Portuguesa de Cardiología (English Edition). 2018;37(12):991-8.
16. Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, et al. Comparison of outcomes after transcatheter aortic valve replacement vs surgical aortic valve replacement among patients with aortic stenosis at low operative risk. JAMA Network Open. 2019;2(6):e195742.
17. Seguel-Soto W, Vera-Calzaretta A, Rubilar H, González R, Stockins A, Ramírez S. Resultados a siete años de la cirugía de reemplazo valvular aórtico en mayores de 80 años. Rev Colomb Cardiol. 2022 [Internet]; 29(3):310-6. [Cited 12 Oct 2024]. http://www.scielo.org.co/scielo.php?script= sci_arttext&pid=S012056332022000300310&lng=en. 9.
18. Inoue S, Nakao K, Hanyu M, Hayashida K, Shibahara H, Kobayashi M, et al. Cost-effectiveness of transcatheter aortic valve implantation using a balloon-expandable valve in Japan: Experience From the Japanese Pilot Health Technology Assessment. Value in Health Regional Issues. 2020;21:82-90.
19. See-Toh RS, Wong XY, Mahboobani KS. Cost-effectiveness of transcatheter aortic valve implantation in patients with severe symptomatic aortic stenosis of intermediate surgical risk in Singapore. BMC Health Serv Res. 2022;22:994.
20. Permsuwan U, Yoodee V, Buddhari W, Wongpraparut N, Thonghong T, Cheewatanakornkul S, et al. Cost-utility analysis of transcatheter aortic valve implantation versus surgery in high-risk severe aortic stenosis patients in Thailand. Clinicoecon Outcomes Res. 2022;14:487-98.

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

Check for updates

ORIGINAL ARTICLE

The association between risk scores and clinical outcome in acute coronary syndrome patients

La asociación entre las puntuaciones de riesgo y el resultado clínico en pacientes con síndrome coronario agudo

Shereen Farag, Shaimaa Mostafa, Khaled El-Rabbat, and Ahmed Abd El-Aziz*

Cardiology Department, Faculty of Medicine, Benha University, Benha, Egypt

Abstract

Introduction: *acute coronary syndrome (ACS) and its complication are one of the major health problems worldwide. Numerous clinical risk scores have been used to stratify ACS patients.* **Objective:** *To evaluate the relationship between risk scores (TIMI, PURSUIT, and GRACE) and short-term outcomes in acute coronary syndrome (ACS) patients.* **Method:** *the study enrolled 500 patients with ACS. Risk scores were evaluated on admission and correlated with outcomes during the hospital stay and three months after discharge.* **Results:** *the study included 500 patients with ACS, and a mean age of 57.4 ± 11.8 years. The mean TIMI, GRACE, and PURSUIT score was 2.7±1.9, 138.8 ± 39.6, and 10.9 ± 4.9, respectively. Higher TIMI, GRACE, and PURSUIT scores were associated with higher inpatient and short-term morbidity and mortality. Of the three, the PURSUIT score was the most significant predictor of inpatient heart failure, using a cut-off value > 15.5 with a sensitivity of 82.2% and specificity of 96.9%. At the same time, the GRACE score was the most accurate predictor of recurrent ischemia and heart failure during three months of follow-up, using cut-off values>117.5 and >118.5, with a sensitivity of 100%, and 100%, and a specificity of 64% and 62.2% respectively* **Conclusion:** *risk scores are straightforward, bedside-applicable, and capable of predicting adverse outcomes during hospitalization and in the subsequent three months.*

Keywords: *Acute coronary syndrome. TIMI score. GRACE score. PURSUIT score.*

Resumen

Introducción: *el síndrome coronario agudo (SCA) y sus complicaciones son uno de los principales problemas de salud a nivel mundial. Se han utilizado numerosos puntajes de riesgo clínico para estratificar a los pacientes con SCA.* **Objetivo:** *evaluar la relación entre las puntuaciones de riesgo (TIMI, PURSUIT y GRACE) y los resultados a corto plazo en pacientes con síndrome coronario agudo.* **Método:** *el estudio inscribió a 500 pacientes con SCA. Las puntuaciones de riesgo se evaluaron al ingreso y se correlacionaron con los resultados durante el ingreso hospitalario y tres meses después del alta.* **Resultados:** *el estudio incluyó a 500 pacientes con SCA, la edad media fue de 57.4 ± 11.8 años. La puntuación media de TIMI, GRACE y PURSUIT fue de 2.7 ± 1.9, 138.8 ± 39.6 y 10.9 ± 4.9, respectivamente. Las puntuaciones más altas de TIMI, GRACE y PURSUIT se asociaron con una mayor morbilidad y mortalidad hospitalaria y a corto plazo. La puntuación PURSUIT fue el predictor más significativo entre las tres puntuaciones para la incidencia de insuficiencia cardíaca intrahospitalaria utilizando un valor de corte > 15.5 con una sensibilidad del 82.2 % y una especificidad del 96.9 %. A su vez, el score GRACE fue el predictor más preciso de isquemia recurrente e insuficiencia cardíaca durante tres meses de seguimiento, utilizando*

***Correspondence:**
Shereen Farag
E-mail: dr.shereenfarag@gmail.com

Date of recepcion: 22-06-2023
Date of acceptance: 22-10-2024
DOI: 10.24875/RCCARE.M24000139
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):31-37
www.rccardiologia.com

valores de corte >117.5 y >118.5, con una sensibilidad del 100%, 100% y especificidad del 64 %, 62.2% respectivamente. **Conclusión:** *los puntajes de riesgo son sencillos, aplicables al lado de la cama y capaces de predecir malos resultados durante la hospitalización y los tres meses.*

Palabras clave: *El síndrome coronario agudo. Puntuación de TIMI. Puntuación de GRACE. Puntuación de PURSUIT.*

Background

Acute coronary syndrome (ACS) and its major adverse complication are major health problems worldwide. They accounts for almost seven million fatalities per year[1,2].

Initial chest pain assessment aims to identify patients with ACS to expedite necessary therapy. Numerous well-established clinical risk scores have been utilized to stratify risk in undifferentiated individuals with chest pain[3,4].

Prognostic scoring systems, including GRACE, TIMI, and PURSUIT risk scores (RSs), have been shown to predict long-term morbidity, mortality, and inpatient outcomes among ACS patients[5,6].

Risk scores were created as a predictive tool for short-term outcomes: the GRACE RS for inpatient complications, TIMI RS for 14-day complications, and PURSUIT RS for 30-day complications. However, a substantial fraction of complications in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients occur after the first month. It is unknown whether these RSs can also predict their occurrence[7].

The objective of the study was to determine the relationship between RSs (TIMI, PURSUIT, and GRACE) and ACS patients' outcomes during their hospital stay and three months post-discharge.

Patients and methods

Study design and patient selection

This single-center, observational study was conducted in the coronary care unit at Benha University Hospital from December 2019 to March 2021. The study included adult male and female patients who presented with NSTE-ACS. Following approval from the human research ethics committee at Benha University's Faculty of Medicine, all participants signed informed consent forms.

Patients with ST elevation myocardial infarction, rheumatic heart disease, end-stage renal disease, end-stage liver disease, or those who refused to participate were excluded from the study.

Method

All patients underwent the following:

History taking: including age, gender, and coronary artery disease (CAD) (hypertension, diabetes mellitus, smoking, dyslipidemia, family history of premature CAD). Clinical evaluation: including Killip class assessment on admission.

Studies

- Laboratory tests: complete blood count, serum creatinine, urea, lipid profile, and cardiac enzymes (troponin & CK-MB).
- Electrocardiogram (ECG): evaluated for the presence or absence of ST segment deviation (elevation or depression), sinus or non-sinus rhythm (such as atrial fibrillation, ventricular tachycardia, junctional rhythm or AV block), and standard or aberrant QRS complexes (such as LBBB, RBBB or pacemaker).
- Echocardiography: all patients were assessed using Philips EPIQ 7C, Release 1.7 (Philips Healthcare, Andover, MA, USA) machine. Two-dimensional breath-holding images were obtained and saved for offline analysis. Left ventricular end-systolic volume (ESV), Left ventricular end-diastolic volume (EDV), and left ventricular ejection fraction (LVEF) were calculated using the biplane Simpson' method[8].
- Risk scores: we utilized the TIMI, PURSUIT, and GRACE RSs. Each score was derived from the clinical history, ECG, and laboratory values collected on admission[9-11].

Management

All patients received appropriate anti-ischemic therapy, including anticoagulants, anti-platelets, beta-blockers, angiotensin-converting enzyme inhibitors, and statins.

Outcome

Patient outcomes were evaluated twice; first, during the hospital stay, for heart failure, arrhythmia, stroke, and death. Then during a three-month follow-up: for mortality, heart failure, and recurrent ischemia.

Statistical analysis

Statistical analysis was done using SPSS version 22. Categorical data were presented as frequencies and percentage and compared using the Chi2 test. Continuous data were shown as means ± Standard Deviation (SD) and compared using the Mann Whitney U test, and Kruskal Wallis test after testing for normality.

Sensitivity analysis was conducted using the ROC curve to determine the cut-off points of the TIMI, GRACE, and PURSUIT RSs, as well as the sensitivity and specificity of this cut-off point.

Results

The study included 500 patients who met the inclusion criteria and completed the follow-up evaluation; the mean age was 57.4 ± 11.8 years old, 70.6% were male, 37.6% were diabetic, 35.2% were hypertensive, 57.2% were smokers, 2.8% had a history of stroke, and 0.6% had a family history of premature CAD. Baseline demographic, risk factors, clinical examination, results and laboratory findings are shown in table 1.

The average TIMI score was 2.7 ± 1.9, the average GRACE score was 138.8 ± 39.6, and the average PURSUIT score was 10.9 ± 4.9.

Table 1. Demographic characters and risk factors of the included patients

	n	%
Age (Mean ± SD)	57.4	11.8
Sex		
Male	353	70.6%
Female	147	29.4%
Obesity (BMI ≥ 30)	164	32.8%
Diabetes mellitus	188	37.6%
Hypertension	176	35.2%
Smoking	286	57.2%
Old stroke	14	2.8%
Positive family history	3	0.6%
Use of ASA last 7 days	37	7.4%
> 1 episode of resting angina in ≤ 24 hours	212	42.4%
Arrest at admission	11	2.2%
ST segment deviation	422	84.4%
Left bundle branch block (LBBB)	5	1.0%
Elevated troponin	438	87.6%
Serum creatinine (mean ± SD)	1.1 ± 0.5	
Mean heart rate (beats/min)	84.4 ± 18.3	
Mean systolic blood pressure (mmHg)	129 ± 29	
Killip class		
I	405	81%
II	59	11.8%
III	18	3.4%
IV	18	3.4%

ACS: acute coronary syndrome; ASA: acetyl salicylic acid; BMI: body mass index

In-hospital outcome

Heart failure was the most common inpatient complication (17.8%), followed by arrhythmia (14.8%) and death (1.6%).

Correlation between scores and in-hospital outcomes

The TIMI, GRACE, and PURSUIT scores were positively correlated with the incidence of inpatient heart failure, with r = 0.51, 0.46, and 0.53, respectively, and p = 0.0001. The correlation between the PURSUIT score and the development of inpatient arrhythmia was minimal, with p = 0.003 and r = 0.24. Inpatient mortality was significantly correlated with TIMI and GRACE scores (r = 0.11, and 0.18, and p=0.01, and 0.0001, respectively) (Table 2).

Outcome after three months' follow up

Eight patients died during hospitalization therefore, only 492 patients were included for follow-up after hospitalization. Within three months of hospital discharge, 4.8% of patients died, 18.9% developed heart failure, and 28.6% had another ischemic attack.

Mortality during the three-month follow-up period was positively correlated with TIMI, GRACE, and PURSUIT scores, with r = 0.26, 0.29, and 0.15, respectively, and p = 0.0001. The incidence of heart failure during the three-month follow-up period was directly linked with the TIMI, GRACE, and PURSUIT scores (r = 0.45, 0.40, and 0.35, and p = 0.0001). In addition, recurrent ischemia was significantly correlated with TIMI, GRACE, and PURSUIT scores, with r = 0.22, 0.49, and 0.44, respectively, and p = 0.0001 (Table 3).

Cut-off values > 2.5 for the TIMI score, > 155 for the GRACE score, and > 15.5 for the PURSUIT score had

Table 2. Correlation matrix between inpatient complications and risk scores

Inpatient complications	TIMI	GRACE	PURSUIT
Heart failure			
r	0.512	0.465	0.533
p	0.0001	0.0001	0.0001
Arrhythmia			
r	0.055	0.055	0.247
p	0.220	0.217	0.003
Death			
r	0.113	0.187	.
p	0.011	0.0001	.

Table 3. Correlation matrix between three months follow-up complications and risk scores

Three months follow-up complications	TIMI	GRACE	PURSUIT
Mortality			
r	0.267	0.298	0.152
p	0.0001	0.0001	0.067
Heart failure			
r	0.452	0.405	0.359
p	0.0001	0.0001	0.0001
Recurrent ischemia			
r	0.220	0.493	0.447
p	0.0001	0.0001	0.0001

the highest diagnostic accuracy in predicting inpatient heart failure, with sensitivities of 82.4%, 100% and 88.2%, and specificities of 78.3%, 92.2%, and 96.9% respectively. Of the three, the PURSUIT score was the most significant predictor of inpatient heart failure (Fig. 1).

The prediction of recurrent ischemia was substantially related to all studied scores; a cut-off value > 1.5 for TIMI, > 117.5 for GRACE, and > 10.5 for PURSUIT scores had the highest diagnostic accuracy, with sensitivities of 100%, 100% and 100%, and specificities of 36%, 64%, and 40%, respectively. The GRACE score was the most accurate predictor of recurrent ischemia within three months (Fig. 2).

Sensitivity analysis revealed that a TIMI score cut-off value of > 1.5 predicts the incidence of heart failure during three month follow-up, with a sensitivity of 100% and a specificity of 33.1%. Using a GRACE score cut-off value > 118.5 will significantly predict the occurrence of heart failure during three months of follow-up, with 100% sensitivity and 62.2% specificity. Finally, for the

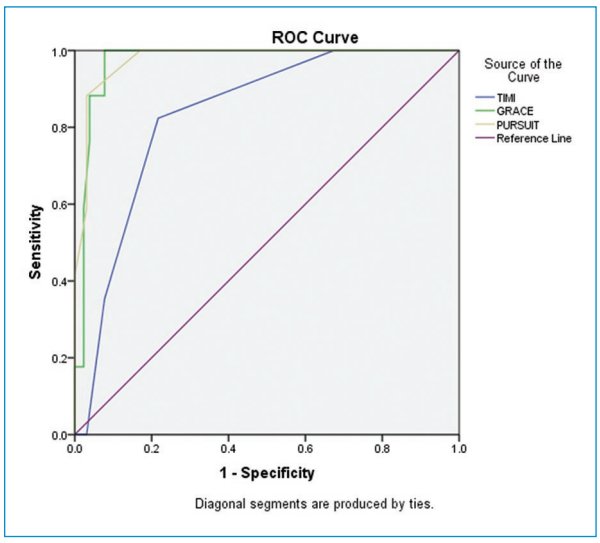


Figure 1. ROC curve showing the predictability of in-hospital heart failure using the three investigated scores studied (PURSUIT score was the most significant predictor among the three scores for the incidence of in-hospital heart failure).

PURSUIT score, a cut-off value >9.5 strongly predicts the occurrence of heart failure during follow-up with 100% sensitivity and 30% specificity (Fig. 3). The GRACE score was the most accurate for heart failure within three months.

Discussion

Acute coronary syndrome covers a broad spectrum of distinct clinical entities with a common etiology that ranges in severity from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI)[12].

Despite the advances in management strategies, ACS is a significant cause of death, worldwide[13]. Identifying high-risk patients and selecting those who would benefit from more aggressive therapy and close follow-up is essential for managing ACS[14,15].

Multiple RSs have been developed based on clinical parameters to aid physicians in risk stratification, as a complement to clinical judgment[16]. Risk stratification of patients with ACS using RSs models is recommended by the guidelines[17]. Our study aimed to correlate coronary RSs and outcomes during hospital admission and after three months of follow-up.

Our findings showed that higher TIMI scores were associated with higher inpatient complications, with a cut-off value of > 2.5. This concurs with Torralba et al.[18],

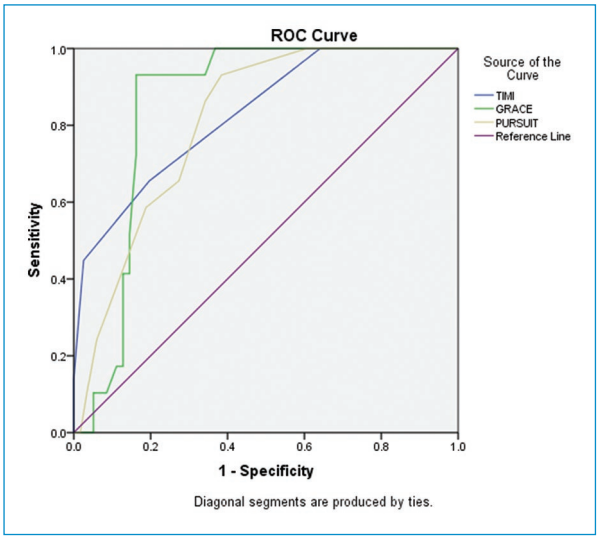


Figure 2. ROC curve showing the predictability of recurrent ischemia using the three scores studied (the GRACE score was the most accurate predictor of recurrent ischemia within three months).

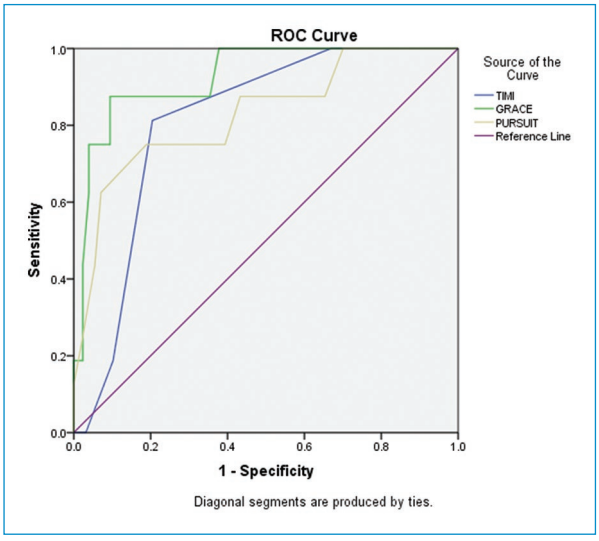


Figure 3. ROC curve for predicting heart failure based on the scores (the GRACE score was the most accurate for heart failure within three months).

Backus et al.[19], Six et al.[20], and Sakamoto et al.[21], who revealed that higher TIMI scores were associated with increased inpatient and short-term complications. In addition, our results were concordant with the result obtained by Iltaf et al.[22], which revealed that a high TIMI RS correlates significantly with death and complications like cardiogenic shock and arrhythmias in the early post-infarction period. Also, Kumar et al.[1] found that a TIMI score ≥4 had the best diagnostic accuracy in predicting short-term mortality outcomes, with a sensitivity of 77.78% and a specificity of 68.09%. The TIMI RS is a simple and practical tool for identifying NSTE-ACS patients at high risk for 14-day mortality[23]. This tool has the potential to save lives and reduce healthcare costs in cardiac care settings, if utilized correctly[24]. Therefore, we recommend its use by clinicians for monitoring these patients with planned and targeted therapies.

The current study's GRACE score was the best predictor of recurrent ischemia and heart failure within three months of follow-up. This was concordant with Yanqiao et al.[6], who found that the GRACE score had higher predictive accuracy than TIMI for inpatient and long-term outcomes among East Asian NSTEMI patients. Also, Kota et al.[5] revealed that, for Japanese patients with STEMI or NSTEMI, there was a significant association between the GRACE RS and inpatient mortality.

In addition, our results were concordant with the result obtained by Chotechuang et al.[25], which revealed that Intermediate-high GRACE risk STEMI patients who underwent delayed coronary intervention in facilities with restricted PCI capabilities had better 30-day and 6-month cardiovascular outcomes than low GRACE risk patients.

Our finding revealed that the higher the PURSUIT score, the higher incidence of inpatient complications, and that was concordant with results obtained by Brilakis et al.[26], which revealed that a higher PURSUIT RS correlates with a lower pre-discharge ejection fraction (EF), more severe coronary artery disease stenosis detected by coronary angiography, and greater early and late mortality of non-selected patients with NSTE-ACS.

Our results were also concordant with the result obtained by Chen et al.[27], which revealed fair to good discriminatory accuracy in predicting major adverse cardiac events when using RSs established from clinical trials (TIMI) or registry (GRACE) databases for the risk stratification of patients with ACS in Western countries.

Study limitation

The capacity of physicians to stratify patients according to risk may depend on their knowledge and experience; however, this individual variation could not be determined in the present investigation. The whole risk

classification process will probably be enhanced by the more widespread and systematic implementation of a verified RS.

Although our data imply that validated risk ratings may improve risk assessment by clinicians, it is yet unknown if they will ultimately lead to improved treatment decisions, resource allocation, and patient outcomes.

Conclusion

Risk scores are simple, bedside-applicable, and easy to use, with the ability to predict adverse outcomes during hospital admission and three months post-discharge, with high sensitivity and specificity.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Human and animal protection. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study design was reviewed and approved by the ethical committee at Benha Faculty of Medicine (MS 1-12-2019) following the Declaration of Helsinki, last updated in 2008. The patients consented through written informed consent as regards participation, and they accepted.

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

References

1. Kumar D, Saghir T, Zahid M, Ashok A, Kumar M, Ali Shah A, et al. Validity of TIMI Score for Predicting 14-Day Mortality of Non-ST Elevation Myocardial Infarction Patients. Cureus. 2021 Jan 6; 13(1):e12518.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019 Mar 5; 139(10):e56-e528.
3. Al-Zaiti SS, Faramand Z, Alrawashdeh MO, Sereika SM, Martin-Gill C, Callaway C. Comparison of clinical risk scores for triaging high-risk chest pain patients at the emergency department. Am J Emerg Med. 2019 Mar; 37(3):461-467.
4. Pocock S, Bueno H, Licour M, Medina J, Zhang L, Annemans L, et al. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: A new risk score from the EPICOR (long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients) study. Eur Heart J Acute Cardiovasc Care. 2015 Dec; 4(6):509-17.
5. Komiyama K, Nakamura M, Tanabe K, Niikura H, Fujimoto H, Oikawa K, et al. In-hospital mortality analysis of Japanese patients with acute coronary syndrome using the Tokyo CCU Network database: Applicability of the GRACE risk score. J Cardiol. 2018 Mar; 71(3):251-258.
6. Yanqiao L, Shen L, Yutong M, Linghong S, Ben H. Comparison of GRACE and TIMI risk scores in the prediction of in-hospital and long-term outcomes among East Asian non-ST-elevation myocardial infarction patients. BMC Cardiovasc Disord. 2022 Jan 7; 22(1):4.
7. De Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005 May; 26(9):865-72.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan; 28(1):1-39.e14.
9. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000 Oct 24; 102(17):2031-7.
10. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation. 2000 Jun 6; 101(22):2557-67.
11. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000 Aug 16; 284(7):835-42.
12. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009 Dec 1; 54(23):2205-41.
13. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7; 42(14):1289-1367.
14. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J. 2013 Apr; 165(4):441-50.
15. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006 Nov 25; 333(7578):1091.
16. Chan Pin Yin D, Azzahhafi J, James S. Risk Assessment Using Risk Scores in Patients with Acute Coronary Syndrome. J Clin Med. 2020 Sep 21; 9(9):3039.
17. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology; Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007 Jul; 28(13):1598-660.
18. Torralba F, Navarro A, la Hoz JC, Ortiz C, Botero A, Alarcón F, et al. HEART, TIMI, and GRACE Scores for Prediction of 30-Day Major Adverse Cardiovascular Events in the Era of High-Sensitivity Troponin. Arq Bras Cardiol. 2020 Mar 13; 114(5):795-802.
19. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol. 2013 Oct 3; 168(3):2153-8.
20. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol. 2013 Sep; 12(3):121-6.

21. Sakamoto JT, Liu N, Koh ZX, Fung NX, Heldeweg ML, Ng JC, et al. Comparing HEART, TIMI, and GRACE scores for prediction of 30-day major adverse cardiac events in high acuity chest pain patients in the emergency department. Int J Cardiol. 2016 Oct 15; 221:759-64.
22. Iltaf K, Dar MH, Khan I, Ali U, Hafizullah M, Shah S. Frequency of high TIMI score and its short term clinical outcomes. Pak Heart J. 2019; 52 (01):80-84.
23. Chan Pin Yin D, Azzahhafi J, James S. Risk Assessment Using Risk Scores in Patients with Acute Coronary Syndrome. J Clin Med. 2020 Sep 21; 9(9):3039.
24. Greenslade JH, Chung K, Parsonage WA, Hawkins T, Than M, Pickering JW, et al. Modification of the Thrombolysis in Myocardial Infarction risk score for patients presenting with chest pain to the emergency department. Emerg Med Australas. 2018 Feb; 30(1):47-54.
25. Chotechuang Y, Phrommintikul A, Kuanprasert S, Muenpa R, Ruengorn C, Patumanond J, et al. GRACE score and cardiovascular outcomes prediction among the delayed coronary intervention after post-fibrinolytic STEMI patients in a limited PCI-capable hospital. Open Heart. 2020 Mar 18; 7(1):e001133.
26. Brilakis ES, Wright RS, Kopecky SL, Mavrogiorgos NC, Reeder GS, Rihal CS, et al. Association of the PURSUIT risk score with pre-discharge ejection fraction, angiographic severity of coronary artery disease, and mortality in a non-selected, community-based population with non-ST-elevation acute myocardial infarction. Am Heart J. 2003 Nov; 146(5):811-8.
27. Chen YH, Huang SS, Lin SJ. TIMI and GRACE Risk Scores Predict Both Short-Term and Long-Term Outcomes in Chinese Patients with Acute Myocardial Infarction. Acta Cardiol Sin. 2018 Jan; 34(1):4-12.

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

Check for updates

ORIGINAL ARTICLE

Prevalence and characterization of tetralogy of Fallot: a comprehensive study

Prevalencia y caracterización de la tetralogía de Fallot: un estudio integral

Pablo Pineda-Sanabria[1], María C. León-Sanabria[2,5], Catalina Arbelaez-Hoyos[1], Vyara Harizanov-Parra[1], Ana Ma. Urueña-Serrano[3], Karen Sarmiento[4], and Ignacio Zarante[2,5]

[1]Faculty of Medicine, Pontificia Universidad Javeriana; [2]Faculty of Medicine, Institute of Human Genetics, Pontificia Universidad Javeriana; [3]Congenital Defects Surveillance, Ministry of Health; [4]Department of Physiologic Sciences, Faculty of Medicine, Pontificia Universidad Javeriana; [5]Genetics Department, Hospital Universitario San Ignacio. Bogotá, Colombia

Abstract

Introduction: *Tetralogy of Fallot (TOF) is a congenital heart defect (CHD) with a global prevalence of 3.56 cases per 10,000 live births (LBs), according to Liu et. al in 2019.* **Objective:** *This study aimed to determine the prevalence of and describe TOF cases in Bogotá, Colombia from 2015 to 2021.* **Method:** *A retrospective cross-sectional study, based on data obtained from the Public Health Surveillance System database. Birth defects were classified according to the International Classification of Diseases (ICD-10), and cases were defined as all LBs with TOF, with a birth weight over 500 grams.* **Results:** *The estimated prevalence of TOF was 2.21 cases (confidence interval [CI] 1.85-2.61) per 10,000 LBs, with a total of 137 cases. The maximum prevalence was found in 2017, with 3.15 (CI 2.11-4.53), and the lowest prevalence in 2015, with 1.26 (CI 0.67-2.18) per 10,000 LBs. The mean birth weight was 2,575.9 g (standard deviation [SD] 660.5), and the average gestational age at birth was 35.85 weeks (SD 3.95). The average maternal age was 29.1 years (SD 7.05). The mortality rate was estimated at 17.51%. Regarding health insurance, 10.95% of cases did not have insurance. Down syndrome and Edwards syndrome were found in nine and three cases, respectively.* **Conclusions:** *The prevalence of TOF in our city was lower than that reported in current global estimates. Nonetheless, there was an increase with regard to previous local data. This change in prevalence trends may be attributed to improvements in surveillance programs.*

Keywords: *Tetralogy of Fallot. Congenital heart defects. Birth defects. Congenital abnormalities. Epidemiology. Public health surveillance.*

Resumen

Introducción: *La tetralogía de Fallot (TF) es una anomalía congénita cardiovascular con una prevalencia global de 3.56 casos por 10.0000 nacidos vivos (NV), según Liu et. Al en el 2019.* **Objetivo:** *Este estudio tiene como objetivo determina la prevalencia y describir los casos de TF en Bogotá, Colombia desde el 2015-2021.* **Método:** *Se realizó un estudio retrospectivo de corte transversal, con datos obtenidos del Sistema nacional de vigilancia en salud pública (SIVIGILA). Los casos fueron definidos como el total de NV con TF, con un peso al nacer mayor a 500gr.* **Resultados:** *La prevalencia estimada para la*

***Correspondence:**
Pablo Pineda-Sanabria
E-mail: pablo_pineda@javeriana.edu.co

Date of reception: 04-11-2023
Date of acceptance: 08-11-2024
DOI: 10.24875/RCCARE.M24000140
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):38-43
www.rccardiologia.com

TF fue de 2.21 (IC 1.85-2.61) casos por 10,000 NV, con un total de 137 casos. La prevalencia máxima se observó en el 2015, con una tasa de 1.26 (IC 0.67-2.18) por 10,000 NV. La media de peso al nacer fue de 2575.9 g (DE 660.5), con una media de edad gestacional al nacer de 35.85 semanas (DE 3.95). La media de edad materna fue de 29.1 años (DE 7.05). Se observó una tasa de mortalidad de 17.51%. Se observó que el 10.95% de los casos no se encontraban afiliados al sistema de salud. Se identificaron casos de Síndrome de Down (n=9) y Edwards (n = 4). **Conclusiones:** *Le prevalencia de la TF en nuestra ciudad fue inferior a la reportada en estimaciones globales existentes. Sin embargo, se observó un aumento en la prevalencia con respecto a estimaciones previas en la ciudad de Bogotá, atribuible a mejoras en el sistema de vigilancia.*

Palabras clave: *Tetralogía de Fallot. Defectos cardíacos congénitos. Defectos de nacimiento. Anomalías congénitas. Epidemiología. Vigilancia de la salud pública.*

Introduction

Congenital heart defects (CHDs) are considered the most prevalent type of birth defect (BD), with an estimated prevalence rate of 82.4 cases per 10,000 live births (LBs)[1]. Among CHDs, tetralogy of Fallot (TOF) is characterized by a tetrad of anomalies: ventricular septal defect, an overriding aorta, right ventricular outflow obstruction, and right ventricular hypertrophy[2]. Tetralogy of Fallot accounts for approximately 4.4% of all reported CHD cases, ranking as the fifth most frequent CHD, with a prevalence rate of 3.56 (3.26-3.88) per 10,000 LBs[1]. The global prevalence, as reported by Orphanet, stands at around 2.5 cases per 10,000 LBs[3]. In Bogotá, Colombia, a comprehensive analysis of 405,408 births between 2001 and 2014 found 17 TOF cases, corresponding to a prevalence of 0.4 cases per 10,000 LBs[4].

Tetralogy of Fallot is classified as a conotruncal heart defect, arising from abnormal septation of the outflow tract in the embryonic heart. The primary hypothesis, known as the malseptation hypothesis, suggests an anterocephalic deviation of the conus arteriosus, resulting in a small infundibulum and a ventricular septal defect. Additionally, abnormal morphology of the septoparietal trabeculations contributes to right ventricular outflow tract obstruction[3].

Recent studies on conotruncal heart defects have identified genetic variants as major contributors to the development of this group of CHDs, with variants in Notch and Wnt pathways being the most frequently identified[5]. Additionally, an association has been found between TOF and both DiGeorge and Down syndromes [6,7]. When left untreated, TOF can cause severe complications, potentially leading to premature death or disability in early adulthood.

A study conducted in Spain reported a mean age of death of 16.28 years among TOF cases. Notably, children under the age of five accounted for 48.5% of all recorded fatalities[8]. However, the majority of TOF cases can be successfully addressed through surgery, yielding favorable outcomes with low mortality rates in adulthood[9]. Nonetheless, certain factors have been identified as potential contributors to increased post-surgical mortality, including low weight ($p = 0.008$), short stature ($p = 0.002$), and arterial oxygen saturation below 75% ($p = 0.018$)[10].

The objective of this study was to estimate the prevalence of TOF in Bogotá, Colombia, between 2015 and 2021. The primary aim was to identify and characterize cases of TOF to enhance healthcare decision-making and positively influence patient prognosis[1].

Method

A retrospective cross-sectional study was conducted, gathering information from the mandatory notification of birth defects (BDs) database within the Public Health Surveillance System (PHSS) in Bogotá, Colombia. Passive surveillance is done, with individual notification of probable and confirmed cases using a notification form with additional data provided to the PHSS. Birth defects are classified and described based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Cases were selected based on the following criteria: all newborns (LBs or stillbirths) born in Bogotá, Colombia, with a weight equal to or greater than 500g, who were diagnosed with TOF using ICD-10 code Q213 and notified in the prenatal stage and up to 12 months after birth, from 2015 to 2021. As an official surveillance and notification database, the PHSS makes the necessary adjustments for reported cases of BD. Adjustment 3 specifically addresses cases that have received official laboratory confirmation, and Adjustment 4 addresses cases that have received clinical confirmation[11].

The prevalence of TOF was determined using the birth data provided by Bogota´s Secretariaty of Health for each year. The prevalence rate was calculated for each year and is expressed as the number of TOF

cases per 10,000 LBs per year between 2015 and 2021. To assess the precision of the prevalence estimates, a 95% confidence interval (CI) was calculated using the Poisson distribution. Additionally, historical analysis was conducted by estimating the linear trend of TOF rates over the studied years.

Quantitative variables, categorized as both nominal and continuous, were analyzed using frequency distribution. Continuous variables, including maternal age, gestational age at diagnosis, number of pregnancies, and birth weight, were assessed based on their average values and standard deviations (SDs). Nominal study variables encompassed sex at birth (female, male, or indeterminate), prenatal diagnosis, prenatal notification, and the presence of multiple pregnancies. The distinction between prenatal diagnosis and prenatal notification in the mandatory reporting form should be noted. Prenatal diagnosis reports refer to postnatal cases diagnosed with TOF whos mothers recalled that they had been informed during pregnancy that their babies had a suspected diagnosis of TOF. On the other hand, prenatal notification cases were fetuses with suspected TOF who were reported to the PHSS during gestation. This latter parameter is of vital importance for the surveillance system as it allows for appropriate monitoring and tracking of the pregnancy.

Cases were classified as preterm births if the gestational age at delivery was less than 37 weeks. Birth weight was classified as low (below the 5th percentile), normal (from the 5th to 95th percentile), or high (above the 95th percentile) for gestational age, based on the updated 2013 Fenton Growth Chart[12].

Cases were categorized into different groups based on their characteristics. These categories included isolated cases (LBs with only TOF), complex cases (LBs with TOF and other cardiovascular defects), polymalformed cases (LBs with TOF and other BDs in a system other than the cardiovascular system), and syndromic cases (LBs with TOF and other anomalies that correlate with each other in a known syndrome). In addition, the type of health insurance coverage was analyzed and classified into three categories: private, public, and no insurance.

Furthermore, the mortality rate was calculated and classified into specific categories. Neonatal deaths were defined as those occurring between birth and 28 days of age. Within this category, further divisions were made: early neonatal deaths, which occurred during the initial seven days of life (0 - 6 days), and late neonatal deaths, occurring 7 to 27 days after birth. Post-neonatal deaths were characterized as those occurring between 28 and 365 days of age.

Data was analyzed using Microsoft Excel 2021. The descriptive statistics tool was used to calculate measures of central tendency and dispersion. Nominal variables were analyzed using the PivotTable function. The local ethics committee granted a waiver for ethical approval due to the retrospective nature of the study and the fact that all procedures performed were part of routine care. The approval code assigned was FM-CIE-8324-14.

Results

Among the 12,089 reports recorded in the PHSS from 2015 to 2021, a total of 137 cases of TOF were identified using the Q213 code (ICD-10). The estimated prevalence rate for the 2015-2021 period was 2.21 cases per 10,000 LBs. The analysis of prevalence rates over the years did not show a linear trend, but rather had two notable peaks in 2017 and 2020. The highest prevalence rate was observed in 2017, with a rate of 3.15 cases per 10,000 LBs. For a detailed overview of the prevalence rates by year, please refer to figure 1.

Out of the total number of cases, 84.67% (n = 116) were LBs, 8.76% (n = 12) were stillbirths (SB), and 6.57% (n = 9) did not have a recorded outcome at the time of notification (unknown outcome at birth). The mean gestational age at birth was 35.85 weeks (standard deviation [SD] 3.95), with 43.27% of cases classified as preterm births. Prenatal diagnosis was available in 59.12% (n = 81) of cases, while postnatal diagnosis occurred in 40.88% (n = 56) of cases. The rate of prenatal notification was 6.57% (n = 9). The mean age at diagnosis was 1.2 months after birth (SD 2.15). Concerning birth weight, 48.39% of cases had a weight below 2,500 grams, 23.67% were born with a low weight for gestational age, 73.12% had a normal weight for gestational age, and 3.23% had a high weight for gestational age at birth.

Regarding maternal characteristics, 12.41% were under 20 old years, 44.53% were over 30, and 26.28% were over 35 years of age. Please refer to table 1 for the demographic characteristics of the selected cases.

When categorizing the cases according to associated BDs, 61.31% (n = 84) were classified as isolated cases, 22.63% (n = 31) as polymalformated, 6.57% (n = 9) as complex cases, and 9.49% (n = 13) as syndromic cases. Among the syndromic cases, 69.23% (n = 9) were attributed to Down syndrome, while 30.77% (n =

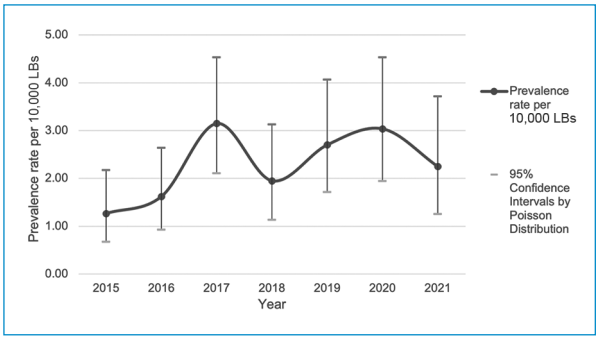


Figure 1. Tetralogy of Fallot. Prevalence in Bogotá, Colombia (2015-2021). Prevalence was calculated as a rate per 10,000 live births. A 95% confidence interval (CI) was computed using the Poisson distribution.

4) were associated with Edwards syndrome. Systems affected by associated BDs in polymalformated and complex cases can be found in table 2.

A total of 24 deaths were documented in the reported cases, resulting in a mortality rate of 17.51%. Examining the deaths based on the time of occurrence, 18 were classified as early neonatal deaths (75%), 1 as a late neonatal death (4.17%), and 5 as post-neonatal deaths (20.83%).

Discussion

The literature on the prevalence of TOF, both globally and within specific regions, shows considerable variation. The reported prevalence rates are influenced by factors such as the effectiveness of neonatal screening programs, the diagnostic methods employed, and the available economic resources. In a study by Liu et al., the estimated global prevalence rate for TOF between 1970 and 2017 was 3.56 cases per 10,000 LBs[1]. This data differs significantly from the prevalence rate observed in our study, which was calculated at 2.21 cases per 10,000 LBs.

Similarly, the estimated prevalence rates from studies conducted in the USA and Europe differ from the rate observed in our study. The National Birth Defects Prevention Network (NBDPN) conducted a study covering the period from 2010 to 2014 in the USA, which calculated a prevalence rate of 4.61 cases per 10,000 LBs[13]. According to the European Network of Population-Based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) the prevalence rate in Europe between 2015 and 2020 was estimated to be 4.06 (3.86-4.26) cases per 10,000 LBs[14]. However,

Table 1. Demographic characteristics of cases

Continuous Variable	Mean	Standard deviation
Maternal age (years)	29.1	7.05
Gestational age at diagnosis (weeks)	30.36	8.08
Gestational age at birth (weeks)	35.85	3.95
Number of pregnancies	2.07	1.23
Birth weight (grams)	2570.98	678.01
Nominal Variable	**Count**	**Percentage**
Sex at birth Male Female Indeterminate	 70 62 5	 51.09% 45.26% 3.65%
Multiple pregnancy	9	6.56%
Prenatal diagnosis	81	59.12%
Prenatal notification to the PHSS*	9	6.57%

*PHSS: public health surveillance system.

Table 2. Associated birth defects classified by system

System	Count	Percentage
Gastrointestinal	10	20.83%
Cardiovascular	9	18.75%
Genitourinary	7	14.58%
Other	6	12.50%
Musculoskeletal	5	10.42%
Nervous	5	10.42%
Cleft lip-palate	5	10.42%
Pulmonary	1	2.08

a study by Cavero-Carbonell et al. in the Valencia district of Spain between 2007 and 2017 reported a prevalence rate of 2.2 cases per 10,000 LBs, which is very similar to the rate found in our study[15].

In Colombia, the prevalence reported by national health authorities in 2021 was 0.9 cases per 10,000 LB[15,16], wich differs from our estimates for the city of Bogotá. Our study shows an increased the prevalence rate compared to previous studies conducted in Bogotá. For instance, a study by Tassinari between 2001 and 2014 estimated prevalence rate to be 0.4 cases per 10,000 LBs[4].

The observed differences in prevalence rates may be attributed to improvements in nationwide surveillance programs, which have likely contributed to better case

identification and reporting. Additionally, it is important to interpret the prevalence rate for Bogotá cautiously, considering its role as a reference city for the diagnosis and treatment of various pathologies in our country. This may lead to a potential overestimation of the prevalence rate in Bogotá compared to other regions. Furthermore, the higher prevalence rate could also be influenced by improved healthcare access and diagnostic resources, including prenatal checkups, which provide more opportunities for early detection and diagnosis.

As mentioned in the results, there was no stable trend in the prevalence rate of TOF during the years studied. This finding is consistent with the national trend observed in Colombia, as reported by the National Institute of Health, which also noted fluctuations in the rates of TOF between 2015 and 2018[17]. It is important to consider that Colombia is an upper-middle-income country with significant regional disparities, which can contribute to variations in the prevalence rates of BD, including TOF, between different regions within the country.

In terms of demographic characteristics, the population in our study exhibited some similarities to the population in the study by Cavero-Carbonell in Valencia, Spain[15]. Firstly, the distribution of sex at birth was similar in both studies. However, it is important to note that the study in Valencia reported a higher frequency of indeterminate sex due to the inclusion of cases involving induced abortion, which is not recorded in the PHSS in Colombia. Secondly, both studies had a high percentage of mothers over the age of 30, although the percentage (67.3%) in the Spanish study was higher than the percentage in our study. At the same time, there were some differences between the two studies. In terms of birth weight, our study had a higher percentage of newborns with a weight below 2,500 grams, which could be attributed to poor maternal conditions in the perinatal period due to social determinants of health. The percentage of preterm births was similar between the two studies.[15]

In terms of associated BDs, our study had a higher percentage of cases with gastrointestinal system malformations compared to musculoskeletal system malformations in the study from Valencia. However, the three most frequent systems involved in associated BDs were congruent between both studies, namely the musculoskeletal, gastrointestinal, and genitourinary systems.

Our study reported a lower rate of syndromic cases due to chromosomal abnormalities compared to the study by Muñoz et al. (2016), which reported that 30-40% of cases diagnosed prenatally had chromosomal abnormalities, particularly DiGeorge syndrome. These findings are not congruent with our results, as in our study, the most frequently associated syndromes were Down syndrome and Edwards syndrome.[18]

Our study found a lower rate of prenatal diagnosis for TOF, which aligns with the findings by Muñoz et al. (2016). Tetralogy of Fallot accounts for 3-7% of prenatally diagnosed CHDs, despite being the most common conotruncal malformation. Obstetric ultrasound, particularly with the four-chamber view of the heart, can detect over 50% of severe cardiac malformations during mid-gestation, with detection sensitivity potentially reaching 90%. Fetal echocardiography is the primary tool for prenatal CHD diagnosis, detecting up to 90% of severe cases from the late first trimester to term[18].

In our study, the rate of prenatal diagnosis and notification was below the threshold set by the Bogotá Secretariaty of health's "Investment Project 7830: Unstoppable Childhood". The project aims to increase early detection and comprehensive care for children with BDs by 20% in 2024 through interventions focused on promoting health and managing preconception, prenatal, and postnatal risks[19]. Improving these indicators is crucial for enhancing preconception care, follow-up, prognosis, mortality, and other important outcomes[18].

According to Gaitan-Duarte, H. et al. (2021), health services often exhibit deficiencies in terms of access, quality, and sufficiency, particularly affecting certain population sectors such as women, indigenous people, migrants, people of African descent, and marginalized groups who face discrimination and rights violations. Health inequity contributes to increased maternal and infant mortality and creates disparities in health indicators both within and between countries. In our study, we analyzed the impact of the type of health insurance on health outcomes, finding that pregnant women with public health insurance had a higher risk of adverse outcomes than those with private insurance[20]. We do not have specific information about maternal chronic diseases present before or during pregnancy, due to incomplete data in the PHSS registry.

Conclusions

This study's limitations primarily stem from the incomplete data available in the PHSS database. This limitation is a result of incomplete recording and reporting. For instance, not all records were made by physicians, potentially impacting the coding and description of anomalies. Additionally, human errors during manual registration could impose constraints on future analysis

and the formulation of study conclusions. Furthermore, barriers to healthcare can contribute to underreporting, spanning from preconception care to postnatal diagnosis, thereby hindering case follow-up and timely treatment. The absence of a formal follow-up program during the study period restricts the analysis of outcomes.

However, the significant improvements observed in case reporting to the healthcare system in our country are worth noting. This study is a unique contribution to the existing literature on the subject in our country. These advancements inspire high expectations for further research in this field and a possible TOF follow-up program that could impact the outcomes and prognosis of this condition.

Acknowledgments

The authors would like to thank the Secretaría de Salud de Bogotá and the Programa de Prevención y Vigilancia de Defectos Congénitos y Enfermedades Raras (PREVERDEC) for providing the data used in this study.

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. This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The local Ethics Committee of Pontificia Universidad Javeriana granted a waiver for ethical approval due to the retrospective nature of the study and the fact that all procedures performed were part of routine care. The approval code assigned was FM-CIE-8324-14.

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

References

1. Liu Y, Chen S, Zühlke L, Black GC, Choy M, Li N, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019;48:455–63.
2. Krieger EV, Valente AM. Tetralogy of Fallot. Cardiol Clin 2020;38:365–77.
3. Anderson R, Bailliard F. Orphanet: Tetralogía de Fallot n.d. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=3303&lng=ES (accessed November 13, 2022).
4. Tassinari S, Martínez-Vernaza S, Erazo-Morera N, Pinzón-Arciniegas MC, Gracia G, Zarante I. Epidemiology of congenital heart diseases in Bogotá, Colombia, from 2001 to 2014: Improved surveillance or increased prevalence? Biomédica 2017;38:148–55.
5. Bittel DC, Butler MG, Kibiryeva N, Marshall JA, Chen J, Lofland GK, et al. Gene expression in cardiac tissues from infants with idiopathic conotruncal defects. BMC Med Genomics 2011;4:1.
6. Michielon G, Marino B, Formigari R, Gargiulo G, Picchio F, Digilio MC, et al. Genetic Syndromes and Outcome After Surgical Correction of TETRALOGY OF FALLOT. Ann Thorac Surg 2006;81:968–75.
7. Athanasiadis DI, Mylonas KS, Kasparian K, Ziogas IA, Vlachopoulou D, Sfyridis PG, et al. Surgical Outcomes in Syndromic TETRALOGY OF FALLOT: A Systematic Review and Evidence Quality Assessment. Pediatr Cardiol 2019;40:1105–12.
8. Llamosas-Falcón L, Bermejo-Sánchez E, Sánchez-Díaz G, Villaverde-Hueso A, Posada de la Paz M, Alonso-Ferreira V. TETRALOGY OF FALLOT in Spain: a nationwide registry-based mortality study across 36 years. Orphanet J Rare Dis 2019;14:79.
9. Dennis M, Moore B, Kotchetkova I, Pressley L, Cordina R, Celermajer DS. Adults with repaired tetralogy: low mortality but high morbidity up to middle age. Open Heart 2017;4:e000564.
10. Juliana J, Sembiring YE, Rahman MA, Soebroto H. Mortality Risk Factors in TETRALOGY OF FALLOT Patients Undergoing Total Correction. Folia Medica Indones 2021;57:151.
11. Grupo de Vigilancia y Control de Enfermedades No Transmisibles. Protocolo de Vigilancia de Defectos Congénitos. Instituto Nacional de Salud; 2022.
12. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
13. Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, et al. National population□based estimates for major birth defects, 2010–2014. Birth Defects Res 2019;111:1420–35.
14. European Platform on Rare Disease Registration- Prevalence n.d. https://eu-rd-platform.jrc.ec.europa.eu (accessed February 19, 2023).
15. Cavero-Carbonell C, García-Villodre L, Barrachina-Bonet L, Moreno-Marro S, Páramo-Rodríguez L, Guardiola-Vilarroig S. Vigilancia Epidemiológica De Las Anomalías Congénitas Cardíacas: La Tetralogía De Fallot en la Comunitat Valenciana, 2007-2017. Rev Esp Salud Pública n.d.:12.
16. Defectos Congénitos: Periodo epidemiológico IX. Colombia 2021. Bogotá D.C.: Instituto Nacional de Salud; 2021.
17. Mellizo GAA. Informe De Evento Defectos Congénitos, Colombia, Año 2018 2019:19.
18. Muñoz H, Copado Y, Díaz C, Muñoz G, Enríquez G, Aguilera S. Diagnóstico y Manejo Prenatal de Patología Cardíaca Fetal. Rev Médica Clínica Las Condes 2016;27:447–75.
19. Chacón N, Lara H. Ficha Técnica del Indicador: Tasa de mortalidad por defectos congénitos en niños menores de 5 años en Bogotá D.C. Secretaría de Salud de Bogotá; 2022.
20. Gaitán-Duarte H, Estrada-Orozco K. La seguridad en los servicios de salud, un problema prioritario en la atención de la mujer a nivel mundial. Rev Colomb Obstet Ginecol 2021;72:141–8.

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

Check for updates

REVIEW ARTICLE

Consumption of cocaine and cardiovascular diseases in young adults

Consumo de cocaína y enfermedades cardiovasculares en adultos jóvenes

Ezequiel García-Ballestas[1,2], Sandra L. Angulo-Mariño[3], Guillermo Olaya[4], Camilo E. Palencia-Tejedor[5], Nicolás R. Rojas-Quintero[6], Gabriel A. Quiñones-Ossa[2], Fernando Manzur[1], and Luis R. Moscote-Salazar[1,2]*

[1]Centro de Investigaciones Biomédicas (CIB), Universidad de Cartagena, Cartagena de Indias; [2]Consejo Latinoamericano de Neurointensivismo-CLaNi, Cartagena; [3]Faculty of Medicine, Universidad El Bosque, Bogotá; [4]Departament of Internal Medicine, Universidad de Cartagena, Cartagena de Indias; [5]Servicio de Medicina Interna, Clínica Medical Duarte, Universidad de Santander-Sede Cúcuta, Cúcuta; [6]Faculty of Medicine, Universidad de Santander-Sede Cúcuta, Cúcuta. Colombia

Abstract

Cocaine use is currently a national and international public health problem related to high mortality and morbidity rates. The increase in cocaine use by young adults over the last decades has caused multiple medical problems related to its consumption. Although alterations have been found in all body systems, it is especially in the cardiovascular system where cocaine exerts its greatest effects, which can be as serious as death. This drug may induce arrhythmias, coronary vasospasm, myocardial ischemia, acute myocardial infarction, and sudden death. The following article presents a descriptive review of the effects of cocaine on the different body systems while emphasizing the cardiovascular effects that are associated with higher mortality, so as to provide an updated and complete information of this phenomenon that affects a large part of the world's population and, above all, young people.

Keywords: *Cocaine. Cardiovascular diseases. Young adults.*

Resumen

En la actualidad, el consumo mundial de cocaína es un problema de salud pública relacionado con altas tasas de morbilidad y mortalidad. Dicho consumo ha aumentado en las últimas décadas, sobre todo en los adultos jóvenes, y es el responsable de la aparición de múltiples enfermedades relacionadas con su uso y consumo. Aunque se han demostrado alteraciones en todos los sistemas del organismo, es en especial en el sistema cardiovascular donde la cocaína ejerce sus mayores efectos, los cuales pueden ser tan graves como la muerte. Esta droga puede inducir arritmias, vasoespasmos coronarios, isquemia del miocardio, infarto agudo de miocardio y muerte súbita. En este artículo se hace una revisión descriptiva de los efectos que ejerce la cocaína sobre los diferentes sistemas del cuerpo y se hace énfasis en los efectos cardiovasculares (que son los asociados a mayor mortalidad) de tal manera que se brinde una información actualizada y completa de este fenómeno que afecta a gran parte de la población mundial, más exactamente a la población joven.

Palabras clave: *Cocaína. Enfermedades cardiovasculares. Adultos jóvenes.*

***Correspondence:**
Ezequiel García-Ballestas
E-mail: ezegames@hotmail.es

Date of reception: 28-08-2024
Date of acceptance: 08-11-2024
DOI: 10.24875/RCCARE.M24000146
Available online: 13-05-2025
Rev Colomb Cardiol. 2025;32(1):44-51
www.rccardiologia.com

Introduction

Cocaine use dates back to 1500 B.C., when the Incas chewed or macerated the leaves to improve their physical capacity and work longer hours[1]. Albert Niemann isolated and described cocaine in 1859; later, in 1884, Karl Koller used it as a local anesthetic for some surgical procedures and finally, in 1855, Friedrich Gaedcke continued the work begun by Albert Niemann to isolate cocaine and turn it into the alkaloid compound we know today. However, the first complications due to its use were reported in 1886, and therefore it was restricted to medical use in 1914; despite this, it is used as a narcotic today[2-6].

Global cocaine use has proved to be a public health problem with high rates of morbidity and mortality[7]. This is compounded by the socioeconomic impact associated with high consumption rates in developed countries and its production by developing countries. Unfortunately, Colombia is the second largest exporter of cocaine in the world, after Peru[8-11]. This high global consumption over the last few decades, which has grown exponentially, has led to the onset of multiple clinical disorders related to the use of this drug[6,10,12]. In regard to illegal substance use, the latest census report by the Colombian Drug Observatory (ODC, in Spanish) in 2013 stated that 484,109 people consumed any type of narcotic, for a prevalence of 12.2%[13-15].

Parkin et al.'s study established that risk factors (in vulnerable populations, such as poverty, difficulty in accessing health care and education, and unemployment, among others) determine dependence on highly addictive psychoactive substances like cocaine and crack, which is a cocaine subproduct (dirty cocaine waste)[11,16]. This reflects a public health problem, especially in young adults, who are the main consumers and have higher morbidity and mortality rates[11,17]. These reasons led to a detailed analysis of the cardiovascular effects in this population. The goal of this document is to describe the pertinent evidence related to the systemic effects (especially cardiovascular effects) associated with cocaine use, through a comprehensive review of the literature, seeking to stimulate reflection on this problem, particularly in young readers who are training to be tomorrow's physicians, and the professionals who are guiding this new generation.

Method

We conducted a review of the current literature through a search of scientific articles published between 2010 and 2024, available in the Scientific Electronic Library Online (SciELO), PubMed, Cochrane, LILACS, Embase, Elsevier, Scopus, ScienceDirect and Ovid databases. In addition, we used descriptors such as cocaine use, cardiovascular diseases, young adults and cardiovascular effects of cocaine. Articles addressing the topic of cardiovascular diseases and their relationship to cocaine use in young adults between the ages of 18 and 40 were included. References were gleaned from the lists of references in the articles found. Studies that analyzed patients over the age of 40, patients with cardiovascular diseases with other etiologies, and those with chronic kidney disease and rheumatologic disease, were excluded.

Results

Epidemiology

Over the last few decades, the exponential growth in cocaine consumption has become a global public health problem, with a mortality rate of 76%, which causes a high socioeconomic impact, according to the drug report published in 2018 by the United Nations Office on Drugs and Crime[6,9]. In 2017, approximately 271 million people, that is, 5.5% of the world's population between the ages of 15 and 64, had used psychoactive substances in the previous year; a long-term projection of the number of people who use these illegal substances shows an increase of approximately 30% compared to the 2009 rates, when 210 million people had used them[9,18].

Regarding cocaine consumption in Latin America, the countries with the highest consumption are Argentina and Uruguay, with 1.6%, followed by Mexico, Costa Rica, Chile, Brazil, Colombia and Venezuela, with averages ranging from 0.5 to 1.1%[19,20]. However, it should be noted that Colombia is the highest producer of cocaine, with an average of 70% relative to the global average[21]. The 2013 National Study on the Consumption of Psychoactive Substances (done by the Ministry of Justice and Law) highlighted the significant growth in the use of any illegal substance (marijuana, cocaine, crack, ecstasy or heroin), both in lifetime prevalence, which was 8.8% in 2008 and rose to 12.2% in 2013, as well as use during the previous year, which rose from 2.6 to 3.6%[14,18]. The 2017 Colombian Drug Report (emitted by the ODC) stated that 484,109 people consumed psychoactive substances, including marijuana, cocaine and crack[14]. Cocaine use had increased compared to 2011, going from 2.4 to 2.6% in 2016[22]. Illegal

drug use was most frequent in the 18-24-year-old age group, with 8.4% of the general population in 2013. The highest prevalence of illegal drug use by departments was in Antioquia, with 8.2%, while the lowest was in Córdoba, with 0.3%; Norte de Santander was below the Colombian average (3.6%) at 2.8%, and Bogotá, the nation's capital, was at 5%, and this drug use was more common in men, with 2.54%, than in women, with 0.53%[14,18,19,23,24].

General characteristics of cocaine

Cocaine is a highly addictive alkaloid derived from coca plant leaves belonging to the *Erythroxylum coca* species, native to South America[25,26]. It has psychopathological as well as central nervous system (CNS), gastrointestinal, respiratory, endocrine and cardiovascular effects[12,27]. In the cardiovascular system, it causes many complications like arrhythmias, myocarditis, cardiomyopathies, hypertension, aortic dissection, endocarditis, acute myocardial infarction, and, in the worst case, sudden death[2-29].

It is also a local anesthetic and powerful stimulant that increases extracellular and presynaptic levels of monoamine neurotransmitters like dopamine, noradrenaline and serotonin, involved in the mesocorticolimbic circuit, where it inhibits reuptake by binding to the monoamine transporters at the nerve terminals[25,30-32]. The main mechanisms of action are: first, noradrenaline reuptake inhibition at the peripheral sympathetic nerve terminals, thus increasing noradrenaline uptake in the alpha-1 and beta-1 postsynaptic adrenergic receptors (this effect is potentiated with the use of other substances); second, dopamine reuptake inhibition, increasing its release, which stimulates the CNS and triggers a euphoric effect; and, finally, sodium channel blocking, which inhibits action potential generation and simultaneously blocks the potassium channels, altering nervous and cardiac tissue[33-35]. Continuous cocaine use triggers decreased dopamine levels and leads to serotonin reuptake inhibition, which causes depressive disorders, decreased libido, more craving and sleep-wake cycle disorders[30,36-38].

Cardiovascular effects

Cocaine use triggers many systemic complications, but cardiovascular system involvement is notable, with the highest-impact damage depending on the hemodynamic effect caused by a sympathomimetic response that stimulates alpha-1 and beta-1 adrenergic receptors, triggering early cardiovascular effects like tachycardia and hypertension, as well as late effects like bradycardia and circulatory failure[39,40] (Table 1).

Blood pressure and heart rate

Cocaine raises blood pressure (BP) in proportion to the dose consumed which, in turn, increases ventricular afterload, altering contractility and increasing the heart rate (HR). This occurs due to the response to the myocardial oxygen demand [41]. Fischman et al.'s study evaluated the dose vs. HR relationship, with intravenous cocaine administered to young, healthy patients with an average HR of 74 beats per minute (bpm), in which the effect of doses higher than 16 and 32 mg increased the HR by 100 bpm and 112 bpm, respectively. The effects began within an average of two to five minutes, peaking 10 minutes after drug administration, and returning to a normal HR 46 minutes later[42]. This same study analyzed the dose vs. systolic arterial pressure (SAP), where doses of 4 to 8 mg had no effect, unlike the administration of 16 to 32 mg, which caused a 10 to 15% change, with a SAP of 130-140 mmHg and an initial effect at 10 minutes[42]. Some studies maintain that simultaneous cocaine and ethanol consumption (whose mechanism of action is similar to that of cocaine, blocking dopamine reuptake at the synaptic gap) potentiates cocaine's systemic effects, such that this combination exacerbates myocardial oxygen demand, which is ultimately compensated by increasing the HR and SAP[43,44].

Hypertension (HTN) is a common manifestation in cocaine use and its mechanism of action is linked to potentiation of the sympathomimetic effects through a reflex increase in inotropic and chronotropic activity, coupled with an increase in factors that cause peripheral vasoconstriction. This produces medium and long-term consequences like atherosclerosis, vascular smooth muscle cell apoptosis, abnormal vasorelaxation, calcium channel blocking and nitric oxide synthase blocking[39,45,46]. According to studies, intranasal consumption of 2 mg/kg of cocaine increases blood pressure by 10 to 25%, due to damage to the baroreceptors that regulate BP elevation. It should be noted that it takes 72 hours to eliminate cocaine from the body, and therefore elevated BP begins to decrease as time passes[47,48]. Although HTN may resolve spontaneously, it is important to remember that frequent users or those who combine alcohol and cocaine use may have a higher risk of complications like hypertensive emergencies, ischemic events and acute aortic dissection[36,49,50].

Table 1. Acute effects of cocaine on the cardiovascular system

Effect	Mechanism of action	Time of onset	Reference studies
Tachycardia	Beta-1 adrenergic receptor stimulation and increased myocardial oxygen demand.	2-5 minutes	Fischman et al.[42]
Hypertension	Alpha-1 adrenergic activation and increased ventricular afterload.	10 minutes	Fischman et al.[42]
Vasoconstriction	Smooth muscle adrenergic receptor stimulation and increased endothelin-1 and thromboxane-A2.	Rapid	Lange et al., Turillazzi et al.
Increased HR and BP	Potentiated by simultaneous ethanol consumption, greater oxygen demand.	Variable	Mendoza et al.

In 2004, Mendoza et al. reported the clinical case of a patient with HTN due to indiscriminate cocaine use. The patient developed hemorrhages and exudates compatible with grade III hypertensive retinopathy, along with elevated BP figures. After 24 months of follow up, he maintained a normal BP along with pharmacological treatment with lisinopril and hydrochlorothiazide plus a low sodium diet and cocaine abstinence, with which he achieved target levels.

Vascular tone

Cocaine-induced vasoconstriction is caused by adrenergic receptor stimulation in the smooth muscle cells of the coronary arterial bed and increased vascular endothelial permeability due to direct effects on endothelin-1 (ET-1) and thromboxane-A2 (TXA2) production, which foster endothelial dysfunction. On the other hand, nitric oxide (NO) is reduced by this vascular damage, thus favoring platelet aggregation[38,41]. These effects support the acute coronary thrombosis mechanism found in patients with acute myocardial infarction (AMI) following cocaine consumption, which was seen after early coronary angiography confirmed thrombotic coronary obstruction which, when resolved (either spontaneously or with fibrinolysis), revealed a normal vascular tree. Lange et al.[44] analyzed the hemodynamic parameters of the coronary arteries after administering cocaine and found an acute reduction in vessel caliber and blood flow in the coronary sinus, which led them to the conclusion that cocaine, by increasing HR and BP, leads to increased myocardial oxygen demand, due to local vasoconstriction. Furthermore, Turillazzi et al.[51] evaluated coronary artery diameter, which is directly affected by a low concentration of cocaine in the blood, more specifically, by its metabolites: benzoylecgonine and ecgonine methyl ester, which are responsible for the arterial vasoconstriction, thus supporting the previously mentioned theories. Cocaine-induced early vascular smooth muscle cell apoptosis signaling pathways have been reported. This process could be mediated by a calcium ion overload and low magnesium which promotes cell death by the production of calcium and magnesium-dependent endonucleases.

Induction of myocardial ischemia and acute myocardial infarction

Acute myocardial infarction (according to the fourth universal definition) is an acute myocardial injury with clinical evidence of acute myocardial ischemia and a rise or fall in cardiac troponin levels with at least one figure above the upper reference limit of the 99th percentile and at least one of the five clinical conditions mentioned in the 2018 consensus. Coupled with the above, cocaine use is related to the development of AMI, which manifests mainly with the onset of arrhythmias that tend to appear due to a prolonged QT interval associated with sodium channel blocking, which allows it to act as a local anesthetic and, in turn, block the potassium channels, altering the interaction between these channels[40]. Deep vein thrombosis and bacterial endocarditis are also complications of intravenous cocaine use. There is evidence of arterial thrombosis facilitated by an antithrombin-3 and protein C deficit in chronic cocaine users. However, the risk of these complications decreases when consumption ceases[27].

As already mentioned, this alkaloid exacerbates the chronotropic and inotropic response, as it increases the HR and BP and triggers increased cardiac output and myocardial oxygen demand, as a first step, to trigger serious cardiovascular system complications[5,39,]; cocaine users may or may not develop significant coronary artery vasospasms. In addition, sodium channel

blocking depresses the myocardium and induces myocardial ischemia[41].There are four factors involved in the generation of ischemia, as follows:

– Increased myocardial oxygen demand due to the previously mentioned factors and the sympathomimetic effect, which causes ischemia with significant coronary stenosis, with an increased effect if the user has a history of smoking.
– Alpha-1-adrenergic coronary vasoconstriction; an exacerbation of the vasoconstrictive effect on the epicardial arteries and the arterioles[34,46].
– Coronary thrombosis: since the alkaloid increases platelet aggregation due to the effect of TXA2, it allows thrombi to be formed and also causes endothelial dysfunction through the procoagulant effect, thus decreasing antithrombin III and protein C synthesis[34,46].
– Coronary artery aneurysms: in Rodríguez et al.'s study, in which 112 cocaine consuming patients (who were symptomatic at the time) were examined and underwent coronary angiography, 30.4% had coronary artery aneurysms, compared to the control group with 7.6%[40].

Thus, these factors trigger myocardial ischemia, coupled with a prothrombotic state that ends in AMI. However, it is pertinent to clarify that excessive consumption of this substance causes a 24 times greater risk of AMI within the first hour of consumption[40,46]. When a cocaine user is admitted to the emergency room for precordial pain, two aspects should be understood: first, a simple electrocardiogram will always show a pathological result because ST segment elevation is common; and second, creatine phosphokinase (CPK) is usually elevated in users due to the side effects of consumption (hyperthermia and muscle damage), and therefore troponins should always be used, specifically troponin I, as the best diagnostic marker[39].

Furthermore, the study by Veas et al. analyzed coronary microcirculation damage in cocaine users after undergoing primary angioplasty, with a group of 59 patients and a non-user control group of 142 patients. After a TIMI frame count (which evaluates epicardial flow and microcirculation), the evidence showed that the user group had a higher count than the control group, and therefore the investigators concluded that users have a higher risk of endothelial damage and microcirculation impairment caused by primary angioplasty. Bosch et al conducted an observational study of 1,240 patients with an average age under 55 and a complaint of chest pain, in which they analyzed the relationship between cocaine use and precordial pain and determined that 63 patients reported cocaine use associated with precordial pain, and 6% of these ultimately suffered an AMI. An autopsy study[39] showed that those who died from acute coronary thrombosis had elevated mastocytes in the coronary segment, a finding suggestive of a local proinflammatory state in frequent cocaine users. However, this study did not consider the history of tobacco addiction.

Arrhythmia induction

Cocaine can cause arrhythmias due to its pharmacological properties, as it acts as a local anesthetic and sympathomimetic agent (as mentioned previously), thus promoting vasoconstriction of the coronary arteries and, therefore, reducing oxygen delivery to the myocardium. Coupled with this alteration, there are prolonged PR, QRS and QT intervals on the electrocardiogram (EKG). These changes are linked to electrical disturbances due to the direct effect on the sodium, potassium and calcium channels. The most common arrhythmias in cocaine users are sinus tachycardia, sinus bradycardia, supraventricular tachycardia, ventricular tachycardia, bundle branch block, complete heart block, accelerated idioventricular rhythm, ventricular fibrillation, and asystole[46].

In addition, we have already mentioned some of the complications caused by chronic cocaine use; for example, acute myocardial ischemia is associated with an elevated extracellular potassium concentration within the ischemic area, causing potassium-induced depolarization of the membrane potential, as a result of sodium channel inactivation; subsequently, there is an increased proportion of these inactivated channels under resting conditions. Cocaine has been found to bind to inactivated sodium channels, reducing even further their availability in the involved ischemic area, which alters electrical conduction and increases the onset of arrhythmias, producing QRS complex prolongation, ST segment elevation (which can even lead to a Brugada syndrome) and a predisposition to ventricular fibrillation on the EKG. Another cause that exacerbates sodium channel inhibition is vasoconstriction, which patients will compensate with an increased HR[3]. On the other hand, potassium and calcium channels are blocked and repolarization is affected by a prolonged QT interval and other complications, like ventricular fibrillation and torsades de pointes (rhythms that can be seen on the EKG), associated with bradycardia derived from the simultaneous channel blocking[3]. It should

be noted that the potassium channels may be altered by a direct relationship with human ether-a-go-go-related gene (hERG) mutations, which is a direct cause of long QT.

Myocarditis and endocarditis

Cocaine addiction increases left ventricular pressure and dilation and decreases contractility, which, together with the adrenergic impact of cocaine, could mimic pheochromocytoma-induced cardiomyopathy or takotsubo syndrome (takotsubo cardiomyopathy). In some cases, myocardial dysfunction is reversible if consumption is stopped, but if it is resumed, the heart damage and complications reappear. Dilated cardiomyopathy is the most frequent complication of chronic cocaine use, due to catecholamine reuptake blockade in the presynaptic neuron which causes subendocardial ischemic and myocytic necrosis, together with hyperadrenergic abnormalities leading to myocardial contraction band necrosis, followed by heart failure and heart valve defects.

On the other hand, some studies employing endomyocardial biopsies indicate that focal myocarditis and dilated cardiomyopathy are caused by the toxic effect of elevated plasma catecholamines which ultimately cause subendocardial ischemia and myocytic necrosis in the myocardium[34,46]. The relationship between intravenous cocaine consumption and the onset of infective endocarditis is clear when the procoagulant effects, endothelial dysfunction and valve abnormalities or disease are taken into account. Autopsies of some cocaine users have found myocarditis with lymphocytic infiltrates dependent on an inflammatory reaction at myocardial necrosis or vascular injury points. There are also other myocardial lesions, both fibrotic and necrotic; the latter are more evident in patients with pheochromocytoma (considering the catecholaminergic hyperstimulation produced by cocaine). The study by Aguilar et al.[52] included eight patients who reported intravenous cocaine use, with no history of cardiovascular problems. Transthoracic echocardiograms showed masses adhered to the chordae tendineae, with greater prevalence of tricuspid valve involvement. Finally, the direct toxic effect of cocaine on the heart and myocardium makes this alkaloid a potential risk factor for cardiomyopathies, and if this is aggravated by the presence of contaminants like heavy metals (manganese) that are often mixed with cocaine, its risk contribution increases exponentially[46].

Great vessel dissection or rupture

Keeping in mind the mechanism of action of cocaine and the acute complications it causes, vasoconstriction is triggered by increased shear stress in the vessel walls, leading to a heightened risk of intimal rupture and, ultimately, acute aortic dissection[49]. There are some predisposing factors for this condition that are exacerbated by cocaine consumption, such as male sex, being a young adult, being of African descent, smoking and having untreated HTN[49].

Hypertensive crises are one of the most common complications of chronic cocaine use and are often accompanied by aortic dissection due to cell apoptosis and smooth muscle necrosis. This leads to endothelial dysfunction and vessel wall weakness that produce aortic dissection, which can cause sudden death and require immediate surgery. Out of 3,584 acute aortic dissections registered in the International Registry for Aortic Dissection (IRAD) database from 1996 to 2012, 1.8% were associated with cocaine use. The same institute obtained data from 17 international centers in which the prevalence of cocaine addicts in acute aortic dissection cases was only 0.5%; however, two single-center studies reported that 3.7 and 9.8% of the prevalence of cocaine addiction in acute aortic dissection cases occurs in young adults. The study by Pérez et al.[53] reported the case of a 25-year-old cocaine user who was admitted for cocaine-related AMI and whose subsequent coronary angiography showed spontaneous dissection of the proximal segment, along with a superimposed thrombus and TIMI-III distal flow. He was therefore treated pharmacologically, and monitoring was ordered one week later to verify dissection closure.

Conclusion

Cocaine addiction is the main cardiovascular disease threat in young adults, as it produces effects that vary depending on the route of administration and dose consumed, causing anywhere from bradycardia due to vagal stimulation to sudden death. Cocaine, unlike other drugs (like heroin or methamphetamines), can cause harmful effects through different pathophysiological pathways. It is important to note that there are frequent complications of chronic use, like rhinitis, nasal mucosa erosion, nasal septum perforation, bacterial sinusitis, respiratory diseases, heart arrhythmias, seizures, weight loss and malnutrition syndrome, as well as systemic involvement with neurologic, respiratory, cardiovascular, obstetric, gastrointestinal, renal

and endocrine complications. Cocaine use is not just a health problem, but also a social threat. It is important to promote the ongoing search for treatments to prevent relapses in chronic users, and for this to become a commitment and challenge for healthcare professionals.

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 involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study did not involve patient personal data nor did it require ethical approval. The SAGER guidelines do not apply.

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

References

1. Barrie Fairley H. La “anestesia” en el imperio incaico. Rev española Anestesiol y Reanim ISSN 0034-9356, Vol 54, No 9, 2007, págs 556-562 [Internet]. 2007 [cited 2024 Oct 23];54(9):556–62. Available from: https://dialnet.unirioja.es/servlet/articulo?codigo=3546180
2. MacGowan GA, Dark JH, Corris PA, Nair AR. Effects of drug abuse, smoking and alcohol on donor hearts and lungs. Vol. 32, Transplant International. Blackwell Publishing Ltd; 2019. p. 1019–27.
3. Politi T, Fallabrino M, Abella L, Cortínez D, Crippa E, Failo D. Complicaciones arritmicas del consumo de cocaína. Rev Iberoam Arritmología. 2013;4(40-55).
4. Bosque J, Mainera A, Bruno D, Espinola M, Loredo A, Alvarado N. La cocaína: consumo y consecuencias. Salud mental, 37(5), 381-389
5. Cortés Valerio A, Cortés Bejarano F, Quesada Campos J, Vargas Cedeño JD, Xu Carranza D. Efectos cardiovasculares en usuarios de cocaína. Rev costarric salud pública. 2019;28:105–16.
6. Rezkalla SH, Hale S, Kloner RA. Cocaine-induced heart diseases. Am Heart J. 1990;120(6 PART 1):1403–8.
7. Degenhardt L, Baxter AJ, Lee YY, Hall W, Sara GE, Johns N, et al. The global epidemiology and burden of psychostimulant dependence: findings from the Global Burden of Disease Study 2010. Drug Alcohol Depend [Internet]. 2014 [cited 2024 Oct 23];137(1):36–47. Available from: https://pubmed.ncbi.nlm.nih.gov/24559607
8. Pollin W. The Danger of Cocaine. JAMA J Am Med Assoc. 1985 Jul;254(1):98.
9. Oficina de las Naciones Unidas contra la Droga y el Delito. Informe Mundial de Drogas 2018: crisis de opioides, abuso de medicamentos y niveles récord de opio y cocaína. UNODC. 2018.
10. Hoffman R. Cocaína epidemia siglo XXI. Rev Toxicol. 2009;26(1):15.
11. Parkin J. Bogotá tackles basuco addiction. Lancet. 2015 Sep ;386(9998):1027–8.
12. Castroseiros E, Penas M, Castro A. Patología del corazón de origen extracardíaco (VIII) Cocaína y corazón. Rev Española Cardiol. 1998 ;51(5):396–401.
13. Ministerio de Justicia de Colombia. Reporte de drogas 2015. Ministerio de Justicia y del Derecho - Observatorio de Drogas de Colombia (2015), Bogota, Colombia.
14. Medina Ramírez C, Rodríguez Padilla R, Paredes Rosero M, Patricia Crispín Amorocho G, Fagua Duarte Jaime Flórez Murcia Jaime Mendoza Gómez Camila Patiño Rodríguez Gonzalo Sosa Gutiérrez Angélica Valencia Masmela J. Reporte de Drogas Colombia 2017. Colombia; Ministerio de Justicia y del Derecho - Observatorio de Drogas de Colombia (2017). Bogotá, Colombia.
15. Bartolucci J, Carolina NN, Verdugo FJ, Carlos Prieto J, Sepúlveda P, Corbalán R. Características, manejo y evolución intrahospitalaria de usuarios de drogas ilícitas con infarto agudo del miocardio. Rev Med Chil. 2016;144(1):36–46.
16. Villatoro Velazquez JA, Medina-Mora Icaza ME, Campo Sánchez RM del, Fregoso Ito DA, Bustos Gamiño MN, Resendiz Escobar E, et al. El consumo de drogas en estudiantes de México: tendencias y magnitud del problema. Salud Ment. 2016;193–203.
17. Dürsteler KM, Vogel M. Effective drug therapy for cocaine dependence: A milestone. Lancet. 2016 May;387(10034):2171–3.
18. Oficina de las Naciones Unidas contra la Droga y el Delito, Informe Mundial sobre las Drogas 2015 (publicación de las Naciones Unidas, núm. de venta S.15.XI.6).
19. Informe sobre el consumo de drogas en las Américas 2019. Comisión Interamericana para el Control del Abuso de Drogas (CICAD) Secretaría de Seguridad Multidimensional (SSM) Organización de los Estados Americanos (OEA). Washington, D.C; 2019. 139–212 p.
20. Sandoval LE, López Á, Cárdenas C. Determinantes y características de la oferta de cocaína en Colombia. Rev la Fac Ciencias Económicas Investig y Reflexión. 2009;XVII(2):199–208.
21. Oficina de las Naciones Unidas contra la Droga y el Delito. Informe Mundial sobre las Drogas 2019 (publicación de las Naciones Unidas).
22. Distribución de drogas ilegales y su consumo en Colombia - ¿Cuál es el problema y qué hacer para enfrentarlo?; 2019. Fundacion Ideas para la Paz, Bogota, Colombia.
23. Oficina de las Naciones Unidas contra la Droga y el Delito, Informe Mundial sobre las Drogas 2016 (publicación de las Naciones Unidas, núm. de venta S.16.XI.7).
24. Universidad de los Andes - Facultad de Economía. Consumo de Drogas: comparación Medellín y Bogotá. Bogotá; 2018. p. 1–11.
25. En M, Pública S, Pušković I. Complicaciones médicas asociadas al consumo de cocína. 2010. Repositorio Universidad Nacional de Cordoba (2009) pp 1-146
26. Calabuig G. Medicina legal y toxicología. 7ma ed. Elsevier, España; 2018. Capítulo 74, 1093-1122.
27. Kloner RA, Hale S, Alker K, Rezkalla S. The effects of acute and chronic cocaine use on the heart. Circulation. 1992;85(2):407–19.
28. Ambrosio Flores E. Efectos de la cocaína en el ser humano. Vol. 10, Trastornos Adictivos. Ediciones Doyma, S.L.; 2008. p. 151–65.
29. Jerí RE. Cocaína 1980: Actas del Seminario Interamericano sobre Coca y Cocaína. Repos Inst - CEDRO. 2018.
30. Ryan S. Cocaine Use in Adolescents and Young Adults. Pediatr Clin North Am. 2019;66(6):1135–47.
31. Peacock A, Bruno R, Gisev N, Degenhardt L, Hall W, Sedefov R, et al. New psychoactive substances: challenges for drug surveillance, control, and public health responses. Vol. 394, The Lancet. Lancet Publishing Group; 2019. p. 1668–84.
32. Nanji AA, Filipenko JD. Asystole and ventricular fibrillation associated with cocaine intoxication. Chest. 1984;85(1):132–3.
33. Billman GE. Mechanisms responsible for the cardiotoxic effects of cocaine. FASEB J. 1990 May;4(8):2469–75.
34. Kim ST, Park T. Acute and chronic effects of cocaine on cardiovascular health. Int J Mol Sci. 2019 Feb;20(3).
35. Crumb WJ, Clarkson CW. Characterization of cocaine-induced block of cardiac sodium channels. Biophys J. 1990;57(3):589–99.
36. Roverano S, Gallo J, Ortiz A, Paira S. Manifestaciones sistémicas asociadas al consumo de cocaína: comunicación de un caso. Rev argent Reumatol. 2016;27(3):50–2.
37. Xiao Y-F, Morgan JP. Cocaine Blockade of the Acetylcholine-Activated Muscarinic K+ Channel in Ferret Cardiac Myocytes. J Pharmacol Exp Ther. 1998;284(10-18).
38. Havranek EP, Nademanee K, Grayburn PA, Eichhorn EJ. Endothelium-dependent vasorelaxation is impaired in cocaine arteriopathy. J Am Coll Cardiol. 1996 Nov;28(5):1168–74.
39. Havakuk O, Rezkalla SH, Kloner RA. The Cardiovascular Effects of Cocaine. Vol. 70, Journal of the American College of Cardiology. 2017.
40. Guarda E, Rodríguez M, Solari S, León L, Ramírez J, Pérez O. Complicaciones cardiovasculares por uso de cocaína. Rev Chil Cardiol. 2007;26 (459-466).
41. Dávila J. Intoxicación con cocaína: reporte de caso. Med Leg Costa Rica. 2013;30(1-7).
42. Fischman MW, Schuster CR, Resnekov L, Shick JFE, Krasnegor NA, Fennell W, et al. Cardiovascular and Subjective Effects of Intravenous Cocaine Administration in Humans. Arch Gen Psychiatry. 1976;33(8):983–9.

43. Kelkar AH, Smith NA, Martial A, Moole H, Tarantino MD, Roberts JC. An Outbreak of Synthetic Cannabinoid–Associated Coagulopathy in Illinois. N Engl J Med. 2018 Sep;379(13):1216–23.
44. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. N Engl J Med. 2001 Aug 2;345(5):351-8.
45. Duflou J. Psychostimulant use disorder and the heart. Addiction. 2020 Jan;115(1):175-183.
46. Rener A, Figueroa S. Efectos cardiovasculares de la cocaína. A propósito de dos casos. Rev Urug Cardiol 2014; 29: 60-66.
47. Heesch CM, Wilhelm CR, Ristich J, Adnane J, Bontempo FA, Wagner WR. Cocaine activates platelets and increases the formation of circulating platelet containing microaggregates in humans. Heart. 2000 Jun;83(6):688–95.
48. Sánchez MP, Pérez MC, Romero FM, Lorman RS. Consumo de cocaína, hipertensión arterial y enfermedad renal crónica. Nefrologia 2010; 30(6):698-713.
49. Dewar K, Nolan S. Chronic hypertension, recreational cocaine use and a subsequent acute aortic dissection in a young adult. BMJ Case Rep. 2017 Oct;2017.
50. Stennett BA, Padovan-Hernandez Y, Knackstedt LA. Sequential cocaine-alcohol self-administration produces adaptations in rat nucleus accumbens core glutamate homeostasis that are distinct from those produced by cocaine self-administration alone. Neuropsychopharmacology. 2019; 45(3):441-450.
51. Turillazzi E, Bello S, Neri M, Pomara C, Riezzo I, Fineschi V. Cardiovascular Effects of Cocaine: Cellular, Ionic and Molecular Mechanisms. Curr Med Chem. 2012 Nov;19(33):5664–76.
52. Aguilar JA, Summerson C. Endocarditis infecciosa en adictos a drogas intravenosas. Arch Cardiol Mex. 2000;70(4):384-390.
53. Pérez-Díaz P, Bermejo-Calvillo N, López-Lluva MT, Jurado-Román A. Cocaine not only fears the myocardium. Rev Colomb Cardiol. 2018 Sep;25(5):343.e1-343.e2.