ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 90 N° 3 JUNE 2022
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar
web site: www.sac.org.ar / http://ppct.caicyt.gov.ar/index.php/rac
Editorial and graphic production
CF Brand Design & Communication- e-mail: estanislao@cfdisenografico.com.ar / www.cfdisenografico.com.ar
Printing: Pymedia - Gandolfo 1106, Victoria, San Fernando - www.pymedia.com.ar
This paper meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper)

VOL 90 Nº 3
JUNE 2022

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EDITORIAL

From Guidelines to Real World: Knowledge as a Solution to Implement the Evidence

De las guías al mundo real: el conocimiento como solución para implementar la evidencia

CLARA INÉS SALDARRIAGA GIRALDO

The last decade has been, perhaps, one of the most exciting times, considering how heart failure treatment has evolved: we have witnessed the introduction of new drugs that change the clinical course of the disease, and re-evaluated old concepts of multi-step, long-duration schemes for initiating drug therapy, up to the emergence of the concept of foundational drugs for heart failure or quadruple therapy. (1) However, while guidelines are rapidly updated and concepts change, the implementation of this knowledge in the real world seems to move at slow pace. This gap between guidelines and the real world has been demonstrated in registries such as the CHAMP-HF (2) and the European Society of Cardiology Heart Failure Long-Term Registry (3) which found suboptimal use of heart failure therapies.

Identifying the usual clinical practice and the existing gaps in the disease approach is a very valuable solution, because it leads us to the daily healthcare practice setting and allows us to find practical solutions to the problem of implementing therapies; and this is the perfect niche to develop educational strategies to address the problem.

In this sense, the article Attitudes and Clinical Practice in Heart Failure Among Physicians in Argentina, by Burgos et al., is a novel approach that lets us take a new look at an old problem. This study presents a survey conducted on a group of healthcare professionals, mostly cardiologists in Argentina, about their usual practice in managing heart failure patients. This survey presents several highly relevant results: only a quarter of the surveyed population initiates treatment with quadruple therapy and 50% does not achieve the goal of treating their patients with this combination of drugs. Forty-four percent feel uncertain about the diagnosis of heart failure with preserved ejection fraction and only 46% considered relevant to identify and treat anemia and iron deficiency. (4) This information is novel because there are no previous reports on the usual practices of Latin American cardiologists in the

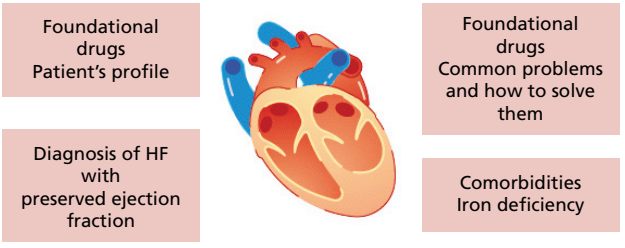

Fig. 1. Opportunities in education in heart failure according to Burgos et al. findings

management of heart failure and coincides with the results reported by authors from other regions worldwide, as Erhardt et al., (5) who found that although most cardiologists surveyed in 7 European countries knew the guidelines, less than 25% of them followed their recommendations. In turn, the CORE initiative investigated the clinical practice patterns among physicians in Australia and several European countries and found low recognition of the signs and symptoms of the disease, limited use of diagnostic tests, underuse of recommended agents and sub-therapeutic dosing. (6)

In this sense, the study by Burgos et al. is a starting point for improving the implementation of heart failure guidelines, pointing out 4 key aspects on which we should focus our educational strategies for physicians: 1) identify the clinical profiles of heart failure patients for foundational drugs and their importance; 2) the most common problems that can occur when starting medications, and how to solve them; 3) how to diagnose heart failure with preserved ejection fraction; and 4) the importance of comorbidities in heart failure, in particular iron deficiency. It would also be very interesting to approach the reality of other specialties involved in heart failure treatment in Argentina and other countries of the region, as a second step towards the lessons that this work has generated, and thus conclude that knowledge and education can be

Rev Argent Cardiol 2022;90:163-164. http://dx.doi.org/10.7775/rac.v90.i3.20531

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:193-205. http://dx.doi.org/10.7775/rac.v90.i3.20522

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the answer to how we can move forward from guidelines to their implementation in the real world.

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EDITORIAL

Bilateral internal thoracic artery grafts in left main coronary artery disease

Doble puente mamario en la revascularización de tronco de coronaria izquierda

MANUEL ROQUE CERVETTI[1], SIAMAK MOHAMMADI[1]

"Our surgical technique should be adapted to the patient and not the patient to our technique"

Bilateral internal mammary artery (BIMA) grafting remains as a niche, rather than a routine. Observational studies have demonstrated the benefits of BIMA, however randomized trial did not corroborate these advantages (1). For the BIMA enthusiasts, the Arterial Revascularization Trial (ART) was a huge disappointment (2). Will ROMA trial change the history?

Dr. Navia and colleagues compare whether CABG without extracorporeal circulation using both mammary arteries has an additional benefit to conventional revascularization using only one mammary (SIMA) in terms of long-term survival for left main coronary artery disease. This is a risk adjusted retrospective observational study (n = 723), in which SIMA was used in 144 patients and BIMA in 579. Survival at 10 years was significantly higher in unadjusted group of patients with BIMA compared to SIMA surgical strategy (79.0% ± 3.4% vs 67.0% ± 4.9%, respectively, p log-rank <0.01). This benefit was also seen in the risk-adjusted analysis (93.0% ± 4.6 vs 69.0% ± 5.7 respectively, p = 0.03). The use of BIMA was an independent predictor of 10-year survival (HR 0.57, IC 95%: 0.37-0.87; p = 0.01).

The authors at the Cardiovascular Institute of Buenos Aires should be congratulated on their continuous efforts to use BIMA off-pump bypass strategy for majority for their patients needing CABG surgery. It is not necessary to emphasize that this factor is a crucial element in order to obtain an excellent clinical result. However, the additional better outcomes in any surgical approach depend strictly to the patient's selection. In the present study, the usual risk factors for CABG surgery which negatively affect the long-term outcomes are less frequent among BIMA patients compared to the general CABG patient's population. Only 15% of patients were female, 25.2% were diabetic, 2,8% had COPD, 18,7% had low ejection fraction (EF, <45%), and 5,6% had kidney failure. The mean body mass index among BIMA patients was approximately 27. Another aspect to take in consideration is that from 3,757 patients, only 20% fulfilled with inclusion criteria and from this 20%, 80% were treated with BIMA technique, and the remaining 20% with SIMA technique. So, it is very clear that there was a high selection process. Therefore, BIMA strategy is an excellent choice in well selected low risk patients who have a very high life expectancy. In our hospital, at Quebec Heart and Lung Institute, Mohammadi et al. demonstrated that the use of a second internal Mammary artery does not prolong late survival in patients with low EF undergoing CABG, despite a similar operative mortality between matched BIMA and SIMA groups (n = 2, 1.8% vs n = 1, 0.9%, respectively, P = 0.6) (3). Farkash et al. also shown that there were not short or long-term benefit derived by the use of BIMA grafting for myocardial revascularization in patients with low LVEF (4). In adittion, Mohammadi et al. found that insulin-dependent diabetes mellitus, chronic renal failure, peripheral vascular disease, and low ejection fraction were all independent risk factors for late cardiac death (all P<0.0001) among patients undergoing CABG (5). These factors are significantly higher among SIMA patients and despite all statistical adjustment methods play an important negative role on the long-term survival.

Finally, we should mention the RAPCO trials (Radial Artery Patency and Clinical Outcomes) where the long-term patency of the radial artery (RA), the right internal mammary artery (RIMA) and the saphenous vein (SV) were analyzed as a second conduit. The estimated 10-year patency and late survival rate were significantly higher among RA compared to the free RITA and the SV grafts (6). It seems that RA could be potentially an excellent arterial graft option in patient at higher risk of sternal wound complications.

In conclusion, there is little doubt that with multiple artery revascularization, we provide one of the best surgical quality in terms of conduits. However, to claim

Rev Argent Cardiol 2022;90:165-166. http://dx.doi.org/10.7775/rac.v90.i3.20532

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:173-178. http://dx.doi.org/10.7775/rac.v90.i3.20517

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that conduit is the only important prognostic factor is to deny the incredibly nuanced complexity of contemporary coronary surgery, which depends on many different factors including degree of coronary stenosis, size and quality of target vessel and distal run-off and not only on the type of conduits used. Thus, it would be judicious to analyze on a case-by-case basis for the sake of better early and late clinical outcomes. Patients' comorbidities, coronary arteries quality, age, sex, weight should be taking in consideration at the moment of selecting our CABG graft strategy.

We would like to encourage and congratulate Dr. Navia and his team for the tireless effort in the myocardial revascularization surgery improvement.

Conflict of interest

None declared.

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

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ORIGINAL ARTICLE

Evaluation of the Orbit Bleeding Risk Score as Predictor of Major Bleeding in Patients with Acute Coronary Syndrome

Evaluación del Orbit Bleeding Risk Score como predictor de sangrado mayor en pacientes con síndrome coronario agudo

DANIEL A. CHIRINO NAVARTA[1,2, MTSAC], SEBASTIÁN PINEL[1], FEDERICO L. VITALE[1], JULIETA S. IGLESIAS[2], MARIELA LEONARDI[1,2], FRANCISCO E. TELLECHEA[2, MTSAC], GUSTAVO J. CALDERÓN[1, MTSAC], CLAUDIO DIZEO[1,2, MTSAC]

ABSTRACT

Background: Major bleeding is the most important complication of antithrombotic treatment in acute coronary syndrome (ACS) and is associated with higher mortality. Assessing the risk of bleeding is a challenge. The usefulness of the Orbit Bleeding Score (ORBIT) to assess the risk of bleeding in ACS has been scarcely studied.
Objective: The aim of this study was to evaluate the ORBIT score as a predictor of major bleeding in patients hospitalized for ACS in whom anticoagulation is decided as part of the antithrombotic strategy.
Methods: Patients admitted to two coronary care units with diagnosis of ACS who received anticoagulation as part of the antithrombotic therapy were retrospectively included in the study. The CRUSADE, ACTION-GWTG and ORBIT scores were calculated using the admission clinical data. The primary endpoint was major bleeding, defined as BARC 3 or 5 classification.
Results: The study included 762 patients. Major bleeding occurred in 3.4% of cases. In the univariate analysis, the three scores were predictors of major bleeding, while in the multivariate analysis only the ORBIT score was an independent predictor of major bleeding (OR: 2.46, 95% CI 1.61-3.97, p <0.001). The area under the ROC curve was 0.70, 0.68 and 0.80 for the ACTION-GWTG, CRUSADE and ORBIT scores, respectively. The ORBIT score presented a higher area under the curve than the CRUSADE score (p=0.03) but without significant difference with the ACTION-GWTG score (p=0.06)
Conclusions: The ORBIT score was the only independent predictor of major bleeding, presenting a better discrimination capacity than the CRUSADE score and a tendency to better capacity than the ACTION-GWTG score.

Key words: Acute Coronary Syndrome - Risk Assessment - Hemorrhage

RESUMEN

Introducción: El sangrado mayor es la complicación más importante del tratamiento antitrombótico en el síndrome coronario agudo (SCA), y se asocia a mayor mortalidad. Evaluar el riesgo de sangrado es un desafío. La utilidad del *Orbit Bleeding score* (ORBIT) para evaluar el riesgo de sangrado en SCA ha sido poco estudiada.
Objetivo: Evaluar al ORBIT como predictor de sangrado mayor en pacientes internados por SCA en los que se decide la anticoagulación como parte de la estrategia antitrombótica.
Materiales y métodos: Se incluyeron en forma retrospectiva pacientes internados en dos unidades coronarias con diagnóstico de SCA que recibieron anticoagulación como parte de la terapia antitrombótica. A todos se les calcularon los *scores* CRUSADE, ACTION-GWTG y ORBIT con los datos clínicos del ingreso. Se analizo el punto primario de sangrado mayor, definido como una clasificación de BARC 3 o 5.
Resultados: Se incluyeron 762 pacientes. El sangrado mayor se presentó en el 3.4%. En el análisis univariado los tres *scores* fueron predictores de sangrado mayor, mientras que en el multivariado sólo el ORBIT fue predictor independiente de sangrado mayor, con OR 2,46, IC95% 1,61-3,97, p<0,001. El área bajo la curva ROC fue de 0,70, 0,68 y 0,80 para los *scores* ACTION-GWTG, CRUSADE y ORBIT, respectivamente. El ORBIT presento una mayor área bajo la curva que el CRUSADE (p=0,03) sin diferencia significativa con el ACTION-GWTG (p=0,06)
Conclusiones: El ORBIT fue el único predictor independiente de sangrado mayor, con una mejor capacidad de discriminación que el CRUSADE, y tendencia a mejor capacidad que el ACTION-GWTG.

Palabras clave: Síndrome coronario agudo - Hemorragia - Medición de Riesgo

Rev Argent Cardiol 2022;90:167-172. http://dx.doi.org/10.7775/rac.v90.i3.20521

Received: 02/10/2022 – *Accepted:* 04/27/2022

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Sources of Support and Funding: None.

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INTRODUCTION

Antithrombotic treatment is imperative in acute coronary syndromes (ACS), regardless of invasive management. Antiplatelet and anticoagulation therapies are a fundamental part of ACS management and their implementation has been shown to reduce morbidity and mortality in coronary heart disease. (1,2) Bleeding is the most important complication of this treatment, both due to its frequency and its clinical implications. Major bleeding is associated with an increased risk of mortality and other adverse events. (3,4) For this reason, different risk scores have been developed to predict major bleeding in patients with ACS. One of the most used scores is the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) (5), developed to predict bleeding in patients with non-ST-segment elevation ACS (NSTEACS). The Acute Coronary Treatment and Intervention Outcomes Network Registry-Get with the Guidelines (ACTION-GWTG) is another risk model developed from a cohort of patients with ACS with and without ST-segment elevation. (6) These scores have moderate predictive capacity and relative calculation complexity.

On the other hand, risk models initially developed to predict bleeding in patients with atrial fibrillation (AF) have also been evaluated in the context of ACS. HAS-BLED is the most widely used bleeding score in AF and has also been evaluated in ACS, where it has a similar predictive capacity as the CRUSADE score, with the advantage of being easier to calculate. (7, 8) The Outcomes Registry for Better Informed Treatment Bleeding risk score (ORBIT) is also a simple risk model developed to predict bleeding in patients with AF. (9) Recently, the National Institute of Health and Care Excellence (NICE) guidelines recommend this model to assess the risk of bleeding in AF due to its greater predictive capacity. (10) The usefulness of this risk model in ACS has been scarcely studied.

The objective of the present study was to evaluate the ORBIT score as a predictor of major bleeding in patients hospitalized for ACS in whom anticoagulation is decided as part of the antithrombotic strategy.

METHODS

An observational, retrospective study was carried out in two coronary care units in Buenos Aires, Argentina, including patients with a diagnosis of ACS hospitalized between January 2015 and January 2021. The inclusion criteria were as follows: patients with a diagnosis of NSTEACS, with use of anticoagulation as an antithrombotic strategy on admission (with low molecular weight heparin, sodium heparin or fondaparinux) and antiplatelet therapy with aspirin and/or P2Y12 receptor inhibitors. Patients who did not receive anticoagulation as antithrombotic treatment and those with insufficient data to calculate risk scores were excluded from the study

Medical histories were reviewed and background information, clinical admission data of interest to calculate scores and in-hospital evolution were collected.

Risk score calculation

The CRUSADE, (5) ACTION-GWTG (6) and ORBIT (9) risk scores were calculated based on the variables considered in the original publications. Due to the procedural protocol in both services where the study was carried out, the CRUSADE score is routinely calculated in all patients admitted with a diagnosis of ACS since 2014. Therefore, the value calculated on admission was considered for the analysis. The data was not found in 95 patients, so it was calculated retrospectively with the admission clinical data. The ACTION-GWTG and ORBIT scores were totally calculated retrospectively. The points for each variable were assigned, and the total score of each individual patient was calculated by adding the variable points corresponding to each score model.

The CRUSADE score (5) includes hematocrit (Hct), creatinine clearance (ClCr) measured by the Cockcroft-Gault formula, heart rate (HR), systolic blood pressure (SBP), female gender, presence of signs of heart failure on admission, history of previous vascular disease (peripheral arterial disease and/or stroke) and previous diagnosis of diabetes variables.

The ACTION-GWTG (6) includes age, HR, SBP, creatinine, hemoglobin (Hb), female gender, body weight, history of diabetes, peripheral artery disease, presence of ST-segment elevation or depression, signs of heart failure or shock on admission and prior treatment with warfarin variables. On this last point, we consider treatment with oral anticoagulation with either warfarin, acenocoumarol or non-vitamin K antagonist anticoagulants.

The ORBIT score (9) considers age >74 years, presence of Hb <12 g/dL in women or <13 g/dL in men, or Hct <40% in men or <36% in women, or history of anemia, previous history of bleeding (gastrointestinal, intracranial or hemorrhagic stroke), estimated glomerular filtration rate (eGFR) by the CKD-EPI formula <60 mL/min/1.73m^2 and prior use of antiplatelet agents.

Based on the original publications, the patients were classified into risk categories. In the case of the CRUSADE and ACTION-GWTG models, they were classified into five risk categories (very low, low, moderate, high and very high risk), while for the ORBIT three risk categories were considered (low, moderate and high risk).

Primary endpoint of major bleeding

To define the primary endpoint of in-hospital major bleeding, the Bleeding Academic Research Consortium Definition of Bleeding (BARC) classification was used. (11) BARC classification type 3 or 5 was considered major bleeding. Type 3 is divided into A (drop in Hb between 3 and 5 g/dL or need for transfusion), B (drop in Hb >5 g/dL or cardiac tamponade, or surgical requirement) and C (intracranial or retinal hemorrhage). Type 5 is fatal bleeding (probable, 5-A, or definite, 5-B). Bleeding in the context of cardiac surgery (type 4 of the BARC classification) was not considered.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation (SD), or as median and interquartile range (IQR) in the case of non-normal distribution. Categorical variables are expressed as percentage.

Univariate analysis was performed by logistic regression using major bleeding as the dependent variable and each score as the independent variable. In a later stage, a multivariate analysis was performed exploring the three scores simultaneously in a logistic regression model. As previously mentioned, the scores were analyzed as continuous and cate-

gorical variables divided into the risk categories corresponding to each score.

In order to determine the discrimination power of the scores, ROC (receiver operating characteristic) curves were built to establish the area under the curve (AUC) with its corresponding 95% confidence interval (95% CI). The scores' AUC were compared using the chi-square test for homogeneity of areas. A p value <0.05 was considered significant. Statistix 7 and Epidat 3.1 softwares were used for the analysis.

Statistical analysis

Continuous variables are described as mean ± standard deviation or median and interquartile range according to their distribution, and categorical variables are expressed as numbers and percentages. For the biva.

RESULTS

A total of 890 patients were recruited, 53 of which were excluded for not having received anticoagulation and 75 for lack of data to calculate the scores; so 762 patients were finally included in the study. The admission diagnosis was NSTEACS in 580 patients (450 diagnosed with non-ST-segment elevation myocardial infarction and 130 with unstable angina) and ST-segment elevation ACS (STEACS) in 182 patients.

Mean age was 68±11 years, and 35% were women; the remaining population characteristics are shown in Table 1.

One hundred percent of patients received aspirin as antithrombotic treatment, and 96.3% (n=734) P2Y12 receptor inhibitors (clopidogrel in 85% of cases, ticagrelor in 13%, and prasugrel in 2%). All patients had anticoagulation with enoxaparin and 9.5% fibrinolytics (n=72); among the latter, 65 patients received rTPA and 7 streptokinase. Coronary angiography was performed during hospitalization in 89% of the patients, (n=685) and 69.9% underwent revascularization (n=533).

The major bleeding endpoint occurred in 3.4% of the patients (n=26), 20 of which were classified as BARC 3 A, 4 as BARC 3 B and 2 as BARC 3 C. No patient presented fatal bleeding.

The median CRUSADE score was 25 (IQR 15-36), for the ACTION-GWTW score it was 25 (IQR 20-29), and for the ORBIT score 1 (IQR 1-2). Table 2 shows the risk categories of each score and the rate of major bleeding according to each category. As shown in Table 3, in the univariate analysis, the three scores were predictors of major bleeding when analyzed as continuous variables: ACTION-GWTW (OR 1.12, CI 95% 1.02-1.19, p=0.001); CRUSADE (OR 1.06, CI 95% 1.03-1.08, p=0.01), and ORBIT (OR 2.56, CI 95% 1.81-3.36, p<0.01), while in the multivariate analysis, only the ORBIT score was an independent predictor of major bleeding (OR: 2.46, 95% CI 1.61-3.97, p<0.001). Table 4 presents the univariate and multivariate analysis considering the different risk categories.

The ACTION-GWTG score presented an AUC of 0.70 (95% CI 0.58-0.82), the CRUSADE score an AUC of 0.68 (95% CI 0.57-0.80) and the ORBIT score an AUC of 0.80 (95% CI 0.72-0.90). The ORBIT score presented higher AUC than the CRUSADE score (p=0.03) without significant differences with the ACTION-GWTG score (p=0.06) (Figure 1).

Table 1. Baseline population characteristics (n=762)

Variables	
Age (years)	68±11
Women, n (%)	269 (35.3)
History	
Hypertension, n (%)	587 (77)
Diabetes, n. (%)	220 (28.8)
Current smoking, n (%)	190 (24.9)
Dyslipidemia, n (%)	388 (50.9)
Previous PCI, n (%)	92 (12)
Previous CABG, n (%)	65 (8.5)
PAD, n (%)	70 (9.1)
Previous stroke, n (%)	31 (4)
History of bleeding, n (%)	7 (0.9)
VKA treatment, n (%)	34 (4.4)
Admission Data	
SBP – mmHg (mean ± SD)	142±27
HR – bpm (mean ± SD)	76±16
Weight – Kg (mean ± SD)	79±11
Hct - % (mean ± SD)	39 ±16
Hb mg/dL (mean ± SD)	13.8±2.6
Creatinine - mg/mL (median and IQR)	0.98 (0.78–1.11)
CrCl < 60 ml/min/1,73m^2, n (%)	76 (9.9)
eGFR < 60 ml/min/1,73m^2, n (%)	61 (8)
Cardiogenic shock, n (%)	7 (0.9)
Signs of HF, n (%)	32 (4.1)
ST segment elevation, n (%)	182 (23.8)
ST segment depression, n (%)	202 (26.5)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; PAD: peripheral arterial disease; VKA: Vitamin K antagonists; SBP: Systolic blood pressure; HR: Heart rate; Hct: Hematocrit; Hb: Hemoglobin; CrCl: Creatinine clearance measured using the Cockroft Gault formula; eGFR: Glomerular filtration rate estimated using the CKD-EPI formula; HF: Heart failure; SD: standard deviation.

DISCUSSION

In our work we analyzed the performance of three risk scores to predict bleeding in a population of patients with NSTEACS, in whom anticoagulation was used as part of the antithrombotic treatment. In our population, only the ORBIT score resulted an independent predictor of major bleeding, with a good predictive capacity (AUC 0.80). The CRUSADE and ACTION-GWTG scores were predictors in the univariate analysis, but they were not independent predictors in the multivariate analysis. The predictive capacity of the ACTION-GWTG score was moderate (AUC 0.70), while that of the CRUSADE score was fair (AUC 0.68). When comparing the curves, the ORBIT score showed greater predictive capacity than the CRUSADE score, and a tendency to better capacity than the ACTION-GWTG score.

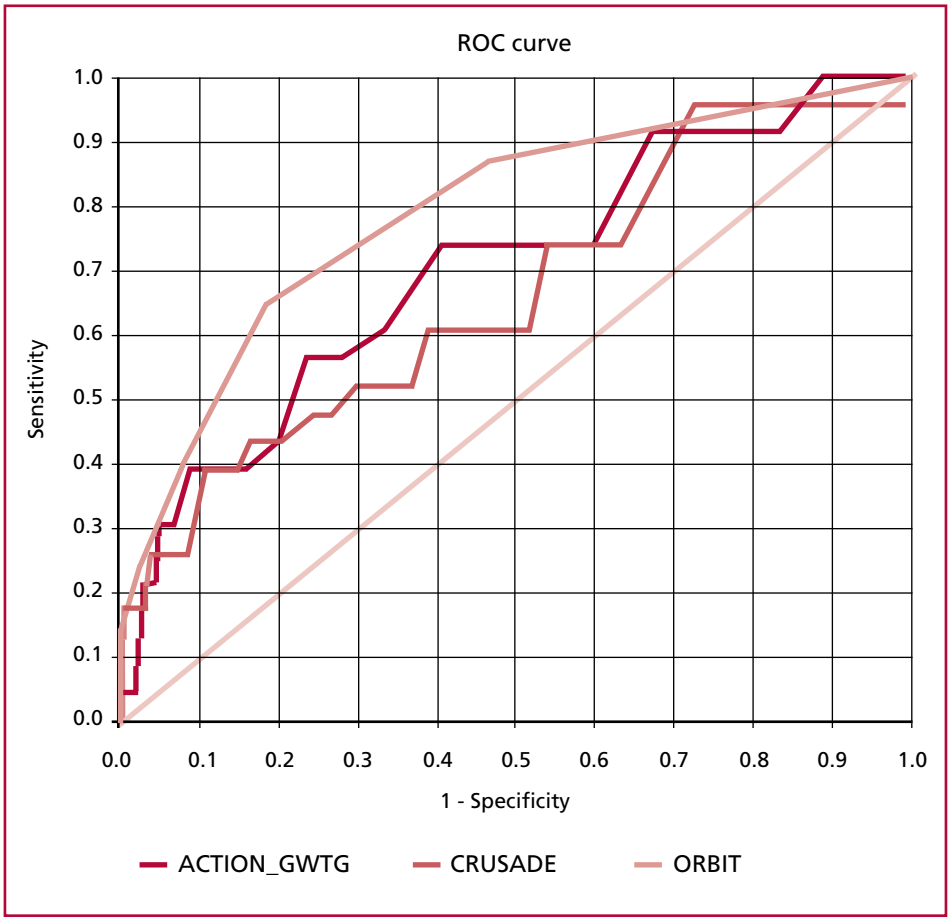

Fig. 1. Comparison of ROC curves

ORBIT categories	Total population n	Total population %	Major bleeding n	Major bleeding %
Low (0-2)	601	79	9	1.5
Moderate (3)	76	10	6	7.8
High (4 or more)	85	11	11	12.9
ACTION-GWTG categories				
Very low (<20)	198	26	2	1
Low (21-30)	403	52.9	12	2.9
Moderate (31-40)	137	18	9	6.5
High (41-50)	16	2.1	2	12.5
Very high (>50)	8	1	1	12.5
CRUSADE categories				
Very low (<20)	304	40	6	1.9
Low (21-30)	190	25	4	2.1
Moderate (31-40)	153	20	5	3.2
High (41-50)	69	9	5	7.2
Very high (>50)	46	6	6	13

Table 2. Distribution of bleeding according to the risk category.

The first thing to highlight is that, of the three scores evaluated, the one with the best performance, ORBIT, was developed to predict bleeding in anticoagulated patients for AF and not for ACS. However, this model uses variables strongly associated with an increased risk of bleeding, such as age, kidney function, anemia, and history of previous bleeding. Age is an important predictor of bleeding in ACS. (12) An analysis of more than 24 000 patients enrolled in the GRACE registry published several years ago showed that the adjusted risk of major bleeding increases by 30% for each decade of life. (13) In the ORBIT model,

Table 3. Univariate and Multivariate Analysis for Major Bleeding. Scores as continuous variable

	UNIVARIATE			MULTIVARIATE		
	OR	95% CI	p	OR	95% CI	p
ACTION-GWTG	1.12	1.02 - 1.19	0.001	0.99	0.90-1.08	0.782
CRUSADE	1.06	1.03 - 1.08	0.012	1.01	0.98-1.05	0.122
ORBIT	2.56	1.81 - 3.36	<0.001	2.56	2.62-3.97	<0.001

Table 4. Univariate and Multivariate Analysis for Major Bleeding. Scores according to risk categories

	UNIVARIATE			MULTIVARIATE		
	OR	95% CI	p	OR	95% CI	p
ACTION-GWTG	2.27	1.31 -2.12	0.003	1.19	0.98–2.43	0.629
CRUSADE	1.56	1.15- 2.12	0.004	1.01	0.66–2.43	0.925
ORBIT	3.26	2.06-5.17	<0.001	3.06	1.69–5.52	<0.001

age has an important weight in the score, since it assigns 1 point to age >74 years, out of a maximum total of 7 points. On the other hand, the CRUSADE score does not consider this parameter and in the ACTION-GWTG model, age has less weight within the total score. Renal function and anemia are considered in all three scores. However, anemia is defined differently in the three models. The CRUSADE model includes only the Hct value and the ACTION-GWTG model that of Hb, while in the ORBIT model the definition is broader, considering both Hb and Hct (both differentiated according to female/male gender) and it includes the history of anemia. This may result in more patients adding points for this variable. In addition, anemia has a very important weight in this score, adding 2 points out of a total of 7. In the CRUSADE and ACTION-GWTG models, anemia has less weight in the final score. Several studies have shown that the presence of anemia in ACS is an important prognostic marker for both cardiovascular events and bleeding. (14,15)

Renal dysfunction is an important predictor of bleeding. In the previously mentioned analysis of the GRACE registry, it was documented that kidney failure increases the risk of bleeding by 50%. (13) Although it is considered in the three risk models, the variables that define renal function are different. The ACTION-GWTG score incorporates the isolated creatinine value, while the CRUSADE and the ORBIT scores include the calculation of glomerular filtration rate, which is more specific to assess renal function. (16)

Another aspect that can explain the performance of the ORBIT score is that it takes into account the history of bleeding, not included in the other two. In the analysis of the GRACE registry, a history of bleeding almost triplicates the risk of in-hospital bleeding in ACS. (13) Although this antecedent was very infrequent in our patients, among the 7 who presented it, 2 had major bleeding, representing a warning signal regarding the choice of antithrombotic strategy in these patients.

CRUSADE is the most used score in clinical practice and is recommended in different guidelines. (2,17) Although it was developed for NSTEACS, it has been extensively studied in the entire spectrum of ACS. (18,19) The ACTION-GWTG model was built including patients with and without STEACS. Several studies have compared both scores, finding a similar predictive capacity. (20,21) A recent meta-analysis, (19) of 17 studies with more than 18 thousand patients, reported a moderate predictive capacity of both scores (AUC 0.71 and 0.76, respectively), somewhat higher than that found in our work (0.68 and 0.70).

On the other hand, the CRUSADE and the ACTION-GWTG scores share several variables such as female gender, renal function, signs of heart failure, diabetes, SBP and HR, which could partly explain why in the multivariate analysis they tend to cancel each other as predictors. In addition, our population presented relatively few events for the multivariate analysis (26 bleedings for 3 scores), although the bleeding rate is similar to that reported in other studies. (3,5,6,12)

ORBIT is not the first score developed for AF that is studied in ACS. HASBLED has been studied as a predictor of bleeding in ACS, (7,8) with a similar predictive capacity than the CRUSADE score, although in the aforementioned meta-analysis, (19) the performance was somewhat lower. Considering that bleeding predictors are similar in patients with ACS and AF, and that the scores developed for the latter pathology are easy to calculate at the patient's bedside, it is reasonable to assess their usefulness in ACS.

Limitations

Our work has several limitations. It is a retrospective study carried out in only two centers, so the results cannot be extrapolated to other populations. Although the size of the study is moderate, relatively few events were recorded for the variables analyzed (26 events for 3 scores), which may influence the results.

CONCLUSIONS

In conclusion, the three scores evaluated were predictors in the univariate analysis, but the ORBIT score was the only independent predictor of major bleeding, presenting a better discrimination capacity than the CRUSADE score and a tendency to better capacity

than the ACTION-GWTG score. ORBIT is an easy score to calculate at the patient's bedside, and may be useful for predicting bleeding in patients with ACS.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Off-Pump Coronary Artery Bypass Graft Surgery with Bilateral Internal Mammary Arteries in Left Main Coronary Artery Disease. Is There Any Benefit in 10-Year Mortality?

Cirugía de revascularización coronaria sin bomba con 2 arterias mamarias en la enfermedad del tronco ¿genera beneficio en la mortalidad a 10 años?

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ABSTRACT

Background: The randomized controlled trials comparing coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI) included all types of surgical techniques (on-pump and off-pump) and different conduits (arterial and venous). Is it reasonable to assume that all surgical techniques are equal in terms of late mortality?
Objectives: The aim of this study was to evaluate whether off-pump CABG surgery using both mammary arteries provides additional benefit over conventional revascularization using single mammary artery in terms of long-term survival for left main coronary artery (LMCA) disease.
Methods: We conducted a retrospective, observational and comparative study (n = 723) adjusted for risk. A stratified analysis was performed according to the use of single internal thoracic artery (SITA, n = 144) or bilateral internal thoracic arteries (BITA, n = 579) analyzing survival at 10 years after the intervention.
Results: Survival at 10 years was significantly higher in BITA group (79.0% ± 3.4% vs 67.0% ± 4.9%, log-rank test, p <0.01). This advantage was also observed in the risk-adjusted analysis (93.0% ± 4.6 vs 69.0% ± 5.7 respectively, p = 0.03). The use of BITA was an independent predictor of 10-year survival (HR 0.57, 95% CI 0.37-0.87, p = 0.01).
Conclusion: The use of bilateral internal mammary arteries in patients with left main coronary artery disease undergoing off-pump coronary artery bypass grafting was associated with higher survival at 10 years.

Key words: Coronary Artery Bypass, Off-Pump - Coronary Artery Disease - Coronary Artery Bypass - Mammary Arteries

RESUMEN

Introducción: Los ensayos clínicos aleatorizados que compararon la cirugía de revascularización miocárdica (CRM) con la angioplastia transluminal coronaria (ATC) incluyeron todo tipo de técnicas quirúrgicas (con y sin bomba de circulación extracorpórea) y diversos conductos (arteriales y venosos). ¿Es razonable suponer que todas las técnicas quirúrgicas son iguales en términos de mortalidad tardía?
Objetivos: Evaluar si la CRM sin circulación extracorpórea y con el empleo de ambas arterias mamarias tiene un beneficio adicional a la revascularización convencional utilizando una sola arteria mamaria en términos de sobrevida a largo plazo para la enfermedad del tronco de la coronaria izquierda (TCI).
Material y métodos: Estudio observacional retrospectivo comparativo (n = 723) ajustado por riesgo. Se realizó análisis estratificado según el uso de arteria mamaria interna única (SITA, n = 144) o ambas arterias mamarias internas (BITA, n = 579). Se analizó la sobrevida a los 10 años de la intervención.
Resultados: La supervivencia a los 10 años fue significativamente mayor en el grupo en que se utilizaron ambas arterias mamarias (79,0% ± 3,4% vs 67,0% ± 4,9%, log-rank test, p <0,01). Este beneficio también se observó en el análisis ajustado por riesgo (93,0% ± 4,6 vs 69,0% ± 5,7 respectivamente, p = 0,03). El uso de ambas arterias mamarias fue un predictor independiente de sobrevida a 10 años (HR 0,57, IC 95% 0,37-0,87; p = 0,01).
Conclusión: El uso de ambas arterias mamarias internas en pacientes con enfermedad del tronco coronario izquierdo sometidos a revascularización coronaria sin circulación extracorpórea se asoció con mayor sobrevida a los 10 años.

Palabras claves: Cirugía de revascularización coronaria - Cirugía coronaria sin bomba - Enfermedad coronaria - Puente de arteria coronaria - Cirugía con doble mamaria

Rev Argent Cardiol 2022;90:173-178. http://dx.doi.org/10.7775/rac.v90.i3.20517

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Received: 10/11/2021 – *Accepted:* 02/08/2022

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INTRODUCTION

Coronary artery bypass graft (CABG) surgery has been established as the gold standard treatment for coronary artery disease and is the standard of care to validate percutaneous coronary interventions (PCIs) in randomized clinical trials (RCTs). However, studies comparing CABG surgery versus PCI included all types of surgical techniques (on-pump and off-pump) and different conduits (arterial and venous). Is it reasonable to assume that all surgical techniques are equal in terms of long-term mortality?

There is still disagreement about which conduits are the best for CABG, particularly in left main coronary artery (LMCA) disease. Pooled data from large observational studies have demonstrated the superiority of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) (1) for multivessel coronary artery disease. Although these studies included patients with LMCA disease, they were not primarily focused on this subgroup of patients. Despite the significant long-term benefit, the use of BITA has not been universally adopted, mainly because it is technically more demanding, and the benefit has not been confirmed in RCTs. The Arterial Revascularization Trial (ART) was designed to answer the question if BITA was superior to SITA in multivessel disease but failed to demonstrate a significant benefit in the long-term survival. (2) It neither specified how many patients included had LMCA disease, making it difficult to extrapolate these results to clinical practice in this group of patients. (3)

The results of other RCTs focused on patients with LMCA disease also failed to demonstrate any benefit. The sub-analysis of a RCT (EXCEL trial), designed to evaluate if PCI was noninferior to CABG in LMCA disease, explored if BITA was superior to SITA in the group of patients included in the CABG surgery arm. (4) Although the study had poor statistical power to detect a significant difference because of the study design and the important statistically significant differences in the baseline characteristics (11 of 22 variables reported in Table 1), the authors concluded that there was no evidence of benefit in the composite outcome of mortality, myocardial infarction and stroke at 3-year follow-up. Thus, there is still controversy about the best surgical technique to manage LMCA disease.

Considering that CABG surgery is the standard of care (gold standard) to test new therapeutic technologies, such as implantation of new-generation stents to treat LMCA disease, and the heterogeneity of the different techniques for CABG surgery worldwide and in our country, it is extremely important to determine which is the best surgical technique in terms of long-term survival (10 years). Therefore, the aim of our study was to evaluate if BITA is associated with greater long-term survival in LMCA disease.

METHODS

We conducted a comparative observational analysis adjusted for risk, of data prospectively collected from November 1996 to May 2014 at a single center. The cohort was made up of consecutive patients with LMCA disease and involvement of at least two coronary artery territories who underwent off-pump CABG surgery and received at least one bypass graft with at least one in situ mammary artery graft which is universally accepted as the gold standard in CABG. Off-pump surgery is the standard of care in our institution. Patients requiring emergency surgery (within 24 hours), on-pump surgeries, and patients with history of CABG surgery were excluded. Patients were stratified according to the number of internal mammary arteries used, into BITA Group (2 thoracic arteries) and SITA Group (1 thoracic artery + another conduit). The surgical technique used in both groups has already been described. (5) The primary endpoint was all-cause mortality at 10 years since it is less amenable to interpretation.

All patient data were prospectively collected in our customized database (Microsoft Access; Microsoft Corp, Redmond, WA), which is used in our daily practice. Preoperative, intraoperative, and postoperative data were obtained by retrospective review of the clinical reports in the database and cross-checked with all the medical records. The preoperative characteristics of the patients in these study groups were summarized as mean ± standard deviation, median and interquartile range (IQR) or incidence (percentage), as appropriate. Continuous variables were compared using the Student's t test for independent samples or Mann-Whitney U test, and the chi-square test or Fisher's exact test were used to compare categorical variables.

A propensity score for having BITA grafting was calculated for each patient using a logistic regression model that included all the preoperative variables listed in Table 1. Patients were matched 1:1 by the propensity scores using the greedy matching technique without replacement. A nearest-neighbor–matching algorithm was used with a caliper distance of 0.1. Outcomes of interest between the matched groups were compared using the paired t test for continuous variables and the McNemar test for categorical variables. After matching, we examined the balance of all observed covariates, interactions among all covariates, and quadratic terms of all covariates. Preoperative differences between the groups were evaluated using standardized differences. Changes in imbalance were plotted (before and after propensity score matching). Event-free survival curves were estimated using the Kaplan-Meier method. A stratified multivariate Cox regression model was used to estimate the effect of BITA on long-term survival among the matched groups. The first block of the regression model included the type of conduit used and the second block included the operative variables using the backward stepwise likelihood ratio method to account for matching.

Univariate and multivariate Cox proportional hazard analyses were performed to investigate the significant predictors of late mortality. The variables used for univariate analysis were the clinical variables listed in Table 1. Variables with a p value < 0.2 on univariate analysis were included in the multivariate model. Three statistical tests (likelihood ratio test, Wald test, and logrank test) were used to ensure the goodness of fit of the model. Global Schoenfeld test and covariate specific Schoenfeld individual test were applied to evaluate the proportional hazards assumption in the Cox proportional hazards model.

Long-term survival was evaluated by direct communication with the patient, family and treating physicians. The medical records were also reviewed.

Ethical considerations

All the patients signed an informed consent form regarding the surgical method, the postoperative evaluations and the

Table 1. Patients' characteristics

	UNADJUSTED RISK DATA			UNADJUSTED RISK DATA			
	SITA (n = 144)	BITA (n = 579)	p	SITA (n = 107)	BITA (n = 107)	p	MSD‡
Age, years, m (SD)	70.0 (9.3)	65.3 (9.0)	<0.001	68.9 (9.3)	69.2 (9.7)	0.831	0.029
Female sex,	20.10%	8.80%	<0.001	24.30%	15.00%	0.121	0.137
Weight, kg, m (SD)	79.4 (19.0)	81.6 (12.9)	0.254	80.9 (20.4)	78.5 (12.5)	0.352	0.142
Height, cm, m (SD)	168.3 (8.7)	172.1 (7.3)	<0.001	168.3 (9.0)	170.5 (8.8)	0.115	0.145
Hypertension	79.20%	79.40%	0.941	78.50%	79.40%	0.867	0.023
Dyslipidemia	73.60%	79.80%	0.106	72.90%	73.80%	0.877	0.021
Family history	26.40%	27.50%	0.796	25.20%	24.30%	0.874	0.022
Diabetes mellitus	25.70%	26.60%	0.826	28.00%	25.20%	0.643	0.063
Smoking habits (current or former smoker)	54.90%	67.0%	0.009	55.1	63.6	0.266	0.172
Previous stroke	1.40%	4.50%	0.084	0.90%	3.70%	0.175	0.186
COPD	5.60%	4.50%	0.589	4.70%	2.80%	0.471	0.099
Chronic kidney disease (including dialysis requirement)	6.30%	4.30%	0.327	7.50%	5.60%	0.581	0.076
LVEF < 45%	22.90%	13.30%	0.004	18.70%	18.70%	>0.99	<0.001
History of myocardial infarction	21.50%	25.40%	0.336	21.50%	26.20%	0.422	0.110
Previous PCI	17.40%	16.90%	0.901	17.80%	21.50%	0.491	0.094
Peripheral artery disease Lower extremities	6.30%	3.30%	0.099	4.70%	2.80%	0.471	0.099
Carotid artery disease (only medical treatment),	4.20%	5.70%	0.466	3.70%	2.80%	0.701	0.053
Carotid artery disease (treated with surgery/ endovascular procedure),	0.00%	1.90%	0.096	0.00%	0.00%	>0.99	<0.001
Abdominal artery disease	2.80%	1.00%	0.109	1.90%	0.90%	0.561	0.080
Elective surgery	40.30%	46.60%	0.171	38.30%	46.70%	0.213	0.171
Two-vessel coronary artery disease	28.50%	31.30%	0.516	26.20%	35.50%	0.139	0.132
Three-vessel coronary artery disease	71.50%	68.70%	0.516	73.80%	64.50%	0.139	0.132
Previous cardiac surgery							
Valve replacement + CABG	1.40%	0.00%	0.005	0.00%	0.00%	>0.99	<0.001
Isolated heart valve surgery	1.40%	0.00%	0.005	0.00%	0.00%	>0.99	<0.001

SITA: single internal thoracic artery; BITA: bilateral internal thoracic artery; SDM: standardized differences in means; SD: standard deviation; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

use of anonymized clinical data for academic purposes. The study was approved by the institutional review board of *Instituto Cardiovascular de Buenos Aires*.

RESULTS

Of 3,757 patients undergoing elective or urgent CABG surgery due to multivessel disease, 723 met the inclusion criteria (19.2%) and were stratified according to the number of internal mammary arteries used into BITA group (2 mammary arteries, n=579, 80.1%) and SITA group (1 mammary artery + another conduit, n=144, 19.9%). The preoperative characteristics of the study population are presented in Table 1. Patients in the BITA group were younger (BITA, 65.3 ± 9.1 years versus SITA, 70.0 ± 9.9 years; p <0.0001) and taller (p < 0.001); the history of CABG surgery was less common (p <0.01) and fewer patients had moderate or severe left ventricular dysfunction (p = 0.004).

After propensity score matching, 107 comparable matched sets were obtained (n=214), with no significant differences in their baseline characteristics (Table 1). The preoperative differences between the groups were evaluated using standardized differences. There were no imbalances as assessed through univariate and multivariate tests. The overall chi-square balance test (Hansen and Bowers) (6) was also not significant (chi-square [degrees of freedom: 18] = 8.474 ; p = 0.998).The multivariate imbalance measure (Iacus, King, and Porro, L1) was larger in the unmatched sample (0.972) than in the matched sample (0.935), also indicating that matching improved overall balance. (7)

Follow-up of hospital survivors was complete in

96.2 %: BITA group vs. SITA group, 91.8 % vs. 95.6 %, with no significant differences (p = 0.136). Median follow-up of all the patients was 5.2 years (IQR 2.2 - 8.1 years), with no significant difference between both groups (p = 0.189). Figure 1 shows the unadjusted 10-year outcomes with greater 10-year survival for the BITA group (79.0 % ± 3.4% vs. 67.0% ± 4.9%, p log-rank test = 0.008).

In addition, in the risk-adjusted population (according to propensity score) BITA patients had significantly higher survival than SITA patients at the end of follow-up, 93.0% ± 4.6 vs. 69.0% ± 5.7 respectively (HR: 0.27, 95%CI: 0.07-0.76, p = 0.016, univariate Cox model). BITA grafting was also a predictor of better survival on multivariate analysis (HR 0.26, 95% CI, 0.08-0.89, p = 0.03, Cox multivariate model).

Time-to-event analysis using multivariate Cox regression identified better 10-year survival in the BITA group (HR 0.57, 95% CI, 0.37-0.87, p<0.01) (Table 2). Long-term survival was significantly higher in the BITA group vs. the SITA group. The Schoenfeld test was not statistically significant for each of the covariates, and the global test was also not statistically significant (p = 0.6595). Therefore, we can assume the proportional hazards of the Cox model.

DISCUSSION

The use of both internal thoracic arteries with an off-pump technique seems to improve long-term survival of patients with LMCA disease compared with a more traditional revascularization surgery using a single internal thoracic artery plus another conduit (radial artery graft or saphenous vein graft).

There is significant discrepancy between large risk-adjusted observational trials and RCTs regarding both surgical techniques. Four RCTs comparing BITA and SITA in multivessel disease reported no differences in mid-term survival at 5 years. (8-11) None of these studies mentioned LMCA disease in their design, (3) so it would not be reasonable to extrapolate their conclusions to LMCA disease. In addition, mid-term follow-up could be insufficient to show better survival with the use of the arterial conduit. Other important methodological issues, as on-pump or off-pump interventions, could have also modified the treatment effect. The surgical techniques were not standardized or homogeneous, so that the surgeon could perform on-pump or off-pump procedures, which is still a major issue of controversy for long-term survival. (12-14) Of these RCTs, the ART trial was not only the largest trial but also had the longest follow-up (10 years). Unfortunately, there are other methodological concerns about this trial. Although the primary analysis used the intention-to-treat principle, crossover between groups was > 36%; therefore, only 64% of the randomized patients received the assigned treatment and only 40.9% (1259 patients out of 3078) were off-pump procedures. (15) Considering these limitations, we designed the present study including only off-pump operations to standardize the surgical technique and because it is the standard of care in our institution.

On the other hand, evidence from large observational studies supported the use of both mammary arteries in multivessel disease, as demonstrated in 6 meta-analyses. (16-21) The largest meta-analysis included 29 observational studies, with a total of 89 399 patients. Pooled data yielded a significantly higher long-term survival (10 years) for the BITA group compared with that of the SITA group (82.1% vs. 70.5%, HR 0.78; p<0.00001). In the present study, performed exclusively in patients with LMCA disease, we observed a similar benefit.

Fig. 1. Unadjusted long-term all-cause mortality. BITA: bilateral internal thoracic artery; SITA: single internal thoracic artery.

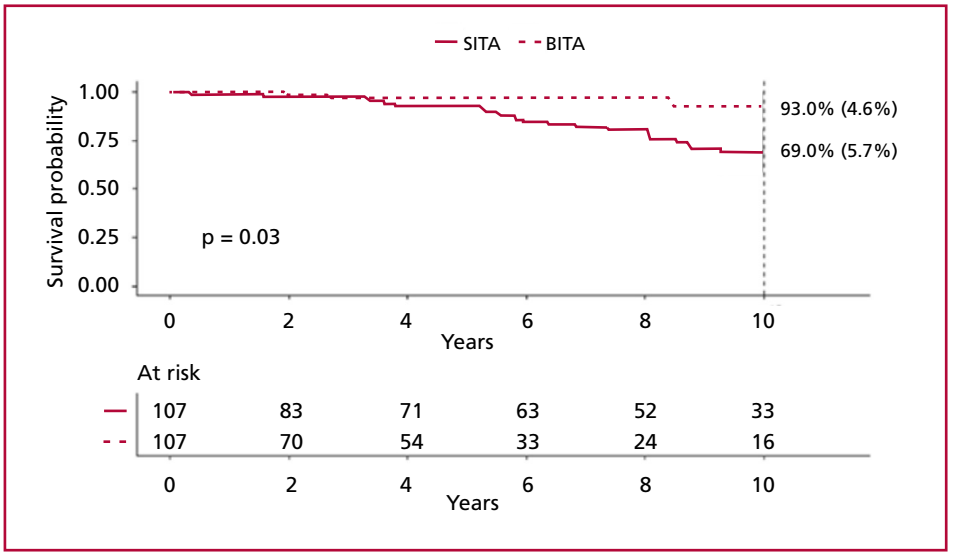

Fig. 2. Risk-adjusted long-term all-cause mortality (propensity score matching). BITA: bilateral internal thoracic artery; SITA: single internal thoracic artery.

Table 2. Multivariate Cox proportional hazard regression for all-cause mortality at 10 years

	HR	95% CI		p
Peripheral artery disease	2.06	1.07 -	3.99	0.032
Chronic kidney disease (including dialysis requirement)	3.06	1.55 -	6.03	0.001
Elective surgery	0.56	0.36 -	0.87	0.010
Postoperative myocardial infarction	3.43	1.32 -	8.87	0.011
BITA	0.57	0.37 -	0.87	0.010

BITA: bilateral internal thoracic artery

The evidence about the best surgical strategy for managing LMCA disease is still limited. One could argue that it is not so different from multivessel disease. Although this may be true from the surgeon's point of view, it is very different for interventional cardiologists. Surgery treats the vessel affected by atherosclerosis, whereas percutaneous coronary intervention treats each lesion of the vessel. In this regard, some RCTs compared new technologies used in PCIs with CABG surgery, including any surgical strategy. These methodological designs imply accepting that all surgical techniques provide the same benefits. But is it really true? In the present study, we observed a significant difference in favor of BITA versus SITA in 10-year all-cause mortality, providing further evidence that not all CABG surgeries offer the same benefits. A sub-analysis of the EXCEL trial addressed this issue by analyzing only the surgical arm. Among the 905 patients undergoing CABG, 688 (76.0%) underwent SITA and 217 (24.0%) underwent BITA. There were no significant differences in 3-year survival (HR 1.36; 95% CI, 0.60-3.12; p = 0.46). Probably this short follow-up was insufficient to demonstrate the benefit of the second arterial conduit. In fact, in the present study the probability of survival at 3-year follow-up was not significantly different between the two groups (97.0% ± 0.8% vs. 94.0% ± 2.1%, p = 0.1); with significant differences at 10 years (79.0% ± 3.4% vs. 67.0% ± 4.9%, p = 0.008).

This study has several limitations. The main limitation is its design, a retrospective observational comparative study conducted in a single center. To mitigate the confounding effect, two different and independent statistical methods were used (propensity score matching and multivariate Cox regression). In addition, we only included patients who underwent off-pump CABG surgery to reduce the possible effect of on-pump or off-pump on the outcome. However, although every effort was made to minimize the effect of confounders, we cannot rule out the effect of those unmeasured. (21)

In conclusion, this study suggests that coronary artery bypass graft surgery for LMCA disease exclusively with BITA as composite T-graft and off-pump technique can be safely performed and could be associated with improved long-term survival compared with the more traditional strategy using a mammary artery graft plus another conduit.

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ORIGINAL ARTICLE

Long-term Outcomes of Coronary Artery Bypass Surgery According to the Presence or Absence of Left Main Coronary Artery Disease

Resultados a largo plazo de la cirugía de revascularización coronaria según la presencia o no de enfermedad del tronco de la arteria coronaria izquierda

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ABSTRACT

Background: Coronary artery bypass grafting (CABG) has modified the natural evolution of patients with left main coronary artery (LMCA) disease. There is little information in our setting regarding the mid- and long-term follow-up of operated patients.
Objective: The aim of this study was to evaluate the implication of LMCA disease in the long-term evolution of patients operated on with CABG, and to assess the mortality and incidence of myocardial infarction (AMI) and/or stroke.
Results: Follow-up was completed in 438 patients (95.6%) with a median of 58 months [interquartile range (IQR) 35-88 months]. Actuarial survival at 10 years was 91.8% for the entire population, with no significant differences between the LMCA group (91.57%) vs. the non-LMCA group (91.86%), HR 1,008 95% CI 0.38-2.65, p=0.98. In multivariate analysis, preoperative left ventricular ejection fraction (HR = 0.95; 95% CI 0.93-0.97; p < 0.001), age (HR 1.1, 95% CI 1.04-1.13, p<0.001) and non-elective priority of surgery (HR=3.71; 95% CI 1.3-10.35; p=0.01) were independent predictors of long-term mortality. AMI-free survival was 96.8% (LMCA 94% vs. non-LMCA 97.4%, p=0.8) and freedom from stroke was 98% (LMCA 97.8% vs. non-LMCA 98.1 %, p=0.8).
Conclusion: In patients undergoing CABG, the presence of LMCA disease did not increase the rate of hard events (death, AMI, and stroke) at the long-term follow-up. The results obtained in this series of patients are similar to those published in the international literature used to develop myocardial revascularization guidelines.

Key words: Myocardial Revascularization - Follow-Up Studies - Coronary Artery Bypass - Left Main Coronary Artery Disease

RESUMEN

Introducción: La cirugía de revascularización miocárdica (CRM) ha modificado la evolución natural de los pacientes con enfermedad de tronco de la arteria coronaria izquierda (TCI). En nuestro medio es escasa la información relacionada con el seguimiento a mediano y largo plazo de los pacientes intervenidos.
Objetivo: Evaluar la implicancia de la enfermedad del TCI en la evolución alejada de los pacientes intervenidos con CRM, y conocer la mortalidad e incidencia de infarto de miocardio (IAM) y/o accidente cerebrovascular (ACV).
Resultados: El seguimiento se completó en 438 pacientes (95,6%) con una mediana de 58 meses [Rango intercuartilo (RIC) 35-88 meses]. La sobrevida actuarial fue a 10 años del 91,8% para toda la población, sin diferencias significativas entre el grupo TCI (91,57%) vs grupo no TCI (91,86%), HR 1,008, IC 95% 0,38-2,65, p=0,98. En el análisis multivariado se encontraron como predictores de mortalidad alejada la fracción de eyección ventricular izquierda preoperatoria (HR = 0,95; IC 95% 0,93-0,97; p < 0,001), la edad (HR 1,1, IC 95% 1,04 - 1,13, p< 0,001) y la prioridad no electiva de la cirugía (HR = 3,71; IC 95% 1,3-10,35; p = 0,01). La sobrevida libre de IAM fue del 96,8% (TCI 94% vs no TCI 97,4%, p= 0,8) y la libertad de ACV fue del 98% (TCI 97,8% vs no TCI 98,1%, p= 0,8).
Conclusión: En los pacientes sometidos a CRM, la presencia de enfermedad del TCI no incrementó la tasa de eventos duros (muerte, IAM y ACV) en el seguimiento alejado. Los resultados obtenidos en esta serie de pacientes son similares a los publicados en la bibliografía internacional utilizada para desarrollar las guías de revascularización miocárdica.

Palabras clave: Revascularización miocárdica - Estudios de Seguimiento - Puente de Arteria Coronaria - Enfermedad de tronco de arteria coronaria izquierda

INTRODUCTION

The results of coronary artery bypass grafting (CABG) in patients with multivessel disease have been previously documented, and the presence or absence of left main coronary artery (LMCA) disease in the preoperative coronary angiography has been analyzed. Moreover, the development of the surgical technique and changes in anesthetic and postoperative management have contributed to reduce the morbidity and mortality of the procedure. In our patients, the LMCA disease group did not have a higher incidence of isolated death, myocardial infarction (AMI) and/or stroke; however, when these hard events were combined there was a higher incidence of the composite endpoint com-

Rev Argent Cardiol 2022;90:179-184. http://dx.doi.org/10.7775/rac.v90.i3.20518

Received: 02/08/2022 – *Accepted:* 04/13/2022

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pared with the non-LMCA disease group. (1) Knowing the immediate perioperative results of LMCA disease, evaluating the long-term follow-up is the next step to assess its quality. The evidence shows the advantages of this strategy and we should have reference information to compare it with new revascularization procedures. (2,3) The objective of our work was to evaluate mortality and the incidence of AMI and stroke at 10 years in patients treated with CABG, analyzed according to the presence or absence of LMCA disease.

METHODS

This was a retrospective cohort study of consecutive patients undergoing isolated CABG (single procedure) from January 1, 2011 to March 31,2020 at Hospital Universitario Austral (HUA). Patients included were over 18 years of age, and the presence of significant coronary artery disease was defined in the LMCA by an obstruction greater than 50%, and in the rest of the coronary arteries by an obstructive lesion ≥70%. Patients who received an additional procedure to CABG were excluded from the analysis.

Data from the electronic medical records of HUA were collected and an exclusive database was created for this study. The registry was approved by the independent Evaluation and Ethics Committee of the institution which waived the need for individual consent since the patients were not identified, nor was sensitive data required (according to Law 25,326 of Habeas Data on the Protection of Personal Data).

Mid-term survival and events were evaluated from the follow-up carried out and documented in the medical records of our institution and epicrisis in case of hospitalization outside HUA, as well as from communication with the patient, family, and treating physicians. Data on death, AMI, and stroke at follow-up were collected.

Statistical analysis

Continuous variables are described as mean ± standard deviation or median and interquartile range according to their distribution, and categorical variables are expressed as numbers and percentages. For the bivariate analysis, Student's t test or the Mann Whitney U test was used to compare continuous variables, as appropriate, and the chi square test or Fischer's exact test with Yates' correction, for dichotomous variables. A survival analysis was performed using Kaplan-Meier curves to assess the occurrence of death during follow-up between both groups, evaluating the difference between curves with the log-rank test. A Cox model was created to evaluate the relationship between age, preoperative ventricular function, diabetes and elective status of surgery with the incidence of mortality. The proportional hazards assumption was verified by means of graphs and statistical tests (Schoenfeld test). The discrimination capacity of the model was evaluated using the C index. The same analysis was repeated for the occurrence of AMI and stroke during follow-up. Significant differences between variables were considered for $p < 0.05$.

Final endpoint

The endpoint was defined as the occurrence of isolated events and the composite of death, stroke and/or AMI in the long-term follow-up of CABG, including results within 30 days after surgery.

The following definitions were used:

Perioperative AMI: Development of new persistent Q waves of at least 0.04 s duration in two or more consecutive leads and/or a decrease in the precordial R wave voltage >25%, with >10-fold increase in troponin and/or wall abnormalities on the echocardiogram consistent with electrocardiographic disorders.

AMI during follow-up: The criteria of the fourth definition of infarction or the diagnosis referred to in the epicrisis of the patient when he/she had been admitted to another institution were considered. (4)

Stroke: Focal and/or diffuse brain injury confirmed by clinical findings and computed tomography with sequelae at patient discharge.

RESULTS

Among a total of 458 consecutive patients operated on for isolated CABG between January 2011 and March 2020, 187 (40.82%) had LMCA disease and 271 (59.18%) did not. As previously reported, overall hospital results were as follows: mortality 1.96%, stroke 0.65%, AMI 1.74%, with no statistically significant differences between the two groups analyzed depending on the presence or not of LMCA disease. However, in the univariate analysis, patients in the LMCA disease group had a higher incidence of major adverse cardiovascular events (MACE): 3.93% vs. 2.2%, p=0.022. (1)

Long-term follow-up was completed in 438 patients (95.6%) with a median of 58 months (IQR 35-88 months). The overall survival of the LMCA disease group at 120 months was 91.57%, with no significant difference with the non LMCA disease population (91.86%) (HR 1,008 95% CI 0,38-2,65, p= 0,98) (Figure 1). Independent predictors of death were evaluated in a multivariate analysis, including impaired ventricular function, age, diabetes, and non-elective surgery status as covariates. Impairment of ventricular function (HR 0.95, 95% CI 0.93-0.97, $p < 0.001$), age (HR 1.1, 95% CI 1.04 - 1.13, $p < 0.001$) and the non-elective priority of surgery (HR = 3.71; 95% CI 1.3-10.35; p = 0.01) were significantly associated with mortality, but not diabetes. The proportional hazards assumption was verified by graphical and statistical methods (Schoenfeld test) (Table 1).

AMI-free overall survival in the LMCA disease group was 96%, with no significant difference compared with 97.4% in the non-LMCA disease group (Log-rank p=0.8) (Figure 2). Neither ventricular function nor age or diabetes were significantly associated with AMI occurrence. Stroke-free survival at 120 months was 97.8% for the LMCA disease group vs. 98.1% for the non-LMCA disease group, with no statistically significant difference. (Log-rank p= 0.86) (Figure 3). Also in this case, the variables mentioned were not significantly associated with the incidence of this outcome.

When analyzing the composite endpoint events, no worse outcome was observed in patients with preoperative LMCA disease (table 2).

DISCUSSION

There is solid evidence to indicate CABG in multivessel coronary and LMCA disease. This is summarized

in the meta-analysis by Yusuf et al. published in 1994, which considered 7 randomized trials of CABG vs. medical treatment, involving 2650 patients followed up for 10 years (5). Although these works are now obsolete compared with better current surgical techniques and medical therapy, they established certain principles that are still valid today. Studies showed that there was longer survival and improved symptom relief in patients undergoing CABG who had three-vessel disease or LMCA disease, especially when the proximal anterior descending artery was mainly affected

Clearly, CABG has been improving from that time to the present with the use of arterial conduits, the advent of surgery without cardiopulmonary bypass (CPB), improvement of the perioperative process, and use of optimized medical treatment during follow-up according to the comorbidities of each patient, as well as the management of secondary prevention of cardiovascular disease with drugs tested for this purpose.

In the multicenter ART study (Arterial Revascularization Trial), by Taggart et al., with random assignment to the use of one or two internal thoracic artery arteries, two groups including 1260 patients each were generated, divided by the use or not of CPB for CABG (6). Mortality recorded at 30 days was comparable between CABG without and with CPB (1% vs. 1.2%; p=0.7). All-cause mortality at 5 years was 8.9% vs. 8.3%, respectively, with no significant differences (HR 1.14; 95% CI, 0.86-1.52; p=0.35), and cardiovascular mortality 4.1% vs. 3.1%, respectively (HR 1.39; 95% CI 0.90-2.13; p=0.13). There were no statistically significant differences in long-term AMI between CABG without CPB, 3%, and with CPB, 4.1% (HR 0.66; 95% CI 0.43-1.02; p=0.06), nor in the occurrence of late stroke 3.3% vs. 2.6%, respectively (HR 1.32; 95% CI 0.83-2.11; p=0.24).

These ART results are of great value since they demonstrate that CABG without CPB is a safe treatment with a 5-year follow-up comparable to CABG with CPB, similar to those reported in our current experience (1).

In a subsequent ART analysis, it was concluded that low-volume CABG centers without CPB are asso-

Table 1. Multivariate analysis of long-term mortality predictors

Variables	HR	95% CI	*p* value
Age	1.1	1.04-1.13	<0.001
Diabetes	1.28	0.85-1.94	0.228
LVEF	0.95	0.93-0.97	<0.001
Status			
Elective	Reference		
Non elective	3.71	1.30-10.35	0.01

LVEF: Left ventricular ejection fraction

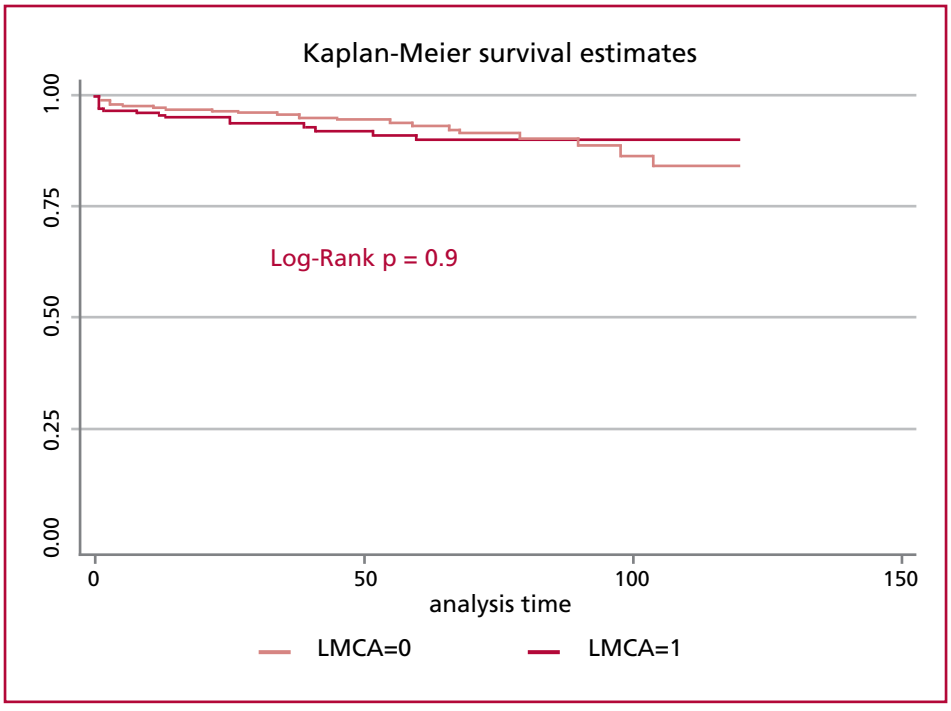

Fig. 1. Actuarial survival at 10 years. Kaplan-Meier curve. Comparison in coronary patients operated on with coronary artery bypass grafting with and without left main coronary artery (LMCA) disease (LMCA=1 and LMCA=0, respectively)

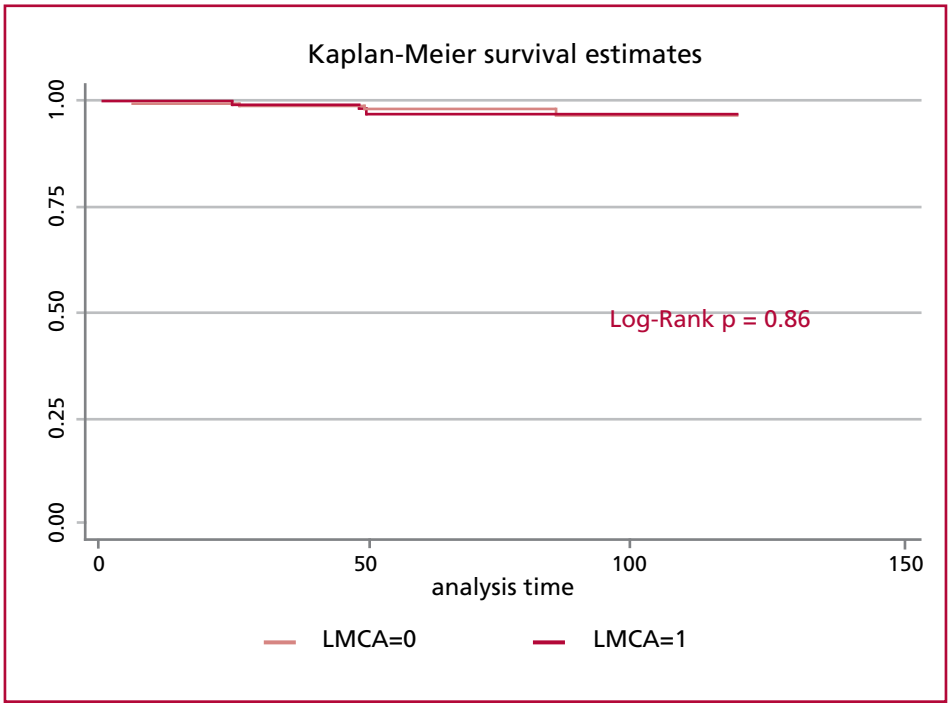

Fig. 2. AMI-free survival. Kaplan-Meier curve. Comparison in coronary patients undergoing coronary artery bypass grafting with and without left main coronary artery (LMCA) disease (LMCA=1 and LMCA=0, respectively).

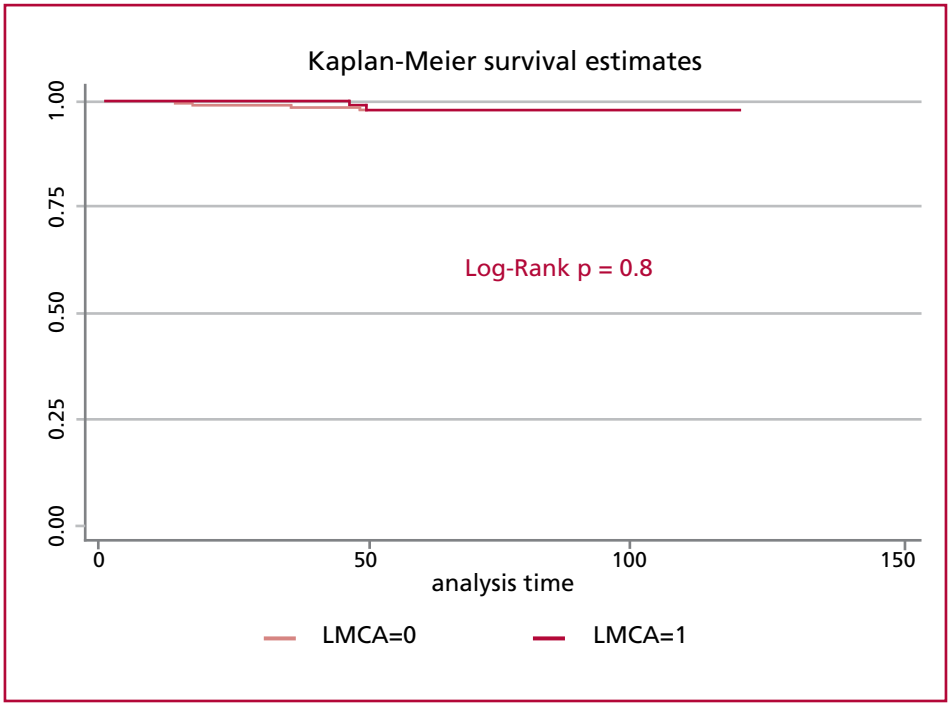

Fig. 3. Stroke-free survival. Kaplan-Meier curve. Comparison in coronary patients undergoing coronary artery bypass grafting with and without left main coronary artery (LMCA) disease (LMCA=1 and LMCA=0, respectively).

ciated with fewer bridges, a higher rate of conversion to surgery with CPB, and increased cardiovascular risk (7). Moreover, Benedetto refers that CABG without CPB is as safe as with CPB in the short. and long-term in highly experienced surgical teams. (8)

In the EXCEL percutaneous coronary intervention (PCI) vs. CABG in LMCA disease study, randomization was stopped prematurely with 1900 instead of the 2600 patients initially planned. (9) Patients included should have a low to moderate coronary anatomy complexity. The 5-year results showed no difference in the composite endpoint of death, AMI, and stroke (PCI 22% vs. CABG 19.2%; OR 1.19; 95% CI 0.9-1.5; p=0.13). All-cause mortality occurred more frequently in the PCI group (13% vs. 9.9%; (OR 1.38, 95% CI 1.03–1.85); however, cardiovascular mortality was similar in both groups (5% and 4.5%, respectively; OR 1.26, 95% CI 0.85-1.85), and AMI rate was also similar (10.6% and 9.1%, respectively; OR 1.14; 95% CI 0.84–1.55). There was also no difference in the in-

Table 2. Baseline characteristics of the population

	LMCA group	Non-LMCA group	Total	*p* value
Patients	175	263	438	
AMI	7 (4%)	7 (2.6%)	14 (3.2%)	NS
Stroke	4 (2.2%)	5 (1.9%)	9 (2%)	NS
Death	15 (8.5%)	21 (8%)	36 (8.2%)	NS
MACE	26 (15.8%)	33 (12.5%)	59 (13.5%)	NS

LMCA: Left main coronary artery. AMI: Acute myocardial infarction. MACE: Major adverse cardiovascular events.

cidence of stroke (CABG 3.7% vs. PCI 2.9%, OR 0.78; 95% CI 0.46-1.31). Ischemia-driven revascularization was more common after PCI than after CABG (16.9% vs. 10.0%; OR 1.84; 95% CI 1.39-2.44; p <0.001).

The SYNTAX study included 1800 patients with three-vessel lesion or LMCA randomly assigned to PCI (n=903) or CABG (n=897). Coronary artery bypass grafting treatment showed lower rates of death and AMI at 5 years in patients with three-vessel disease; therefore, CABG should continue to be the standard of care for three-vessel coronary lesions. (10) It would seem that patients with more complex coronary artery disease would benefit from CABG while PCI would be a valid treatment option in patients with less complex disease, although with a higher rate of subsequent re-intervention.

In this study, a follow-up greater than 93% was achieved at 10 years, (11) with long-term mortality of 248 patients (28%) after PCI and 212 (24%) after CABG (OR 1.19; CI 95 % 0.99–1.43, p=0.06). Among patients with three-vessel disease, 153 (28%) out of 546 had died after PCI vs. 114 (21%) out of 549 after CABG (OR 1.42, 95% CI 1.11–1.81); however, there were no differences in mortality among patients with LMCA disease: 27% with PCI and 28% with CABG (OR 0.92, 95% CI 0.69–1.22; p for interaction=0.023).

The long-term evolution of patients undergoing CABG clearly depends on the type of grafts used. In this case, the great contribution of the work by Lytle et al., in which superiority in long-term survival was observed in those patients with bilateral vs. single internal thoracic artery bypass grafts for CABG, was having promoted a change in the revascularization strategy with a greater tendency to use more than one arterial conduit for revascularization. (12) Taggart in the editorial comment about our publication in Rev Argent Cardiol, precisely highlights the need to investigate and publish the surgical results of both the perioperative and the follow-up periods to analyze the surgical strategies used. (13)

Gaudino et al. carried out a meta-analysis including 35 studies with 149 902 patients in which venous and arterial conduits were used. (14) Mean follow-up time was 6.9 years. The use of arterial conduits (internal thoracic and radial) was associated with a decrease in operative mortality (OR 0.68; 95% CI 0.55–0.83), perioperative AMI (OR 0.77; 95% CI 0.64–0.92) and perioperative stroke (OR 0.80; 95% CI 0.65–0.98) with respect to the use of venous conduits. They also observed lower long-term mortality in CABG with arterial conduits (OR 0.80; 95% CI 0.75–0.85).

The evidence obtained in this meta-analysis did not reveal statistically significant differences between the use of the radial artery or the right internal thoracic artery as the second conduit (the left internal thoracic artery in situ is the first conduit) regarding operative mortality (OR 0.96; CI 95% 0.83– 1.11), perioperative stroke (OR 0.87; 95% CI 0.45–1.68) or perioperative AMI (OR 0.32; 95% CI 0.03–3.13). Moreover, they observed that using the internal thoracic artery skeletonization technique did not increase the risk of mediastinitis.

These data show that surgical groups should increasingly perform CABG, preferably using arterial grafts. In our study population, 82.5% of patients underwent CABG exclusively with arterial grafts, with an average of 3 per patient. This type of surgical technique obviously has an impact and would help reduce cardiovascular risks in the immediate perioperative period and long-term follow-up. We believe that the satisfactory results obtained in our series are comparable to international reference centers with higher volume of surgeries per year. The performance of CABG without CPB with preferably multiple arterial conduits (internal thoracic and radial arteries) should be the background to compare new revascularization procedures. It should be noted that at the beginning of the experience, the learning curve by the surgical group performing CABG without CPB should be considered, perhaps with a selection bias for this surgical modality.

Furthermore, it is important to clarify that there has been no selection of patients for CABG according to the distribution of coronary disease, an aspect that should be taken into account in the analysis of results of other comparative treatment strategy studies for LMCA disease in selected anatomies. In this sense, not all the cases are the same.

Limitations

The greatest limitation of this analysis is its single-center, observational, and retrospective design. Most patients were directed to CABG according to the current recommendations of the American and European revascularization guidelines, as well as according to the consensus reached between the cardiology, endo-

vascular therapy and cardiac surgery services of our hospital. For this reason, strict considerations cannot be made regarding the indication of the therapy indicated due to prior selection bias.

CONCLUSIONS

In our experience, in patients with multivessel coronary artery disease operated on with CABG, the presence of LMCA disease did not increase the rate of serious events (death, infarction and stroke) both in the immediate perioperative period as in the long-term follow-up. The results obtained in this series of patients are similar to those published in the literature used to develop cardiovascular practice guidelines and constitute a local reference to evaluate long-term results.

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ORIGINAL ARTICLE

INOCA: Non-Invasive Assessment of the Pathophysiological Mechanisms Using CZT-SPECT

INOCA: Evaluación no invasiva de los mecanismos fisiopatológicos mediante CZT-SPECT

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ABSTRACT

Background: One of the causes of INOCA (Ischemia with Non- Obstructive Coronary Arteries) is microvascular dysfunction (MVD), which can be noninvasively assessed through the quantification of myocardial blood flow (MBF) and myocardial flow reserve (MFR). Dynamic myocardial perfusion imaging (MPI) by CZT-SPECT at rest, with dipyridamole stress test and cold pressor test (CPT) can establish the presence of two different pathophysiological mechanisms of MVD: endothelium-independent or endothelium-dependent, respectively.
Objectives: The aim of this study was to evaluate the usefulness of CZT-SPECT for the diagnosis of MVD and the different mechanisms involved in patients with INOCA.
Materials and Methods: A total of 93 consecutive INOCA patients were prospectively included and underwent dynamic MPI with CZT-SPECT at rest and with dipyridamole stress test and CPT. THe MBF was quantified using 4DM® software. A MFR response to dipyridamole <2, and changes in MBF (ΔMBF) <1.5 with CPT were considered abnormal responses. MVD was defined in the presence of one abnormal response or both.
Results: CZT-SPECT detected MVD in 85% (n = 79) of the patients with INOCA. Forty-two percent had an abnormal response to both stressors while 43% presented an abnormal response of MBF only with CPT.
Conclusion: The use of CZT-SPECT with both stress tests allowed the evaluation of different possible pathophysiological mechanisms of MVD present in most patients with INOCA.

Key Words: Microvascular blood flow- Vascular endothelium-Vascular smooth muscle-SPECT

RESUMEN

Introducción: Una de las causas propuestas del síndrome INOCA (por sus siglas en inglés: *Ischemia with Non-Obstructive Coronary Arteries*) es la disfunción microvascular (DMV), la cual puede evaluarse en forma no invasiva, mediante la cuantificación del flujo sanguíneo miocárdico (FSM) y la reserva de flujo miocárdica (RFM).
Las imágenes de perfusión miocárdica (IPM) y dinámicas con CZT-SPECT en reposo- dipiridamol - y prueba de frio (PF), permiten establecer la presencia de DMV evaluando diferentes mecanismos fisiopatológicos: endotelio independiente o dependiente, respectivamente.
Objetivos: Evaluar la utilidad de CZT-SPECT en el diagnóstico de DMV y los diferentes mecanismos patológicos involucrados, en pacientes con diagnóstico de INOCA.
Material y métodos: Se incluyeron en forma prospectiva 93 pacientes consecutivos con diagnóstico de INOCA, a los que se les realizó IPM e imágenes dinámicas con CZT-SPECT en reposo-dipiridamol-PF. El FSM se cuantificó con el software 4DM. Se consideró respuesta anormal al dipiridamol una RFM <2 y a la variación del FSM (ΔFSM) <1,5 con PF. Se definió DMV a la presencia de una o ambas respuestas anormales.
Resultados: El CZT-SPECT detectó DMV en un 85% (n=79) de los pacientes con INOCA. El 42% tuvo respuesta anormal con ambos apremios mientras que el 43% restante, mostró una respuesta alterada del FSM sólo con PF.
Conclusiones: El uso de CZT-SPECT empleando ambos apremios,
permitió evaluar diferentes mecanismos fisiopatológicos que causan DMV presente en la mayoría de los pacientes con INOCA.

Palabras Clave: Flujo sanguíneo microvascular - Endotelio vascular - Músculo liso vascular - SPECT

Rev Argent Cardiol 2022;90:185-192. http://dx.doi.org/10.7775/rac.v90.i3.20515

Received: 04/08/2022 – *Accepted:* 05/15/2022

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INTRODUCTION

Ischemia with Non- Obstructive Coronary Arteries (INOCA), a syndrome defined by the presence of signs or symptoms of myocardial ischemia without obstruction of the epicardial coronary arteries, is an increasingly common finding, particularly in women. (1-3)

The overall prevalence is estimated to be close to 39%; however, it varies considerably according to sex, with a prevalence of 33% in men and up to 65% in symptomatic women undergoing elective coronary angiography. (1-3)

Among the different pathophysiological causes explaining these syndromes, vasospasm and microvascular dysfunction (MVD) are the two main mechanisms proposed. (4,5)

Coronary artery vasoreactivity can be invasively assessed by coronary angiography. Microvascular function can also be evaluated by noninvasive imaging methods; among these, cardiac positron emission tomography (PET) imaging is currently the gold standard and most validated method, as it allows quantification of myocardial blood flow (MBF) and myocardial flow reserve (MFR). (6-10)

The novel CZT cameras have higher sensitivity and energy resolution than the conventional SPECT cameras with sodium iodide crystal scintillation detectors, and allow dynamic quantification of MBF and estimation of MFR comparable to PET. (11-13)

Myocardial blood flow and MFR can be quantified after inducing maximal hyperemia which can be attained by different stimuli evaluating different physiological mechanisms. Dipyridamole inhibits endogenous adenosine reuptake, thereby causing microvascular vasodilation by inhibiting calcium influx into the smooth muscle cells, while cold pressor test (CPT) is a powerful sympathetic nervous system stressor that, like acetylcholine, leads to the release of nitric oxide and endothelium-derived hyperpolarizing factors. (7, 14-17)

Noninvasive imaging tests using both stressors to measure MBF and MFR could be useful to establish the diagnosis of MVD and differentiate the mechanisms involved.

The aim of this investigation was to determine the prevalence of MVD in INOCA patients using noninvasive imaging tests with estimation of MFR after dipyridamole stress and changes in MBF (ΔMBF) to CPT.

METHODS

Study design: we conducted a prospective, single-center cohort study.

Population: the study population was made up of 93 consecutive patients with INOCA in the absence of a ≥ 50% diameter stenosis documented by elective conventional coronary angiography (n = 83) or computed tomography coronary angiography (n = 10). Patients with evidence of myocardial infarction, cardiomyopathies, left ventricular dysfunction and valvular heart disease were excluded from the study.

Method for image acquisition and processing

All the patients underwent CZT-SPECT myocardial perfusion scintigraphy using a 2-day protocol without discontinuing their usual medication.

On the first day, 7mCi of Tc^{99m}-MIBI were injected at rest, and dynamic images were obtained for determining baseline MBF, followed by conventional myocardial perfusion imaging (MPI) protocol. At 60 minutes, 0.56 mg/kg of dipyridamole were administered intravenously over 4 minutes; thereafter, 21mCi of Tc^{99m}-MIBI were injected. The hemodynamic values and dynamic images were obtained again to determine MBF after dipyridamole stress and MPI.

On the second day, the baseline hemodynamic values were obtained again and compared with those measured on the previous day. As there were no significant variations (see appendix) and, in agreement with the institutional review board to follow the standard regulations of administering the lowest possible radiation dose, Tc^{99m}-MIBI was not re-injected at rest, and the protocol was directly initiated with the second stressor.

For the CPT, each patient immersed his/her hand into a cold water container with a temperature of 4 °C over 2 minutes. Then, 21 mCi of Tc^{99m}-MIBI were injected and dynamic images were obtained to determine MBF, followed by conventional MPI protocol.

The 4DM® software was used for image processing and MBF quantification at rest and after both stressors. The MBF was expressed in mL/min/g. The MFR was calculated as the ratio of MBF during dipyridamole stress test to resting MBF, and the ΔMBF response to CPT as the ratio of MBF during CPT to resting MBF.

A value of MFR <2 and a ΔMBF to CPT <1.5 were considered abnormal. (14-17) Microvascular dysfunction was defined in the presence of one abnormal response or both. Four groups were obtained after combining the results obtained in our sample of patients: 1) normal MFR and abnormal ΔMBF; 2) abnormal MFR and abnormal ΔMBF; 3) abnormal MFR and normal ΔMBF, and) normal MFR and normal ΔMBF.

Statistical analysis

Quantitative variables were expressed as median and interquartile range (IQR), according to their distribution, and were compared using the Kruskal-Wallis test. Qualitative variables were expressed as percentage and compared using multiple chi-square test. The Bonferroni test was used for comparing groups.

A p value <0.05 was considered statistically significant. All the calculations were performed using StatsDirect 3.3.5 software package.

Ethical considerations

The study was approved by the institutional review board and all the subjects signed and informed consent form.

RESULTS

A total of 93 patients were analyzed. There were no significant differences in patients' baseline characteristics or medications between the different groups, except for the use of statins (Table 1). There were no patients in group 3.

Eighty-eight patients were symptomatic. MVD was evaluated after the first episode of precordial pain in 32, while in the remaining 56 the evaluation was carried out after several symptomatic episodes. Even 18 of them underwent diagnostic angiography on more than one occasion. All cases had the last episode

Table 1. Baseline characteristics of the patients

	Group 1 (n = 40)	Group 2 (n = 39)	Group 4 (n = 14)	p
Age (yrs), mean±SD	59±11	58±12	56±10	ns
Sex				
Male	12 (30%)	16 (41%)	6 (43%)	ns
Female	28 (70%)	23 (59%)	8 (57%)	ns
Symptoms or ECG changes				
Atypical angina	34 (74%)	28 (72%)	10 (71%)	ns
Typical angina	3 (8%)	9 (23%)	4 (29%)	ns
STD >3 mm	3 (8%)	2 (5%)	0	ns
CVRF present				
Diabetes	5 (12%)	5 (13%)	1 (7%)	ns
Hypertension	19 (48%)	19 (48%)	6 (43%)	ns
Smoking habit	14 (35%)	15 (38%)	5 (36%)	ns
Dyslipidemia	24 (60%)	24 (62%)	7 (50%)	ns
4 CVRF	1 (2%)	3 (8%)	0	ns
3 CVRF	5 (12%)	6 (16%)	3 (21%)	ns
2 CVRF	17 (43%)	10 (25%)	3 (21%)	ns
1 CVRF	9 (23%)	13 (33%)	4 (29%)	ns
No CVRF	8 (20%)	7 (18%)	4 (29%)	ns
Menopause	25 (89%)	18 (78%)	8 (100%)	ns
Usual medication				
Aspirin	16 (40%)	17 (44%)	7 (50%)	ns
Beta blockers	11(28%)	15 (38%)	9 (64%)	ns
ACEI	11(28%)	9 (23%)	9 (64%)	ns
ARB	6 (15%)	5 (13%)	0	ns
Clopidogrel	2 (5%)	2 (5%)	2 (5%)	ns
Calcium channel blockers	6 (15%)	12 (31%)	2 (5%)	ns
Trimetazidine	4 (10%)	6 (15%)	2 (5%)	ns
Isosorbide dinitrate	2 (5%)	7 (18%)	0	ns
Statins	25 (63%)	20 (51%)	14 (100%)	0.005

SD: standard deviation ECG: electrocardiogram; STD: ST-segment depression; CVRF: cardiovascular risk factor. ACEI: angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blockers

of precordial pain, at least 30 days prior to the study. Five patients were considered INOCA due to a history of asymptomatic ST segment depression (STD) in stress tests (3 patients in group 1 and 2 patients in group 2).

Myocardial perfusion images were normal at rest and after both stress tests in all the cases. Normal MPI was defined as absence of segmental uptake defects of Tc^{99m}-MIBI, assessed quantitatively by a sum score of zero after each stress and at rest, and qualitatively by comparing the polar maps of each patient with those of the software program. In addition, the normal MPI definition included absence of regional or global wall motion abnormalities or a left ventricular ejection fraction < 55%.

Five patients reported chest discomfort during dipyridamole stress test and none of them presented electrocardiographic changes with both stressors.

Microvascular dysfunction occurred in 79 patients (85%). There were 40 patients (43%) in group 1, 39 (42%) in group 2, no patients in group 3, and 14 patients (15%) in group 4.

Hemodynamic parameters at baseline and after stress tests did not show statistically significant differences between groups, except for MBF at rest between groups 2 and 4 ($p<0.05$), after dipyridamole between group 1 vs 2 ($p< 0.0001$) and vs group 4 ($p<0.05$), as well as between groups 2 and 4 ($p<0.05$), and in CPT between groups 1 and 2 vs group 4 ($p<0.0001$).

We found a significant difference in the MFR between group 1 and 2 ($p < 0.0001$) and between group 2 and 4 ($p < 0.0001$), as well as in the CPT ΔMBF between group 1 vs. group 2 ($p = 0.0013$), group 1 vs. group 4 ($p < 0.0001$) and between group 2 vs. group 4 ($p < 0.0001$). ΔMBF values less than 1 also showed a significant difference between groups 1 and 2 ($p<0.0001$) (Table 2)

DISCUSSION

In our study, most INOCA patients (n=79) evaluated with CZT-SPECT had an abnormal vasodilator response with CPT, which demonstrates an endothelium-dependent MVD. In addition, patients in group 2 had decreased MFR after dipyridamole stress test,

showing a dual pathophysiological component in this subgroup (Figure 1).

The use of both stressors in our patients allowed the evaluation of different possible pathophysiological mechanisms of MVD: endothelium-dependent or smooth muscle-dependent. The CPT was useful to detect MVD in most cases, even in patients with normal vasodilator response to dipyridamole, as patients in group 1.

The MBF response to CPT was abnormal not only because it did not increase by 50% as expected, but also because the MBF decreased compared with the baseline value in 38 patients, which could be interpreted as an endothelium-dependent microvascular vasospasm (Figure 2). Twelve of these 38 patients (32%) belonged to group 1 and 26 patients (68%) to group 2 ($p < 0.0001$), which could reflect that the microvascular involvement was greater in the latter group of patients, with both functional and structural impairment.

We failed to establish the clinical and methodological characteristics of the 14 patients with normal ΔMBF with CPT and normal MFR with dipyridamole stress test to explain a difference with the rest of the patients. However, it could be related with the presence of vasospastic angina, not detectable by this method, or to other causes of chest pain, such as neuropathic pain. We can only mention as a distinctive finding that this group of patients were all medicated with statins.

We did not perform intracoronary injection of acetylcholine or ergonovine during the index invasive coronary angiography in any of our patients; therefore, we cannot affirm that MVD is the only pathophysiological mechanism involved, since a small percentage of patients with this syndrome may present vasospastic angina associated with microvascular angina. (8,9)

The current evidence demonstrates that MVD is present in the early stages of atherogenesis due to structural and functional changes that occur in the walls of arterioles and intramural capillaries, often related with the presence of cardiovascular risk factors (CVRF). (7)

CVRF increase reactive oxygen species production, leading to endothelial dysfunction. In consequence, the release of vasodilator substances such as nitric oxide is reduced, resulting in a reduction in smooth muscle cell relaxation. Thus, the assessment of the endothelium-dependent vasodilator response with CPT could detect earlier stages of MVD even if smooth

Table 2. Hemodynamic values and results obtained by groups.

	Group 1 (n = 40)	Group 2 (n = 39)	Group 4 (n = 14)
Rest:			
HR (bpm)	65 (58-75)	64 (59-70)	62 (59-71)
SBP (mm Hg)	130 (120-135)	130 (120-130)	130 (120-140)
DBP (mm Hg)	80 (80-80)	80 (80-80)	80 (70-90)
RPP	7975 (7450-10010)	8160 (7200-9100)	8305 (7080-9230)
LVEF (%)	75 (68-83)	71 (66-71)	70 (67-77)
MBF (mL/min/g)	1,05 (0,81-1,29)	1,18 (0,93-1,32) *vs G4	0,71 (0,66-1,15)
Dipyridamole:			
HR (bpm)	80 (68-93)	74 (68-80)	75 (64-86)
SBP (mm Hg)	120 (117-130)	130 (120-140)	125 (110-140)
DBP (mm Hg)	80 (75-80)	80 (80-80)	80 (70-80)
RPP	9615 (8425-11850)	9000 (8360-10200)	9030 (7920- 10360)
LVEF (%)	73 (70- 82%)	74 (70-80%)	75 (70-81)
MBF (mL/min/g)	2.69 (2.15-3.32) †vs G2 *vs G4	1.84 (1.49-2.07) *vs G4	2.09 (1.72-2.84)
CPT:			
HR (bpm)	70 (61-80)	72 (67-78)	70 (66-80)
SBP (mm Hg)	120 (110-130)	120 (120-130)	125 (120-140)
DBP (mm Hg)	80 (75-80)	80 (70-80)	80 (80-80)
RPP	8400 (7250-9610)	8760 (8040-9620)	9045 (8260-9940)
LVEF (%)	74 (69-81)	72 (67-77)	73 (69-80)
MBF (mL/min/g)	1.04 (0.83-1.59) †vs G4	0.99 (0.77-1.23) †vs G4	1.70 (1.19-1.96)
MFR	2.58 (2.13-3.26)	1.56 (1.41-1.69) †vs G1 and G4	2.53 (2.25-3.18)
ΔMBF	1.08 (0.95-1.26) * vs G2, †vs G4	0.87 (0.72-1.11) †vs G4	1.79 (1.54-2.02)
ΔMBF <1	0.87 (0.71-0.94)	0.79 (0.69-0.87) †	-

*p<0.05 †p < 0.0001
All the results expressed as median and interquartile range.
HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure
RPP: rate pressure product (maximum SBP x maximum HR); LVEF: left ventricular ejection fraction; MBF: myocardial blood flow; MFR: myocardial flow reserve; ΔMBF: changes in myocardial blood flow ; CPT: cold pressor test.

muscle-dependent vasodilator response is normal. Moreover, vascular impairment will be greater as the exposure time to these CVRF increases. (7)

The population evaluated in our study had one or more CVRF. Of the 19 patients without any traditional CVRF, 9 were postmenopausal women. Several studies with PET demonstrated that the reduction in estrogen levels in postmenopausal women predisposes to a reduction in coronary artery vasodilation similar to that observed in premenopausal women with diabetes. (19-21)

The clinical manifestations of MVD include typical exercise-induced angina, angina in the immediate recovery after exercise or even at rest, atypical chest pain or angina equivalents such as exercise-induced dyspnea. Because of this wide variety of symptoms, different criteria were established for the diagnosis of microvascular angina, considering not only the clinical aspects, but also the abnormal values of coronary vasoreactivity according to different methods, as MBF and MFR. (9, 21,22)

Although MVD can worsen the prognosis in patients with or without obstructive coronary artery disease, particularly in the presence of symptoms, there is currently no specific treatment. This leads to multiple combinations of different drugs, some of them with no clear evidence of benefit, as in our patients. (23,24)

The importance of knowing the pathophysiological mechanisms involved in INOCA syndromes lies in tailoring the treatment to each particular case. Several studies have demonstrated that the quality of life of these patients improves when the different mechanisms are evaluated and treatment is based on the pathophysiological cause involved. The CormicA trial evaluated invasive coronary function testing at time of

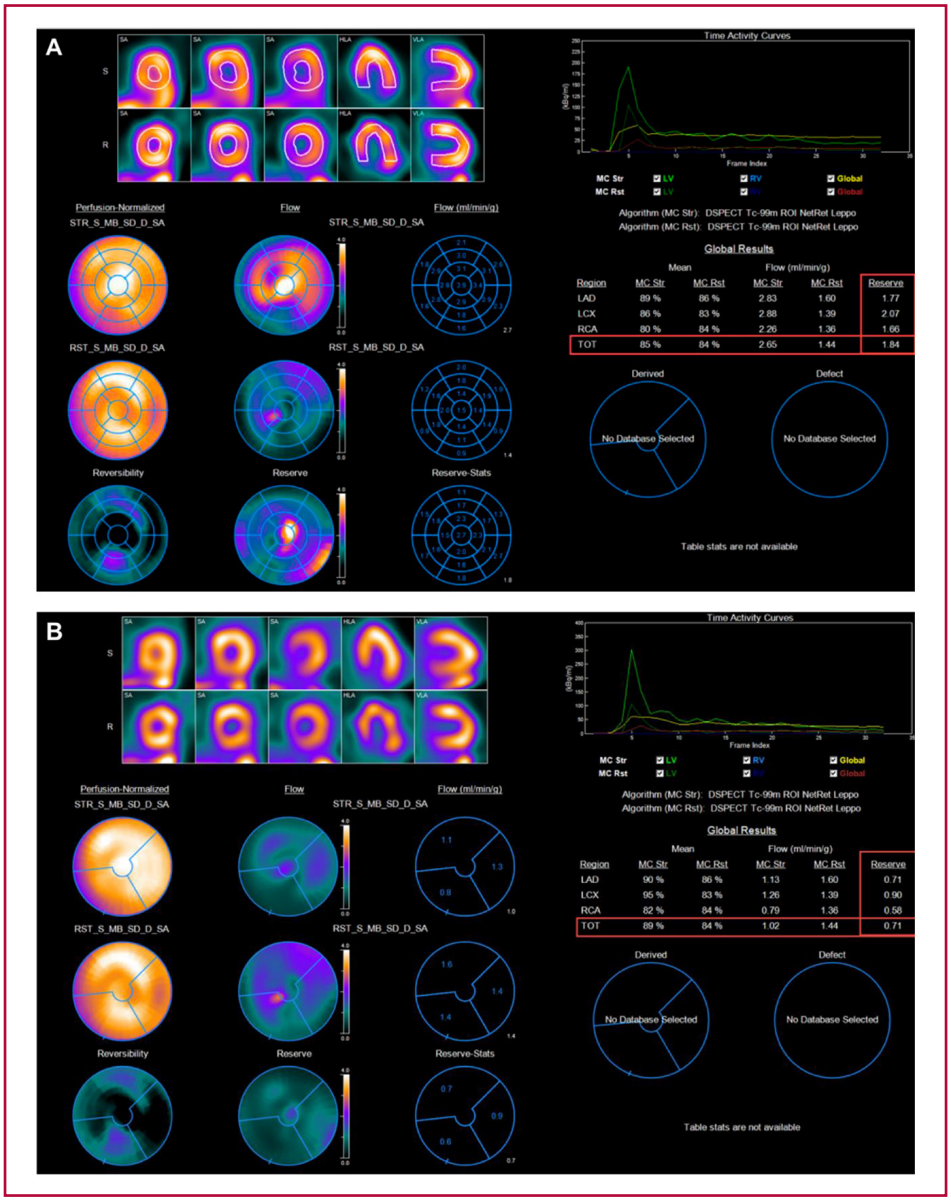

Fig. 1. Patient with smooth-muscle dependent and endothelium-dependent MVD. **A.** Dipyridamole (MFR: 1.84). **B.** Cold pressor test (ΔMBF: 0.71)

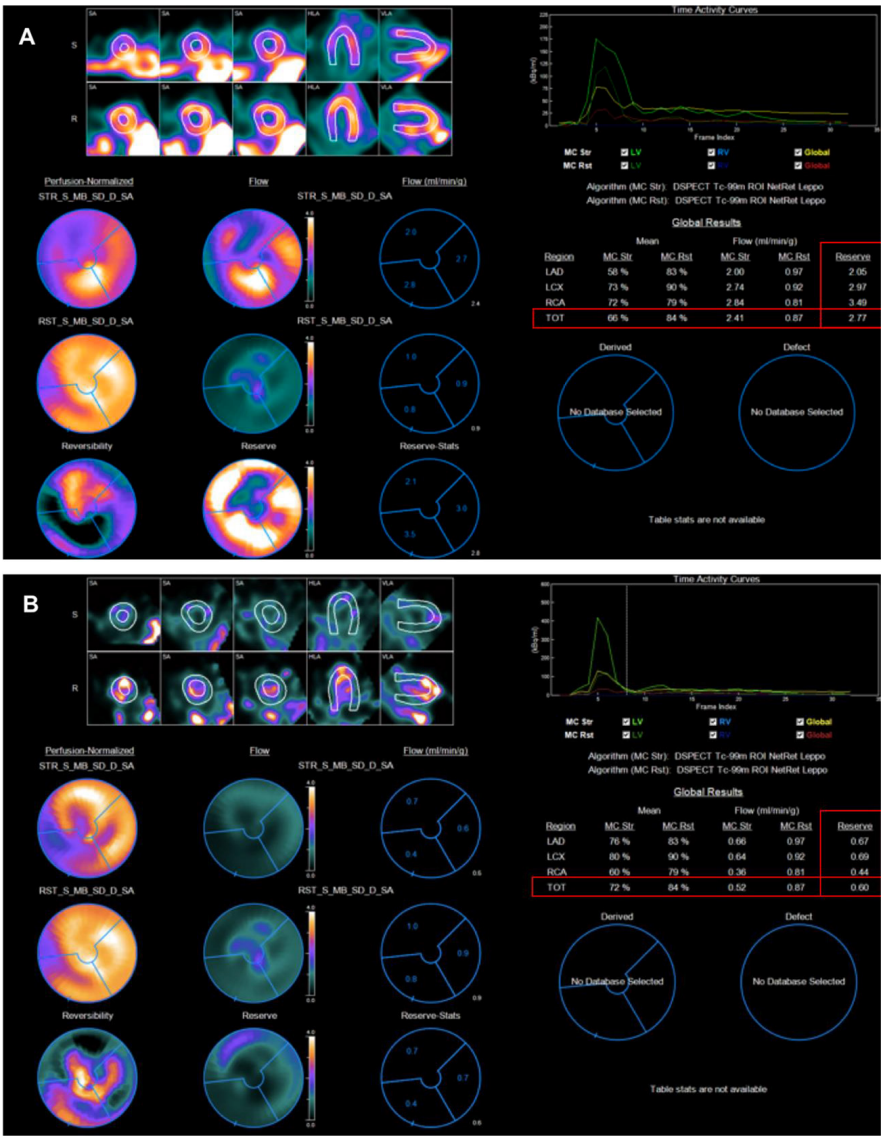

Fig. 2. Patient with endothelium-dependent microvascular vasospasm. **A.** Dipyridamole (MFR: 2.77) **B.** Cold pressor test (ΔMBF: 0.60)

the index diagnostic angiography in 151 patients with INOCA randomized to medical therapy guided by an interventional diagnostic procedure (group 1) versus control group (group 2). Quality of life and clinical events at 1 year were compared in both groups. Group 1 showed marked and sustained clinical improvement and better quality of life compared with the control group. (2,25).

We present a simple, noninvasive diagnostic algorithm, which includes the evaluation of the two possible mechanisms of coronary vasoreactivity that produce MVD in patients with INOCA (Figure 3).

Study limitations:

The sample size is small and the method used is relatively new, although its validation and reproducibility are currently accepted. Future studies in larger populations will be necessary to evaluate the usefulness of this approach in patients with INOCA.

Although invasive functional coronary testing is not routinely performed in our country in patients with INOCA, we consider that such evaluation should be performed during diagnostic coronary angiography to rule out epicardial coronary vasospasm as a probable or concomitant cause.

CONCLUSIONS

In our experience, the use of CZT-SPECT devices detected MVD in 85% of patients with INOCA.

The use of both stress tests allowed the evaluation of two different pathophysiological mechanisms of MVD: endothelium-dependent or smooth muscle-dependent.

Evaluation with CPT should be included in the

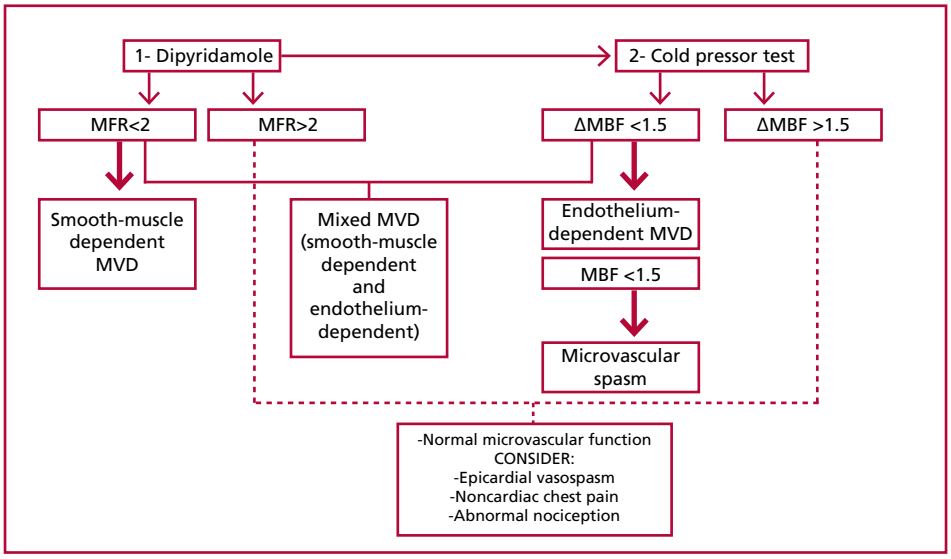

Fig. 3. Diagnostic algorithm proposed to for non-invasive assessment of microvascular function in patients with INOCA.

MFR: myocardial flow reserve. Δ MBF: myocardial blood flow variation. MVD: microvascular dysfunction

noninvasive assessment of INOCA patients, as MVD may be present even with normal MFR with dipyridamole stress test.

Conflicts of interest

None declared.

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

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Appendix

Comparison between the resting hemodynamic values (day 1 vs. day 2) across the different groups

	Rest Day 1	Rest Day 2	p
Group 1			
HR (bpm)	65 (58.5-75.5)	67 (58.5-76)	ns
SBP (mm Hg)	130 (120-135)	130 (120-130)	ns
DBP (mm Hg)	80 (80-80)	80 (75-80)	ns
RPP	7975 (7450-10010)	8140 (7285-9755)	ns
Group 2			
HR (bpm)	64 (59-70)	64 (59-68)	ns
SBP (mm Hg)	130 (120-130)	130 (120-140)	ns
DBP (mm Hg)	80 (80-80)	80 (80-80)	ns
RPP	8160 (7200-9100)	8260 (7370-9100)	ns
Group 4			
HR (bpm)	62 (59-71)	68 (62-77)	ns
SBP (mm Hg)	130 (120-140)	125 (120-140)	ns
DBP (mm Hg)	80 (70-90)	80 (80-80)	ns
RPP	8305 (7080-9230)	8400 (7680-10140)	ns

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate pressure product

ORIGINAL ARTICLE

Attitudes and Clinical Practice in Heart Failure Among Physicians in Argentina

Actitudes y prácticas clínicas en la insuficiencia cardiaca en médicos de Argentina

LUCRECIA MARÍA BURGOS[1], MARÍA LORENA CORONEL[2], JORGE THIERER[3]

ABSTRACT

Background: It is necessary to identify areas of improvement in the care of heart failure (HF) patients and thus implement educational interventions to optimize quality of care and their clinical outcomes.
Objective: The aim of this study was to evaluate attitudes, knowledge, confidence and care pathways of patients with HF among physicians in Argentina.
Methods: We conducted a cross-sectional study using a self-administered survey to evaluate clinical practice patterns, and attitudes/perceptions regarding the diagnosis, treatment and follow-up of HF patients in the outpatient and inpatient setting. The survey respondents were physicians from 22 centers in Argentina who participated in a comprehensive educational program for the care of HF patients carried out between March and July 2021.
Results: A total of 50 physicians were surveyed; mean age was 41 ± 8 years and 86% were cardiologists. In patients with reduced left ventricular ejection fraction, 24% of the respondents reporting starting with quadruple therapy; 88% chose beta-blockers, 72% dual angiotensin receptor-neprilysin inhibitors, 48% mineralocorticoid receptor antagonists and 34% sodium-glucose cotransporter-2 inhibitors. Fifty percent of the survey respondents answered that they do not reach quadruple therapy. Forty-four percent of physicians reported they felt very uncertain about the diagnosis of HF with preserved ejection fraction, and 46% considered relevant to evaluate the presence of anemia or iron deficiency
Conclusion: There are knowledge gaps in the diagnosis and treatment of HF, especially in the diagnosis of HF with preserved ejection fraction, and in the indication of quadruple therapy. This highlights the need for implementing educational strategies that focus on knowledge, confidence, and care pathways.

Keywords: Heart failure - Quality of care, Ambulatory Care, Ventricular Dysfunction, Argentina

RESUMEN

Introducción: Es necesario identificar áreas de mejora en la atención de los pacientes con insuficiencia cardíaca (IC), para implementar intervenciones educativas con el fin de optimizar la calidad de atención y los resultados clínicos.
Objetivo: Evaluar las actitudes, conocimiento, confianza y formas de atención a pacientes con IC, de médicos de Argentina.
Material y métodos: Estudio de corte transversal a través de una encuesta auto administrada para evaluar los patrones de práctica clínica y las actitudes/percepciones relacionadas con el diagnóstico, tratamiento y seguimiento de pacientes con IC en el ámbito ambulatorio y el hospitalario. Se incluyeron médicos de 22 centros de Argentina que participaron de un programa integral educativo de IC entre marzo y julio de 2021.
Resultados: Se encuestaron 50 médicos, con edad media de 41 (±8) años; el 86% eran cardiólogos. En pacientes con fracción de eyección ventricular izquierda deprimida, el 24% inicia con la terapia cuádruple, y privilegia en un 88% los betabloqueantes, 72% los inhibidores duales de la neprilisina y la angiotensina II, 48% los antagonistas de los receptores mineralocorticoides y en el 34% los inhibidores del cotrasportador sodio glucosa 2. El 50% de los encuestados refiere que no llega a alcanzar la cuádruple terapia. El 44% refiere sentirse muy inseguro con el diagnóstico de IC con fracción de eyección preservada. El 46% de los médicos considera relevante la determinación de anemia o ferropenia.
Conclusión: Se identificaron brechas de conocimiento en el diagnóstico y tratamiento de la IC, especialmente en el diagnóstico de IC con fracción de eyección preservada, y la cuádruple terapia. Esto refuerza la necesidad de implementar estrategias educativas que tengan como foco el conocimiento y seguridad, y las formas de atención.

Palabras clave: Insuficiencia cardíaca - calidad de atención - Atención Ambulatoria - Disfunción Ventricular - Argentina

Rev Argent Cardiol 2022;90:193-205. http://dx.doi.org/10.7775/rac.v90.i3.20520

Received: 04/16/2022 – *Accepted:* 05/18/2022

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INTRODUCTION

Despite important therapeutic advances, the prevalence of heart failure (HF) is still a major healthcare issue (1, 2) and is associated with frequent hospitalizations, high morbidity and mortality rates, and elevated healthcare costs. (3) Furthermore, HF prevalence and burden to the health care system are expected to increase due to population aging and prolonged survival of patients with cardiovascular diseases. (4)

Therefore, the effective diagnosis and treatment based on clinical practice guideline recommendations for HF patients is essential; (5-8) however, translation to clinical practice is suboptimal and many HF patients do not receive adequate treatments or doses. (10-12)

In Argentina, the available information about medical attitudes and opinion regarding diagnostic and therapeutic practices in chronic and decompensated HF comes from the 2005 DIME-IC national survey, which found a wide disparity between most of the strategies used for diagnosis, evaluation and therapy. (13)

Therefore, the aim of this initiative was to obtain updated information on the attitudes, knowledge and care pathways for the contemporary diagnosis and management of HF among physicians in the secondary and tertiary level of care in Argentina.

METHODS

Study design and population

The study had a cross-sectional design. The physicians included represented 22 public and private healthcare centers of the second and third levels of care in Argentina who voluntarily participated in a comprehensive educational program for the care of HF patients carried out between March and July 2021. The aim of the educational intervention was to optimize the diagnosis and treatment of HF patients in the outpatient and inpatient settings, based on a training program in heart failure clinics with a total training load of 30 hours and a final exam.

Development of the survey

A baseline survey was performed in March 2021. The online questionnaire was created, distributed and administered using Google Forms (Mountain View, CA). The link to the questionnaire was submitted via e-mail. When the participants received and clicked on the link, they were automatically directed to the information about the study and the informed consent.

The information collected included demographics, educational background of the participants, their place of practice and the characteristics of the patients they treated. In addition, key areas on attitudes and general and specific clinical practice for the management of HF according to national and international clinical practice guidelines were evaluated.

The online, self-administered survey used several question formats to measure confidence, clinical practice patterns, and attitudes/perceptions regarding the diagnosis, treatment, follow-up, long-term management, and multidisciplinary care of outpatients and inpatients with HF. The 55 questions of the survey were developed based on a review of the literature and on the recommendations of clinical practice guidelines (5-8,14), and expert opinions (supplementary appendix). Self-reported confidence in knowledge and practice decisions was rated on a 5-point scale, where 1 was not at all confident, 2 to 4 somewhat confident and 5 completely confident.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, or median and interquartile range (IQR), according to their distribution. Categorical variables were expressed as numbers and percentages. Data obtained from multiple choice questions were analyzed using descriptive statistics. All the statistical calculations were performed using IBM® SPSS® Statistics 25.0 statistical package (IBM Corp., Armonk, NY, USA).

Ethical considerations

The authors developed the report without the participation of the sponsor of the educational program (AstraZeneca laboratory). We did not obtain approval from the institutional or central review board because our study was designed to examine the perceptions and knowledge of physicians rather than to collect information from patients. The professionals answered the survey for free, and the survey was completely anonymous.

RESULTS

Characteristics of the physicians and healthcare centers

Of the 50 physicians participating in the educational intervention, 100% responded to the requests and completed the survey.

Twenty-four percent of survey respondents worked in the City of Buenos Aires, 21% in Cordoba, 12% in Corrientes, 10% in Buenos Aires, 7% in Chaco and Misiones, 5% in La Pampa, Neuquen and Santa Fe, and the remaining 4% in Mendoza and Tucuman.

Mean age was 4 ± 8 years, with a median time since graduation from medical school of 13 years (IQR 7-20).

Eighty-six percent were cardiologists, 12% were internists, and 2% were endocrinologists. Ninety-two percent worked in a multidisciplinary healthcare center. Thirty-four percent of the professionals worked in a private center or with social security coverage, 14% in the public sector and the remaining 52% in both sectors. All the professionals reported that their diagnostic and therapeutic management was based on clinical practice guidelines.

The median number of total beds available in the center where they worked was 65 (IQR 16-150), with 12 (IQR 8-25) beds dedicated to patients with cardiovascular diseases.

The physicians surveyed saw 8 patients (IQR 4-10) with HF per week on an outpatient basis, and 74% of those dealing with hospitalized patients saw a median of 4 patients (IQR 2-6) with acute HF.

Regarding HF services and availability of resources, 80% of the respondents worked in centers with critical care units, and 28% had HF units. In addition, 59% had a specific a HF clinic, 18% had palliative care services and 12% counted with a hospital day-case unit.

The centers had several specialties available for

consultation: pulmonology (98%), diabetology (98%), nephrology (94%), neurology (92%) and hematology (88%).

The diagnostic tests available in more than 90% of the centers where the physicians surveyed worked were electrocardiogram (ECG), echocardiography, scale, 24-hour Holter monitoring, laboratory tests including troponin (Figure 1), and 60-70% had availability of natriuretic peptides and right and left heart catheterization.

The therapeutic options available in more than 70% of the centers were renal replacement therapies, intravenous iron infusion, implantable cardioverter defibrillators (ICDs) or cardiac resynchronization therapies (CRTs), and percutaneous coronary interventions. Only 10% had heart transplantation capabilities and 15% counted with ventricular assist devices (Figure 1, supplementary material).

Characteristics of the patients with heart failure treated

Among HF patients treated, 40% (IQR 30-60) were 50-70 years old and 43% (IQR 25-60) were > 70 years.

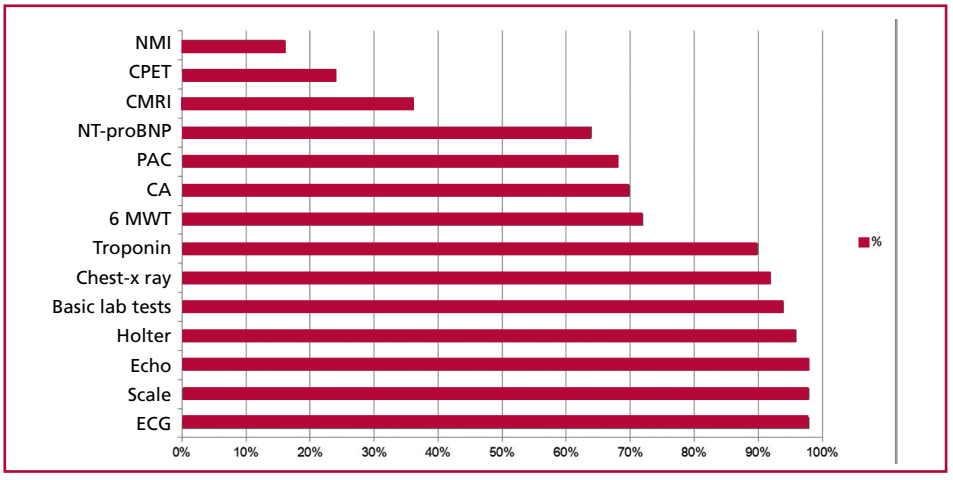
Comorbidities as anemia, iron deficiency and diabetes were common. Most patients had left ventricular ejection fraction (LVEF) < 40% and the most common etiology was ischemic cardiomyopathy, followed by hypertensive heart disease (Table 1).

In terms of medical coverage, 40% (IQR 20-50) counted with the national social security system, 20% (IQR 5-40) had provincial social security coverage and 10% (0-20) prepaid medical insurance.

Diagnosis

The physicians were asked about the signs and symptoms they consider for the diagnosis of HF in daily clinical practice. The most ranked symptoms were paroxysmal nocturnal dyspnea (98%), orthopnea and

Fig. 1. Complementary tests available in the centers.



NMI: Nuclear medicine images; CPET: cardiopulmonary exercise testing; CMRI: cardiac magnetic resonance imaging; PAC: pulmonary artery catheter; CA: coronary angiography; 6MWT: 6 minute-walk test; Echo: echocardiography; ECG: electrocardiogram

Table 1. Baseline characteristics of the population with heart failure treated by the physicians surveyed.

	Median (IQR)
Comorbidities	
Anemia	30% (15-50)
Iron deficiency	20% (10-40)
Diabetes	60% (30-80)
Hyperkalemia	10% (5-20)
Chronic kidney failure with creatinine clearance < 60 mL/min/m^2 or creatinine levels > 1.5 mg/dL	30% (20-50)
LV ejection fraction < 40%	60% (45-75)
Etiology	
Ischemic	50% (40-60)
Hypertensive	20% (10-35)
Valvular heart disease	10% (5-20)
Idiopathic	5% (5-15)
Undetermined	5% (1-10)
Chagas' disease	4% (1-10)
Other	6% (2-10)

the presence of pulmonary rales (both 96%), while heart murmurs (42%) and palpitations (28%) were the least ranked.

The most relevant diagnostic tests were the determination of LVEF and renal function, followed by functional class and etiology of heart disease. Only 46% considered relevant to evaluate the presence of anemia or iron deficiency (Figure 2).

Forty-four percent of physicians reported feeling very uncertain about the diagnosis of HF with preserved ejection fraction (HFpEF) and 24% felt very uncertain about the diagnosis of HF in the patient with comorbidities (Figure 3).

As for hospitalizations, 82% considered very important to find the decompensating factor.

Treatment

When physicians were asked which drugs they prioritized when initiating treatment of patients with HF with reduced LVEF (HFrEF) in the outpatient setting, 88% chose beta-blockers (BBs), 78% angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), 72% dual angiotensin receptor-neprilysin inhibitors (ARNIs), 48% mineralocorticoid receptor antagonists (MRAs) and 34% sodium-glucose cotransporter-2 (SGLT2) inhibitors.

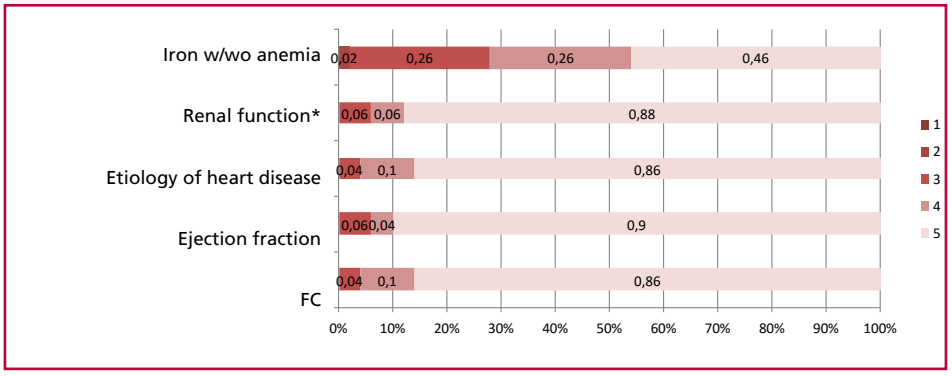
The drug combinations preferred at the initiation of treatment were quadruple therapy (BB; SGLT2; MRA and ACE inhibitor/ARB/ARNI) 24%, triple therapy 32%, double therapy 30%, and monotherapy 14%. The classic combination of an ACE inhibitor/ARA II, BB and MRA was the scheme most used.

The median time to reach 50% of the target dose of each drug in a patient with HFrEF with quadruple therapy is 4 weeks (RIC 2-8), and a median of 8 weeks (4-12) for the target dose. Fifty-percent of the survey respondents answered that they do not reach quadruple therapy.

Fifty percent of physicians felt confident to identify patients with indication for cardiovascular rehabilitation; however, only 20% felt confident to indicate cardiac transplantation (Figure 4).

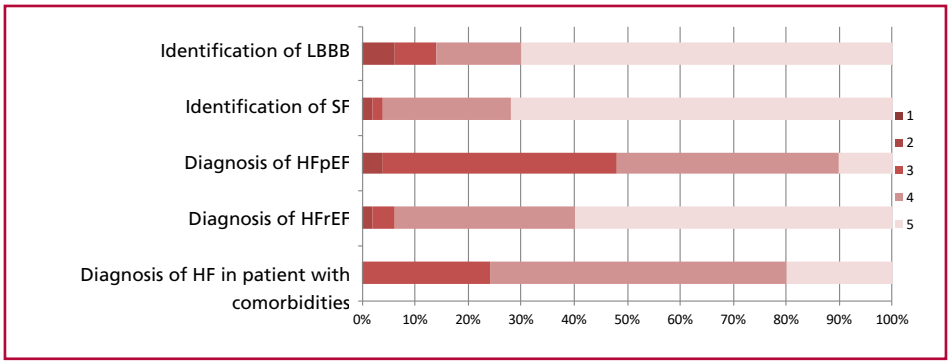
Among hospitalized patients, 84% titrate their medication before hospital discharge and 16% prefer to make modifications on an outpatient basis. The importance of administering hypertonic saline and intravenous iron in patients hospitalized for HF was investigated. Only 12% and 6% of the physicians surveyed considered that the administration of iron and hypertonic saline, respectively, were essential.

As for the signs or methods to assess congestion in patients hospitalized for HF to define hospital discharge, 100% use physical examination, 82% evaluate weight loss and functional class, 62% perform echo-



5-point scale: 1 "not relevant at all", and 5 "absolutely essential". w/wo: with or without; FC: functional class *BUN; creatinine; creatinine clearance.

Fig. 2. Relevance of diagnostic practices.



5-point scale: 1 "not confident at all in the diagnosis" and 5 "absolutely confident with my diagnosis" HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; AF: atrial fibrillation; LBBB: left bundle branch block.

Fig. 3. Certainty and confidence about the diagnosis of HF in the outpatient setting.

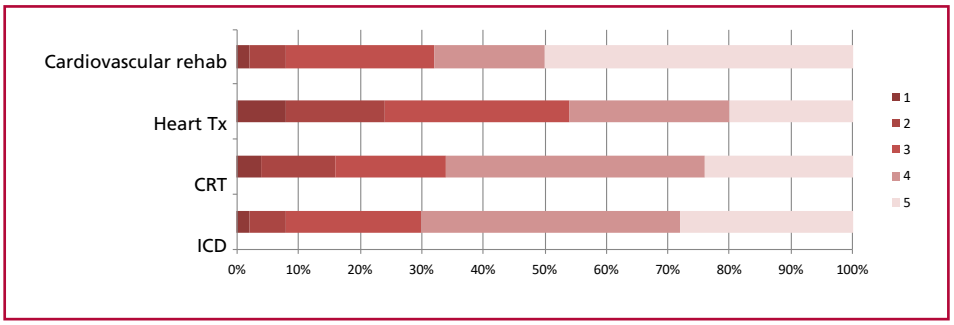


Fig. 4. Certainty and confidence about identifying of HF patient who may benefit from different treatments

5-point scale: 1 "not confident at all in identifying" and 5 "absolutely confident in identifying". rehab: rehabilitation; TX: transplantation; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator.

cardiography, and 42% measure biomarkers or use lung ultrasound.

Follow-up

The survey respondents felt that the median time from the initiation of outpatient treatment to the next follow-up visit was 14 days (IQR 7-15); 18% reported scheduling a second visit within 1 week, 64% within 7-15 days, and the remaining 18% after 15 days. Once treatment for HF was initiated, the median time to monitoring laboratory tests was 15 days (IQR 7-30) and 68% ordered the laboratory tests after 2 weeks. Median time to repeat echocardiography after initiation of treatment was 3 months (IQR 1-6) and 60% consider that consultation with other specialists is essential.

As for hospital discharge, 74% did not count with a discharge checklist. Most professionals (86%) agreed that it is extremely important to provide general written instructions at the time of hospital discharge. Fifty percent reported scheduling outpatient follow-up appointments within 7 days of hospital discharge, and 34% between 10 and 30 days.

DISCUSSION

Based on this study, we were able to evaluate the attitudes, knowledge, confidence and care pathways regarding the diagnosis, treatment and follow-up of patients with HF in the outpatient and inpatient settings among physicians, mostly cardiologists, in 22 medium complexity centers in Argentina.

Despite the wide availability of evidence-based HF guidelines, and that 100% of the survey respondents reported that their diagnostic and therapeutic decisions were based on these guidelines, we found some gaps between guideline recommendations and real-world practice. These differences were evident in both outpatient and inpatient settings.

There are certain findings worthy of note.

First, in terms of the services of the institutions considered, there was a low rate of HF units, with a considerable absence of palliative care services. HF is a chronic and progressive disease that affects people's quality and quantity of life. (15,16)

The creation of specialized care systems, such as HF units, has improved the management of these patients, as reflected in several meta-analyses. (17-19) For this reason, they have been included as a recommendation in the European Society of Cardiology Guidelines for the treatment of chronic HF more than a decade ago: (20) class I, level of evidence A to reduce hospital admissions, and class IIa, level of evidence B to reduce mortality.

These systems do not require high complexity and could be set up in medium and low complexity centers. Palliative care significantly improves the quality of life of heart failure patients and their families and should therefore be considered from the moment the diagnosis is made and not only in the final stages of the disease, providing patients with active information and promoting their involvement in decision-making.

Second, in terms of disease diagnosis, we noted that most professionals feel confident in the diagnosis of HFrEF but not with HFpEF or comorbidities. Among them, anemia poses the greatest difficulty for its diagnosis, classification, and treatment. The association between anemia and HF is well known but rarely considered in clinical practice; it is sometimes a cause of HF but is usually a consequence of the disease. In the Euro Heart Failure Survey, the estimated prevalence of anemia increased to 33% at a hemoglobin cutoff of 12 g/dL. Anemia significantly affects morbidity and mortality of patients with HF, so its detection and treatment are essential for these patients. (21)

Third, we noted great disparity in terms of indications upon discharge and strict post-discharge follow-up after hospitalization.

After a first hospitalization, the patient enters a vulnerable phase with high risk of readmission, followed by a plateau of false stability which will end in the final period of the disease, in which death is often preceded by recurrent hospitalizations. (22-24) To address this vulnerability, it is essential to act on the patient's transition before and after discharge, integrating organizational measures and improving treatment capable of modifying the disease. We believe that standardizing the recommendations at discharge,

systematic post-discharge monitoring and follow-up guidelines can help the mapped centers to counteract this difficulty. Providing centers with standardized protocols, as a discharge checklist, is a simple measure that can result in a significant impact to improve patients' outcome during this vulnerable phase.

An additional shortcoming was the timely referral of patients to a higher complexity center for the evaluation for a potential heart transplantation. As part of the educational program, we will generate simple roadmaps to help fight against the deficiencies found, facilitating the diagnosis, follow-up, management of comorbidities and diagnostic criteria.

The study has several limitations that should be mentioned. First, the study design was an observational survey that included physicians, mostly cardiologists with extensive experience, and who had graduated from medical school in a range of 7 to 20 years. Secondly, although the professionals surveyed represent more than 20 centers nationwide, they are part of an education and training program, which could represent a bias towards physicians who are more motivated to participate in this type of academic activities. The interpretation of the questions of the survey was left to the discretion of the responding physicians.

In summary, our study highlights an important need for improving the education and confidence among physicians about the clinical diagnosis, investigation, and treatment of HF in the outpatient and inpatient settings. Importantly, targeted HF continuing medical education is required, with a clinical focus on proper clinical diagnosis and the use of diagnostic tests for confirmation, along with knowledge translation of practice guidelines. Preceptorships in specialized HF clinics might inspire further confidence in HF management. (25) Continuing medical education programs will need to be tailored to varying learning needs, including traditional didactic lectures, podcasts, case-based tutorials, and learning programs that incorporate assessments of performance. Multifaceted educational programs and practice audit programs have been shown to improve confidence and clinical performance among health care practitioners. (26)

Based on the information gathered, we believe that, by detecting weak areas, we have found windows of opportunity for improvement. We will carry out the interventions previously proposed and we will conduct the same survey to the professionals after their continuing education during these months to evaluate and measure the impact of the project.

CONCLUSIONS

We obtained updated information on the management of HF among physicians in Argentina. Knowledge gaps were identified in the diagnosis and treatment of HF, especially in the diagnosis of HF with preserved ejection fraction, and indication of quadruple therapy.

The availability of actual information on how patients are managed in our country is a key starting point for improving the early diagnosis and prevention of this disease and the interaction between the three levels of care to obtain standardized treatment and finally reduce the high morbidity and mortality rate of HF patients

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SUPPLEMENTARY MATERIAL

Identification

Age
Years since graduation
Did you complete a residency program in any medical specialty?
Do you base your daily clinical practice on the recommendations of national/international clinical practice guidelines? (Yes/No)

Workplace

1. You work in a
   A. Specialized center
   B. Multidisciplinary center
2. Office and hospital practice
   a. Private practice/social security system
   b. Public center
   c. Both
3. The health center where you work has (please check all the appropriate options)
   a. Hart failure unit or service
   b. Heat failure clinic
   c. Hospital day-case unit/heart failure observation unit
   d. Critical care unit (intensive care unit, coronary care unit)
   e. Heart failure specialist nurse
   f. Palliative care
   g. None of the above
4. Your center has a general ward exclusively dedicated to the treatment of patients with cardiovascular diseases
   a. Yes
   b. No
5. How many beds are available in your center?
   Numeric field
6. How many beds are allocated to patients with cardiovascular diseases in your center?
   Numeric field
7. Regarding the complementary tests for the diagnosis/evaluation and/or management of heart failure patients, your center/clinic counts with (please check all the appropriate options)
   a. Basic laboratory tests
   b. Electrocardiogram
   c. Scale
   d. BNP/NT-proBNP
   e. Cardiac troponin
   f. Chest X-ray
   g. Echocardiography
   h. 24-hour Holter monitoring
   i. Nuclear medicine images
   j. 6-minute walk test
   k. Cardiopulmonary exercise testing
   l. Cardiac magnetic resonance imaging
   m. Coronary angiography
   n. Pulmonary artery catheter
   o. I do not count with.....(please enter the corresponding letter) but the test can be rapidly performed in another center.
8. Regarding the different types of therapeutic procedures that patients with heart failure may require, your center/clinic offers
   a. Bolus infusion of furosemide
   b. Continuous infusion of furosemide
   c. Ambulatory inotrope infusion
   d. Hypertonic saline administration

e. Dialysis/ultrafiltration
f. Intravenous iron administration
g. Percutaneous coronary intervention
h. Heart surgery
i. Pacemaker/cardiac resynchronization therapy/implantable cardioverter defibrillator
j. Transcatheter aortic valve implantation/mitraclip
k. Mechanical circulatory assistance device
l. Heart transplantation
m. I do not count with.....(please enter the corresponding letter) but the procedure can be rapidly performed in another center.

9. Please, indicate if any of the following consultants are available in your center/office
   a. Hematologist
   b. Nefrologist
   c. Pulmonologist
   d. Diabetologist
   e. Other: please, indicate

The following questions are related with your population of heart failure patients

1. On average, how many heart failure patients do you see per week in your outpatient practice?
   Numeric field
2. On average, how many patients hospitalized for heart failure do you see per week?
   Numeric field

Of your patient population with heart failure, please describe the approximate proportion of the following comorbidities:
Anemia: ___%
Iron deficiency: ___%
Diabetes:____%
Chronic kidney failure with creatinine clearance < 60 mL/min/m2 or creatinine levels > 1.5 mg/dL: ___%

3. Proportion of heart failure patients in each age range
   a. < 50 years; 50-70 years; >70 years
4. Of your total heart failure patient population, which proportion of patients have an ejection fraction <40%?
5. Distribution of patients by etiology
   a. Ischemic cardiomyopathy
   b. Hypertensive cardiomyopathy
   c. Valvular heart disease
   d. Undetermined
   e. Other
6. Please, indicate the proportion of your patients by medical coverage
   a. Provincial social security
   b. National social security system (PAMI; Incluir Salud)
   c. Prepaid medical inssurance
   d. Without medical coverage

The following survey does not have a correct answer; the aim of the survey is to know your opinion of the management the heart failure patients in the outpatient and inpatient settings.

Management of HF patients in the office (outpatient setting)
In your daily clinical practice in your office, which of the following signs and symptoms do you consider for the diagnosis of heart failure (please check all that you consider appropriate)

a) Jugular venous pressure > 8 cm
b) Fatigue
c) Memory loss
d) Cardiac murmur
e) Nicturia

f) Orthopnea
g) Palpitations
h) Paroxysmal nocturnal dyspnea
i) Pulmonary rales
j) Reduced exercise tolerance
k) Sputum
l) Tachycardia
m) Third heart sound
n) Ankle swelling
o) Abdominal bloating

Based on signs and symptoms you suspect that your patient has heart failure. Do you perform any complementary tests to confirm this diagnosis?
I do not perform any complementary tests; the presence of signs and symptoms consistent with heart failure, the patient's history and comorbidities are enough for the diagnosis.
Chest X-ray
Electrocardiogram
Lipid panel and glycemia
Laboratory tests to evaluate renal function and electrolytes
Liver panel
Thyroid panel
Echocardiography
Natriuretic peptides
Spirometry
Coronary angiography
Computed tomography coronary angiography

1. How relevant do you consider the determination of functional class in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
2. How relevant do you consider the determination of ejection fraction in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
3. How relevant do you consider the determination of etiology of the heart disease in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
4. How relevant do you consider the determination of renal function (BUN, creatinine level, creatinine clearance) in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
5. How relevant do you consider the determination of iron deficiency with or without anemia in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
6. How certain/confident do you feel about your diagnosis of heart failure in the setting of a patient with several comorbidities. On the following scale, please check a value between 1 and 5, where 1 is "not confident at all in the diagnosis" and 5 is "absolutely confident with my diagnosis" 1 - 2 - 3 - 3 - 4 - 5
7. How certain/confident do you feel about your diagnosis of heart failure with reduced ejection fraction. On the following scale, please check a value between 1 and 5, where 1 is "not confident at all in the diagnosis" and 5 is "absolutely confident with my diagnosis" 1 - 2 - 3 - 3 - 4 - 5
8. How certain/confident do you feel about your diagnosis of heart failure with preserved ejection fraction. On the following scale, please check a value between 1 and 5, where 1 is "not confident at all in the diagnosis" and 5 is "absolutely confident with my diagnosis" 1 - 2 - 3 - 3 - 4 - 5
9. How certain/confident do you feel about identifying atrial fibrillation. On the following scale, please check a value between 1 and 5, where 1 is "not confident at all in the diagnosis" and 5 is "absolutely confident with my diagnosis" 1 - 2 - 3 - 3 - 4 - 5
10. How certain/confident do you feel about identifying left bundle branch block. On the following scale, please check a value between 1 and 5, where 1 is "not confident at all in the diagnosis" and 5 is "absolutely confident with my diagnosis" 1 - 2 - 3 - 3 - 4 - 5
11. Please indicate which drugs you prioritize when initiating treatment of a patient with reduced ejection fraction (you can check more than one option)

a. Beta blockers
b. SGLT2 inhibitors
c. Mineralocorticoid receptor antoagonists
d. ACE inhibitors/ARBs
e. Sacubitril/valsartan
f. None of the above

12. Describe with a number, the time elapsed from treatment initiation to the next visit: ___days; ___months
13. After initiating treatment for heart failure, when do you monitor laboratory tests? ___days; ___months; ___years
14. After initiating treatment for heart failure, when do you monitor echocardiography? ___days; ___months; ___years
15. How relevant do you consider consultation with other specialists in your patient with a diagnosis of heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
16. Describe with a number the time elapsed until a patient with heart failure and reduced ejection fraction reaches full treatment with quadruple therapy (quadruple therapy refers to beta-blockers; SGLT2 inhibitors; mineralocorticoid receptor antagonists; ACE inhibitors/ARBs/ARNIs)
    a. at any dose: ___days; ___months; ___years
    b. at least 50% dose: ___days; ___months; ___years
    c. with target dose: ___days; ___months; ___years
    d. I do not reach quadruple therapy
17. How certain/confident do you feel about identifying patients requiring an implantable cardioverter defibrillator? On the following scale, please check a value between 1 and 5, where 1 is "not confident at all" and 5 is "absolutely confident" 1 - 2 - 3 - 3 - 4 - 5
18. How certain/confident do you feel about identifying patients requiring cardiac resynchronization therapy? On the following scale, please check a value between 1 and 5, where 1 is "not confident at all" and 5 is "absolutely confident" 1 - 2 - 3 - 3 - 4 - 5
19. How certain/confident do you feel about identifying patients heart transplantation? On the following scale, please check a value between 1 and 5, where 1 is "not confident at all" and 5 is "absolutely confident" 1 - 2 - 3 - 3 - 4 - 5
20. How certain/confident do you feel about identifying patients who may benefit from cardiac rehabilitation? On the following scale, please check a value between 1 and 5, where 1 is "not confident at all" and 5 is "absolutely confident" 1 - 2 - 3 - 3 - 4 - 5

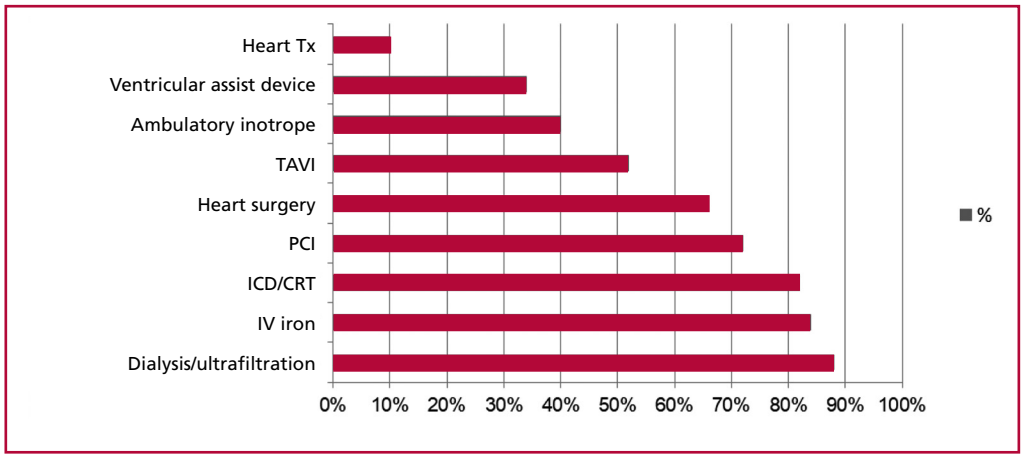
Management of hospitalized HF patients (inpatient setting, hospital day-case unit)

Do you see patients hospitalized for HF:
Yes (go on with the survey) / No (end the survey)

1. In your daily clinical practice with hospitalized patients, which of the following signs and symptoms do you consider for the diagnosis of heart failure (please check all that you consider appropriate)
    a. Jugular venous pressure > 8 cm
    b. Fatigue
    c. Memory loss
    d. Cardiac murmur
    e. Nicturia
    f. Orthopnea
    g. Palpitations
    h. Paroxysmal nocturnal dyspnea
    i. Pulmonary rales
    j. Reduced exercise tolerance
    k. Sputum
    l. Tachycardia
    m. Third heart sound
2. Based on signs and symptoms you suspect that your patient has heart failure. Do you perform any complementary test to confirm this diagnosis?
    a. I do not perform any complementary tests; the presence of signs and symptoms consistent with heart failure, the patient's history and comorbidities are enough for the diagnosis.
    b. Chest X-ray

   c. Electrocardiogram
   d. Lipid panel and glycemia
   e. Laboratory tests to evaluate renal function and electrolytes
   f. Liver panel
   g. Thyroid panel
   h. Echocardiography
   i. Natriuretic peptides
   j. Spirometry
   k. Coronary angiography
   l. Computed tomography coronary angiography
3. How relevant do you consider finding the decompensating factor that caused acute heart failure and led to patient's hospitalization? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
4. Check the method(s) you consider appropriate to follow up a patient hospitalized for heart failure.
   a. Physical examination and vital signs
   b. Weight
   c. Renal function and electrolytes
   d. Diuresis output
5. Check the method(s) you consider appropriate to assess congestion in a patient hospitalized for heart failure to define hospital discharge.
   a. Physical examination
   b. Functional class
   c. Echocardiography
   d. Lung ultrasound (comets)
   e. Biomarkers
   f. Weight loss
6. How relevant do you consider hypertonic saline administration in a patient hospitalized for heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
7. How relevant do you consider intravenous iron administration in a patient hospitalized for heart failure? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
8. Please check the drug treatment adjustments you make before discharge
   a. Titration of drugs recommended in clinical practice guidelines for the treatment of heart failure.
   b. I add drugs
   c. I reduce drug dose
   d. I prefer to modify drug regimens during outpatient visits
9. Please check the recommendations you give upon discharge.
   a. Dietary sodium restriction
   b. Physical activity
   c. Fluid restriction
   d. Daily weight control
   e. Signs of alarm
   f. Flexible diuretic dosing regimen
10. Please indicate which drugs you prioritize when you discharge a patient with reduced ejection fraction (you can check more than one option)
   a. Beta blockers
   b. SGLT2 inhibitors
   c. Mineralocorticoid receptor antoagonists
   d. ACE inhibitors/ARBs
   e. Sacubitril/valsartan
   f. None of the above
11. Do you have a specific discharge checklist for patients hospitalized for heart failure? Yes/No

12. How relevant do you consider providing general written instructions at the time of hospital discharge? On the following scale, please check a value between 1 and 5, where 1 is "not relevant at all" and 5 is "absolutely essential" 1 - 2 - 3 - 3 - 4 - 5
13. When do you schedule outpatient follow-up appointment after hospital discharge:___days; ___months



TX: transplantation; TAVI: transcatheter aortic valve implantation; PCI: percutaneous coronary intervention ICD: implantable cardioverter defibrillator. CRT: cardiac resynchronization therapy. IV: intravenous

Fig. 1. Treatments available in the centers

BRIEF ARTICLE

Early Hospital Discharge (Within Six Hours) for Patients Undergoing Coronary Angioplasty

Estudio AHORA 6: Angioplastia coronaria con alta HOspitalaria RÁpida en 6 horas

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ABSTRACT

Background: 24-hour hospitalization is common practice in patients (P) who underwent scheduled coronary angioplasty (PCI). Previous experiences propose same-day discharge in selected P.
Methods: Prospective, comparative, randomized, single-blind study. P aged 18 to 75 years were included as candidates for a scheduled radial-access PCI with the possibility of accessing the emergency system in less than 40 minutes. P with left ventricular ejection fraction < 30%, creatinine > 1.5 mg/dL, heart failure, chronic obstructive pulmonary disease, decompensated diabetes or very complex coronary anatomy were excluded. The population was divided in two groups (G). G 1: same-day discharge in 6 hours. G2: discharge the next day. Primary endpoint: death or need for rehospitalization within 24 hours of the procedure. Follow-up was carried out by phone the night of the procedure and the next morning, in person at 48 hours, and by telephone after a month, six months and a year. Continuous variables were expressed as median and their respective interquartile range, and qualitative variables as percentages.
Results: 80 P were randomized. Six P (7.5%) presented exclusion criteria during the procedure. There were no deaths or major cardiovascular events in either groups. At one year of follow-up, 3.75% of in-stent restenosis was detected. Troponin elevation was detected in 20 P (25%); 4 were P excluded due to complications during PCI, in the remaining 16 it had no clinical repercussion.
Conclusion: In a population of patients between 55 and 75 years old, mostly male, with a high prevalence of previous myocardial infarction, and ventricular function depression, a scheduled radial-access PCI could be performed with same day discharge in 6 hours, with an adequate safety margin.

Keywords: Angioplastia - Length of Stay - Time Factors - Patient Discharge

RESUMEN

Introducción: Es de práctica habitual la internación durante 24 h en los pacientes (P) intervenidos con una angioplastia coronaria (ATC) programada. Experiencias previas proponen el alta post ATC en el mismo día en P seleccionados.
Material y métodos: Estudio prospectivo, aleatorizado, controlado, simple ciego. Se incluyeron P de 18 a 75 años candidatos a una ATC programada por acceso radial, con posibilidad de acceder al sistema de emergencias en menos de 40 minutos. Se excluyeron los P con fracción de eyección ventricular izquierda < 30%, creatinina > 1,5 mg/dL, insuficiencia cardíaca, enfermedad pulmonar obstructiva crónica, diabetes descompensada o anatomía coronaria muy compleja. Se dividió a la población en dos grupos (G). G 1: alta en 6 horas. G2: alta al día siguiente. Punto final primario: muerte o necesidad de rehospitalización dentro de las 24 h de realizado el procedimiento. Se realizó seguimiento telefónico la noche del procedimiento y a la mañana siguiente, presencial a las 48 h, y telefónico al mes, seis meses y un año.
Resultados: Se adjudicaron aleatoriamente 80 P. Seis P (7,5%) presentaron criterios de exclusión durante el procedimiento. No se produjo ninguna muerte ni evento cardiovascular mayor en ninguno de ambos grupos. Al año de seguimiento se detectó 3,75% de reestenosis intra stent. Se detectó elevación de troponina en 20 P (25%) de los cuales 4 habían sido excluidos por complicaciones durante la ATC. En los restantes 16, la elevación de la troponina no tuvo repercusión clínica.
Conclusión: En una población de pacientes entre 55 y 75 años, en su mayoría de género masculino, con alta prevalencia de infarto de miocardio previo, y depresión de la función ventricular, pudo realizarse una angioplastia programada por acceso radial con alta en 6 horas, con un adecuado margen de seguridad.

Palabras clave: Angioplastia - Tiempo de Internación - Factores de Tiempo - Alta del Paciente

INTRODUCTION

Cardiovascular diseases are the leading health problem in industrialized countries. (1) In this context, transluminal coronary angioplasty (PCI) is a safe and effective therapeutic method. (2)

Scheduled PCI is a procedure with very low chances of serious complications in the first 24 hours. (3) Associated with the above, radial access allows for rapid recovery and avoids bleeding due to femoral access site, which could cause serious complications. (2)

Rev Argent Cardiol 2022;90:206-209. http://dx.doi.org/10.7775/rac.v90.i3.20520

Received: 03/23/2022 – *Accepted:* 05/19/2022

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In 2009, the Society for Cardiac Angiography and Interventions (SCAI), with the approval of the American College of Cardiology Foundation, developed a consensus defining the criteria patients should meet to be considered for outpatient intervention. The April 2016 SCAI consensus on "Good Practice in the Cardiac Catheterization Laboratory" considered same-day discharge post-PCI as a standard practice. (5)

In 2021, the American College of Cardiology published new recommendations that provide a framework for the development of a same-day discharge PCI approach, excluding from this strategy only patients with acute coronary syndrome. (6)

Several studies on radial or femoral access for PCI with percutaneous closure devices have been published, in which same-day discharge could be granted, with positive outcomes. (7-10)

A recent multicenter study demonstrated the safety of same-day discharge after radial access PCI, even in complex procedures (multivessel PCI > 50%, bifurcations > 20%). (10) In Argentina, the ACA I and ACA II studies, published in 2009 and 2016 respectively, proposed this practice in selected patients, with successful outcomes. (12)

In this context, we conducted a study to assess the safety of early discharge (defined as discharge within 6 hours following the procedure) after scheduled radial access coronary angioplasty in low to moderate risk patients.

METHODS

We conducted a prospective, randomized, single-blind study. Patients aged 18 to 75 years with moderate clinical and angiographic risk were candidates for scheduled radial-access PCI.

The study population was divided into two groups (G): G1 or early discharge: the patient went home on the same day the procedure was performed, after a 6-hour stay in the recovery room; G2 or control: the patient stayed 3 hours in the recovery room, and then was admitted to the Cardiology ward until the following morning. Candidates did not know whether they would be discharged or not.

Patients had to come exclusively from the hospital program area, be accessible by telephone for follow-up, and have access to the emergency system in a vehicle (private, hired, or from the emergency system) in less than 40 minutes.

There were clinical, angiographic, procedure related and socioeconomic exclusion criteria.

- Clinical criteria:

a. Age < 18 or > 75 years
b. Acute coronary syndrome
c. Allergy to iodinated contrast
d. Coagulopathy or contraindication to dual antiplatelet therapy
e. Chronic kidney failure (creatinine >1.5 mg/dL or eGFR< 60mL/min)
f. Decompensated heart failure or chronic obstructive pulmonary disease (COPD)
g. Left ventricular ejection fraction (LVEF) < 30%
h. Diabetes without adequate control
i. Lack of optimized treatment

- Angiographic criteria:

a. Complex anatomy (lesion of the left main coronary artery, ostium of the circumflex and the anterior descending arteries, venous bypass graft to internal mammary artery, single patent vessel, coronary bifurcation treatment)

- Procedure-related criteria:

a. Hemodynamic instability
b. Need for glycoprotein-IIb/IIIa inhibitors or intra-aortic balloon pump
c. No reflow or TIMI flow < 3
d. Acute occlusion
e. Thrombus
f. Persistent coronary artery dissection
g. Conversion to femoral access
h. Occlusion of a major branch (> 2 mm, or causing symptoms)
i. Distal embolism
j. New, persistent ventricular or atrial arrhythmia

- Socioeconomic criteria:

a. Lack of adequate social support (family or caregiver to provide immediate care the night of the procedure)
b. No telephone for follow-up
c. Unable to access the emergency unit

The study primary endpoint was death or rehospitalization within 24 h of the procedure. Combined secondary endpoint included all-cause admission to the Coronary Care Unit, need for coronary reintervention and/or any vascular or non-vascular event leading to corrective intervention after PCI.

At each stage of the study, patients were evaluated by a group of interventional cardiologists (evaluation group, EG), including those directly involved in the procedure and the on-call interventional cardiologist.

The study was developed in consecutive scenarios.

a) Scenario 1: Interventional Cardiology Office

Routine evaluations for any procedure were performed: clinical status and the need for angioplasty, associated diseases, complementary and laboratory tests (blood count, blood chemistry with renal function and coagulation profile). For this purpose, the checklist approved by the SCAI in 2016 was used, translated into Spanish (Annex 1). A pre-procedural radial Doppler scanning was performed to all patients. Next, it was determined whether patients met any exclusion criteria to participate in the study. Admission to the study was proposed, and a general Informed Consent and a study-specific Informed Consent —approved by the Education and Research Committee and the Ethics Committee of our center— were signed. Dual antiplatelet therapy was then initiated.

b) Scenario 2: Interventional Cardiology Unit

Between 8-9 am, prior to PCI, the patient was reevaluated by the EG to confirm whether dual antiplatelet therapy had been administered. ECG was performed and a blood sample was drawn to measure baseline troponin levels. The risk of contrast-induced nephropathy, bleeding complications and death was calculated according to the SCAI 1:1 randomization score using a simple randomization program (OxMaR). At this time, the patient and the interventional cardiologist in charge of the procedure were unaware of the

randomization results.

Patients randomized to G1 continued with PCI. In the case of G2, inpatient bed availability was checked before continuing with PCI. If the bed was unavailable, the procedure was postponed up to a maximum of three times. On the third opportunity, patients were switched to G1 by protocol.

The patient was taken to the catheterization laboratory for radial access PCI, according to the approach followed. If any of the procedural complications listed in the exclusion criteria occurred, the patient was excluded from the study. Otherwise, PCI was terminated. Following the PCI procedure, the radial sheath was removed, and a compressive bandage was applied. Complications at the puncture site were ruled out.

c) Scenario 3: Recovery

The patient was taken to the recovery room, vital signs were checked, and the patient was asked for symptoms of ischemia and complications related to the procedure. An ECG was performed to rule out acute ischemic changes. The patient was allowed to ambulate after two hours with an accompanying person. After 3 hours in the recovery room, EG reevaluation was conducted. In case of good progress, G1 patients stayed in the recovery room until discharge (6 hours).

G2 patients were referred to the Cardiology ward for routine check. As in G1, the same procedures were performed and the same variables were recorded in G2. Patients received the usual post PCI care, and were discharged 24 hours post procedure.

Follow-up included telephone calls at night and in the morning after the procedure. In-person follow-up was also performed on the first working day, 48-72 hours post-procedure, including lab tests. Telephone follow-up was carried out at 1, 6 and 12 months..

RESULTS

A total of 80 patients were randomized. Baseline characteristics are summarized in Table 1. Six patients (7.5%) met the exclusion criteria during the procedure —3 in G1 (1 conversion to femoral access, 1 persistent dissection, 1 branch occlusion) and 3 in G2 (2 branch occlusions, 1 persistent pain)— and were transferred to the coronary unit after PCI. All patients were discharged within 24 hours.

No major cardiovascular events or deaths were detected at 1 month and 6 month follow- up in either group. At 1-year follow-up, angina was detected in 5% (4 patients in G1, none in G2), with 3.75% in-stent restenosis (3 patients in G1, none in G2).

Most patients (61, 76%) were tested for high-sensitivity troponin (HsT), and the rest for troponin I, showing high levels in 25% of the cases (n=20, 15 of them tested for HsT). Four patients were excluded due to complications during PCI (3 with lateral branch occlusion); in the remaining 16 patients, elevation had no clinical impact on the outcomes.

DISCUSSION

In many cases, the systematic post-PCI hospitalization for at least 24 h limits the scope for performing the procedure, with the resulting delay in solving the patient's problem.

When analyzing our previous experience, we found out that, in an unselected group of patients, the frequency of unwanted events was low. Importantly, more than 90% of those patients required no more than one day of hospitalization.

With the exclusion of those subjects for "high-risk coronary angioplasty" based on the SCAI consensus selection criteria, more than one third of the sample met criteria for scheduled low- or moderate-risk PCI. (2, 4) No deaths, major bleeding complications or contrast-induced nephropathy were found in this group of patients.

Additionally, the COVID-19 pandemic exposes cardiac patients to a double risk: the risk inherent to their disease and the risk associated with increased likelihood of infection during hospitalization. Postponing procedures in the context of the pandemic has already shown to increase cardiovascular mortality. (13)

The systematic care of these patients should be carefully followed, as we believe that the key to implementing a same-day discharge coronary angioplasty approach lies in ensuring patient safety.

Limitations

Unlike other experiences carried out in Argentina, we decided to conduct a randomized study; however, the low number of patients included and the low rate of events detected in this population prevented us from drawing definitive conclusions. Nevertheless,

Table 1. Baseline characteristics of the population

Variables	G1 (n=43)	G2 (n=37)	p
Age, years	65 ± 8	64 ± 10	ns
Female	21%	16%	ns
HBP	81.4%	86.5%	ns
DM	34.9%	40.5%	ns
DLP	58.1%	45.9%	ns
SMK	34.9%	24.3%	ns
Prior myocardial infarction	46.5%	56.8%	ns
Stroke	2.3%	2.7%	ns
Depressed LVEF	45.5%	66.7%	ns

HBP: high blood pressure; DM: diabetes mellitus; DLP: dyslipidemia; SMK: smoking; LVEF: left ventricular ejection fraction

Variables	GLOBAL	G1	G2	p
PEP	0	0	0	--
SEP	0	0	0	--
TROPONIN E.	25%	20.9%	29.7%	ns
Postponed due to UB	11.2%	0	24.2%	--
D&MCE at 30 days	0	0	0	--
D&MCE at 6 months	0	0	0	--
D&MCE at 12 months	5%	9.3%	0	ns
ISR	5%	6.97%	0	ns

Table 2. Results. PEP: primary endpoint; SEP: secondary endpoint; TROPONIN E.: troponin elevation; UB: unavailable bed; D&MCE: death and major cardiovascular events; ISR: intra-stent restenosis

the selected design prevented the physician-operator from deciding to include the patient in the same-day discharge group based on subjective elements, and allowed strict criteria for safety and follow-up to be established. Further studies with a larger number of patients may contribute to change the paradigm of post-procedural management in these cases.

CONCLUSIONS

In a population of patients between 55 and 75 years of age, mostly male, with a high prevalence of previous myocardial infarction and mild to moderate depression of ventricular function, scheduled radial access PCI within 6-hour discharge could be performed with an adequate safety margin.

The fact that nine procedures were postponed due to unavailable inpatient bed in the 24 h discharge group confirms the importance of new strategies in the management of these patients, even more during the COVID-19 pandemic.

Troponin elevation, predominantly high-sensitivity troponin, was observed in a high number of cases, but it had no impact on patient progress.

On the other hand, G2 patients undergoing PCI were hospitalized in the general Cardiology ward and not in the Coronary Care Unit, which, in itself, represents a significant change in post-PCI management

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BRIEF ARTICLE

Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS) Patient Characteristics Admitted to the Coronary Care Unit of Hospital Provincial Neuquén

Características de pacientes hospitalizados en Unidad Coronaria del Hospital Provincial Neuquén por síndrome coronario agudo sin elevación del segmento ST (SCASEST)

LEONARDO M VILLALBA, VICTORIA A PARRELLO, LILIAN BAEZ

ABSTRACT

Background: Acute coronary syndromes (ACS) are part of the clinical presentation spectrum of coronary heart disease, and patients presenting with these syndromes constitute a heterogeneous population in which prognosis differs according to clinical and laboratory variables.
Objective: The aim of this study was to describe the clinical characteristics of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who were admitted to Hospital Provincial Neuquén (HPN) coronary care unit (CCU) from 2017 to 2019.
Methods: This was an observational, retrospective, longitudinal and single-center study of patients hospitalized in HPN CCU between January 1, 2017 and December 31, 2019. Data collected from the epicrisis and medical records were used. Six months after hospital discharge, a new contact was made to corroborate data on mortality after the event.
Results: A total of 107 patients diagnosed with NSTE-ACS, with mean age of 62.2 ±-10.51 years (65.4% male gender) were included in the study. Among them, 45.8% were smokers and 46.7% had comorbidities, the most prevalent being hypertension (69.2%) and diabetes mellitus (36.4%). In 35.5% of cases, patients had a previous heart attack, 7.5% heart failure, 85% received anti-ischemic therapy, 35.5% vasodilator treatment, 70.1% required coronary angiography, 91.6% presented positive high-sensitivity troponin levels and 22.4% required coronary stent placement. The most frequent lesion corresponded to the anterior descending artery in 12.1% of patients.
Conclusions: The most prevalent characteristics of patients with NSTE-ACS, as well as the clinical presentation and risk of in-hospital mortality, were similar to those reported by other centers.

Key words: Acute Coronary Syndrome – Acute Coronary Syndrome without ST elevation – Intrahospital Mortality – Cardiovascular Risk

RESUMEN

Introducción: Los síndromes coronarios agudos (SCA) son parte del espectro de presentación clínica de la enfermedad coronaria, y estos pacientes constituyen una población heterogénea en la cual el pronóstico difiere según las variables clínicas y de laboratorio.
Objetivo: Describir las características clínicas de los pacientes con síndrome coronario agudo sin elevación del segmento ST (SCASEST) que ingresaron a la Unidad Coronaria (UCO) del Hospital Provincial Neuquén (HPN) en el período 2017-2019.
Métodos: Estudio observacional, retrospectivo, longitudinal y unicéntrico de pacientes hospitalizados en UCO del HPN entre 1 de enero de 2017 y 31 de diciembre de 2019. Se utilizaron datos recabados de las epicrisis e historias clínicas. A 6 meses del egreso hospitalario, se realizó un nuevo contacto para corroborar datos sobre la mortalidad posterior al evento.
Resultados: se registraron 107 pacientes con diagnóstico de SCASEST, con edad promedio de 62,2 ± 10,5 años (65,4% de sexo masculino). El 45,8% era tabaquista y el 46,7% presentaba comorbilidades, siendo las más prevalentes la hipertensión arterial (HTA, 69,2%) y la diabetes Mellitus (DM, 36;4%). El 35,5% tenía infarto previo, y el 7,5% insuficiencia cardíaca. El 91,6% presentó Troponinas Ultrasensibles (T-us) positivas; el 85% recibió terapia antiisquémica, el 35,5% tratamiento vasodilatador y el 70,1% fue sometido cinecoronariografía (CCG). El 22,4% requirió la colocación de al menos 1 stent coronario. La lesión más prevalente fue de la Arteria Descendente Anterior (ADA) en 12,1%.
Conclusiones: Las características más prevalentes de los pacientes con SCASEST en nuestro centro, así como la presentación clínica y el riesgo de mortalidad intrahospitalaria (MIH) fueron similares a los reportados en otros centros.

Palabras claves: Síndrome Coronario Agudo – Síndrome Coronario Agudo Sin Elevación Del ST – Mortalidad Intrahospitalaria – Riesgo Cardiovascular

Rev Argent Cardiol 2022;90:210-214. http://dx.doi.org/10.7775/rac.v90.i3.20519

Received: 02/14/2022 – *Accepted:* 06/03/2022

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INTRODUCTION

Ischemic heart disease is still the main cause of death worldwide. Acute coronary syndromes (ACS) are part of the clinical presentation spectrum of coronary heart disease and patients presenting with these syndromes constitute a heterogenous population in which the diagnosis differs according to clinical and laboratory variables. (1)

Acute coronary syndromes involve acute myocardial infarction (AMI) with or without ST-segment elevation, with or without Q wave, and unstable angina (UA). (2) While ST-segment elevation AMI (STEMI) is at present a clear pathophysiological entity with established treatment strategies, UA and non-ST-segment elevation AMI (NSTEMI) have been grouped under different names and are currently defined as non-ST-segment elevation ACS (NSTE-ACS). (3)

Based on the information of recent ACS registries in our country, we assume that the number of NSTE-ACS is markedly higher than that of ST-elevation ACS (STE-ACS). Gagliardi et al. published the EPI-Cardio registry in which they detected 2855 patients with STE-ACS (37.96%) and 4667 with NSTE-ACS (62.04%). (4) The recently published EPICOR study shows 40.64% of patients with STE-ACS and the rest with NSTE-ACS. (5) The two cited registries were performed in different public, private and university center networks. Since 31 425 patients with STE-ACS were estimated from data of a population registry in Argentina, it is probable that a clearly higher number is hospitalized with NSTE-ACS per year. (6)

In response to the need of adjusting treatment as a function of the individual risk of adverse cardiovascular outcomes, predictive systems such as the Global Registry of Acute Coronary Events (GRACE) scales have been developed. (7-9) The high prevalence of coronary risk factors and worldwide population ageing are two aspects that have increased AMI mortality in the last years.

Identifying the different factors associated with increased mortality risk for AMI has helped to develop diverse scores or scales to stratify risk in these patients. (10)

Consequently, to understand the current reality regarding the way to approach NSTE-ACS, an epidemiological study was carried out in a small, developing coronary care unit (CCU) (10 beds) of the highest complexity center of the city of Neuquén [Hospital Provincial de Neuquén (HPN)], with data obtained from patients hospitalized during a 2-year period and their corresponding death risk stratification.

We considered it was highly relevant to obtain data that allows local casuistry evaluation to improve working methods and the self-evaluation of the health teams that are employed in this labor, and also to serve as parameter for other institutions in the same situation.

METHODS

This was an observational, retrospective, longitudinal, single-center study of patients hospitalized in HPN CCU performed by a research group from the Internal Medicine and Cardiology Division of HPN between January 1, 2017 and December 31, 2019.

It should be mentioned that the patients included in the study were admitted to a small CCU, with a fully developing hemodynamics service. Data were collected from the epicrises and completed with information from the clinical histories.

Six months after discharge, a new telephone or in-person contact was made to confirm data on mortality after the event.

The inclusion criteria were:

Patients admitted to CCU during the period between January 2017 and December 2019, who fulfilled NSTE-ACS diagnostic criteria: chest pain in the last 48 hours, associated with high-sensitivity troponin (hs-Tn) levels above the 99 percentile, or electrocardiographic changes compatible with ischemia, defined as T-wave inversion, ST-depression >1 mm or transient ST elevation (less than 20 minutes) on discharge.

The exclusion criteria were:

- Patients with UA clinical diagnosis requiring hospitalization, but with negative troponins.
- Patients with ACS diagnosis and electrocardiogram compatible with STE-ACS.
- Patient self-discharge.

Cardiovascular risk factors and relevant clinical history were obtained from patient interrogation on hospital admission. History of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking (active or passive, current or past), alcohol consumption, relevant medical history and cardiovascular history were assessed.

The following variables were considered:

- Admission heart rate
- Admission blood pressure
- Admission serum creatinine
- Admission Killip and Kimball classification
- ECG with acute ischemic signs: presence of electrocardiographic abnormalities suggesting acute ischemia during the course of hospitalization
- Echocardiogram with acute ischemic signs: presence or absence of echocardiographic signs of acute ischemia in in-hospital evaluations
- Anti-ischemic therapy: need for anti-ischemic therapy in hospitalized patients (nitrates, aspirin, beta-blockers, calcium antagonists, oxygen).
- Vasodilator therapy: need for specific nitrate use during the acute NSTE-ACS period
- Positive troponins: Troponin elevations considered clinically relevant according to their cut-off point and the clinical context of NSTE-ACS
- Need for coronary angiography (CA) during hospitalization
- CA findings
- Need for coronary stent placement
- Length of stay in CCU
- Percentage of risk according to the GRACE score: Mortality risk category 6 months after discharge according to the GRACE score.

Statistical analysis

Data were collected in an online Kobotoolbox database and analyzed using SPSS 21 statistical package. Qualitative variables were described as frequencies and percentages, and mean and standard deviation were calculated for quantitative variables. Parametric or non-parametric variable distri-

bution was established using the Kolmogorov-Smirnov or Shapiro Wilk tests.

Results were expressed as percentages, means (with standard deviation) and medians [with interquartile range (IQR)].

Ethical considerations

Patient informed consent was waived as usual medical practices of the center were respected, without interventions. Data were automatically anonymized upon being sent to the coordinating center.

RESULTS

A total of 107 patients with NSTE-ACS diagnosis and mean age of 62.2±10.5 years (65.4% male) were admitted to HPN CCU between January 2017 and December 2019. In 45.8% of cases patients referred current or prior tobacco smoking and 46.7% presented comorbidities, the most prevalent being HTN (69.2%) and DM (36.4%). Among these patients, 35.5% had previous infarction and 7.5% presented history of heart failure (Table 1).

In-hospital evolution

Median hospital stay was 3 days (IQR 2-4). Seventy -two percent of patients presented with angina, and almost all individuals were included in Killip and Kimball class I. Also, 65.4% of patients had electrocardiographic signs of acute ischemia, with T wave abnormalities as the most frequent manifestation in 38.3% of cases, and 32.7% showed echocardiographic changes compatible with acute ischemia.

Positive hs-Tn levels were found in 91.6% of patients during the acute phase and diagnosed as NSTEMI, 85% of cases received anti-ischemic therapy, 35.5% required specific treatment with vasodilators, 70.1% underwent CA during hospitalization and only 22.4% required stent placement (Table 2). The most frequently involved artery was the anterior descending artery, in 12% of the patients (37.3% of the lesions found).

Only 12.1% of patients were at high risk (>3%) of in-hospital mortality (IHM) estimated with the GRACE score. The mean GRACE score was 133.8±52.1. However, none of the patients died during hospitalization. Table 3 shows the remaining risk categories.

Table 1. Baseline population characteristics (n=107)

Variables	Value
Age, years – mean±SD	62.2 ± 10.51
Male gender – n (%)	70 (65.4%)
Smoking – n (%)	49 (45.8%)
Alcohol consumption – n (%)	2 (1.9%)
Comorbidities – n (%)	50 (46.7%)
DM – n (%)	39 (36.4%)
HTN – n (%)	74 (69.2%)
Heart failure – n (%)	8 (7.5%)
CKD – n (%)	10 (9.3%)
Overweight/Obesity – n (%)	30 (28%)
Dyslipidemia – n (%)	34 (31.8%)
COPD – n (%)	2 (1.9%)
AMI – n (%)	38 (35.5%)
PVD – n (%)	2 (1.9%)

SD: Standard deviation. DM: Diabetes Mellitus. HTN: Hypertension. CKD: Chronic kidney disease. COPD: Chronic obstructive pulmonary disease. AMI: Acute myocardial infarction. PVD: Peripheral vascular disease.

DISCUSSION

The present work allows understanding the characteristics of patients admitted and discharged from HPN CCU, consisting of approximately 10 beds and a fully developing hemodynamics service. It also shows the wide spectrum of NSTE-ACS presentation and analyzes the diagnostic and therapeutic strategies used. Although the total number of patients in our work is not equivalent to that in other reports, we consider that it is not negligible with respect to the number of beds in our center.

Compared with the study by Costabel et al., their average age of event occurrence coincided with our mean age of 62 years, as well as its more frequent presentation in the male gender in 70% of patients. (11), also similar to other reports in the literature. Regarding comorbidities, comparable data were also found for the prevalence of prior DM and AMI, close to 30%. History of HTN prevailed in our population, with almost 70% of cases, as well as smoking, similar to the study by Mauro et al. (12)

Length of hospital stay for this condition is usually short, and in our study, it was 3 days, as described in other studies. As in other reports, almost all our patients were in Killip and Kimball class I.

Compared with the study by Mauro et al, electrocardiographic abnormalities were more prevalent in our patients (65.4% vs. 46%) and T-wave abnormalities were the most frequent manifestation in both studies (38.3% vs. 25%). (12) However, we encountered higher positive hs-Tn (91.6% vs 65%) though there could be discrepancies in the cut-off point and methodology.

Our center performed a lower number of CA than that reported by Costabel et al. (70% vs. 87%), perhaps due to differences in equipment criteria, but unfortunately, we do not have data on the time to CA performance. Six-month mortality was higher in our case (12.1% vs. 5.7%), which could be due to the great number of comorbidities present in our patients, and that a high percentage, close to 35%, had anterior descending artery involvement.

The need for coronary stent placement (22.4%) was much lower than that presented in the previously cited study (79.6%) and in other national and international registries, where it is close to 100%. We have no record of the type of coronary stent used in our center.

The mean GRACE score of the study by Garmendia et al. was 133.8±52.1, while that of our data was lower, 112.5±23.8, maybe justified because the former population had more comorbidities. (13)

Characteristic of the event	Value
Length of hospital stay in days (median and IQR)	3 (2-4)
Typical chest pain, n (%)	77 (72%)
Heart rate – bpm, mean ± SD	74.7 ± 15.7
SBP – mmHg ±SD	140.0 ± 26.7
Serum creatinine – mg/dl ± SD	1.2 ±0.9
Killip & Kimball I, n (%)	106 (99.1%)
ECG with acute ischemic signs, n (%)	70 (65.4%)
Electrocardiographic abnormality, n (%)	
T-wave abnormality	41 (38.3%)
ST depression	19 (17.8%)
ST depression + T-wave abnormality	6 (5.6%)
Q wave	3 (2.8%)
Echocardiogram with acute ischemic signs, n (%)	35 (32.7%)
Anti-ischemic therapy, n (%)	91 (85%)
Vasodilator therapy, n (%)	38 (35.5%)
Need for CA, n (%)	75 (70.1%)
Positive high-sensitivity troponins, n (%)	98 (91.6%)
Need for coronary stent, n (%)	24 (22.4%)

SD: Standard deviation. SBP: Systolic blood pressure. ECG: Electrocardiogram. CA: Coronary angiography.

Table 2. Characteristics of the NSTE-ACS event

In-hospital GRACE risk category	IHM (%)	Percentage of patients
Low	<1	39.3%
Intermediate	1-3	48.6%
High	>3	12.1%

IHM: In-hospital mortality. Mortality at 6 months after hospital discharge was 12.1%.

Table 3. Stratification of in-hospital mortality risk

CONCLUSIONS

Our registry provides data that do not differ considerably from those of centers with more complex CCU and from studies with a larger number of patients. These data allow to identify that, regardless the center, the most prevalent characteristics of NSTE-ACS patients, as well as the clinical presentation and IHM risk, continue to be similar. The present registry is very useful to complement the database of multi-center studies, as the ones cited here, to have a more real population information.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

High Lipoprotein(a) Levels and Risk of Aortic Valve Stenosis Related Clinical Events: A Systematic Review

Niveles elevados de lipoproteína(a) y riesgo de eventos clínicos relacionados con la estenosis valvular aórtica: una revisión sistemática

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ABSTRACT

Background: Several studies have evaluated the association between lipoprotein(a) plasma levels [Lp(a)] and the occurrence of aortic valve stenosis related events, with contradictory results.
Objective: The main objective of this systematic review was to analyze the predictive capacity of elevated Lp(a) levels on major clinical events associated with aortic valve stenosis.
Methods: This systematic review was conducted in accordance with PRISMA and STROBE recommendations. A search was carried out in order to identify studies with a cohort design evaluating the association between Lp(a) levels and the events of interest. The primary endpoint was the incidence of clinical events related with aortic valve stenosis (aortic valve replacement, death or hospitalization). This review was registered in PROSPERO.
Results: Seven observational studies with a total of 58 783 patients were eligible for analysis. Our findings showed that the presence of elevated Lp(a) levels was associated with an increased risk of events related with aortic valve stenosis in most of the studies evaluated (between 70% and approximately 3-fold higher risk), despite adjusting for other risk factors.
Conclusion: This review suggests that elevated Lp(a) levels are associated with a higher incidence of aortic valve stenosis related clinical events. However, considering the limitations of this study, the clinical usefulness of Lp(a) as a prognostic marker in aortic valve disease should be confirmed in future investigations.

Keywords: Lipoprotein (a) - Aortic valve stenosis - Aortic valve replacement - Mortality - Systematic review.

RESUMEN

Introducción: Varios estudios han evaluado la asociación entre los niveles plasmáticos de lipoproteína (a) [Lp(a)] y la aparición de eventos relacionados con la estenosis valvular aórtica, aunque los resultados fueron contradictorios.
Objetivo: El objetivo de esta revisión fue analizar la capacidad predictiva de los niveles elevados de Lp(a) sobre los eventos clínicos relacionados con la estenosis valvular aórtica.
Material y métodos: Esta revisión sistemática se realizó de acuerdo con las recomendaciones PRISMA y STROBE. Se realizó una búsqueda en diferentes bases de datos con el objetivo de identificar estudios de cohorte que evaluaran la asociación entre los niveles de Lp(a) y los eventos de interés. El punto final primario fue la incidencia de eventos clínicos relacionados con la estenosis aórtica (reemplazo valvular aórtico, muerte u hospitalización). Esta revisión fue registrada en PROSPERO.
Resultados: Se consideraron elegibles para el análisis siete estudios observacionales con un total de 58 783 pacientes. Los valores elevados de Lp(a) se asociaron con un mayor riesgo de eventos relacionados con la estenosis valvular aórtica en la mayoría de los estudios evaluados (entre un 70% y aproximadamente 3 veces más riesgo), a pesar de ajustar por otros factores de riesgo.
Conclusión: Esta revisión sugiere que los niveles elevados de Lp(a) se asocian con una mayor incidencia de eventos clínicos relacionados con la estenosis valvular aórtica. Sin embargo, y considerando las limitaciones de este estudio, la utilidad clínica de la Lp(a) como marcador pronóstico en la enfermedad valvular aórtica deberá confirmarse en futuras investigaciones.

Palabras clave: Lipoproteina (a) - Estenosis valvular aórtica - Reemplazo valvular aórtico - Mortalidad - Revisión sistemática

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL) variant containing an apolipoprotein B molecule, covalently bonded to a glycoprotein of variable molecular weight, apolipoprotein(a), through a disulfide bond. (1,2) Based on current evidence, it is well established that high Lp(a) levels confer greater risk of cardiovascular disease (mainly coronary heart

Rev Argent Cardiol 2022;90:215-221. http://dx.doi.org/10.7775/rac.v90.i3.20516

Received: 01/24/2022 – *Accepted:* 04/08/2022

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disease). Epidemiological and genetic studies indicate an association between high Lp(a) levels and increased cardiovascular risk. (3-5)

Aortic valve stenosis is associated with the progressive reduction of the aortic valve orifice and impaired leaflet motion. It is the most common type of valvular disease and the most prevalent in the elderly population, with degenerative calcification being the most frequent acquired cause. (6)

Interestingly, lipoprotein or lipidic precursor accumulation has been observed within the stenotic aortic valves, including conventional LDL, oxidized LDL and oxidized phospholipid particles. (7,8) In addition, several observational studies have evaluated the relationship between Lp(a) levels and calcific aortic valve. (9) Moreover, various reports, mostly from cohort studies, have analyzed whether high Lp(a) levels are an independent risk factor for the progression of aortic valve stenosis or the occurrence of clinical events, though with contradictory results. (10-17) The identification of Lp(a) as a potential risk factor to develop cardiovascular disease (including aortic valve disease) has awakened the interest to develop pharmacological therapies specifically targeting the reduction of its levels.

Consequently, the main purpose of the present systematic review was to analyze the ability of high Lp(a) levels to predict the occurrence of clinical events related with aortic valve disease.

METHODS

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations developed to steer the performance of systematic reviews and analyze observational studies in epidemiology, respectively. (18,19)

A systematic bibliographic search was carried out to identify studies evaluating the association between Lp(a) levels and clinical events related with aortic valve stenosis. Two independent reviewers performed the search in PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar and Cochrane Controlled Trials electronic databases, using the term "lipoprotein(a)", alone or combined with the following terms: "aortic valve stenosis", "aortic valve replacement", "aortic stenosis mortality", "aortic stenosis hospitalization", "aortic valvulopathy" and "aortic valve calcification".

The following inclusion criteria were used to select the studies:

1) Observational cohort design studies (prospective or retrospective). No case series, cross-sectional o case control-studies were included.
2) Studies comparing patients with or without high LP(a) levels. No specific cut-off point was established; some studies used the highest Lp(a) tertile, and others analyzed preestablished cut-off points (e.g.: 50 mg/dL).
3) Studies evaluating the relationship between Lp(a) levels and risk of clinical events associated with valvular disease.

The primary endpoint of the study was the incidence of events related with aortic valve stenosis. This endpoint, defined according to the events reported in each selected study, was a composite of clinically relevant events, as aortic valve replacement, death or hospitalization associated with valvular disease. The hazard ratio (HR) was the measure of association used, with its corresponding 95% confidence interval (95% CI).

Two independent reviewers assessed the quality of the studies included, using the QUIPS (Quality in Prognostic Studies) tool criteria. (20) Any discrepancy between the two reviewers was solved though the participation of a third reviewer.

This systematic review was registered in PROSPERO.

The performance of a quantitative analysis (meta-analysis) was not possible due to the heterogeneity of the populations included, the different Lp(a) cut-off points and diagnostic methods used, and the type of clinical events reported.

RESULTS

A total of 7 studies, including 58 783 patients, were identified and considered eligible for the qualitative analysis. Figure 1 shows the flow diagram of the studies' selection process.

All included studies were observational cohort studies (prospective or retrospective). The risk of bias was evaluated in all studies. Only one study was identified as low risk of bias, and in the remaining 6 studies a moderate risk was observed. These studies had methodological issues more frequently related with study discontinuation and statistical analysis or reporting. The quality of the assessed studies is shown in Figure 2.

Mean age and the proportion of women ranged between 58 and 70.3 years and between 31.7% and 72.7%, respectively. Three studies included patients with mild to moderate aortic valve stenosis, (10-12) one study analyzed subjects with familial hypercholesterolemia (13) and three studies evaluated individuals belonging to the general population. (14-16) Mean follow-up ranged between 3.2 and 19.8 years.

Three studies considered the highest Lp(a) tertile as cut-off point, (10-12) and another three analyzed a preestablished Lp(a) level of 50 mg/dL as their cut-off point. (13-15) In the case of the study published by Kamstrup et al., the subgroup of patients with Lp(a) levels between 67 and 89 mg/dL was selected for this analysis and compared with reference values (<22 mg/dL). (16) Table 1 depicts the characteristics of the studies included.

The qualitative analysis showed that two studies did not report a significant association between high Lp(a) levels and the primary endpoint, although the trend was markedly in favor of the association in one of them. Conversely, the remaining five studies reported a greater risk of events associated with aortic valve stenosis in those patients with elevated Lp(a) levels, ranging between 70% and approximately 3-fold higher risk, despite adjusting for traditional risk factors (Figure 3).

DISCUSSION

In this systematic review, high compared with lower Lp(a) levels were associated with greater incidence of

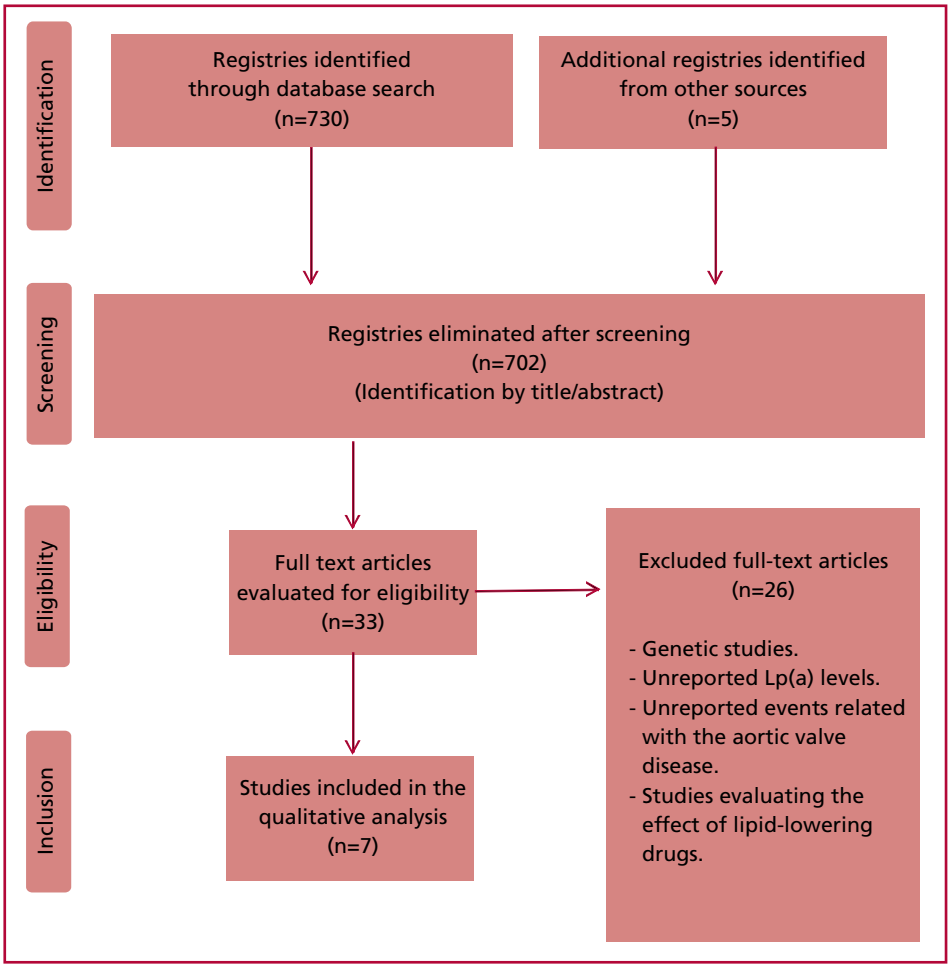

Fig. 1. Flow diagram of studies' selection process.

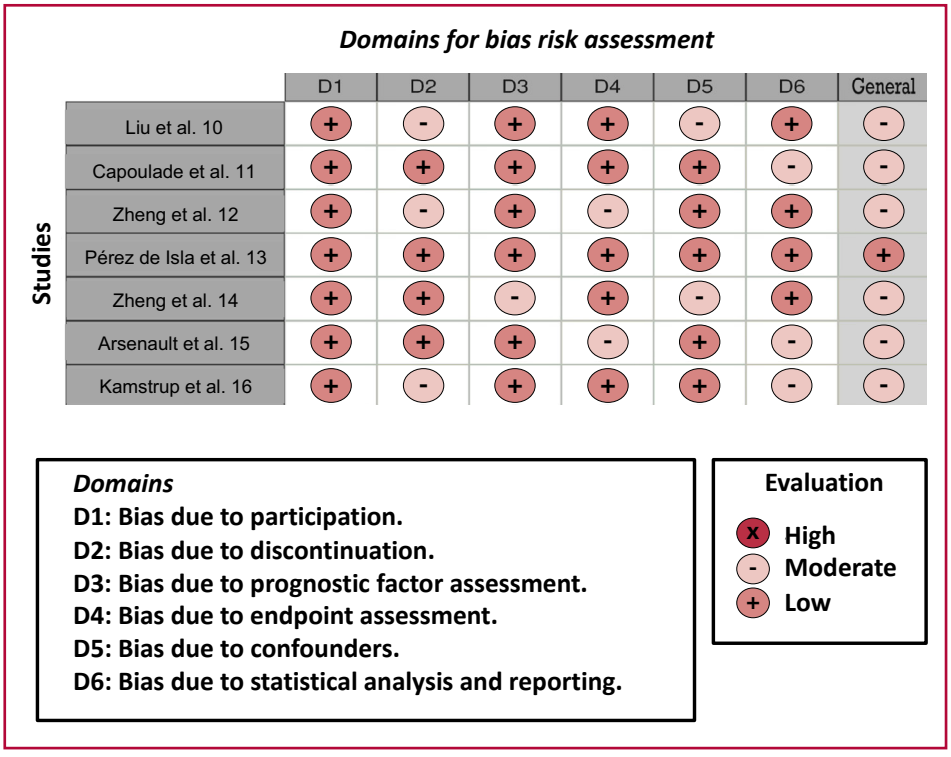

Fig. 2. Bias assessment in the included studies.

Table 1. Characteristics of the studies analyzed

Study	N	Population	Lp(a) groups evaluated (mg/dL)	Study methodology	Events evaluated related with aortic valve stenosis	Follow-up (years)
Liu et al.[10]	359	>18 years. Mild to moderate aortic valve stenosis (peak velocity >2.5 and <4m/s). Men: 58.3%	>38.15 vs. ≤38.15	Cox regression analysis. Adjusted for age, sex and traditional risk factors.	AVR or cardiac death.	3.2
Capoulade et al.[11]	219	>18 years. Mild to moderate aortic valve stenosis (peak velocity >2.5 and <4m/s). Men: 60%	>58.5 vs. ≤58.5	Cox regression analysis. Adjusted for age, sex and baseline aortic stenosis severity.	AVR or cardiac death.	3.5
Zheng et al.[12]	145	> 50 years. Aortic valve stenosis with peak velocity > 2.5 m/s and aortic calcification. Men: 68.3%	>35 vs. ≤35	Cox regression analysis. Adjusted for age, sex, traditional risk factors, history of CVD and baseline aortic stenosis severity.	AVR or death.	5
Pérez de Isla et al.[13]	3712	>18 years. Familial hypercholesterolemia Men: 65.7%.	>50 vs. ≤50	Cox regression analysis. Adjusted for age, sex, history of CVD and traditional risk factors.	AVR	7.5
Zheng et al.[14]	17 745	General population 39 -79 years. Men: 55.1%.	>50 vs. ≤50	Cox regression analysis. Adjusted for age, sex, history of CVD and LDL-C.	Death or hospitalization	19.8
Arsenault et al.[15]	17 553	General population between 39 and 79 years. Men: 44%.	≥50 vs. <50	Cox regression analysis. Adjusted for age, sex, smoking and LDL-C.	Death or hospitalization	11.7
Kamstrup et al.[16]	19050	General population >20 years. Men: 44%.	67-89 vs. <22	Cox regression analysis. Adjusted for age, sex and traditional risk factors.	AVR	5

LDL-C: Low-density lipoprotein cholesterol; CVD: Cardiovascular disease; AVR: Aortic valve replacement

clinical events related with aortic valve stenosis in almost all the studies evaluated.

Growing information suggests that lipids could play a role in the pathophysiology of aortic valve stenosis. (6) Furthermore, a genomic study revealed that certain polymorphisms in the Lp(a) gene locus are associated with greater risk of valvular calcification. (21)

The main blood transporter of oxidized phospholipids is Lp(a). It has been shown that these modified phospholipids promote valvular mineralization and calcification through the positive regulation of reactive oxygen species and inflammatory cytokines released by macrophages. (6,22) Also, within the valve, lipoprotein-associated phospholipase A2 uses oxidized phospholipids to generate lysophosphatidylcholine, an enzyme which has demonstrated in vitro an effect on mineralization. (23,24) Conversely, other mechanisms

not related with oxidized phospholipids have been proposed: Lp(a) significantly increases the activity of alkaline phosphatase, phosphate release, calcium deposits, hydroxyapatite, cellular apoptosis, vesicle formation in the extracellular matrix and phosphorylation of certain proteins involved in signal transduction. (22)

Calcification is one of the most relevant processes which determine the progression of aortic stenosis. Previously published reports showed that the presence of valvular calcification has significant prognostic value. (25-27) In this sense, high Lp(a) values could favor valvular calcification and, consequently, increase the risk of clinical events related with valvular disease. In line with previously mentioned pathophysiological findings, most studies evaluated in this review showed a positive and significant association between Lp(a) levels and clinical events related with aortic valve disease.

The individual analysis of the studies included in this systematic review revealed that they did not always concur. On the one hand, the analysis of two studies evaluating populations with a previous degree of aortic stenosis showed a significant association between high Lp(a) levels and the primary endpoint, (11,12) whereas a third study did not. (10) In the latter case, the study only included Chinese patients [potential ethnic variation of the Lp(a) effect], the Lp(a) cut-off point was low and the follow-up time was lower compared with the other two studies. On the other hand, two of the studies evaluating the same association in the general population found a significant relationship (14,15), but not a third study. The result of this last case showed a clear trend in favor of the association, and it should be considered that the follow-up time was markedly shorter in this study compared with the other two. (16) The only study evaluating patients with familial hypercholesterolemia showed a significant association between elevated Lp(a) levels and valvular events. A previously published review showed similar findings to those of our investigation. (9) However, this review mostly included studies with a cross-sectional or case-control design. Also, a meta-analysis evaluated the association between aortic stenosis and the different genetic Lp(a) variants. (28) Consequently, to the best of our knowledge, this is the first systematic review based on observational cohort studies, specifically examining the Lp(a) effect on clinical events related with aortic valve stenosis.

Lp(a) concentrations vary widely among individuals within the same population, as well as between different ethnic groups. (29) This variation complicates establishing a universal clinical risk threshold, which is currently considered >50 mg/dL. The studies included in our analysis considered different cut-off points for this lipidic marker. Therefore, we cannot ascertain, from this review, which would be the Lp(a) cut-off point with greatest predictive power. In addition, and taking into account the variations of this marker in the different populations, it would be good practice to have local investigations and not extrapolate results obtained in other regions.

To date, there are no effective medical treatments for aortic valve stenosis. The evidence from randomized controlled trials showed that statin-based lipid-lowering therapy was not associated with a reduction of events related with calcific aortic stenosis. (30) As is well known, statins are inefficient or may even increase Lp(a) serum levels. (31,32) Niacin reduces Lp(a) between 20% and 25%. However, clinical trials with these agents did not evidence a reduction of major cardiovascular events and currently their use is not recommended. (33) Different from niacin, PCSK9 inhibitors have been demonstrated to decrease Lp(a) levels and reduce cardiovascular events. Moreover, a recent study with these drugs has shown promising results regarding a decreased rate of aortic stenosis progression. (34) The greater reduction of Lp(a) levels with PCSK9 inhibitors, compared with statins, would explain the benefit of these drugs

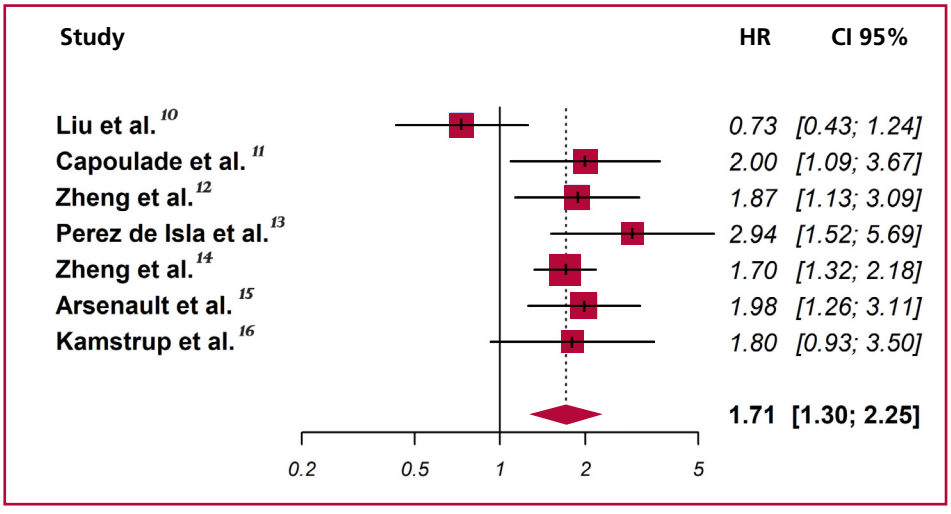

Fig. 3. Effect of high Lp(a) levels on events related with aortic valve stenosis. Hazard ratios (HR) and 95% confidence intervals (CI).

in aortic stenosis. (35) New therapies are being developed to reduce Lp(a) levels, including an antisense oligonucleotide that selectively binds to the messenger RNA that codifies the Lp(a). (36) Nevertheless, future clinical trials should demonstrate its potential role in the treatment of aortic stenosis.

This systematic review presents some limitations. Firstly, we were unable to perform a quantitative analysis (meta-analysis) due to the clinical heterogeneity (population characteristics, different Lp(a) cut-off points, aortic events reported and follow-up times). Secondly, although the number of patients in the studies published by Zheng et al. (14) and Arsenault et al. (15) were not exactly the same and the follow-up time was different, they were probably obtained from the same database. Consequently, we cannot rule out some degree of overlap in the events identified in the first follow-up years. Thirdly, our review included only observational studies. Therefore, there are probably biases and confounding factors related with this type of design. Finally, the review included few studies. However, until more and better-quality studies are developed, our review analyzed the best available evidence so far.

CONCLUSION

Our data suggest that high Lp(a) levels are associated with greater incidence of aortic valve stenosis related clinical events. However, and considering the limitations of this review, the clinical usefulness of Lp(a) as a prognostic marker in aortic valve disease should be confirmed in future investigations.

Conflicts of interest

None declared.

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

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The Rejection of Harvey's Discovery

El rechazo al descubrimiento de Harvey

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Despite the anti-dogmatic and liberal atmosphere of the Renaissance, the publication of "*De motu cordis*" (1628), at the time when **Harvey** was 50 years old, provoked lively controversies. It was not easy that fourteen centuries of Galenic hegemony, despite the partial contributions on circulation due to the studies of **Vesalius, Cesalpino, Valverde** and **Colombo**, should be overthrown without any opposition. **Harvey** must surely have foreseen this contingency, since twelve years passed from his first manuscripts the "*Lumleian Lectures*" (1616) to the publication of the text.

"*De motu cordis*" had challengers and supporters. Among the latter we must mention his close friend **George Ent** (London, 1604-1689); the famous Dutch physiologist **Franz de le Boë Silvio** (1614-1672); **Francis Glisson** (London, 1597-1677); the Belgian **Vopisius Fortunatus Plemp** (1601-1671), **René Descartes** (Egmond, 1596-1650); **Anton Deusing** (Groningen, 1612-1666); **Werner Rolfink** (Jena, 1599-1673) and **Hermann Conring** (Hellsmstadt, 1606-1681).

His most famous critics included **Jacques Primrose** (London, died 1659), **Emilio Parisano** (Rome, 1567-1643), **Gaspar Hoffmann** (Germany, 1572-1648), **Jean Riolano** (Paris, 1580-1657), **Guy Patin** (1602-1672), **Francisco Folli** (Venice, 1624-1685), and **Marco Severino** (Naples, 1580-1656). **Harvey** did not argue with all of them, but only replied to **Hoffmann** and **Riolano**.

The opposition of the Englishman **Jacques Primrose**, a disciple of **Riolano**, was carried out through the text "*Exercitations animadversions in librium de Motu Cordis*" (1630), but it does not reveal any scientific quality. It was based on the fact that since ancient times patients had been cured with no need to know the alleged theory of circulation.

Moreover, from Rome, **Emilio Parisan**o, with his text "*Nobilium exercitationum*" (1653) held that the existence of venous valves could not justify the movement of blood. On the other hand, this assertion by **Parisano**, in the analysis of the "*De Motu Cordis*", indicates that the teachings Harvey had received from his teacher Fabrizio d'Acquapendente with respect to the venous valves was an important contribution to his discovery. This concept was also confirmed by the English scientist **Robert Boyle** (1627-1691).

In 1636, on his way to Vienna, **Harvey** learned that Gaspar Hoffmann had criticized him with the following words for having assumed, "*that Nature was so clumsy and inefficient an artificer, in suffering the blood to become recrudescent, and making it return again and again to the heart in order to be recon-cocted, to grow enfeebled as often in the general system, thus uselessly spoiling the perfectly-made blood, merely to find her in something to do*". For this reason, he met Hoffmann in Altdorf and had a debate, in which he resorted to reasoning by working on a corpse. Faced with the unperturbed refusal of his interlocutor, exasperated, he stuck his dagger in the table and left immediately. He subsequently sent him a letter inviting him to reread "*De Motu Cordis*".

Guy Patin, Dean of the Faculty of Paris, openly declared himself to be "*anti-circulation*". Thus, he wrote: "*Circulation is paradoxical, useless to medicine, false, impossible, unintelligible, absurd, harmful to the life of man*".

With **Jean Riolano** he had a longer discussion. Professor in Paris, **Riolano** wrote two texts, in 1648 "*Enchiridium anatomicum et pathologicum*" (Paris), and in 1649 "*Opuscula Anatomica Nova*", in which he maintained a Galenist position despite certain concessions. He accepted the major circulation only in the large arteries and veins, but not in the small ones, which would have a nourishing function. "*The blood,*" wrote **Riolano**, "*remains in them for nutrition and does not back flow into the larger vessels*". While he agreed, except for the above caveats, with the systemic circulation, he denied the minor one. In his concept the blood in the pulmonary artery served exclusively for pulmonary nutrition, while the blood flow emptied from the right ventricle into the left ventricle through the pores of the septum.

Harvey replied with two epistles in 1649 published in Rotterdam under the title "Exercitations dual anatomicae de circulatione sanguinis ad **J. Riolanum**, filium". In the first one he is polite, but in the second one his arguments acquire a virulent tone. In the latter he presents a summary of the circulation. He strictly says: "*The blood which is contained in the veins and which accumulates especially in the part of the vena cava neighboring the base of the heart and*

the right atrium, is heated there by a caloric faculty inherent in it, bubbles into vapor and rises in the manner of fermenting substances, thus filling the atrium. This contracts by its own contractility, immediately expelling the blood into the right ventricle of the heart, which, in turn, once filled, expels by its systole the blood it has received. Faced with the obstacle that the tricuspid valves oppose to blood backflow, the ventricle expels it into the vena arteriosa, which opens its door. Once in the vena arteriosa, the blood is impeded by the sigmoid valves to return backwards. By inspiration and expiration, the lungs are mobilized and with them their vessels, thus offering this blood the way and passage to the venous artery and from this to the left atrium, which has movement, rhythm, purpose and synchronous functions with the right atrium, pouring its blood into the left ventricle. Immediately the left ventricle propels its blood into the opening of the aorta and from it to all its branches".

Criticisms of the blood circulation, such as the one made by the Portuguese Lima in 1761, were widespread until the 18th century.

Digital Ischemic Necrosis of the Upper Limb Due to Thoracic Outlet Syndrome

Thoracic outlet syndrome encompasses diverse clinical disorders resulting from compression of the neurovascular structures running from the base of the neck to the upper limbs at its thoracic outlet. Arterial involvement in thoracic outlet syndrome is infrequent but serious due to the potential risk of thromboembolic complications that threatens the functionality and viability of the extremity. (1) Digital ischemic necrosis is a form of presentation of this condition.

This is the case of a 32-year-old woman, heavy smoker, with a 4-month history of intermittent left upper limb claudication associated with hand paresthesia. The patient progressed with pain at rest and dry ischemic necrosis in the third finger of the left hand (Figure 1A). Evaluation and treatment were performed by a multidisciplinary team (Traumatology, Internal Medicine, Rheumatology, Emergency); the patient was referred to the Vascular Surgery Division. Physical examination revealed coolness and pallor of the left forearm and hand; absence of axillary, humeral, radial and ulnar pulses with contralateral pulses present; a painful non-pulsatile hard-stony mass in the left supraclavicular fossa, which the chest X-ray revealed to be a supernumerary cervical rib. Doppler ultrasound showed subclavian, humeral, radial and left ulnar arteries with a post-obstructive monophasic flow pattern, with very low velocity (20 cm/sec in the subclavian artery) and reduced resistance. CT angiography revealed an anterior costal fusion of the bilateral cervical rib and the first costal arch only on the left side, associated with thrombosis of the subclavian artery (Figure 2A). Angiography evidenced recanalization of a thrombosed aneurysm of the left subclavian artery distal to the vertebral artery through collaterals in the axillary artery, distal occlusion of the humeral artery, but patency in the deep humeral artery and recanalization through collaterals in the ulnar and radial arteries with incomplete palmar arch (Figure 2B). It was decided to perform surgical resection of the cervical and first thoracic ribs, anterior and middle scalenectomy, exclusion of the subclavian aneurysm and arterial reconstruction with subclavian-axillary bypass with a ringed 6 mm-polytetrafluoroethylene (PTFE) prosthesis.

The patient was referred to a smoking cessation program. After one and a half-year follow-up, the patient is asymptomatic, with healing of the digital trophic lesion (Figure 1B) and patent bypass.

Upper limb ischemia is less common than lower limb ischemia. (2, 3) Depending on the time of evolution, ischemia can be acute or chronic, the latter being less common. Vascular trauma, embolism and arterial thrombosis are causes of acute ischemia, whereas subclavian artery atherosclerosis and thoracic outlet

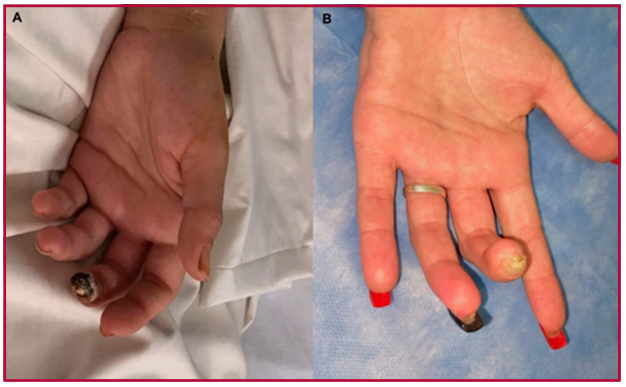

Fig. 1. A. Digital ischemic necrosis of the third finger. **B.** Trophic lesion healing following revascularization

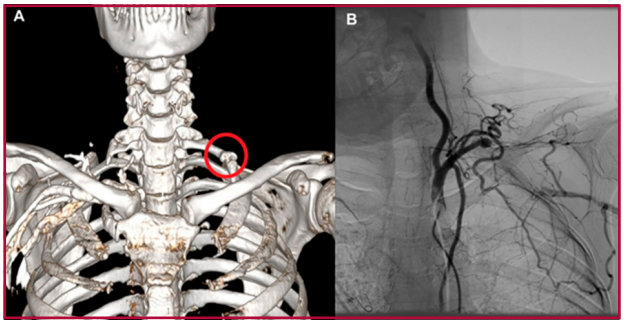

Fig. 2. A. CT Angiography: Anterior costal fusion of the bilateral cervical rib and the first costal arch only on the left side. **B. Angiography:** Recanalization of a thrombosed aneurysm of the left subclavian artery distal to the vertebral artery through collaterals in the axillary artery

syndrome often present with chronic upper limb ischemia. (2, 3)

Thoracic outlet syndrome is a complex entity characterized by extrinsic compression of the brachial plexus and/or subclavian vessels (vein or artery), by bony abnormalities or by hypertrophy of the scalene and/or subclavian muscles. Depending on which structures are compressed, it can be neurogenic (95%), venous or arterial TOS. Arterial thoracic outlet syndrome is characterized by subclavian artery disease in the setting of anatomic factors that produce compression, most commonly bony abnormalities such as a cervical rib, first hypoplastic rib, clavicle fracture, rib or hypertrophic calluses from healed fractures. (1, 4) It is the least frequent form of thoracic outlet, representing only 1-3% of patients in the largest reported series, and occurring mostly in young women. (1)

Arterial complications at the thoracic outlet represent the end stage of an undiagnosed condition in which the subclavian artery has been chronically compressed and wall changes develop, including intimal injury with or without post-stenotic dilatation or aneurysm formation, and thrombus formation leading

to distal embolization and serious complications, such as upper limb ischemia and posterior circulation ischemic stroke. (1, 4, 5)

Unilateral hand or digital ischemia is a common clinical presentation in patients with arterial outlet syndrome, which may be accompanied by numbness, tingling, temperature and impaired sensitivity. It is important to point out that these findings can be observed even with palpable radial and ulnar pulses. Loss of ulnar, radial or humeral pulses, as well as decreased blood pressure measurement in the affected limb, may also occur. (4)

Digital ischemia attributable to microembolization is the most common presentation of arterial thoracic outlet syndrome; however, this clinical presentation remains a challenge for physicians due to differential diagnoses, as it can also occur in other conditions such as vasculitis, thromboangitis obliterans, Raynaud's syndrome, ergotamine intoxication, and upper limb atherosclerosis. (4, 6)

The presence of bilateral symptoms suggests a systemic etiology, but the arterial thoracic outlet syndrome should not be ruled out, because cervical ribs tend to occur bilaterally in 50% of cases. (6)

Patients with significant subclavian or axillary artery stenosis, in the absence of acute ischemic complication, may present with typical symptoms of upper extremity claudication. Vemuri et al reported 42% of patients with images of chronic thoracic outlet arterial compression, but with associated symptoms of neurogenic compression, or even asymptomatic, concluding that the incidence of arterial thoracic outlet syndrome is underestimated. (1, 5) Al-Jundi et al suggest that smoking might be a predisposing factor for the symptomatic presentation of arterial thoracic outlet syndrome due to increased risk of thrombosis . (6)

An initial assessment with a chest X-ray including cervical spine views can demonstrate aneurysmal changes or elevated flow velocities correlated with a compressive stenosis of the subclavian artery. (6) Analysis of the causes of embolization should include transthoracic echocardiography, as well as computed angiotomography of the aortic arch and upper limbs, the most readily available modality that provides anatomical details regarding the presence of a bony abnormality and a subclavian artery post-stenotic dilatation. (4) However, for treatment planning purposes, angiography remains more sensitive for assessing the degree of subclavian artery involvement, distal vascular beds and level of embolization. (4, 6) In asymptomatic patients, it also confirms extrinsic compression of the subclavian artery in early stages, when there are no lesions of the arterial wall, performing the procedure during hyperextension maneuvers of the upper limb.

Surgical treatment for arterial thoracic outlet syndrome consisted of supraclavicular thoracic outlet decompression with complete anterior and middle scalenectomy with bone resection (resection of cervical rib and/or first rib or other bony abnormality) plus vascular reconstruction depending on the degree of subclavian artery involvement (stenosis/aneurysm) and the presence or absence of distal embolism. Revascularization of the upper limb is performed using bypass surgery with saphenous vein or ringed PTFE graft, associated with distal embolectomy to treat the embolic complication. (1, 4)

In summary, thoracic outlet syndrome is a rare cause of upper limb arterial ischemia that should be suspected in young patients; early surgical treatment (outlet decompression surgery and arterial reconstruction) is indicated to achieve limb salvage and avoid functional sequelae.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

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Management of a Premature Infant (1460 g) with Ductal-Dependent Tetralogy of Fallot

Patients with a diagnosis of Tetralogy of Fallot (TOF) requiring early intervention are those who are prostaglandin dependent, or with severe cyanosis due to

decreased pulmonary blood flow resulting from unfavorable right ventricular outflow tract (RVOT) or pulmonary arteries anatomy. Management of these patients with associated risk factors (low weight, prematurity, age < 3 months, unfavorable pulmonary artery anatomy, anomalous coronary distribution and critical preoperative conditions) continues to raise debate. Palliative procedures may include RVOT opening, systemic pulmonary anastomosis, pulmonary valve replacement, or patent ductus arteriosus or RVOT stenting. Early repair in these patients can be performed successfully; however, despite its many advantages, it is associated with a great number of postoperative complications and subsequent reinterventions. (1-4)

The purpose of this study is to describe the management of a TOF patient with multiple risk factors, who underwent successful surgery without complications at the Hospital Interzonal Especializado Materno Infantil in the city of Mar del Plata, Buenos Aires, Argentina.

It was an infant born at 32 weeks of gestation (weight 1460 g), with trisomy 21 on karyotype, delivered by emergency cesarean section due to large anterior ventricular septal defect (VSD), infundibular and valvular pulmonary stenosis (valve Z-score -4), confluent good size pulmonary arteries, overriding aorta, small atrial septal defect (ASD) and patent ductus arteriosus, diagnosed by fetal Doppler echocardiography. Due to the unfavorable cardiac anatomy, continuous prostaglandins infusion was indicated to maintain ductal patency.

At 20 days of life, the patient developed Escherichia Coli bacteremia and sepsis, associated with severe respiratory distress syndrome. After 7 days of sepsis treatment, a 7x7 mm vegetation was found in the right atrium; the condition was assumed to be infective endocarditis due to Escherichia Coli. After 4 more weeks of antibiotic therapy, follow-up echocardiography showed no vegetation. After 58 days on mechanical ventilation and neonatal intensive care unit discharge, the patient required oxygen therapy due to bronchopulmonary dysplasia. Patient comorbidities included chronic diarrhea due to protein-losing enteropathy, for which he was fed with hydrolyzed milk via parenteral nutrition (a total of 68 days). Lab tests showed hypoproteinemia, hypogammaglobulinemia and hypoalbuminemia.

Due to the multiple risk factors described above (ductus-dependent TOF, prematurity, low weight, respiratory distress syndrome, and hypoproteinemia), and once infective endocarditis resolved, RVOT stenting appeared to be the safest option to postpone surgical repair and perform it with more favorable clinical features.

Stent implantation

The right femoral vein was punctured, and a 6 French introducer was deployed. A 15 mm-long outflow tract was observed, with a marked dynamic systolic narrowing at 4 mm from the pulmonary valve plane. It was decided to place a 4x16 cobalt chromium coronary stent. The stent was progressed taking the valvular plane and the RVOT. The balloon was inflated and a stable infundibular diameter of 4 mm was achieved. Subsequent angiography showed good flow through the stent and severe pulmonary valve regurgitation due to collapse of the valve by the stent.

After the procedure, the patient was transferred to the neonatal ward; arterial oxygen saturation was between 93-95%; prostaglandin was discontinued, and closure of the arterial ductus was confirmed 48 h post-procedure, with saturation dropping to 90%. The patient remained in the pediatric ward for nutritional recovery.

At the age of 7 months, arterial oxygen saturation was 85%, requiring 0.5 L oxygen through a nasal cannula. Physical examination showed chronic malnutrition (weight 3.4 kg), active precordium, presence of Dressler's syndrome, and systolic murmur in pulmonary focus 3-4/6. Echocardiography revealed a large subaortic VSD, RVOT stent gradient of 55 mmHg, right ventricular hypertrophy, confluent good size pulmonary arteries, overriding aorta, and small ASD. A surgical repair was decided.

Surgical procedure

It was performed by median sternotomy. A patch was reserved for pulmonary artery repair, and the patient was heparinized. Cannulation of the aorta and the superior and inferior vena cava was performed, temperature was lowered to 28°C, the aorta was clamped, cardioplegia was infused antegrade, and a left heart vent cannula was placed. The main pulmonary artery was opened at the level of the annulus, extending to the bifurcation of the pulmonary branches (Figure 1). The stent was attached to the posterior wall, at the level of the RVOT and pulmonary valve; it was completely resected without complications (Figure 2). Infundibular resection was performed due to right ventricular hypertrophy, and the large VSD was closed with a 0.6 mm polytetrafluoroethylene patch. A monocusp autologous pericardial valve was sutured to the pulmonary annulus and transannular patch, from the ventriculotomy to the bifurcation of the pulmonary branches. Air was purged from the left heart and the aorta was declamped after 61min. The patient recovered sinus rhythm. When the patient reached 36.5ºC, he was weaned from cardiopulmonary bypass after 100 min, and was decannulated.

Immediate postoperative course required low doses of inotropes. The patient was extubated 48 hours after surgery, and was on nasal cannula oxygen due to his bronchopulmonary dysplasia. On the 5th postoperative day, he was transferred to a less complex area for nutritional recovery. Echocardiography 1 month after surgery showed closed VSD, no residual VSD, closed ASD, mild pulmonary stenosis, mild to moder-

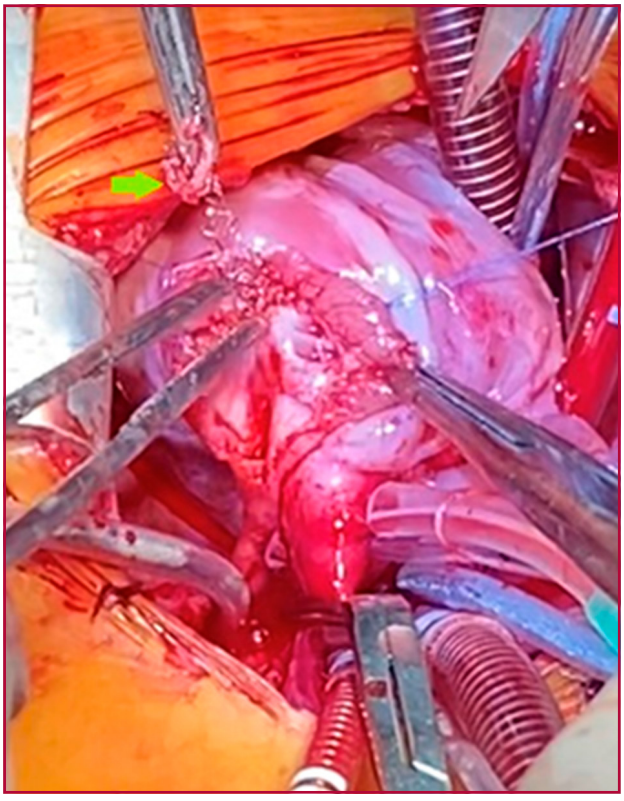

Fig. 1. The stent is removed (green arrow) through ventriculotomy; it is attached to the posterior wall of the right ventricular outflow tract

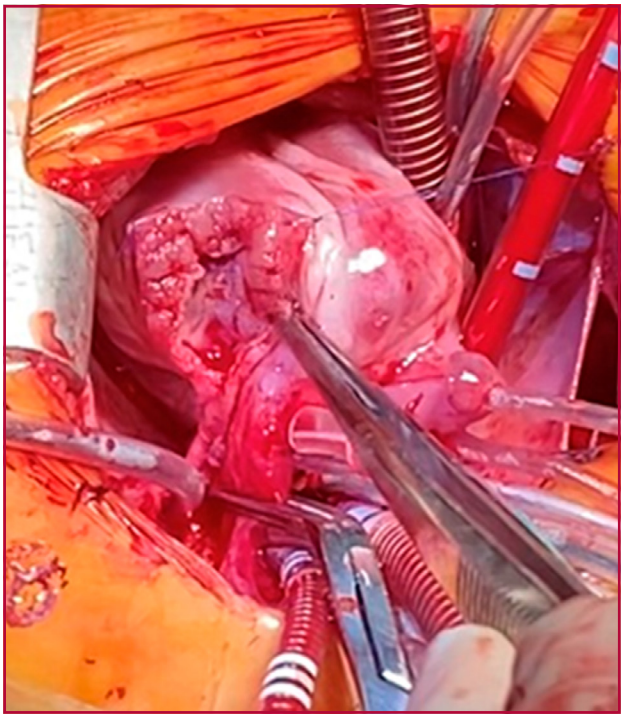

Fig. 2. Complete stent removal, without complications

ate pulmonary insufficiency, and good-caliber confluent pulmonary branches.

TOF is characterized by large subaortic VSD, pulmonary stenosis, right ventricular hypertrophy, and overriding aorta. Surgery in these patients with confluent, and of good caliber, pulmonary branches, usually allows primary repair without complications, with excellent results. Those prostaglandin-dependent patients with severe cyanosis due to severely decreased antegrade pulmonary blood flow require early intervention. In patients with coexisting comorbidities, primary repair can be performed successfully with low mortality rate, but it is associated with more postoperative complications and reinterventions. (1-4) Systemic pulmonary anastomosis is the most common palliative procedure for premature infants with low weight or pulmonary branches hypoplasia; however, it is associated with a higher rate of complications, such as pulmonary artery stenosis. (5) In these patients, RVOT stenting is the bridging option to repair surgery. (6) Surgical repair with RVOT stenting in TOF patients can be performed without complications. Complete intraoperative stent removal can be achieved in up to 95% of the patients, requiring longer cardiopulmonary bypass. (6)

In premature, low-weight patients with coexisting comorbidities, RVOT stenting improves cyanosis, does not alter the anatomy of the pulmonary branches, and allows to solve non-cardiac comorbidities in order to then perform the uncomplicated reconstructive surgery.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable.

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Rev Argent Cardiol 2022;90:225-228.
http://dx.doi.org/10.7775/rac.v90.i3.20525

Dasatinib Induced Pulmonary Arterial Hypertension in a Patient from the Peruvian Andes at 3660 m

Pulmonary arterial hypertension (PAH) incidence ranges from 1.5 to 32 patients per million, with poor prognosis, (standardized U.S. mortality rate between 4.5 and 12.3 per 100 00 inhabitants, and a five-year survival rate of 56%). (1) PAH is defined when pulmonary systolic pressure is > 30 mmHg, or mean pulmonary artery pressure (mPAP) is ≥ 25 mmHg; its etiology is varied and includes PAH secondary to drugs (group 1 of the 6th World Symposium on PAH Clinical Classification: drug/toxin induced).

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI), approved by the FDA in 2010 as first-line treatment of chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Several clinical trials have shown that dasatinib is more effective than imatinib in treating CML as it can produce fast and sustained clinical, hematological and molecular remissions. However, cardiovascular adverse events with dasatinib have been reported, including QTc prolongation, pleural and pericardial effusion, pulmonary parenchymal infiltrates, and PAH.

Considering that there are no literature reports on PAH and dasatinib in subjects inhabiting high altitude settings, our purpose is to describe the case of a patient born in a city at 3660 m high, who was diagnosed with CML and treated with dasatinib, and who developed PAH, in order to determine whether altitude contributed to such development.

This was a 42-year-old male patient from Huancavelica, Peru, diagnosed with CML by flow cytometry in 2009. Imatinib 400 mg/day was prescribed in March 2011. Since the patient was unresponsive to imatinib, in September 2014 he was switched to dasatinib 100 mg/day for 21 months, followed by 140 mg every other day for 25 months. In June 2019, the patient reported dyspnea, fatigue, headache, and weight loss (5 kg), and was admitted to the emergency room for acute respiratory distress and fever. Chest computed tomography (CT) revealed mild pericardial effusion and bilateral pleural effusion requiring drainage, with clinical improvement. ECG showed right bundle branch conduction disturbances (Figure 1). Echocardiography revealed severe right ventricular enlargement, normal contractility, and 3D ejection fraction 42%; marked right atrium enlargement and moderate tricuspid regurgitation. Left ventricular function was normal, with ventricular septal displacement associated with right ventricular overload. Severe pulmonary hypertension, systolic PAP 100 mmHg, and mild pericardial effusion were also detected (Figure 2). Pulmonary CT angiography showed bilateral pleural effusion without pulmonary thromboembolism.

A medical peer review decided to discontinue dasatinib and switch to nilotinib. Medical check-ups were performed every 3 months; no progression of PAH was observed. Symptoms completely resolved within 9 months after dasatinib discontinuation, ECG was normal; systolic PAP on echocardiography reverted to baseline and right chambers returned to normal.

Our patient had baseline systolic PAP of 40 mmHg, typical of an Andean native resident. Peru is a country traversed by the Andes mountains; 8,726,000 people (28.1% of the Peruvian population) live in this region, and are adapted to altitudes above 3500 m. At this altitude, low barometric pressure results in low partial pressure of inspired oxygen compared to coastal residents; hypoxia causes physiological changes in the pulmonary circulation —first described by the Peruvian researcher Dante Peñaloza 62 years ago—, (2) with increased smooth muscle cells (SMC) in the small pulmonary arteries and muscularization of the arterioles, increased pulmonary vascular resistance, and development of PAH. Mean PAP describes a parabolic curve: at 2000 m the value is 15 mmHg and at 4500 m it is 30 mmHg, and can reach up to 40 mmHg, as was the case in our patient. (3) The prevalence of altitude-induced PAH is 5-18% in South America.

A second mechanism of altitude-induced PAH would be vasoconstriction of the pulmonary precapillary vessels, accounting for 80% of increased pulmonary vascular resistance, and of the small pulmonary veins (< 900μm), which determine the remaining 20%. This vasoconstrictor response to hypobaric hypoxia has an initial stage within seconds of exposure to alveolar oxygen deprivation that reaches its maximum value at 15 minutes, followed by a second stage with a more gradual increase in pulmonary arterial pressure that reaches a plateau at 2 hours and is maintained for 8 hours. The first stage would be a consequence of reactive oxygen species (ROS) generated by mitochondria of SMCs in the middle layer of the arterioles; this excess of ROS induces alterations in the potassium channels, intracellular calcium increase and subsequent vasoconstriction. The second stage would be regulated by alterations in the endothelial function: enhanced endothelin-1 production and thromboxane A2, with reduced prostacyclin and nitric oxide synthesis. (3)

Imatinib, a first-generation TKI, is the treatment for CML. However, second-generation TKIs such as

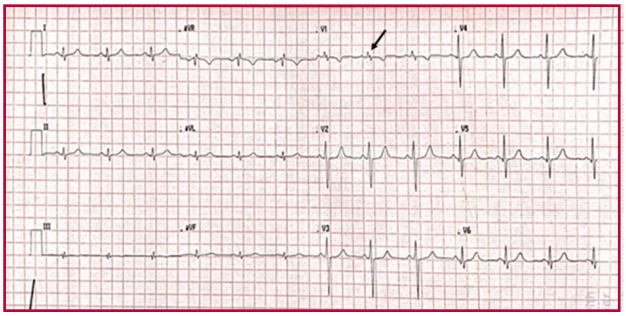

Fig. 1. ECG. Findings on admission: arrow showing right bundle branch conduction disturbances, with QRS complex with rSr' morphology in V1.

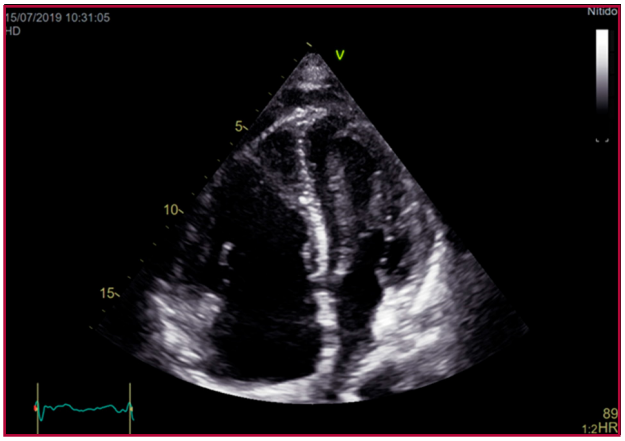

Fig. 2. Echocardiography. Transthoracic echocardiography showing enlargement of the right ventricle and right atrium, ventricular septal displacement to the left, compression of the left ventricle, and mild pericardial effusion.

dasatinib have been approved as first-line treatment for CML since November 2007 in USA, because they produce improved molecular and clinical response due to their potency on non-mutated BCR-ABL1, 325-fold greater than imatinib, with early disease control. (4)

Both imatinib and dasatinib are TKIs that act on BCR-ABL kinase; however, their effects are opposite. Imatinib improves PAH, while dasatinib causes PAH (incidence 0.2-5%). (5) This is a late complication, occurring at around 34 months (range 8-48 months). In our patient, this complication occurred at 46 months of treatment; the fact that he was an Andean resident did not determine earlier presentation or more severe symptoms. The mechanism responsible for PAH in dasatinib-treated patients is still unclear. Dasatinib differs from other TKIs in that it strongly inhibits the Src family kinases, which degrade activated platelet-derived growth factor receptors (PDGFR) and other growth factors, encouraging the proliferation of SMCs in pulmonary artery branches. It has also been demonstrated that increased oxidative stress is a determinant of pulmonary endothelial dysfunction and vascular injury. (5)

Our patient developed pleural effusion, one of the most common adverse reactions caused by dasatinib (incidence 14-60%); 90% of cases occur within one year; the reaction disappears after dasatinib withdrawal. The mechanism may be autoimmune or by inhibition of PDGFR-beta, which would cause fluid retention, and alteration of pulmonary endothelial permeability. Several studies report that PAH is the major comorbidity in patients with dasatinib-induced pleural effusion. Patients with pleural effusion may also develop pericardial effusion (29%). (6)

PAH symptoms are nonspecific, including shortness of breath, dyspnea, chest pain, cough, and hemoptysis. Physical examination is useful but nonspecific. ECG is poorly sensitive in the detection of right ventricular enlargement (20%). Echocardiography features high sensitivity and specificity. Hemodynamic manifestations improve when the drug is discontinued; however, some patients will require PAH treatment. Our patient showed clinical improvement after drug discontinuation; ECG and echocardiography were normal without treatment.

In conclusion, living at high altitude was not associated with changes in the progression of dasatinib-induced PAH.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material).

Ethical considerations

Not applicable.

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Rev Argent Cardiol 2022;90:228-230.
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Surgical results in the rehabilitation of Continuous hypoplastic pulmonary branches in patients younger than 6 months. Experience of a center

Severe hypoplasia of the pulmonary branches is life-threatening, unless pulmonary flow through the ductus arteriosus or aortopulmonary collaterals is maintained.

It is vital to reestablish pulmonary flow in the first year of life to prevent final lung development from being permanently affected. To this end, a number of surgical techniques that promote the development of pulmonary arteries have been proposed.

This paper describes our experience in rehabilitating continuous hypoplastic pulmonary branches in infants < 6 months of age.

In a retrospective cohort study, we reviewed electronic medical records of patients < 6 months of age with hypoplastic pulmonary branches undergoing surgery to ensure adequate pulmonary flow between January 2015 and December 2020 at the Children's Hospital Dr. Roberto Gilbert Elizalde.

Patients with previous procedures or discontinuous pulmonary arteries were excluded. Pulmonary branches with an echocardiographic Z-score < -2 were defined as hypoplastic. Parameter Z (Children's Hospital of Michigan) was used to calculate the Z-score.

Operative mortality was defined as deaths occurring within 30 days after surgery —or after 30 days if the patient remained in hospital—, and late mortality as those occurring beyond 30 days post-surgery if the patient was discharged.

All therapeutic catheterization or surgical procedures performed after surgery were considered reinterventions.

Ten patients met the inclusion criteria; 70% were male infants. Mean age was 1.87 ± 1.7 months; mean weight 4.04 ± 1.28 kg; mean height, 52.95 ± 5.48 cm; and body surface area, 0.23 ± 0.04 m2. Pulmonary atresia was the most common condition (30% of cases); mean Z-score of the right and left pulmonary branches prior to the procedure was -3.99 ± 1.98 and -2.36 ± 1.67 respectively.

The modified Blalock-Taussig shunt (subclavian pulmonary anastomosis using a 3-4 mm-polytetrafluoroethylene [PTFE] tube) was the preferred procedure (7 cases); 2 central shunts were used in 2 cases, and a 12 mm-valved biological conduit from the right ventricle to the pulmonary artery, with pulmonary branch plasty, was required in the remaining patient.

Mean Z-score of the right and left pulmonary branches after the procedure was -0.6 ± 2.37 and 0.09 ± 1.55 respectively (difference from preoperative values: p = 0.006 and p = 0.007 respectively).

Five patients required reintervention: a surgical reintervention with pulmonary branch plasty and a new central shunt, and four therapeutic catheterizations.

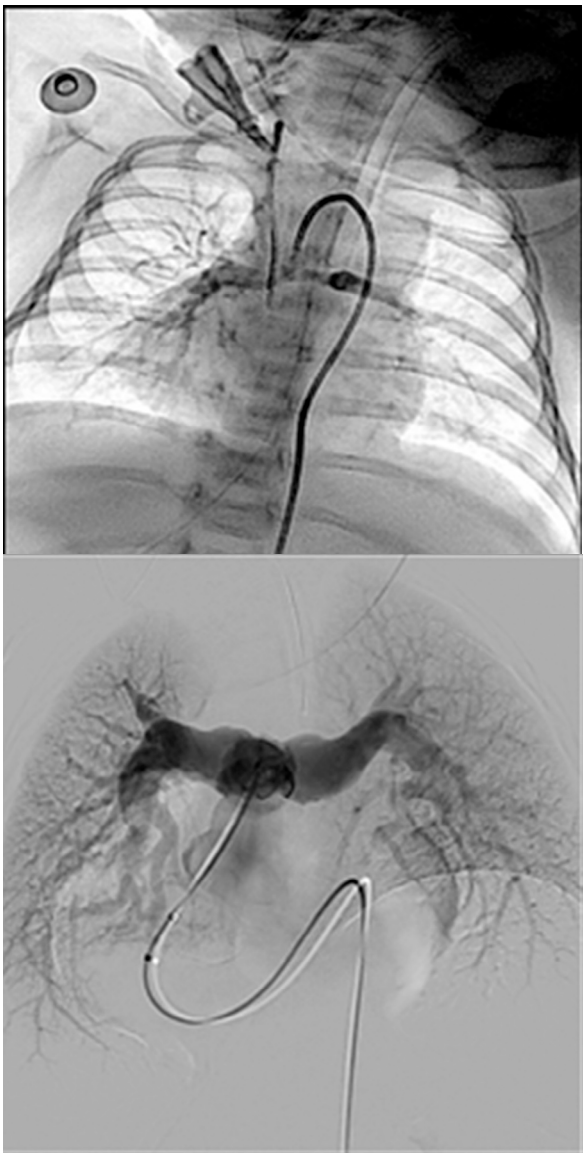
Table 1. Surgical procedures and outcomes.

n	Diagnosis	Z-score Preoperative		Surgery	Catheterization	Postoperative Z-score		Survival
		RPB	LPB			RPB	LPB	
1	Ia TA	-2.66	0.47	BT (3mm)	Yes	.	.	-
2	IIa TA VSD	-2.99	-2.47	BT (3.5 mm)	No	-1.77	0.29	+
3	PA VSD	-2.8	-3.8	RV tube PA + branch plasty	Yes	0.41	1.86	+
4	TOF	-2.73	-2.25	BT (3.5 mm)	No	-2.45	.	+
5	DORV TOF	-2.3	0.37	Central shunt	Yes	0.7	1.3	+
6	UAVC PS	-3.68	-3.4	BT (4 mm)	No	4.14	0.28	+
7	AVC TOF	-4.6	-1.78	BT (3 mm)	No	-0.92	0.32	+
8	PA IS	-7.8	-4.38	BT 4 mm + branch plasty	No	.	.	+
9	PA VSD	-7.3	-3.8	Central shunt 4 mm	Yes	-3.52	2.93	+
10	TOF	-3.12	-2.58	BT (3mm)	No	-1.39	0.73	+

TA: tricuspid atresia; Ia TA: tricuspid atresia with pulmonary atresia; IIa TA VSD: tricuspid atresia with transposition of the great arteries plus pulmonary atresia and ventricular septal defect; PA: pulmonary atresia; IS: intact septum; BT: Blalock Taussig; AVC: atrioventricular canal; UAVC: unbalanced atrioventricular canal; VSD: ventricular septal defect; PS: pulmonary stenosis; TOF: tetralogy of Fallot; RV: right ventricle. RPB: right pulmonary branch; LPB: left pulmonary branch; DORV

During mean follow-up of 7.66 ± 5.63 months, there was one operative death 21 days after surgery (Blalock-Taussig shunt with a 4-mm PTFE tube), and one late death 3 months after the procedure (Blalock-Taussig shunt with a 3-mm PTFE tube) in a patient who was readmitted with severe dehydration due to diarrhea. Both of them were cases of pulmonary atresia with intact septum.

Pulmonary artery rehabilitation was achieved in 60% of the patients, but was unsuccessful in two patients, whose pulmonary branches were disconnected.



Diagnostic catheterization: Angiography of pulmonary branches in anteroposterior view.

Fig. 1. A. 4-month-old patient with dextrocardia, double-outlet right ventricle (RV), severe pulmonary stenosis. Hypoplasia of the pulmonary branches. **B.** Post-surgery with right ventricle to pulmonary artery conduit, pulmonary branch plasty, and subsequent pulmonary branch angioplasty

Table 1 includes a summary of the surgical procedures and outcomes.

The modified Blalock-Taussig shunt was the preferred technique in our series. This procedure is the most widely used in the world, since it ensures controlled pulmonary flow with limited coronary diastolic steal, provided the tube size is chosen correctly; it is also easy to be controlled in subsequent surgeries. (1)

The central shunt (aortopulmonary septal defect through a PTFE tube or with a direct window) would offer some advantages: less chances of obstruction, more symmetrical flow, less distortion, and better postoperative management. Both methods may result in pulmonary congestion —due to improper shunt size— and in coronary steal, particularly with the central shunt. (1)

Some studies compared systemic to pulmonary shunts with the right ventricle to pulmonary artery connection, finding no differences in the development of the pulmonary tree. (2, 3)

Depending on the different series, overall mortality with Blalock-Taussig shunt varies between 2.3% and 16%, and between 9% and 11% in neonates. (4) The only operative death in our series was a patient with Blalock-Taussig shunt, who died 21 days after surgery.

Two central shunts were performed. This procedure is an effective option for diminutive pulmonary arteries, offering a pulsatile, symmetrical flow that encourages pulmonary arteries growth. (1, 5) However, one of these patients required therapeutic catheterization, reoperation with a new central shunt and pulmonary branch plasty, but the branches were disconnected during follow-up.

The right ventricle to pulmonary artery conduit is very popular in patients with pulmonary atresia, ventricular septal defect and hypoplastic pulmonary branches with aortopulmonary collaterals, and despite the advantage of enhancing pulmonary artery development has not been demonstrated in all studies, it does ensure greater stability, improved saturation, and decreased time between palliative surgery and the final procedure, with less obstruction, no coronary diastolic steal and less distortion of the pulmonary branches. (3, 6-8) This technique has the disadvantage of requiring cardiopulmonary bypass during surgery; in rare cases, aneurysm due to right ventricular outflow tract patch may occur. (3) It was used in a case of pulmonary atresia and ventricular septal defect, with positive outcomes.

Pulmonary artery rehabilitation was achieved in 60% of our patients. Various studies report ranges of success between 37% and 78% for pulmonary branch repair. (2, 8)

We had a significant number of reinterventions (50%): one surgical reintervention and four therapeutic catheterizations, which highlights the importance of catheterization (Figure 1).

All the procedures performed had been shown to

be useful in encouraging pulmonary arteries growth in all the publications reviewed.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable

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Rev Argent Cardiol 2022;90:230-232.
http://dx.doi.org/10.7775/rac.v90.i3.20524

Aneurysm of the Brachiocephalic Trunk. A Rare Entity

Injuries of the innominate artery, or brachiocephalic trunk (BCT), are exceedingly rare, and are associated with high blood pressure, smoking, syphilis, and

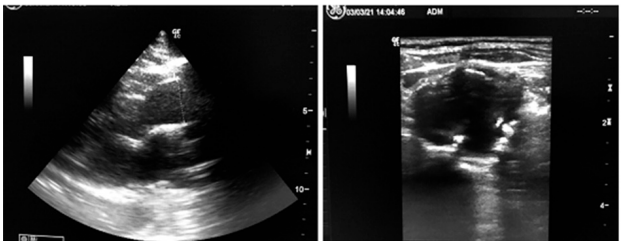

Fig. 1. Echocardiography. **A (left)**. Left parasternal long axis view showing mild elongation of the supravalvular aorta. **B (right)**. Fibro-lipid plaques at the aneurysmal level.

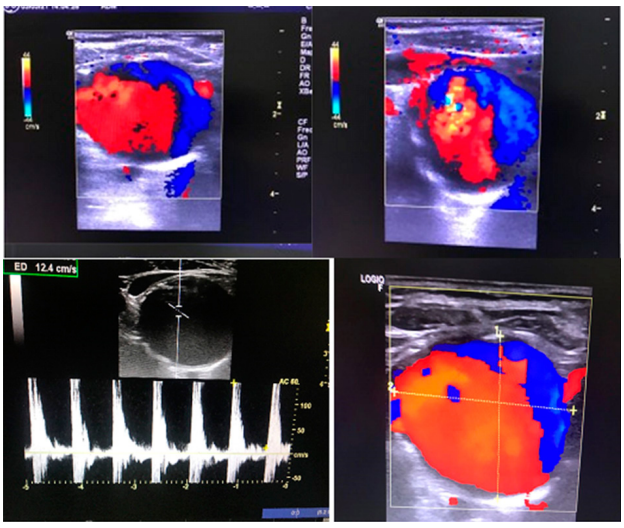

Fig. 2. Doppler ultrasound of the neck vessels. **A** (upper left). Two-dimensional ultrasound confirming BCT aneurysm. **B** (upper right). Color Doppler: bidirectional blue and red flow in Yin Yang. **C** (inferior left). Doppler flow with abnormal, monophasic waveform at the aneurysmal level. **D** (inferior right). Two-dimensional ultrasound showing fibro-lipid plaques and aneurysm size

probably other cardiovascular risk factors. Semiologically, they are detected as asymptomatic pulsatile masses. Clinically, BCT aneurysms are evidenced by their mass effect, compressing neighboring structures (dyspnea, dysphonia, stridor, dysphagia, superior vena cava syndrome). BCT aneurysms may present as arteriovenous fistulas, pseudoaneurysms, dissections or true aneurysms, and the rupture, with or without fistula formation, to the airway or gastrointestinal tract —particularly the esophagus— is the most dreaded complication. They can potentially result in systemic, central nervous system or right upper limb embolisms. Diagnosis is based on clinical suspicion and diagnostic imaging, mainly computed angiotomography, and thoracic and supra-aortic trunk angiography.

We describe the case of a 50-year-old female patient, 1.50 m tall and 64 kg, with a history of controlled hypertension under treatment. The patient started coughing, and a chest X-ray and computed tomography (CT) scan were requested as per protocol

to rule out COVID-19. Chest X-ray profile revealed a superior mediastinal mass compressing and displacing the trachea. CT scan reported BCT aneurysm; the patient was referred to our vascular ultrasound service to decide the course of action to follow.

Physical examination showed a right-suprasternal pulsatile mass and a systolic-diastolic murmur. Vascular ultrasound revealed a 35 x 28 mm BCT aneurysm and hyperechoic fibro-lipid plaques, with no significant obstructions. No aneurysmal dilatations were found in the remaining neck vessels. Echocardiography showed mild supravalvular elongation (33 mm) but no aortic dilatation (Figure 1). Color Doppler showed the Yin-Yang effect filling the aneurysm (Figure 2). No aneurysmal dilations were found in the upper and lower limb arteries. In view of this data, routine laboratory tests, thyroid hormones, glycemia, Hb A1C, and VDRL were requested. Antiplatelet drugs and rosuvastatin 20 mg/day were prescribed. The patient was referred to vascular surgery for either surgical or endovascular approach, but was admitted to hospital due to community-acquired pneumopathy, with good response to antibiotic treatment. After discharge, her case was discussed in a grand round, and it was decided to perform aneurysmal surgery. The patient is currently on the surgery waiting list.

BCT aneurysms are rare entities that may cause life-threatening complications, including rupture, fistulas or thromboembolism that may cause strokes; hence the importance of diagnosis and adequate treatment to prevent these complications. (1) Degenerative aneurysms are the most common type and are associated with thoracic and abdominal aortic aneurysms, with the BTC involvement in cases of type-A aneurysmal dissection. Jiménez et al reported a case of a 52 x 55 x 48 mm BCT aneurysm with intramural thrombus and mild tracheal compression, and visualization of about 6 x 6 cm right-suprasternal, soft, pulsating, non-tender mass in the carotid triangle, with thrill and murmur radiating to the neck. (1) It was associated with a second aneurysm > 5 cm diameter in the descending aorta. Both aneurysms were successfully treated by conventional surgery in two stages.

In a 40-year retrospective study, Bauer et al detected only six true BCT aneurysms from 73 surgeries of supra-aortic trunks and neck vessels. (2)

Pseudoaneurysms are more common due to motorbike or car accidents, and open trauma of the great intrathoracic vessels. Rupture is mainly associated with the presence of posttraumatic pseudoaneurysms. (3)

Autoimmune diseases, such as Takayasu arteritis, Kawasaki disease, giant cell arteritis, Marfan syndrome, or Behcet's disease, can also involve the innominate artery. (4) Surgical or endovascular treatment may be followed, depending on the case. (5) Kieffer et al (6) consider that the approach depends on the extent of the aneurysm. BCT aneurysms are therefore classified into three types: A: aneurysms not involving the origin of the BCT; although they are the most uncommon, they would be the easiest to treat using a termino-terminal bypass or an endovascular prosthesis. B: aneurysms involving the origin of the BCT; they are the most common ones. An aorto-BCT or aorto-carotid subclavian bypass originating from the ascending aorta is performed, and the origin of the BCT is sutured with a patch. C: aneurysms involving the entire BCT and the ascending aorta, requiring ascending aorta replacement, with or without aortic valve replacement.

While case reports are rare, BCT aneurysm is currently uncommon; we must be trained to determine its etiology and surgical timing. Surgical treatment is suggested for all symptomatic or ruptured aneurysms and for those > 3 cm. Surgery in these patients should be performed immediately, due to the risk of rupture and of secondary compression, which can be very serious.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable

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Rev Argent Cardiol 2022;90:232-233.
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Continuing Medical Education as Mainstay for Development

La educación médica continua como eje del desarrollo

As physicians, we walk through successive stages during our training. The first stage is undergraduate education at the university, which provides us with the necessary tools to begin our journey to become professionals. With the logical enthusiasm and the medical degree, we begin the next stage: training as specialists in which we enhance and expand our knowledge in the area we choose, which in our case is cardiology. Thereafter, there is a long and wide road ahead of us that we will have to travel for the rest of our professional life. This path of continuous training and updating has particular characteristics: it involves permanent transformation and we constantly incorporate new knowledge and sometimes we observe how what we believed to be established facts fall apart. It is at this stage that formal education with courses, seminars, among others, necessarily coexist with another less formal but no less important training tool, which is continuing education through peer-to-peer knowledge sharing, in which we are sometimes trainees and sometimes trainers of other colleagues. This is where the scientific societies play an extremely important role.

Continuing medical education is the only recognized treatment to prevent the progressive obsolescence of professional competence; it is an ethical responsibility of all healthcare professionals to ensure safe and scientifically supported healthcare for their patients.

Amanda Galli

In this permanent communication and sharing of knowledge, we adopt, internalize, and incorporate useful and essential knowledge for our professional practice. Each of us has a level of development within our training with established knowledge that allows for the incorporation of new concepts and approaches when the necessary tools are available to us. This zone of development that is close, at hand, can be reached by using our existing skills with the guidance or support provided by a more capable peer, adapting Lev Vygotzky's concept of learning. A pair that will give us the necessary scaffolding to climb one more step on the ascending path of our knowledge.

This is the fundamental and irreplaceable role of scientific societies in the current world. A world that is no longer limited to our daily work environment. We need our peers in our daily relationships but also in regional and international interrelationships to reach that "zone of proximal development" that is so necessary in a world in permanent change and evolution.

The SAC is committed to this target and has developed high-level courses that are offered, whenever possible, twice a year and in a virtual format that allows equal opportunities regardless of the place of residence.

We also organize workshops and case conferences with free access where opinions are fluently shared.

We also develop webinars, conferences and congresses with the participation of colleagues from other societies.

The recent congress on Imaging in Cardiology was attended online by more than 50 foreign guests, and hands-on workshops were held on a variety of topics.

The Argentine Congress of Cardiology will recover its usual face-to-face setting, with the active participation of several national and international guests. It will be a refreshing opportunity to strengthen bonds with our fellow countrymen and with cardiologists from sister regional societies.

We all need each other. Sharing makes us richer. The SAC gives you the opportunity to participate.

Dr. Héctor Deschle[MTSAC, FACC, FESC]
President of the Argentine Society of Cardiology