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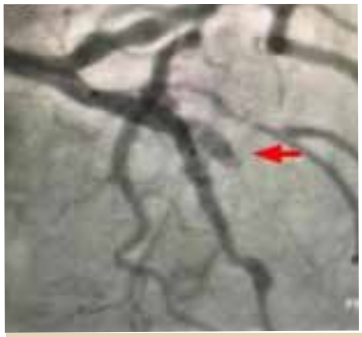

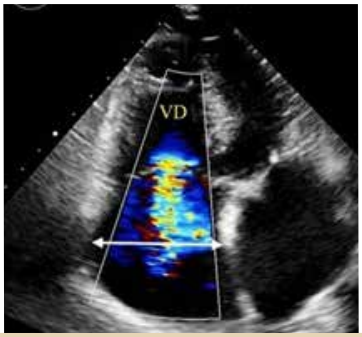

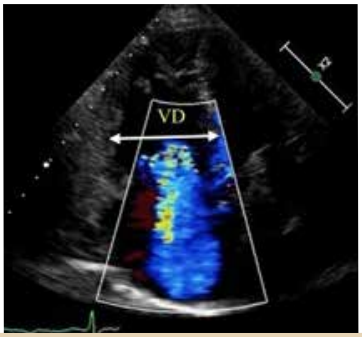

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> N° **1** · March 30th
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> N° **3** · September 30th
> N° **4** · December 20th

> **Supplement 1**
Manejo de la congestión en pacientes con insuficiencia cardíaca

> **Supplement 2**
Shock cardiogénico complicando al infarto agudo de miocardio 2025

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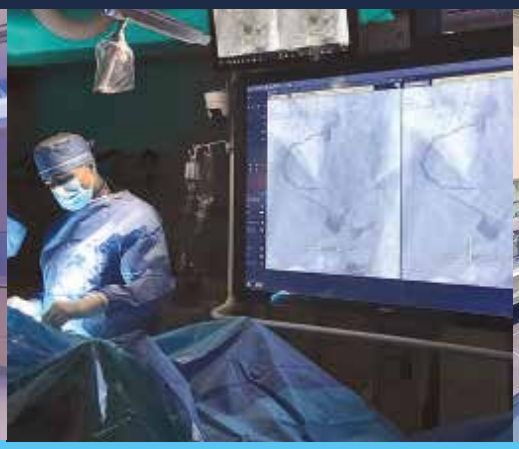
INNOVACIÓN

CARDIO LOUNGE

El primer espacio en Argentina diseñado para realizar ***procedimientos cardiovasculares de alta complejidad de forma ambulatoria*** *de manera* ***segura,*** *posibilitando* ***internaciones breves*** *y potenciando la integración entre el paciente, su acompañante y el equipo de salud.*



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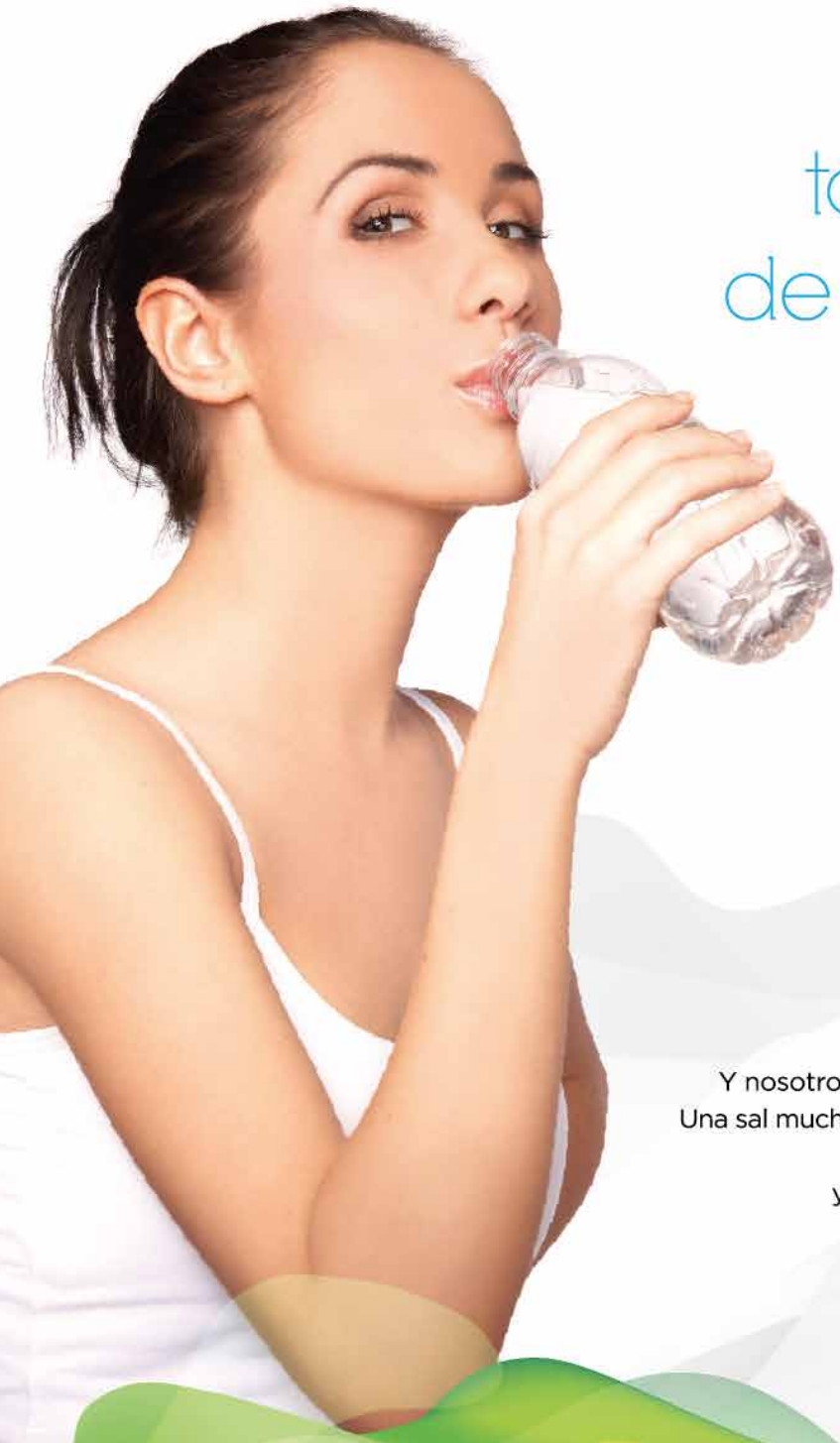

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Editorial

Research leadership of the Argentine Federation of Cardiology: role of scientific organizations in promoting medical publications.

Eduardo R. Perna.

Associate Editor – Journal of the Argentine Federation of Cardiology (Revista de la Federación Argentina de Cardiología). Division of Heart Failure and Pulmonary Hypertension - Instituto de Cardiología "Juana F. Cabral". Corrientes.

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ABSTRACT

Research is one of the many activities that a doctor is able to perform, and it requires the dissemination of the results as the essential final step. The availability of scientific literature is constantly growing without a ceiling, so the Argentine Federation of Cardiology (FAC) should encourage the publication of original articles. The FAC Journal (Revista de FAC - RevFAC) represents the appropriate tool for this purpose, demonstrating continuous activities, with an increase in the production of supplements, editorials, female authorship and foreign articles; with international scope and adequately complying with various criteria that evaluate biomedical journals. The quality has been reflected in the constant increase in its article views.

In its innovative enthusiasm to reduce the gap between research and quality publication, FAC first created the Secretariat of Medical Research, which provides methodological advice to internal projects, and later, designed and carried out two editions of the Tutoring for Writing Scientific Articles (TRAC) course. This instrument allowed an interaction between students and FAC mentors with experience in writing articles, with satisfactory results.

Scientific publication should be considered a component of routine medical activity, which requires training to develop a skill that can be acquired and improved. FAC is committed to making this task easier for its members.

"Writing a scientific paper properly is not a life or death issue; it is much more serious." (Day RA. How to write and publish a scientific paper. 4th edition. The Oryx Press. Phoenix, AZ 1994).

Among the numerous activities that a physician is capable of carrying out, there is research, whose necessary and indispensable culmination is dissemination of the results obtained to the scientific community, in a clear way, with methodological strictness, an impeccable presentation of results and a clear, concise and reliable discussion, that would position the findings in a particular context and, particularly, in the generalization of its applicability in the corresponding area. One of the main challenges for the investigator appears in relation to this aspect: writing a document with a language according to current times, useful, interesting, that may be included in the vast bibliographic repository. As an example of the magnitude of information available, PubMed is a free-access database, specialized in health sciences, with more than 37 million biomedical references.

Scientific information grows exponentially and holds a relevant place, requiring different skills that are not necessarily innate and could be learned. Unlike literary writing, scientific writing has the single purpose of reporting on the result of an investigation[1]. In the last 25 years, the number of citations in 4 extensive areas of cardiology: hypertension, heart failure, coronary artery disease and atrial fibrillation increased 3.4, 4.9, 2.6 and 7.1 times, respectively *(Figure 1)*. This shows, on one hand, an ongoing increase in the literature available, and on the other hand, that a limit has not been reached yet on the possibility of communicating scientific findings in a wide degree of relevance. This last thought should be taken as the encouragement to foster the publication of original articles in the Argentine Federation of Cardiology (FAC).

The *Revista* (Journal) of FAC as a tool for scientific dissemination

Scientific communication is a means to share advancements, challenges and experiences with a wide cardiological audience. The *Revista* of FAC (RevFAC) is the official publication of the Argentine Federation of Cardiology, created in year 1970. Since year 1997 the electronic format has been added, which is the one currently available. Under the supervision of the Department of Scientific Publications, the FAC through this journal brings consensuses, recommendations and guidelines of professional care, as

Corresponding author's address: **Dr. Eduardo R. Perna.** Bolívar 1334. 3400. Corrientes. *e-mail:* pernaucic@hotmail.com

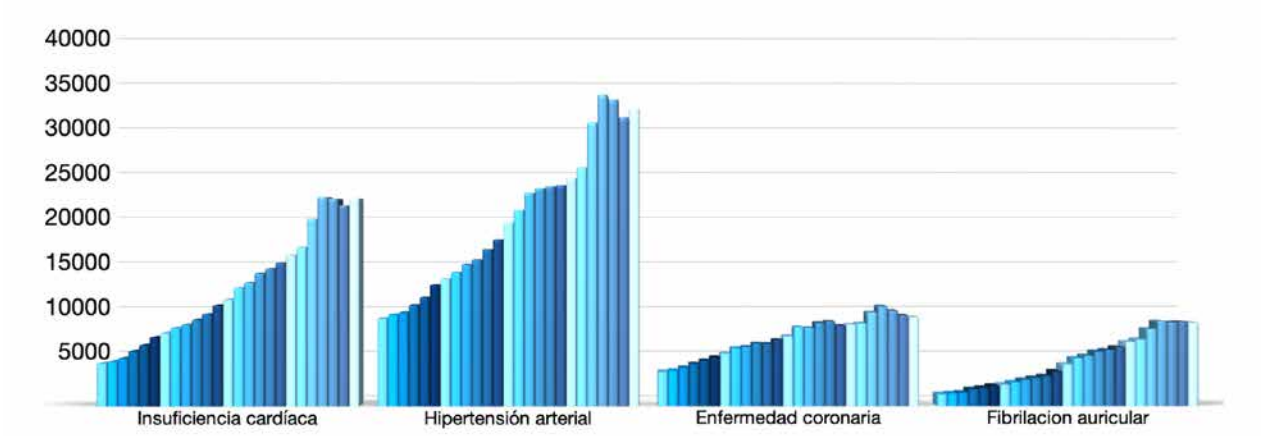

FIGURE 1.
Number of bibliographical references in PubMed in the 2020-2024 period, in 4 areas of cardiology .
Taken from: https://pubmed.ncbi.nlm.nih.gov

well as scientific production and opinions by important national and international leaders in the area, to its members and the medical community. Its editorial team includes an Editor in Chief, an Associate Editor, Associate Editors in 9 thematic areas and the National and International Editorial Committees, made up by outstanding cardiology leaders in our country and overseas. Furthermore, it is important to highlight the unwavering secretary, design, translation and dissemination team who carry out the work daily, and who allow obtaining an excellent final product.

Between 2019 and 2024, a total of 48 fascicles, 24 quarterly issues with a total of 255 articles and 24 supplements were published. The supplements increased from 2 in 2019 to 7 in 2023 and 6 in 2024, with a total of 44 articles. The yearly evolution in the number and type of articles published in the fascicles and the proportion of female first authors and foreign authors is shown in *Figures 1 and 2*. Gender equality has been an aspect of particular interest for FAC. This has been analyzed from different aspects of the operation of the FAC, and published in a document where obstacles were identified and future strategies were designed[2].

These results show the steadfast work in the last 6 years of the RevFAC, with an increase in the production of supplements. Although the publication of original articles has scarcely increased, probably due to a limitation in space, a significant increase was observed in editorials and articles from foreign authors, reflecting the international dissemination of the journal. Female authorship occurred in half of the articles in supplements and in a fourth of the issues, showing the acknowledgement to female leadership entailed by the invitation to lead review articles and institutional documents. Another piece of information to highlight is that the number of visualizations increased constantly from 2019 to 2024: 1521, 2871, 3372, 15,991, 28,091 and 12,486, with an average of 254, 479, 422, 1999, 2554 and 1249 per fascicle.

Recently, Buendía Hernández and Koretzky analyzed the challenges for publications in Latin American journals of cardiology[3]. The RevFAC meets many of the criteria by which a biomedical journal is evaluated: peer review, indexation in databases, editorial quality, open access and bibliometric evaluations[3]. The databases where it is indexed are: Free Medical Journals, IMBIOMED, Latindex, Lilacs, Periódica UNAM and Scopus. Additionally, it is one of the Latin American cardiology journals that are included in the Web of Science of Clarivate®.

Leadership of the Argentine Federation of Cardiology in the area of medical publications: the TRAC course

Although there has been a sustained growth of the RevFAC, it is far from being a faithful reflection of research in the FAC area. On the contrary, there is a disproportion between the number of abstracts presented in scientific events and the number of original articles in the RevFAC. In the National Conferences of the last 3 years, more than 750 studies have been presented, 75% of which are potentially publishable brief communications.

It is evident that there are obstacles hindering the publication of research projects results. Among them, we can mention aspects related to authors: scarce time availability due to work needs, absence of motivation, procrastination, lack of training about how to prepare and write an article; characteristics of the study conducted: lack of originality, already known data, small samples, insufficient data, inadequate statistical analysis, frustration by failed previous attempts to publish, disproportion between the effort to publish and the acknowledgement generated at professional and institutional level, etc.

An innovative step of FAC to contribute to changing this reality was the creation of the Department of Medical Investigation, with the goals of providing methodological advice to all projects emerging from the different FAC fields: committees, federated societies or individually, with national and regional scope. In 2017, the project of organization and operation was written and published, which dealt with the basic structure of the projects presented to the Department for their evaluation[4].

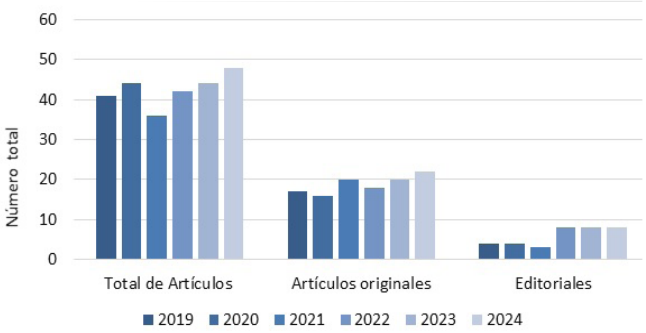

FIGURE 2.
Yearly total of articles, original papers and editorials in the 2019-2024 period.

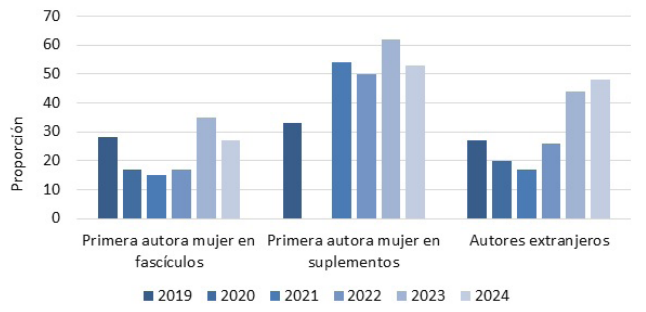

FIGURE 3.
Percentages of female first authors and foreign authors in the 2019-2024 period.

Acknowledging that scientific articles are of interest and relevant for most health care professionals, and that it is extremely important to know the foundations for an appropriate publication, FAC planned in year 2021 a theory and practice course called Tutorship for Writing Scientific Papers (TRAC). The goals of it was to provide the necessary keys for students to learn the elements required to publish articles related to our specialty, with the level of demand that national and international scientific societies demand. The aims are presented in *Table 1*.

As a distinctive characteristic, the students had to present the abstract of an article they would write during the course. The modality was completely online, with prerecorded theory classes and synchronic virtual workshops. Another original aspect of the course was the participation of tutors that would keep a permanent exchange with authors, outside of classes and workshops. The lecturers of classes and the tutors were particularly selected for their skill and experience in preparing and publishing scientific articles in national and international journals. The requirement to approve the course was the presentation of the finished article, which was evaluated by a jury of experts in publications.

With this TRAC course delivered for the first time, 7 articles were presented, with one of them winning. Urrutia et al, analyzed the female participation in articles published in 4 Argentinian scientific journals related to cardiology over a term of 5 years, reaching the conclusion that the presence of women in cardiological scientific literature is limited, with underrepresentation and no changes in the last five years[5]. Lopez et al, evaluated characteristics and anatomical and functional modifications in a retrospective study on 864 children with no pathologies, concluding that there are cardiovascular modifications in athletes performing a systematic sports activity, even at early ages, which start in the prepuberty stage but are more intense during puberty[6].

In the second TRAC course, 5 papers were finished. From them, the article by Hubely et al was winner[7]. This study evaluated the right ventricular outflow tract by pulmonary annular plane systolic excursion by echocardiogram, and its relationship with ejection fraction by resonance, in 70 patients; concluding that pulmonary annulus excursion is related to ejection fraction and with most right ventricular systolic function indices.

TABLE 1.
Goals of the TRAC course

Goals
Introducing the fundamental concepts of scientific communication in health care sciences.
Increasing awareness on the need to report the results of an investigation and clinical observation.
Learning the principles and guidelines ruling adequate writing of reports and scientific papers.
Learning to identify the quality of the published scientific texts.
Learning about the basic statistical elements to interpret and write an article.
Identifying the structure of an article and the rules to be followed so that a publication is clear and methodical, communicating the topic to the reader in an accurate manner.
Writing in an accurate, clear and concise manner articles that can be published in academic and scientific media.
Applying principles, methods, techniques and tools that experts in the topic offer to write academic texts.
Using essential elements to achieve good communication and selecting, with clear steps and outlines, the most appropriate medium for the publication of an article and other academic texts.
Applying the professional guidelines that are required to present a text to an academic publishing institution or an indexed journal.

Final messages

FAC has assumed an active role of leadership to overcome obstacles to increase the scientific production of its members. There are still pending tasks to be done, such as enhancing the availability of advising in the design and execution area of investigation projects, writing of articles, statistical analysis, improvement of educational options, indexation of the RevFAC in new databases such as PubMed, increasing the number of fascicles, etc.

The publication of a scientific article should be considered a component of the usual medical activity, requiring training to enable the development of a skill that could be acquired and, essentially, improved. Scientific entities have to fulfill a facilitating role to reduce the gap between national scientific production and the final presentation of an article in well renowned journals.

FAC has assumed its commitment in different stages of this process: two departments involved directly (Scientific Publications and Medical Research), National Conferences and satellite events where the medical community may present their work and share experiences, and a RevFAC with national and international renown. Furthermore, today it established a bridge between them with the TRAC course, which provides the basic tools so that publishing doesn't turn into something more serious than a life or death issue[8].

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Editorial

Prognosis and evolution in the right ventricular infarction

Gabriela Borrayo Sánchez, Leslie Maribel Hernández Mercado.

School of Medicine, UNAM, México

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prognosis

ABSTRACT

The clinical evaluation, hemodynamic, and progression of patients with ST-segment elevation acute myocardial infarction (STEMI) and right ventricular involvement remains a challenge.

Timely reperfusion changes the prognosis; however, there are other determining factors of evolution, such as the presence of greater hemodynamic deterioration requiring invasive management, increased biventricular failure, complications such as atrioventricular block, renal failure, and higher mortality.

The authors observed a worse prognosis in the right ventricular infarction (RVI) group in a cohort of 1,126 patients, of which 9.6% (149 patients) had this condition. Although between 75% and 76% underwent primary angioplasty and 5% fibrinolytic therapy, with no significant difference between both groups, mortality was three times higher in patients with right ventricular infarction (15.4% vs 5.1%, p<0.0001), which implies other pathophysiological and therapeutic conditions in this group of patients.

INTRODUCTION

Right ventricular infarction (RVI) significantly impacts on prognosis, and up to 20% course with permanent RVI and low right ventricular function by obstruction of the right coronary artery, associated to a more extensive left ventricular infarction and microvascular damage documented by MRI[1]. It is associated to inferior infarctions in 10 to 30%; the authors report 9.6% in their cohort[2].

In the age of reperfusion, mortality by ST-elevation myocardial infarction has reduced with an improvement in timely and sustained reperfusion; however, there are still challenges to implement the infarction code in low and medium income countries, as 30% or more do not receive reperfusion[3,4]. The authors report between 75 and 76% of primary angioplasty, not providing details on success and timing, not finding significant differences[2].

ELECTROCARDIOGRAPHIC DATA

ST-segment elevation in the V4R lead of more than 1.0 mm defines RV compromise. It is remarkable that just 7.1% had electrocardiographic compromise, which casts a doubt as to how diagnosis was made in 2.5% of cases[2,5]. In the presence of inferior infarction with ST-segment elevation, international guidelines recommend using 16 leads[6]. Identifying RVI allows high risk stratification and focusing the treatment with more volume and preventing using nitrates that reduce preload even more[7].

HEMODYNAMIC REPERCUSSIONS

RVI with hemodynamic repercussion is characterized by three clinical data: hypotension, increase in jugular venous pressure (between 40 and 60% of cases) and clear lung fields (Cohn's triad); the authors point out that from 9.6% to 6.1% had hemodynamic repercussion, more presence of atrial fibrillation and complete heart block in a significant manner[2,8], as well as a greater increase in serum creatinine due to kidney failure by low output.

ECHOCARDIOGRAPHIC EVALUATION

Echocardiographic evaluation of right and left ventricular function is essential, as it allows evaluating the extent of infarction and make a follow-up on the management of the acute phase[9]. Ventricular interdependence manifests in the presence of RVI, when residual volume increases in the right ventricle pushing the interventricular septum, which contributes to reducing beat volume in the left side. The authors do not mention echocardiographic tests in their patients, which are accessible in the intensive care unit and could guide the treatment along with Swan Ganz monitoring[2]. There are new techniques for function assessment with 3D echocardiography or right ventricular free wall strain, which are not usually used in an emergency scenario, but provide very useful information.

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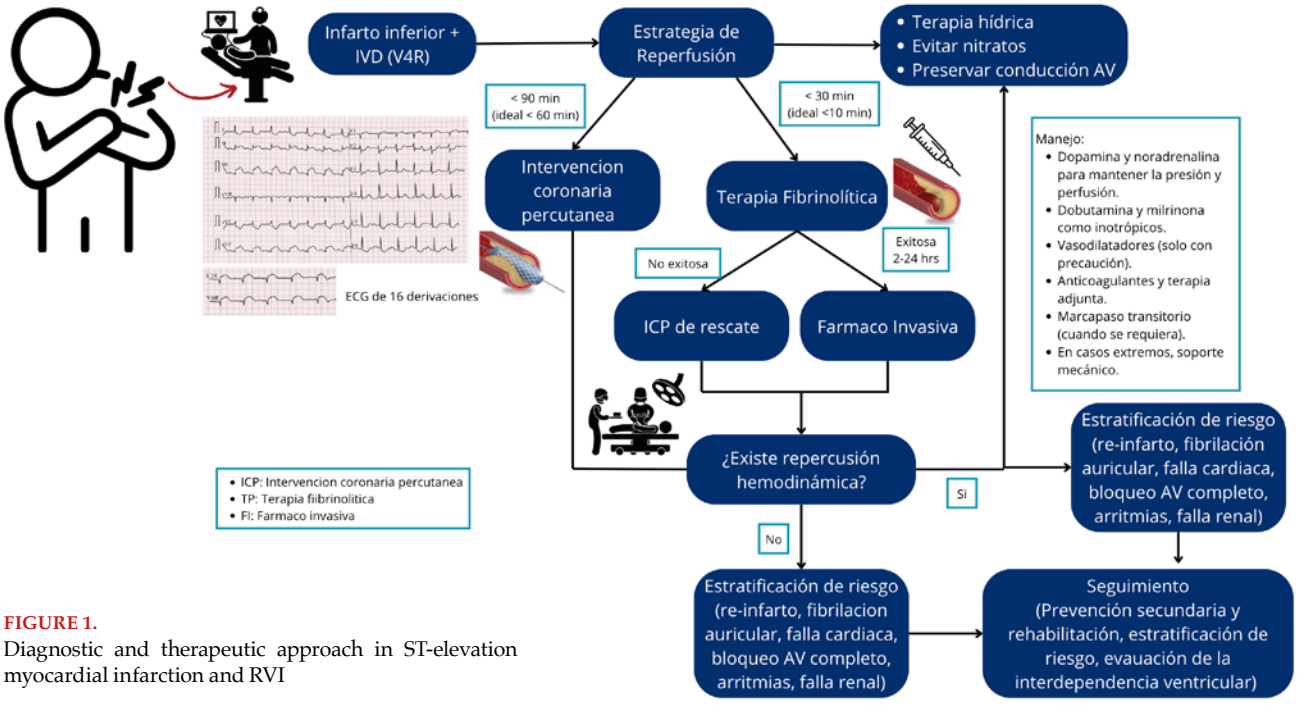

FIGURE 1.
Diagnostic and therapeutic approach in ST-elevation myocardial infarction and RVI

RVI COMPLICATIONS

A table with the clinical and hemodynamic data of both groups is not included, which could be fundamental in early mortality and to determine risk associations. The authors, as in other studies, point out a greater extent of infarction by troponin level, as well as more complications in patients with RVI, such as reinfarction 8.1 vs 4.6% (p = 0.048), atrial fibrillation 16.8 vs 9.1% (p = 0.004), atrioventricular block 13.4 vs 2.3% (p =< 0.001) and higher requirement of mechanical ventilation 13.4 vs 7.9% (p = 0.020)[2]. These complications are associated with a more severe prognosis and a higher rate of mortality, as shown in multivariate analysis, where independent mortality factors were an advanced age (OR 1062, 95% CI 1031-1094, p = 0.001), Killip ≥ 2 (OR 2.1, 95% CI 1.88-4.73, p = 0.004), elevated creatinine (OR 1.55, 95% CI 1.10-2.18, p = 0.015) and RVI (OR 2.82, 95% CI, 1.17-5.6, p = 0.003). This entails identifying from the very beginning this group of patients as in high risk, and acting more timely with successful and permanent reperfusion by primary angioplasty or pharmaco-invasive strategy, as well as biventricular evaluation, interdependence by echocardiography and fluid management, preserving atrioventricular conduction with use of transient dual chamber pacemaker, proper management with inotropic agents and auxiliary therapy. Early stratification, secondary and tertiary prevention and using echocardiography and MRI could be a great help for long-term treatment *(Figure 1)*[10].

CONCLUSION

The published study shows relevant data from the clinical point of view in anterior infarction with RVI, with a higher risk of complications, including up to 3 times more death in spite of having more than 75% of primary angioplasty. Undoubtedly, there are pathophysiological and therapeutic data, particularly timely reperfusion, which should be considered in the presence of RVI, entailing a specialized diagnostic and therapeutic approach in a group in high risk.

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Review Article

From metabolic syndrome to cardiovascular-nephro-metabolic syndrome

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ABSTRACT

The term "metabolic syndrome" has been the subject of considerable debate as to its suitability and usefulness in clinical practice. Despite its widespread use, there are significant concerns about the accuracy of its definition, the certainty of its pathogenesis, and its value as a marker of CVD risk.

More recently, it has been proposed to speak of metabolic cardiorenal syndrome because it is more explanatory of the chain of pathophysiological events that lead from an increase in adiposity to an increased risk of cardiovascular and renal disease. In this article, we update the current concepts of adipocyte dysfunction as the original cause of this condition, analyze the correct way to evaluate overweight or obese patients and propose some diagnostic and therapeutic considerations from primary prevention to secondary prevention of new events.

INTRODUCTION

Cardiovascular diseases (CVD) are still the main cause of death throughout the world, particularly in low and medium income regions, such as Latin America. This is because of the combination and interaction in different proportions of a high prevalence of cardiometabolic risk factors and socioeconomic, educational and cultural conditions. This reality propositions the need to change some paradigms, to consistently and systematically promote cardiovascular prevention as the most cost-effective strategy in the mid and long term, with the goal of reducing its prevalence in mid and low income countries, not just Latin America, but also other regions in the world.

Cardiometabolic diseases (CMD) and their clinical manifestations (in other words, CVD, cerebrovascular disease, peripheral artery disease and chronic kidney disease) are, jointly, the main cause of morbidity and mortality throughout the world[1]. In general, it is estimated that more than 17 million individuals die yearly due to this conditions, representing 31% of all world deaths. CVDs have reached epidemic proportions and are associated to very high social and financial costs, both due to significant direct costs due to sanitary intervention, and significant indirect costs that emerge from death and disability.

We should highlight that the load of CVD is higher in mid and low income countries respectively, in comparison with high income countries[2]. For instance, although CVD represent 23% of deaths in high income countries, they cause more than 42% of deaths in mid and low income countries. This corresponds to a risk of death by CVD, between two and four times higher in mid and low income countries than in high income ones. The most frequent pathophysiological substrate in the mentioned pathologies is atherosclerotic cardiovascular disease (ASCVD), a pathological process secondary to changes in artery walls including endothelial dysfunction, oxidative stress, inflammation and atherothrombosis[3]. These changes are the consequence of a sustained and long-term effect by a group of risk factors, known jointly as cardiometabolic risk factors (CMRF), highly related with abdominal obesity and ectopic fat, specifically hypertension (HTN), dyslipidemia including atherogenic dyslipidemia, diabetes mellitus (DM) and prediabetes. Other risk factors are modifiable behaviors, such as smoking in all its forms (active and passing smoker, chewing, vaping, cannabis consumption), high alcohol consumption, sedentary life, inadequate diet and other genetic and hereditary factors. Two standardized international studies of cases and controls on modifiable risk factors associated to myocardial infarction (INTERHEART) and stroke (INTERSTROKE), showed that CMRF are responsible for more than 80% of CV events[4,5]. Furthermore, both studies showed that these risk factors do not occur in isolation, but they are frequently grouped in a single individual, and the addition of different factors exponentially increases the risk of a CV events[4,5].

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From this scenario, the notion of cardiometabolic risk (CMR) emerges, which is defined as the probability of developing DM, subclinical or clinical ASCVD, or a CV event in the presence of CMRF. Current evidence shows consistently that an early diagnosis and strict control of CMRF significantly reduces the chance of a new CV event[6].

FROM METABOLIC SYNDROME TO HEPATO-CARDIO-RENAL SYNDROME

Metabolic syndrome (MS) was originally defined as a group of interrelated factors that increase the probability of developing cardiovascular disease, type 2 diabetes mellitus (T2DM) and other health complications. The syndrome is characterized by central obesity, insulin resistance, glucose intolerance, hypertension and atherogenic dyslipidemia, including high triglycerides and low cholesterol levels of high-density lipoproteins (HDL) and normal or slightly high levels of low-density lipoproteins (LDL) cholesterol, with a higher proportion of type B LDL which is smaller and denser, but more atherogenic[7,8]. The prevalence of metabolic syndrome is increasing throughout the world, fostered by factors such as urbanization, sedentary lifestyles and inappropriate changes in diet[8].

The diagnostic criteria for metabolic syndrome generally require the presence of three or more of the following components: abdominal obesity (often evaluated by waist circumference), high blood pressure, high glucose levels in a fasting state, high triglyceride levels and low HDL cholesterol levels[9]. Insulin resistance and central obesity are considered key factors contributing to the syndrome[9,10].

Metabolic syndrome treatment is focused on lifestyle modifications, including changes in diet, increase in physical activity and weight loss, mainly abdominal obesity, with the aim of improving sensitivity to insulin and reducing visceral fat[11]. Jointly with healthy habits, there are different pharmacological treatments and surgical options. MS is also related to an increase in other conditions, such as nonalcoholic fatty liver disease, nowadays called metabolic-associated fatty liver disease, heart failure, cognitive deterioration and obstructive sleep apnea, turning it into an important public health problem.

In spite of the great dissemination of the term metabolic syndrome, there is debate as to whether it is ideal or useful.

The American Diabetes Association and the European Association for the Study of Diabetes have critically evaluated the concept, emphasizing that, although these risk factors are often grouped, the definition of MS is inaccurate and its pathogenicity does not support this concept, and there is no single treatment. Its value is also questioned as a risk marker for CVD, suggesting that physicians should focus on evaluating and treating individual risk factors instead of relying in the diagnosis of metabolic syndrome[11,12].

Moreover, the World Health Organization (WHO) has pointed out that, although the concept of metabolic syndrome could be useful with educational goals, it has a limited practical usefulness as a diagnostic or treatment tool. The WHO suggests that it should be considered a premorbid condition instead of a clinical diagnosis, and emphasizes the need to investigate the common metabolic pathways underlying diabetes and cardiovascular diseases[13].

Experts propose redefining MS to better reflect its pathophysiology. For instance, a perspective suggesting considering it a "fat storing condition", aligning it with the biological processes that animals use to store fat, which may provide information on obesity and diabetes[14].

In brief, although the term "metabolic syndrome" is well known, its suitability is debatable, and more accurate clinical definitions are needed, as well as an approach based on a comprehensive treatment of individual risk factors.

As a consequence of these reasonable criticisms, we prefer the concept of cardiometabolic risk as an entity where there is a set of risk factors in a patient with a pathophysiology that could be common, and is based or at least closely related to an increase in visceral fat. From a practical point of view, we prefer the approach that prioritizes the relationship between cardiovascular, metabolic, renal and hepatic health.

This view would enable a better understanding of the interrelated nature of cardiovascular, renal and metabolic health (CRM), besides the development of new risk prediction equations and the availability of new and powerful pharmacological therapies that would provide the chance to changing the course of CRM health. Achieving this change at population level will require a change in the conceptual and clinical paradigm to offer interdisciplinary care.

CRM health reflects the interaction between metabolic risk factors, chronic kidney disease and the cardiovascular system, and has a deep impact on morbidity and mortality. There are multisystemic consequences of a poor cardiovascular-renal-metabolic health, with the high associated incidence of disease events and cardiovascular mortality being the most significant clinical impact. There is a high prevalence of poor cardiovascular, renal and metabolic health in the population, with a disproportionate load between those with adverse social determinants of health. However, there is also a growing number of novel therapeutic options that favorably improve the metabolic risk factors, renal function or both, and that also have cardioprotective effects.

PATHOPHYSIOLOGICAL CONSIDERATIONS

Although these syndromes are well known, there is awareness, beyond the initial hemodynamic considerations as a cause for cardiac and renal alterations, that nowadays metabolic anomalies are increasingly acknowledged to play a significant pathophysiological role in bidirectional cardiovascular-renal and hepatic interactions[15,16]. Moreover, renal dysfunction is increasingly acknowledged as a key mediator of the relationship between metabolic risk factors and CVD, particularly heart failure (HF)[17]. Therefore, instead of simply considering cardiorenal syndrome and cardiometabolic disease as separate entities, it is increasingly clear that we should consider their overlapping as a wider construct, the CRM syndrome[18].

This article does not attempt to thoroughly define the molecular causes of CRM syndrome pathophysiology, but undoubtedly, fatty tissue alteration, which we will call adiposopathy, characterized by adipocyte excess and dysfunction, particularly, those located in intra-abdominal visceral white adipose tissue (AT) and other ectopic, perivascular, pericardial, peripancreatic, perirenal, hepatic, intramuscular fat deposits, may cause inflammation, insulin resistance and the appearance of metabolic risk factors, and a myriad of systemic effects, including a greater risk of CVD[19]. In turn, this adiposopathy generates insulin resistance, hyperglycemia, inflammation and oxidation; key elements in the chain of pathophysiological events that trigger CRM syndrome. This places the biology of adipocytes in the epicenter of the pathophysiology of metabolic diseases.

ADIPOSOPATHY AS GENESIS OF THE SO-CALLED HEPATO-CARDIO-RENAL SYNDROME

The contribution of AT constituted by adipocytes of different types, inflammatory cells and fibroblasts, to normal physiology and complications related to obesity is key. We could say that one of the most significant discoveries in the last two decades of investigation of adipocytes is that they not only release endocrine hormones, but adipocytes and adipose tissue jointly secrete a variety of effectors, including exosomes, microRNA, lipids, inflammatory cytokines and peptide hormones that act in a paracrine and endocrine way, affecting the local and systemic metabolic responses. There are several types of adipocytes classified by color; the best known ones are the white ones, with storing and secretion functions; the brown ones, with thermoregulation functions and production of energy; and recently, two more have been described, beige ones also with heat-generation functions, and pink ones, with functions related to the production of milk during pregnancy and lactation[20].

The type of adipocyte that constitutes the highest volume of AT in the human body, and experiences the greatest expansion in ectopic TA in patients with visceral obesity, is white adipocyte, which secretes a variety of substances: adipocytokines, pro-inflammatory and anti-inflammatory cytokines, and peptide hormones that have paracrine and endocrine functions, affecting local and systemic metabolic responses *(Table 1)*. The set of substances produced and secreted by AT in physiological or pathophysiological scenarios is called secretome[19,20,21]. The AT whose secretome shifts toward an antiatherogenic and anti-inflammatory profile is considered "metabolically healthy". In the presence of insulin resistance, white adipose tissue changes not just its volume but its genetic expression, and consequently, its secretome toward production and secretion of pro-inflammatory cytokines, which have proatherogenic and pro-inflammatory effects; when these molecules are secreted by large deposits of AT and start circulating, they may exert endocrine effects on the vascular wall and the myocardium, affecting their normal physiology[22]. The molecules secreted by perivascular AT also exert paracrine effects (through diffusion) and possibly vasocrine effects (through microcirculation) on the vascular wall[23,24]. Similar paracrine effects are observed between the epicardial adipose tissue and the heart; in normal conditions, it fulfills functions of energy regulation and it buffers the possible damage to the free fatty acids in the myocardium, in patients with obesity and/or insulin resistance, pro-inflammatory cytokines induce coronary and cardiomyocyte dysfunction, increasing the risk of ASCVD and heart failure (HF).

TABLE 1.
Main adipokines secreted by adipose tissue and their functions.
Note: the first three are secreted by adipocytes, the rest by other types of cells.

Leptin: it controls appetite through the central nervous system. It influences on the feeling of satiation
Adiponectin: it has antiinflammatory and endothelial protective effects, and it increases sensitivity to insulin
Resistin: it promotes insulin resistance and inflammation
Apelin: it modulates blood pressure favoring nitric oxide release. It improves myocardial contractility; its expression is increased in the left ventricle in patients with heart failure
Chemerin: it increases fat deposits, insulin resistance. Proinflammatory.
Interleukins (IL): IL-6, IL-8, IL-10
Monocyte chemotactic protein-1 (MCP-1): it attracts monocytes to adipose tissue
Plasminogen activator inhibitor-1 (PAI-1).
Retinol binding protein 4 (RBP4): involved in insulin resistance
Tumor necrosis factor-alpha (TNFα): proinflammatory and antagonist of insulin signaling
Visfatin: it favors adipogenesis, inflammation and insulin resistance
Omentin: antiinflammatory, it improves insulin resistance
Vaspin (SERPINA12): it activates the Glut4 receptor, improves insulin resistance, increases acetylcholine levels and nitric oxide, it inhibits NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), antiinflammatory
Progranulin: antiinflammatory effects
Angiopoietin 1 and 2 (ANG1 and ANG2): angiogenesis and vascular function[8].

Likewise, these substances are responsible for the induction of insulin resistance and atherogenic dyslipidemia. Renal function is also affected by pathological fatty tissue infiltration. Leptin, adiponectin and resistin are exclusively secreted by adipocytes, while other factors may also be secreted from other types of cells, as for instance the immune system cells *(Table 1)*.

Not all adipokines are damaging to the cardiovascular system, and do not necessarily induce cardiac dysfunction *(Table 1)*. Adiponectin or IL-10 secretion exert protective effects by suppressing inflammation and reducing CV oxidative stress[20,21]. Because of everything that has been described, visceral obesity should be considered as an adipocyte disease or dysfunction, adiposopathy, and it is considered by different publications as the genesis of CRM syndrome.

DYSGLYCEMIA AND INSULIN RESISTANCE

The mechanisms of damage induced by hyperglycemia on the cardiorenal system are well studied. In hyperglycemic states, characteristic of insulin resistance, the excessive flow of intracellular glucose leads to cytoplasmic oxidative stress, the main event proposed as triggering organic damage induced by DM[25]. The production of reactive species of oxygen causes damage in tissues through several mechanisms: activation of polyol and hexosamine pathways, which exacerbate oxidative stress in a vicious circle, activation of protein kinase C (PKC), formation of advanced glycation end-products (AGE), as a result of nonenzymatic glycation of proteins.

In turn, AGEs may directly damage the heart, the endothelium, the vascular wall, the kidney and the liver, generating inflammation and fibrosis[26]. Therefore, AGEs are involved in the pathogenesis of the organic damage related to diabetes, such as diabetic cardiomyopathy, diabetic kidney disease, atherosclerosis and metabolically-associated fatty liver disease[27]. Moreover, hyperglycemia is associated with the local renin-angiotensin-aldosterone system activation in myocardium and the kidney, promoting vasoconstriction, fibrosis and exacerbation of organ dysfunction[28,29,30].

It has been proven that glomerular podocytes, cells responsible for the glomerular basement membrane integrity and a proper operation of the capillary loop, have their function altered in DM, and are responsible of conditions characteristic of diabetic kidney disease, such as proteinuria and mesangial expansion[31].

In a parallel way to glucotoxicity, insulin resistance is associated to a metabolic change in cell energy, shifting toward oxidation of free fatty acids (FFA), consuming more oxygen than glucose oxidation, making the cells less efficient. The increase in FFA absorption, when excessive, leads to accumulation of intracellular triacylglycerols, promoting oxidative stress, lipotoxicity and apoptosis[26].

Thus, the bidirectionality of interaction and the vicious circle between obesity, insulin resistance and CRM syndrome is understood.

CLINICAL APPROACH

Classification and diagnosis

The increasing understanding of the complex pathophysiology and interrelation between obesity, insulin resistance, adiposopathy and heart, renal and liver disease demand a change in the clinical approach to patients with CRM syndrome; in fact, the definition of obesity is even changed, and it is understood that the key is body composition and a higher or lower proportional content of fat. Overweight and obesity should be defined as an abnormal or excessive accumulation of fat that could harm health.

Body mass index (BMI) has been the gold standard to define and classify obesity; in fact, the classification of obesity by the WHO is based on this parameter. BMI has been used in many studies to define and classify obesity, which facilitates the comparisons between populations and studies. Although BMI provides the most useful measure at population level on overweight and obesity, it is possible that it may not correspond to the same degree of adiposity in different individuals. BMI does not cover the complex biology of adiposity excess, as it does not take into account muscle or bone mass, nor the amount and distribution of fat. People with a similar BMI may have a different cardiometabolic risk. For instance, women usually have a higher percentage of body fat and less muscle mass in comparison to men with the same BMI[32]. Simple measurements like waist circumference, waist-to-hip ratio or waist to height ratio, better reflect adiposity and visceral adipose tissue, which can better predict CVD than BMI per se. therefore, it has been proposed that these anthropometric measures should supplement BMI for a phenotypical characterization of obesity, keeping BMI as an essential anthropometric measure for epidemiology and population studies.

The American Heart Association (AHA) proposes classifying patients in 5 stages with CRM syndrome, integrating pathophysiology, risk range and opportunities for prevention, and optimization of care for CRM syndrome *(Table 2)*[33].

Stage 0, patient with no risk factors; **stage 1,** patient with excessive or dysfunctional adiposity; **stage 2,** patient with metabolic risk factors present (hypertriglyceridemia, hypertension, diabetes) or chronic kidney disease of moderate to high risk; **stage 3,** subclinical CVD in CRM syndrome or risk equivalent (high risk of CVD or CKD of very high risk); and **stage 4,** clinical CVD in CRM syndrome. Furthermore, the factors that increase risk affect the chance of progression through the CRM syndrome stages.

Supplementing the classification, factors increasing risk are also proposed: the proposal includes the need to start an early diagnosis of CRM disease, in the preconceptional period or during childhood, to be able to identify children in risk and be able to start primary prevention programs early, promoting a healthy diet, minimization of sedentary activities (screen time) and regular physical activity, essential bases for any therapy for the prevention and treatment for excessive increase in weight in childhood and adolescence *(Table 3)*. We can add that the true essential prevention is guaranteed by a healthy preconception and pregnancy; hence the importance of promoting preconceptional medical consultation since adolescence, and in couples or individuals who wish to have children.

Patients with CRM syndrome also have an increased risk of metabolically-mediated liver disease or metabolically-associated fatty liver; for this reason, in the routine evaluation of these patients, an early diagnosis should be made on this condition with clinical tools very easy to use, as for instance the FIB4 score, which uses simple parameters such as transaminases, platelets, BMI and patient's age to yield an estimation of the probability of having a fatty liver, to finally refer these patients to evaluation by the hepatology service[34].

THERAPY

Once identified the stage, therapy should be specific to each and guided by the individual risk of patients. Health

TABLE 2.
Classification of CRM syndrome in stages according to the American Heart Association[34].

Stage	Definition and characteristics
0	Normal BMI and waist circumference, normal glycemia and blood pressure, normal lipid profile and no evidence of subclinical or clinical CKD or CVD
1 Excessive or dysfunctional adiposity	Overweight/obesity, abdominal obesity or dysfunctional adipose tissue, with no presence of other metabolic risk factors. BMI ≥25 kg/m2; abdominal circumference ≥88/102 cm in women/men, or glycemia in a fasting state ≥100-124 mg/dL or HbA1c between 5.7% and 6.4%
2 Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia ≥135 mg/dL, hypertension, diabetes) or CKD
3 Subclinical CKD	Subclinical ASCVD or HF in individuals with excessive/dysfunctional adiposity, other metabolic risk factors or CKD. Subclinical ASCVD defined as coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets the criteria). Subclinical HF defined as elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 that indicate a higher risk of HF. Equivalents of risk of subclinical CVD in CKD: very high risk (CKD in stage G4 or G5 or very high risk according to the KDIGO classification). High risk of CVD expected in 10 years
4 Clinical CVD in CKM	Clinical CVD (CAD, HF, stroke, peripheral artery disease, atrial fibrillation) between individuals with excessive/dysfunctional adiposity, other risk factors of CRM or CKD. Stage 4a: no kidney failure.

BMI: body mass index; **CKD:** chronic kidney disease; **CVD:** cardiovascular disease; **ASCVD:** atherosclerotic cardiovascular disease; **CCTA:** coronary computed tomography angiography; **HF:** heart failure.

promotion has to be the foundation of any therapy in all CRM syndrome stages.

Stage 0: health promotion is key, emphasizing healthy nutrition, physical activity, sleep hygiene, quitting smoking, maintaining weight and ideal body composition, periodically learning BP values, glycemia and lipids.

Stage 1: patients with obesity or fat dysfunction, but with no risk factors. The goal should be weight loss, improvement of body composition and prevention of DM development, HTN and dyslipidemia in patients with obesity or dysglycemia. A weight loss should be achieved of at least 5%, with the benefit being greater the more weight is lost. Pharmacotherapies and bariatric surgery are supplementary options for people with BMI ≥30 and less than 40 kg/m2, who cannot reach the goals of weight loss by modifying their lifestyle. For people with persistent or progressive intolerance to glucose, in spite of lifestyle modification, it is possible to consider use of metformin, which may prevent progression to diabetes. rGLP1 agonists are not approved for these patients.

TABLE 3.
Factors increasing risk in patients with CRM syndrome.

1. Chronic inflammatory conditions (e.g.: psoriasis, RA, lupus, HIV/AIDS)
2. Low socio-economic level, psycho-social stress
3. High load of mental health disorders (e.g.: depression and anxiety)
4. Sleep disorders (e.g.: obstructive sleep apnea)
5. History of premature menopause (age <40 years), complicated pregnancies (e.g.: hypertensive disorders during pregnancy, premature delivery, small for gestational age, gestational DM), polycystic ovaries
6. hs-CRP ≥2.0 mg/L
7. Family history of DM and/or CKD
8. Smoking in all its forms: cigarettes, cigars, vaping, and cannabis included
9. Metabolically-associated fatty liver

From 1 through 7, those proposed by AHA; 8 and 9 suggested by the authors. **RA:** rheumatoid arthritis; **HIV/AIDS:** human immunodeficiency virus/acquired immunodeficiency syndrome; **DM:** diabetes mellitus; hs-CRP; high-sensitivity C-reactive protein; **CKD:** chronic kidney disease

Stage 2: the aim of the treatment is to approach collectively CMRF and CKD, with the main aim of preventing progression to subclinical and clinical CVD. The treatment should be with the therapies that have the best evidence of cardio-renal-metabolic protection, based on local or international guidelines for each pathology or condition (HTN, DM, atherogenic dyslipidemia).

Stage 3: the goal of the treatment is to intensify preventive interventions, always according to individual risk for CVD. These patients, due to having subclinical CVD and/or CKD, should be considered as in very high risk and efforts should be made to prevent progression to clinical CVD and kidney failure, which is the most important goal. Likewise, therapies should be applied with the best evidence and according to the recommendations and approvals from each country.

Stage 4: the aim in these patients is optimizing care and secondary prevention for patients with CVD and CMRF, CKD or both. In all patients with ASCVD, use of aspirin or P2Y12 inhibitors is indicated, besides therapy with high-intensity statins. Taking into account that the goals for LDL and non-HDL are increasingly lower, the chance of using other LDL-reducing agents in combination, like ezetimibe, bempedoic acid, PCSK9 inhibitors or inclisiran, should be proposed as long as it is necessary and financially feasible.

Similarly, in patients with proven intolerance to statins, using non-statin drugs such as ezetimibe, bempedoic acid or PCSK9 inhibitors and inclisiran should be considered if financially feasible.

Optimal medical therapy is also indicated in all patients with HF and reduced ejection fraction, with a particular focus on 4 pillars: β-blockers, angiotensin receptor blockers/

neprilysin, mineralocorticoid receptor antagonists and SGLT2 inhibitors or GLP1 agonists.

CONCLUSIONS

The epidemic of obesity and overweight presents, as a consequence, a significant increase of patients with increased cardiometabolic risk, and consequently, risk of ASCVD, HF and CKD. The initial concept of metabolic syndrome is increasingly being questioned, and we should start talking about cardiovascular-kidney-metabolic syndrome based on pathophysiology and on clinical symptoms, as well as in the new therapeutic strategies that increasingly reduce risk. The best strategy is preventive, starting since the first 1000 days of life (pregnancy and the first 2 years of life), childhood and even preconception, with education in teenagers. The preventive and curative treatment of these individuals will be incomplete when not based on adequate lifestyle changes.

The final goal should be reducing CM risk globally, so the choice of drugs to treat each particular condition (obesity, HTN, DM, dyslipidemia, CVD, CKD, HF) should be based on those with proven risk reduction, attempting to follow clinical practice guidelines to be able to achieve this goal.

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Review Article

Tricuspid valve regurgitation: as the years go by

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ABSTRACT

Tricuspid valve insufficiency is increasingly gaining relevance in the field of valve diseases. This is due to the growing number of studies and publications demonstrating that it is not merely a bystander but rather has prognostic implications and impacts the quality of life of those affected. In addition to the advancement in diagnostic methods with echocardiography and cardiac magnetic resonance imaging, surgical techniques have been improved, and new percutaneous treatment devices have been developed, which will likely change the future management of this valvular disease. Therefore, we believe it is important to understand anatomy and different etiologies, in order to comprehend the mechanisms involved in the insufficiency and consider appropriate therapeutic options.

INTRODUCTION

Tricuspid regurgitation (TR) has been underestimated for many years, being one of the most neglected in comprehensive evaluation of heart diseases. In the initial descriptions, it was categorized as a safety valve of the right ventricle (RV) that was designed to be incompetent. It was even considered that moderate or severe TR was benign in many scenarios.

However, it has been proven that significant TR may lead to progressive RV function deterioration, being an independent predictor of morbimortality in several scenarios.

Interest in the diagnosis and treatment of this disease has increased because of the new technologies available and an increased survival of patients with heart failure (HF).

The aim of this review is to understand the anatomy and physiology of the tricuspid valve (TV), learning about the main diagnostic methods and updating on the therapeutic options available currently.

ANATOMY AND PHYSIOLOGY OF TV

TV is made up by a fibrous ring, usually three thin and membranous leaflets (anterior, septal and posterior), tendinous cords, papillary muscles and the myocardium of the right chambers of the heart.

The tricuspid annulus (TA) is difficult to delimit in comparison with the mitral annulus. However, its dilatation is the main cause of TR and what determines the need for a surgical or percutaneous intervention[1]. It is described as an asymmetrical ellipsoid, shaped like a saddle, with smaller and more resistant segment related to the interventricular septum and the septal valve[2]. Its behavior is dynamic during the cardiac cycle, decreasing size in up to 25% during systole.

It is the valve with the largest transversal area of the heart, measuring approximately between 7 and 9 $cm2^3$. Due to its large diameter and the small difference in RV and RA pressures, the normal peak diastolic measure is less than 1 m/sec, with a mean gradient of less than 2 mmHg.

The TV leaflets are thin and membranous, with a triangular or semicircular morphology. The anterior leaflet is the largest, and it adheres to the annulus between the RV infundibulum and the inferolateral wall. The posterior leaflet is inserted in the posterior margin of the annulus, between the inferolateral wall and the interventricular septum. The septal leaflet is smallest, and it is located on the interventricular septum, more apical than the mitral anterior leaflet, but usually at less than 10 mm[3].

The classical 3-leaflet arrangement presents in approximately 54% of patients. The new classifications described valves of up to seven leaflets, with accessory leaflets, smaller than the main ones[4].

The tendinous cords usually anchor the leaflets to the three papillary muscles, although in 20% of healthy people, there are only the anterior and posterior leaflets. The anterior papillary muscle emerges from the moderator band or the adjacent myocardial wall, and it is the most prominent one.

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The TV is closely related to the His bundle, which crosses the TA at 5 mm from the anteroseptal commissure, with the right coronary artery in its trajectory through the right atrioventricular sulcus, and with the right Valsalva sinus at the level of the aortic root.

CLASSIFICATION OF TRICUSPID REGURGITATION

The presence of some degree of TR is a very frequent finding in transthoracic echocardiogram (TTE); however, the presence of significant TR (moderate or greater) has a prevalence of 0.6-0.8%[5]. It is up to 4 times more frequent in women than in men, and its incidence increases with age, so that around 4% of individuals of more than 75 years may have it.

SECONDARY OR FUNCTIONAL TRICUSPID REGURGITATION

Secondary or functional TR (FTR) occurs in absence of significant structural alteration of the TV apparatus. It is the most frequent cause of TR (80-90% according to the series)[6]. There are two main mechanisms causing it: geometrical deformation of the valve apparatus or TA dilatation.

ETIOLOGY

The most frequent cause of FTR is the left pathology (cardiomyopathies, ventricular dysfunction and/or heart valve disease), which in advanced stages leads to pulmonary hypertension[7].

FTR of atrial origin is an increasingly identified entity, with a 14-17% prevalence in patients with permanent atrial fibrillation (AF), and up to 25% in those with an evolution of their AF longer than 10 years[8].

There are other causes of FTR included in *Table 1*.

PATHOPHYSIOLOGY

As mentioned before, two different pathophysiological models lead to the development of FTR: tethering and/or dilatation *(Figure 1)*.

The first one occurs mainly in scenarios with RV dilatation and systolic dysfunction, along with pulmonary remodeling and hypertension. This remodeling causes a shift in papillary muscles, which in turn produces the tethering of the cords and the tenting of the leaflets, resulting in coaptation above the TA plane.

The other mechanism is TA dilatation, which may exist both by RV dilatation and by isolated right atrium dilatation. In these cases, TA acquires a flatter and more circular shape, and regurgitation is due to a decrease in leaflet coaptation surface.

Once the RV and AD remodeling process starts, any of the two pathways leads to volume overload, which in turn causes a greater dilatation of the annulus and worsening of the FTR. This volume overload produces more RV remodeling, worsening the leaflet tethering, and producing a greater degree of regurgitation, and therefore, more RV dilatation. In brief, FTR generates more FTR, and both mechanisms coexist and a feedback loop occurs.

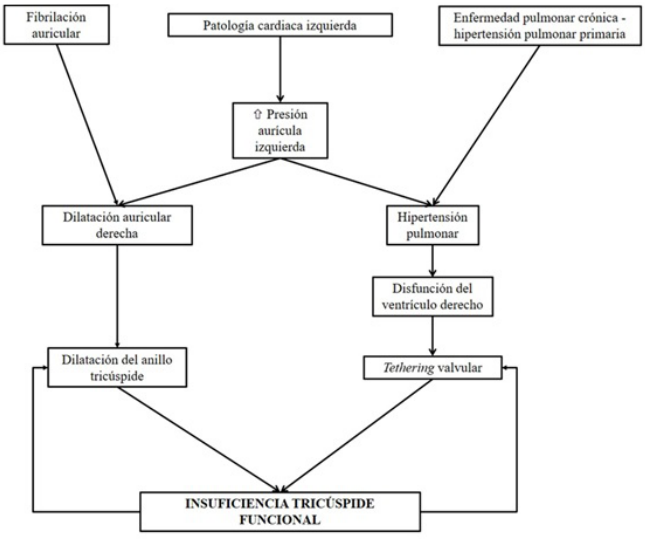

FIGURE 1.
Pathophysiological mechanisms of functional tricuspid regurgitation

CLASSIFICATION

Based on pathophysiology, a new FTR classification has been proposed[6]. It takes into account leaflet mobility and its form of coaptation (similar to Carpentier's classification used for mitral valve), added to the TA characteristics and remodeling both in the RA and the RV.

Thus, within FTR there are 2 main categories:

- Ventricular, where the tethering mechanism prevails, with restriction of normal mobility of the leaflets in systole (Carpentier type IIIb), with great RV remodeling, presenting a round or elliptical morphology.
- Atrial, where TA dilatation is protagonist and leaflet movement is normal (Carpentier type I). The level of coaptation of the leaflets is normal and the RV preserves its conical morphology, although its basal portion could be dilated.

It is important to highlight that atrial FTR is a diagnosis of exclusion that should be made in absence of TV leaflet pathology, left structural cardiac pathology, significant pulmonary hypertension or presence of devices of intracardiac pacing, and usually in a context of AF of long evolution[6]. The differentiation of atrial FTR has prognostic and therapeutic implications, as a proper rhythm control may contribute to inverse remodeling of TA dilatation in this group of patients. On the other hand, the annuloplasty devices may play an essential role in their treatment in selected cases.

PROGNOSTIC IMPACT

Classically, medical efforts are focused on repairing or correcting left heart compromise, as FTR was considered a mere bystander in this scenario. It is known currently that this TR does not resolve spontaneously after left pathology treatment, and that the presence of significant TR or TA dilatation after left valve surgery is associated with regurgita-

TABLE 1.
Tricuspid regurgitation classification, etiology and pathophysiology[12,13].
Modified and adapted

	Etiology	Fisiopatología y hallazgos
VENTRICULAR FUNCTIONAL TR	- Left heart pathology (valve diseases, cardiomyopathies). - Primary pulmonary hypertension. - Secondary pulmonary hypertension (chronic parenchymal lung disease, pulmonary embolism, left-to-right shunts). - RV dysfunction (cardiomyopathies, ischemic heart disease).	- RV dilatation and dysfunction, RV remodeling . - Marked leaflet tethering . - Restricted leaflet mobility in systole (Carpentier type III B)
ATRIAL FUNCTIONAL TR	- Atrial fibrillation . HF with preserved LVEF	- Increase in atrial filling pressures . - RA and TA dilatation . - Normal leaflet movements (Carpentier type I). - Tethering usually absent (except in advanced stages). - RV with normal dimensions (except in advanced stages)
TR BY CARDIAC TUMORS	- Right atrial myxoma	- Interference with valve closure
TR RELATED WITH DEVICES	- Primary: - Secondary:	- Direct interference of lead on the tricuspid valve apparatus (adhesion, laceration, perforation, impaction). - TR by functional cause or remodeling secondary to pacing by the device . - Leaflet mobility is variable. - Frequent RA, RV and TA dilatation
PRIMARY OR ORGANIC TR	- Degenerative (myxomatous or prolapse). - Congenital (Ebstein anomaly, dysplastic valves). - Rheumatic pathology . - Carcinoid syndrome . - Infectious endocarditis . - Trauma. - Endomyocardial fibrosis . - Iatrogenic (leaflet damage in invasive procedures). - Pharmacological . - Associated to radiotherapy. - Valve damage induced by drugs (anorexigenic agents, dopamine antagonists, ergot alkaloids)	- Valve structural alterations proper of each pathology. - Annular dilatation or leaflet perforation (Carpentier I): congenital, endocarditis. - Excessive leaflet mobility (Carpentier type II): degenerative, trauma, iatrogenic. - Restricted leaflet mobility in systole and diastole (Carpentier IIIA): rheumatic, carcinoid, radiotherapy. - Frequent RA, RV and TA dilatation

tion progression during follow-up. Furthermore, FTR may appear a long time after the cause originating it has disappeared. This means that in patients who have undergone left valve surgery with mild TR at the time of intervention, there is a risk between 7-25% of developing significant TR in the future.

For this reason, many patients with FTR who have not received a targeted treatment in recent decades are referred to an intervention when the disease is in advanced stages of RV damage, entailing a high surgical risk, which in many cases is considered inoperable.

Different retrospective series based on the review of thousands of TTE have shown that significant FTR is a factor associated to worse survival, regardless of pulmonary artery systolic pressure (PASP) and RV function[9]. Besides, its prognostic impact has been studied in different particular clinical contexts. In the case of patients with HF and reduced left ventricular ejection fraction, the presence of moderate or severe TR presence was an independent prognostic factor of mortality[10]. Likewise, in patients who have undergone left valve disease, the presence of significant TR is an independent predictor of mortality, both in those treated surgically and with percutaneous intervention techniques[11]. Finally, in the case of atrial FTR, its detection has been associated to worse prognosis, regardless of other comorbidities and the presence of AF[12].

Therefore, whatever the underlying cause, the presence of significant FTR worsens the prognosis of patients, and should be treated in a targeted manner.

ORGANIC OR PRIMARY TRICUSPID REGURGITATION

Organic or primary TR has an estimated frequency of 8 to 10% in all TV regurgitations. An organic anomaly may present or interfere in any of the valve apparatus components, and the causes could be congenital or acquired *(Table 1)*[1].

The clinical suspicion is essential to guide the etiological diagnosis in this type of TR, as valve compromise is usually part of more complex diseases. The most frequent congenital cause is Ebstein anomaly. Between acquired causes, the one induced by pacemaker leads is one of the main ones.

EBSTEIN ANOMALY

It is a congenital heart disease mainly affecting the TV and the RV. It is characterized by variable adhesion of the posterior and septal leaflet of the RV endocardium plus elongation of the anterior leaflet in the shape of a "sail". This leads to apical shift of the valve orifice, which makes a variable portion of the RV to be atrialized and dysfunctional. It is responsible for approximately 0.5% of all congenital defects of the heart and 40% of congenital TV anomalies.

The degree of TR may vary, and its clinical behavior mainly depends on the degree of adherence and septal and posterior valves shift toward the RV chamber. In mild cases, only basal portions are adhered, so valve function is usually almost normal. In severe cases of TR, it is usually severe and there is important adherence of posterior and septal leaflets, and marked anterior leaflet elongation.

Diagnosis is made by measuring the apical shift of the septal valve by TTE or cardiac magnetic resonance. The normal distance with the mitral anterior leaflet is less than 8 mm/m2[13,14]. Besides, RV size, remodeling and function should be evaluated, as well as volume overload and its possible association with other congenital heart diseases, to decide on the proper time for intervention.

Prognosis is related to the anatomical compromise of TV and the degree of RV hypoplasia. In mild cases, symptoms are usually scant and there is a good course. In severe cases presenting in newborn babies, symptoms are usually serious and prognosis depends on the severity of the clinical symptoms, the anatomical characteristics of valve compromise and the associated congenital anomalies.

NON-CONGENITAL ETIOLOGIES

TV, as well as the mitral valve, may present different degrees of myxomatous compromise, and approximately 0.3% of TR causes are related to prolapse. It is more common in the anterior and septal leaflets. A >2 mm prolapse toward the RA in a parasternal view of the short axis is one of the diagnostic criteria for TV prolapse, which is associated with TR of a higher degree and RV remodeling. In turn, it could be associated to concomitant mitral valve prolapse.

Rheumatic compromise of TV is rare in isolation. However, up to 20% is associated to left disease. TR is the most common affection, and less than 50% of cases present stenosis. Valve apparatus compromise is characterized by diffuse thickening, cord fusion and calcium deposits of variable degree. Leaflet retraction and tendinous cords may cause an opening in the dome and a coaptation deficit with the subsequent TR.

Isolated infectious endocarditis is a rare affection, with a 2% incidence. To the typical symptoms, pulmonary embolism can be added. It is usually related to the use of injectable medications and/or IV devices. The main causal agent is Staphylococcus aureus. It is diagnosed when vegetations are observed, usually isoechoic, and with erratic movements. They are usually adhered to intracardiac devices and/or central accesses, as well as the atrial wall of the TV. Rupture or perforation can be observed in leaflets, tendinous cords or papillary muscles, as well as in abscesses, pseudoaneurysms and fistulae adjacent to the valve apparatus.

Carcinoid heart disease is rare and is associated with neuroendocrine tumors in 30-40% of patients. Right heart valves may suffer fibrosis with leaflet thickening, shortening and rigidity. This prevents normal movements during systole and diastole, remaining virtually immobile in advanced stages. TR is generated by increased transvalvular gradient. The few patients with carcinoid compromise in left leaflets usually present patent foramen ovale and right carcinoid compromise in up to 87% of cases.

TR ASSOCIATED TO DEVICES

The implant of pacemaker or cardioverter defibrillator leads by percutaneous venous access is the most common cause of acquired TR.

The trajectory of a catheter through the TV and the location of the lead in the RV could be associated to potential risk of valve dysfunction, generating significant TR in up to 25 to 38% of patients during a 1 to 1.5-year follow-up. It is considered that the lead could be the cause or contribute to TR in 7-45% of patients carriers of devices.

Those in whom the catheter stands at the level of the septal or posterior leaflets present a higher chance of developing significant TR than those in whom it is located near the anterior leaflet or the commissures.

When the tip of the lead is located in the interventricular septum, it is more likely that the device may interfere with normal mobility of the valves and is associated to significant TR. The wires located on the RV apex or in the outflow tract present less interference with valve operation.

TTE allows to visualize the position of the electrode in up to 94% of cases. This reinforces the need to make thorough testing and in real time, in patients who develop significant TR after the implant of catheters, leads or other devices.

Cardiac pacing devices may cause both primary and functional TR *(Table 1)*[15]. These two etiologies may coexist, and in some cases, primary TR caused by the devices may lead to RV dilatation and FTR.

DIAGNOSIS OF TR

There are diverse tests that allow evaluating TV anatomy and function. Using a comprehensive approach allows to determine the severity and prognosis of the valve disease. The different methods will be analyzed based on their complexity:

ECHOCARDIOGRAPHY

TTE is the first option to evaluate TV. It allows to analyze valve anatomy (leaflet degree of mobility and coaptation, presence of tethering, TA diameter and dimensions), the severity of the disease and its impact on right chambers (RA and RV volume and function, estimation of the systolic pressure in the RV). Furthermore, it allows assessing the left chambers and the mitral and aortic valves.

To evaluate the RV, four main views are used:

1. Short axis view at the aortic valve level;
2. Parasternal view of the RV inflow tract;
3. Apical view of the four chambers focused on the RV;
4. Subcostal four-chamber view.

By a thorough analysis of its anatomy, it is possible to make an assessment of the TV to establish number of leaflets, and in the case of appropriate acoustic windows, it is also possible to establish if there are segmentations in them.

Spatial orientation makes it difficult to see all leaflets simultaneously (only 5-10% of patients, and generally with modified subcostal view), so it is important to be meticulous about the identification and morphology of each leaflet when describing valve anatomy.

A study of leaflet structure and function allows to identify the cause and mechanism of TR, to classify it according to what is observed in *Table 1 and Figure 2*.

The presence of a permanent pacemaker makes it necessary to conduct a thorough examination to determine if regurgitation is caused by lead interaction (mechanical obstacle, adherence, perforation, laceration, papillary muscle or tendinous cords transection) or by ventricular remodeling due to pacing.

In the cases of suspicion of congenital disease, the distance between the tricuspid septal leaflet and the mitral anterior leaflet can be measured. The normal value is <8 mm/m2. Furthermore, the tenting area can be measured, where a value >1 cm2 is considered severe. Measurement of TA in the 2-dimensional plane is made in the apical 4-chamber view at the end of diastole, and it is considered normal when up to 39 mm or 21 mm/m2. Normal thickness of leaflets is less than 1 mm in diastole and overlapping at the coaptation point should be >5 mm in a competent valve.

Similarly to mitral valve, leaflet mobility can be evaluated in TR by Carpentier's classification, allowing to establish a possible etiology of the mechanism involved in the heart valve disease.

Three-dimensional (3D) TTE is a valuable tool, as it allows to make multiplanar reconstructions, achieving a full view of the valve and its ring. The resulting image is similar to the surgical view, allowing the identification of problems with prolapses, vegetations and perforations, among others. The 3D study is more accurate than the 2D one in the evaluation of TR severity, and it allows to estimate the effective regurgitant orifice directly, which is particularly useful in the cases of eccentric or multiple jets.

A change has been suggested in the classical stratification of TR, to include the "very severe" and "torrential" degrees. This allows for a better evaluation of the severity of the regurgitation and can guide the most appropriate choice of treatment.

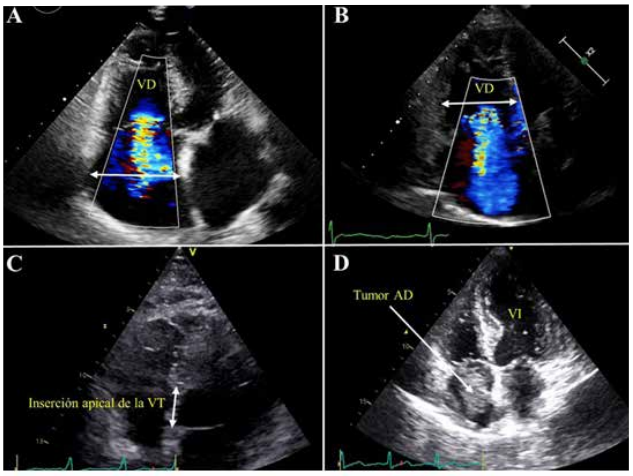

FIGURE 2.
Mechanisms related to different types of tricuspid regurgitation A) Functional TR by right atrium dilatation; B) functional TR by right ventricular dilatation; C) TR in patients with Ebstein anomaly; D) TR in patients with right atrial myxoma

TR severity can be evaluated using a combination of qualitative, semiquantitative and quantitative methods, and cutoff values are presented in *Table 2*[16].

The measurement of right chambers dimensions is essential for prognostic goals. The presence of normal values does not usually correlate with severe TR. Additional parameters such as TAPSE, RV fractional shortening area, S wave velocity in tissue Doppler echocardiogram and longitudinal deformation of the free wall are valuable to evaluate systolic function. The assessment of the inferior vena cava and the estimation of PASP are also necessary and possible through this method. Three-dimensional TTE is an efficient tool to evaluate volumes and ejection fraction, so if available it is very useful, with a performance comparable to cardiac MRI.

Transesophageal echocardiogram can provide valuable information in cases in which TTE results are inconclusive, especially in terms of the cause, mechanism and probability of an effective interventionist treatment. However, the quality of images is not better than TTE made by experts.

CARDIAC MRI

Cardiac magnetic resonance imaging allows to evaluate RV morphology and function due to their high spatial resolution and clarity to delimit endocardial edges. It is the method of choice to quantify cardiac volumes, so it allows to stratify the severity of TR by the quantification of regurgitant volume.

Although performance is comparable to 3D TTE when evaluating RV and TR, there may be differences of up to

TABLE 2.
Echocardiographic criteria for TR severity grading[16].

	Mild	Moderate	Severe	Very severe (massive)	Torrential
Qualitative parameters					
TV morphology	Normal or mild leaflet anomalies		Severe lesions (flail valve, severe coaptation defects, marked tenting)		
TR color flow Doppler jet echocardiography	Central and small	Central and medium	Central and important or eccentric with Coanda effect		
Flow convergence area	Not visible or small and transient	Intermediate	Large and holosystolic		
Continuous-wave Doppler spectral density	Transient, mild density, parabolic	Parabolic and dense, sometimes triangular	Dense and usually triangular with early acceleration peak		
Semiquantitave parameters					
Flow in liver veins	Systolic dominance	Systolic flattening	Reverse systolic flow		
Anterograde TV flow	Dominant A wave	Variable	Dominant E wave (> 1 m/sec)		
PISA method	<5	6 –9	>9		
Vena contracta width (mm)	<3	3 – 6.9	7 – 13	14 – 20	≥21
Quantitative parameters					
ERO (mm2)	<20	20 – 39	40 – 59	60 – 79	≥80
Regurgitant volume (ml)	<30	30 – 44	45 – 59	60 – 74	≥75
Vena contracta 3D (mm2)			75 – 94	95 – 114	≥115

one degree of severity between both, an important fact when making a comprehensive evaluation of the results of patients.

It allows to evaluate the extent of fibrosis in the cardiac muscle through late gadolinium enhancement and the T1 mapping modality, managing to establish the underlying myocardial damage.

In general, it is recommended to consider magnetic resonance as an option when the results from other tests, such as 2D and 3D TTE do not yield conclusive results in terms of the severity of the heart valve disease in patients in whom the clinical suspicion remains high.

COMPUTED TOMOGRAPHY

Computed tomography is very useful when planning interventional treatments, as it allows clearly visualizing linear structures, such as TA and its relation with the right coronary artery, as well as determining accurately the extent of valve or subvalvular calcifications.

TREATMENT FOR TR

In recent decades, the appearance of new evidence changed the management of TR to a more aggressive approach[13].

The presence of significant TR is usually properly tolerated in the absence of significant pulmonary hypertension or liver damage. Diuretics and vasodilators are effective to reduce symptoms and slow down progression to the right HF. However, in the long term TR is associated to high morbimortality, recurrent hospital admissions and progressive reduction of functional capacity[17].

Regardless of clinical presentation, patients with significant TR should initially be treated for their underlying disease, followed by a new anatomical and functional evaluation of TV when compensated. Likewise, repositioning or extracting pacemaker leads could be considered in selected patients.

Most recommendations of treatment are based on the opinion of experts due to the absence of randomized clinical trials in a large scale, so the ideal time for surgery is still controversial.

In patients with severe TR, concomitant treatment is indicated at the time of left valve surgeries, as persistent TR is associated to a worse outcome[18]. In the cases of moderate TR or less, a concomitant intervention should be evaluated carefully in every patient, as if there is TA dilatation, annuloplasty leads to less progression to severe TR in 2 years, and therefore to a better outcome. For this reason, if TA dilatation >39 mm or ≥21 mm/m2 is observed, we should consider performing a simultaneous intervention in the TV[19]. Another group of patients that may benefit from a

TABLE 3.
TV lesions[22]

Anatomical region of tricuspid valve	Type of lesion
Annulus	Dilatation Abscesses
Valves	Tissue excess Thickening Vegetations Perforation Rupture
Commissures	Fusion Thickening
Cords	Rupture Elongation Thickening Shortening
Papillary muscles	Rupture Elongation
Ventricle	Infarction Fibrosis Dilatation

concomitant treatment are those presenting mild or moderate TR associated to symptoms of right HF, regardless of TA diameter[17]. Finally, surgery is also possible in the case of mild TR associated with permanent HF and TA dilatation[20].

In the case of significant TR, if surgery was not made during treatment of a left valve disease, a surgery can be considered in patients with recurrent episodes of HF in spite of the optimal pharmacological treatment, as long as there is no severe RV dysfunction, irreversible pulmonary hypertension or severe liver dysfunction[19].

In-hospital mortality rates for isolated TV surgery are not consistent in literature, but are around between 2-9.8%. Moreover, in spite of the improvement in surgical techniques, mortality in patients with combined surgery (with left valves) or isolated TR who undergo valve replacement or repair remains high and is around 11.6% and 7.1%, respectively[21].

Recurrence of moderate to severe TR with previous surgery may reach up to 60% in 5 years, and a new surgery is necessary in approximately 20% of patients in 10 years. Although surgical reintervention is the treatment of choice for prosthetic dysfunction or deterioration of annuloplasty, it is associated to a very high mortality rate, reaching 35% in 30 days[13].

It is very frequent for patients with severe isolated TR, associated to severe RV dysfunction, and those who have been previously operated for left valve disease, to be rejected by cardiac surgeons due to the high mortality in surgical interventions in this scenario. In some of these patients, it is possible to consider transcatheter percutaneous treatment in a center with experience in TV pathology.

Next, the types of surgeries and devices available will be reviewed, along with their main indications and results to this date.

TV SURGERY

At surgical level, TV disease etiology may vary, but lesions are defined by affected components, as observed in *Table 3*[22]. Surgical treatment has as its goal to solve these problems, so the evaluation by TTE with functional approach allows assessing the different valve components and provide accurate information to surgeons. During surgery, it will be determined whether reconstructing or repairing the valve is feasible or if a replacement will be necessary.

TA annuloplasty is considered the most common technique for TV repair. It is carried out by the use of rings in most patients. They are usually incomplete due to the strict topographic relationship of TA with the atrioventricular node.

There are flexible, semi-rigid and rigid rings, which will be used depending on the clinical scenario and the degree of alteration in the normal TA morphology. Flexible ones reduce the size of TA without restoring their original elliptical shape (known as reduction annuloplasty). Rigid prosthetic rings can restore the original shape of the annulus without affecting leaflet movement (known as annular remodeling). Nonetheless, rigid rings have been associated to dehiscence, so semi-rigid rings have been used in an attempt to reduce the risk of this complication.

Usually, a 32 mm ring is used in male patients, and a 30 mm one in female patients, although direct calibration can be made and is preferred whenever possible.

David et al, after reviewing their cases, propose personal criteria for a more aggressive treatment of TR at the time of surgery over the mitral valve, performing annuloplasty in all patients with moderate TR, chronic AF, and mean chamber diameter of the RV >30 mm by TTE.

The rings do not correct valve tethering or shortening. This makes them less effective in the long term, if used in isolation in patients with this type of valve damage. In these cases, even annuloplasty with a smaller ring size are usually not enough to correct TR. For this reason, it is necessary to use techniques that would allow increasing coaptation surface such as pericardial patches, or even tricuspid valve replacement could be considered.

There are other valve repair techniques, but they will not be analyzed in this review as they are mainly surgical and technical.

The choice of surgical technique will depend on the stage of the TR in natural evolution. In the presence of TA dilatation without significant tethering (coaptation level <8 mm), annuloplasty with prosthetic rings is preferred. Rings used in the cases of severe TA dilatation should be undermeasured (>45 mm)[23].

To treat mild TR, reduction annuloplasty with flexible ring can be carried out. Instead, in cases of severe TR, remodel annuloplasty with rigid ring is usually more effective. Up to 95% of patients who undergo annuloplasty with ring will remain free from moderate or major TR for several years after the surgery.

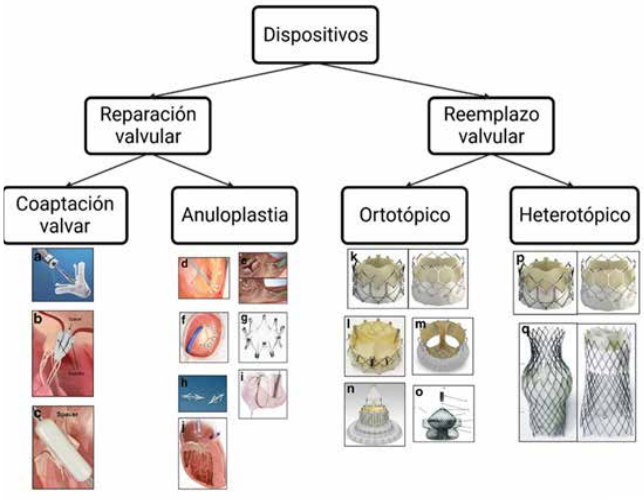

FIGURE 3.
Transcatheter therapies for tricuspid valve repair and replacement, currently being used or in development[25].
(a) MitraClip; (b) PASCAL; (c) FORMA; (d) Trialign; (e) TriCinch; (f) Cardioband; (g) Iris; (h) minimally invasive annuloplasty device (MIA); (i) transatrial intrapericardial tricuspid annuloplasty (TRAIPTA); (j) percutaneous pledget-assisted suture tricuspid annuloplasty (PASTA); (k) and (p) SAPIEN XT/SAPIEN 3 valves; (l) tricuspid valve stent GATE; (m) Trisol valve; (n) LUXValve; (o) TriCares valve; (q) TricValve (superior and inferior vena cava valves).
RA: right atrium; **RV:** right ventricle; **TV:** tricuspid valve; **LV:** left ventricle

PERCUTANEOUS TREATMENT

To this date, limited clinical data are available in regard to the efficacy of interventional options, but feasibility and safety of most techniques have been proven, among which annuloplasty devices, valve coaptation and even valve replacement devices (orthotopic and heterotopic) are included.

The indication to perform an intervention of this type should come from a multidisciplinary heart team. The clinical benefits and success of the procedure should be evaluated in patients categorized as inoperable. These interventions are superior to the full pharmacological treatment in patients who remain symptomatic[24].

There are multiple devices in the market, many of them still being studied currently, so it is extremely important, before planning any procedure, to make an exhaustive evaluation of the TR physiology and underlying valve damage, as the device to be used will depend on this. In *Figure 3 and Table 4,* the main options are observed and their results in the main studies on each one[25,26].

There are multiple criteria for a proper selection of the prosthesis to be used, which were detailed in the article published by Praz et al[27].

As this is an investigation field, indications will surely be enhanced as years go by, and patients will benefit from these procedures increasingly.

TABLE 4.
Basal characteristics and main results of studies on each device[26]

Device	Study	Number of patients	Design	Age	Functional class (NYHA III/IV)	FTR	Success of procedure	Residual TR >3	Mortality in 30 days – n (%)
TricCLip	Trivalve	85	Randomized	77 ± 9	96%	90%	77%	23%	-
	TRILUMINATE	85	Randomized	78 ± 8	75%	84%	91%	43%	0%
Pascal	Fam et al.	28	Randomized	78 ± 6	100%	92%	86%	15%	2 (7%)
	CLASP-TR	34	Randomized	76 ± 10	79%	88%	80%	81%	0%
Forma	Perlmann et al.	18	Prospective registry	76 ± 10	94%	100%	89%	44%	0%
	Kodali S et al.	29	Prospective registry	76 ± 8	86%	100%	93%	-	2 (7%)
Mistral	Planer et al.	7	Prospective registry	73 ± 7	-	100%	100%	-	0%
Trialing	SCOUT	25	Prospective registry	74 ± 7	67%	100%	100%	-	0%
TriCinch	PREVENT	24	Prospective registry	74 ± 8	58%	-	81%	~45%	0%
Cardioband	TRI-REPAIR	30	Prospective registry	75 ± 7	83%	100%	100%	28%	0%
	Davidson et al.	30	Prospective	77 ± 8	70%	100%	93%	55%	0%
Caval Devices	Lauten et al.	25	Observational multicenter	78 ± 7	100%	96%	92%	-	3 (12%)
	TRICAVAL	14	Randomized	77 (68-82)	86%	-	100%	-	3 (21%)
Navigate	Hahn et al.	30	Prospective registry	78 (70-80)	86%	100%	87%	0%	3 (10%)
Evoque	Fam et al.	25	Randomized	76± 3	88%	76%	92%	4%	0%
Lux Valve	lu et al.	12	Prospective registry	69 (66-74)	100%	-	100%	8%	0%

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Systematic Review

Dual antiplatelet therapy in secondary prevention for coronary and cerebrovascular disease and thrombocytopenia: A Systematic Review

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stroke,
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thrombocytopenia.

ABSTRACT

Introduction: Coronary heart disease and cerebrovascular disease are the main causes of mortality and disability. Association with thrombocytopenia increases the risk of complications. Single and dual antiplatelet therapy are part of secondary prevention. However, antiplatelet therapy in patients with thrombocytopenia raises the risk of bleeding.

Objective: The objective of this systematic review is to synthesize information on the potential risks and benefits of dual antiplatelet therapy compared to single or no antiplatelet therapy, in adults with thrombocytopenia in secondary prevention of coronary heart disease and cerebrovascular disease.

Methods: A systematic literature review of randomized and non-randomized studies reporting efficacy and safety outcomes was performed in the main databases. Evidence quality was evaluated with the ROBINS I tool, and outcomes were reported through evidence profile tables.

Results: Given the heterogeneity between studies, a meta-analysis of the data was not possible. Two studies indicated a lower rate of mortality and ischemic events with clopidogrel-based dual antiplatelet therapy, while one study found higher mortality with ticagrelor-based therapy. Major bleeding events were more frequent with ticagrelor-based therapy, while they were lower with clopidogrel-ASA.

Conclusions: Evidence suggests a possible benefit of dual antiplatelet therapy in patients with thrombocytopenia in secondary prevention of coronary heart disease and cerebrovascular disease, especially with clopidogrel-ASA. The absence of randomized clinical trials and the limited information from non-randomized studies limits the possibility of making solid recommendations. The decision to use dual antiplatelet therapy should be guided by clinical judgment, considering individualized risks and benefits.

LIST OF ABBREVIATIONS

ACS: acute coronary syndrome
CAD: coronary artery disease
CVD: cerebrovascular disease
CKD: chronic kidney disease
DAPT: dual antiplatelet therapy
HTN: hypertension
SAPT: single antiplatelet therapy

INTRODUCTION

Coronary artery and cerebrovascular diseases are the two main causes of mortality and disability at world level, with an estimate of 7 million deaths per year and 129 million disability-adjusted life years (DALY) and 6 million deaths and 143 millions of DALY, respectively[1,2]. However, advancements in their treatment have increased survival in these patients, which favors the coexistence with other comorbidities, including thrombocytopenia.

Up to 5% of patients with acute coronary syndrome (ACS) have base thrombocytopenia, and up to 13% of them develop it later[3]. Likewise, a low platelet count has been reported in 2.3% of patients with ischemic cerebrovascular disease (CVD), being a prognostic factor that increases up to six times the risk of in-hospital mortality[4]. In fact, the conditions that lead to thrombocytopenia increase the risk of developing CAD and CVD by multiple mechanisms, including different infectious diseases, autoimmune diseases, cancer, nutrition deficiencies, hypersplenism and related to medications, which entails a cardiovascular risk of up to 38% more[3].

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It has been shown that dual antiplatelet therapy (DAPT) decreases up to 50% the risk of mortality and thrombotic events after an acute ischemic event, a benefit that could be particularly important during the first month of management[5,6]. However, in the population with thrombocytopenia, its use generates the dilemma of administering an antiplatelet treatment to a population with an inherent risk of bleeding. To this date, few studies have sought to assess the benefit and risks of DAPT in this population, and the evidence they show has not been summarized systematically[7,8,9]. This has conditioned a lack of consensuses from scientific societies about which is the ideal management of these patients, representing a challenge in clinical practice[10,11,12,13].

The aim of this systematic review is to summarize the information on the potential risks and benefits of DAPT in comparison with SAPT or with no antiplatelet therapy, in adult patients with thrombocytopenia who are in secondary prevention for acute coronary syndrome and cerebrovascular event.

MATERIALS AND METHODS

Design and approval

A systematic review was made on the literature, including randomized and non-randomized studies, taking into account specific recommendations for the combined summaries of both types of studies[14,15]. The study was approved by the committee on ethics of the Pontificia Universidad Javeriana (Article N° FM-CIE-0595-24). The protocol was published in PROSPERO (CRD42024544138).

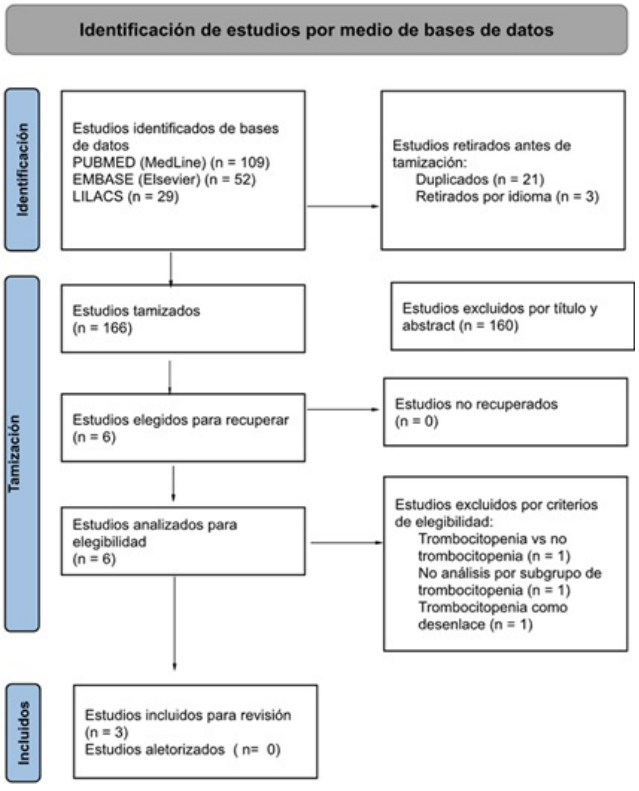

FIGURE 1.
PRISM flowchart[18].

Inclusion and exclusion criteria

To be included, the studies had to evaluate patients older than 18 years, with thrombocytopenia (defined as a platelet count <150,00 cell/μL), in secondary prevention for acute coronary syndrome, acute ischemic stroke or transient ischemic attack. Furthermore, they had to compare two treatment arms: DAPT (defined as aspirin plus a P2Y12 receptor inhibitor), with SAPT (defined as aspirin or clopidogrel or ticagrelor or prasugrel individually) or no therapy. Finally, they had to report at least one of the follow outcomes of interest: death, reinfarction, new cerebrovascular event, major bleeding, minor bleeding or hypersensitivity to medication. One-arm studies or those reporting the combination of anticoagulation with DAPT or 3 or more antiplatelet drugs were excluded.

Search and selection

The following databases were consulted: PubMed (MedLine), EMBASE (Elsevier) and LILACs until May 2024. Randomized clinical studies and observational studies were included, that had been published in Spanish and English since 1997, a time when FDA approved clopidogrel to be used. The search terms used were: "Thrombocytopenia", "Blood Platelet Disorders", "Coronary Disease", "Acute Coronary Syndrome", "Myocardial Infarction", "Stroke", "Ischemic Attack, Transient", "Aspirin", "Acetylsalicylic acid", "Clopidogrel", "Prasugrel Hydrochloride", and "Ticagrelor". The search strategies for each database can be checked in Appendix 1. Duplicate references were removed with the Mendeley tool.

Two investigators (MMS and MIG) independently selected the articles by title and abstract. From the potentially eligible articles, the full text was evaluated. All discrepancies that emerged were identified and solved by consensus or by a third investigator (OMM). The selection process is shown according to the PRISMA recommendation in *Figure 1.*

Data extraction

Once the initial selection was made, data extraction was made in a paired, independent and standardized manner by two reviewers (MMS and MIG). Once again, the discrepancies that emerged were identified and solved by consensus or by a third investigator (OMM). The relevant data collected from the articles were: author, year of publication, type of study, intervention used (DAPT), control (SAPT), number of participants, indication of therapy, age, gender, etiology and degree of thrombocytopenia, comorbidities (hypertension, diabetes mellitus, CAD, diabetes, previous CVD, cancer, cirrhosis, chronic kidney disease and anemia), previous bleeding and time of follow-up.

Evaluation of quality

For the randomized studies, the plan was to use version 2 of the Cochrane tool (RoB2)[16]. For nonrandomized stu-

TABLE 1.
Characteristics of the studies included

Author	Type of study	Intervention	Control	Number of patients	Indication of therapy	Age	Male gender	Etiology of thrombocytopenia	Degree of thrombocytopenia*	Previous bleeding	Comorbidities	Time of follow-up
Yu-Ying, 2022	Observational retrospective	ASA + clopidogrel 64%	ASA 21% or Clopidogrel 15%	468	ACS	SAPT 72.52 (+13.6) DAPT 70.77 (+12.5)	73%	Decrease in production: 62 (13.2%) Hypersplenism: 87 (18.5%%) Unknown: 319 (68.3%)	Mild 83.7% Moderate 13.7% Severe 2.6%	NR	DM 35%, previous CVD 15.5%, CAD 23.5%.	30 days
Chen, 2021	Observational retrospective	ASA + ticagrelor 4%	ASA or Clopidogrel 96%	936	ACS	67:1 ± 10:2	81%	NR	Average 85 x 103/μL (IQR 74-94 x 103/μL)	NR	HTN 55%, CKD 6%, chronic liver disease 2%, previous CVD 2.2%	In-hospital. Median 5 days (IQR 3-7 days)
Iliescu, 2018	Observational retrospective	ASA + clopidogrel 28%	SAPT 42% No therapy 31%	98	ACS	66.9 (+8.52)	83%	Cancer 100%	Mild-Moderate 42.9% Severe 20.4% Deep 36.7%	NR	HTN 86%, cancer 100%	22 months

ASA: acetylsalicylic acid; **DAPT:** dual antiplatelet therapy; **DAPTica:** dual antiplatelet therapy with ticagrelor; **DM:** diabetes mellitus; **CAD:** coronary artery disease; **CVD:** cerebrovascular disease; **CKD:** chronic kidney disease; **SAPT:** single antiplatelet therapy; **HTN:** hypertension; **NR:** not reported; **IQR:** interquartile range; **ACS:** acute coronary syndrome. *Mild thrombocytopenia 100,000-150,000 cell/μL, moderate 50,000-100,000 cell/μL, severe 30,000-50,000 cell/μL, deep <30,000 cell/μL

dies, the plan was to conduct a quality evaluation by the ROBINS I tool[17]. This tool allows to classify the global bias risk for each study and each outcome, defining it as "low", "moderate", "severe" or "critical", according to the three domains of the study: "before the intervention", "at the time of intervention" and "after the intervention"[17].

DATA ANALYSIS

The summary of the results from the primary studies was planned by meta-analysis of information, if clinical heterogeneity was low in terms of the population, interventions implemented, measured results or follow-up time, using the RevMan software (Review Manager), recommended by Cochrane with a model of random effects. If high clinical variability was identified, the plan was to summarize the information by evidence profile tables for each outcome evaluated, with no meta-analysis, differentiating the results from randomized and nonrandomized studies. Additionally, making an analysis by subgroups was proposed, according to the type of P2Y12 receptor inhibitor, the degree of thrombocytopenia, the presence of cancer and the indication of DAPT, if the collected information allowed it. Finally, in the case of finding more than 10 studies evaluating the same outcome, an analysis by funnel plot was planned, to assess the risk of publication.

RESULTS

A total of 109 studies were identified, of which 3 nonrandomized studies were included in the analysis[7,8,9]. These studies were made in the United States, Taiwan and China[7,8,9]. No randomized study was included and just one evaluated cerebrovascular outcomes. The selection process is presented in the PRISMA diagram *(Figure 1)*[18]. The characteristics of the patients included in the studies and the evaluated outcomes are presented in *Table 1*.

The three analyzed studies were observational and retrospective, analyzed patients with CAD preferably, and with DAPT based to a great extent on ASA combined with clopidogrel. The age average was similar in the three studies, around 70 years, and most of the population were men. The most frequently reported comorbidities were hypertension and diabetes mellitus. Most patients had an average of platelets between 50,000 and 150,000, so most patients had mild to moderate thrombocytopenia.

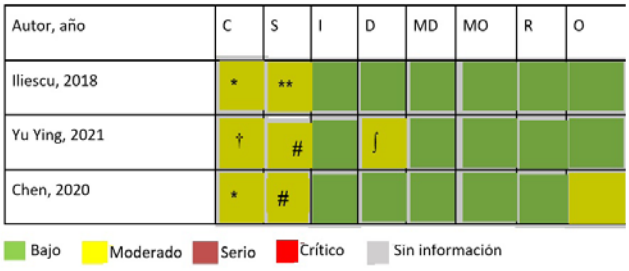

FIGURE 2.
ROBINS I tool
* Not controlled by diabetes, age, HTN; ** There is no way to evaluate the arm rate of changes; † There is a difference in the severity of thrombocytopenia between the arms of the study; # There is no way to evaluate the arm rate of change; ∫ No evaluation could be made on the effect of adhering to the intervention
C: confusion bias; **B:** bias in the selection of participants in the study; **I:** bias in the classification of interventions; **D:** bias due to deviations from the expected interventions; **MD:** bias due to missing data; **MO:** bias due to outcome measurement; **R:** bias in the selection of informed outcomes; **O:** general risk of bias

DAPT was mainly made up by aspirin and clopidogrel. Only in one study ticagrelor was used[9]. ST-segment elevation myocardial infarction was the most frequent indication for DAPT in two of the studies. One of the studies exclusively included patients with cancer, most with hematological neoplasms[9]. However, the etiology of thrombocytopenia in most was not known.

The follow-up periods in the three studies were different, with follow-ups of 5 days in-hospital for Chen et al, 30 days in Yu Ying et al, and 22 months for Iliescu, which prevented data meta-analysis given the high heterogeneity between evaluation times[7,8,9].

QUALITY EVALUATION

The quality evaluation of the studies was carried out with the ROBINS I tool, as only nonrandomized studies were found. This process is presented in *Figure 2*. In regard to the study population, in the Yu Ying Li et al group, statistically significant differences were identified in the baseline characteristics between the two groups, including gender, use of beta blockers and statins[8]. Likewise, patients in SAPT presented greater risk of bleeding in spite of the adjustment by known factors, which may have generated a confusion bias. Only in one study, the cause of thrombocytopenia was reported, understanding that its etiology could be an independent variable of mortality and higher risk of bleeding, which may lead to a confusion bias.

Two studies were classified with low risk and one study with moderate risk. The results of the risk of bias evaluation are presented in *Figure 2*.

CLINICAL OUTCOMES

Death

In *Table 2a*, mortality results are shown. Two of the studies reported mortality rates and one of them survival analysis. A lower rate of mortality and better survival were found with use of DAPT for the 2 studies that evaluated it with ASA-clopidogrel; however, estimations were imprecise. In a study evaluating the use of ASA-ticagrelor as DAPT, the mortality rate was higher with DAPT (OR 2.67; 95% CI 0.39-18.23, p = 0.5)[7].

Reinfarction

In *Table 2b*, a single study is shown to have evaluated a new ischemic myocardial event[7,8]. Similarly to mortality findings, there were less events with DAPT with ASA-clopidogrel, once again, with imprecise estimations.

New cerebrovascular event

In *Table 2c*, results are shown from the 2 studies evaluating a new cerebrovascular event[7,8]. Again, there were less cerebrovascular events with DAPT with ASA-clopidogrel compared with SAPT, and more with the ASA-ticagrelor combination.

TABLE 2A.
Evidence profiles for mortality and effectiveness. **A:** death

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	8	300	2.67	9	168	5.3	HRa 0.55 (0.19-1.54) p=0.2536	30 days
Chen, 2021	3	41	7.3%	13	895	1.5%	ORa 2.67 (0.39-18.23) p=0.5	In-hospital. Median 5 days (IQR 3-7 days)
Iliescu, 2018	Survival HR 0.601 (95% CI 0.33-1.07; p = 0.087) in favor of DAPT							22 months

TABLE 2B.
Evidence profiles for mortality and effectiveness. **B:** reinfarction

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	22	300	7.3	14	168	8.3	HRa 0.86 (0.41-1.81) p=0.6904	30 days

TABLE 2C.
Evidence profiles for mortality and effectiveness. **C:** new cerebrovascular event

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	3	300	1	5	168	2.98	HRa 0.35 (0.07-1.68) 0.1894	30 days
Chen, 2021	4	41	9.8	24	895	2.7	ORa 2.67 (0.68-10.48) p=0.2	In-hospital. Median 5 days (IQR 3-7 days)

TABLE 3A.
Perfiles de evidencia para eventos de seguridad. **A:** Sangrado mayor

		DAPT			SAPT				
	Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Major bleeding	**Yu-Ying, 2022**	18	300	6	18	168	10.6	HRa 0.66 (0.32-1.36) p=0.2573	30 days
	Chen, 2021	3	41	7.3	9	895	1	ORa 9.7 (1.57-60.4) p=0.025	In-hospital. Median 5 days (IQR 3-7 days)
	Iliescu, 2018	0	27	0	0	41	0	-	-
Total bleeding	**Chen, 2021**	3	41	7.3	11	895	1.2	ORa 6.48 (1.12-37.66) p= 0.08	In-hospital. Median 5 days (IQR 3-7 days)

TABLE 3B.
Perfiles de evidencia para eventos de seguridad. **B:** Sangrado menor

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Chen, 2021	0	41	0	2	895	0.2%	-	In-hospital. Median 5 days (IQR 3-7 days)

Major bleeding

In *Table 3a*, the results of major bleeding events are shown. In the Yu Ying study, less major and total bleeding events were found in patients with DAPT (ASA-clopidogrel), unlike the reports from Chen et al, who found more in-hospital major bleeding events in the DAPT group (ASA-ticagrelor)[8].

Minor bleeding

Only the Chen et al study evaluated minor bleeding events, finding less events in patients with DAPT, being so few that a confidence interval estimation was not possible *(Table 3b)*[7].

Hypersensitivity

Hypersensitivity events were not reported in any of the three studies.

DISCUSSION

In this systematic review, evidence available on DAPT was evaluated in comparison with SAPT or no antiplatelet therapy, in adult patients with thrombocytopenia, who were in secondary prevention for acute coronary syndrome and cerebrovascular event. It was found that there is scant information and it differs between studies. Heterogeneity could be mainly explained by the type of medication evaluated and follow-up periods, so the use of DAPT remains controversial.

Few studies were found, all of them nonrandomized, with risk of biases mainly associated to basal characteristics between groups, which may condition confusion biases. Although a tendency was observed toward a benefit with DAPT (ASA-clopidogrel) in terms of outcomes, up to now there is not enough evidence to be able to make a strong recommendation on the benefits and damages with the use of this therapy in patients with thrombocytopenia.

In the Yu Ying study, DAPT showed a tendency towards a benefit in the outcomes of death, reinfarction and new CVD, not reaching statistical significance[8]. However, in the Chen study, DAPT showed a non-significant tendency to an increase in the risk of mortality[7]. This disparity could be explained by factors such as follow-up period (quite a short period of evaluation in the Chen study), a greater risk of bleeding with ticagrelor and patients in whom a stronger P2Y12 receptor inhibitor was prescribed, then having a higher base thrombotic and mortality risk. It is for this reason that the heterogeneity found may be due to a clinical situation rather than statistical. The findings are in agreement with the recommendations by experts of preferring clopidogrel over ticagrelor in patients in high risk of bleeding, and in those with thrombocytopenia[3,13]. Besides, clopidogrel is the P2Y12 receptor inhibitor that has been most evaluated in shortened therapies for patients in high risk of bleeding[19,20,21,22]. Finally, the findings support the results of previous studies, including MATCH, where a decrease in the frequency of cerebrovascular events

was observed in DAPT with ASA-clopidogrel in patients without thrombocytopenia[23,24].

Total and major bleeding is the highest in patients with DAPT based on ticagrelor, which is in agreement with previous studies like THALES, where there were higher rates of bleeding with DAPT[25]. On the other hand, DAPT based on clopidogrel seems to be safe in the evaluated population. Previous studies like CHANCE found similar results, where there were no higher rates of bleeding with the use of DAPT, which may favor a safe use of this therapy, even in patients with high risk of bleeding[26]. In fact, in Iliescu's study, where half of patients had severe or deep thrombocytopenia, no major bleeding was documented in the arm of patients with DAPT[9].

As to minor bleeding, although it was only measured in the Chen study, there were less bleeding events with DAPT, which could be underestimated given the size of the evaluated population. Previous studies have shown that there are higher rates of minor bleeding in patients with DAPT, so in the future, studies are required that would take into account this outcome and its implications in clinical practice[27].

The greater risk of bleeding in the population with thrombocytopenia and DAPT is a consistent finding in studies and even in a meta-analysis[28]t the time of prescribing this therapy in low platelet counts. The degree of severe thrombocytopenia was minimum in the three studies, generating limitations in evidence for patients with major hematological compromise and major risk of bleeding.

Finally, there were no studies evaluating DAPT with prasugrel, so that for the time being, it shouldn't be used, as its effects are unknown in patients with thrombocytopenia in secondary prevention for ACS or CVD. Additionally, DAPT indication was exclusively evaluated in patients with ACS, so outcomes may not be extrapolated to CVD patients.

This systematic review is the first to summarize outcomes in patients receiving DAPT or SAPT associated to thrombocytopenia; however, several limitations should be acknowledged. First, in spite of what was planned, a summary with information by meta-analysis was not achieved because of the significant heterogeneity between studies. This could be explained by the difference in the degree of thrombocytopenia of participants, its etiology (with different rates of cancer) and the antiplatelet drug used for DAPT. On the other hand, the follow-up periods were different between the evaluated studies. The results could not be individualized due to the degree of thrombocytopenia, as the number of patients with severe thrombocytopenia was minimal, and outcomes were not reported in a differential way for such patients. The authors consider that it is important to evaluate by these subgroups in future summaries of information, as different clinical outcomes are expected at lower platelet counts. Finally, the number of patients with cancer was minimal, and it comes from a single study. Information on this growing population is still limited and management with DAPT should be cautious, and risks and benefits should be analyzed individually.

CONCLUSIONS

There is evidence suggesting a benefit from DAPT in patients with thrombocytopenia in secondary prevention of ACS in comparison with SAPT or no therapy. There is not enough evidence to evaluate if there is a benefit from DAPT in patients with thrombocytopenia in secondary prevention for CVD. The population with CAD may benefit from DAPT based on clopidogrel as it has proven to be safe in observational studies; however, there is no robust evidence to recommend it over ticagrelor-based therapy to decrease clinical outcomes. Finally, no evidence was found on the effectiveness or safety of prasugrel in this population.

Absence of randomized clinical trials and the scarce information in non-randomized studies with risk of significant bias shows the need for additional studies to evaluate the use of these therapies in patients with thrombocytopenia. So, for the time being, the best clinical criteria should still guide therapy.

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Original Investigation Reports

Assessment of streptokinase effectiveness and mortality predictors in patients with ST-segment elevation myocardial infarction in a Latin-American center

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ABSTRACT

Introduction: thrombolysis reduces mortality and improves patient's outcomes with ST-elevation myocardial infarction (STEMI).

Objectives: assess clinical outcomes in STEMI patients treated with streptokinase (STK), and risk factors predictors of mortality.

Methods: observational, cohort study, with a follow-up for 1 month. We assessed 177 STEMI patients, divided into 2 groups, those that received STK (49%) and those that didn't: No STK (51%), who were admitted at Ciudad Hospitalaria "Dr. Enrique Tejera", from April to August 2022.

Results: the mean age was 63 ±10 years, there were 67% males and 79% had hypertension. Successful reperfusion was 41%, mortality in patients with Reperfusion vs No reperfusion was 6.7% vs 93.3% (p=0.001). Groups STK vs No STK at 1 month had heart failure hospitalizations of 25.9% vs 74.1% (p=0.004). Risks factors predictors of mortality at 1 month were hypertension with HR: 10.23 (p=0.002), female sex HR: 3.57 (p=0,001), family history HR: 2.28 (p=0.021) and diabetes HR: 2.02 (p=0.04). The mean age, and the KK, GRACE and TIMI score values were higher in patients that died.

Conclusions: reperfusion with STK was low. Patients with successful myocardial reperfusion had significantly lower mortality. Risk factors predictors of mortality were hypertension, female sex, family history, diabetes, age and KK, GRACE and TIMI scores.

INTRODUCTION

In the countries with low or medium level of economic development, within which we find Venezuela, chronic noncommunicable diseases constitute the main causes of mortality. Ischemic heart disease is one of them, specifically acute myocardial infarction (AMI), which holds the first place, so some authors call it the epidemic of the century[1]. A series of factors related to atherogenesis are known: cardiovascular risk factors of atherosclerosis. There is a direct relationship between cardiovascular mortality and major risk factors: diabetes, smoking, hypercholesterolemia, hypertension and family history of early coronary artery disease (CAD)[2].

Thrombolytic therapy (TT) in patients with ST-segment elevation myocardial infarction (STEMI) is one alternative, when primary angioplasty is not available or if a delay of more than 2 hours is expected to apply it[3].

Thrombolytic agents proved to be effective in terms of reduction of major cardiovascular events. It is advisable to infuse fibrin-specific thrombolytics within the first 6 hours, and streptokinase (STK) with a therapeutic window of up to 12 hours. The highest success rates are always obtained when administering the treatment within the first 2 to 3 hours from the onset of symptoms, when it is more likely that the fresh occlusive thrombus may dissolve pharmacologically, thus achieving a quick recovery of ischemic myocardial tissue. After this window period, the impact on mortality reduction is lower. In this situation, a rapid care for the opening of the artery related to the infarction is the main goal, with primary angioplasty with stent implant being the most effective method, and therefore, the preferred one whenever possible[2,3,4].

In Venezuela, there are a few prospective epidemiological studies with representative samples of the behavior of thrombolytic therapy, in terms of the therapeutic window, door-to-needle times, or degree of effectiveness according to cardiovascular risk factors.

By understanding the importance of thrombolytic therapy with streptokinase in patients with STEMI, in our center, where there is percutaneous coronary interventionism (PCI), we set out to perform a study whose main goal was to assess the effectiveness of STK in terms of: rate of myocardial reperfusion, evolution in terms of outcomes, and in turn, determine the cardiovascular risk factors predictors of mortality, in patients admitted to the coronary care unit of the cardiology service of the Ciudad Hospitalaria Dr. "En-

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rique Tejera" with diagnosis of STEMI, who received streptokinase in comparison with those that did not receive it, in an in-hospital follow-up and at one month.

MATERIALS AND METHODS

Observational, prospective study, with a quantitative approach and comparative analysis, with in-hospital follow-up and at one month. The population was made up by 286 patients with acute coronary syndrome (ACS), of whom patients with ST-segment elevation myocardial infarction (STEMI) were analyzed, who were admitted in the coronary care unit of the Ciudad Hospitalaria Dr. Enrique Tejera (CHET), Valencia, Venezuela, in the term April to August, 2022.

The sample was constituted by 177 patients with diagnosis of STEMI, both in those that received thrombolytic therapy with streptokinase and in those that could not receive it for different reasons. The following were exclusion criteria: patients with STEACS, acute myocardial infarction with ambiguous ST-segment alterations (ST-segment elevations in borderline contiguous leads: less than 2 mm in men and 1.5 mm in women), patients with contraindication to receive thrombolytics and patients with sudden cardiac death before receiving thrombolytics.

The electrocardiographic criterion for reperfusion was the European guideline for STEMI management from 2017, which establishes a successful reperfusion when ST segment ≥50% drops or is solved between 60 and 90 minutes after having applied TT, with improvement of symptoms and/or the presence of hemodynamic stabilization[5].

In this study, electrocardiographic criteria were used as operational definition of reperfusion, for logistic reasons, similarly to other studies[6,7].

Streptokinase was administered with the standard protocol of 1.5 million U over 60 minutes (min) intravenously by infusion pump. It was suspended if patients presented hypotension with systolic blood pressure <90 mmHg or moderate to severe allergic reaction and/or bronchospasm, administering hydrocortisone 250 mg and fluid replacement.

The first electrocardiogram (ECG) was made at the onset of STK administration, the second ECG by the end of infusion, and 90 minutes later with a 2 to 4-hour window.

Vertical ST-segment elevation was measured in the lead with the highest ST elevation, before delivering STK, 60 and 90 minutes later. ST-segment elevation measurement was made at 80 ms of the J point, corresponding to ST elevation peak. The success of reperfusion by STK was defined as a ≥50% drop of the ST segment and improvement of symptoms at 90 min with a 2 to 4-hour window; and its failure as the absence of this ECG parameter, with no improvement of symptoms[6].

The sample was divided into 2 groups of patients: those receiving streptokinase: STK: 87 (49.2%) patients; and those who did not receive it, group NoSTK: 91 (50.8%) patients.

Also, patients receiving STK who presented ECG criteria for reperfusion (Rep) were analyzed vs those without reperfusion criteria (NRep). Cardiovascular risk factors and post-STEMI Killip and Kimball, GRACE and TIMI scores were recorded.

They are defined as combined cardiovascular events: as absolute value and their percentage expression of the combined cardiovascular death, reinfarction, recurrent angina and hospital admissions due to heart failure.

Statistical analysis: categorical variables are expressed in absolute frequencies and ratios. Continuous variables are expressed in mean and standard deviation (SD). For the analysis of differences between groups and to establish risk ratios: hazard ratio (HR), chi-square (X2) test was used with categorical variables and considering a Gaussian distribution for continuous variables, the Student's t-test was used, establishing a statistically significant value of $p<0.05$.

When collecting data, systematization was made by the creation of a database in the Excel program of Microsoft®, and later analyzed by the statistical analysis program Epi-Info of the CDC in Atlanta, and the Past program[8,9].

The study was conducted after the approval by the Committee of Research and Ethics of the CHET, No. BE-00253-22;

TABLE 1.
Baseline characteristics

CHARACTERISTICS	G N=177	STK n=87	No STK N=90	P
Age (μ, SD)	63±12	61±10	65 ±12	0.049
Male	67,8%	68.9%	65,0%	0.261
Hypertension	79.1%	74.7 %	83.3%	0.082
Family history	49.1%	49.4%	48.8%	0.471
Smoking	48.8%	44.8%	38.8%	0.214
Diabetes mellitus	33.3%	29.8%	36.6%	0.172
Dyslipidemia	32.7%	33.3%	32.2%	0.438
Previous MI	19.8%	17.4%	22.2%	0.217
Previous angina	4.3%	7.5%	1.6%	0.077
SBP (μ, SD)	136±36	142±36	130±35	0.031
HR (μ, SD)	82±20	83±19	82 ±20	0.686
LVEF (%, SD)	49,80%	50,3±9	49,2±10,4	0.485
KK ≥2 (%)	15.8%	12.6%	18.8%	0.335
TIMI (μ, SD)	3.7±1.7	3.3±1.6	4 ± 1.8	0.006
GRACE (μ, SD)	147±32	143 ±28	154 ±34	0.076
TYPE OF MI				
Extensive anterior (%)	53%	55,0%	51,2%	0.296
Lateral (%)	8,6%	9,4%	7,7%	0.372
Inferior (%)	38,4%	35,6%	41,1%	0.229
MEDICATION				
Aspirin (%)	99.4%	97.0%	96,0%	0.235
Clopidogrel (%)	98.8%	98,1%	97,8%	0.491
ACEI (%)	36.1%	33,0%	38,0%	0.223
ARB (%)	36.7%	39,0%	34,0%	0.263
Atorvastatin (%)	97.7%	98,0%	98,0%	0.487
Beta blockers (%)	70,0%	70,0%	66,0%	0.161

G: global; **STK:** streptokinase; μ: mean; **SD:** standard deviation; **SBP:** systolic blood pressure; **HR:** heart rate; **LVEF:** left ventricular ejection fraction; **ACEI:** angiotensin-converting enzyme inhibitors; **ARB:** angiotensin II receptor blockers

taking into account ethical guidelines, whose main foundation was based on respect to human rights, stated in the Nuremberg code, and the declaration of Helsinki of the World Medical Association for medical investigations in human beings, where also the confidentiality of participants is guaranteed[10,11].

RESULTS

From the 177 patients evaluated, the mean age was 63±12 years, the male gender predominated with 67%, hypertension was 79%, followed by active smoking 48.8%, with no significant differences between STK and NoSTK groups *(Table 1).*

In relation to Killip and Kimball (KK) and GRACE risk stratification scores upon admission, there were no significant statistical differences between STK vs NoSTK. In the TIMI score of STEMI, the score average was higher in the NoSTK group vs STK group: 4.0±1.8 vs 3.3±1.6 (p=0.006).

In relation to the affected left ventricular wall, extensive anterior myocardial infarction (MI) was the most frequent one, 53%, and inferior MI was 38.4%, while lateral MI was 8.6%.

Patients with electrocardiographic reperfusion (Rep) were in average 5±2 years (p=0.01) younger than those with no reperfusion (NRep). The average door-to-needle time was 47±3.8 minutes, with an average time window (TW) of 4.7±1.5 hours. The reperfusion rate was 41.4%, with an average TW between the Rep vs NRep groups of 4.0±1.7 vs 5.2±2.5 hours (p=0.001). In terms of outcomes, mortality by month was significantly lower in patients with Rep vs NRep: 1 (6.7%) vs 14 (93.3%) p = 0.001; the rest of the variables did not present significant differences *(Table 2).*

From the patients that presented with STEMI, 50.8% could not receive STK; from these, 83% presented to the ER outside the therapeutic window period, followed by 8.8% who received primary angioplasty, and 6.7% who had contraindication for its administration.

We found that 19.5% (17/87) of patients that received STK presented upon admission SBP <100 mmHg; from these 29.4% (5/17) died due to cardiogenic shock.

There was no statistically significant difference in terms of combined or individual in-hospital cardiovascular events (death, reinfarction, recurrent angina and acute heart failure) between STK vs NoSTK groups: combined events: 19 (45.2%) vs 23 (54.8%), p = 0.283; death: 12 (48%) vs 13 (52%), p = 0.452; reinfarction: 1 (50%) vs 1 (50%), p = 0.74; recurrent angina: 4 (80%) vs 1 (20%), p = 0.17; and acute heart failure: 12 (41.4%) vs 17 (58.6%), p = 0.23.

Combined major cardiovascular events (recurrent angina, reinfarction, death and readmission by heart failure) within one month of follow-up between the STK and NoSTK groups were: 40.0% vs 28.2% (p=0.061), hospitalizations by heart failure, in STK vs NoSTK groups were: 25-9% vs 74.1% (p=0.004). The remaining isolated variables analyzed: reinfarction, recurrent angina and death were not statistically significant between groups *(Table 3).*

When analyzing predictors of death within one month in the global sample, a high hazard ratio (HR) was evident in female patients: HR 3.57 (p = 0.001), patients with hypertension: HR 10.23 (p = 0.002), family history of early CAD: HR 2.28 (p = 0.021), and diabetes: HR 2.02 (p = 0.041) *(Table 4).*

The mean age and the Killip and Kimball (KK), GRACE and TIMI scores were significantly higher in patients who died over the month of follow-up *(Table 5).*

DISCUSSION

In this study, it was possible to observe a low rate of reperfusion with STK. The patients presenting electrocardiographic reperfusion had a significantly lower mortality.

TABLE 2.
Characteristics of patients with electrocardiographic reperfusion vs no reperfusion and major cardiovascular outcomes within a month.

VARIABLES	Rep. n=36 (41,4%)	NRep. N=51 (58,6%)	P
Age (μ, SD)	58 ± 1	63 ± 4	0,01
Male	25 (40,9%)	36 (59%)	0,45
Hypertension	25 (38,5%)	40 (61,5%)	0,17
Family history	14 (32,6%)	29 (67,4%)	0,05
Smoking	15 (38,5%)	24 (61,5%)	0,31
Diabetes mellitus	9 (34,6%)	17 (65,4%)	0,21
Dyslipidemia	12 (41,4%)	17 (58,6%)	0.49
Previous MI	5 (33,3%)	10 (66,7%)	0,24
Previous angina	2 (50%)	2 (50%)	0,42
GRACE (μ, SD)	138 ± 23	147 ± 32	0,149
TIMI score (μ, SD)	3,0 ± 1,3	3,5 ± 1,8	0,127
Therapeutic window (μ, SD)	4,0 ± 1,7	5,2 ± 2,5	0,001
Door-to-needle time (μ, SD)	45,1 ± 10,9	48,7 ± 11,0	0,136
MAJOR OUTCOMES			
Combined events	14 (43,8%)	18 (56,3%)	0,49
Recurrent angina	7 (46,7%)	8 (53,3%)	0,46
Reinfarction	2 (33,3%)	1 (66,7%)	0.33
Re-Adm HF	3 (42,8%)	4 (57,1%)	0,46
Death	1 (6,7%)	14 (93,3%)	0,001

Rep: reperfusion; **NRep:** no reperfusion; **μ**: mean; **SD:** standard deviation; **ReIM:** reinfarction; **Re-Adm HF:** readmissions due to heart failure

TABLE 3.
Major cardiovascular events accumulated within one month of follow-up in patients receiving STK vs those who did not receive it .

Events	STK	No STK	HR (IC)	P
Combined	40%	28,1%	1,69 (0,87-3,30)	0,061
Death	17,2%	18,8%	0,89 (0,41-1,92)	0,390
Recurrent angina	20%	16,7%	1,25 (0,54-2,84)	0,301
Re-infarction	4%	2,56%	1,58 (0,25-9,75)	0,326
Re-Adm HF	25,9%	74,1%	0,29 (0,11-0,75)	0,004

STK: streptokinase; **HR:** hazard ratio; **CI:** 95% confidence interval; **Re-Adm HF:** readmissions due to heart failure . Significant p <0.05

Mortality predictors were: hypertension, female gender, family history of early CAD, diabetes, age and KK, GRACE and TIMI scores.

Streptokinase presents limitations, not just in terms of pharmacological effectiveness; moreover, in this study a large number of patients received the thrombolytic agent at the end of the therapeutic window. It is well known that one the most critical aspects to achieve more TT effectiveness is the rapid application of it within the first 2 hours. We should highlight that with TT only a small number of patients achieved an optimal reperfusion in AMI, with substantial deterioration of benefits in many patients, as late arterial recanalization, incomplete arterial permeability by critical residual stenosis, absence of myocardial tissue perfusion by microcirculation obstruction, intermittent arterial reocclusion and tissue injury by reperfusion may also occur[12]. For these reasons, in the centers where PCI is not available (as in our case), and being located at distance of more than 2 hours from a center with it, it is the option available, as well as many of the other public centers at national level. Currently, the recommended strategy is the pharmacoinvasive one whenever possible, with PCI within the first 24 hours after application of thrombolytic therapy, which provides better results in terms of reduction of symptom recurrence and major cardiovascular events[5,13].

Evaluating the effectiveness of therapeutic strategy with streptokinase in STEMI in the center, it is essential to be able to assess its impact in the population, and from there, be able to define according to results, the degree of benefits obtained, or if on the contrary, it would be necessary to make modifications to improve its efficacy or rather consider a change in strategy.

Several epidemiological studies, both in developed countries and in Latin America, have proved that patients with STEMI present in an age range from 50 to 75 years, with greater prevalence of male gender, hypertension and smoking, very similar to that found in our study, where there was an average age of 63±12 years, with male gender predominance (67%) and most were hypertensive, 79.1%, and smokers, 48.8%[14,15,16,17,18].

In terms of the risk profile in the global sample of this study, according to stratification scales, the GRACE scale had a percentage of 147, placing it in moderate to elevated risk, with in-hospital mortality in this cohort of 14%, which predicts mortality in 6 months between 10 to 20%, similar to the study by Bozbeyoğlu E. et al [19]. In the overall sample, the TIMI score of prediction of events was in a range between 3 to 4 points, which predicts a moderate risk of death within 30 days between 4.4% to 8%, which means that the GRACE scale in this case was closer to the findings than the post-MI risk TIMI score, as in other studies[20,21,22].

Fifty-three percent of patients presented extensive anterior MI. These data agree with many other studies, where a higher prevalence of extensive anterior myocardial infarction is observed[16,19,20,21].

We observed that from 50.8% of patients that did not receive STK, most (83%) was because they presented outside the therapeutic window, and few patients that presented within the TW, did it at the end of it, reducing the possibility of reperfusion *(Table 2)*. In the study of Achiong F. et al, from 122 patients, only 35 patients (28.7%) received thrombolysis[23]. The reasons for not receiving thrombolysis were similar to those of our study, with a time window of more than 6 hours being predominant. Other studies show similar data[23,24,25].

The electrocardiographic reperfusion rate of 41.8% was below other studies. This could be related to other factors as has already been pointed out, to patients receiving STK at the end of the TW beyond 4 hours[14,16,19,25]. It is known that thrombolytics lose their effectiveness the later they are administered, and STK loses its effectiveness exponentially for each hour of delay. In this study, there was 59% reperfusion failure. Lee Y. et al, in year 2008, report reperfusion failure in 56.8% with STK, similar to this cohort; and diabetes, hypertension, anterior MI, more prolonged window periods and a high leukocyte count were highly predictive of thrombolysis failure[6]. This supports the fact that thrombolytic therapy does not achieve the expected results, particularly when there is delay in their use, taking into account that the ideal window period is in the first 2 to 3 hours[5,15,19]. Delay in the application of thrombolysis is not just due to the delay of patients to go to the ER, but largely to the absence of health care networks and effective referrals to specialized centers, which would enable a rapid access to the-

TABLE 4.
Risk factors predicting mortality within one month

F. DE RIESGO	HR	IC95%	p
SEXO FEMENINO	3,57	(1,58-7,69)	0,001
HAS	10,23	(1,34-77,70)	0,002
HISTORIA FAMILIAR	2,28	(1,02-5,08)	0,021
DIABETES	2,02	(0,92-4,41)	0,041
TABAQUISMO	1,28	(0,59-2,77)	0,258
DISLIPIDEMIA	1,29	(0,58-2,86)	0,267
IM PREVIO	1,04	(0,39-2,75)	0,454

SHT: systemic hypertension; **HR:** hazard ratio; **CI:** confidence interval
Significant P <0.05

TABLE 5.
Mortality assessment in patients with STEMI within one month

Parámetro	Muerte	Vivo	p
Edad ($\mu \pm$ DE)	71,2 ± 10,9	61,2 ± 10,9	0,0001
KK ($\mu \pm$ DE)	1,6 ± 0,9	1,1 ± 0,3	0,0071
GRACE ($\mu \pm$ DE)	176 ± 32,6	141 ± 28,3	0,0001
TIMI ($\mu \pm$ DE)	4,5 ± 1,6	3,5 ± 1,7	0,0038

μ: mean; **SD:** standard deviation; **KK:** Killip and Kimball score; **GRACE:** GRACE score; **TIMI:** TIMI score

rapy in the proper window period. Another determinant factor at population level is lack of knowledge about the need for immediate care, and learning that a delay of more than 1 to 2 hours to receive TT entails an increase in mortality and subsequent cardiovascular complications[5,23]. Hence, the importance of education programs and promotion of this particular aspect.

Patients that presented electrocardiographic criteria of reperfusion were in average younger and had a significantly lower mortality in one month: 1 (6.7%) vs 14 (93.3%); HR: 0.55 (0.42-0.71) p<0.001; however, there was no reduction in recurrent angina, reinfarction, readmissions by heart failure *(Table 2)*. These results are in agreement with the first large study with STK, the GISSI trial, which showed a greater survival in patients who had reperfusion with STK[26].

It is known that STK is the least effective of thrombolytics, and if applied in average 4 hours after the TW its effectiveness decreases in terms of reduction of the MI size, and therefore of mortality *(Table 2)*[16,23,24,25,26].

Classically, the factors related to mortality increase in STEMI are: an advanced age, delay in reperfusion therapy, heart failure with Killip and Kimball III and IV, decreased left ventricular ejection fraction, hemodynamic instability, extensive anterior infarction, diabetes, history of previous infarction, chronic kidney disease[20,21,27]. Several studies show that while initially women appear to have a greater mortality, these differences are mainly attributed to an advanced age and more comorbidities[27,28]. Xi et al, recently, in a meta-analysis confirmed that after adjusting by risk factors and clinical profile, mortality in the short term remains high in women, but in the long term there is no significant difference between genders[29].

This study shows that the risk factors related to a significant increase in the mortality of patients with STEMI in 30 days were hypertension, with HR: 10.23 (p = 0.002), female gender, HR: 3.57 (p = 0.001); family history, HR: 2.28 (p = 0.021) and diabetes, HR: 2.02 (p = 0.041) *(Table 4)*. Furthermore, similarly to what has been known and reported in several studies, the following appeared as mortality predictors in a 30-day follow-up: age, and high values in Killip and Kimball, GRACE and TIMI scales for STEMI *(Table 5)*[30,31,32,33].

Based on this results, in terms of use of STK, it would be convenient to propose again more effective strategies for the reduction of morbimortality related to STEMI.

Limitations

It should be taken into account that this was an observational study in a single center, which is the largest reference center in the state.

The size of the sample of the study is appropriate to obtain a global evaluation of the center proper, in relation to the diagnosis and management of ACS; however, larger samples and local studies with follow-ups in a larger scale are needed, that would enable to define thrombolytic strategies with more accuracy and certainty.

Regrettably, the proportion of patients that present outside the therapeutic window is very high. Now, in terms of the door-to-needle time determined in this study of 47±3.8 min, which is very late according to the current recommendations stating that it should be in average ≤30 min; it is nonetheless comparable to other studies where STK was used[6,15,34]. On the other hand, by not having public centers with PCI in the state, it is not possible to apply the pharmaco-invasive strategy in most patients as it has already been established in treatment guidelines for ACS[5].

From the health care point of view, there are limitations in terms of obtaining serial biomarkers in appropriate times, to establish kinetic curves that would allow diagnosing myocardial infarction with more accuracy, and start myocardial reperfusion when thrombolytics are used according to treatment guidelines[4,5].

CONCLUSIONS

This study shows that the proportion of the patients with STEMI that does not receive TT is high: 50.8%, and in most, 83%, it is because they present outside the therapeutic window. The patients that do receive STK, do it late in most, in average 4.7±1.5 beyond the 2 hours that are optimal. The rate of electrocardiographic myocardial reperfusion with STK was just 41.8%; in whom, mortality was significantly less in comparison with those who were not reperfused, with HR 0.55 (p = 0.001).

The risk factors related to mortality increase were hypertension, female gender, family history, diabetes, age and elevated valued in the KK, GRACE and TIMI risk scores.

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Original Investigation Reports

Infarction with right ventricular compromise and relationship with hospital outcome

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ABSTRACT

Introduction: acute myocardial infarction (AMI) with right ventricular (RV) compromise is a challenge in patients' management.

Objectives: to evaluate clinical characteristics and hospital evolution of patients (pts) with ST-elevation myocardial infarction (STEMI) and RV compromise hospitalized at the Institute of Cardiology of the City of Corrientes.

Material and methods: prospective, observational registry, 1,126 consecutive patients with STEMI, admitted from 01-01-2017 to 12-31-2022. Anterior AMI was present in 51.9%, 9.6% (149 pts) presented RV compromise. The population was separated into 2 Groups: I) with and II) without RV compromise.

Results: the mean age was 64.9 vs 62.8 ± 12 years (p=0.10), diabetes 31.5 vs 39.7 (p=0.63). Mean blood glucose 188.2 vs 167.8 mg/d (p=0.042), hs-TnT 4659 vs 2822 ng/dl (p=0.003). In-hospital mortality in both groups was 15.4 vs 5.1% (p<0.001), reinfarction 8.1 vs 4.6% (p=0.048), atrial fibrillation 16.8 vs 9.1% (p=0.004), 3rd degree AV block (AVB), 13.4 vs 2.3% (p=<0.001) Swan Gans was applied in 18.1 vs 5.5% (p=0001); mechanical respiratory assistance in 13.4 vs 7.9 % (p=0.020), angiography 95.2 vs 96.9% (p=0.28), thrombolytic therapy 5.4 vs 5.2% (p=0.92) and primary angioplasty 75 vs 76.1% (p=0.32). Multivariate analysis showed predictors of mortality: age OR (1.062 95% CI 1.031-1.094, p=0.001), Killip ≥2 OR=2.1 (95% CI 1.88-4.73, p=0.004), creatinine OR=1.55 (95% CI 1.10-2.18 p=0.015), and RV OR=2.82 (95% CI 1.17-5.6, p=0.003). The risk of RV compromise, anterior ST depression and complete AVB was analyzed; with RV compromise, mortality was 15.4%, with 2 factors 20.5% and with 3 it increased to 28.2%.

Conclusions: RV compromise triples in-hospital mortality, it has a worst outcome and was dependent on mortality, which was greater with RV compromise, complete AV block and anterior ST depression.

INTRODUCTION

Clinical results and the prognosis of patients (pts) with ST-segment elevation myocardial infarction (STEMI) have significantly improved since the implementation of primary angioplasty (TCA)[1]. However, the location of the culprit lesion is an important determinant of clinical course and the outcome[2]. In approximately 50% of pts with STEMI, the culprit lesion is located in the right coronary artery (RCA) and may cause inferior STEMI. These infarctions may complicate with bradycardia and right ventricular (RV) compromise[2,3]. The role of the RV is known in prognosis and functional state, and its compromise is associated to a poor outcome[4,5]. However, it is not known whether the presence of RV compromise affects LV size and function independently, or if it is only an indication of a large myocardial infarction per se. The role of RV infarction within the framework of inferior STEMI is little known, and much less in Argentina, so the objectives of this study were evaluating the clinical characteristics and in-hospital course of patients with ST-segment elevation acute coronary syndrome and RV compromise, admitted to the Coronary Unit of the Instituto de Cardiología de Corrientes.

MATERIALS AND METHODS

Observational and prospective study of consecutive pts admitted to the Coronary Unit of the Instituto de Cardiología "JF Cabral" by STEMI. The population was divided into 2 groups: with RV compromise (Group I) and without RV compromise (Group 2).

Data were obtained from the characteristics of pts (age, gender, risk factors, history, comorbidities), clinical scenario (location of infarction, Killip and Kimball upon admis-

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sion, time of evolution), treatment applied (reperfusion, antiplatelet drugs, adjuvant medications), in-hospital clinical course (heart failure, post-infarction angina, shock, death) and delays until an effective treatment is applied.

The period of inclusion was from January 1, 2017, to December 31, 2022.

The inclusion criteria were suspicion of AMI and some of the following: 1) ST-segment elevation ≥1 mV in at least two limb leads or ≥2 mV in at least two contiguous precordial leads; 2) AMI evolving with new Q waves of less than 24 h since the onset of symptoms; 3) suspicion of infero-posterior AMI (horizontal ST depression from V1 through V3, suggestive of acute circumflex coronary artery occlusion); or 4) new or allegedly new complete left bundle branch block (CLBBB).

The exclusion criteria were diagnosis of non-ST elevation ACS and infarctions with more than 24 hours of evolution.

DEFINITIONS

Electrocardiographic right ventricular infarction: patients with spontaneous infarction in Group I, with ST elevation >1.0 mm in lead V4R, suggestive of proximal RCA occlusion.

Hemodynamic RV compromise: ischemic systolic dysfunction in the right ventricle (RV), which decreases the left ventricular preload, and leads to hypotension with low cardiac output and clean lungs and disproportionate right heart failure.

RESULTS

There were 1126 consecutive pts admitted to the Coronary Unit of the Instituto de Cardiología JF Cabral, since January 1, 2017 to December 31, 2022, with diagnosis of STEMI. The average age of the population was 62±12 years, 78% were of male gender; 51.9% (584 pts) were anterior AMI and 48.1% (542 pts) non-anterior AMI *(Figure 1)*.

RV commitment was present in 9.6% (149 pts), 7.1% (80 pts) presented electrocardiographic compromise and 6.1% (69 pts) ECG and hemodynamic compromise *(Figure 2)*.

The population was separated into 2 groups: I with RV and II without RV. The average age in both groups was 64.9 vs 62.8±12 years (p = 0.10), diabetes was present in 31.5 vs 39.7 (p = 0.63) and female patients 26.2 vs 22.5% (p = 0.31), respectively. Patients in Group I had more history of previous ACS 21.1 vs 12.1% (p = 0.005), and equal prevalence of peripheral vascular disease 7.4 vs 5% (p = 0.24). The average of glycemia upon admission was 188.2 vs 167.8 mg/d (p = 0.042), hs-TnT 4659 vs 2822 ng/dl (p = 0.003). In-hospital mortality in Groups I and II were 15.4 vs 5.1% (p<0.001) *(Table 1)*. In-hospital complications were: reinfarction 8.1 vs 4.6% (p = 0.048), atrial fibrillation (AF) 16.8 vs 9.1% (p = 0.004), complete heart block (CHB) 13.4 vs 2.3% (p =<0.001) *(Figure 3)*. Swan Ganz was required in 18.1 vs 5.5% (p = 0001); mechanical ventilation (MV) 13.4 vs 7.9 (p = 0.020). Coronary angiography (CAG) was applied in 95.2 vs 96.9% (p = 0.28), thrombolytics (TBL) in 5.4 vs 5.2% (p = 0.92) and primary angioplasty (TCA) in 75 vs 76.1% (p = 0.32). There were no differences in the coronary anatomy in both groups *(Table 1)*.

In multiple logistic regression analysis, mortality predictors were age OR 1062 (95% CI 1031-1094, p = 0.001), Killip ≥ 2 OR 2.1 (95% CI 1.88-4.73, p = 0.004), creatinine OR 1.55 (95% CI 1.10-2.18, p = 0.015) and RV compromise 2.82 (95% CI 1.17-5.6, p = 0.003) *(Table 2)*. The risk ascribed to STEMI with RV was analyzed, as well as anterior ST depression and CHB, in the presence of RV mortality was

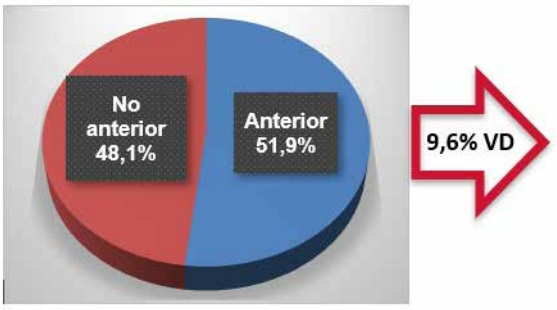

FIGURE 1.
Location of infarction.

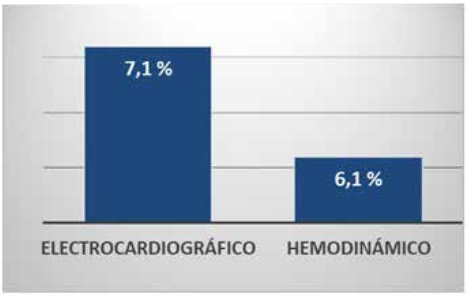

FIGURE 2.
Electrocardiographic findings of inferior infarction and RV, with electrocardiographic and hemodynamic compromise.

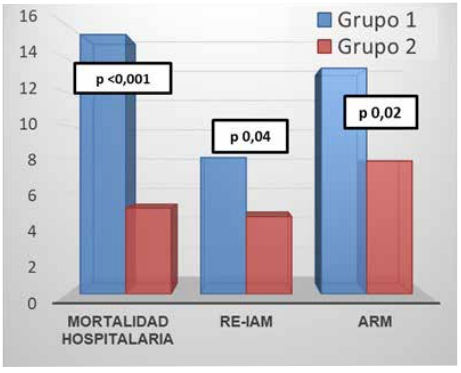

FIGURE 3.
In-hospital events
Re-MI: reinfarction; **MV:** mechanical ventilation

TABLE 1.
Characteristics of the population

	Group 1	Group 2	p
Age (years)	64,9	62,8	NS
Female gender (%)	26,2	22,5	NS
Previous ACS (%)	21,1	12,1	0,005
Peripheral vascular disease (%)	7,4	5	NS
CAD of 2 and 3 vessels (%)	62	61,8	NS
Female gender (%)	26,2	22,5	NS
Thombolytics (%)	5,4	5,2	NS
Primary TCA (%)	75	76,1	NS
Pharmaco-invasive TCA (%)	5.1	5	NS
Delayed TCA (%)	15.2	15.1	NS
Atrial fibrillation (%)	16,8	9,1	0,004
Complete heart block (%)	13,4	2,3	<0,001

TABLE 2.
Multivariate analysis

Multivariate analysis	OR	p=
Age	1,062 (IC 95% 1,031-1,094)	0.001
Killip ≥2	2,1 (IC 95% 1,88-4,73)	0.004
Creatinine	1,55 (IC 95% 1,10-2,18)	0.015
RV compromise	2,82 (IC 95% 1,17-5,6)	0.003

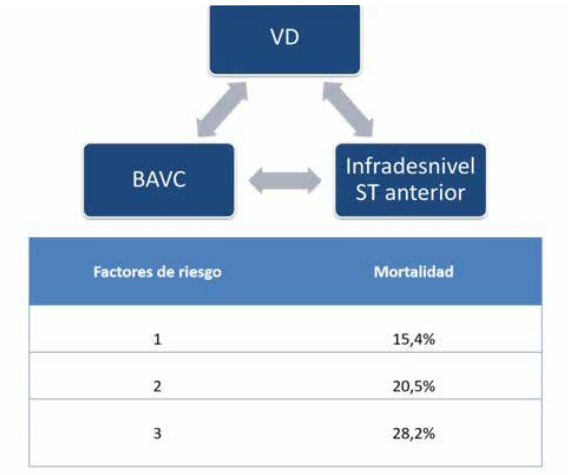

FIGURE 4.
High risk inferior infarction: RV, CHB and ST depression
RV: right ventricle; **CHB:** complete heart block

15.4%, and if there were 2 factors associated it increased to 20.5% and in the presence of 3, mortality increased to 28.2% *(Figure 4)*.

DISCUSSION

RV compromise in STEMI triples in-hospital mortality, it has a worse course during hospital stay and was an independent predictor of mortality. Mortality increased when RV was associated to CHB and anterior ST depression.

Between 30 and 50% of patients who experienced inferior wall infarction may present right ventricular compromise. Right ventricular infarctions rarely occur in isolation; they are nearly always associated to inferior infarction. The coronary artery affected is usually RCA[6]. The proximal segment of RCA irrigates the sinoatrial (SA) node and the right atrial wall, the middle segment irrigates the lateral and inferior right ventricle (RV), and the posterior portion of the left ventricle, the inferior septum, the inferior wall of the left ventricle and the atrioventricular (AV) node are perfused by the distal segment of the RCA. Ten percent may have a right ventricle irrigated by the circumflex artery[7].

The RV produces a hemodynamic form of shock, characterized by low output, hypotension with clean lungs and high pressures of right heart filling, with very poor in-hospital prognosis, and those who overcome this phase display a good subsequent evolution[8]. Hemodynamic compromise in this scenario is a "history of two ventricles" with unequal conditions where the right ventricle is ischemic, dilated and in failure, while the left ventricle is typically "dry" and contracts vigorously, unless it is damaged by previous ischemic aggressions of by the infarction proper in 2% percentage. Acute occlusion of the RCA proximal to the RV branches induces ischemic systolic dysfunction in the RV, altering the transpulmonary delivery of left ventricular (LV) preload, resulting in a reduction of cardiac output and hypotension[6]. The ischemic right ventricle is rigid, dilated and depends on the volume, which produces pandiastolic dysfunction in the RV and elevated pressures in right heart filling. The systolic performance of the RV depends to a large extent from the LV septal contractions, generating pressure and RV systolic output through systolic interactions mediated by the paradoxical septal motion. A severely deteriorated systolic function of the LV limits this contribution offsetting the RV performance, and is associated to a more significant hemodynamic compromise[9].

In patients with a culprit RCA and inferior STEMI, 1 in every 5 had evidence of RV infarction detected by MRI[10]. Goldstein et al, found that pts with RV infarction had a lower RV function in the follow-up in comparison to patients without it, and incomplete ST resolution was independently associated with RV infarction immediately after STEMI[11,12].

PROGNOSTIC MARKERS

First, in inferior infarction, a prognostic marker is the early identification of RV compromise, clinically significant to guarantee not just a proper management, but also to prevent a contraindicated treatment[13]. In this study, in-hospital mortality in the group of patients with RV compromise was 3 times higher (15.4 vs 5.1%, p<0.001).

Second, the presence of CHB is a prognostic marker. Approximately 8% of all patients with inferior infarction have a high degree AV block[14]. Heart block during inferior infarction is associated with a rate of in-hospital mortality of more than 20%. Inferior infarctions associated with heart block are larger than those without heart block, based on the estimation by cardiac enzymes, left and right ventricular ejection fraction, and analysis of left and right ventricular wall motion determined by echocardiography. They have more in-hospital complications, twice more reinfarctions (8.1 vs 4.6%, p = 0.048), twice more atrial fibrillation (16.8 vs 9.1, p = 0.004) and 5 more times of CHB (13.4 vs 2.3%, p =<0.001).

Third, another important prognostic marker in inferior infarction is ST-segment depression in anterior wall, which is associated to a higher percentage of patients with anterior descending artery lesion or more extensive CAD, and therefore, more extensive infarctions as determined by hs-TnT levels, more severe anomalies in regional wall motion and left ventricular ejection fraction[15]. In inferior infarction complicated by heart block, concomitant precordial ST-segment depression and RV compromise indicate larger infarctions and worse prognosis in comparison to those without these characteristics[16]. Moreover, they could be prone to presenting complications in the short and long term in regard to those without ST-segment depression[17]. They had higher in-hospital mortality (13% vs 4%, p<0.001) and a significantly higher incidence of "urgent and non-deadly complications" (defined as reinfarction, persistent hypotension, Killip class III or IV, congestive heart failure and ventricular tachycardia or fibrillation) than patients with non-ST-segment depression (46% vs 29%, p = 0.026). This was one of the studies that revealed a statistically significant ratio in the mortality of patients with inferior infarction associated to anterior ST-segment depression.

In this study, in the analysis of multiple logistic regression, mortality predictors were age OR 1062 (95% CI 1031-1094, p = 0.001), Killip >=2 OR 2.1 (95% CI 1.88-4.73, p = 0.004), creatinine OR 1.55 (95% CI 1.10-2.18, p = 0.015) and RV compromise OR 2.82 (95% CI 1.17-5.6, p = 0.003). The risk ascribed to STEMI with RV, anterior ST depression and CHB was analyzed; in the presence of RV mortality was 15.4%; if there were 2 factors associated it increased to 20.5%, and in the presence of 3, mortality increased to 28.2%.

Patients with RV compromise required a more invasive management: Swan Ganz 18.1 vs 5.5% (p = 0001); MV 13.4 vs 7.9% (p = 0.020). However, there were no differences in regard to interventionism with coronary angiography 95.2 vs 96.9% (p = 0.28), or about the use of thrombolytics 5.4 vs 5.2% (p = 0.92) and primary angioplasty 75 vs 76.1% (p = 0.32).

RV compromise in a scenario of inferior wall myocardial infarction is a risk factor independent from the increase in mortality (17% vs 6.3%)[18].

Refractory cardiogenic shock is the main determinant of poor outcomes in these patients. Percutaneous revascularization has improved the general prognosis in the short term in comparison to fibrinolysis (7% vs 9%)[19,20,21].

CLINICAL IMPLICATIONS

An early identification of right ventricular compromise is important because it entails a specific therapy, initially an aggressive administration of volume to improve preload. Clinical evidence of inferior or posterior infarction that responds with hypotension to nitrates should arise a strong suspicion of associated right ventricular infarction[22]. Management by central venous access or Swan Ganz catheter is essential to document the value of central venous pressure and start volume expansion until reaching a central venous pressure of 14 mmHg, to later administer inotropic agents of the dobutamine type. The beginning of cardiogenic shock requires a rapid stabilization of aortic pressure; therefore, an agent exerting alpha-agonist vasopressor properties along with inotropic properties (norepinephrine and dopamine) should be the initial agent of choice with a rapid administration of volume[23,24].

CONCLUSIONS

Right ventricular compromise in STEMI triples in-hospital mortality, is associated to a worse outcome, and was an independent predictor of mortality.

Mortality increased when right ventricular compromise was associated to CHB and anterior ST depression.

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Original Investigation Reports

Characterization of pacemakers pmplanted in a high-complexity hospital, 2018-2023

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ABSTRACT

Introduction: the prevalence of pacemaker implantation has increased, primarily due to the rising life expectancy of patients. There are few studies that provide a characterization of pacemakers used in recent years.

Methodology: an observational, retrospective, and correlational study was conducted following the STROBE guidelines for observational studies. Data were analyzed from a high-complexity hospital's pacemaker procedures between 2018 and 2023.

Results: there was a 150% increase in procedures between 2018 and 2023, with a total of 646 pacemaker procedures: 59% of the procedures were performed on men, with a higher prevalence in those aged 66 to 80 years; dual-chamber pacemakers accounted for 60.2% of the implants. In single-chamber pacemakers, 49.8% of cases are due to atrioventricular block with atrial fibrillation, followed by second-degree and complete atrioventricular block in similar proportions. For dual-chamber pacemakers, 48.6% of cases corresponded to complete atrioventricular block, followed by sick sinus syndrome. There is a statistically significant relationship between the type of pacemaker and gender, as well as between the type of pacemaker and the fixation system (active electrodes).

Conclusions: the placement of pacemakers has increased significantly in recent years. There is a higher prevalence of implantation in male patients, dual-chamber pacemakers, and active fixation leads.

INTRODUCTION

In recent years, there has been an increase in heart rhythm disorders and other pathologies requiring permanent pacemaker implant[1]. One of the reasons is an increase in the life expectancy of patients. This means that those suffering heart rhythm alterations, infiltrative and inflammatory heart diseases, some cardiomyopathies and other pathologies require permanent cardiac pacing at an advanced age, besides the physiological changes associated to ageing in the cardiac conduction system[2,3].

On the other hand, in many countries, the prevalence of pacemaker implant is unknown[4]. Thus, there are studies made based on database estimations, or else based on previous observational studies[5].

The last world survey about pacemakers was made in year 2009, with the participation of 61 countries, published in 2011. An increase in pacemaker implants stands out in this study, in all countries in the last 4 years before conducting it. Nearly all countries showed a greater percentage of active pacing leads[6].

In the United States, there has been a constant increase in the implant of pacemakers. Within 10 years, there have been 42% more procedures according to Medicare data[7]. Other countries show completely opposite data, with very low pacemaker implant rates in countries like Egypt or Uzbekistan, to very high ones (<1000 implants per million people) in France or Sweden[8].

In a study made in Ecuador, there is evidence of a higher rate of implanted pacemakers in male patients, and in those older than 65 years[9]. In Chile, a historical study on pacemakers implants also shows a higher proportion of male patients. This study also shows the evolution over time, where the primary tendency was implanting pacemakers with single-chamber pacing. Later, this tendency reverted, and currently the implant of dual-chamber pacemakers is more usual[10].

In contrast, in Colombia, a 13-year study with 2590 patients shows that the most prevalent pacing mode is single-chamber (66.2%) in comparison to dual-chamber (27.7%), in spite of current guidelines recommending the latter more[4,11].

Finally, there is a great advancement in cardiac pacing devices. Since the first external models to conventional transvenous ones, and the most recent ones, wireless generators[12,13]. In such scenario, we set out to review the

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TABLE 1.
Type of pacemaker (only implants) implanted in years 2018-2023

IMPLANT	2018		2019		2020		2021		2022		2023		TOTAL
	n	%	n	%	n	%	n	%	n	%	n	%	
Single-chamber	16	37%	37	64%	21	37%	33	41%	42	39%	52	40%	201
Dual-chamber	27	63%	21	36%	36	63%	47	59%	66	61%	77	60%	274
TOTAL	43	100%	58	100%	57	100%	80	100%	108	100%	129	100%	475

most recent years of pacemaker implanting in a high-complexity hospital.

The aim of our study was to characterize the population of patients requiring pacemakers between years 2018 to 2023 in a high-complexity hospital in Chile.

MATERIALS AND METHODS

A quantitative, descriptive, correlational and retrospective study was carried out. This study followed the international STROBE guideline for observational studies[14,15].

An anonymous data sheet was used, from a high-complexity hospital in Chile, with all the pacemaker implant data between years 2018 and 2023. This spreadsheet includes data on gender, age, type of intervention that could be implantations, replacement, reimplantation/relocation (in single- or dual-chamber pacemakers), types of pacemakers (single- or dual-chamber), type of lead (active or passive) and state of patients (alive or deceased).

For the analysis of data, frequency and percentage of each variable were applied. In relation to the association of variables, a chi-square analysis was made with 95% confidence intervals.

In regards to ethical aspects, this investigation followed international guidelines and the declaration of Helsinki. The data used correspond to data provided in an anonymous spreadsheet.

RESULTS

In the period between 2018 and 2023, 646 pacemaker implant procedures were carried out. There is a growing tendency of procedures, with a 150% increase between 2018 and 2023 *(Table 1)*. From the total of procedures in these 5 years, 59% of them were done in men, and 41% in women. After the procedure, 4.8% passed away. The age with highest prevalence of pacemaker procedures was between 66 and 80 years, with 48.14%. In the age range of 80 plus years, 36.22% procedures were conducted. The most common type of pacemakers is dual-chamber, with 60.2%. Among dual-chamber ones, the most prevalent are implants with 42.4%. In terms of the diagnosis originating the indication of cardiac pacing, in single-chamber ones, 49.8% correspond to atrioventricular block with atrial fibrillation. Next in frequency and in an almost equal proportion, second degree atrioventricular block and complete heart block. For dual-chamber pacemakers, 48.6% correspond to complete heart block, and next in frequency, sick sinus syndrome *(Table 2)*.

TABLE 2.
Characteristics of the population in a 2018-2023 study

Variable	n	%
Gender		
Men	381	59
Women	265	41
Total	646	100
Age		
20-40	4	0,61
41-65	97	15,01
66-80	311	48,14
80 and more	234	36,22
Type of intervention		
Single-chamber		
Implants	201	31,11
Replacements	44	6,81
Reimplantation/relocation	12	1,85
Dual-chamber		
Implants	274	42,41
Replacements	36	5,57
Reimplantation/relocation	79	12,22
Type of pacemakers		
Single-chamber (VVIR)	257	39.8
Dual-chamber (DDDR)	389	60.2
Type of pacemaker according to diagnosis		
Single-chamber		
AV block with atrial fibrillation	128	49.8
2nd degree AV block	67	26.0
Complete heart block	62	24.1
Type of pacemaker according to diagnosis		
Dual-chamber		
2nd degree AV block	54	13.8
Complete heart block	189	48.6
Sick sinus syndrome	137	35.2
Trifascicular block	9	2.3
State		
Alive	615	95.2%
Deceased	31	4.8%

In *Table 3,* lead fixation systems are shown. The most widely used fixation method is for active dual-chamber pacemakers in atrial implant.

In regards to the relationship between variables, it was only detected between gender and type of pacemaker (single/dual chamber), and between the lead fixation system (active/passive) and type of pacemaker (single/dual chamber) *(Table 4).*

TABLE 3.
Lead fixation system

Type of lead in single-chamber PMs		n	%
Implants	**Active**	124	19,19
	Passive	77	11,91
Relocations	**Active**	4	0,61
	Passive	8	1,23
Type of lead in dual-chamber PMs			
Atrial implant	**Active**	240	37,15
	Passive	34	5,26
Ventricular implant	**Active**	2	0,30
	Passive	157	24,30

TABLE 4.
Relationship between variables

	Type of pacemaker (single-chamber/ dual-chamber) Chi square	Type of intervention (implant, replacement/ reimplantation) Chi square
Gender	0,002	0,700
Lead fixation (active/ passive)	0,000	0,877
Age	0,512	0,494

DISCUSSION

The tendency shown in this study to an increase in pacemaker procedures within the last 5 years is shown to be global[6]. This prevalence increase in an older population attest to the significance of researching this topic.

In relation to the diagnosis justifying the need of a pacemaker, the cases requiring single-chamber pacemakers are, in general, the same described usually in scientific literature[13]. These are patients with atrial fibrillation and atrioventricular block. On the other hand, according to the current clinical practice guidelines on cardiac pacing and resynchronization therapy, dual-chamber pacemakers are mainly indicated in cases of complete heart block, with the aim of preventing recurrent syncopes[4].

The study showed that there is a relationship between the type of pacemaker and gender, with the highest amount being implanted in men. Similar results have been observed in other investigations[9,10,16]. A recent study that has examined a data series shows that pacemaker implant is more frequent in men, but the complications of this procedure are more frequent in women (as they have thinner and smaller blood vessels, with narrower chests)[17].

Thus, the relationship between type of pacemakers and gender found in the study is relevant to the world tendency in recent years, and is based on the fact that cardiac conduction system pathologies are more prevalent in men[18].

About the relationship between the type of pacemaker and lead fixation, this is due to most ventricular leads used in single- and dual-chamber pacemakers being active, located in the chamber that generates cardiac output, so guaranteeing pacing is required when using a lead with low displacement rate. It is not the case of dual-chamber pacemaker, which besides the ventricular lead, uses atrial leads, which by being passive and pre-shaped in a "j" outline facilitate their placement in the atrial appendage. The indication of active atrial leads is recommended by lead manufacturers in the case of patients presenting a distortion of the right atrial anatomy, as in the case of cardiac surgery (valvuloplasties). Therefore, this study follows the tendency of other countries, where the most prevalent fixation system is the active one[6].

No relationship was observed between the types of pacemakers and the age of patients. Currently, the type of pacemaker (single- or dual-chamber) is determined by the need of the patients of atrioventricular synchronicity prevalence, which in turn is determined by the type of heart rhythm disorder. Thus, it is considered that in patients with chronic atrial fibrillation, using dual-chamber pacemakers makes no sense, as these devices turn to VVI mode automatically when they detect atrial alteration, so the atrial lead never generates an impulse. Furthermore, there is no evidence of a better quality of life for elderly patients in terms of single- or dual-chamber pacemakers[19,20]. Another study that compares patients younger than 85 years with those older than 85 does not show statistically significant differences between the groups and the type of pacemaker implanted[21].

The type of intervention does not show a relationship to gender, as this is related to patients presenting pacemaker battery exhaustion or lead dysfunction. In the case of battery exhaustion, the determinants are according to the pacemaker parameter programming, as for instance minimal rate, voltage, pulse width, lead resistance, percentage distribution of pacemaker use given by the sensed cardiac chamber-paced cardiac chamber, which project device longevity, regardless of age and gender of patients.

In terms of lead dysfunction, it is related to the physiological response to the lead contact area (passive or active) with myocardial tissue, and patients presenting a significant inflammatory reaction may develop lead dysfunction in capturing or sensing, having to relocate the lead and place it elsewhere. This depends on each patient. Pacemaker manufacturers found a way to help with this complication by making passive and active leads with steroid-eluting tips, to decrease or minimize the inflammatory reaction of the tissue in contact with the lead[22,23].

The limitations of this study are related to it being observational, where only some relationships between variables are described or established, not being able to establish causality. Another limitation is that between the data, year 2021 is included, which due to the COVID-19 pandemic could not yield a reflection of reality in terms of patterns of intervention, and many procedures were delayed due to the established quarantines.

CONCLUSIONS

Pacemaker implantation has been increasing considerably in recent years. There is a higher prevalence of implants in male patients, of dual-chamber pacemakers and active fixation leads.

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Original Investigation Reports

Costs of an early reperfusion project for the treatment of ST-segment elevation acute coronary syndrome in the public sector of the Alto Valle, Province of Río Negro

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ABSTRACT

Introduction: in the public sector of the Alto Valle of Rio Negro (RN), a healthcare issue has been identified concerning the management of ST-segment elevation acute coronary syndrome (STEACS). An opportunity to improve this situation would be the implementation of an early reperfusion project.

Objective: to estimate the costs of an early reperfusion project with prehospital/hospital thrombolysis and primary PCI (pPCI) in patients with STEACS.

Methodology: the study is framed as a health economic evaluation (HEE). The cost estimation was conducted using a macro-costing technique with a cost-of-illness approach.

Results: the total estimated cost of the project was US$ 2,422,783.91. According to the expected cases and based on the projections made, in the first year of the project, we would expect to treat 66 STEMI patients, with a program cost per patient of US$ 10,791.19, a cost per day of stay of US$ 1,640.01, and an average stay of 6.58 days. By the end of the program, we would aim to treat 131 patients at a cost per patient of US$ 2,066.93 and a cost per day of stay of US$ 645.92, with an average stay of 3 days.

Conclusions: In the public healthcare sector of the Alto Valle of RN, reperfusion times for STEMI are prolonged, highlighting the need for the implementation of an early reperfusion project. For patients undergoing pPCI, initial costs are high, but they are offset by a shorter length of hospital stay. In the case of treatment with thrombolysis (TL), costs are higher due to the need for coronary angiography (CAG) with a probable PCI.

INTRODUCTION

Caring for acute myocardial infarction (AMI) in the public sector of the Alto Valle de Río Negro (RN) presents opportunities for improvement, according to a research made. A sanitary problem has been detected, as hospitals do not usually use fibrinolytic agents for the immediate care of infarction, and patients are referred to private centers to undergo primary percutaneous coronary intervention (pPCI), regardless of the time elapsed since diagnosis[1,2]. In the development of the study, it was observed that the time window for pPCI was prolonged, with a median of 200 minutes (IQR: 120-480) or a median of 336±290, and only 26 patients were treated in year 2017; of these, 25 with good evolution and one patient deceased, representing a total of 15 years of potential life lost (YPLL), taking into account the population and incidence of AMI; a total of 50.5 YPLL were not registered due to a lack of treated patients in 2017[1,2].

ST-segment elevation acute coronary syndrome (STEACS) presents in the public sector of RN multiple barriers preventing a proper treatment: causes attributable to the patients, as delaying consultation, deficit in pre-hospital/in-hospital care, lack of human resources (HR) in number and quality, deficit in technological resources, lack of training and education for the staff, and absence of coordinated regional health care networks.

An improvement in this situation would be formulating an early reperfusion project; planning it is a continuous process of estimation of financial resources and services necessary to achieve specific goals according to established priorities, thus enabling the choice of optimal solution(s)

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between plenty of alternatives, considering a scenario of internal and external difficulties currently known or expected in the future[3,4].

Economic evaluation (EE) is an essential tool to make decisions related to sanitary projects and programs financing and regulation, within a health care system where resources are always scarce. In the health care services, EE establishes that resources should be applied to the alternatives that generate more benefits in relation to costs[5].

The hypothesis is that carrying out a project of early reperfusion within 5 years would achieve reducing YPLL, more life years gained (LYG) would be obtained, and a higher number of patients with STEACS would be treated in Alto Valle de RN. The costs of the project could be high in the first year of implementation, but then they diminish.

General aim: estimating the costs of a project of early reperfusion by pre-hospital/in-hospital thrombolysis and pPCI in patients with STEACS in the public sector of Alto Valle de RN.

MATERIALS AND METHODS

The study is included in an EE of health, on a project of early reperfusion for STEACS in 5 years in Alto Valle de RN, to achieve more LYG and treating more patients, decreasing the times to reperfusion and increasing the population to be reperfused.

The estimation of the costs of the project was made by a macrocost model focused on cost-disease.

The costs of equipment were obtained following the bidding processes of the province of RN and usual providers of public health, requesting budgets to different companies according to the area. Direct costs (DC) were added, associated to additional medications required at the time of diagnosis of STEACS and during the year of follow-up in an outpatient. For the estimation of costs of education, an average teaching hour was used, between the Universidad Nacional de Comahue (UNCo), the Argentine Federation of Cardiology (FAC) and the Argentine Society of Intensive Care (SATI).

For the staff costs, the payment values of the province for Public Health staff were applied; in the case of Advanced Emergency Medical Technicians (AEMTs), the values provided by the Emergency Hospital of the city of Córdoba were used. The staff that was estimated based on the nursing and managerial staff of category 6 hospitals, and according to estimation guide for care index, taking it as basis plus categorization[6].

Costs update (June 2017-June 2024) was made based on two indicators: SIPIM (Sistema de Índice de Precio Interno Mayorista – System of Wholesale Internal Cost Index) and the salary variation index for this period, which were expressed in the official dollars (US$) rate of Argentina.

For the development of the reperfusion project, we started from the health scenario observed in the population of Alto Valle of RN in 2017, and it was decided to propose pPCI as a priority strategy, and in the cases of thrombolysis (TBL), use tPA (Alteplase) as it is fibrin-specific[1,2]. Objectives and goals were set, activities were prepared, actions and the necessary resources were estimated (physical, human, financial), approaching from macromanagement and applying the methodology of formulation of socio-sanitary projects, where decisions related to public health care policies are the framework and condition the implementation of budgets and coverage[7,8].

Based on the higher time window (TW) obtained in the studied population (2017) and following the percentage of patients treated observed in the city of Rosario, a reduction in YPLL was estimated, assuming that the project would enable decreasing reperfusion time until reaching a recommended time of 120 minutes, along with a higher number of treated patients[9]. The proportion of patients per year was projected, that would reach a reduction in times as the program advanced, where in the first year, only 5% would reach 120 minutes until reperfusion, second year 10%, third year 25%, fourth year 30% and 60% in the last year of the project.

LYG were obtained from the subtraction between YPLL with/without project according to the following formula[2]:

N° of expected cases x rate of increase in indirect costs in Rosario[9]

N° of expected cases = 40% of the total of patients with diagnosis of AMI expected according to the population for the year of analysis, incidence of STEACS, % of patients with hospital coverage and the corresponding proportion was assigned according to delay time.

$$LYG = YPLL(t) - YPLL\ (t+1)$$
$$YPLL = Def * provincial\ YPLL$$
$$t = year\ of\ project$$
$$(t+1) = subsequent\ year$$

The following were considered indicators: pain-to-hospital time, time window (TW), door-to-needle time (DTNT) and door-to-balloon time (DTBT).

DEFINITIONS

Cost: value of used resources to produce or reach the value of a good or service. Sacrificed, consumed or lost resources until reaching a specific goal, expressed in monetary terms.

Direct costs (DC): they constitute the value of goods, services and other resources that are consumed in the supply of an intervention or treating adverse effects or any other present or future consequence linked to the intervention: capital costs, fixed or variable costs.

- *Medical direct costs:* use of sanitary system resources. E.g.: medications.
- *Non-medical direct costs:* costs absorbed outside of the sanitary system, as the use of non-sanitary resources. E.g.: travel allowances.

Indirect costs (IC): costs supported by patients and their families, as a consequence of disease sequelae. They are re-

lated to changes in the productive capacity of the individual or relatives, essentially the loss of work days, whether due to mortality or morbidity, e.g.: treatment time, time off from work, time of relatives dedicated to the patient's care, transportation, food, etc.[10,11].

Productivity costs: financial implications of the disease in the use of time, as a consequence of the sequelae of a disease. In this case, the effect of receiving treatment is not considered, but rather the subsequent effects of the disease.

Future costs related or not with the project: they include the different types of direct costs that emerge as a consequence of the sanitary intervention or the higher life expectancy of patients.

Other definitions:

Pain-to-hospital time: time elapsed since the onset of symptoms suggestive of ischemia and the first medical contact (FMC), expressed in minutes.

Time window (TW): time interval in minutes after the onset of symptoms until the onset of infusion or until the start of TCA.

Door-to-needle time (DTNT): time interval in minutes since arrival at the institution and the onset of the infusion.

Door-to-balloon time (DTBT): time interval in minutes since arrival to the institution until balloon inflation.

TABLE 1.
Budget Human Resources

HR	Number	Pesos	Dollars
Specialists in cardiology	6	$ 89,658,230.93	U$D 96,354.90
Nurses	18	$ 189,154,708.20	U$D 203,282.87
AEMTs	18	$ 283,131,087.94	U$D 304,278.44
Total		$ 561,944,027.08	U$D 603,916.20

STATISTICAL ANALYSIS

Statistical analysis was based on the definition of costs considering the day/stay average as base indicator expressed in the official US$ rate in Argentina.

To formulate tables, estimations and graphs, the SPS and Excel programs were used.

Ethical considerations: the authors state knowing about and having followed the international, national and provincial legal and ethical regulations: the Nuremberg Code, the Declaration of Helsinki, the International Ethical Guidelines for biomedical research involving Human Subjects of the CIOMS/WHO; the International Ethical Guidelines for Epidemiological Studies of the CIOMS/WHO, the Operational Guidelines for Ethics Committees that review Bio-

TABLE 2.
Budget supplies, equipment, medications

Equipment/supplies	Number	Pesos	Dollars
SPRINTER 415 ambulances	12	$ 956,785,091.26	U$D 1,028,248.35
CardioPrint ECG devices	12	$ 20,967,867.30	U$D 22,533.98
Cobas h 232 analyzers	12	$ 125,807,203.80	U$D 135,203.87
Cardiac POC troponin T x 10 measurements	12	$ 2,981,285.58	U$D 3,203.96
Cardiac CK MB x 10 measurements	12	$ 2,522,137.06	U$D 2,710.52
Cardiac D-Dimer x 10 measurements	12	$ 3,273,427.31	U$D 3,517.92
Pulse oximeters	24	$ 1,797,893.35	U$D 1,932.18
Adult sphygmomanometers	12	$ 753,503.28	U$D 809.78
Adult single-head stethoscopes	12	$ 185,650.36	U$D 199.52
PCs with printers	12	$ 15,643,441.76	U$D 16,811.87
Pharmacy supplies, disposable material, supplies, etc.	12	$ 13,259,497.19	U$D 14,249.86
Promotion activities (publicity campaigns, stationery, posters)		$ 21,673,519.67	U$D 23,292.34
Printing + FD. Guidelines, protocols	160	$ 1,133,922.94	U$D 1,218.62
Mobility and travel allowances 5% total		$ 60,790,969.11	U$D 65,331.51
Overhead and unforeseen circumstances		$ 382,983,105.40	U$D 411,588.51
Training		$ 11,842,875.00	U$D 12,727.43
Medications		$ 37,192,066.41	U$D 39,969.98
Total		$ 1,659,593,456.78	U$D 1,783,550.20

medical Research of the WHO 2000, the UNESCO Universal Declaration on Bioethics and Human Rights from 2005, and the valid national guidelines of the Ministry of Health of Argentina.

RESULTS

The implementation of an early reperfusion project in a real scenario would have a financial variability influenced by multiple and different factors. The requirements will be according to an increase in demand, by identifying more candidates to early reperfusion, as proven in the experience of the city of Rosario[9].

The project was proposed with pPCI as a priority treatment, and in the case of not meeting the recommended times, thrombolytic therapy with Alteplase was chosen (unless contraindicated)[12].

The necessary staff for the different areas would be hired and trained, supplies, medications and technology would be bought; about the existing buildings, only the emergency wards would be modified to adapt them to manage STEACS. The hemodynamics services already existing in private centers would be used, improving coordination with them, through a network and optimizing with the coordination center, a 24/7 coverage area with the private (interventionist) staff available, under the Infarction Code (IC) protocol of action[2].

The budget for human resources, supplies, equipment, medications and total costs is described in *Tables 1-2.*

The total cost estimated of the project was US$ 2,422,783.91, with a distribution of payments in 5 stages, as described in *Table 3.*

The group of studied patients in the Alto Valle was low in comparison to the expected cases of STEACS; however, after estimating the expected cases taking into account the incidence of STEACS in the population of Alto Valle de RN, and the projections prepared and described previously in the investigation, we will show how they will affect the implementation costs of an early reperfusion project with an average of stay days of 6.58, according to what was found in the studied population, and when the program ends, an average time of hospital stay of 3 days, according to recommendations[1,2,12].

In the first year of the project, 66 patients with STEACS would be expected to be treated, the program cost per patient would be US$ 10,791.19, with a cost/day/stay of US$ 1640,01, with an average of 6.58 days of stay; by the end of the program, 131 patients should be treated, at a cost per patient of US$ 2066.93, and a cost/day/stay of US$ 645.92, reaching a time of average hospital stay of 3 days, as detailed in *Table 4.*

According to the same proportion of expected treated cases, and according to the geographical location and type of treatment according to rate of use, at the beginning of the project 59 patients would be registered as undergoing pPCI, with 6.58 days of hospital stay, with a cost/day/stay of US$ 1443.20; at the end of the program, 116 patients would be registered as undergoing pPCI with a cost/day/stay of US$ 276.43, with 3 days of stay, and in the case of patients who undergo thrombolysis and subsequent PCI (of rescue or delayed), 5 days of stay would be estimated in total per patient (assuming that no complications appear); in this case, there would be a total of 15 patients with a cost/day/stay of US$ 413.37, as detailed in *Table 5* and *Figures 1 and 2.*

DISCUSSION

In this study, we observed that the program/patient cost would be US$ 10,791.19, with a cost/day/stay of US$ 1640.00 US$ in the first year of the project, with an average of 6.58 days/stay and, by the end of the program, the cost/patient would be US$ 2066.93 and a cost/day/stay of US$ 314.12, reaching an average time of stay of 3 days.

The evaluation of costs is important for all types of EE; one of the central concerns is the impact of using scarce health resources, and thus, costs are central for the critical analysis of any type of EE[10,11].

There are two essential concepts in economy: scarcity and choice. Scarcity indicates that the resources individuals and societies have available are limited, while needs are infinite. The financial activity consists of the social organization to deal with scarcity, using scant resources to satisfy

TABLE 3.
Total cost of capital and periods with payments

Period	Useful life	Total cost of capital	Yearly cost of capital with r=0,15
	n	(cost of replacement)	
1	5	U$D 2,387,466.40	U$D 712,218.36
2	4	U$D 1,675,248.04	U$D 586,781.34
3	3	U$D 1,088,466.70	U$D 476,723.34
4	2	U$D 611,743.36	U$D 376,293.30
5	1	U$D 235,450.06	U$D 270,767.57
Total			U$D 2,422,783.91

r: discount rate.

TABLE 4.
Treatment of patients with project, patient cost/day of stay cost

Year	Treated patients	Cost of program	Cost of patient	Cost of day of stay with projection
1	66	US$ 712,218.36	US$ 10,791.19	US$ 1,640.01
2	99	US$ 586,781.34	US$ 5,927.08	US$ 1,384.83
3	108	U$D 476,723.34	U$D 4,414.10	U$D 1,146.51
4	124	U$D 376,293.30	U$D 3,034.62	U$D 916.81
5	131	U$D 270,767.57	U$D 2,066.93	U$D 645.92

TABLE 5.
Estimation of costs with pPCI and TBL with project

				pPCI			TBL and PCI		
Year	**Patient cost**	**Day of stay cost**	**Patients**	**Patients**	**Day of stay cost**	**Cost of day of stay**	**Patients**	**Day of stay cost**	**Cost of day of stay**
Año 2	U$D 5,927.08	U$D 900.77	99	88	4.28	U$D 792.68	11	5.91	U$D 1,002.89
Año 3	U$D 4,414.10	U$D 670.84	108	96	3.85	U$D 590.34	13	5.82	U$D 758.43
Año 4	U$D 3,034.62	U$D 461.19	124	109	3.31	U$D 405.85	14	5.70	U$D 532.39
Año 5	U$D 2,066.93	U$D 314.12	131	116	3.20	U$D 276.43	15	5.00	U$D 413.37

PCI: Percutaneous coronary intervention. **TBL:** thrombolysis. **US$:** Dollars

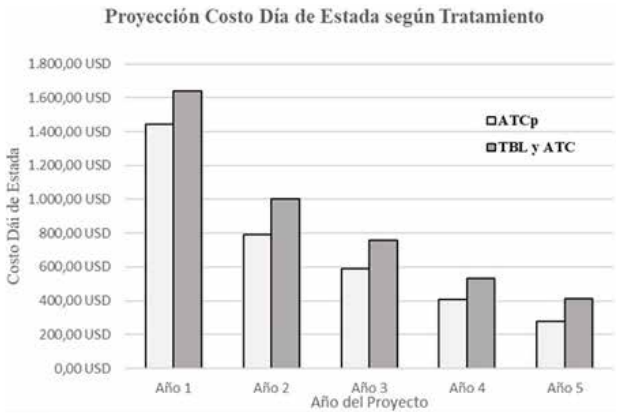

FIGURE 1.
Projection of costs according to days of stay and treatment

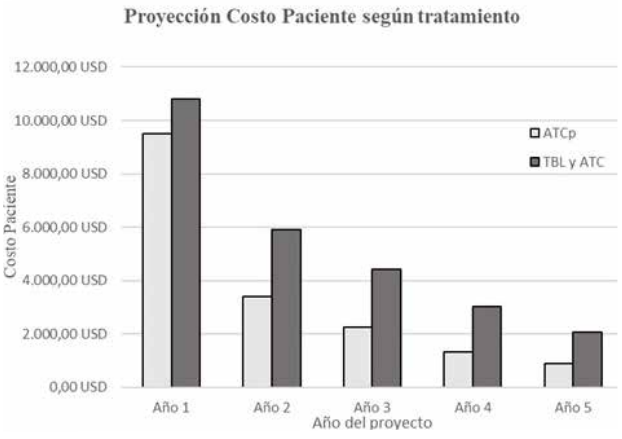

FIGURE 2.
Projection of costs according to the type of treatment

virtually infinite needs. All these resources are applied to different uses to generate health, a need that is also infinite.

The implementation of these resources constitutes a cost, as a financial sacrifice is being generated (use of a scant resource). The concept of cost then refers to using a scarce resource in a given economic activity. It is important to take into account that the cost is generally measured in money, but it is not money: costs are the real resources used in a specific economic activity[13].

A concept closely related with scarcity and choice is the cost of opportunity, when a new resource is consumed, applied to a given use and not to others; there is an opportunity seized by the use of such resource and many opportunities lost. The cost of opportunity seeks to reflect that, in every financial decision, there is a sacrifice made, as the resources used to consume or invest will not be available for another use. The cost of opportunity is usually identified with the best alternative dismissed (they constitute lost benefits).

In bibliography, publications have emerged that assess the profitability of the networks in the treatment of AMI, as Catalonia, that is creating a regional STEMI network with the IC action protocol[14]. The authors made an EE before and after the implementation of the network, and observed that this implementation modified the distribution of the procedures, with a significant decrease in patients treated by thrombolysis (37% vs 3%; p<0.01), rescue PCI (11% vs 4%; p<0.01) and patients not reperfused (21% vs 4%; p<0.01), in comparison with a significant increase in pPCI (31% vs 89%; p<0.01).

In terms of costs, fibrinolytic treatment generated the lowest average of hospitalization expenditures, rescue PCI was the most expensive procedure, followed by pPCI. As a result of the substitution effect generated by the implementation of the network, costs increased by € 1656 per patient with STEACS, from € 2284 to € 3940. Simultaneously, however, improvement in the efficiency of the pPCI procedure allowed a decrease of € 1458 per patient in hospital costs, from € 5397 to € 3939. The effect of the combined cost was a light increase (2.6%) of € 198 in cost/patients/STEACS, from € 7681 to € 7879.

In England, the National Infarct Angioplasty Project (NIAP) evaluated the implementation of pPCI[15,16]. There were 2072 patients with STEACS enrolled, 70% admitted directly for pPCI, and the remaining 30% were admitted to a hospital with no hemodynamics service (called "non-primary PCI site"); from those admitted directly to a hemodynamics center, 67% received pPCI, 16% thrombolysis and 17% did not receive reperfusion treatment. From

those admitted in a "non-primary PCI" site, 70% were referred to another hospital for the procedure, 14% received thrombolysis and 16% did not receive reperfusion therapy. In-hospital mortality was 6.8% and the average duration of the stay was a little less than six days.

The patients treated by thrombolysis in control sites (£ 2983) were less expensive than those treated by thrombolysis in the NIAP sites (£ 3945) (p<0.01), or those treated with pPCI in the NIAP sites (£ 4900) (p<0.01). Hospitalization was the costliest category for any group of patients, even patients treated with pPCI, where the duration of the stay was shorter, it represented 41% of the total cost. The average stay duration was greater in NIAP sites for patients treated with thrombolytics (8.4 vs 6.9 days, p<0.01) or with pPCI (5.66 vs 4.44 days, p = 0.047).

The patients that received thrombolysis presented substantial differences in costs between the thrombolytic drugs available. Streptokinase (STK) of £ 81 per dose in comparison with a minimum £ 612 for other thrombolytics. For these patients, the mean cost was £ 3509, but it was greater in NIAP sites in £ 852. For the patients treated with pPCI, the mean cost was £ 5176 for those admitted during work hours, and it was higher for patients treated outside these hours: £ 245. The mean shortest time, of 20 minutes, was recorded between patients taken directly to hemodynamics. The delays generated due to the referrals to centers with pPCI would change the financial benefits, highlighting the importance of minimizing delays and diagnostic errors that would also increase costs.

Birkemeyer et al, analyzed the profitability in the short term of a STEMI network in a rural area of Germany, where its implementation led to using reperfusion methods differently[17]. In 2002, 27% of patients received thrombolytics and 53% pPCI; while 21% of patients did not receive any reperfusion treatment; in 2008, the impact of the network was confirmed with 1% of thrombolytics, 89% pPCI and 10% with no reperfusion treatment, decreasing in-hospital mortality from 16% to 7%. The highest costs were mainly due to the higher number of patients that received intensive care after STEACS complicated by cardiac arrest and/or shock. Besides, a higher number of complex pPCI procedures were made in a parallel way to a decrease in the number of patients with post-AMI revascularization surgery (RVS). The mean initial costs per life saved during the stay were € 7727.

The Concannon et al study evaluated the comparative effectiveness of STEACS regionalization strategies to increase use of pPCI in comparison with transportation and standard emergency care. It was observed that in the patients receiving pPCI, the saved costs of care and years of life adjusted by quality were profitable in a variety of conditions[18]. A strategy based on emergency medical services to transport patients to a center with existing interventionism was less expensive and more effective.

Le May et al, studied the costs of hospital admission due to pPCI with stent placement vs thrombolysis with tPA in the treatment of AMI (STAT study), in the initial admission and in 6 months of follow-up. There were 61 patients in pPCI with stent enrolled, and 62 in thrombolysis. The duration of initial hospitalization was 6.7±11.3 days in the stent group and 8.7±6.7 days in the tPA group (P=0.001)[19]. The total days of hospitalization in 6 months were 8.3±13 in the stent group and 12.1±14.0 in the tPA group (P=0.001). The costs of hospitalization were lower in the stent for the initial admission, CA$ 6354±6382 vs CA$ 7893±4429 (P=0.001), and in 6 months, CA$ 7100±7111 vs CA$ 9559±6933 (P=0.001), expressed in Canadian dollars.

The composite primary endpoint (death, reinfarction, stroke, restenosis) within 6 months was reduced in the stent group: 24.2% vs 55.7% (P<0.001); the increase in the thrombolysis group was mainly due to less revascularization of the culprit vessel: 14.5% vs 49.2%, P<0.001. Recurrent ischemia was lower in the stent group, 9.7% vs 26.2%. Within 2 years, the composite endpoint remained low in the stent group, 32.2% vs 57.3% of tPA (P=0.005). The authors concluded that, in centers with proper facilities and experienced staff, the placement of stents in pPCI is less expensive and more effective than applying thrombolysis, but such results may not be applicable to centers using streptokinase; however, any saving in costs with STK would probably be compensated with worse clinical results as it is considered less effective[19].

Other authors describe a risk score in the cases of STEACS to decrease costs and maintain optimal results for patients. This score added 6 clinical and angiographic variables (age, time of ischemia, KK class, number of vessels with CAD, if the vessel involved led to anterior infarction and TIMI flow after pPCI), each variable with an analyzed point value. The scores from 0 to 3 were classified as of low risk of mortality in 30 days or after discharge, while scores ≥4 were considered of high risk. Patients in low risk presented a shorter mean stay and lower general costs (low risk US$ 6720 [US$ 5280-9030] vs high risk US$ 11,783 [US$ 7953-25,359]; P<0.001), achieving a reduction in costs not affecting the quality of care[20]. Other authors also coincide in that patients with low risk STEACS who undergo pPCI could be considered for an early discharge, being safe and profitable in this group of patients[21,22].

Sanitary technological evaluation (STE) is also defined as a multidisciplinary process that summarizes information on medical, social, financial and ethical aspects related to using sanitary technology, by a systematic and transparent process, free of biases. Health care systems add new technologies daily; in some cases, this addition has no scientific basis, with the consequence of a poor use of resources, affecting both quality and costs of sanitary services. This reality leads to the birth and the development of the concept of STE, which is defined as the set of evaluation research with the aim of reporting, based on scientific knowledge and the reality of scenarios, on the different decisions that should be made in a health care system, whether at the level of sanitary and research policies, planning, purchases, resources or financing; in some places in the world these evaluations

are mandatory at the time of approving a medication or technologies[11,23].

In the analysis of costs in interventions for coronary syndromes after the emergence of thrombolysis with STK, the cost per LYG in these cases should be compared to another treatment, for instance, dialysis in the US, which costs US$ 50,000/patient/year. Programs up to this amount are considered positive from the financial point of view and there are no doubts on the benefits of STK. Later, recombinant tissue plasminogen activator (rTPA) appeared, which in comparison to the former, proved to yield a better survival, although there were no differences found in hospital stay expenses between both groups of patients, just the cost of thrombolysis (US$ 2200 for rTPA and US$ 270 for STK). The cost-effectiveness (CE) ratio for rTPA was US$ 27,000/LYG, which is very convenient when compared with dialysis, but much less when compared with STK[24,25].

When pPCI is compared with thrombolytic treatment, different results occur, with advantages in terms of survival, but different in terms of CE, as with this strategy, all patients went to CAG, with few differences with thrombolytics, because plenty of these patients were later studied by hemodynamics; therefore, the final cost was not increase. When a CE analysis is made on pPCI as initial strategy, it is very good in centers that already have hemodynamic services available[24,25].

In the PAMI Trial study, when pPCI was compared with rTPA, a reduction was observed in in-hospital mortality, reinfarction and stroke rates with a shorter hospital stay. In spite of the initial costs of CAG, the mean total hospital charges were lower per patient with pPCI than with rTPA, mainly due to a reduction in adverse results in the hospital. In terms of in-hospital events, 83% of patients treated with pPCI were alive and free from reinfarction at the end of the follow-up, in comparison with 74% of patients treated with rTPA[26].

For Wailoo A et al, the primary care of STEACS based on pPCI is considered profitable in a threshold of £ 20,000 per QALY gained, mainly if patients were directly admitted to the hemodynamic service, than if they were referred to other hospitals[16].

About pre-hospital and in-hospital thrombolysis, the meta-analysis by Morrison et al, shows a decrease in all cases of mortality by STEACS with pre-hospital treatment, in comparison with in-hospital thrombolysis. There is also evidence that the sooner the patients arrive to the hospital and receive thrombolysis, the better the results[27]. The GREAT (Grampian Region Early Anistreplase Trial) study directly approached early pre-hospital thrombolysis and compared it with treatment administered in the hospital, where pre-hospital thrombolysis had a life expectancy for 12.48 years and in-hospital one had an average life-expectancy of 12.39 years. Costs were £ 361 for pre-hospital treatment and £ 300 for in-hospital one. Therefore, incremental cost-effectiveness ratio (ICER) per LYG for pre-hospital thrombolysis over the in-hospital one was £ 667[28,29].

In an EE analysis of the pharmacoinvasive strategy (PhIS) in Mexico, the authors assessed costs and their impact on hospital stay comparing it with pPCI. From all patients included (1747), 26.9% received PhIS, 24.7% pPCI and 48.3% were not reperfused (NR). In relation to the hospital stay in 30 days, PhIS and pPCI, 5 (3-10) / (3-9) days did not show significant differences; however, the NR group showed a stay of 9 (5-15) days. Mortality in 30 days was 5.8% in pPCI and 4.3% in PhIS, but higher in the NR group (11.4%). When costs were adjusted per age, gender, diabetes, smoking, previous AMI, heart failure, TIMI score, MACE, hospital stay and mortality in 30 days, a similar cost was found between PhIS and pPCI (US$ 4534.25 vs US$ 4446.61), but higher costs when comparing NR patients with PhIS (US$ 5428.90 vs US$ 4534.25) or with pPCI (US$ 5428.90 vs US$ 4446.61).

In this study, it was observed that PhIS is similar in terms of costs, mortality and duration of hospital stay, with less incidence of MACE in comparison with pPCI. In environments where pPCI could not be implemented properly, PhIS is financially feasible[30].

Learning about the costs and benefits of the different cardiovascular therapies is a vast challenge for the medical community: in the case of patients who undergo pPCI, costs are high initially, but are compensated with a lower amount of days of hospital stay; in the case of patients receiving thrombolytic treatment, costs are higher, as in all cases a subsequent coronary angiography (CAG) will be made, and likely PCI.

CONCLUSIONS

In the public sector of Alto Valle de RN, reperfusion times in STEACS are very prolonged and less patients are treated than expected for the population; thus, the implementation of an early reperfusion project is necessary, focused on improving pre-hospital/in-hospital care for these patients, increasing their treatment and improving reperfusion times by using pre-hospital/in-hospital fibrinolysis and/or pPCI as it may correspond, strengthening a regional care network.

The total cost of the project would amount to US$ 2,422,783.91; the patient cost and cost/day of stay at the beginning of the project would be US$ 10,791.19 and US$ 1640.01, respectively, with an average of 6.58 days of stay and 66 patients treated within the first year of the project. Patient cost and cost/day of stay by the end of it would be US$ 2066.93 and US$ 645.92, respectively, with an average of 3 days of stay and 131 patients treated in the last year of the program.

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Original Investigation Reports

Post-COVID clinical syndrome: how deep is the damage? Preliminary results of a cohort of 2252 cases evaluated in an outpatient center in the city of La Plata, province of Buenos Aires, Argentina

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ABSTRACT

Introduction: the post-COVID-19 condition is a chronic condition that occurs after a SARS-CoV-2 infection, which is present for at least 3 months as a continuous, intermittent or progressive disease, affecting one or more organ systems.

Objectives: The objective of this research was to explore the initial and delayed symptoms after SARS-CoV-2 infection, describe its impact and quantify the residual damage.

Materials and methods: from July 1, 2020 to September 1, 2022, patients who had presented a positive result in a test for COVID-19 or a diagnosis under epidemiological criteria were included in an outpatient care center in the city of La Plata, evaluating risk factors, symptoms of their disease, persistent symptoms and findings in auxiliary cardiovascular, respiratory and neurocognitive tests.

Results: 2252 patients with an average age of 42.21 years (SD: 14.17, range: 17-89) were evaluated. Patients with post-COVID-19 clinical syndrome were 1090 (48.4%), while 1162 (51.6%) had no symptoms. Among the post-COVID-19 symptoms, fatigue, dyspnea and cough were the most frequent, described in 28.2%, 21.8% and 14.4% respectively; while memory failure and concentration failure were reported in 10.2% of the patients questioned. An evaluation of the respiratory, cardiovascular and neurological test performance impact (Montreal Test, PHQ-9 and GAD-7) was also carried out. Patients with persistent symptoms were predominantly female, with an older average age and a higher smoking rate.

Conclusions: no significant differences were observed in the cardiovascular or respiratory aspects between those who presented post-COVID-19 syndrome and those who did not. There was also no worse performance in neurocognitive tests when assessing post-COVID-19 symptoms compared to those who did not suffer from it; although when performing a subgroup analysis adjusted for age, those over 50 years of age showed worse performance.

INTRODUCTION

Long COVID has constituted a public health problem that requires being defined, quantified and described[1,2,3,4]. The post-COVID-19 condition occurs in people with a history of probable or confirmed infection by SARS-CoV-2, generally within 3 months from the onset of COVID-19, with symptoms that last at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, respiratory and cognitive difficulties, but also may refer to an impact in daily performance. Symptoms may appear from the onset or after recovery from an acute episode of COVID-19, or persist from the initial disease. The symptoms may also fluctuate or recur over time[5,6].

Evidence to this moment suggests that long COVID prevalence in low and medium income countries could be similar to richer countries, although numbers vary a lot in both. A recent publication found that between 8% and 41% of people who had an infection by SARS-CoV-2 and had not been admitted presented symptoms[7]. There is scarce research on this condition in less rich countries, and the absence of data also presents obstacles for the efforts to seek the mechanisms of this disease and advance with personalized treatments.

The aim of this research work was to explore the initial and distant symptoms of the SARS-CoV-2 infection, to describe its impact and quantify the residual damage in an ambulatory center in the province of Buenos Aires.

MATERIALS AND METHODS

Since July 1, 2020, to September 1, 2022, patients were included that presented a positive result in the COVID-19 test

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TABLE 1.
Basal characteristics of the sample

	Total 2252	NO post-COVID-19 1162 (48.4%)	WITH post-COVID-19 1090 (51.6%)	p
Age	42.21 (DS: 14.17)	40.6 (14.5)	43.33 (13.83)	<0.001
Sex	M 928 (41.2%)	605 (52.1%)	366 (33.6%)	<0.001
	F 1324 (58.8%)	557 (47.9%)	724 (66.4%)	
HTN	313 (13.9%)	152 (13.1%)	161 14.7%	0.560
Diabetes	85 (3.8%)	38 (3.2%)	47 (4.2%)	0.302
Dyslipidemia	11.5%	11.8%	11.3%	0.803
Asthma	6.6%	6.3%	6.8%	0.780
COPD	1.3%	0.8%	1.7%	0.165
Smoking	15.5%	12.5%	18.7%	<0.001
Former smoking	18.1%	17.4%	18.9%	0.120
Hypothyroidism	12.1%	13.8%	9.8%	0.110
Hyperthyroidism	13.8%	11.9%	15.1%	0.066
Obesity	26.8%	25.4%	28.2%	0.078
Alcoholism	36.5%	35.8%	37.2%	0.140
Vaccination	52.9%	52%	53.8%	0.560

or diagnosis under epidemiological criteria, and had met long COVID criteria, defined as the presence of signs and symptoms that develop during or after an infection compatible with COVID-19 and last for more than 12 weeks, and are not explained by an alternative diagnosis, in the Centro Médico Capital of the city of La Plata, province of Buenos Aires, Argentina, as part of the comprehensive evaluation program for this pathology[8]. It consisted of an interview and a complete clinical history, detection of co-morbidities, vaccination schedule, lab routine (including reactants of the acute phase), electrocardiogram by ECG View resting Ecco-Sur 2017® device, transthoracic 2D Doppler Color Philipps Affiniti 50 echocardiogram, respiratory function MGC Diagnostics 2017 laboratory, and neurocognitive tests (Montreal, PHQ-9, GAD-7) (Annex)[9,10,11]. All patients consented on using their data with the purpose of academic analysis. They were included in a database of the type Microsoft Excel 2021, version 16.57.

The distribution of continuous quantitative variables was analyzed, and presented as mean and standard deviation or as medians depending on their distribution. Categorical variables are expressed in absolute variables or proportions. The comparison of means between groups was made between Student's t-test or Wilcoxon test, as it may correspond. For the categorical variables, the proportions were analyzed by Chi square test or Fisher's exact test, as it corresponded.

RESULTS

The data from 2252 patients, included between July 1, 2020 and September 1, 2022, were analyzed. Male patients: 928 (41.2%) and female: 1324 (58.8%), with an average age of 42.21 years (SD: 14.17, range: 17-89), and a mean time since acute infection of 8.3 weeks. Patients with post-COVID-19 syndrome were 1090 (48.4%); while 1162 (51.6%) did not present symptoms. The following associated risk factors were found: a high presence of alcoholism (36.5%), obesity (26.8%), hypertension (HTN) (13.9%), smoking (15.5%) and being a former smoker (18.1%). As a possible protective factor, the rate of immunizations against SARS-CoV-2 was analyzed, which was 52.9% (1191 patients), vaccinated with at least one dose at the time of evaluation, with no differences between those presenting post-COVID-19 and those who didn't. From these, 209 (9.3%) had received a single dose, 570 (25.3%) two doses, 342 (15.2%) three doses and 72 (3.2%) four doses *(Table 1)*.

In regard to the initial symptoms of acute infection (two weeks before), we should mention that fever was present in 56.7% of cases, headache in 39.5%, anosmia-hyposmia in 30.2% and odynophagia in 32.1% as the most frequent ones, although the symptoms mentioned by patients were very varied, and included manifestations of different clinical fields, such as cough, fatigue, precordial pain, rapid or intense beating, irritability, difficulties to sleep, loss of hair, diarrhea, vomits, abdominal pain, loss or decrease in the sense of taste, loss of memory or concentration *(Table 2)*. In no case there were significant differences observed between those who later present post-COVID-19 and those who didn't. In this sample, only 33 (1.8%) patients required hospital admission during the acute phase of their infection by SARS-CoV-2.

In the case of the post-COVID symptoms fatigue, dyspnea and cough, they were described in 28.2%, 21.8% and 14.4%, respectively, and were the most frequent. On the other hand, loss of memory or concentration were reported in 10.2% of the interviewed patients.

TABLE 2.
Initial post-COVID-10 symptoms

Initial symptoms	Total 2252
Fever	1277 (56.7%)
Headache	890 (39.5%)
Anosmia/hyposmia	680 (30.2%)
Odynophagia	477 (21.2%)
Cough	471 (20.9%)
Fatigue	421 (18.7%)
Precordial pain	77 (3.4%)
Rapid or strong beating	216 (9.6%)
Hair loss	160 (7.1%)
Irritability	135 (6.0%)
Diarrhea	97 (4.3%)
Vomits	50 (2.2%)
Abdominal pain	38 (1.7%)
Trouble sleeping	149 (6.6%)
Loss or decrease of taste sense	331 (14.7%)
Loss of memory or concentration	311 (13.8%)

Finally, an evaluation of the respiratory and cardiovascular impact was made, as well as the performance compromise on neurological tests (Montreal test, PHQ-9 and GAD-7) *(Table 3)*.

It is important to mention that although no differences were observed in neurocognitive tests between both groups, when making an analysis of subgroups, in people older than 50 years, a worse performance was observed in the Montreal test between people with post-COVID-19 syndrome than in those with no post-COVID-19 symptoms: mean 20.5 vs 22.6, respectively ($p<0.01$).

DISCUSSION

Long COVID (defined as occurring 12 weeks after the original infection) is characterized by symptoms lasting several months in individuals who have undergone a severe, moderate or mild form of COVID-19[12,13].

The most commonly described symptoms have been persistent fatigue, difficulties to breath, tachycardia and palpitations, anosmia, muscle weakness, brain fog, headache, vomits and nausea, fever and skin rash[14,15].

Persistence of COVID-19 symptoms has also been reported in several studies. Huang et al, evaluated 1733 patients (nearly half were men) in Wuhan, China, with a mean follow-up of 186 days, where 76% of patients reported at least one persistent symptom, particularly in women, where the most frequently reported were muscle weakness and fatigue (63%), followed by difficulties to sleep (26%) and anxiety or depression (23%)[16].

As highlighted in the consensus document issued by the American College of Cardiology (ACC), in patients with COVID-19 and myocarditis, the most common symptoms were the presence of fever, dyspnea, cough and pain chest[17].

Other symptoms include different types of precordial discomfort, post-strain fatigue, palpitations and syncope. Although symptoms may resolve within the 3 months after the initial diagnosis, sometimes they may persist for more than 12 months.

COVID progression is related to different risk factors such as ageing, asthma, obesity, general state of health before the pandemic and female gender. In fact, young people and/or women present a higher risk of developing long COVID than men, but the level of risk is similar around the sixth decade of life[18]. In this regard, the finding in this cohort coincide and reproduce the same symptoms reported as the most frequent.

Formally, COVID-19 sequelae are usually grouped in "prolonged post-acute COVID-19 pathologies", if observed between the fourth and the twelfth week after the onset or

TABLE 3.
Tests made on the sample

Auxiliary tests	Total 2252	NO post-COVID-19 1162 (48.4%)	WITH post-COVID-19 1090 (51.6%)	p
Adjusted DLCO	24.81	25.08	24.54	0.09
VEF1/CVF	82.03	82.5	81.6	0.16
Abnormal ECG	1137 (50.5%)	578 (49.7%)	559 (51.3%)	0.70
TAPSE (mm)	21	21	21	0.50
PASP (mmHg)	15.6	15.2	16	0.55
LVEF (%)	64	62	65	0.43
GAD-7	5	4	5	0.09
PHQ-9	5	4	5	0.12
Montreal test	22.07	22.58	21.56	0.08

healing of viral infections[19]. The unspecific symptoms could be common with other viral infections, such as mild discomfort, weakness, headache, joint pain; while other specific signs, inherent to a previous disease by SARS-CoV-2, include cough, strain dyspnea, chest pain, dysgeusia and anosmia.

Between the tissues affected by COVID-19 are lung parenchyma. In the initial invasion by COVID-19, the virus binds with ACE2 receptors (angiotensin-converting enzyme 2) in the endothelial cells of the lung, leading to different types of injuries that trigger inflammatory cell recruitment and cytokine release[20]. Chronic inflammation is related to prolonged elevation of this cell strain, among which we may include IL-1β, IL-6 and TNF-α, as well as IL-8 and reactive oxygen species. These pro-inflammatory cytokines entail a profibrotic state in the long run, leading to a tissue environment prone to collagen deposition and structural changes in lung parenchyma[21].

Cardiovascular complications have also been described in patients with long COVID by direct vascular injury, stimulation of adhesion and increase in procoagulants[22,23].

In this regard, transthoracic color 2D Doppler echocardiography has enabled performing a comprehensive evaluation of structural sequelae, with most being unspecific. Patterns have been observed compatible with different degrees of ventricular dysfunction, myocardial infarctions, myocarditis and Takotsubo cardiomyopathy in a minority of patients[24]. The results of echocardiography modified the therapeutic behavior in a third of the cases, including the specific management of the disease, hemodynamic support and level of care received by patients. In this study, an impact was observed on different echocardiographic variables in a scenario of long COVID, particularly in PASP, although with no differences between vaccinated and not vaccinated people.

Within the context of the microcirculatory system, "endotheliitis" usually continues with an extracellular accumulation of "neutrophils" and evolves toward hyperimmune vasculitis of a more complex "leukocytoclastic" type. In mid to large caliber vessels, endothelial dysfunction entails an accelerated progression toward preexisting atherothrombotic plaques through an increase of platelet deposits, circulating inflammatory cells associated to an immune and procoagulant reaction[23]. These conditions may directly cause arterial or venous thromboembolic complications that should be considered at the time of assuming a diagnosis.

Another significant finding observed has been the difference in the performance of neurological tests made between immunized patients and those who weren't. In this study, a better performance was observed for the three tests: Montreal ($p<0.001$), GAD-7 ($p<0.044$) and PHQ-9 ($p<0.021$) in patients who had been vaccinated. These results were observed both in the global sample and in people older than 65 years. One of the possible reasons that could explain this behavior is the protection provided by the different vaccines, preventing a cascade of inflammatory events of COVID-19. The main factors underlying the pathophysiology of brain effects include direct viral infection, hypoxic injury secondary to pulmonary compromise, cytokine storm, microglial alteration and neuroinflammation, hypercoagulability, neural pathway inflammation, post-infection autoimmunity, intestinal microbiota translocation and negative ACE2 regulation, among other conditioning factors[25].

CONCLUSIONS

In this study, the prevalence of long COVID-19 symptoms in an ambulatory care center of the province of Buenos Aires.

Although the population sample is not representative, it has an important size, highlights the heterogeneity of persistent symptoms and a significant functional impact of the disease, which extends over time after the confirmation or suspicion of infection by SARS-CoV-2, with some significant differences between people having been previously vaccinated and those who had not. To study prevalence, the predictors and the prognosis, an investigation is necessary on a population sample using standardized case definitions.

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ANNEX:

Definitions

Montreal Test or Montreal Cognitive Assessment (MoCA):

It is a tool for evaluation designed to detect mild cognitive deterioration. It covers domains such as memory, attention, language, visuospatial abilities and executive function. It is widely used because of its sensitivity to identify subtle cognitive changes, particularly in patients in risk of dementia.

Generalized Anxiety Disorder-7 (GAD-7):

It is a questionnaire of 7 items evaluating the severity of the generalized anxiety disorder. Every item measures symptoms such as an excessive concern or a difficulty to relax, and the total score indicates the severity of symptoms (mild, moderate or severe). It is a simple tool, validated for clinical and research use.

Patient Health Questionnaire-9 (PHQ-9):

It is a self-administered score of 9 items to measure the presence and severity of depression symptoms. It is based on diagnostic criteria of the DSM questionnaire, and it enables an efficient monitoring of symptoms over time, with scores categorized in ranges of severity (minimum to severe).

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Position Statement

Cardiovascular effects of doping substances, medicines and ergogenic supplements in relation to sports

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ABSTRACT

The benefits of physical activity on health are undoubted and indisputable. However, certain sports have been covered by a blanket of suspicion due to the use of ergogenic substances that overshadow and call into question sporting merits and talent. The ease to obtain them and industrial marketing have made this a business of intangible magnitude for the common people. With the aim of improving performance, increasing muscle mass or losing weight, these substances are used, the effects of which are not always proven and can be harmful to health. Elite athletes, amateurs and even more young non-athletes misuse them, due to lack of knowledge, lack of professional support and being easily obtained in the market.

In this review, the effects of the most used substances in sports practice will be summarized, emphasizing the impact at cardiovascular level.

INTRODUCTION

Doping can be defined, according to Law 26,912, as the use of substances or methods to improve sports performance with a potential risk for health[1]. To promote a doping-free activity, WADA (World Antidoping Agency) was created in 1991. With a code established in 2004 and updated in 2021, it includes around 700 sports organizations. WADA updates yearly the lists of prohibited substances[2]. Since 2004, and as there is a gap between the time when athletes start experimenting with new substances and the time where their use is identified, the regulations allow sanctions to be retroactive. Samples are kept for at least 10 years, so that in 2020, the medals obtained in London 2012 were confirmed.

The prevalence of doping in competitive sports ranges between 0% to 73%; most fall below 5%, it affects all levels and more in amateurs who experience less surveillance[3,4,5]. Doping identification demands important expenses, but the real problem is not just revoking a prize, but the health of sportspeople[3]. A retrospective analysis of antidoping rules violations in the samples collected in the Olympic Games between 1968 and 2012 revealed that the positive samples for prohibited substances that were analyzed again, contained exogenous anabolic steroids or their metabolites in 90% *(Figure 1)*[6]. The goal of this positioning is raising awareness and informing cardiologists, physicians and sports enthusiasts on the possible cardiovascular complications associated to a bad use of these substances.

ANABOLIC-ANDROGENIC STEROIDS (AAS)

They are the most used illegal drugs, not just by athletes competing in strength sports, but also in resistance sports, as they accelerate post-exercise recovery, increase strength and more training load is tolerated. Likewise, in the environment of fitness, they are also very popular to obtain fast achievements in physical image[3,7]. Using them with erythropoietin is the most efficient combination, and available to improve results in resistance sports. In fact, it is the most used combination in these disciplines[7,8]. As ethical and legal considerations forbid their administration to sportsmen, even with research purposes, all studies published about them are based on self-reports by athletes themselves, which may yield a certain non-validity margin. Many ath-

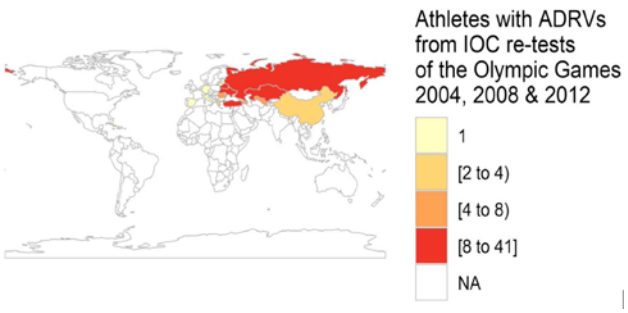

FIGURE 1.
Cases detected subsequently, and that had an impact on the result of medals obtained in the 2004-2008-2012 Olympic Games[6].

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letes would not reveal using them to a physician or discuss it, as the perception is they know very little about the issue[9].

Most studies are small and in elite athletes, who are the main users. Amateurs and non-sportspersons lead statistics, with an image goal. They use a combination of different substances, in such a way that results cannot be attributed solely to AAS. In spite of these limitations, the results from 49 studies in the last 10 years in 1467 athletes show that most attributable disorders include: an early onset of CAD, hypertension, myocardial infarction and arrhythmias, plus other non-cardiovascular effects summarized in *Figure 2*[10].

AAS activate androgen receptors (AR) signaling, causing modifications at nuclear level via DNA, as well as direct effects on other tissues at a distance, AR-dependent or not *(Figure 3).*

These mechanisms, in combination with growth hormone and insulin-like growth factor 1 (IGF-1) stimulation, cause formation of muscle proteins[11]. These effects are promoted by a combination with training, leading to an increase in muscle mass and strength. A bad use and prolonged abuse may lead to adverse cardiovascular effects, some of them severe, such as sudden cardiac death and CAD[11,12]. The samples from autopsies showed that cardiovascular disease is very extensive in these cases. Other series have revealed the same findings: systolic function deterioration, atherosclerotic CAD, pulmonary thromboembolism, coronary and endocavitary thrombi and inflammatory infiltrates. Also, myocyte hypertrophy has been found, as well as focal cell damage, myofibrillar loss and interstitial fibrosis, preferably located in a subepicardial area and damage in small vessels *(Figures 4 and 5)*[13].

It is estimated that mortality between athletes using AAS is from 6 to 20 times greater, and around 30% of deaths may be attributed to cardiovascular causes[10].

There is cardiomyopathy by AAS, confirmed by data from autopsies, echocardiography and cardiac MRI; furthermore, the typical cardiac remodeling of athletes changes into another type of remodeling, of pathological characteristics, that predispose to severe arrhythmias, sharing characteristics with hypertrophic cardiomyopathy[10,14,15]. The complications are related to doses and time of use. The most used AAS in our area are: testosterone (testoviron-sustanon) 250-1000 mg. It is quickly metabolized, but its esterification of the 17-hydroxy group by enanthate or cypionate makes its release to be slower due to its lipophilic base. Its main characteristic is its low cost and that it is easily obtained. Its therapeutic use is hormone replacement at a dose to normalize testosterone level, in an average of 250-500 mg every 3-4 weeks. As doping it should exceed by far this range, reaching doses of at least 250-500 mg per week.

By removing the 19-methyl group of testosterone, 19-nortestosterone (nandrolone) is obtained, with a much greater anabolic effect (deca-durabolin 50-100 mg), also easy to obtain, with a low cost and good results. It is the one most found in anti-doping controls[16].

17β-alkylated anabolic steroids make the testosterone molecule to be resistant to degradation and can be administered orally or by injection. In the case of stanozolol (winstrol) administered orally, it is hepatotoxic, but the most consumed one. It is also the one easiest to get. This drug cannot be aromatized, which means that it is not me-

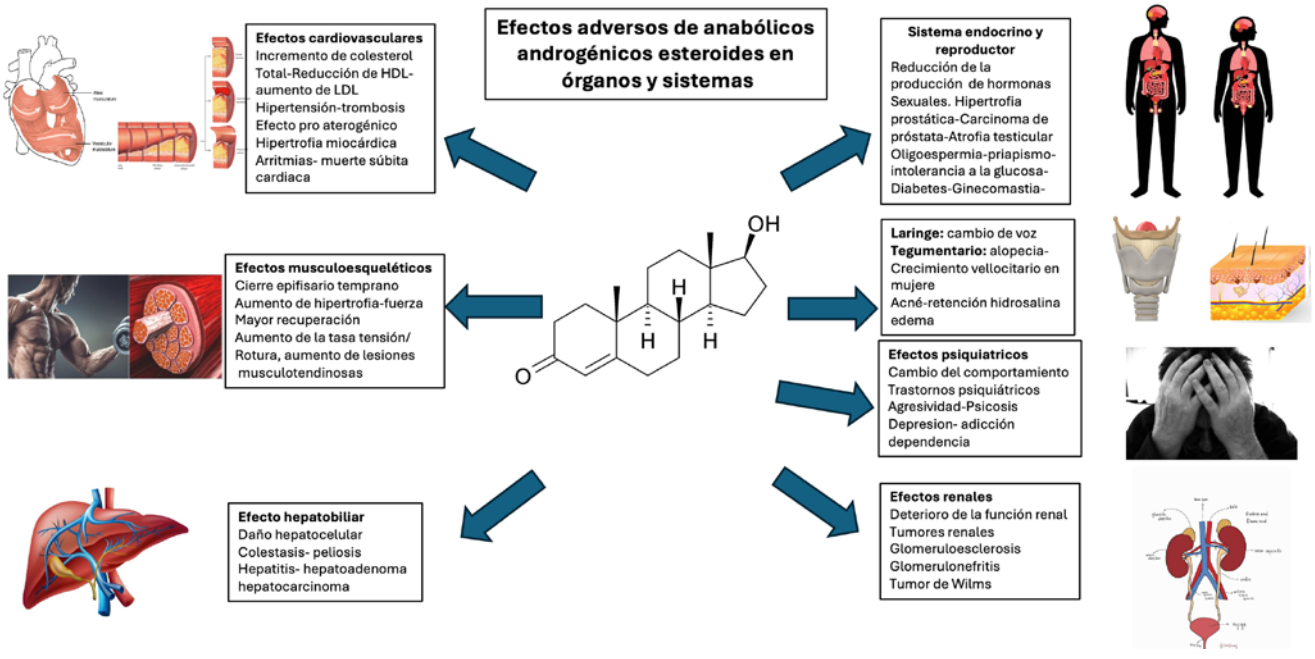

FIGURE 2.
Adverse effects due to AAS may affect numerous organs and systems

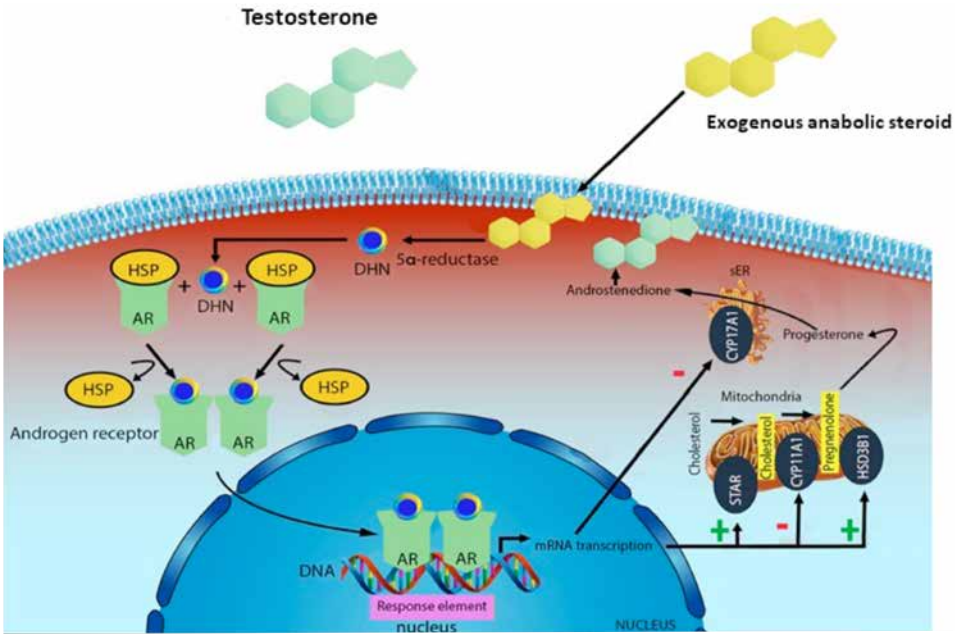

FIGURE 3.
Exogenous anabolic steroids are transported toward the interior of cognate cells, bind to androgen receptors or could be reduced by 5-alpha reductase. The N-receptor complex after structural changes is transported within the nucleus, where it binds with chromosomal DNA nucleotide sequences. The DNA produced interferes with the physiological biosynthesis of testosterone[11].

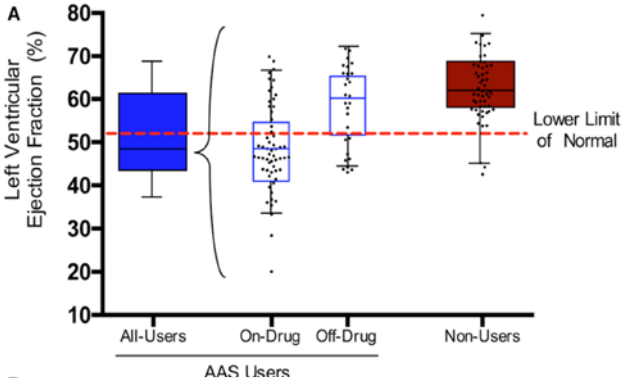

FIGURE 4.
Systolic ventricular function in users vs non-users of AAS

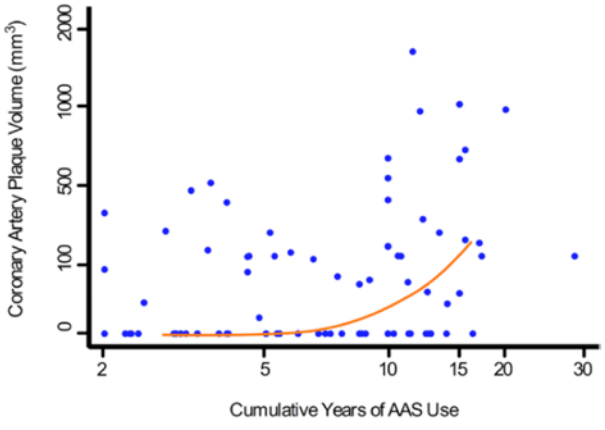

FIGURE 5.
Ratio between plaque volume and exposition to AAS over time

tabolized by aromatase to estrogens. This is a detail not to be overlooked, as most aromatizable AAS generate a high number of estrogens producing gynecomastia, which leads to them being combined with aromatase inhibitors like anastrozole.

HUMAN GROWTH HORMONE (HGH)

Besides the known effects of long bone growth before the closure of their epiphyseal plate, it has metabolic effects that are vitally important in adults. Its deficit should always be investigated, as it causes an increase in fat mass with abdominal obesity, loss of bone mineral density, decrease of muscle strength and aerobic capacity, reduction in physical performance and quality of life. These cases could be reverted by the administration of recombinant HGH. In sportspersons, its use is based on muscle mass increase, loss of fat mass and acceleration of recovery times. Likewise, AAS may generate severe adverse effects. Most studies are a consequence of the follow-up of patients with acromegaly and not by studies on sportspeople. Due to this, conclusions are relative. A higher probability of developing hypertrophic myocardium, increases in myocardial collagen, fibrosis, cell inflammation and necrosis has been described. These alterations predispose to arrhythmias and risk of heart failure[7,10].

NEW DOPING TENDENCIES

Synthetic peptides and AR modulators are modern drugs to improve performance. They trigger stimulation of natural secretion of anabolic hormones or stimulate their receptor. Although there is a greater potential risk than using AAS or other forbidden drugs, they are also used in spite of not having been proven to be safe in humans[17].

Selective androgen receptor modulators (SARM) are a new class of substances designed to stimulate directly the androgen receptor, with anabolic effects similar to AAS, but with very superior power and less androgenic effect. They are considered experimental in humans, with possible side effects, including carcinogenicity and potential cardiovascular problems[18]. The best known are ostarine, andarine and cardarine, which are also obtained on the internet and sports supplements shops as a nonsteroidal product, with no adverse effects. Their administration is by pills.

Just as with modulators, peptides are designed to generate an increase in natural production of AAS and HGH anabolic hormones. These novel products obviously lack information on their results in the long term, and are promoted as natural products, as many of them derive from plants. In this regard, arginine-based formulations have been studied as HG release modulators with favorable results[19].

INSULIN

Insulin plays a key role in the synthesis of muscle proteins, specifically after a session of strength training. Insulin is essential to add amino acids to muscles, as well as minimizing protein degradation during and after exercise. Ingestion of carbohydrates during and after a session stimulates its release, and associated to proteins it prevents muscle degradation and ensures an anabolism that favors muscle recovery and growth[20].

STIMULANTS

Amphetamines and methylphenidate are prescribed for the treatment of attention deficit/hyperactivity disorder (ADHD). They are contraindicated in people with history of arrhythmias, particularly in those who have a genetic basis[21]. They have deep effects on the cardiovascular system, which leads to congestive heart failure, acute myocardial infarction, cardiac chamber dilatation, valve fibrosis, pulmonary hypertension and cerebral infarction[10].

BETA-2 AGONISTS

Salbutamol and clenbuterol are prescribed for the treatment of asthma. Although there are no studies to back its use as performance improvers, in high doses there are reports stating the contrary[22].

Clenbuterol has recently emerged as a useful drug by its effect on beta-3 receptors (lipolytic), as well as by its anabolic effect in elite and recreational sports groups. It is used in bodybuilding to achieve muscle definition. Doses are much higher than therapeutic ones. It is forbidden by WADA.

GLUCOCORTICOIDS

Glucocorticoids are classified as doping substances. It has been suggested that they may increase the availability of metabolic substrates and improve the use of energy sources during resistance exercises. Cardiovascular effects are already known, so we will not go into detail.

INCREASE IN MUSCLE OXYGEN SUPPLY, BLOOD DOPING

In general, it entails autologous blood transfusion, collected previously to increase the mass of red blood cells. This method was used for many years, but as it is impractical, it is no longer in use, besides requiring a certain infrastructure for implementation.

RECOMBINANT HUMAN ERYTHROPOIETIN (RHUEPO)

It causes an increase in red blood cells mass and hemoglobin (Hb) concentration, similar to blood doping, as well as improvement in maximum oxygen consumption. Increase in hematocrit has been proven, such as VO2max after the administration of rHuEPO over 4 weeks in a small cohort of trained cyclists[23]. In practice, it is used in resistance sports such as cycling or running, mainly at competitive level. It is easily obtained and its cost is high, but not unaffordable.

LEGAL ERGOGENIC SUPPLEMENTS

In contrast with the results found with negative effects at health level with AAs, there are many favorable responses for some substances of legal use such as caffeine, creatine and omega-3 fatty acids, ginkgo biloba and amino acids. Some of these effects include more excitation, better memory and cognition, brain protection and depression reduction. Unfortunately, it is difficult to draw definitive conclusions due to small scale studies and possible publication biases[20].

Using legal ergogenic aids is well extended between athletes and sportspeople by pleasure, with statistics ranging between 40 and 100%. These supplements are aimed at improving performance or losing fat mass in many cases.

CAFFEINE

Caffeine per se is efficient to improve aerobic capacity in resistance athletes. Benefits in physical performance are achieved by ingesting from 3 to 6 mg/kg (2 to 4 cups of coffee, 200-400 mg). Secondary effects become more common with doses of more than 9 mg/kg of body mass. Overdose may lead to cardiotoxicity and digestive disorders with significant cardiovascular side effects, such as tachycardia, hypertension and coronary vasoconstriction. It may cause diarrhea, colics and diuresis increase. Stimulus on the hypothalamic-pituitary-adrenal system, similar to intense physical or mental stress, may generate an additional load and cardiovascular complications[20]. It is freely sold in 200 mg pills.

CREATINE (CR)

α-methyl guanidine-acetic acid is an organic nitrogenated acid present in muscles and nervous cells of some living organisms. It can be obtained natural or artificially as a supplement. It is a molecule made up by the amino acids arginine, methionine and glycine. It is synthesized naturally in the liver, pancreas and kidneys. It acts as in-

termediary in energy transference. Phosphocreatine (PCr) delivers high energy phosphate in cytosol to ADP to regenerate ATP. The reaction is catalyzed by cytosolic or mitochondrial creatine phosphokinase (CPK) in a reverse process, where the ATP generated in the mitochondria delivers phosphate to creatine to regenerate PCr, which will come out from the mitochondria into cytosol to regenerate ATP from ADP. This so-called "shuttle" of PCr is a very important process in energy regeneration, as ADP is larger, depending on a saturable transporter in the mitochondrial membrane, with the Cr-PCr dynamic being much faster[24]. Thus, the ATP/ADP levels are maintained (necessary to develop muscle energy). Because of an intense and persistent demand, adenylate kinase will form from two ADP, one ATP and one AMP; the latter will stimulate key enzymes of glycolysis.

The amount of Cr in the body decreases with the advancement of age. In terms of sports use, it has become the most popular non-stimulating legal ergogenic aid since the early 1990s, after the Barcelona Olympic Games of 1992, where the winners of medals in sprint and strength publicly announced that they believed their performance had benefitted from using it.

There are few adverse effects and they are dose-dependent, including weight gain (1.6-2.4 kg), cramps, gastrointestinal discomfort and dehydration. There have been two case reports of transient compromise of renal function by glomerular compromise and nephritis, respectively, and for this reason it should be closely monitored. There are no adverse cardiovascular effects or significant toxicity. However, case reports have associated it with the presentation of deep vein thrombosis, cardiac arrhythmias, chest pain and even sudden cardiac death[25]. The studies were mostly in the short term and on healthy individuals.

CARBOHYDRATES (CHO)

The intensity and duration of exercise justify a proper use of carbohydrate supplements to restore energy, in efforts that last longer than 1 hour. There are no cardiovascular effects, except in excess when combined with caffeine[26].

PROTEINS

One of the most sought goals in sports performance is reaching and maintaining muscle mass. All supplements ingested have this as one of their main goals. Strength exercise provides a stimulus for muscle growth through specific genes. Along with the transcription of these genes in mRNA, there should be other factors to convert this mRNA into skeletal muscle protein. The role of amino acids, insulin, CHO and proteins in the promotion of protein synthesis of the skeletal muscle with exercise is crucial to elucidate the mechanism regulating muscle hypertrophy[20].

Supplementation with high-quality whey protein (20-30 gr, one measure) increases muscle mass and strength during strength exercise training when ingested before, and mainly after exercise within a window period of around 30 min.

No cardiovascular side effects have been reported in sportspeople, so they could be consumed with no problems even in children and the elderly. In some cases, only digestive effects may appear.

ENERGY DRINKS

The World Health Organization has categorized the use of energy drinks as a public health problem. They predominantly contain caffeine in combination with other alleged energy booster ingredients, being particularly consumed by teenagers and young adults[27]. The ingredients are caffeine, guarana, taurine and ginseng. The caffeine content per 250 ml can is around 80 mg. Consuming them excessively may increase blood pressure, produce platelet aggregation and endothelial dysfunction[28]. Moreover, it has been reported that in vitro, taurine acts as a triggering factor to improve hemodynamic results, presenting both a positive inotropic effect and enhanced cardiac muscle contraction, induced by caffeine[29]. The combination with alcohol is common, increasing the risk of complications, mainly arrhythmias such as paroxysmal atrial fibrillation. Depending on the product and amount ingested, the caffeine dose may easily exceed 1000 mg. Energy drinks put people in risk when they have a genetic heart disease. There is evidence that drinking two cans of an energy drink increases the risk of cardiac arrest by 20% in individuals with underlying heart disease, such as patients with long QT syndrome.

GENETIC DOPING

Genetic doping (method forbidden by WADA) includes the use of normal or genetically modified cells, as well as gene transference technologies, gene silencing and gene editing. More than 200 genes are associated to human performance and play a role in muscle development, oxygen supply to tissues, neuromuscular coordination or even pain control[30]. The severe side effects expected for health include lethal immunodeficiency and leukemia. The risks for health may also be caused by gene overexpression, a common issue in gene therapy.

KEY POINTS FOR ATHLETES

A natural supplement is not necessarily a safe supplement. Supplements should be used if necessary for known deficiencies and prescribed by specialists, and products should be from manufacturers with a good quality standard. Athletes are personally responsible for any substance they consume. Ignorance is not accepted as an excuse for a positive doping test. Athletes with established heart diseases should be paying even more attention and consulting with their physicians before using any supplement or ergogenic aid.

Doping in the search for success is a multidimensional issue, and the fight against an arbitrary use in professional and recreational sports practice should involve all the interested parties of the system: athletes, clubs, scientists, the audience, sponsors, the media, family and official authorities.

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Letter

Antiplatelet treatment in patients with dengue and coronary artery disease: clinical considerations and risks

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ABSTRACT

Dengue infection has increased in recent years and is currently a public health problem. Although the majority of those infected usually present asymptomatically or mildly, those who develop severe forms present potentially fatal complications, such as thrombotic and/or hemorrhagic events. That is why, in patients treated with antiplatelet agents, special caution must be taken. This is of special interest given the magnitude of the prevalence of coronary heart disease. Currently, there are no local guidelines for the management of antiplatelet therapy in these patients, however, certain factors must be considered when evaluating each patient: indication for antiplatelet treatment (primary versus secondary prevention), previous revascularization (recent or long-standing), and signs of bleeding and platelet count. A management algorithm is proposed according to these variables.

Dengue has considerably increased in recent decades, turning into a public health problem in recent years. Between 75-80% of cases usually course asymptomatically, and the remaining 20-25% present a fever phase. From the latter, only 0.1-5% manifest a severe form[1]. According to the current epidemiology bulletin of the Ministry of Health of the Nation, in the current season (2024-2025), there have been 162 confirmed cases to date, from whom 153 did not present history of travelling (autochthonous)[2].

The management of hematological alterations constitute a challenge from the medical point of view, mainly if patients are under antiplatelet and/or anticoagulant therapy, due to the risk of bleeding. The severe forms of dengue are characterized by hemostasis alterations and vascular dysfunction, originating two main complications: hemorrhagic or thrombotic phenomena[3,4]. Within hemorrhagic complications, there are skin symptoms such as petechiae, ecchymosis, spontaneous bruising, mucosal bleeding (epistaxis, gingival, gastrointestinal, vaginal bleeding and others), as well as potentially fatal internal bleeding[5].

The excessive activation of coagulation may lead to diverse thrombotic events: disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolisms, infarctions (AMI) and ischemic strokes. Between the described pathophysiological mechanisms, the following stand out: structural and functional dysfunction of the vascular endothelium, oxidative stress and systemic inflammation, immunological phenomena, protein depletion and coagulation factors, platelet decrease and function alteration, as well as fibrinolysis inhibition. Endothelial injury results in increase of capillary permeability, tissue edema and serous effusion. Cytokine storm promotes intravascular coagulation with factor consumption. All of this entails a delicate balance between bleeding and thrombosis[6,7]. Dengue induces both vasculopathy and coagulopathy, interfering with coagulation and fibrinolysis. The activation of both systems is more emphatic in cases of dengue hemorrhagic fever and dengue shock syndrome, in comparison to the classical forms[8,9].

The management of patients who under antiplatelet treatment, both aspirin and P2Y12 (P2Y12) receptor inhibitors or their combination (DAPT) is delicate. This situation presents challenges and situations that should be considered[10]:

1- Temporary antiplatelet suspension: although it constitutes a systematic recommendation, mainly during the first week to prevent the possibility of developing Reye's syndrome, the time relationship of the patient in regard to the event that caused the onset of treatment should be thoroughly evaluated (e.g.: acute coronary syndrome [ACS] or revascularization).
2- Risk evaluation: as mentioned above, the patient should be stratified in terms of thrombotic risk. Patients who have undergone coronary revascularization with stent (TCA) recently are under a greater risk of complications if DAPT is suspended. The most vulnerable time will

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FIGURE 1
Outline of antiplatelet therapy management in patients with dengue
DAPT: dual antiplatelet therapy; **PLT:** platelet count.

be between 1 and 3 months after TCA, depending also on other factors like the type of stent implanted (pharmacological or conventional, number of stents, length, location, among others) and the reason that led to revascularization (stable or in ACS).

3- Close monitoring: constant monitoring of platelet count (PLT) and signs of bleeding. If there are signs of bleeding, measures for immediate support should be taken.
4- Restart of antiplatelet therapy: if it was suspended, they can be restarted after the critical phase of dengue (after 5-7 days of fever) and when the platelet levels have returned to a safe range level.

Although there is no formula to estimate bleeding risk versus thrombotic risk in patients in high risk that simultaneously course with thrombocytopenia, the following management guidelines are proposed *(Figure 1)*:

- Both anticoagulation and antiplatelet therapies could be maintained while PLT is >50,000/mm3. Below this value, in-hospital management is advised, with daily evaluation of PLT and coagulation tests, weighing thrombotic risk vs bleeding risk in every case.
- In patients with combined antithrombotic therapy (anticoagulation and antiplatelet therapy), in general, suspension should be considered with PLT <50,000/mm3.
- In patients in high thrombotic risk who have undergone recent TCA (one month for conventional stent and 3-6 months for pharmacological stent), in treatment with DAPT, it is suggested to maintain the management with PLT >50,000/mm3 *(Table 1)*. In the case of presenting levels between 30,000 and 50,000/mm3, DAPT could be maintained with the patient admitted and suspend it in case of reaching PLT levels <30,000/mm3. In the case of bleeding or shock, always suspend DAPT and consider platelet transfusion.
- Patients with recent TCA but in whom the period of highest risk has already passed (more than one month with conventional stent and more than 6 months for pharmacological stent), it is advised to maintain DAPT while PLT >30,000/mm3.
- In stable individuals who are in secondary prevention treatment due to previous ischemic vascular event (in general with aspirin), antiplatelet therapy should be suspended for 7 days with PLT values <50,000/mm3, to restart it once such levels are recovered.
- A multidisciplinary approach is suggested (cardiology, internal medicine, infectious diseases, hematology and hemotherapy) for the management of complex cases.

It is important to highlight that each case should be analyzed individually, particularly in patients in high thrombotic risk. It is important for this management to be made under medical supervision, as both infection by dengue and suspension of DAPT may present significant risks for patients.

TABLE 1.
Risk stratification

HIGH RISK	LOW RISK
• Recent ACS - Within the first 6 months	• Chronic coronary syndrome
• Recent TCA - One month in the case of BMS - Three months in the case of DES	• Non-revascularized patients • Antiplatelet therapy with CV prevention

ACS: acute coronary syndrome; **TCA:** transluminal coronary angioplasty; **BMS:** bare metal stent; **DES:** drug-eluting stent; **CV:** cardiovascular.

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Clinical Case

Coronary artery perforation, an unusual complication during percutaneous coronary intervention. Cases report

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ABSTRACT

Coronary artery perforation (CAP) during percutaneous intervention is a rare but serious complication due to the risk of cardiac tamponade. It can be visible immediately (perforation secondary to balloon inflation, stent implantation or the creation of a false channel), but it can also manifest secondarily in hemodynamic deterioration during the course of angioplasty (distal perforation by the angioplasty guidewire). The Ellis classification categorizes the types of perforations, and according to it, it enables the management and resolution of the complication. Type III perforation is associated with the treatment of complex injuries. We report 3 cases in our series that presented coronary perforation, one due to stent expansion during optimization of its implantation in the main vessel, and two cases due to distal perforation by the coronary guidewire. The three cases were resolved in the ward using different techniques. One CAP was resolved by embolization with Spongostan, another CAP was controlled by releasing a coil and the third CAP was solved with the implantation of two covered stents. Only one of the patients required pericardiocentesis due to cardiac tamponade. It is essential to bear predictive factors for CAP in mind, make early diagnoses and resolve using therapeutic options according to the type of perforation. .

INTRODUCTION

Coronary artery perforation (CAP) is a rare complication, but with high morbimortality, which may present over an ongoing percutaneous coronary intervention. According to bibliographic reports, its incidence is 0.2% to 0.8% of coronary interventions.

PAC could be caused by angioplasty guidewires, inflation of coronary balloons at high pressure, stent implantations and use of atherectomy techniques[1,2,3].

Diagnosis is generally immediate, with extravasation of contrast medium being observed during the procedure[4,5].

Signs and symptoms range from chest pain, vertigo, nausea, vomits, tachycardia, blood pressure drop to an increase in central venous pressure as cardiac tamponade develops. Bradycardia of vagal origin may also occur. ST-segment modifications in ECG may appear because of vessel occlusion at the level of the perforation or distal to it[6].

Tamponade occurs in average in 20% of cases of CAP, and in general immediately after CAP. However, this complication of CAP may appear in a subacute manner, within hours after the intervention, mainly in cases of distal perforation by angioplasty guide wire[7,8].

Between the predicting factors we find: 1) clinical variables (advanced age, female gender, kidney failure); 2) angiographic variables (calcification and tortuosity of coronary arteries, C-type lesions, total chronic occlusion); and 3) variables related to the technique (use of hydrophilic guidewires, atherectomy devices, optimization of the result of angioplasty by intracoronary echography, after stent dilatation at high pressures)[9,10].

There is unanimity in that when faced with a CAP, the first thing to do is inflating a coronary balloon proximal or at the level of the perforation, with the aim of sealing the leak, and performing pericardiocentesis in the case of cardiac tamponade. IV protamine could be administered to offset unfractionated heparin. Conservative management could be chosen if, with the previously explained measures, the problem is solved; on the contrary, patients may require the implementation of other alternatives that may include using conventional or covered stents (particularly with PTFE), and embolization with different materials: metal coils, thrombin, polyvinyl alcohol particles, or even embolization by coagulated blood or subcutaneous fat from patients themselves[11,12,13,14,15].

PRESENTATION OF CASES

During the period from January 1, 2019 to June 30, 2024, there were 917 percutaneous coronary interventions made. Three patients (0.32%) presented coronary artery perforation as a complication during the procedure.

Case 1: female, 90-year-old patient. She is hypertensive, dyslipidemic, with history of coronary angioplasty to the

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anterior descending artery and carotid artery angioplasty (right internal carotid artery), peripheral vascular disease of inferior limbs. As she presented unstable chest angina, coronary angiography (CAG) was conducted, showing severely calcified lesions in tandem, in the third mid-proximal section of the right coronary artery (RCA).

Angioplasty was carried in the RCA, facilitated by intravascular lithotripsy (IVL) and intravascular ultrasound (IVUS), with implant of two pharmacological coronary stents (3.0 x 28 and 3.0 x 24 mm of length).

After implant of the second stent, extravasation of contrast medium was observed in the distal segment of the artery (posterior descending branch) due to laceration of the artery by hydrophilic guidewire of 0.014".

The patient evolved with symptoms of sustained hypotension and bradycardia. Immediately, balloon 2.5 was inflated at low pressure for a few minutes in distal segment of right coronary artery. Significant pericardial effusion was verified by cardiac Doppler ultrasound. Emergency pericardial puncture was made, as well as placement of transient pacemaker by femoral access. Subsequently, a microcatheter was pushed to the posterior descending branch, and Spongostan was released, achieving contrast medium extravasation containment. She evolved satisfactorily, and after 7 days she was discharged *(Figure 1).*

Case 2: male, 56-year-old patient. He is hypertensive, dyslipidemic. Functional class II chronic stable angina. Spect+ antero-apical ischemia. CAG showed 90% lesion in bifurcation of RCA with diagonal branch (Dg). Severe 80% proximal lesion in Cx artery. Angioplasty was made with 2-stent technique (3.5 x 16 mm and 2.5 x 12 mm) and finally kissing balloon to RCA-Dg guided by IVUS. In final angiographic control, contrast medium extravasation was observed in distal diagonal branch. Balloon of 1.5 mm was inflated in a prolonged manner. Next, a microcatheter was pushed and then embolization was carried out, releasing 2.0 x 3 cm coil successfully. Angiographic and cardiac Doppler echocardiography was conducted, with mild pericardial effusion. He was discharged in 48 hours *(Figure 2).*

Case 3: female, 72-year-old patient. She was hypertensive, dyslipidemic, type II diabetic. History of VVI pacemaker implant because of complete heart block. In a scenario of non-ST-segment elevation acute coronary syndrome, severe 95% lesion was observed in RCA-Dg. Percutaneous coronary intervention was made on the RCA-Dg. Pre-dilatation with 3.0 noncompliant balloon in RCA. After the pre-dilatation, contrast medium extravasation was observed with hemodynamic compensation. Graft Master covered stent of 3.0 x 18 mm was implanted urgently. In angiographic control, there was still mild ex-

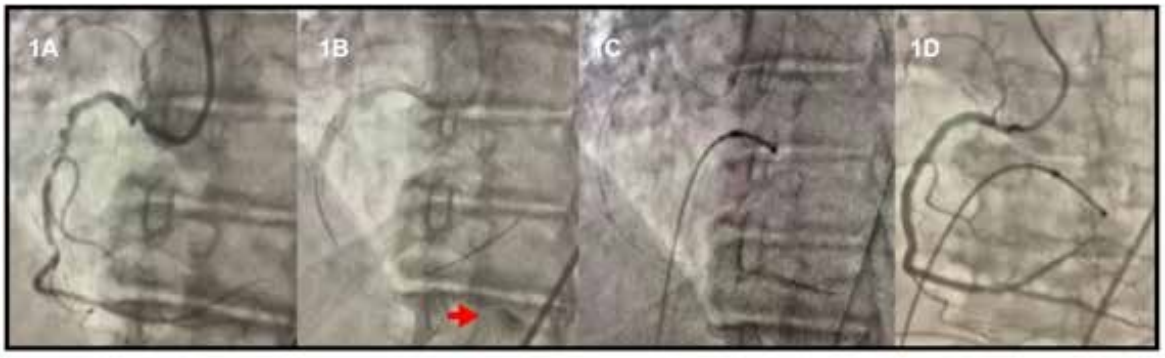

FIGURE 1
A) Severely calcified lesions in proximal-mid third of the right coronary artery; B) dilatation with balloon (lithotripsy) and stents implant. Perforation at distal level (posterior descending branch); C) embolization with Spongostan; D) final result.

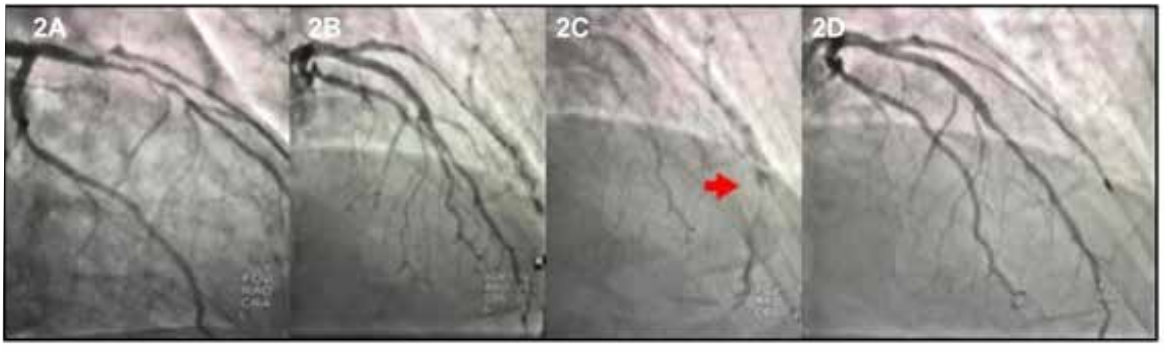

FIGURE 2
A) Severe lesions in bifurcation (RCA-Dg); B) angioplasty with 2 stents; C) perforation of distal diagonal branch; D) embolization with coil.

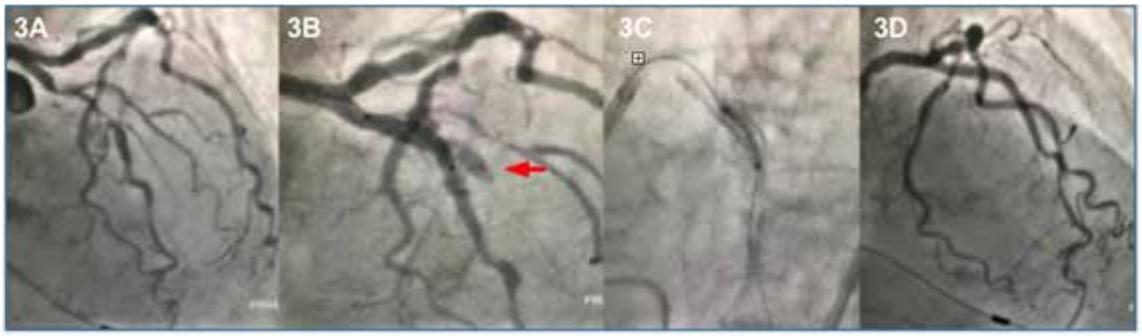

FIGURE 3
A) Severe lesions in RCA; B) extensive contrast medium extravasation in RCA; C) covered stents implant; D) final result.

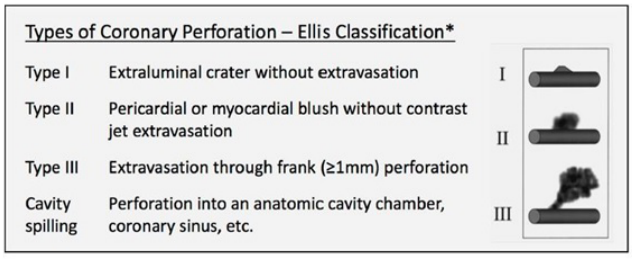

FIGURE 4
Ellis classification. Outline of different types of coronary artery perforation.

travasation in a distal direction, so a second Papirus® covered stent of 2.5 x 20 mm was implanted overlapping the other one. The patient evolved favorably with discharge in 72 hours *(Figure 3)*.

DISCUSSION

According to the experience of our group, CAP related to PCI was a rare complication.

Percutaneous procedures approach increasingly complex scenarios, with extensively calcified lesions, which has also entailed a higher incidence of this type of complications.

The diagnosis of CAP is angiographic. According to Ellis, cardiac perforations are classified into 4 types. Type I: extraluminal crater with no extravasation; type II: blush in the pericardium or myocardium with no jet extravasation; type III: extravasation through >1 mm perforation with jet extravasation, and cavity spilling (CS) type when extravasation heads toward an anatomical chamber *(Figure 4)*[16].

Its treatment depends on the type of perforation, location, vessel diameter and mechanism of it.

Most often it occurs during optimization of angioplasty in proximal perforations, which are most frequent than distal ones, which are related to the use of aggressive guidewires.

This is an absolute urgency that may complicate quickly with tamponade and death, hence the significance of being equipped with a pericardial drainage kit.

Initially, hemodynamic support should be provided.

Heparin is always antagonized after pericardial drainage.

The first impulse is hemostasis by balloon inflation while preparing an appropriate hemostatic treatment. Type I perforations are generally solved with prolonged balloon inflation (the balloon should be inflated at a lower pressure that would achieve hemostasis, being verified by contrast medium injection regularly for 5 to 10 minutes).

When perforation occurs in the main vessels of a good diameter (>2.5 mm), using polytetrafluoroethylene (PTFE) covered stents may solve the problem. Covered stents have significantly reduced the rate of tamponade, the need for emergency surgery and mortality associated to this complication. These stents provide hemostasis in approximately 85% of type III perforations of Ellis. Within its limitations we may find a difficult navigability in the presence of tortuous and/or calcified arteries, and the possibility of occlusion of secondary branches after implant[17].

When the perforation occurs in small vessels and/or distal segments, embolization with thrombin, coils, fat clots or particles may lead to a satisfactory outcome[18].

CONCLUSIONS

Coronary perforation is a rare complication, but potentially deadly, with a high rate of morbidity and mortality if not identified and treated immediately. An early diagnosis and fast treatment are key to obtain successful results.

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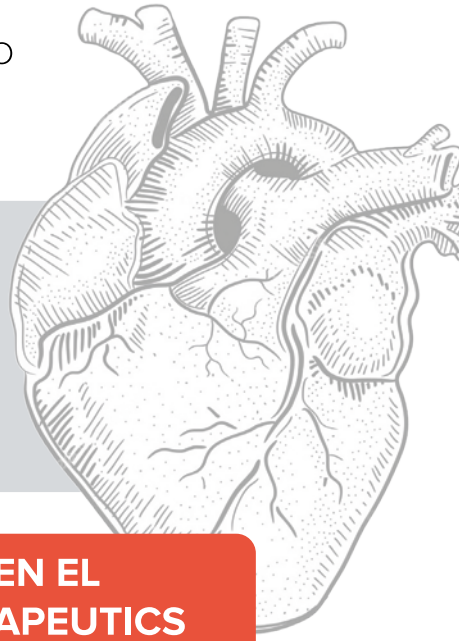

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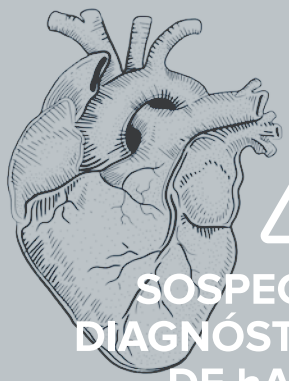

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